Chronic Pain: Tom's Agonizing Feet

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Persistent pain is a major cause of disability and suffering, as well as a treatment challenge for the busy clinician. Approximately 29% of Canadians report persistent pain and at any one time, seven million Canadians are taking pain medication.[1] Both the perception of pain and its response to analgesic therapy widely vary and there exists no objective laboratory test that can measure or quantify pain. Thus, clinicians must treat pain based on the patient's reported perceptions and pain descriptors.

Tom's Case

- Tom, 58, is a male doctor and university professor who has a one-year history of Type 2 diabetes mellitus
- He has had bilateral burning pain in his legs and feet for the last two years
- The pain is worse at night. Tom cannot tolerate bed sheets touching his skin and therefore, is sleeping poorly
- He is irritable and distracted at work
- Tom has clinical and electrophysiological evidence of mixed distal sensory-motor peripheral neuropathy

Does Tom have chronic pain?

There is no universally accepted definition of chronic pain. Pain that exists longer than expected due to tissue injury could be considered chronic, as could pain secondary to ongoing disease processes, such as in diabetic neuropathy. However, with advances in research on the mechanisms of chronic pain, it is now known that physiologic changes occur in both the peripheral and central nervous systems in response to the injury or disease that lead to the continued generation of pain.

Is Tom's pain "nerve pain?"

Pain can generally be considered to be nociceptive, neuropathic, or mixed. Neuropathic pain is pain initiated or caused by a primary lesion or dysfunction in the nervous system, *i.e.*, in diabetic peripheral neuropathy or postherpetic neuralgia. Neuropathic pain descriptors include:

- burning,
- electrical,
- shooting and
- pins and needles

Nociceptive pain is pain that arises from normal activation of peripheral nociceptors at tissue injury site, such as that caused by inflammation. Descriptors include aching and throbbing pain.

Recognize the role of pharmacologic therapy

Research supports a holistic approach to pain management with pharmacologic treatment as part of a comprehensive management plan. Recent published reviews of best-evidence in pharmacotherapy for chronic and neuropathic pain support this approach,[2,3] which includes:

- education,
- identification of treatment objectives,
- aerobic activity,
- modalities as appropriate,
- lifestyle modifications,
- sleep restoration,
- psychosocial assessment and interventions as needed.

To date, there is no single agent that provides complete pain relief and treatment will often require the use of combination therapy. Most studies that evaluate the efficacy of pharmacologic agents have considered a

Table 1

First-line medications for treating chronic neuropathic pain

	Starting dose	Titration	Therapeutic range	Side effects	Indications
Amitriptyline	10 mg to 25 mg q.d.	10 mg to 25mg 5 days to 7 days	10 mg to 150 mg q.d.	• Sedation • Weight gain	• Neuropathy • Myofascial pain • Tension headaches
Nortriptyline	10 mg to 25 mg q.d	10 mg to 25 mg	10 mg to 100 mg q.d. 5 days to 7 days	• Sedation • Weight gain	• Neuropathy • Myofascial pain • Tension headaches
Gabapentin	300 mg q.d.	300 mg q.5.d.	1800 mg to 3600 mg q.d. in 4 doses to 5 doses	• Dizziness • Somnolence • Ataxia • Confusion	• Neuropathic pain • Spinal cord injury • Neuropathy
Pregabalin	50 mg to 75 mg b.i.d.	75 mg to 150 mg	150 mg to 600 mg 3 days to 7 days, b.i.d. to t.i.d.	• Dizziness • Somnolence	• Postherpetic neuralgia • Diabetic neuropathy
Carbamazepine	100 mg CR b.i.d.	100 mg to 200 mg	400 mg to 800 mg q.d. (up to 2000 mg q.d.)	• Sedation • Rash • Hepatitis • Migraine	• Trigeminal neuralgia • Prophylaxis • Diabetic neuropathy

reduction in pain of at least 30% to 50% as a positive result. Therefore, patients need to be educated about the expectations of pain treatment. For an individual patient, the success of treatment should be evaluated in the context of functional outcomes and mutually agreed upon objectives, such as improved sleep or the ability to return to work.

Pain transmission occurs via ascending and descending neurons and processing at the brain and spinal cord levels. In reaction to injury or disease, physiologic changes occur in these pain pathways which result in the generation of persisting pain. These changes include peripheral and central sensitization, loss of descending inhibition and structural reorganization. For example, nociceptors (neurons that normally respond to pain stimuli) may now fire in response to non-noxious stimuli, such as light touch. Neurons previously responsive only to non-painful stimuli may now be active in pain transmission pathways.

Agents used in the treatment of chronic pain can be divided according to their major antineuralgic mechanisms of action:

1. Agents that modulate peripheral sensitization by their effects on the sodium channels, including:
   - carbamazepine,
   - phenytoin,
   - topiramate,
   - lamotrigine,
   - mexiletine and
   - lidocaine.

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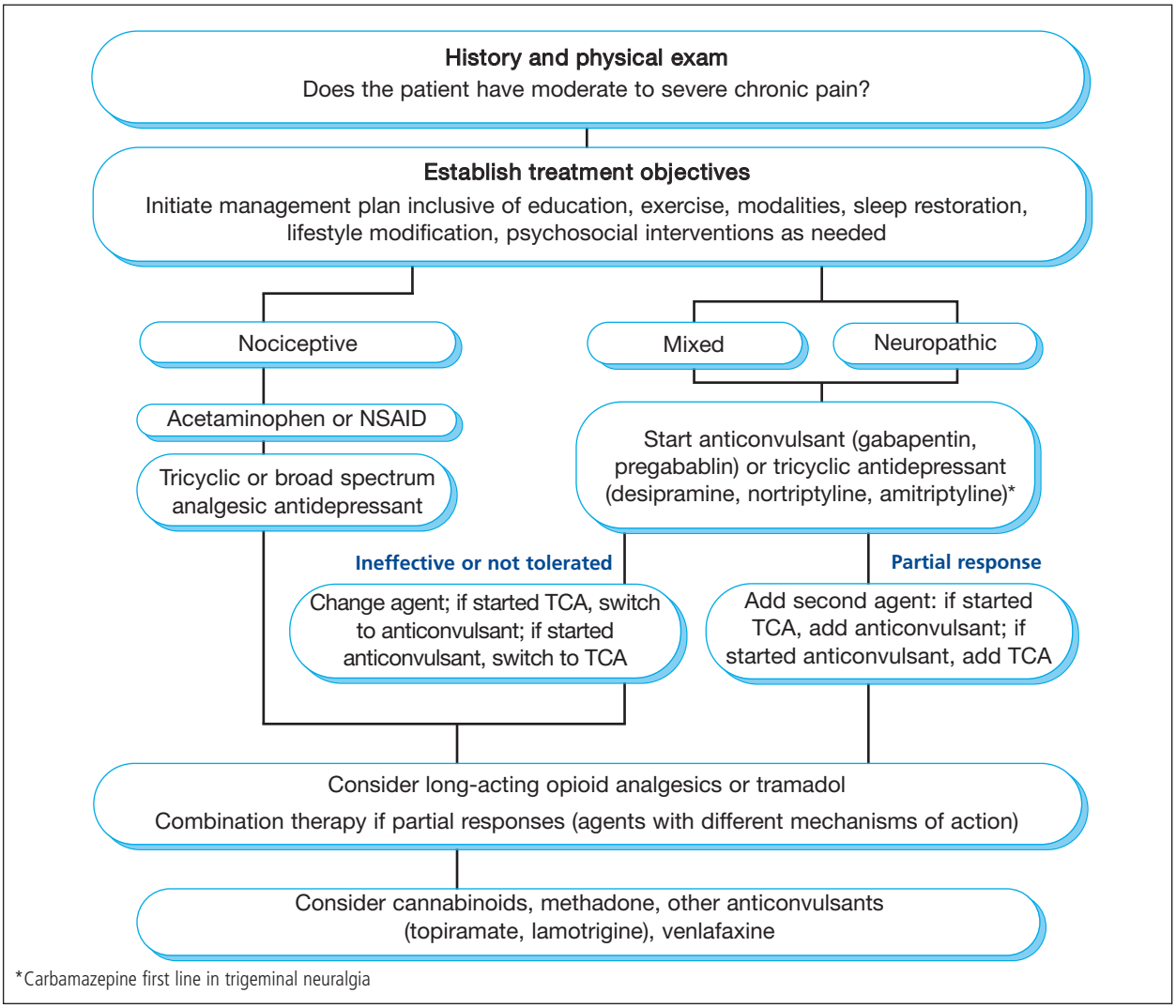

Figure 1. Algorithm for pharmacotherapy in chronic pain.

2. Agents that enhance the descending inhibitory pathways from the brain to the spinal cord by inhibiting the reuptake of biogenic amines or by interacting with the opiate receptors, including:
   - tricyclic antidepressants (TCAs),
   - selective norepinephrine reuptake inhibitors (SNRIs),
   - tramadol and
   - opiates.
3. Agents that modulate central sensitization, as well as N-methyl-D-aspartic acid antagonists, include:
   - ketamine,
   - dextromethorphan,
   - methadone and topiramate, as well as
   - agents that affect the calcium channels (*e.g.*, gabapentin and pregabalin).

Should Dr. Tom be prescribed morphine for bedtime?

First-line therapy in chronic neuropathic or mixed pain includes TCAs and the calcium-channel modulating anticonvulsants gabapentin and pregabalin (Table 1), in randomized, controlled trials (RCTs), TCAs have clear evidence of efficacy in a number of pain conditions, including diabetic neuropathy, lower back pain and postherpetic neuralgia.[2-5] The main disadvantage is the side-effect profile, resulting in anticholinergic effects and sedation, which are generally less with desipramine or nortriptyline. The use of gabapentin and pregabalin for chronic neuropathic pain, is supported by a number of RCTs including spinal cord injury, diabetic neuropathy mixed neuropathic pain disorders.

Take-home message

1. Educate your patient
2. Establish treatment objectives
3. Pharmacotherapy should only be instituted as part of a comprehensive pain management plan
4. Tricyclic antidepressants and anticonvulsants remain first-line therapy for most patients
5. Combination therapy may be required

The decision to start therapy with a TCA vs. an anticonvulsant is a clinical one, based on the patient's symptoms, co-morbidities, financial resources and compliance. For patients with sleep impairment, a TCA may be the better starting choice. Patients who poorly tolerate anticholinergic side-effects may do better with the anticonvulsants. Patients for whom compliance is an issue may not do well with dosing requirements of gabapentin.

For nociceptive pain, first-line agents include the non-opioid analgesics (*i.e.*, acetaminophen, non-steroidal anti-inflammatory drugs [NSAIDs]), or TCAs for diagnoses such as low back pain. Recent research on NSAIDs has demonstrated a central mechanism of analgesic action in addition to the anti-inflammatory effect.[2]

Opioids are effective in chronic pain conditions and are a reasonable choice for select patients. Clinicians should follow clinical practice guidelines for opioid use, such as that from the Canadian Pain Society.[6]

Tramadol has a dual mechanism of action, with weak μ-opioid agonism and inhibition of both serotonin and noradrenalin reuptake. It has demonstrated efficacy in both nociceptive and neuropathic pain conditions, with dosing of 50 mg to 100 mg every four hours to six hours, with a maximum dose of 400 mg q.d. With low respiratory depressant effect and low abuse potential, it is a reasonable choice for chronic pain treatment.

Venlafaxine has both strong serotonin and noradrenalin reuptake inhibition and is structurally similar to tramadol. There is trial evidence to support the use of 150 mg to 225 mg q.d. of venlafaxine in neuropathic pain and it may be considered when TCAs fail.

Dosing should start low, with gradual titration to therapeutic levels, monitoring for benefit and side effects. For patients with a partial response, once stable at therapeutic level, a second agent from a different class may be added. For patients who do not respond despite therapeutic levels, or who do not tolerate the medication, the first agent should be tapered to discontinue, then a second agent trialed. Remember the mechanisms by which the medication acts; if one agent is ineffective, or only partially effective, agents with a different mechanism of action should be considered. As chronic and neuropathic pain arise from a number of physiologic changes in the nervous system, combination therapy with agents that act at different sites is often required (Figure 1).

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