Opioid Therapy in Chronic Pain

Jane C. Ballantyne, MD, FRCA

INTRODUCTION

Opioids have a long history of use for the treatment of pain, and despite efforts to find alternatives, they remain the strongest and most effective analgesics available. The downside is that they are addictive and potentially dangerous, especially when used not as prescribed, and there are many complex reasons why opioids used to treat pain in outpatients, who control their own use, may not be taken strictly as prescribed. Throughout history, although recognizing the value of opioids in treating serious pain, especially acute pain and pain at the end of life, there has been caution about using opioids to treat chronic pain. This caution existed because of the perceived increased risk of addiction when opioids are used long term and at home. There has been a surge in prescribing of opioids for chronic pain, especially in the United States, and this surge has been produced by a combination of increased availability, production of new opioids and new formulations that have been aggressively marketed, and changed beliefs about whether the risk of addiction for some should preclude use when it might help the many who do not become addicted.1 The surge in prescribing for chronic pain has produced a parallel increase in cases of opioid abuse and related deaths,1-3 and despite what is now more than 2 decades of experience, it is still unclear whether, and under what conditions, opioids can be used to treat chronic...
pain safely and effectively. Many questions remain, but what this article presents is how opioids should be used to treat chronic pain considering recent concerns about their efficacy and safety.

PATIENT SELECTION

Not all patients are suitable candidates for opioids. In fact, proper selection of candidates for the treatment can do more to improve efficacy and safety than any other aspect of managing the treatment. It is tempting to think that a patient’s complaint of severe pain is enough to warrant use of strong pain medications. Recent teaching has been that a report of severe pain warrants treatment with opioids if all efforts to use alternative treatments have failed. But recent evidence shows that for some pain conditions, opioids not only may not work well but also may hinder the progress toward recovery that can be achieved by other means.4–9 It is becoming clear that this is true for several pain conditions and is particularly true for musculoskeletal pain. Opioids allow people to rest comfortably and are useful for providing comfort.10 They are also useful during acute onset or acute exacerbations of pain when they can reduce pain enough to start the process of active rehabilitation. With long-term usage, however, they may have a different role. Analgesia is not always maintained long term, and the numbing effect of opioids tends to make people less inclined to move even when exercise, or at least maintained activity, is the intervention most likely to achieve recovery. There are many musculoskeletal conditions and so-called centralized pain states such as nonstructural low back pain or fibromyalgia, where the numbing effects of opioids can actually lessen the likelihood of recovery.11–15 At the same time, when there is significant damage due to disease, trauma, or surgery, and normal activity is not a realistic goal, the numbing effect of opioids can be helpful and may even improve function in patients with serious functional incapacity. Opioids at low doses can also be helpful in low-risk patients who are intolerant of alternative treatments and cannot realistically be active, for example, the elderly. Choosing candidates for opioid therapy based on their disease state and not on their reported pain severity has several advantages. It allows one to exclude cases that are more likely to recover without opioids. It allows one to target opioids only toward cases that can be improved. It removes the need to make judgments about pain severity and what a report of pain suggests. Past teaching was that because pain is a subjective experience, “pain is what the reporting person says it is.” Although this is indisputable, severe pain that would be better managed without opioids should not be treated with opioids simply because of a report of severe pain. Decisions about the suitability of opioid treatment must always be made on an individual patient basis, but Table 1 attempts to summarize some of the broad categories of suitability for long-term opioid treatment.

BASIC PRINCIPLES OF CHRONIC OPIOID MANAGEMENT

- Decisions about opioid treatment always take place after a full history and physical examination and after reaching and documenting a pain diagnosis.
- Continuous treatment with an opioid for 90 days or longer is COT.16
- At 90 days, or preferably sooner, a process of shared decision making needs to occur concerning whether COT is a good choice.17–21
- Before offering COT21
  - Patient completes a screening instrument for addiction risk.
  - Baseline urine drug toxicology screen is done.
  - If available, active or prior usage is checked in prescription monitoring system.
Decision to treat is made based on benefit versus risk.

If COT is chosen, the following safeguards are necessary:

- Patient studies and signs a treatment agreement that includes a statement of agreed goals.
- Patient receives prescriptions in person on a monthly basis or more frequently if high risk.
- Once effective dose is established, dose escalation is avoided.
- Either long-acting opioid or short-acting opioid is used but not both.
- Concomitant sedatives should not be used, especially benzodiazepines or alcohol.
- Goals are reassessed regularly (at least 3 monthly).
- Urine drug test (UDT) is repeated according to clinic standards.
- Opioid is weaned if goals are not met or for noncompliance.
- The lowest effective dose should always be used and should not exceed 100 mg morphine equivalent daily dose (MEDD) (see the “Opioid Medication Choices” section for definition of MEDD).
- Safe-keeping practices and disposal of unused opioid should be encouraged.

**Starting Chronic Opioid Therapy**

Most COT begins with short-term opioid therapy. For example, the opioid is used to treat an acute exacerbation of chronic back pain or pain after surgery or trauma. Occasionally, administration of opioids is started in the absence of an acute exacerbation. Short-term opioid therapy should not be allowed to become COT without a formal...
decision that COT is indicated. When using opioids to treat acute pain, the likely duration of pain should be kept in mind and only the amount and duration that is necessary should be prescribed. Most routine surgery and trauma do not require opioids after 3 days. Sometimes longer is needed, but prescribing for acute pain should never be open-ended. Susceptible individuals may rapidly progress to dependence or addiction.22

Evidence suggests that patients treated with opioids for 90 days or longer are likely to continue treatment for life.17–20 Ninety days is also the point at which persistent pain is termed chronic.16 If opioids have been provided continuously for 90 days, this would be a reasonable stopping place, or a time to define the treatment as COT if the decision is to continue the opioid.

Before starting COT, there must always be a fully documented history and physical examination (repeated if the patient is inherited), culminating in a pain diagnosis. Screening for addiction risk should ideally take place before starting an opioid (ie, before short-term treatment is started), but failing that, screening should take place before starting COT. Table 2 lists some commonly available screening tools.23–27 The simplest and most commonly used is the Opioid Risk Tool (Fig. 1). A baseline UDT should also be performed before starting COT (see the “Urine Toxicology” section for more details on urine drug toxicology). COT may be contraindicated in patients with high risk of addiction or with illicit drugs in the urine.

**Decision to Treat**

The decision to use COT should never be considered trivial. COT has huge implications for patients’ lives, including the likelihood that they will not return to work,7,20,28–32 they will be infertile and lose libido,33–35 they risk becoming dependent,36,37 they may become cognitively impaired, and pain relief will be partial at best.38 Ideally, family members should be included in the decision. COT also has huge implications for the prescriber, because neither is COT simple nor are the patients who receive this treatment simple: the treatment can be draining of both resources and time. For the right indications, COT can be tremendously valuable, and worth the effort, but COT should never be undertaken lightly.

**Reducing the Risks of Chronic Opioid Therapy**

**Written agreements**

The best way to reduce the risk of COT is to ensure that the patient is well informed about the limitations and risks of COT, as well as the safe keeping of the medications.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Commonly used opioid risk screening instruments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butler et al,63 2004</td>
<td>Screener and Opioid Assessment for Patients with Pain (SOAPP) 5-, 14-, or 24-item questionnaire. Completed by patients</td>
</tr>
<tr>
<td>Webster &amp; Webster,25 2005</td>
<td>Opioid Risk Tool (ORT) 5-item questionnaire. Completed by patients</td>
</tr>
<tr>
<td>Passik et al,26 2005</td>
<td>Pain Assessment and Documentation Tool (PADT) Assesses 4 domains. Completed by physicians</td>
</tr>
<tr>
<td>Belgrade et al,27 2006</td>
<td>Scoring system to predict outcome (DIRE) Assesses 4 domains (diagnosis, intractability, risk, efficacy). Completed by physicians</td>
</tr>
<tr>
<td>Butler et al,24 2007</td>
<td>Current Opioid Misuse Measure (COMM) 17-item questionnaire. Complete by patients</td>
</tr>
</tbody>
</table>

Data from Refs.24–27,63
Written agreements can be useful as educational tools, as well as for documenting patients’ acceptance of the terms of treatment and their stated goals. Many other educational tools are available, including more comprehensive written materials, videos, and Web sites, and patients should be encouraged to pursue these. However, a simple and short written agreement in lay language is probably preferable as a starting point. Box 1 lists the principles that should be present in a written agreement. Fig. 2 is an example of a written agreement.

**Fig. 1.** Stratifying risk: opioid risk tool. (*Adapted from* Webster LR, Webster RM. Predicting aberrant behaviors in opioid treated patients: preliminary validation of the opioid risk tool. *Pain Med* 2005;6(6):433.)
Urine toxicology

Urine toxicologic tests are imperfect and complex but have become a standard of care during COT. Simple dipsticks that can be used in the clinic are notoriously inaccurate; there is a high rate of both false-positive and false-negative results. Nevertheless, they are much cheaper than the laboratory-based tests, and it is reasonable to use a simple test before progressing to a laboratory test, particularly as a means of familiarizing patients on COT with the process of giving urine and the need to give urine as a routine part of COT. The least likely compounds to give false-positive results are cocaine and amphetamines, so if these are found at initial simple in-house screening, that may be a reason to postpone starting COT until confirmatory tests can be completed and further history sought if necessary. Opioids are the most likely to show false-positive and false-negative results. No action should be taken on dipstick testing, and even after confirmatory laboratory testing, no action should be taken without discussing the result with the laboratory because there are many reasons that an unexpected test result may be due to factors other than taking a nonprescribed substance or not taking the prescribed opioid.

For medical purposes, giving urine is usually done unobserved. Urine specimens can easily be adulterated or swapped. Tampering or swapping can be detected to some extent by shaking the urine to test for frothiness (possible soap contamination), assessing its color, and measuring its temperature and pH immediately after collection.

The appearance of opioid metabolites can be confusing. For example, codeine is metabolized to morphine, hydrocodone may be metabolized to hydromorphone, and oxycodone may be metabolized to oxymorphone. Tests for oxycodone may not have the sensitivity to pick up low levels.

Weaning

It is easy to say if the treatment does not work, stop it. Or if aberrant behaviors arise, stop the treatment. It is not always easy to wean opioids, and in fact, it may not always be appropriate even in the face of poor efficacy or aberrancy. Patients who are given opioids for a long time become dependent on them (see Section “Dependence and Addiction”).37 Not all dependence is addiction, but dependence is often hardwired and difficult to reverse, especially when it accompanies prolonged treatment, which makes it important (1) not to use COT other than for the most refractory of cases in

---

<table>
<thead>
<tr>
<th>Box 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Core features of an opioid care agreement</strong></td>
</tr>
<tr>
<td>1. Pain medications cannot be refilled early.</td>
</tr>
<tr>
<td>2. Refills require a clinic visit by appointment.</td>
</tr>
<tr>
<td>3. No urgent requests for refills. Call to make appointments in advance.</td>
</tr>
<tr>
<td>4. Lost or stolen pain medications or prescriptions cannot be refilled. They must be safeguarded.</td>
</tr>
<tr>
<td>5. Never get pain medication for chronic pain from other clinics or emergency rooms.</td>
</tr>
<tr>
<td>6. If you get any pain medications from another provider for any other reason, you must tell your provider here immediately.</td>
</tr>
<tr>
<td>7. Do not share, sell, or trade your pain medications with anyone.</td>
</tr>
<tr>
<td>8. You must allow your urine to be tested for drugs at any time.</td>
</tr>
<tr>
<td>9. Failure to follow these rules may result in discontinuation of your pain medications.</td>
</tr>
</tbody>
</table>
If I want to get refills of my pain medicine, I have to come to all of my appointments (at least every 6 months).
If I miss more than 2 appointments without calling ahead to cancel, my doctor may stop prescribing this medicine for me.
I cannot get pain medicine from any other doctor or clinic, unless I am in the hospital or my doctor says it is okay.
I should keep my appointments with other doctors, therapists, and other treatments for my pain in order to get refills of my medicine.
I will tell my doctor if the medicine is not helping my pain, and will not take more medicine on my own or run out early.
To get more medicine, I need a paper prescription. These medicines cannot be called into the pharmacy, or filled on a night, holiday, or weekend.
I may get the prescription from my doctor at my regular appointment, or by calling the practice at least 3 business days before I run out. I may not just walk into the office and ask for a refill.
I will keep my medicines in a safe place. If my medicine is lost, damaged or stolen, I may not get a new prescription.
I agree to have a urine drug test at any time. If I don’t take the test, I will stop getting the medicine.
If I share, sell or trade my medicine or use illegal drugs or other pain medicines, my doctor may stop giving me this medicine.
If I act out at the staff or my doctor, I will not get my medicine, and may be asked to leave the clinic.
I understand that this medicine may not work for my pain. If this happens, my doctor may stop giving this type of pain medicine to me.
If I do not follow this agreement, my doctor will stop giving me this type of pain medicine.
I will get my pain medicine at only one pharmacy.

I have read this agreement, understand it, and will follow it.
Patient Signature ________________________________________________________ Date______________
Physician Signature_____________________________________________________      Date______________
Pharmacy ________________________ City _____________________________ Phone ________________________

Fig. 2. Opiate pain medicine agreement. (Courtesy of Robin Canada, MD, David Goldman, MD, Craig Wynn, MD. Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA.)

which the treatment can provide comfort and risks are acceptable and (2) to stop COT early or as soon as it becomes evident that it is not meeting goals of treatment.
Principles of weaning are as follows:

- Patient must agree.
- Structure a weaning protocol (eg, 10% reduction in dose per visit).
- Be prepared to plateau (most patients tolerate a few dose reductions and then stall; it is reasonable to allow a break and then restart the wean later).
• Be prepared to fail (if a wean is not tolerated, be prepared to continue opioid for life).
• If a wean is not tolerated, patient is likely to have complex and persistent dependence; treat this much like addiction, with opioid maintenance and counseling.
• Always consider the possibility of addiction and need for addiction treatment.

DEPENDENCE AND ADDICTION

• There are special considerations when using COT in patients with known risk of substance abuse.
• Dependence or addiction may arise during COT in any patient.

Using Chronic Opioid Therapy in Patients with Risk of or Current Substance Abuse

Neither risk of nor current substance abuse precludes the use of COT. However, in both cases there is a high risk of development or worsening of addiction; this means that COT should not be used without the full understanding of risks by both patients and their families. Full precautions should be taken (eg, only use long-acting opioids, pick up prescriptions weekly or even daily if indicated, use frequent UDTs and random pill counts, involve family in giving medications, involve family in safe keeping of medications, and reevaluate frequently).

Dependence or Addiction Arising During Chronic Opioid Therapy

Dependence on opioids is completely expected during COT, particularly extended COT. Dependence essentially means that there are symptoms of withdrawal if the drug is withdrawn or the dose reduced, when circumstances change and the dose requirement changes, or if tolerance develops and is not satisfied by a dose escalation. For a few patients, withdrawal consists simply of classic withdrawal symptoms such as pupillary dilatation, goose flesh, nausea and vomiting, abdominal pain, tachycardia, worsening pain, and agitation. These physical symptoms of withdrawal usually subside within weeks of discontinuing opioid altogether, although they may recur as circumstances change for a patient receiving COT. But for many patients, there is also a psychological component to withdrawal, which does not reverse easily and may be a strong factor in difficulty weaning patients from opioids, especially when they have been receiving COT for a long time. The combination of physical and psychological dependence can seem much like addiction because the dependence is a strong driver of opioid-seeking behavior, behavior that may even seem compulsive. Some patients on COT exhibit clear signs of true addiction, and if they do, they should be referred for specialty treatment. Many fit into a gray zone between clearly not addicted and clearly addicted (Fig. 3). These patients are dependent and warrant treatment much like addiction treatment. They may do better if their opioid pain treatment is maintained. As mentioned in “Weaning” section, it is always worth trying to wean if the treatment does not seem to be working well, but if the wean is not tolerated, then it may be better to continue the opioid. The other important aspect of treatment of these patients is counseling. In the United States at least, because of the past 2 decades of gross overprescribing of opioids for chronic pain, there are not enough specialty centers that can handle patients at the intersection of chronic pain and opioid dependence, and there are not enough trained counselors to help busy medical practitioners with counseling. This is another reason to be circumspect about the decision to embark on COT.
PHARMACOLOGIC AND DOSE CONSIDERATIONS

Opioid choices, restrictions, precautions, and dose equivalences can be found in any drug reference book to which the reader is referred. This article provides only a broad understanding of the available opioids, how they relate to each other, how and why to move from one opioid to another, and how and why to achieve dose limitation.

Opioid Medication Choices

**Morphine**
- Morphine is the archetypal opioid and the opioid to which all others are compared.
- Morphine is a pure opioid agonist.
- Morphine is a “dirty” drug, meaning it has several active metabolites.
- Dosing of other opioids is often calculated for comparison in terms of MEDD, that being the daily dose of morphine that would be equivalent to the daily dose of the opioid being used.
- Morphine is derived from poppy and accounts for 50% of the active components of opium.
- Morphine utility for chronic pain is related to familiarity with its use and low cost.

**Other naturally occurring opioids**
- Codeine and thebaine are also naturally occurring constituents of opium.
- Codeine is used as an analgesic but is not useful for chronic pain because it causes constipation and has highly variable metabolism and thus highly variable effects.

---

Fig. 3. Spectrum of dependence and addiction. ER, Emergency room; PMP, prescription monitoring program (now available in several states in the United States, in continued development); UDT, urine drug test. Note: Doctor shopping occurs in the United States because many patients have multiple providers, unlike countries with national health systems where patients have a medical “home.”
**Semisynthetic opioids**

- Other pure opioid agonists in common usage are oxycodone, hydrocodone, and hydromorphone.
- These compounds are all synthesized from opium constituents.
- Because they have straightforward metabolism and clearance, they are the first choice for COT.

**Synthetic opioids**

- Fentanyl, meperidine, methadone, and tapentadol are also pure opioid agonists but have limited utility for COT.
- Fentanyl’s kinetics mean that it is only available for outpatients as a transdermal patch or various transmucosal forms. There are disadvantages to both, and fentanyl use is not encouraged for COT. Tolerance develops rapidly requiring dose escalation. The ultrarapid onset of transmucosal form is not needed during chronic pain management and is undesirable because of increased risk of addiction.
- Meperidine is not a good choice for COT because it has a toxic metabolite (normeperidine) and tends to be addictive because of its rapid onset.
- Methadone is a complex drug and can be dangerous because of its variable kinetics, which can lead to accumulation, overdose, and subsequent death. Its use for COT is generally discouraged, unless the therapy has been started and stabilized by an expert.
- Tapentadol is a pure opioid agonist with additional noradrenaline reuptake inhibition. It is a good analgesic but has all the same considerations in terms of addiction risk as other pure opioid agonists and is expensive and not covered by all insurance companies.

**Mixed agonist/antagonists and partial agonists**

- Mixed agonist/antagonists and partial agonists are generally too complicated to use as COT.
- The exception may be buprenorphine, which is a partial agonist/antagonist that is available in patch form for use in chronic pain or sublingual (SL) for addiction treatment.
- It could be argued that buprenorphine, because it has a ceiling dose and rarely causes respiratory depression, should be the first choice for COT.
- Buprenorphine SL is not approved as an analgesic in the United States, restricting use in COT to the patch, which is expensive and not approved by many insurance companies.
- Tramadol is a partial opioid agonist with additional serotonin and noradrenaline reuptake inhibition. It is useful for COT and has a lower risk of addiction than pure agonists, although addiction can still arise.

**Dosing Guidance**

- The lowest recommended dose should be used when starting opioid treatment in an opioid-naive individual.
- Because there is a great deal of interindividual variation, it may be necessary to increase the dose during the first few visits to reach the effective dose.
- Once the effect dose is established, further dose escalation should always be carefully considered. Periodic pain increases, often related to changes in life events, are to be expected in patients with chronic pain (Fig. 4) and often result
in a request for higher dose of opioid in the case of COT. Use of nonopioid interventions rather than dose increase should be encouraged.

- It is widely recognized and supported by evidence that adverse events are more likely to arise when doses are high. In general, doses more than 100 mg MEDD are discouraged.\textsuperscript{19,41–46} Even less than this dose, adverse events do occur, so this dose limitation should not be taken to mean that doses less than this level are completely safe. The safest dose is the stable dose that has been established at the start of treatment.

**Opioid Switching**

- Because of incomplete cross-tolerance at receptor sites, and possibly other factors, switching from one opioid to another can be an effective means of restoring analgesia when effectiveness has diminished because of tolerance.\textsuperscript{47}
- When switching to any opioid except methadone or buprenorphine, 50% of the calculated MEDD should be used.

---

*Fig. 4.* Interdependence of mood, tolerance/dependence, and pain. Even in normal individuals, pain and mood are interdependent, in part through endogenous opioid mechanisms. Individuals taking exogenous opioids long term and continuously adapt by developing tolerance and dependence. Psychological factors such as stress and distress can alter tolerance and thereby induce withdrawal symptoms. For the dependent individual, the need for more opioid becomes the predominant reaction to stress. Although pain is seen as the primary reason to escalate dose, pain is often secondary to other factors. (From Ballantyne JC, Sullivan MD, Kolodny A. Opioid dependence versus addiction: a distinction without a difference. Arch Intern Med 2012;172:1342; with permission.)
• Switches to methadone or buprenorphine are effective but complicated and should only be undertaken by an expert.
• One should be watchful when switching opioids. Adverse effects are more likely to arise when dose or drug is changed. The conservative dosing recommendation (50% reduction in MEDD) is necessary for safety.
• Switching opioid can be remarkably effective, despite drastic dose reduction.

**Long Acting Versus Short Acting**

• There is rarely any need to use long-acting together with short-acting opioids during COT.
• In general, for patients at low risk (eg, elderly patients being treated for osteoarthritis pain), occasional and minimal use of short-acting opioid is best and the best way to maintain opioid efficacy.
• For patients at risk of misuse or addiction, or patients with confusion, 2 or 3 times daily-scheduled long-acting opioid may be preferable.
• The concept of breakthrough pain or use of short-acting opioid to supplement long-acting opioid should not apply during COT. It tends to focus attention on pain and obtaining opioid (a particular problem for at-risk patients), leads to unnecessary and unsafe dose escalation, and may lead to unsafe situations whereby overdose can occur.

**THE ROLE OF NONMEDICAL AND NONPHARMACOLOGICAL INTERVENTIONS**

It is worth mentioning and emphasizing here that there are many approaches to managing chronic pain that are better than COT, and many of these approaches should be used even during COT, to reduce reliance on COT and in hopes to obviate dose escalation. Opioids, as has already been stated, have good analgesic efficacy when first used. All nonopioid interventions, whether pharmacologic, nonpharmacologic, or even nonmedical, take longer to work and require a lot more effort. Opioids are therefore seductive. It may feel as if, in the belief system of patients and their providers, opioids are the only thing that works. But it is now known that analgesia is often not maintained at initial levels over time and that there are many adverse outcomes of COT. Physical pain can be a manifestation of existential suffering, in which case medicine per se may not have any answers. The answer then lies in empowerment by friends, family, priests, and counselors and use of self-management techniques, lifestyle changes, or complementary medical approaches such as acupuncture, yoga, and tai chi. Helpful medical interventions could include injections, dry needling, targeted physical therapy, occupational therapy, nutritional counseling, and nonopioid medications, all of these being particularly helpful given in a multidisciplinary setting. However, there are too few multidisciplinary programs in the United States because of a failure to fund them or to recognize their long-term value. The point to emphasize here is that COT should never be used as sole therapy nor should the decision to initiate COT be taken until all other avenues of treatment have been fully explored. Again, COT is good treatment when it can provide comfort for refractory pain or suffering but not a good choice in the case that functional restoration toward normalcy is the ultimate goal.

**CHRONIC OPIOID THERAPY OUTCOMES**

Ideally, one wants any medical intervention to be evidence based. However, despite many attempts to mine the literature and develop an evidence base in support of COT, there simply is no such evidence. There is a great deal of rhetoric, anecdote,
and widely differing opinions but no strong evidence to support either the efficacy or the safety of COT. In fact, the safety of COT has been brought into question because of an accumulation of population studies that have revealed an alarmingly high incidence of life-threatening adverse outcomes.\textsuperscript{2,3,50–55} It can be argued that population studies cannot show causation, and that is why responses to such alarming statistics have been slow. Nevertheless, a shift in prescribing toward the more conservative regimens is occurring in response to reports on adverse outcomes for COT in both the medical and nonmedical media.

**Efficacy**

Short-term efficacy for opioids is supported by both randomized trials and observational studies.\textsuperscript{56,57} The establishment of long-term efficacy is much more difficult because there simply are no long-term trials in existence.\textsuperscript{48,58} Population studies suggest that COT-treated individuals have more pain, more health care utilization, less return to work, and more adverse effects than nonopioid-treated matched individuals.\textsuperscript{57,59,60} This result suggests that at the least, opioids do not achieve the goal of improving pain and function across the entire population. But that does not mean there are not some within the population study cohorts who do well. Difficulty lies in understanding exactly who they are and how to predict good outcomes. There is a strong suggestion from existing but still inadequate evidence that patients with nonstructural back pain, centralized pain states such as fibromyalgia, and headache do better without COT.

**Adverse or Side Effects**

There are many common adverse effects of opioids, and they are listed in Box 2. Most adverse effects diminish over time, but this is not true of the effects on the bowel, including constipation, or on the endocrine system, including testosterone depletion. A bowel regime should always be offered during COT, as should testosterone replacement when necessary for men.

**Adverse Outcomes and Events**

More concerning perhaps than opioids adverse effects or side effects are adverse outcomes and events that can be catastrophic (Box 3). Catastrophic outcomes of COT have become a concern for government agencies such as the Center for Disease

<table>
<thead>
<tr>
<th>Box 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse or side effects of COT</strong></td>
</tr>
<tr>
<td>Respiratory depression</td>
</tr>
<tr>
<td>Suppression of bowel mobility, constipation</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Drowsiness</td>
</tr>
<tr>
<td>Pruritus</td>
</tr>
<tr>
<td>Dry skin</td>
</tr>
<tr>
<td>Infertility</td>
</tr>
<tr>
<td>Cognitive impairment</td>
</tr>
<tr>
<td>Dependence</td>
</tr>
</tbody>
</table>
Addiction is a catastrophic outcome of COT and underpins many other catastrophic outcomes such as respiratory depression and death, falls and fractures, and cognitive impairment. Losing control of opioid usage is often the reason for accidental overdose. Other factors increase the likelihood of death from opioids, and these are listed in Box 4. The likelihood of accidental death can be minimized by reduction of risk factors as suggested in Box 4. However, that addiction develops in some treated individuals (best estimate, 12%) is inescapable. It may be hard for both patients and their prescribers to recognize and accept that dependence or addiction has arisen. The optimal way to make opioids safer in susceptible individuals is to use safe opioids such as tramadol or buprenorphine patch and to provide strong opioids only in a monitored setting, which would include inpatient settings, methadone or suboxone programs, or responsible family members taking control. Using screening tools and vigilant follow-up are the best methods for identifying individuals at risk, and their use is strongly encouraged.

**Box 3**

**Catastrophic adverse outcomes of COT**

- Respiratory arrest and death
- Addiction
- Ileus
- Falls and fractures
- Accidents

All these catastrophic outcomes are occurring with increasing frequency in the United States and other countries as reported in the literature (see Refs.1–3).

*a* More likely with concomitant administration of benzodiazepines and other sedatives, including alcohol.

Control (Fig. 5). Addiction is a catastrophic outcome of COT and underpins many other catastrophic outcomes such as respiratory depression and death, falls and fractures, and cognitive impairment. Losing control of opioid usage is often the reason for accidental overdose. Other factors increase the likelihood of death from opioids, and these are listed in Box 4. The likelihood of accidental death can be minimized by reduction of risk factors as suggested in Box 4. However, that addiction develops in some treated individuals (best estimate, 12%) is inescapable. It may be hard for both patients and their prescribers to recognize and accept that dependence or addiction has arisen. The optimal way to make opioids safer in susceptible individuals is to use safe opioids such as tramadol or buprenorphine patch and to provide strong opioids only in a monitored setting, which would include inpatient settings, methadone or suboxone programs, or responsible family members taking control. Using screening tools and vigilant follow-up are the best methods for identifying individuals at risk, and their use is strongly encouraged.

SUMMARY

- Carefully select patients for COT. Not all patients are suitable candidates. Patients with nonstructural back pain, centralized pain such as fibromyalgia, and headache are not good candidates.
- Do not let short-term opioid therapy become COT without careful consideration. Most acute pain only warrants a few days opioid therapy; greater than 90 days pain is considered chronic pain, and greater than 90 days opioid therapy is considered COT, but commonly short-term opioid therapy can be stopped much sooner than 90 days.
- Always screen for risk of misuse or addiction before starting COT or ideally before starting short-term opioid therapy.
- Be particularly conservative when risk factors are identified.
- Start at low dose, titrate to effect during initiation, do not dose escalate once stable unless absolutely necessary, and do not exceed 100 mg MEDD.
- Oxycodone, hydrocodone, and hydromorphone are the simplest choice of strong opioid.
- Tramadol or buprenorphine patch may be preferable, especially for patients with known risk, but cost may preclude their use.
- Do not use long-acting and short-acting opioids together during COT. Use long-acting round-the-clock where there are control issues, including confusion, and short-acting as needed in preference when there are no control issues.
- Adhere to the principles of COT outlined in the “Basic Principles of Chronic Opioid Management” section.
- When the treatment is not meeting goals of therapy, or when the dose is too high, discuss tapering with the patient.
- Using these careful precautions, it is hoped that the number of patients taking dangerously high doses of opioids, being dependent on opioids, and having deteriorated quality of life, will go down. In the meantime, there are thousands of patients with the syndrome of chronic pain with opioid dependence, and they need specialty care, which is not always available. In the absence of specialty care, they may need opioid continuation for the treatment of dependence (not pain), together with counseling and maximum use of all suitable nonopioid treatments.

**Box 4**

**Risk factors for adverse outcomes of COT**

When considering risks, addiction is not the only risk. Potentially catastrophic outcomes such as respiratory depression (death), constipation (abdominal obstruction), and cognitive impairment (falls and fractures) can be minimized by being aware of their risk factors.

Watch for the following:

- Obesity and sleep apnea
- Use of central nervous system depressants (especially benzodiazepines) and drugs with anticholinergic properties
- Abdominal disease
- Neurologic and cognitive impairment
- History or family history of substance use disorder
- High anxiety (risk of loss of control over use)
REFERENCES


