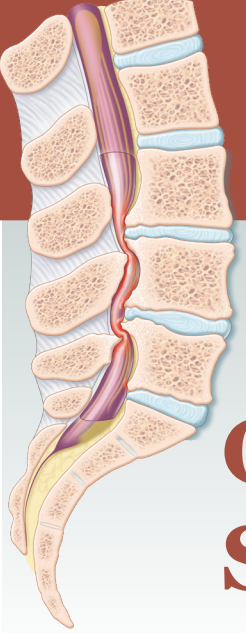

Opioid Use in Patients Undergoing Spine Surgery

ABSTRACT

Opioid medications have long been known for their analgesic properties and play an important role in the treatment of acute post-surgical pain. However, in recent years there has been an increase in chronic opioid therapy (COT) for painful conditions, in particular spinal disorders. These patients can have increased postoperative analgesic requirements and may be at increased risk of complications after surgery. In this evidence-based review, we provide guidance for managing opioid and analgesic medications for patients on COT from the preoperative assessment to post-surgical management including recommendations for appropriate opioid reduction.

KEYWORDS: low back pain, surgery, opioid sparing, peri-operative pain management

CME Pre-test Quiz

Introduction

Opioid containing medications have long been known to be powerful analgesics (See Table 1). These compounds exert their effects centrally to reduce pain and promote pleasure (See Table 2). Opioids have, therefore, been used to treat severe pain, such as surgical pain, and are routinely prescribed to patients undergoing surgery. Many patients with spinal pathology requiring surgery are already on chronic opioid therapy (COT). However, there are significant short- and long-term risks of opioid-use, including addiction (See Table 3) and overdose, both of which have risen alongside opioid prescription rates.[11] The enormity of this problem and its effect on individuals, the healthcare system and society has led to what has in recent years been coined the 'opioid epidemic.'

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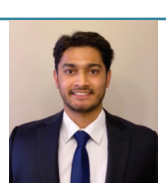

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In addition to their well-established risks, the benefits of opioids have also been called into question, as recent high-level evidence demonstrated that opioids are not better than a placebo at reducing acute low back and neck pain.[16] Furthermore, COT has been shown to negatively impact surgical outcomes and is associated with patient morbidity and mortality.[24,29] Given their unclear benefits, and substantial risks there is a clear need to reduce opioid-use.

The objective of this paper is to present evidence-based strategies to manage and minimize opioid-use through a case-based narrative review (See Figure 1) of opioid management for a patient requiring spine surgery, in particular a patient on COT. We include identifying patients at risk for COT pre-operatively, characterize novel strategies for peri-operative opioid dose reduction, such as erector spinae plane (ESP) blocks, and describe safe post-operative prescription writing.

Pre-Operative Assessment

The use of chronic opioid therapy (COT) in low back pain patients has become increasingly controversial in recent years, with articles challenging the rationale for this treatment option and lack of evidence to support its use.[25] The SPACE randomized controlled trial of the effect of opioids on

Characteristics of Opioids

Table 1: Types of Opioids: Natural, Synthetic & Endogenous

Natural opiates	These are the alkaloids that are principally present in the resin of the opium poppy and include *morphine, codeine,* and *thebain*.
Morphine esters	There are opiates that are more natural than semi-synthetics with small chemical modifications. Among these are *heroin (diacetylmorphine), nicomorphine, dipropanoylmorphine, desomorphine, acetylpropionylmorphine, dibenzoyl morphine,* and *diacetyldihydromorphine,* which are all morphine prodrugs.[10]
Semi-synthetic opioids	These are produced from either morphine esters or natural opiates. *Hydromorphone, hydrocodone, oxycodone, oxymorphone, ethylmorphine,* and *buprenorphine* are examples.
Synthetic opioids	*Fentanyl, pethidine, levorphanol, methadone, tramadol, tapentadol,* and *dextropropoxyphene* are examples
Endogenous opioid peptides	These are synthesized spontaneously in the body and include *endorphins, enkephalins, dynorphins* and *endomorphins*.

Table 2: Opioid Pharmacology

Receptors	• Selective opioid receptors are found in the central nervous system and some other organ systems, such as the alimentary tract. • Opioid receptors fall into three main categories: *mu, kappa, and delta,* with other subtypes including *epsilon, iota, lambda,* and *zeta*. • Morphine, oxycodone, and other opioids have a common mode of action by binding to the *mu* receptor in the central nervous system, which reduces pain perception and the corresponding emotional response. • According to the opioid's affinity and whether it acts as an agonist or antagonist, each receptor type results in a different cellular and physiologic response. • For instance, activation of the 1 receptor is what gives morphine its analgesic effects, whereas activation of the 2 receptor results in respiratory depression and physical dependence.
Metabolism	• Two important enzyme systems with distinct affinities, *Cytochrome P450 (CYP450) and Uridine 5'-diphosph-glucuronosyltransferase (UGTs),* are involved in the metabolism of opioids. • For medications like codeine, fentanyl, methadone, oxycodone, and oxymorphone, the *CYP450* system is important. The *CYP450* system can be impaired by substances that function as substrates, inhibitors, or inducers.
Side Effects	• When opioids are taken for pain relief, common side-effects include nausea, vomiting, sleepiness, itching, dry mouth, disorientation, and constipation.

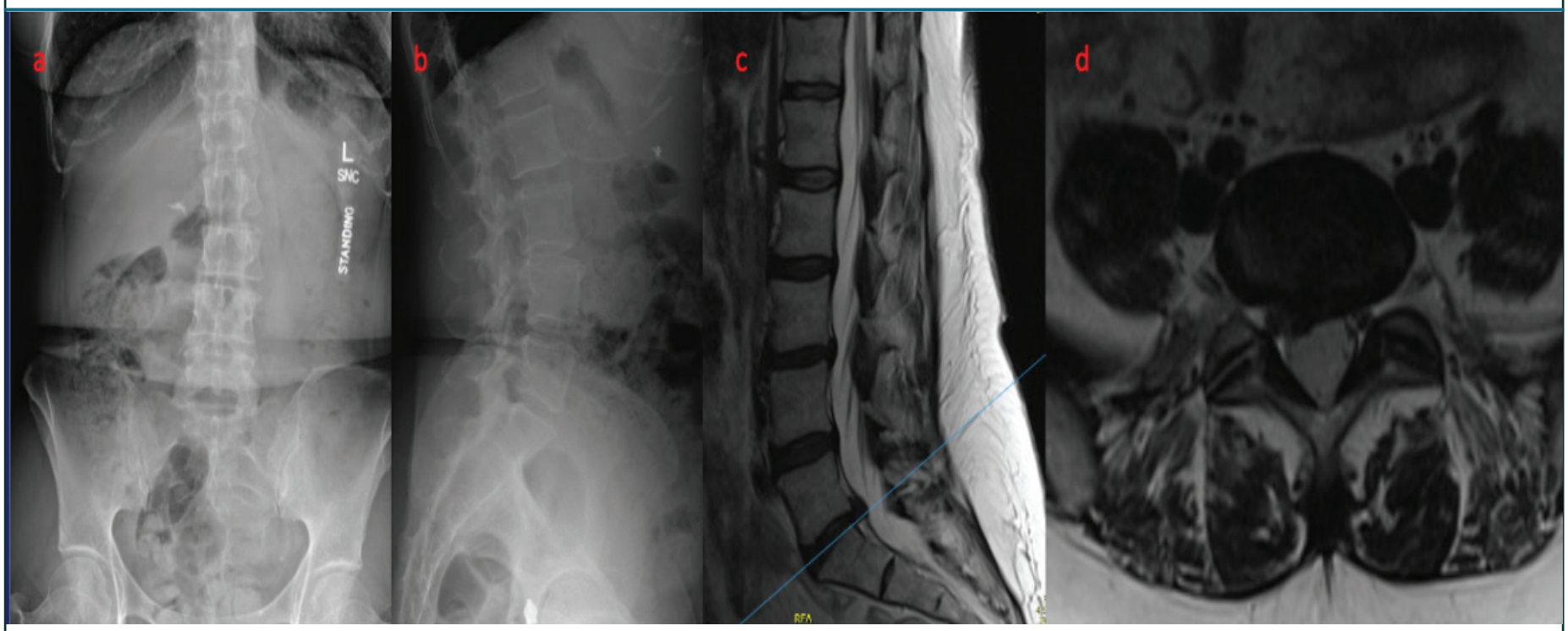
Table 3: Pharmacological Principles of Tolerance, Dependence and Addiction

Tolerance	• This is the gradual reduction of a drug's effects at a given dose. • It doesn't always mean abuse or addiction.
Physical Dependence	• This is when the body becomes habituated to the presence of opioids and experiences withdrawal symptoms when the drug is stopped. • It's a common side effect of some drugs and doesn't indicate addiction.
Addiction	• This is a complex phenomenon that involves psychological responses and a collection of behaviors that lead to gradually increasing drug dosages. • In the context of opioids, this can often lead to the self-administration of opioids through non-oral forms.

pain-related function in patients with hip or knee osteoarthritis or chronic low back pain, demonstrated no improved function over 12 months, and did not support the initiation of opioid therapy for moderate to severe pain with these conditions.[19] More recently, the OPAL trial of opioid analgesia for acute low back and neck pain was a controlled randomized clinical trial in 347 participants over 6 weeks, that found no significant difference between opioids and placebo; it reached the same conclusion that opioids should not be recommended for acute non-specific low back or neck pain.[16]

Unfortunately, it is not uncommon for a family physician in Canada to inherit a patient who has been on COT for several years. The discussion arises as to the benefits versus the risks of continuing

Figure 1: A Case of COT in a Patient Undergoing Spine Surgery



Nancy is a 57-year-old patient who has been in your practice for the past 6 years. When her previous family physician retired and you accepted her into your practice, she had a history of 20 years of low back pain that was being managed by chronic opioid therapy, specifically oxycodone controlled release 80 mg tablets twice daily. She has been maintained on that same dose over most of the past 6 years and has had an opioid agreement in place, random urine drug screens collected in your office at approximately 6 month intervals and has not presented with any behaviours that make you suspicious for diversion such as lost prescriptions or early refills. She has also been on Zopiclone 7.5 mg daily for insomnia through this same interval.

Four months ago she presented with new symptoms of increased low back pain and searing right leg pain, on physical exam had notably decreased left ankle reflex and weakness of ankle plantar flexion. An MRI confirmed a right-sided L5-S1 disc herniation with nerve root impingement. Her pain has not improved with physiotherapy or a targeted transforaminal epidural steroid injection. Based on her persistent and severe symptoms she has consented to have a surgical decompression which is scheduled for 12 weeks from now.

In the past weeks she has been taking oxycodone immediate release for breakthrough pain 5 mg, a total of 8 tablets/day in addition to her previous controlled release oxycodone, and has been started on gabapentin which has not provided notable benefit but has been titrated to a dose of 600 mg three times daily.

treatment or considering an opioid taper or rotation to buprenorphine or methadone. Recent guidelines suggest no preference in choosing either regimen to treat opioid use disorder.[32] Several Canadian provinces require special training and certification to prescribe methadone, these same limitations to not apply to buprenorphine.

Recent clinical practice guidelines from Australia for terminating opioid prescriptions note that it should be considered if there is a lack of overall and clinically meaningful improvement in function, quality of life or pain, or a lack of progress towards meeting agreed therapeutic goals. Cessation should be considered for individuals at high risk of opioid-related harm, including potential drug interactions, comorbidities such as sleep apnea and concomitant use of sedating medicines such as benzodiazepines. The prescription withdrawal plan needs to be voluntary, gradual, and mutually agreed upon by the person taking the medication and the health care professional.[20]

Our case study, Nancy, was on both Zopiclone and gabapentin, both of which are known to increase the risks of opioid-related death. A 2017 article based on Ontario data noted that concomitant treatment with gabapentin was associated with a substantial increase in the risk of opioid-related death, 49% compared to opioids alone. A very high daily dose, 1800 mg of gabapentin or more, had a further 60% increased odds of opioid-related death.[13] The dose of gabapentin should be reduced by 300 mg daily every 3 days until the lowest effective dose is found, or the medication is discontinued. A sudden decrease is not recommended. A clinical toolkit for tapering benzodiazepines can be found on-line at the website of the College of Physicians and Surgeons of Alberta.[2]

A large proportion of patients (as many as 33–70%) seeking elective operations are already using chronic prescription opioids. These patients have been shown to demand greater doses and prolonged duration of opioid therapy postoperatively. Chronic opioid use reliably confers tolerance leading to less effective perioperative pain management and disproportionate pain. Chronic opioid use predisposes to poor immediate surgical outcomes including immediate postoperative complications such as infection, ileus and respiratory suppression with atelectasis and pneumonia. Long-term issues include compromised wound healing and reduced positive outcomes. In a large, methodologically rigorous retrospective analysis of 15,901 opioid-dependent individuals undergoing various arthroplasties or spinal fusion procedures, compared to over 9 million con-

trols, it was demonstrated that opioid dependence had a statistically significant association with increased morbidity and mortality. Preoperative opioid reduction may prove protective. In the same analysis, a subgroup of forty-one patients who successfully weaned their opioid burden by at least 50% prior to surgery were compared to 41 opioid dependent patients who did not, and 41 opioid-naïve controls. The intervention group achieved outcomes comparable to the opioid-naïve group, with both groups demonstrating significantly improved pain and functional outcomes compared to the patient group that did not reduce their opioid use.[24]

The mechanism by which opioids are related to operative complications is likely multifactorial and may be related to the immunosuppressive effects of opioids and to opioid-related endocrinopathies. There is an association with increased superficial and deep surgical site infections, including periprosthetic joint infection. Rates of surgical site infection, prolonged hospital stays, readmissions, emergency room visits, and revision surgery were higher in patients taking opioids for more than 6 months before surgery, but decreased to levels similar to opioid-naive patients if opioids were discontinued 3 months before total hip and knee arthroplasty or lumbar fusion.[29]

There is increasing interest in using buprenorphine in chronic opioid therapy. The updated American Department of Veterans Affairs and Department of Defense guidelines do not recommend opioids for chronic non-cancer pain but for those who are receiving daily opioids, buprenorphine is preferred due to the lower risk of overdose and misuse.[32] A 2019 review on the safety and efficacy of transdermal or transbuccal formulations of buprenorphine supported its use over full mu opioid receptor agonists for effective preferential treatment of chronic pain.[28] Buprenorphine, as a partial mu opioid agonist, has a notably decreased likelihood of respiratory depression constipation, and suicidal tendencies and potentiates anti-depressant and anti-anxiety effects.[28,35] The antagonistic effects of buprenorphine at the δ- and κ-opioid receptors may contribute to its favorable safety and tolerability profile.[28,35] Ten studies examining chronic low back pain and 5 studies on osteoarthritis pain, including one study that examined solely elderly populations, demonstrated effective pain relief for transdermal buprenorphine.[28] Buprenorphine can be used in patients with a dual diagnosis of chronic pain and opioid use disorder, patients requiring concomitant medications (as fewer interactions may occur with other drugs), in the elderly and for those with renal or hepatic impairment.[28]

When considering buprenorphine for surgical patients, recognize that buprenorphine has high potency and a slow rate of dissociation which allows for long lasting analgesia at low doses but has a very high binding affinity at the Mu opioid receptor, a higher attraction than most full agonists, which may complicate the ability of full Mu opioid agonist providing effective pain control in the peri-operative period.[35] The recommended buprenorphine perioperative rotation usually involves the transdermal or transbuccal routes and may not apply to immediate-release, high-dose, sublingual tablets. These are not currently approved for chronic pain but may be used in managing opioid use disorder or as a rotation from high-dose chronic opioid therapy. High-dose strengths may result in higher mu-opioid receptor occupancy, which could reduce the efficacy of concomitant full mu-opioid receptor agonists.[35]

Nancy was taking 200 mg daily of oxycodone, approximately 300 oral morphine equivalents. In this situation, a pre-operative opioid taper is usually recommended. The goal is 90 oral morphine equivalents, the upper limit of the current Canadian Opioid Guidelines, or below.[5]

The Centre for Effective Practice has released an Opioid Tapering Template[1] which includes recommendations to:

- Switch from immediate release opioids to controlled release, on a fixed dosing schedule
- Taper 5-10% every 2–4 weeks, follow the patient frequently even weekly.
- Adjust step size and interval depending on patient response
- Treat withdrawal symptoms as required (See Table 4).

Perioperative Pain Control Strategies

Two evolving approaches with the potential to reduce postoperative opioid-use are multimodal pain management and erector spinae plane (ESP) blocks.[9,14,17,22,23,30,31] A recent randomized controlled trial published in the Journal of the American of Orthopaedic Surgeons, found that in patients undergoing lumbar spinal fusion, a multimodal analgesia regime (ketorolac, orphenadrine and gabapentin) led to decreased opioid use and lower pain scores at 12- and 24-hours post-surgery.[31] This may safely promote early patient discharge.[17]

ESP blocks performed prior to common spine surgery procedures have been reported to offer opioid free anesthesia.[6,18,26] A systematic review published in 2021, which included 12 randomized controlled trials with 828 patients, found that ESP blocks significantly decreased pain, diminished opioid consumption and reduced nausea and vomiting in the 24-hour

Table 4: Symptom Management for Opioid Withdrawal

Symptoms	Management
Muscle pain Slower taper may be required to address these symptoms	• Non-opioid medication (e.g. acetaminophen, ibuprofen, NSAIDs) • Refer to Management of Chronic Non Cancer Pain tool and Opioid Manager tool
Neuropathic pain Slower taper may be required	• Tricyclic antidepressants (e.g. amitriptyline/nortriptyline) • SNRIs (e.g. duloxetine, venlafaxine) • Gabapentinoids (e.g. gabapentin/pregablin) • Refer to Management of Chronic Non Cancer Pain tool and Opioid Manager tool
Physical symptoms of withdrawal	• If BP >90/50 mmHg, may give clonidine 0.1mg. Check BP & HR 1 hour later. If BP <90/50, HR <50 or dizziness, do not prescribe further. May titrate up to qid prn, then taper. • Do not give clonidine if BP <90/50 mmHg or HR <50 bpm
Diarrhea	• Stop stool softeners and/or laxatives (e.g. sennosides, docusate sodium, lactulose) if applicable • Loperamide (if necessary) 4mg STAT, then 2mg after each unformed stool up to a maximum of 16mg per day
Insomnia	• Cognitive Behaviour Therapy for Insomnia (CBT-I) (see Management of Chronic Insomnia tool) • Do not prescribe benzodiazepines, zopiclone or zolpidem • For patients already on benzodiazepine, zopiclone or zolpidem discuss the increased risk of harm and consider tapering once the patients are tapered off opioids.
Nausea/vomiting	• Dimenhydrinate 25–100mg q4h prn • Prochlorperazine 5–10mg q6h prn • Haloperidol 0.5–1mg q12h prn • Metoclopramide 10mg q4–6h prn
Abdominal cramps	• Hyoscine butylbromide 20mg tid-qid prn for 2–3 days
Muscle cramps	• Quinine sulfate 300mg bid prn
Sweating	• Oxybutynin 2.5–5mg bid prn (short-term use) • Ensure patient is well-hydrated
Overdose prevention Tolerance of previous dose of opioids is lost after 1–2 weeks. Patients may inadvertently take the original dose to help with withdrawal symptoms or pain resulting in possible overdose and mortality risk.	• Naloxone kit

period following surgery.[22] Again, responses encouraging an early, safe discharge from hospital.

Postoperative Outpatient Opioid Management

The challenge is to provide adequate postoperative pain control while avoiding the dangers of chronic opioid therapy. Scully et al. evaluated characteristics of postoperative opioid prescribing in a cohort of 565,648 patients undergoing common surgical procedures, including discectomy, from the Military Health System Data Repository and the TRICARE insurance program.[33] This study was specifically focused on opioid naïve patients; patients who had filled an opioid prescription in the 6 months prior to surgery were excluded. Of the 16,647 patients who had a discectomy, the median duration of postoperative opioid prescription was 7 days (range 1-30). In a review by Cook *et al.,* 91-95% of patients undergoing lumbar decompression, transforaminal or posterior interbody fusion, anterior cervical discectomy and fusion or cervical disc arthroplasty, who used opioids preoperatively, filled an opioid prescription postoperatively. Only 63-68% of opioid-naïve patients used postoperative opioids.[8] Patients following spinal decompression who consumed preoperative opioids had a longer postoperative opioid course than opioid-naïve patients.[8] Other factors related to prolonged postoperative opioid use include female sex, anxiety, depression, and alcohol and drug abuse.

Transitioning a postoperative inpatient on COT to an outpatient setting can be complex and must be tailored to the individual patient's physiological and psychosocial needs. The patients on COT will have increased analgesic requirements and pain may be more difficult to control. The American Pain Society recommends education regarding opioid medications, non-narcotics such as acetaminophen and the use of nonpharmacological interventions, such transcutaneous electrical nerve stimulation and cognitive behavioral therapy (CBT). A clear plan for a postoperative opioid reduction, including timing and target dosage, should be agreed to by the patient and their caregivers prior to surgery, and again prior to discharge. Collaboration with a pain management specialist may be beneficial.[7]

According to the US Centers for Disease Control (CDC), patients on opioids for greater than a year should be tapered 10% per month or slower. This can require several months and frequent follow-ups.[12] For patients on opioids for less than a year, a taper of 10% per week is recommended, slowing the reduction if patients exhibit withdrawal symptoms . For refractory withdrawal symptoms physicians should utilize

SUMMARY OF KEY POINTS

1. Pre-operative chronic opioid usage is associated with poorer surgical outcomes.
2. Pre-operative chronic opioid usage is associated with prolonged post-surgical opioid therapy.
3. Pre-operative opioid tapering can achieve clinical surgical outcomes comparable to an opioid-naïve group.
4. Non-pharmacological or non-narcotic medications may help reduce pre-operative opioid usage.
5. A clear plan for a post-surgical opioid taper should be prepared prior to surgery.

treatments targeted at the specific withdrawal symptoms, such as alpha-2 agonists, acetaminophen, NSAIDs, topical medications, trazodone for sleep disturbance, antiemetics for nausea, and GI hypomotility agents for diarrhea. There are a number of published protocols for the medical management of patients on COT, in addition to a number of tools for evaluating withdrawal such as the Clinical Opiate Withdrawal Scale (COWS).[15,34]

The extent of preoperative use of opioids has been shown to be the strongest predictor of postoperative opioid use.[4] In a randomized control trial of spine surgery patients, the authors found that an individualized opioid reduction program along with counseling led to 81% of patients being opioid-free one year after discharge, compared with 61% for patients who were not part of the program.[21] The regimen should be tailored to the specific patient. In cases of opioid

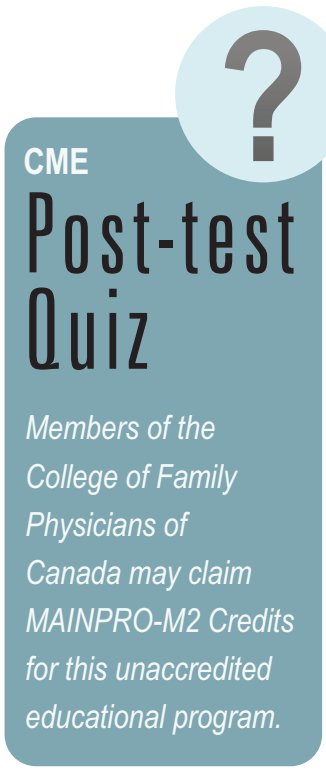
CLINICAL PEARLS

The OPAL trial notes that opioids for acute non-specific low back or neck pain present no significant difference to placebo for pain at 6 weeks.

Buprenorphine is commonly used as an opioid rotation pre-operatively to assist in opioid weaning.

Discontinuing opioid prescriptions should be considered if there is a lack of overall and clinically meaningful improvement in function, quality of life or pain, or lack of progress towards meeting agreed therapeutic goals.

Gabapentin in doses over 1800 mg/day is associated with 60% increased odds of opioid related death.



dependence, the CDC guidelines suggest allowing the patient to play an important role in tapering their opioid dosage, underscoring the importance of patient-centered care, a regular dialogue between the patient and physician.

Beyond withdrawal symptoms, there can be problems with increased pain, dropout, poor overall function and relapse that require medical intervention.[15] Because of the complex psychological aspect of managing COT, psychosocial interventions may increase the effectiveness of pharmacologic treatment. When combined with pharmacological therapy, Cognitive Behavioral Therapy has been shown to be a cost-effective and impactful treatment for COT.[27]

Conclusions

Treating chronic opioid therapy, particularly in the perioperative period demands an evidence-based approach to opioid screening and dose reduction. An open dialogue, which includes addressing patient's expectations is crucial when managing this complex issue in preparation for spine surgery.[3]

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