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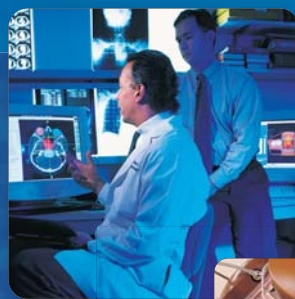
Agence canadienne  
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## T E C H N O L O G Y   O V E R V I E W

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



*Supporting Informed Decisions*

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# 1 Introduction

A damaged or dysfunctional nervous system can result in chronic neuropathic pain. This condition is more common in older people (particularly more than 65 years of age), in women, and in those of lower income.<sup>1-4</sup>

Although the percentage of Canadians with neuropathic pain is unknown, it is estimated to be 1.5% of the population in the US and 1% in the UK. The 2005 Canadian Community Health Survey reported that 10.8% of the population experienced pain or discomfort that prevented them from performing “few, some or most” activities.<sup>1</sup>

Neuropathic pain diminishes patients’ quality of life and burdens the health care system and the economy. People with painful neuropathic disorders experience more comorbidities and need more health care compared with a control group of people without neuropathic pain.<sup>5,6</sup> People with chronic pain are also twice as likely to experience depression.<sup>4</sup> An Australian study estimated that painful neuropathic disorders reduced annual economic productivity by 9.9 million workdays.<sup>7</sup> In the US in 2000, patients with neuropathic pain had health care costs that were three times higher than those of matched control subjects.<sup>8</sup>

The Canadian Pain Society developed guidelines for the pharmacological treatment of neuropathic pain based on the number of patients who need to be treated for one patient to experience at least a 50% reduction in pain.<sup>9</sup> First-line treatments are anticonvulsants (ACs) or tricyclic antidepressants (TCAs). If one fails, the other is tried. ACs can also be used with TCAs. Second-line treatment is based on serotonin-norepinephrine reuptake inhibitors (SNRIs). These include venlafaxine, duloxetine, and topical lidocaine. (Duloxetine was unavailable in Canada when we began this project, as was topical lidocaine 5% patch.) Third- and fourth-line treatment options for neuropathic pain (including tramadol, an opioid analgesic) were not the focus of this study.

## 2 Objectives

The aim of this technology assessment was to assess the clinical and economic impact of first-line drugs in managing neuropathic pain. To achieve that aim, the research focused on answering the following research questions:

- What are the clinical response rates from managing neuropathic pain with TCAs, SNRIs, or ACs?
- What is the existing evidence of cost-effectiveness of using these drugs for managing neuropathic pain?
- What drugs are cost-effective in managing neuropathic pain?
- What would be the impact on public formulary drug budgets if cost-effective technologies were adopted?

### 3 Methods

A protocol was written a priori and followed throughout the review. A librarian at the Hospital for Sick Children in Toronto developed a search strategy and searched the literature on EMBASE, MEDLINE, and The Cochrane Library of Systematic Reviews. References from key reviews and included articles were hand-searched for studies that were not found online. We used the results from a literature search that was done for a Cochrane systematic review of antidepressants for neuropathic pain.<sup>10</sup> For the economic review, we searched the same electronic databases as for the clinical review and Evidence-based Medicine Reviews from 1950 to 2007.

Two reviewers independently screened studies, first by abstracts, then by full text if they were deemed to be relevant. A third reviewer adjudicated disagreements. Clinical studies were included if they were double-blinded randomized controlled trials that compared one or more of TCAs, ACs, and SNRIs in a population of adults who were diagnosed with neuropathic pain. Economic studies were included if they were partial or full economic evaluations and met the same criteria as clinical studies in terms of population, interventions, and comparators.

Two reviewers extracted data independently for the clinical and economic studies. When discrepancies arose, a senior researcher arbitrated or made a final decision. To assess the quality of included clinical studies, two raters used the Jadad scale.<sup>11</sup> Economic studies were evaluated using a checklist by Iskedjian et al.,<sup>12</sup> which is based on Drummond's approach.<sup>13</sup>

We performed a meta-analysis of the clinical studies when three or more had similar characteristics. This provided quantitative summaries of clinical response rates, which we used in a decision tree analysis for our primary economic evaluation. Data were combined using a random effects model. The outcomes of interest were a mean reduction from baseline to endpoint in visual analogue scale (VAS) pain scores, the rate of patients achieving 30% and 50% reduction in VAS pain scores, and rates of withdrawals due to adverse reactions.

For the primary economic evaluation, which had a time horizon of 18 weeks, we adopted ministry of health and societal perspectives and included the direct costs of drugs;<sup>14</sup> costs of physician visits and hospitalizations; and indirect costs of loss of work, leisure, and transportation in the societal perspective. Patients were treated for at least 12 weeks, starting with a drug from one of the three pharmacological groups: ACs (gabapentin, pregabalin, or carbamazepine), TCAs (amitriptyline, clomipramine, nortriptyline, imipramine, or maprotiline), and SNRIs (duloxetine or venlafaxine). We followed the dosing regimen that was presented in Table 1 of Moulin et al.'s<sup>9</sup> report. Depending on their response after six weeks, patients would continue on the same therapy, be put on a higher dose of the same drug, or be switched to a different drug class. Patients who did not respond completely would be given a second agent in addition to the primary drug. Those who still do not respond completely would be treated with tramadol or an opioid as monotherapy.

In addition to the base-case analyses, we performed one-way sensitivity analyses and probabilistic sensitivity analyses (Monte Carlo simulations).

## 4 Results

### *Clinical*

We included 28 articles in our systematic review: 13 evaluated the efficacy and safety of ACs (gabapentin and pregabalin),<sup>15-27</sup> 10 evaluated TCAs,<sup>28-37</sup> four evaluated SNRIs,<sup>38-41</sup> and one study examined an SNRI and a TCA.<sup>42</sup>

The 13 studies of ACs had 20 active treatment arms (gabapentin 5, pregabalin 15) with an average of 81 patients in each. Studies were published between 1998 and 2006 and scored an average of 4.2 in quality. The average trial length was 9.1 weeks. Gabapentin was evaluated in flexible doses ranging from 900 mg/day to 3,600 mg/day. Pregabalin was studied in fixed and flexible doses of between 75 mg/day and 600 mg/day. The average baseline VAS pain score was 6.6.

The 11 clinical trials evaluating TCAs had 15 active treatment arms (10 for amitriptyline, one each for clomipramine, desipramine, imipramine, and nortriptyline, and one with a combination of TCAs). The average number of patients per study arm was 20. Studies were published between 1982 and 2004, averaged 6.6 weeks in duration, and scored an average of 3.6 in quality. The doses ranged from 10 mg/day to 150 mg/day for amitriptyline, 25 mg/day (fixed dose) for clomipramine, 50 mg/day to 150 mg/day for imipramine, and 25 mg/day (fixed dose) for nortriptyline. The dose of desipramine averaged 63 mg/day. The average baseline score for pain was 5.2.

The five trials on SNRIs were published between 2003 and 2006 and had 10 arms of two active treatments (duloxetine 7, venlafaxine 3) with an average of 100 patients per arm. Trials lasted 9.9 weeks and scored a quality of 4.8, on average. Duloxetine was evaluated at fixed doses of 20 mg/day, 60 mg/day, and 120 mg/day. Venlafaxine doses were fixed and flexible and ranged from 75 mg/day to 225 mg/day. The average baseline VAS pain score was 6.2.

For the meta-analyses, we adjusted response rates to compensate for variations in rates of response to placebo. Two methods were used: “from placebo” and “through placebo.”

The number needed to treat (NNT) was 5.0 for ACs and 6.0 for SNRIs in head-to-head trials against placebo for 50% pain reduction. Among the SNRIs, the NNT was 6.0 for duloxetine and 9.0 for venlafaxine. The discrepancy between the two numbers comes from a placebo rate of 27% across the duloxetine studies and 33.8% across the venlafaxine studies.

For 30% pain reduction, the NNT was 3.0 for TCAs, 4.0 for ACs, and 5.0 for SNRIs (duloxetine and venlafaxine were 5.0). When the response rates were adjusted through placebo, the NNT for 50% pain reduction was 3.9 for TCAs, 4.6 for ACs, and 5.7 for SNRIs. For 30% pain reduction the NNT was 3.0, 3.5, and 4.2 for each class respectively.

The dropout rates due to adverse drug reactions were reported in 40 study arms. Meta-analytic dropout rates were similar across drug classes: 12.3% for ACs, 11.7% for TCAs, and 12.0% for SNRIs.

## **Economic**

We included four studies:<sup>5,43-45</sup> one was a cost-effectiveness analysis,<sup>44</sup> one was a cost-utility analysis,<sup>45</sup> one was a cost-effectiveness and cost-utility analysis,<sup>43</sup> and one was a cost-of-illness analysis.<sup>5</sup> All four evaluated chronic neuropathic pain, particularly due to Diabetic Peripheral Neuropathy (DPN) and postherpetic neuralgia.

Wu et al. used a mixed modelling approach,<sup>44</sup> Cepeda and Farrar used a general decision tree,<sup>45</sup> Tarride et al. used a stochastic Markov model,<sup>43</sup> and Lachaine et al. did not reveal the type of model.<sup>5</sup> The time horizon ranged from four to 50 weeks. Two studies adopted a public-payer perspective,<sup>5,43</sup> and two adopted a private (third-party) perspective.<sup>44,45</sup> The studies evaluated pregabalin, gabapentin, amitriptyline, carbamazepine, tramadol, and duloxetine. All the studies were of good to excellent quality with a mean score of 79% using the Iskedjian checklist.<sup>12</sup>

Tarride et al. found that pregabalin was cost-effective compared with other ACs in managing neuropathic pain that was associated with DPN or postherpetic neuralgia.<sup>43</sup> Cepeda and Farrar concluded that amitriptyline (a TCA) was cost-effective compared with carbamazepine, gabapentin, and tramadol.<sup>45</sup> Wu et al. noted the cost-effectiveness of duloxetine compared with routine treatments of DPN (including gabapentin and amitriptyline).<sup>44</sup> While studying patients in Québec with peripheral painful neuropathic disorders, Lachaine et al. reported that these patients consume more medical resources than patients without such disorders.<sup>5</sup>

## **Primary Economic Evaluation**

In the base-case analysis using “from placebo” response rates, the use of TCAs resulted in the highest clinical response, followed by the use of ACs and the use of SNRIs over the 18-week time horizon. The use of TCAs resulted in the highest number of pain-controlled days (49 days on average) compared with 46 days and 43 days for ACs and SNRIs respectively.

In the second base-case analysis using “through placebo” response rates, the use of TCAs resulted in the highest clinical response, followed by ACs and SNRIs. In terms of pain-controlled days, TCAs were the best option (average of 60 days), followed by ACs and SNRIs with 54 and 41 days respectively.

From the ministry of health perspective and using the “from placebo” model, TCAs were the least costly group of drugs for managing neuropathic pain (\$380 in direct medical costs over 18 weeks). SNRIs were second lowest (\$448), and ACs were the most costly (\$560). This was also true from a societal perspective, but the magnitude differed (Table 1).

For the “through placebo” model, TCAs were the least costly and most effective (highest overall response rate and most pain-controlled days) of the three groups of drugs, from a ministry of health perspective and a societal perspective (Table 2).

A total of 128 one-way sensitivity analyses confirmed the robustness and direction of the base-case results. When duloxetine was substituted for venlafaxine as the SNRI in the “from placebo” model, TCAs still had the lowest cost per patient from a ministry of health perspective at \$422. ACs were next at \$610, and duloxetine was highest at \$860. From a societal perspective, TCAs were lowest at a per patient cost of \$1,850, followed by ACs at \$2,112 and duloxetine at \$2,443.

When duloxetine was the SNRI in the “through placebo” model, TCAs were the least costly from the ministry of health perspective at \$355, followed by ACs at \$557 and duloxetine at \$839. The same was true from a societal perspective with TCAs having the lowest cost at \$1,537, followed by ACs at \$1,906 and duloxetine at \$2,504.

TCAs were dominant in all analyses except three scenarios: when the upper level of the 95% confidence interval was applied to the efficacy of ACs in the “from placebo” analyses, when the lower level of the 95% confidence interval was applied to the efficacy of TCAs in the “from placebo” analyses, and when the lower level of the 95% confidence interval was applied to the efficacy of TCAs in the “through placebo” analysis.

If TCAs were not an option, the results were mixed: the use of SNRIs resulted in the lowest cost and lowest efficacy in all analyses except the “through placebo” analyses from the societal perspective. In the other analyses, ACs dominated SNRIs.

Three Monte Carlo simulation analyses confirmed the base-case results, with TCAs dominating the other two classes when the efficacy rates were adjusted relative to placebo. When rates were unadjusted, as in “single arm” analyses, SNRIs dominated.

<b>Table 1: Base-Case Cost-Effectiveness Analysis of ACs, SNRIs, and TCAs for Management of Neuropathic Pain for “From Placebo” Approach</b>							
<b>Approach</b>	<b>Perspective</b>	<b>Strategies</b>	<b>Cost</b>	<b>Incremental Cost</b>	<b>Effectiveness</b>	<b>Incremental Effectiveness</b>	<b>Incremental C/E (ICER)</b>
<b>Indirect “From Placebo”**</b>							
	MOH	TCAs	\$380		79.3% response		
		SNRIs	\$448	\$68	76.4% response	-2.9% response	(Dominated)
		ACs	\$560	\$181	77.8% response	-1.5% response	(Dominated)
	SOC	TCAs	\$1,808		79.3% response		
		SNRIs	\$2,030	\$222	76.4% response	-2.9% response	(Dominated)
		ACs	\$2,063	\$255	77.8% response	-1.5% response	(Dominated)
	MOH	TCAs	\$380		49 PCDs		
		SNRIs	\$448	\$68	43 PCDs	-6 PCDs	(Dominated)
		ACs	\$560	\$181	46 PCDs	-3 PCDs	(Dominated)
	SOC	TCAs	\$1,808		49 PCDs		
		SNRIs	\$2,030	\$222	43 PCDs	-6 PCDs	(Dominated)
		ACs	\$2,063	\$255	46 PCDs	-3 PCDs	(Dominated)

\*Success rates were calculated as follows: meta-analytic average of placebo success rate was calculated across studies for each outcome; meta-analytic average difference from placebo was calculated for each drug; two were added to give an adjusted rate for each drug.

ACs=anticonvulsants; C/E=cost-effectiveness ratio; ICER=incremental cost-effectiveness ratio; MOH=ministry of health; PCDs=pain-controlled days; SNRIs=serotonin-norepinephrine reuptake inhibitors; SOC=society; TCAs=tricyclic antidepressants.

**Table 2: Base-Case Cost-Effectiveness Analysis of ACs, SNRIs, and TCAs for Management of Neuropathic Pain for “Through Placebo” Approach**

Approach	Perspective	Strategies	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Incremental C/E (ICER)
<b>Indirect “Through Placebo”**</b>							
	MOH	TCAs	\$331		88.0% response		
		SNRIs	\$459	\$128	80.6% response	-7.4% response	(Dominated)
		ACs	\$519	\$188	84.3% response	-3.6% response	(Dominated)
	SOC	TCAs	\$1,513		88.0% response		
		ACs	\$1,868	\$355	84.3% response	-3.6% response	(Dominated)
		SNRIs	\$2,125	\$612	80.6% response	-7.4% response	(Dominated)
	MOH	TCAs	\$331		60 PCDs		
		SNRIs	\$459	\$128	41 PCDs	-19 PCDs	(Dominated)
		ACs	\$519	\$188	54 PCDs	-6 PCDs	(Dominated)
	SOC	TCAs	\$1,513		60 PCDs		
		ACs	\$1,868	\$355	54 PCDs	-6 PCDs	(Dominated)
		SNRIs	\$2,125	\$612	41 PCDs	-19 PCDs	(Dominated)

\*Success rates were calculated in same way as for Table 1, but the meta-analytic rate ratio was calculated for each drug against placebo, and these ratios were then multiplied by meta-analytic placebo rates to estimate drug success rates.  
 ACs=anticonvulsants; C/E=cost-effectiveness ratio; ICER=incremental cost-effectiveness ratio; MOH=ministry of health; PCDs=pain-controlled days; SNRIs=serotonin-norepinephrine reuptake inhibitors; SOC=society; TCAs=tricyclic antidepressants.

## 5 Limitations

This review was limited by several factors, including an underestimation of the cost of managing neuropathic pain, because a 50% reduction is incomplete. In addition, although the studies of ACs and SNRIs had sizeable numbers of patients, the sample size for TCAs was 305, which is few enough to give wide confidence intervals and introduce doubt into the sensitivity analyses. Another limitation was the comparison of drugs by class. The combination of data increases sample size and power, but it assumes that all drugs in a class are comparable in efficacy and safety. Different study designs, different types of patients in one study,<sup>44</sup> and different comparators also limit the review’s usefulness. A lack of literature meant that we did not examine the evidence for topical lidocaine, tramadol, or other opioid analgesics, even though they are recommended. Finally, the results of our meta-analyses must be interpreted with caution because one of our analytic approaches (using an unadjusted indirect “single-arm” comparison) may not be valid.<sup>46</sup>

## 6 Health System Implications

If 1% of the Canadian population of 25.3 million adults experience neuropathic pain, as in the UK, then approximately 250,000 people are eligible for treatment. If it is assumed that the government pays for half of them, then TCAs would cost government \$107 million per year in Canada. This is based on the “through placebo” analysis of \$331 per patient for 18 weeks of treatment (\$956 a year), for a total of \$214 million (assuming all patients are covered).

If SNRIs were prescribed instead of TCAs, the cost to the ministry of health would increase by \$128 per patient on average to \$479, or \$1,326 per year, for a total increase of \$59 million. If the SNRI is venlafaxine and only the drug cost is considered at minimum titration doses, the cost increase compared with TCAs is \$17 million. If the SNRI is duloxetine, the daily cost per patient would increase by \$3.76, for a total cost to government of \$171 million annually.

If all patients switched to ACs, it would cost \$519 per patient for 18 weeks, an increase of \$543 per year, resulting in an extra \$68 million per year in drug budget expenditures. If the drug cost alone is considered at minimum standard dose, this estimate would be reduced to \$36 million.

## 7 Conclusions

In the primary clinical analyses, with adjustments from and through placebo, TCAs had the highest efficacy rates, followed by ACs and SNRIs. These measures could not be differentiated from a statistical standpoint, suggesting that more evidence is needed to establish which drug class is superior. The NNT ranged between 3.0 and 6.0.

In the primary pharmacoeconomic analyses (after adjustment from and through placebo for efficacy), TCAs incurred fewer health care costs and produced more health (dominated) than the other two classes in all analyses and remained dominant in most sensitivity analyses (except when response rates were set lower for TCAs). If all Canadian patients were taking TCAs and then were switched to SNRIs or ACs, it would increase annual ministry of health budgets by \$59 million and \$68 million respectively. If these patients were switched from TCAs to duloxetine, assuming a 50% coverage of the market by the ministry of health, it would increase the annual ministry of health budget by \$171 million.

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