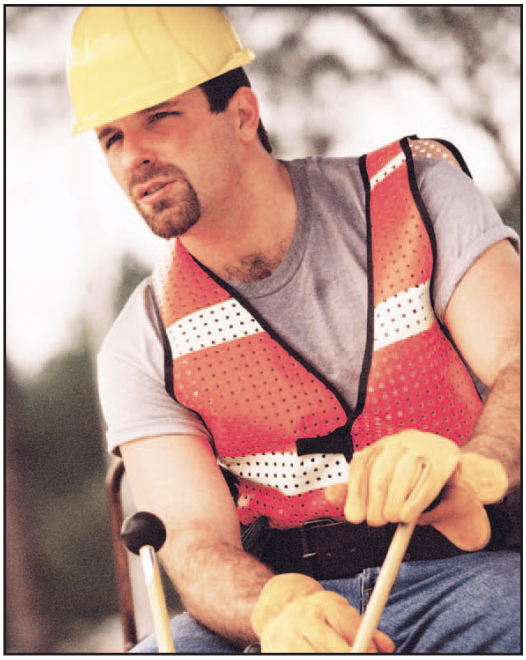
Pain and Dosing: Strike the Balance



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As presented at the Drug Update & Practical Therapeutics Course, November 8, 2002.

David's pain

David, 40, developed back pain which became acute. In 1995, the heavy manual laborer had a discectomy (fifth lumbar vertebrae, sacral nerve 1), and in 1998 he had a spinal fusion.

His pain was alleviated initially by each surgery which was followed by physiotherapy. By March 2003, however, the pain had returned.

Magnetic resonance imaging notes instrumentation, but no impingement of spinal cord or nerve roots. Further surgery was inadvisable.

The pain is now in David's lower back, radiating down his right leg, and worsens when he bends. The pain eases when he is lying down.

David has prolotherapy, as his physiotherapy courses have been completed without benefit.

David's medications:

- Darvon eight capsules per day
- Flexeril 10 mg four times daily

Pain is described as a dull ache in the lower back, and rated at three to four on a verbal analogue scale, with 0 as no pain and 10 as excruciating. The lancinating pain down his right leg rates from five to nine on 10.

David's sleep pattern is poor, as is his appetite. He has gained about 10 pounds. His bowel function is normal, but he reports hesitancy of micturition.

How should David's pain be managed?

For the answers, please go to page 114.

In this article:

Acute or chronic pain is the predominant symptom which takes the patient to the doctor's office or to the emergency department. Prevalence of chronic pain in Canada is 27% in men and 31% in women. The most common type of pain is back pain (35%), followed by leg pain (21%).[1] The way we manage pain not only makes an impact on the patient, but also on the family, and economically on society. Effective treatment of acute pain is less likely to lead to chronic pain syndromes.[2]

Pain and Dosing

David's case discussion

Definitive diagnosis: Failed back syndrome.

Plan:

Pain relief and improvement in mobility.

Treatment starting points:

Oxycontin®: 10 mg every 8-12 hours.
Gabapentin: 300 mg at bedtime on the first day
300 mg twice a day, on the second day
300 mg three times a day on the third day, and thereafter.

Followup:

The medication will need titration. There should be regular monthly appointments, and encouragement for vocational planning. Timely management is unlikely to return David to his previous occupation, but it may reduce the pain enough so that he can train for more sedentary employment.

What about the assessment?

It is imperative to assess the patient's pain and include a functional inquiry, family history, history of medications and allergies, and a social history (Table 1).

Table 1
Considerations for assessing chronic pain

History
- Onset, characteristics
- Variation (exacerbating and relieving factors)
- Severity, using a verbal rating scale, or a visual analogue scale of 0 to 10, where 0 is no pain and 10 is very severe pain

Functional inquiry
- Sleep hygiene
- Appetite
- Weight change
- Bowel and bladder function
- Mood (if depressed, query suicidal ideation)

Family history
- History of alcohol and drug use/misuse

Medications and allergies
- Including present and past medications
- Record doses, schedules, benefits, side-effects and reasons for discontinuation

Social history
- Record the patient's marital status (present and past relationships, and reasons for break ups)
- Documentation of children

Smoking history

Use of alcohol
- Previous "recreational" drug use
- Complete the CAGE questions to screen for alcohol-related problems (if appropriate)

Financial support
- Work
- Disability (workers' compensation)

How do I manage pain with analgesics?

The World Health Organization proposed a stepwise method for ordering analgesics, from mild to strong, to treat cancer pain.[3] This same ladder is used when treating chronic non-cancer pain, although Step 1 would usually have been tried earlier, when pain was acute. The oral route, opposed to parenteral, is definitely the preferred route when treating pain in non-cancer patients. However, on

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occasion this is not possible, as in patients with severe gastrointestinal (GI) absorption problems.

There are three steps to this ladder:

Step 1: Mild Pain

NSAIDs may be indicated for inflammatory pain, as in rheumatoid arthritis, or after acute injury. The safety profile has been improved with the introduction of selective cycloxyegenas-2 (COX-2) inhibitors. However, there are still concerns regarding renal toxicity and GI bleeding, especially with increased age, previous history of bleeding, steroid and low-dose acetylsalicylic acid (ASA) use, and with prolonged use. Proton pump inhibitors should be considered. Both NSAIDs and COX-2 inhibitors can cause fluid retention, hypertension, and congestive heart failure.[4] Acetaminophen has analgesic properties without GI toxicity. Dosing in acute pain can be as high as four grams a day, but should not exceed three grams a day when used chronically. Lower doses should be prescribed for the elderly, frail, and those overusing alcohol (to avoid liver toxicity).[5] It is very important to ask patients about their use of over-the-counter medications and record this information.

Step 2: Moderate Pain

Codeine is available in oral dosing, alone in short-acting and long-acting formulations, or in combination with acetaminophen, and also as an injectable. The analgesic properties are related to its conversion to morphine. However, approximately 10% of the population are poor metabolizers of codeine and, therefore, have no analgesic benefit.[6] Codeine has a ceiling effect, so that doses higher than 60 mg every four hours produce no further benefit for pain control, but may increase side-effects.

Step 3: Severe Pain

Opioids are prescribed for severe pain. There are individual variations and differences in opioid phamacokinetics, which make it impossible to predict which opioid will benefit certain patients. Consequently, it may be necessary to try more than one opioid to realize the benefit.[7]

Morphine: This is the traditional opioid used in palliative care and pain control. Once termed the gold standard, it is now considered the old standard. Newer synthetics and semi-synthetics often have advantages due to improved side-effect profile. Morphine remains readily available for oral dosing, in short-acting and long-acting formulations, suppositories, as well as injectable forms. Morphine-3-glucuronide

Practice Pointers

- It is very important to ask patients about their use of over-the-counter medications. This information should be recorded.
- Patients who are opioid-naïve must first be started on a short-acting opioid, and once stabilized, changed to a long-acting opioid.
- Physicians may choose to have patients (who are prescribed opioids) complete a screening test for substance abuse potential. The patient may also be asked to sign a contract outlining specific rules for the safe use of opioids.

Table 2

When patients should be referred to a specialist

- When acute pain exceeds the normal length of time for healing, and interferes with daily functions. The attending physician may wish to refer the patient after investigations prove negative.
- Post-operative pain management, in patients who are being managed for an existing chronic pain syndrome.
- If the attending physician feels uncomfortable with prescribing or titrating opioids, or if patients are escalating the doses, or side-effects intolerable.
- If pain becomes uncontrollable despite therapy, possibly due to tumour invasion, for example, in cancer pain.
- For special procedures, such as spinal block, epidural stimulator, Medtronic infusion device, botulinum injections.
- If patient is having feelings of worthlessness, or suicidal ideation due to intractable pain.

(M3G) and morphine -6-glucuronide (M6G) are the morphine metabolites which may contribute to toxicity in the elderly and those patients with renal insufficiency.[8,9]

Oxycodone: This is available for oral dosing, either alone in short-acting or long-acting formulations, or in combination with acetaminophen (Percocet®) or with ASA (Percodan®).[10] Combination products can lead to side-effects due to toxicity from acetaminophen or ASA. Oxycodone has no active metabolites and is useful for occasional use or as a breakthrough medication.

OxyContin® is the long-acting or sustained release form of oxycodone. It is an appropriate analgesic in younger populations. In our clinical experience, some patients, particularly the elderly, may experience sleep disturbance or jitteriness. It may be necessary to prescribe a dosing schedule every eight hours rather than every 12 hours, especially when higher doses are ordered.

Hydromorphone: This opioid is a semi-synthetic available in various short-acting formulations, including oral tablets and liquid, rectal suppositories, and injectable. The long-acting formulation is called Hydromorph Contin®. Similar to morphine, it is a mu opioid receptor agonist. Elderly patients and others who have renal impairment or diminished creatinine clearance usually tolerate hydromorphone quite well, with less cognitive impairment and somnolence than with morphine, due to different metabolites.[11]

Transdermal (TTS)-fentanyl: This transdermal patch, called Duragesic®, is available in four different strengths, and is especially useful for patients who have GI absorption problems or poor compliance with oral dosing schedules. It is a long-acting formulation, changed every 48 to 72 hours, so is only recommended to treat chronic pain.

Fentanyl concentrations gradually increase for 12 to 24 hours after the first application, and it takes about 17 hours to reach half-life when the patch is discontinued.[12,13] Duragesic® is particularly helpful for the elderly with stable pain.

Patients who are opioid-naïve must first be started on a short-acting opioid, before the patch is prescribed. The lowest dose of Duragesic® is 25 µg/hr, equivalent to 40 mg to 60 mg of oral morphine per day.

Methadone: This long-acting opioid is best known for its use in addiction medicine but more recently, it has been used in palliative medicine and to treat chronic pain. Methadone is only available in oral formulations in Canada. Physicians must have a special licence approved through their provincial College and Health Canada to prescribe it. This opioid is an N-methyl-D-asparate receptor antagonist, known to be especially useful in treating neuropathic pain syndromes.[14] Methadone is very lipophilic and has a long, but variable half-life (12 to 60 hours); there is much inter-individual variation in pharmacokinetics.[15] Methadone clearance depends on the amount of functional cytochrome P450 isoform 3A4 in the liver, so that its metabolism is either stimulated or inhibited by concomitant medications.[16] Recently it has been found that high doses of methadone can cause serious cardiac arrhythmias.[17] It is a difficult drug to prescribe for the novice physician.[18,19]

What are the potential problems?

There is no evidence that opioids cause organ damage, but there remains the myth that these potent medications cause addiction. However, addiction is a primary neurobiological disease influenced by genetic, psychosocial, and environmental factors. Research has shown the risk for addiction is low in patients who use opioids and who do not have a past history of this disorder.[20,21] Should opioids be required to treat patients with existing addiction problems, special guidelines are recommended, and these patients should be followed very closely.[22] Treating this group of patients can be difficult, but may lead to harm reduction for both the patient and the community.

Pseudoaddiction is a term used to describe abnormal behaviour, similar to that of addiction, as a consequence of inadequate pain management.[23] This ultimately leads to continued suffering and mistrust between the patient and physician.

Tolerance is another potential problem associated with opioids. Tolerance refers to a decrease in analgesia or need for a higher dose to maintain the effect.[24] This phenomenon is not usually the rea-

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Take-home message

- Chronic pain is a biopsychosocial condition.
- The goal of treatment is to relieve pain and improve the quality of life.
- Treatment includes pharmacologic agents (opioids and analgesic adjuvants), and nonpharmacologic therapy (transcutaneous electrical nerve stimulation, physiotherapy, *etc*).
- It is the ethical responsibility of the physician to seek the best possible pain relief for the patient.
- Complete pain relief may not be achievable.

son for opioid dose titration nor does it indicate, on its own, an addiction. It may be the result of disease progression. The analgesic dose may require titration or a change in the opioid.

Physical dependence to opioids is an expected and naturally occurring physiological response when regular use of opioids is abruptly stopped or reduced. Patients should be warned about withdrawal syndrome (like a severe flu) should they discontinue their analgesics abruptly, rather than a gradual reduction under the direction of their physician.

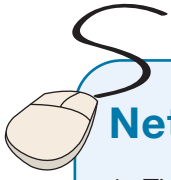
Patients with chronic pain need to balance pain relief with the ability to remain as active as possible. Pharmacologic therapy should not decrease patients' cognitive and physical functioning. When side-effects outweigh the benefits of treatment, new modalities should be tried.

What are the new developments?

Although we have much more knowledge about the complexities of pain and its transmission, new therapies are needed to maximize benefits and minimize side-effects. Strategies for new drugs may arise from improvements on existing treatments (*e.g.,* new formulations and new analogues), or from new targets in the central and peripheral nervous system.[25]

Evidence suggests that combinations of medications, including opioids, may activate different receptors and cellular mechanisms, producing a synergistic effect for analgesia with reduced side-effects.[26] Gabapentin, an anticonvulsant, is a very useful adjuvant to treat neuropathic pain. It has desirable pharmacokinetic properties and is usually well-tolerated. It is prescibed in doses starting at 300 mg the first day, twice daily on the second day, and three times the following day and thereafter. Elderly patients and people who are sensitive to medications should start with 100 mg doses.[27,28] There are some newer adjuvant analgesics, which may be beneficial to treat chronic pain. For example, topiramate, an anticonvulsant, is used as a prophylactic for migraine headaches.[29] It is initially ordered at a dose of 25 mg every hour of sleep for two weeks, increasing to 25 mg twice a day and up to 100 mg twice a day as tolerated. Side-effects may be tingling around the mouth and tips of the fingers. Glaucoma is a contraindication for the use of topiramate.

As previously discussed, the new COX-2 inhibitors are being widely used, but they are not innocuous. Their use needs to be balanced



Net Readings

1. The Canadian Pain Society
   www.canadianpainsociety.ca
2. PainCare.ca
   www.paincare.ca
3. World Health Organization
   www.who.int/cancer/en

between analgesia and risk of complications.[30]

Ongoing studies are reporting that botulinum toxin type A may be a benefit for some pain disorders related to excessive muscle contraction, such as myofascial pain, and as a migraine preventive treatment.[31]

There are ongoing issues around the medical use of cannabinoids. Canadian researchers are hopeful to be involved in studies to determine the analgesic benefits and safety of long-term use of marijuana, using acceptable routes of delivery, such as oral or sublingual.

What about referral to a pain specialist?

There are various situations when patients should be referred to a specialist. To clarify, there is no specific fellowship in Canada for a pain specialist. However, anesthetists are recognized as specialists in pain; they are experts in such procedures as neural blockades and interventions for spinal pain. Other physicians considered specialists are those doctors who have taken a special interest in pain, and, through their clinical experience and personal educational endeavours, have become experts in treating patients with chronic pain.

A multidisciplinary team at a pain clinic is ideal to evaluate the psychosocial issues, but these teams are few and access may be untimely (Table 2). CME

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