



Anticonvulsants, Serotonin-Norepinephrine Reuptake Inhibitors, and Tricyclic Antidepressants in Management of Neuropathic Pain

This document highlights key findings from a CADTH health technology assessment report titled Anticonvulsants, Serotonin-Norepinephrine Reuptake Inhibitors, and Tricyclic Antidepressants in Management of Neuropathic Pain: A Meta-Analysis and Economic Evaluation.

A damaged or dysfunctional nervous system can result in chronic neuropathic pain. The condition is more common in women, people over 65 years of age, and those with lower incomes. Neuropathic pain diminishes quality of life and places burdens on the health care system and the economy.

The Canadian Pain Society has developed guidelines for the pharmacological treatment of neuropathic pain. The first line of treatment is either anticonvulsants (ACs) or tricyclic antidepressants (TCAs), alone or together. Second-line treatment is based on serotonin-norepinephrine reuptake inhibitors (SNRIs). The primary goal of treatment is not to eliminate neuropathic pain, but to make it more tolerable.

All of these drugs can relieve neuropathic pain. But, given scarce resources and the introduction of new treatments, it is timely to assess the recommended treatment options to determine which are clinically optimal and cost-effective.

KEY FINDINGS

- In all scenarios, TCAs dominated the other two drug classes, with lower costs and better patient outcomes.
 - In the primary clinical analyses, TCAs had similar efficacy rates to other classes of drugs.

DRUGS EXAMINED IN THIS REVIEW:

ANTICONVULSANTS

- Carbamazepine, gabapentin, and pregabalin

SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS

- Duloxetine and generic venlafaxine

TRICYCLIC ANTIDEPRESSANTS

- Amitriptyline, clomipramine, nortriptyline, imipramine, and maprotiline



- In the primary pharmacoeconomic analyses, TCAs are associated with fewer health care costs and improved health.
- Uncertainty remains about optimal treatment; the efficacy rates between drug classes could not be distinguished, and there was not enough literature available to enable a review of some recommended drugs.

FOR HEALTH CARE PROVIDERS

- TCAs have the highest efficacy rate, followed by ACs and SNRIs. Patients treated with TCAs had an average of 60 days with controlled pain, compared with ACs with 54 pain-controlled days and SNRIs with 41 pain-controlled days respectively.
- The measures could not be differentiated from a statistical standpoint, indicating that more evidence is needed to establish which drug class is superior.

PHARMACOLOGICAL MANAGEMENT OF CHRONIC NEUROPATHIC PAIN

First Line	Second Line	Third Line	Fourth Line
<ul style="list-style-type: none"> • TCAs • Anticonvulsants <ul style="list-style-type: none"> ◦ Gabapentin ◦ Pregabalin 	<ul style="list-style-type: none"> • SNRIs <ul style="list-style-type: none"> ◦ Venlafaxine ◦ Duloxetine* • Topical lidocaine <ul style="list-style-type: none"> ◦ 5% patch[†] ◦ 5% or 10% gel or cream 	<ul style="list-style-type: none"> • Tramadol • Opioid analgesics 	<ul style="list-style-type: none"> • Cannabinoids • Methadone • SSRI <ul style="list-style-type: none"> ◦ Citalopram ◦ Paroxetine • Other anticonvulsants <ul style="list-style-type: none"> ◦ Lamotrigine ◦ Topiramate ◦ Valproic acid • Miscellaneous agents <ul style="list-style-type: none"> ◦ Mexiletine ◦ Clonidine

SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressants.

*Unavailable in Canada when this project was initiated, duloxetine was selected for estimating overall clinical efficacy of SNRIs.

[†]Unavailable in Canada; 5% or 10% gel or cream can be compounded by pharmacist.

- While the mechanism of TCAs in managing pain is unknown, the drugs may exhibit analgesic properties that are independent of the antidepressant effects.

FOR POLICY MAKERS AND ADMINISTRATORS

- A Canadian economic evaluation that modelled drug use and outcomes over an 18-week period found that TCAs were the least costly group of drugs for first-line management of neuropathic pain; SNRIs were second-least costly and ACs were the most costly.
- If all Canadian patients taking TCAs switched to SNRIs or ACs, annual ministry of health costs would increase by \$59 million and \$68 million respectively.

GLOSSARY

- **Anticonvulsants (ACs):** A class of drugs used to manage epilepsy by suppressing the rapid and excessive firing of neurons.
- **Number needed to treat (NNT):** The number of patients who need to receive treatment to prevent one additional bad outcome.
- **Serotonin-norepinephrine reuptake inhibitors (SNRIs):** A class of antidepressant drugs similar to TCAs, but developed more recently, that act on two neurotransmitters in the brain: serotonin and norepinephrine.
- **Tricyclic antidepressants (TCAs):** A class of antidepressant drugs first developed in the 1950s that work by inhibiting the reuptake of neurotransmitters serotonin and norepinephrine.

What is neuropathic pain?

Neuropathic pain is caused by a dysfunction in the nervous system. It is a form of chronic pain, which refers to continuous or intermittent pain experienced for longer than three months. The prevalence of depression is twice as high among those experiencing chronic pain compared with a population that does not experience such pain.

While there is no Canadian estimate for the prevalence of neuropathic pain, the estimated prevalence in the United States is 1.5%, and in the United Kingdom it is 1%.

PROJECT INFORMATION

Neuropathic pain places a burden on the health care system and the economy and affects patients' quality of life. With the continued introduction of new treatments, there is uncertainty about whether currently recommended treatment options are sustainable. CADTH commissioned an assessment of treatment options to identify optimal clinical- and cost-effective treatments.

The research lead for the project was Michael Iskedjian, BPharm, MSc, President of PharmIdeas Research and Consulting Inc.

CADTH's full-length Technology Report, *Anticonvulsants, Serotonin-Norepinephrine Reuptake Inhibitors, and Tricyclic Antidepressants in Management of Neuropathic Pain: A Meta-Analysis and Economic Evaluation*, as well as a Technology Overview and this Research Highlights tool, are available at www.cadth.ca.

ABOUT CADTH

The Canadian Agency for Drugs and Technologies in Health (CADTH) is a national body that provides Canada's federal, provincial, and territorial health care decision makers with credible, impartial advice and evidence-based information about the effectiveness and efficiency of drugs and other health technologies.

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