Opioids for the Treatment of Chronic Pain: Mistakes Made, Lessons Learned, and Future Directions

Jane C. Ballantyne, MD, FRCA

An overreliance on opioids has impacted all types of pain management, making it undoubtedly a root cause of the “epidemic” of prescription opioid abuse in the United States. Yet, an examination of the statistics that led the US Centers for Disease Control and Prevention to declare that prescription opioid abuse had reached epidemic levels shows that the abuse occurrences and deaths are arising outside the hospital or hospice setting, which strongly implicates the outpatient use of opioids to treat chronic pain. Such abuse and related deaths are occurring in chronic pain patients themselves and also through diversion. Overprescribing to outpatients has afforded distressed and vulnerable individuals access to these highly addictive drugs. The focus of this article is on what we have learned since opioid treatment of chronic pain was first popularized at the end of the 20th century and how this new information can guide chronic pain management in the future. (Anesth Analg 2017;125:1769–78)

The markedly increased prescribing of opioid analgesics in the United States beginning in the 1980s has been a root cause of the US epidemic of prescription opioid abuse and deaths. This increase in opioid prescribing occurred mainly because of increased prescribing for chronic pain. Relatively small increases in prescribing for acute pain concurrently occurred. While opioid prescribing for acute pain is typically finite and within the hospital setting, increased prescribing for acute pain contributed to this epidemic, largely because prescribing for acute pain can be an inadvertent gateway to long-term prescribing. Chronic pain is open-ended and ubiquitous and occurs outside the hospital or hospice. Unlike when opioids are administered in a hospital or hospice, outpatients control their own usage and can readily lose control of their opioid use.

Although the United States is the only country to officially declare opioid abuse an epidemic, it is not the only country either to recognize the problems associated with over-prescribing of opioids or to experience marked increases in opioid prescribing and associated increases in prescription opioid abuse and deaths. Canada is close behind the United States in its increased prescribing and related abuse and death rates. Other developed nations have not seen their levels of abuse and deaths rise, according to local government statistics, but they are seeing trends in prescribing that are similar to the United States and Canada.

In contrast, prescribing of opioids for chronic pain in developing countries is rare. These international differences likely stem from differences in culture, health care systems, health care availability and access, promotional activities by the pharmaceutical industry, drug availability, drug regulations, and clinical practice standards. While it could be argued that overprescribing is seemingly a uniquely North American problem, the insights gained mainly from North America can promote an understanding of the limits of opioid utility for treating chronic pain—lessons that are relevant to all continents and cultures.

As the pitfalls of prescribing opioids for chronic pain have gradually emerged since its expansion in the past 30 years, there has been an evolution away from thinking opioids were generally safe and had often been needlessly denied to the current understanding that safety considerations must be included in prescribing decisions. Initially, assumed rates of opioid abuse were in the order of 5%; newer data suggest rates of 12%–25%. Initially, it was argued that most abuse occurred in individuals obtaining prescription opioids through criminal or careless diversion and that risk mitigation strategies only needed to keep prescription opioids from getting into the wrong hands. The degree to which pain patients themselves were being overtly harmed by inappropriate opioid prescribing for chronic pain was being obscured by good intentions and wishful thinking by clinicians.

Against this backdrop, this article focuses on: (1) the evidence for chronic opioid therapy; (2) analgesic efficacy, dependence, and tolerance; (3) applying palliative care principles to chronic pain management; (4) opioids and the brain; and (5) adverse outcomes and inappropriate patient selection.

**EVIDENCE BASE FOR CHRONIC OPIOID THERAPY**

Because opioids have been recognized as effective analgesics for thousands of years, there was no great urgency to confirm their efficacy with clinical trials. That was until the mid-20th century, when the pharmaceutical industry introduced new opioids and formulations, whose efficacy needed to be compared to the efficacy of a standard like morphine to be approved for clinical use. They also needed to be tested in patients with chronic pain diagnoses, since before the mid-20th century, opioids were generally considered unsafe and ineffective for chronic pain. So began an era during which the number of randomized trials of opioids for chronic pain
increased several fold, subsequently leading to a new evidence base of systematic reviews and meta-analyses.\textsuperscript{36–19} The evidence from these individual trials and systematic reviews/meta-analyses confirms that opioids are effective and safe analgesics for many chronic pain diagnoses—at least during the conduct of controlled trials. No conclusions can be made about associated abuse and addiction risk, and findings on functional improvement and health-related quality of life are mixed. Furthermore, there are several limitations to currently available randomized trials in assessing the utility of chronic opioid therapy. Their duration is not long enough to be able to assess long-term efficacy or adverse outcomes. The study populations are highly selected and thus not representative of the general population. Most importantly, to be eligible, study patients cannot be at risk for substance abuse. Many analgesic trials utilize enriched enrollment, whereby patients who do not respond to the study drug during preenrollment are eliminated from the trial. All told, existing randomized trials, and the systematic reviews and meta-analyses upon which they are based, confirm early analgesic efficacy but do not provide information about real-world opioid utility for the treatment of chronic pain.\textsuperscript{20,21} Not surprisingly, since there were very few randomized trials available when chronic opioid therapy was initially promoted in the 1980s, the supporting evidence consisted mainly of small-scale observational studies, the potential weakness of which is now widely recognized. Looking back, it is somewhat surprising that an entire medical community was convinced by such marginal evidence. A representative 1986 paper by Portenoy and Foley\textsuperscript{11} was seminal in promoting chronic opioid therapy in the 1980s and 1990s. It was a retrospective observational study of 38 cancer survivors with unrelated noncancer chronic pain who had been treated with opioids for up to 6 years. The majority of patients obtained satisfactory analgesia throughout the study period and only 2 patients developed control issues. These authors and others reported substance abuse rates of only 1\% to 5\%. The Portenoy and Foley\textsuperscript{11} study was not the only observational study used to support chronic opioid therapy in the 1980s; however, it was widely cited and was confirmed by other similar observational studies. Opioids seemed to offer satisfactory analgesia for up to 6 years, with low rates of opioid abuse, albeit with mixed findings on function and health-related quality of life—overall supporting chronic opioid therapy.\textsuperscript{20,21} It was not until a decade or so after chronic opioid therapy became widely adopted in the United States and several other countries that an accumulation of larger scale, population-level data began to suggest that there were problems with the therapy. Although prospective longitudinal population studies (like other quantitative observational studies) can be fraught with systematic bias and confounding, they have several major advantages. They can assess what is happening in the real world, over many years, and they can provide an alert to problems. There will always be uncertainty about true causation versus simple association, but with enough consistent data, this type of evidence becomes convincing. In fact, it has been well-designed population studies that have almost exclusively provided the warnings that the rates of opioid-related abuse and deaths have increased to epidemic levels in the United States.\textsuperscript{2–16,22} In addition to providing these warnings, many prospective population studies have now demonstrated that the long-term analgesic and health effects of chronic opioid therapy are poor.\textsuperscript{23–30} One must ask why the outcomes in prospective population studies are so much worse than the outcomes in retrospective observational studies. Likely contributing factors to this difference are: (1) the more diverse population in population studies, not necessarily treated in the highly structured and constrained environment of a prospective observational study; (2) the mix of patients doing well and those doing poorly, whereas many patients doing poorly drop out of observational studies; (3) the length of treatment tends to be much longer in population studies; and (4) variations in practice, including use of monitoring and risk mitigation, occurring in population studies. Concerns about prescription opioid abuse has triggered renewed efforts in many countries to examine the evidence on chronic opioid effects, both positive and negative. Accepting that the risk of abuse is much greater than originally purported (>20\% in several recent studies),\textsuperscript{14,31–33} this begs the question: Do opioids actually work well in providing long-term pain relief? The US Centers for Disease Control and Prevention (CDC) commissioned 2 separate efforts to update the evidence, one a well-designed, intensive systematic review of available trials\textsuperscript{34} and the other a contextual review of population-level data.\textsuperscript{35} In both efforts, evidence could not be found to support long-term efficacy, although there was strong evidence of harm, particularly at high doses. As troubling as the lack of evidence to support long-term effectiveness, there was also no evidence that interventions intended to improve safety (eg, risk mitigation strategies). Nevertheless, there are patients who do well on chronic opioid therapy and whose lives are positively transformed by the treatment. This is supported by multiple anecdotal reports. What is not clear, and an important area for future research, is which patients can be predicted to have good outcomes versus those for whom opioids should be avoided. In summary, there is strong evidence to support short-term analgesic efficacy of opioids for chronic pain, and there is weak evidence to support longer-term analgesic efficacy. However, population studies reveal significant safety concerns and lack of long-term analgesic efficacy across the wider population. Whether long-term opioid therapy improves function and health-related quality of life is uncertain. There is no convincing evidence of long-term analgesic efficacy and strong evidence of harm, especially at high doses of >100 morphine milligram equivalents per day.

**ANALGESIC EFFICACY, DEPENDENCE, AND TOLERANCE**

Clinicians often encounter patients on long-term chronic opioid therapy, even at high doses, who still self-report 10/10 pain. This would seem to be a clear treatment failure. Yet these patients, and often their prescribing providers as well, believe that the opioid is the only thing preventing even worse pain or a return to the pain levels before starting the opioid. Whatever else is happening, it would appear that the opioid is failing as an analgesic.
There may be a substantial difference between continuous and intermittent opioid use. In the drug addiction literature, somewhat misleadingly, the word “abuse” was applied when drug use was intermittent and reversible (Diagnostic and Statistical Manual [DSM] IV).36–38 Intermittent use was a precursor to continuous use or “addiction” (again, misleadingly named “substance dependence”), in which physical dependence and tolerance coupled with aberrant behaviors characterize the disorder. These distinctions are no longer used in the latest addiction criteria (DSM V).39 Nevertheless, the long-established observation that dependence and tolerance go hand in hand with continuous use is relevant not only to addiction but also when opioids are used continuously and long term for pain treatment. Dependence and tolerance are inevitable neuroadaptations to continuous opioid use, and these adaptations could account in large part for analgesic failure.40 At the same time, it is possible that because these adaptations do not occur with intermittent or occasional use of opioids, analgesic efficacy may be better preserved if opioids are not used continuously. Preliminary evidence supports that intermittent use provides equivalent or better analgesia and is preferred by patients.41–44

Extrapolating once more from addiction medicine, when people transition from occasional use to continuous use, instead of providing euphoria, each dose is needed to avoid dysphoria.45 The adaptation is an attempt to restore hedonic homeostasis in the face of continued exogenous drug use. There is a shift from the normal state, in which normal endogenous responses are enough to maintain mood within a normal range, to the dysphoric state, in which only more drug can shift the dysphoria back to normal (Figure 1).

Consistent with this model, a similar process may occur with the analgesic effects of opioids. Again, in an attempt to maintain homeostasis, exogenous opioid that once produced pain relief is now operating in a hyperalgesic state, whereby only exogenous and not endogenous opioid can restore the normal or pain-free state.46 A proposed mechanism for failed analgesia is that patients taking opioids chronically are in a continuous state of withdrawal.47 Some investigators have proposed that chronic pain itself, even without the addition of exogenous opioids, is a state of dependence, tolerance, and continuous withdrawal because of the endogenous opioid response to chronic pain.48

Opioid dependence is understood to be an adaptation that causes withdrawal when the level of opioid use is reduced. Withdrawal comprises certain physical symptoms, such as agitation, nausea, diarrhea, pupillary dilation, and pain (withdrawal hyperalgesia), as well as psychological symptoms such as anhedonia. For pain patients, withdrawal hyperalgesia and anhedonia may be key drivers of their efforts to restore homeostasis through consuming opioid because pain, anxiety, and fear motivated them to take opioids in the first place. Tolerance to opioids is the need to take higher doses to achieve the same effect. Tolerance is far from simple. There are hundreds of molecular and cellular mechanisms occurring along pain pathways and in the “pain connectome,”49 the areas of the brain where simple noiceception is converted into action, that account for tolerance.50

It is especially difficult for the clinician to know how to respond to changes in opioid efficacy because many of the processes that produce tolerance are shared between opioid-induced hyperalgesia (associated with high-dose or high-potency opioid treatment), withdrawal hyperalgesia (associated with continuous opioid therapy), psychological or associative tolerance,51 and pharmacological or nonassociative tolerance (Table 1).51–55

Both dependence and tolerance are adaptations to continuous opioid use, and they cannot be separated. If tolerance develops, whether because of psychological and/or pharmacological factors, withdrawal symptoms, including a worsening of pain, will persist unless the opioid dose is increased (Figure 2). Each dose escalation will restore analgesic efficacy, but multiple dose escalations may be needed, leading to the distressing but all too common state in which no dose is enough.

Thus, we return to the question posed at the beginning of this section: What is happening when we see patients on long-term, continuous opioid therapy, possibly at high doses, who are still reporting 10/10 pain, yet they (and perhaps we) are convinced that their opioid treatment is the only thing that prevents their pain being even worse? The most likely explanation is that they have developed dependence and tolerance, which are impeding their ability to get pain relief from their opioid treatment. The idea that these patients are in a state of continuous withdrawal may explain this clinical scenario, and it is gaining credibility as we learn more about natural endogenous opioid actions.47,48

**APPLYING PALLIATIVE CARE PRINCIPLES TO CHRONIC PAIN MANAGEMENT**

The impetus to more widely prescribe opioids for chronic pain initially came from palliative care; and then from the pharmaceutical industry. Palliative care specialists argued that because cancer pain could be effectively treated with...
also be treated with opioids.\textsuperscript{11} This was largely a moral argument. opioids, chronic pain, which caused equal suffering, should also be treated with opioids.\textsuperscript{33} This was largely a moral argument. The pharmaceutical industry was concomitantly developing and promoting new long-acting opioid formulations like MS Contin (Purdue Pharma LP, Abingdon, MD). The goals of palliative care and industry naturally coincided. The principles of cancer pain treatment suited both stakeholders and their causes.

First proposed in the 1986 World Health Organization analgesic ladder approach for cancer pain, the titrate-to-effect principle (matching dose with effect) was predicated on analgesic doses being escalated to reduce pain levels as much as possible, with no upper dose limit for opioids.\textsuperscript{56,57} Long-acting opioids were developed so that cancer patients would have more sustained pain relief. The concept that opioids will improve rather than worsen dysfunction associated with chronic pain, which may occur if opioids are used in a way that does improve pain. But it appears that paradoxically, high-dose opioids often do not improve pain, and may even make pain worse. This is not a simple paradox. The need for higher doses to achieve the same effect. Tolerance develops to both the euphoric and the analgesic effects of opioid but by different mechanisms and at different rates. The below-listed mechanisms could all contribute to a clinical picture of opioid tolerance.

**Tolerance**
- The need for higher doses to achieve the same effect. Tolerance develops to both the euphoric and the analgesic effects of opioid but by different mechanisms and at different rates. The below-listed mechanisms could all contribute to a clinical picture of opioid tolerance.
- Withdrawal hyperalgesia
- Nonassociative (pharmacological) tolerance

**Opioid-induced hyperalgesia**
- The need for higher doses to achieve the same effect. Tolerance develops to both the euphoric and the analgesic effects of opioid but by different mechanisms and at different rates. The below-listed mechanisms could all contribute to a clinical picture of opioid tolerance.
- Associated (psychological) tolerance
- Can arise in the case of all the central effects of opioids, including euphoria and dysphoria, sedation, analgesia, and nausea. This type of tolerance involves learning, and its development is linked to environmental or contextual cues.\textsuperscript{54,52}
- Nonassociative (pharmacological) tolerance

**Withdrawal hyperalgesia**
- A cardinal sign of physical withdrawal from opioids. Often manifests as flu-like aches and pains or worsening of underlying chronic pain.

**Tolerance and dependence work together. Both tolerance and dependence are adaptations to continuous opioid use, and they cannot be separated. If tolerance arises, whether because of psychological or pharmacological factors or both, withdrawal symptoms, including a worsening of pain, will persist unless the opioid dose is increased. Each dose escalation will restore analgesics efficacy, but multiple dose escalations may be needed, leading to the distressing but all too common state where no dose is enough.

**Table 1. Tolerance to Opioids and Related Definitions**

<table>
<thead>
<tr>
<th>Tolerance</th>
<th>Opioid-induced hyperalgesia</th>
<th>Withdrawal hyperalgesia</th>
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<tr>
<td>A state of nociceptive sensitization caused by exposure to opioids. Often manifests as allodynia.</td>
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**Figure 2. Tolerance and dependence work together. Both tolerance and dependence are adaptations to continuous opioid use, and they cannot be separated. If tolerance arises, whether because of psychological or pharmacological factors or both, withdrawal symptoms, including a worsening of pain, will persist unless the opioid dose is increased. Each dose escalation will restore analgesics efficacy, but multiple dose escalations may be needed, leading to the distressing but all too common state where no dose is enough.**
and cortical areas, now termed the “pain connectome” or involve the endogenous opioid system in reward, limbic, into chronic opioid therapy, pain has become chronicified complex chronic pain patient, who is the most likely to enter ment, surgery, injections, or physical therapy. But for the pain if we oversimplify, or think that its intensity is all there est distress is likely to be the patient with the greatest risk or even any opioid will help. By ignoring the patient behind much a cry for help as it is an indication that a dose increase would probably have been avoided.

The other side of the dose/effect equation is perhaps even more important than the titrate-to-effect principle, tending over time to lead to higher doses that are neither effective nor safe. The effect, a lowering of the pain intensity, may be the wrong goal for chronic pain treatment. It has been argued that a lowering of pain intensity per se is neither sufficient nor necessary for reducing the suffering associated with chronic pain. Reducing a unidimensional pain score using opioids may be the wrong focus, selects the wrong patients, and misunderstands chronic pain. For example, if using increasing doses of opioids to achieve repeated but nonsustained reductions in pain intensity comes at the price of less ability to function, such dose escalation and titrating to effect has not improved health-related quality of life. Had the focus instead been on function and not on pain intensity, excessive dose escalation would probably have been avoided.

A patient’s self-report of high pain intensity may be as much a cry for help as it is an indication that a dose increase or even any opioid will help. By ignoring the patient behind the pain score, we often miss that the patient with the greatest distress is likely to be the patient with the greatest risk for aberrant behavior and poor outcomes. This is the patient who may do better with alternative approaches.

Finally, and most complex, we misunderstand chronic pain if we oversimplify, or think that its intensity is all there is to it. Chronic pain comes in many guises, some of which have obvious solutions such as primary disease management, surgery, injections, or physical therapy. But for the complex chronic pain patient, who is the most likely to enter into chronic opioid therapy, pain has become chronicified largely through adaptations in the brain. These adaptations involve the endogenous opioid system in reward, limbic, and cortical areas, now termed the “pain connectome” or “pain saliency network.” Endogenous and exogenous opioids have a greater effect on the emotional component of pain than the sensory, and that, in this respect, the salience or meaning of pain is more important than its intensity.

OPIOIDS AND THE BRAIN

Despite thousands of years of using plant-derived opiates to treat pain, that opioids work via an endogenous opioid system was not confirmed until as late as the 1970s. Since that discovery, however, our understanding of what opioids do to the brain has advanced rapidly, and completely altered the way we think about pain and its treatment. It is longer postulated that opioid-induced pain relief and addiction occur as distinct processes in distinct areas of the brain. There are many ways in which pain and reward operate together to maintain homeostasis, calculate pain salience, and produce learned protective and survival behaviors, both on an evolutionary and an individual basis. What follows is that whether or not pain relief is the goal of opioid treatment, opioid drugs used continuously will have effects far beyond simple analgesia. Addiction is not inevitable, but alterations in hedonic tone, ability to feel pleasure, ability to socialize, and ability to evaluate and prioritize will all be compromised.

Pain Chronification in the Brain

There are many processes that contribute to chronic pain: inflammatory, neuropathic, central, and psychological. Whatever the contributing causes of chronic pain, the continuous stress of chronic pain will produce responses in the brain that can now be measured with functional magnetic resonance imaging, combined with psychophysical, genetic, and other approaches.

Accumulating evidence suggests that in chronic pain states, the brain undergoes extensive reorganization secondary to aberrant learning. It has been proposed that experienced or perceived chronic pain results from dysfunctional learning, which has been likened to the dysfunctional learning that converts functional rewards into the craving that defines addiction (Table 3). In both cases, the learning is occurring in overlapping reward, limbic, and cortical centers, and is mediated by endogenous opioids and dopamine. This has led some investigators to propose that chronic pain is less a sensory problem and more a reward problem.

The aim of the central processes and endogenous opioid systems is to maintain homeostasis. For some individuals, this successfully suppresses the pain experience; for other more vulnerable individuals, it does not. A recent study in patients with chronic back pain demonstrated how pain can shift from expected sensory regions in the brain into limbic areas like the medial prefrontal cortex and amygdala. Germane to the use of opioids to treat persistent pain is that both endogenous and exogenous opioids suppress pain mainly through their effects in the emotional areas of the brain to which pain shifts as it chronifies, with resulting almost negligible effects on sensory transmission.

It follows that when an opioid is used to treat chronic pain, it is mainly treating the affective and not the sensory component of pain. The treated patient may care less about pain, but the pain itself is unaltered.
Reward Deficiency and Chronic Pain

Expanding upon that chronic pain is less a sensory problem and more a reward problem, Elman and Borsook have suggested that neural changes are similar between chronic pain and long-term substance abuse; thus, the proclivity for addictive behavior is ingrained in pain neuropathology. Chronic pain produces a state of reward deficiency or anhedonia, meaning that chronic pain patients have a reduced capacity to experience pleasure, similar to long-term substance abusers. Not only are the dopamine-mediated wanting and opioid-mediated liking of normal rewards like food and sex diminished, the reward and salience associated with pain relief are increased. This sets the chronic pain patient up for incentive sensitization and craving, which could ultimately lead to addiction. This is one of many credible reasons that rather than protecting from addiction, as we once thought, chronic pain is a risk factor for addiction.

Social Functions of Opioids

Interestingly, as organisms become more dependent on social functions, endogenous opioids play an increasing role in socialization. In amphibians, endogenous opioids have analgesic functions only. In mammals, endogenous opioids play an additional and increasingly complex role in social behaviors that are crucial to survival. In humans, this extends to socialization necessary for the survival of the species, not just the immediate family or social circle. Carr has recently argued that pain modulation by endogenous opioids is secondary in importance for humans to “behavioral fine-tuning to help the population as a whole survive threats beyond trauma to the individual.”

Human social interactions trigger the release of endogenous opioids. Recent human studies have concluded that the reward of social touch is mediated by endogenous opioids. The administration of a μ-opioid receptor antagonist decreases interest in social relationships, highlighting the importance of endogenous opioids in social interactions. Separation elicits distress through low opioid receptor activity, while reunion elicits comfort through high opioid receptor activity. Given that social function is so important for human survival, the reinforcement of social bonds through opioid reward is an essential opioid function.

Individuals who experience repeated social rejection or abuse, particularly in childhood, may develop dysfunctional opioid regulation, which is thought to underlie many neuropsychiatric diseases, including posttraumatic stress disorder, chronic pain, substance abuse, and depression. Early research on “opioidergic” tone suggest that the innate properties of the endogenous opioids system coupled with adaptations that could arise as an individual is confronted with stress could contribute to vulnerability and resilience. Social rejection is thereby a common precursor to risk for opioid craving, use, and abuse.

ADVERSE OUTCOMES AND ADVERSE SELECTION

It has already been highlighted that many of the adverse outcomes of chronic opioid treatment can be linked to high doses (Table 2). The United States may be the only country where overprescribing of opioids has led to an epidemic of abuse and deaths. This overprescribing has fortuitously produced a wealth of data from which the United States and other countries can learn. One clear message is that the patients taking high opioid doses are the same people who could be predicted to have poor outcomes. In other words, their comorbidities predict outcomes such as problematic opioid use, loss of control over use, opioid use disorder, accidental overdose, suicide, and analgesic failure. These specific comorbidities include depression, anxiety, posttraumatic stress disorder, personality disorder, prior substance use disorder, and family history of substance use disorder.

Patients who are taking high doses of opioids and are at risk of adverse outcomes are a self-selected high-risk group. This phenomenon has been termed “adverse selection.” It is possible that adverse outcomes are occurring not because of the high opioid doses per se but because of the risk factors in the patients that tend to be prescribed high doses. They are not the patients taking stable low to moderate doses of opioids that are not escalated. They are also not the up to 40% of people who are started on chronic opioid treatment but discontinue them because they do not like the effects.

Why is this important? First, because it suggests that the pain patients who contribute to the sobering statistics of abuse and deaths start out being at risk, and it is their risk factors that put them on the trajectory to high and unsafe dosing. Second, because it ties in with what new research is discovering, namely, that people with complex refractory chronic pain tend to have reward deficiencies that put them at high risk for craving opioids, losing control of their opioid use, becoming socially isolated, and being unable to carry out normal social functions.

It could be said that the US epidemic of prescription opioid abuse and deaths has occurred because we have put highly addictive drugs into the hands of a distressed population that is at high risk for not being able to control their usage. The question should now be: can we control the epidemic by being more selective about who receives opioid pain treatment?

Many lines of evidence support that it is increased prescribing for chronic pain that has produced the epidemic, not prescribing for acute pain or pain at the end of life. But this is because the amount of opioid used for chronic pain, which is open-ended, is necessarily much higher than the amount used for acute or end-of-life pain, which are time-limited. Moreover, prescribing for chronic pain generally gives control of opioids to patients themselves, whereas prescribing for acute and end-of-life pain is generally more controlled. Nevertheless, the treatment of acute pain with opioids is a common gateway for long-term opioid prescribing and, after surgery or trauma, has been a common source of excess opioids in people’s homes. State governments are now taking matters into their own hands and introducing dose limits for chronic opioid therapy and duration limits for acute pain. But if we understand adverse selection and the effects of chronic pain and opioids on the brain, will either of these initiatives actually control the epidemic?

CONCLUSIONS

This article is written within the context of articles that relate the practice of anesthesia and pain medicine to the opioid
abuse epidemic. Hence, the author has chosen to review new evidence on chronic pain and opioid mechanisms that could help inform why the epidemic happened, how to stop it, and how to avoid it in the future.

Additional topics such as how-to-use-opioids-for-chronic-pain are not discussed here, since this information is available in multiple papers, guidelines, text books, web-based educational materials, and the US Food and Drug Administration Risk Evaluation and Mitigation Strategies (available online for prescribers of long-acting opioids).

The principles of safe prescribing of opioids for chronic pain are summarized in Table 4. This article also does not describe treatment approaches for the millions of patients already dependent on opioids, often taking doses that are higher than those currently recommended, for example, by the US CDC. Although we are learning how difficult it is to motivate patients to taper or discontinue opioid treatment, that not all individuals can be tapered without risk of relapse, that buprenorphine/naloxone is proving to be a useful tool for stabilizing opioid-dependent people, and that these patients need counseling as much as they need an opioid stabilization regime, we do not yet have enough experience to know if we are correct in this approach. This is an area in which research is desperately needed.

What We Can Learn From Existing Basic Science and Clinical Data

1. Opioid analgesic efficacy often declines with continuous use because of the adaptations of dependence and tolerance, theoretically producing a state of continuous withdrawal. This may not be true if opioids are taken intermittently.

2. Applying the treatment principles of palliative care to chronic pain management, namely titrate-to-effect and breakthrough pain principles, has resulted in very high-dose usage. High doses have been shown to be unsafe and ineffective.

3. Chronic pain should be thought of as a stress response involving the endogenous opioid system in reward, limbic, and cortical areas of the brain. Contrary to previous beliefs, people with refractory complex chronic pain are at high risk of abuse.

4. Individuals who most want or need opioids are at the highest risk of poor outcomes, including inadequate pain relief despite repeated dose escalation, problematic use, abuse, and death.

Principles for Opioid Prescribing in the Case of Chronic Pain

Opioids are neither effective nor safe enough to warrant their widespread use.34,35,109 We should begin to think of opioid treatment for chronic pain as the exception rather than the rule. The question of who the best candidates are for chronic opioid therapy is not simple, and not one that has achieved consensus. However, we can turn to early evidence that for many common chronic pain conditions, such as nonstructural low back pain and central pain states (typified by fibromyalgia), alternatives to opioids, particularly behavioral and physical treatments, appear to afford superior efficacy and greater safety.110–115 This suggests that for these common pain conditions, opioids should not be used at all.116

An approach that the author finds helpful is that chronic opioids should be reserved for cases that require comfort care and not functional restoration.117 This idea is based on what is now strong evidence that, again, contrary to what we once believed, chronic opioid therapy delays rather than promotes functional recovery and return to work.218–213 This approach tends to eliminate young people who have many alternative approaches they can use, some tapping into their own powerful endogenous opioid systems.

We also now have the benefit of a wealth of new science that provides insight into what actually happens to the brain when pain becomes chronic, how connected pain and reward systems are through the endogenous opioid system, how this affects basic motivations and social functions, and what happens to the brain when we use exogenous opioids. This all points to what was an emphasis in this article—that brain adaptations to exogenous opioids are more likely to arise with continuous than intermittent opioid use. There are other reasons to avoid long-acting round-the-clock opioids when treating chronic pain, and this indeed has been a recommendation of the CDC,34,108 but the most fundamental reason is that if we put people into a state of continuous withdrawal, we do not help their pain, we compromise safety, and we change their motivations and beliefs.

Table 4. General Principles for Safe Chronic Opioid Prescribing

<table>
<thead>
<tr>
<th>Principle</th>
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<tr>
<td>1. Start with full H&amp;P, including making diagnosis and assessment of risk versus benefit.</td>
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<td>2. Obtain a written agreement or “contract” with established goals.</td>
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<td>3. Risk stratify, and stratify monitoring and treatment accordingly.</td>
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<td>4. Check the prescription monitoring data (PDMP) with each prescription.</td>
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<td>5. Check a baseline UDT. Thereafter, check UDT, do pill counts, etc, as indicated.</td>
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<td>6. Be prepared to taper and discontinue if goals are not met.</td>
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<td>7. Use extra caution at high doses.</td>
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<td>8. Prescribe naloxone if dose is high.</td>
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<td>9. Do not use concomitant sedative hypnotics.</td>
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Abbreviations: H&P, history and physical examination; PDMP, prescription drug monitoring program; UDT, urine drug test.

ACKNOWLEDGMENTS
The author acknowledges Thomas Vetter for his review and input to the manuscript.

DISCLOSURES
Name: Jane C. Ballantyne, MD, FRCA.
Contribution: This author was solely responsible for the manuscript.
This manuscript was handled by: Honorio T. Benzon, MD.

REFERENCES


