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Feature Article

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Initiating Opioid Therapy:
Time to Rewrite the Playbook?

by Dr. Brian Goldman

Feature Article

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CASE: Susan is a 40-year old female with chronic nociceptive pain due to osteoarthritis of both knees as well as tendonitis of the wrist. In the past, she fell and fractured three ribs on the right side. As a result, she suffers from mixed nociceptive and neuropathic pain involving the right upper quadrant and right lower chest regions. On most days, she has 7/10 pain at rest, and 9/10 pain with activity.

The pain has limited greatly the patient's ability to function. Previously, she was training to be a personal care provider. However, her pain has made it difficult to work in her chosen field. She is able to dress and bathe herself. However, she is unable to do housework, shop, or care for her two children.

Trials of most nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen with codeine and amitriptyline have not provided adequate pain relief. Injections of corticosteroids provide temporary relief. Injections of hyaluronic acid have not helped. She has been seen by an orthopedic surgeon, who has concluded that Susan would benefit from bilateral knee arthroplasties. However, the surgeon is unwilling to do the surgery until Susan has lost at least 20-30 pounds. She has had numerous trials of passive physiotherapy without improvement. She is unable to participate in active physiotherapy due to unrelieved pain.

Her other medical problems include hypertension and osteoporosis. She is a non-smoker, and drinks up to 3-4 alcoholic beverages a week.

On physical examination, Susan is moderately obese. She walks with a marked antalgic gait. She has reduced range of motion in both knees, but no effusion. There is no ligamentous laxity. There is hyperalgesia and allodynia involving the right lower anterior chest and right upper quadrant region. Examination of the right wrist reveals reduced range of motion but no allodynia and no evidence of inflammation.

Introduction

For most physicians, the decision to initiate opioid therapy in a patient with chronic non-cancer pain is a momentous one. With fears regarding addiction and diversion, many physicians are already somewhat reluctant to prescribe opioids. When the first opioid prescribed is not a success, the physician may feel even more reluctant to press ahead. What should the second choice be? Should an immediate-release opioid be prescribed, or is it appropriate to start with an oral controlled-release preparation?

This article talks about winning strategies for starting and maintaining opioid therapy. It discusses the potential benefits and pitfalls of the various options for initiating treatment. And it looks at the evidence for starting therapy with long-acting opioids.

General Principles

There is growing evidence that opioid analgesics can provide pain relief and improved function in both nociceptive and neuropathic pain.[1,2,3,4] Numerous guidelines have been established regarding the use of opioid analgesics.[5] In general, a trial of opioid therapy should be considered "when unrelieved pain contributes to a decreased quality of life for the patient and a reasonable, documented trial of other

standard treatment modalities fails to provide adequate relief."[6]

According to most guidelines, treatment with opioid therapy should be part of an overall treatment plan that incorporates non-opioid as well as non-pharmacological treatment. The indications for opioid therapy include pain that has failed to respond to a reasonable trial of other therapies.

The goals of opioid therapy include improved pain control and functional improvement. It is important for the prescribing physician to help the patient develop functional goals.

Which Opioid to Choose?

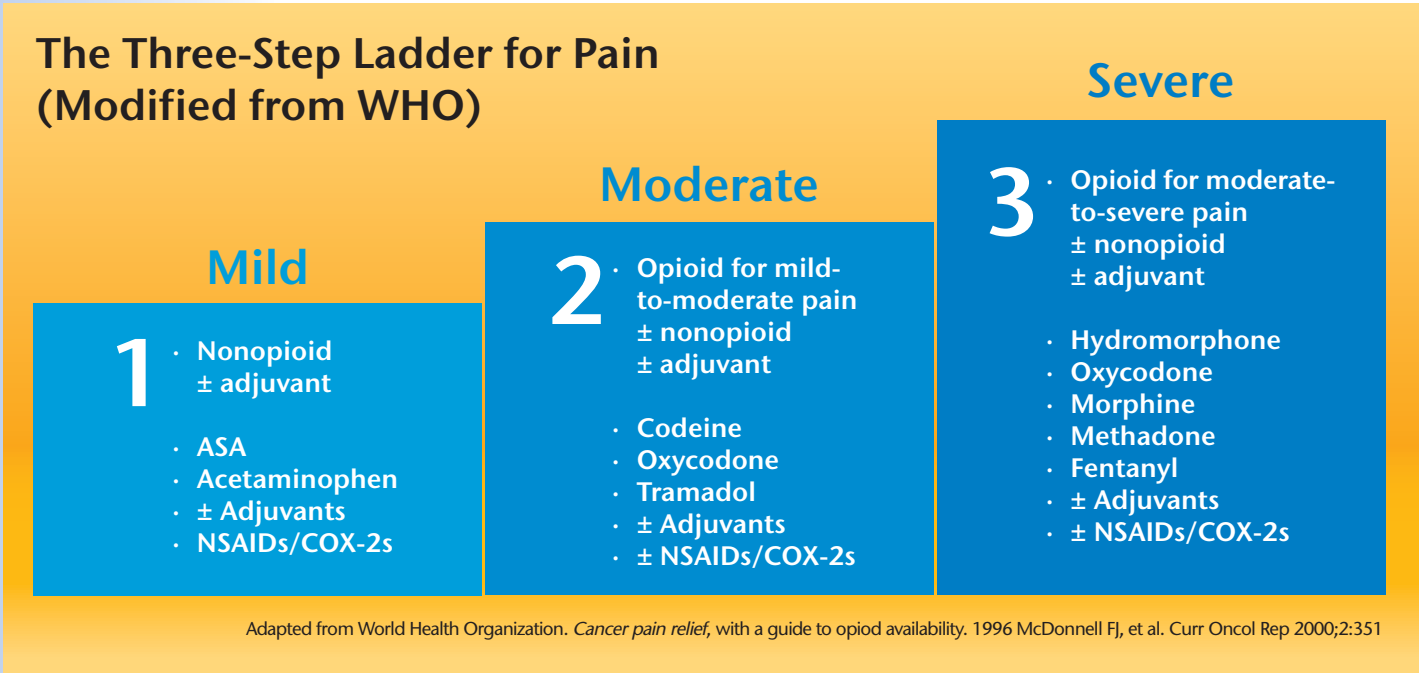
In the management of chronic non-cancer pain, there are numerous opioid options from which to choose. Opioids prescribed commonly in Canada include codeine, morphine, oxycodone, hydromorphone, transdermal fentanyl and methadone. The World Health Organization (WHO) developed an analgesic ladder for managing cancer pain.[7] This analgesic ladder has been adapted to the management of chronic non-cancer pain (*see Figure 1*).

The WHO analgesic ladder uses a recognized method of integrating opioid and non-opioid medications into a unified treatment approach. According to the ladder, 'mild' pain is usually treated with acetaminophen, NSAIDs or coxibs. For 'moderate' pain, opioids such as codeine and oxycodone (with or without acetaminophen) may be introduced into the treatment program. For 'severe' pain, the use of opioid analgesics such as hydromorphone, oxycodone, morphine, fentanyl and methadone may be indicated. Adjuvants are non-opioid medications such as tricyclic antidepressants and anti-epileptic drugs. Where appropriate, they may be prescribed at any time for pain that is mild, moderate or severe.

While a reasonable approach, it is important to remember that it's not necessary to follow the ladder's guidelines exclusively. All opioid analgesics have agonist activity at the μ receptor. In theory, any agent can be used in patients with chronic non-cancer pain, provided one follows the general principle of slow, careful titration and close follow-up and is aware of the relative analgesic potency of the various opioids. Points to consider when selecting an opioid include the patient's previous experience with opioids, allergies and sensitivities, diseases that affect metabolism and clearance of specific opioids, as well as clinical factors that may limit administration and absorption of specific opioids.

When it comes to initiating therapy, a key consideration is the patient's prior use of opioid analgesics. In general, it's a good idea to take a cautious initial approach with opioid-naïve patients with mild to moderate pain. Compound analgesics such as acetaminophen with codeine or oxycodone are a time-honored initial choice. In theory, tramadol with acetaminophen is another option. However, the Health Canada-approved indication for tramadol with acetaminophen (Tramacet®, Janssen-Ortho) is for short-term use of five days or less. Codeine is considered a non-optimal choice for patients with

Figure 1: Modified World Health Organization Analgesic Ladder



Adapted from World Health Organization. *Cancer pain relief,* with a guide to opiod availability. 1996 McDonnell FJ, et al. Curr Oncol Rep 2000;2:351

moderate to severe pain. There is significant inter-individual variation in the metabolism of codeine due to genetically-mediated variability in the cytochrome P450 isoenzyme 2D6 activity.[8]

When prescribing compound analgesics as described above, titration is limited by the maximum recommended daily dose of acetaminophen. For short-term use of ten days or less, a maximum daily dosage of 4000 mg of acetaminophen is recommended. When using acetaminophen longer than ten days, the total daily dosage should be reduced to 3200 mg. For patients on warfarin, fasting, a low protein diet, and those with cardiac or renal disease, consider reducing the maximum daily dosage of acetaminophen to 2600 mg.

Single entity opioid analgesics are available for mild to moderate pain (e.g. codeine) and for moderate to severe pain (e.g., morphine, fentanyl, hydromorphone and oxycodone). Morphine has traditionally been recommended as first line treatment for moderately-severe to severe chronic non-cancer pain. However, it is metabolized to morphine-3-glucuronide (M-3-G) and morphine-6-glucuronide (M-6-G). The former (M-3-G) has no analgesic activity but has been found to have neuro-excitatory attributes; accumulation of M-3-G may lead to myoclonus and hyperalgesia. M-6-G has analgesic activity and has been shown to accumulate in the presence of renal failure and may cause respiratory depression and excess sedation. Despite careful titration, some patients do not achieve optimal analgesia with morphine.

CR preparations have the added advantage of existing in a corresponding IR form as well, which facilitates the initiation of therapy and the provision of short-acting treatment for breakthrough and incident-related pain.

Hydromorphone is a potent opioid analgesic. It is metabolized into hydromorphone-3-glucuronide (H-3-G) and dihydroisomorphine glucuronide. It does not have a 6-glucuronide metabolite. H-3-G appears to have neuro-excitatory properties that are analogous to the effects seen with M-3-G. Although it is an unusual occurrence, H-3-G accumulation can occasionally interfere with titration. This tends to occur at extremely high doses of hydromorphone, and especially in patients with renal failure. This may be attributable to the fact that hydromorphone is five times more potent than morphine, thus having less H-3-G (versus M-3-G) available to accumulate. In addition, the absence of an active 6-glucuronide metabolite may also contribute to a clinical advantage over morphine.[9]

Oxycodone has no toxic metabolites; its principle metabolite, oxymorphone, has 10% of the analgesic activity of oxycodone.

Transdermal fentanyl is another option for patients with moderately-severe to severe chronic non-cancer pain. This formulation provides a set rate of hourly absorption of fentanyl through the skin. As currently formulated, the 25 µg/hr strength patch is roughly equivalent to 60-135 mg of oral morphine per day. Recently a new 12 µg/hr patch was introduced which is to be used for titration and dose adjustment. Transdermal fentanyl, as currently formulated, is contraindicated for the initiation of opioid therapy in opioid-naïve patients. It is also not indicated for use in children under the age of 18.

Methadone is a dual mechanism opioid with activity at the µ and δ receptors, as well as N-methyl-d-aspartic acid (NMDA) antagonist activity. It also inhibits the reuptake of monoamines. There is growing experience in the use of methadone in patients with chronic non-cancer pain.[10] The drug is considered a reasonable choice in patients with severe neuropathic pain. Since methadone has a long half-life and duration of action, it should be titrated extremely slowly and carefully. Methadone exhibits huge inter-individual variation in terms of equianalgesic doses. Extreme care should be taken when switching patients from other opioids to methadone. In addition, methadone has numerous interactions with drugs that act on cytochrome P450 3A4 isoenzyme. Physicians who wish to prescribe methadone must obtain special authorization from Health Canada. Methadone should never be used as a first line drug in opioid-naïve patients. The use of methadone for pain management should be confined to experienced clinicians only.

CASE: Susan's family doctor discussed goals of therapy with her. In the short term, Susan would like to be able to increase her activity around the house, to do more housework, and to be able to play sports with her children. In the long term, she would like to be able to return to part time employment.

Susan's family physician initiated a trial of short acting morphine. However, titration was limited by the development of drowsiness and somnolence that necessitated discontinuing the drug. Her family physician would like to try another opioid, but isn't certain how to proceed.

The IR vs Oral CR/long acting Opioid Dilemma

Oral controlled-release and long-acting preparations have been a boon to patients with chronic non-cancer pain. They have the advantages of improved convenience and compliance, reduced pill burden, fewer peaks and valleys of plasma concentration, and improved sleep (see Table 1). Options in this category include oral controlled-release (CR) opioids, transdermal fentanyl and methadone. CR preparations have the added advantage of existing in a corresponding IR form as well, which facilitates the initiation of therapy and the provision of short-acting treatment for breakthrough and incident-related pain.

Table 1:

Advantages of Controlled-release (CR) Opioids

- **Enhanced convenience and compliance**
- **Fewer peaks and valleys in plasma opioid levels**
- **Fewer persistent adverse effects**
- **More consistent analgesia**
- **Improved quality of life**

Adapted from: Jovey RD. Opioid Analgesics. In: Jovey RD, Ed. Managing Pain. The Canadian Healthcare Professional's Reference. Endorsed by The Canadian Pain Society. Rogers Media, 2002, page 54.

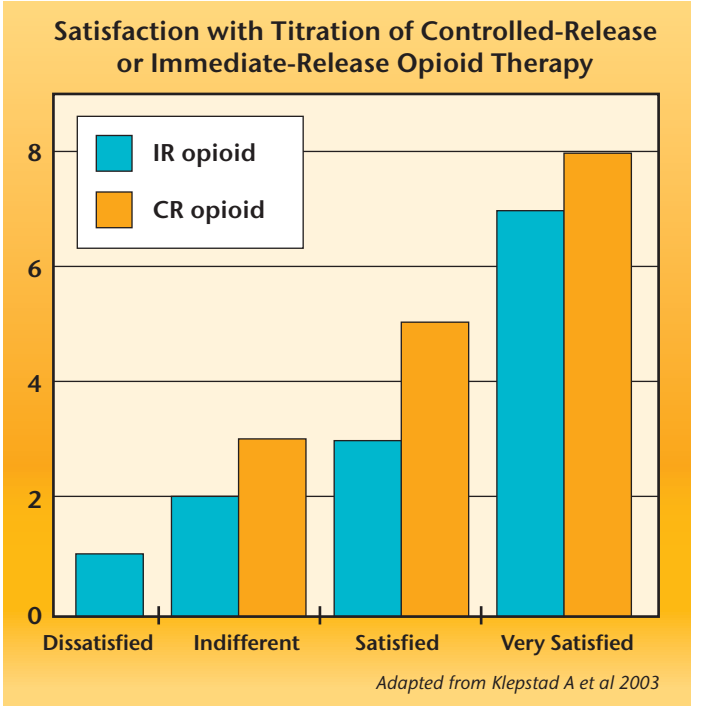
Traditionally, many guidelines have recommended initiating and titrating opioid therapy with immediate-release (IR) products. Afterwards, the patient is converted to the corresponding oral CR or long-acting preparation. The advantage has been that the use of an IR product permits more rapid titration than is usually possible with oral CR products. The major disadvantage of this approach is that some patients report less analgesia after being switched to the CR product.

Therefore, an alternative approach is to initiate and titrate opioid therapy with an oral CR product. There is evidence this approach is a reasonable one. Klepstad did a randomized, double-blind, double-dummy, parallel group study in patients with cancer pain that compared titration with IR morphine to titration with a CR preparation. Patients in either group had comparable pain scores, and there was no difference in the intensity of adverse effects between the two groups. Patients titrated on CR morphine reached stable pain control in a mean of 1.7 days, while patients titrated on IR morphine reached stable pain control in a mean of 2.1 days. Although this was statistically significant, it is not a material difference clinically.

Patients titrated with CR morphine did not experience more adverse effects during the titration than did patients titrated with IR morphine. In fact, patients receiving the oral CR preparation reported statistically significantly less tiredness than patients receiving the IR form. As well, patient satisfaction with analgesia was significantly greater in patients treated with CR opioids (*see Figure 2*). This study demonstrated that initiation with oral CR opioids was just as effective and safe as doing so with IR opioids.[11]

Salzman conducted two separate trials comparing oral CR oxycodone administered every 12 hours to IR oxycodone administered 4 times a day to determine whether patients could be titrated to stable pain control. In one study, 48 patients with cancer pain were randomized to open-label titration with either CR or IR oxycodone (maximum dose 400 mg per day) for a period of up to 21 days. In a second study, 57 patients with low back pain were titrated with either CR or IR oxycodone (maximum 80 mg per day) for a period of up to 10 days. The majority of the patients enrolled in either study were converted from other opioid analgesics. Among cancer patients, 85% achieved stable analgesia; 92% with the CR formulation and 79% with the IR form. In the study involving patients with low back pain, a total of 91% achieved stable pain control; 87% with the CR preparation and 96% with the IR version. Adverse effects associated with opioid analgesics (nausea, vomiting, constipation, somnolence dizziness and pruritus) were similar in both studies and with both formulations.[12]

Figure 2:



Adapted from Klepstad A et al 2003

While not definitive, these studies suggest that the usual approach of determining oral CR opioid dosage by titrating first with the corresponding IR preparation may be unnecessary. Rather, therapy can be initiated and titrated with a CR opioid.

There are several potential advantages to this approach. Patients are spared a multiple dose schedule. CR dosing is generally twice or three times daily. Such a schedule is more convenient to the patient than that of an IR opioid, and may improve patient compliance.

Initiating therapy with a CR product omits the need to convert the patient from an IR to a CR product. Finally, the physician does not need to convince the patient to switch to a CR opioid when the IR product appears to be working well.

Which Oral CR Opioid to Try First?

Traditionally, oral CR morphine has been the treatment of choice for initiating therapy with a long-acting agent. However, the accumulation of active metabolites M-3-G and M-6-G as discussed previously may make CR morphine a problematic choice for some patients. In particular, elderly patients as well as patients with renal failure are at increased risk of accumulation of active metabolites.

For these reasons, it's worthwhile to consider some other options for initiating therapy with CR opioids. CR codeine is one such option for mild to moderate pain. If the pain is moderate to severe, then CR oxycodone is another option for initiating opioid therapy. As discussed previously, oxycodone does not have neuro-excitatory metabolites. Nevertheless, the elimination of oxycodone is delayed in patients with renal and hepatic impairment.[13,14] CR hydromorphone would be another option. There are few published controlled trials studying the effectiveness of hydromorphone in patients with chronic non-cancer pain. However, the drug has been evaluated in patients with cancer pain. A Cochrane Systematic Review demonstrated good evidence for the use of hydromorphone in patients with cancer pain.[15] Recently, a single dose treatment study showed efficacy in patients with chronic non-cancer pain.[16] Based on evidence involving the use of other opioids, it's likely that hydromorphone would be found to be effective in longer duration studies as well.

Something New for Opioid-Naïve Patients?

Recently, a 5 mg tablet of oral CR oxycodone has become available in Canada. Koizumi and colleagues conducted an open-label dose titration study to assess the efficacy and tolerability of CR oxycodone 5 mg in the treatment of patients with cancer pain. Twenty-two patients who had not taken opioid analgesics in the preceding two weeks were enrolled. Eighteen patients in the efficacy population attained stable, adequate pain control. Two-thirds of the patients attained stable, adequate pain control without any dose titration (i.e. at a dosage of 5 mg q12h). The mean duration required to achieve adequate pain control was 1.2 days. Eighty percent of the patients required no rescue medication. Fifteen of the patients reported at least one adverse effect, but only one patient had to withdraw from the study because of an adverse effect.[17]

For the majority of patients with moderate to severe pain, the usual starting dose for oral CR oxycodone should still be 10 mg q12h. However, for certain patients with a low average body weight or who are frail, CR oxycodone 5 mg q12h is a reasonable option.

CASE: Susan's physician decided to try a different opioid analgesic. He started therapy with CR hydromorphone 3 mg q12h. Aside from some initial somnolence, Susan tolerated the medication well. Over the next few months, her doctor titrated the dosage of CR hydromorphone to 9 mg tid. She was started on gabapentin and titrated to 1200 mg qid.

On that regime, Susan has been able to enter active physiotherapy. Though not working, she has resumed looking after her children and is able to play some sports with them. Improved pain management has given her a better outlook on life. She feels she is more productive than she was before, and no longer feels she has to be carried by her family. Susan still retains the long-term goal of returning to gainful employment.

Conclusion

Opioid therapy can provide analgesia to patients with chronic non-cancer pain. The traditional approach has been to avoid oral CR opioids in opioid-naïve patients, to titrate patients with IR opioids, and to reserve oral CR opioids for patients so titrated.

Many clinicians have initiated opioid therapy with oral CR opioids and found this a successful strategy. Taken together, the studies by Koizumi, Klepstad and Salzman suggest that the traditional approach may be reconsidered.

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