Clinical Concerns

Drugs for Chronic Pain:
No Easy Solution

Lori Montgomery, MD, CCFP

Presented at the University of Calgary's Wednesday Evening Course Program, Calgary, Alberta.

When you contemplate the etiology of chronic pain, you can get dizzy from the sheer array of contributing factors. So, it makes sense that there is not one single "magic pill" to eliminate it. A logical approach to a chronic pain patient involves an understanding of:

- the biomechanical factors that perpetuate pain,
- the psychosocial context in which the patient finds themselves and
- the non-medical strategies that they have developed to cope with pain.

But we do have some weapons in our pharmaceutical armoury to help our patients manage the problem.

First principle of chronic pain management

The first principle of chronic pain management is simple: elimination of pain is not a reasonable goal. Given that fact, decisions about which agents to use and when must be guided by functional goals. These should be related to:

- work,
- exercise,
- social activity,
- sleep, or
- mood.

Michael's case

Michael, 44, presents 6 months after a vasectomy. He has had several months of inguinal and testicular pain that is beginning to limit his ability to work. The pain is constant, at an intensity of 8/10. He describes the pain as burning and electric shock-like, associated with numbness, pins and needles and a tingling feeling. On exam, he is allodynic over the area. He is currently taking acetaminophen and codeine phosphate with very little relief. His main goals are to improve his sleep and to eliminate sick days related to pain.

Diagnosis

Michael's history and physical exam are consistent with neuropathic pain. The incidence of chronic pain following vasectomy has been variously estimated at 5% to 33%[1] and this is only one of several well-documented post-surgical pain syndromes that appear to have neuropathic contributors.

Initial treatment

You give Michael a prescription for 10 mg of nortriptyline and a schedule for increasing the dose in 10 mg increments every week, until he reaches the 50 mg to 80 mg range, at which point you plan to reassess his progress.

For more on Michael, look to page 93.

The success of any intervention should be judged by whether or not it improves function.

Do not forget the simple things

There is excellent evidence for simple analgesics like acetaminophen and ibuprofen for mild-to-moderate pain. They are not generally useful for purely neuropathic pain, but most pain is anything but "pure." If there are no contraindications to using them, they are still a good start.

Next steps for neuropathic pain

Pain with a neuropathic component (Table 1) should be addressed with more specific agents. A recent guideline by the Canadian Pain Society offers a review of the evidence for the commonly-used neuropathic pain agents and suggests an algorithm for their use (Figure 1).[2] Tricyclic antidepressants, gabapentin and pregabalin all have very reasonable NNTs (2.5 to 4.5) in the treatment of various neuropathic pain conditions and are well tolerated if the starting dose is small and titration happens slowly.

In the context of chronic pain, we consider strong opioids successful if they reduce pain levels by 30% to 40%.

Second-line agents

Serotonin-norepinephrine reuptake inhibitors and topical lidocaine are considered equally good second-line choices, although the lidocaine patch has not yet been approved for use in Canada; therefore, a 5% gel or cream can be used instead (though this is not ideal as it has not been studied in trials the way the patch has).

Third-line agents

Tramadol and other long-acting opioids have excellent evidence for efficacy, but are relegated to third-line status due to their high cost, the possible side-effects of long-term treatment and their abuse potential. Other agents, like cannabinoids, methadone, topiramate, lamotrigine and valproic acid, have less convincing evidence in neuropathic pain, but can be considered if other agents fail.[3,4]

Michael's case cont'd...

First follow-up

Six weeks later, Michael has increased his nortriptyline to 50 mg but was unable to titrate any further due to sedation side-effects. His pain levels have decreased to an average of 5/10 and he is now sleeping uninterrupted for about 6 hours per night. However, he continues to call in sick regularly due to flares of pain. You decide to continue the nortriptyline and add gabapentin, beginning at 100 mg h.s. and titrating up slowly to a maximum of 3,600 mg q.d. You also give him some reading material on relaxation techniques and pacing his activities.

Second follow-up

Eight weeks later, Michael has titrated the gabapentin to 300 mg t.i.d. His pain levels are now about 2/10 most of the time and he no longer misses work due to pain. He continues to use acetaminophen and codeine phosphate for flares of pain, which only occur about every two months and last for less than a day. You elect to maintain the current doses of his medications, and continue to teach non-pharmacologic coping strategies whenever possible.

Table 1

DN4 neuropathic pain questionnaire[5]

Four or more positive responses suggests neuropathic pain:

1. Does the pain have 1 of the following characteristics?
   a) Burning
   b) Painful cold
   c) Electric shocks
2. Is the pain associated with ≥ 1 of the following symptoms in the same area?
   a) Tingling
   b) Pins and needles
   c) Numbness
   d) Itching
3. Does a physical exam reveal ≥ 1 of the following characteristics?
   a) Hypoesthesia to touch
   b) Hypoesthesia to pinprick
4. In the painful area, can the pain be caused, or increased by the following?
   a) Brushing

Weak opioids

Physicians are very familiar with the side-effect profile and efficacy of codeine, which can be the next step after simple analgesics for non-neuropathic pain. Be aware that a percentage of the population lacks the necessary enzyme to metabolize codeine and another portion are ultra-rapid metabolizers and will be more sensitive to lower doses. Until recently, there were no other options in this class for Canadian patients. However, tramadol (along with codeine) is now available as a useful intermediate step—albeit an expensive one—before considering strong opioids. The immediate-release formulation is supplied as 37.5 mg of tramadol and 325 mg of acetaminophen and the long-acting formulation of tramadol alone starts at 150 mg. The side-effect profile of both the immediate release and long-acting formula

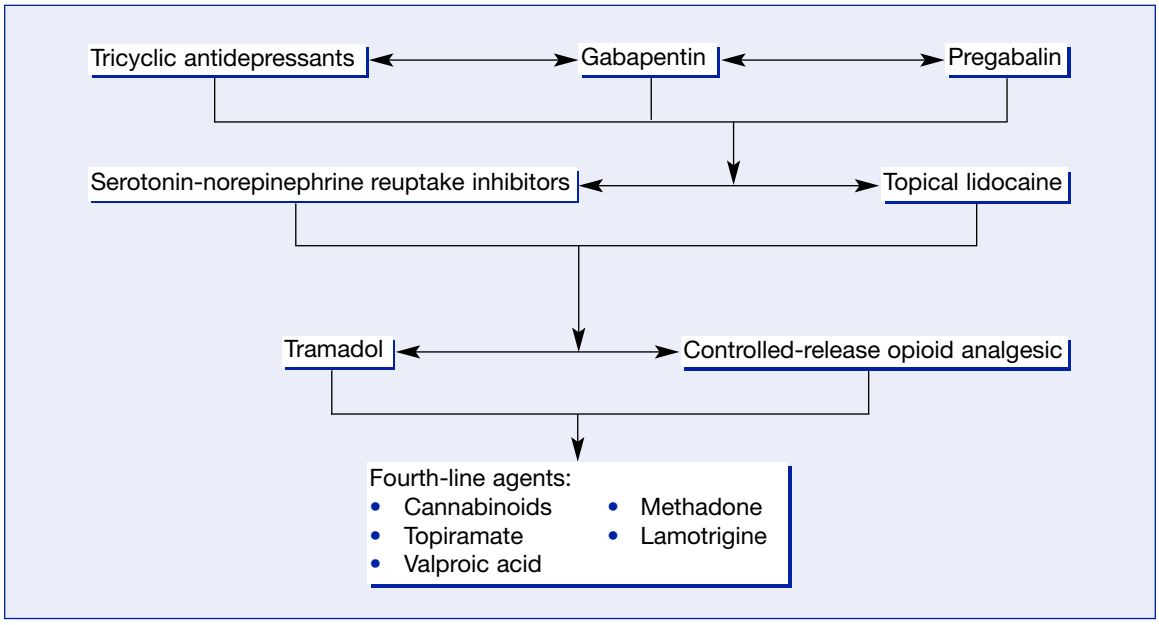

Figure 1. Algorithm from the Canadian Pain Society regarding commonly-used neuropathic pain agents.[2]

is similar to codeine, but many patients report less constipation.

Strong opioids

Sometimes, both physicians and patients have high expectations of strong opioids. They are "pain-killers" so one should have little or no pain after taking them, right? The fact is that in the context of chronic pain, we consider strong opioids successful if they reduce pain levels by 30% to 40%; therefore, dose escalations beyond this level should be attempted on a trial basis and with clear limits.

There is excellent evidence for the use of opioids (including methadone) in many chronic pain conditions, but there is limited evidence for doses > 180 mg q.d. of the morphine equivalent.

Side-effects of strong opioids

Beyond the side-effects that are commonly associated with opioids, it is becoming clear that chronic use can be associated with immune changes, endocrine effects (including low libido) and opioid-induced hyperalgesia. Many physicians are particularly conscious of addiction potential and patients certainly need to be screened for addiction risk factors prior to beginning opioid therapy. A full discussion of opioid dependence and overuse, as compared to addiction, is beyond the scope of this article, but physicians at our facility (the Calgary Health Region Chronic Pain Centre) use a standard opioid agreement for all patients on opioid therapy and employ standardized documentation templates (Table 2) to try to minimize problems.

Table 2

Opioid checklist

- Full history and physical exam?
- Screening tests for addiction/risk factors?
- Pain diagnosis?
- Opioid agreement reviewed and signed?
- Name of pharmacy on file?
- Opioid prescribing flowsheet on file?
  - Date
  - Drug
  - Dose
  - Number dispensed
  - Date refill is due
- Are the 5 'As' addressed at each visit?
  - Analgesia
  - Activity
  - Adherence with treatment
  - Aberrant drug behaviours
  - Adverse effects
- Other options explored?

There is excellent evidence for the use of opioids (including methadone) in many chronic pain conditions, but there is limited evidence for doses > 180 mg q.d. of the morphine equivalent.

Dr. Montgomery is a Chronic Pain Physician, Calgary Health Region, Chronic Pain Centre, Calgary, Alberta.

Patients need to be screened for addiction risk factors prior to beginning opioid therapy.

The bottom line

The science of chronic pain management is an evolving one and many questions remain unanswered. With a couple of exceptions,[6,7] the evidence for combining agents is based on expert consensus and many of the medications available are used for off-label indications. However, there is a growing body of evidence to support many of these interventions, as long as both the patient and physician have realistic expectations. Dx

Acknowledgements
The author would like to thank Dr. Chris Spanswick for reviewing this article and for providing suggestions.

References
1. McMahon AJ, Buckley J, Taylor A, et al: Chronic Testicular Pain Following Vasectomy. Br J Urol 1992; 69(2):188-91.
2. Moulin DE, Clark AJ, Gilron I, et al: Pharmacological Management of Chronic Neuropathic Pain. Consensus Statement and Guidelines from the Canadian Pain Society. Pain Res Manag 2007; 12(1):13-21.
3. Lynch ME: A Review of the Use of Methadone for the Treatment of Chronic Non-Cancer Pain. Pain Res Manag 2005; 10(3):133-44.
4. Ware M, Beaulieu P: Cannabinoids for the Treatment of Pain: An Update on Recent Clinical Trials. Pain Res Manag 2005; 10(Suppl A):27A-30A.
5. Bouhassira D, Attal N, Alchaar H, et al: Comparison of Pain Syndromes Associated with Nervous or Somatic Lesions and Development of a New Neuropathic Pain Diagnostic Questionnaire. Pain 2005; 114(1-2):29-36.
6. Gilron I, Bailey JM, Tu D, et al: Morphine, Gabapentin or Their Combination for Neuropathic Pain. N Engl J Med 2005; 352(13):1324-34.
7. Simpson DA: Gabapentin and Venlafaxine for the Treatment of Painful Diabetic Neuropathy. Journal of Clinical Neuromuscular Disease 2001; 3(2):53-62.

Resource
1. Ballantyne JC, Mao J: Opioid Therapy for Chronic Pain. N Engl J Med 2003; 349(20):1943-53.