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Anticonvulsants, Serotonin-Norepinephrine Reuptake Inhibitors, and Tricyclic Antidepressants in Management of Neuropathic Pain: A Meta-Analysis and Economic Evaluation

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Anticonvulsants, Serotonin-Norepinephrine Reuptake Inhibitors, and Tricyclic Antidepressants in Management of Neuropathic Pain: A Meta-Analysis and Economic Evaluation

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January 2009

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Authorship

Michael Iskedjian was the Research Lead. He contributed conception, design, literature review, development of analysis plan, analysis, and interpretation of results.

Thomas R. Einarson contributed to the conception, design, development of analysis plan and interpretation of results, and writing of report. This included identification of outcomes,

comparators, analytic approach, study horizon, and assistance in developing a pharmacoeconomic model.

John H. Walker contributed to the design, development of analysis plan, modelling, analysis of results, and reviewing of the report.

Roman Jovey contributed to the design and clinical relevance of the proposed data model, report reviews, and revisions for intellectual content.

Dwight Moulin contributed to the design and clinical relevance of the proposed data model, report reviews, and revisions for intellectual content.

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Conflicts of Interest

Michael Iskedjian has received funding for consultancy services and speakers fees, however none has been received from the above manufacturers for the indications in the report. John Walker has provided consultancy services, however none has been received from the above manufacturers for the indications in the report. Thomas Einarson has received funding for consulting services, presentations, seminars, and workshops for industry and government. Roman Jovey has received compensation for speakers fees, participating on advisory boards, consulting services, or writing projects from each of the following companies: Biovail Pharmaceuticals, Boehringer-Ingelheim Canada Ltd., Janssen-Ortho Inc., Merck Frosst Canada Ltd., Nycomed Canada Inc., Pfizer Canada Inc., Paladin Lab Inc., Purdue Pharma, Sanofi-Aventis Canada Inc., and Valeant Canada Ltd. Dwight Moulin has received compensation for speakers fees and consulting services from Purdue Pharma, Pfizer Canada Inc., Janssen-Ortho Inc. , Bayer Inc., Biovail Pharmaceuticals, Boehringer-Ingelheim Ltd. and Merck-Frosst Canada Ltd. and has conducted research for Purdue Pharma, Pfizer Canada Inc. and Janssen-Ortho Inc.

EXECUTIVE SUMMARY

The Issue

Neuropathic pain places a burden on the public-payer health care system, the economy, and on patients' quality of life. With the continued introduction of new treatments, there is uncertainty about whether currently recommended treatment options are sustainable, given scarce resources. An assessment is needed to identify optimal clinical- and cost-effective treatments of neuropathic pain.

Objective

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 tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs), or anticonvulsants (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?

Clinical Review

Methods: Two independent reviewers systematically searched MEDLINE, EMBASE, and Cochrane databases from inception to 2007. The references from retrieved studies and reviews of the topic were hand searched for further potential articles. Quality was assessed using Jadad's method. The homogeneity of effects was determined using χ^2 and I^2. Data were combined using a random effects model.

Results: We identified 13 studies (n=1,257) that evaluated the anticonvulsants (gabapentin and pregabalin), five that studied SNRIs (n=781), and 10 that focused on TCAs (n=249). One study evaluated TCAs and SNRIs. The average quality score was 81%±21%. For partial response rates, we analyzed 17 study arms (n=1,439), nine involving anticonvulsants (n=870), four that examined SNRIs (n=458), and four that studied TCAs (n=111). Rates for SNRIs were 66.0% [standard error (SE) 2.2%], for anticonvulsants they were 54.5% (SE 3.7%), and for TCAs they were 49.2% (SE 6.6%). For full response rates, 23 study arms were summarized. SNRIs had the higher response rate of 45.9% (SE 2.3%) and ACs had a response rate of 36.3% (SE 3.2%). No rates were available for TCAs. When adjusted against placebo rates and pro-rated against partial response rates, the response rates for TCAs became the highest for both outcomes, and ACs had higher success rates than SNRIs. A significant difference could not be detected between these rates with appropriate statistical analyses. The numbers needed to treat ranged between 3.0 and 6.0, lowest for TCAs and highest for SNRIs.

Economic Analysis

Economic Review: Four previously conducted economic evaluations of pregabalin, gabapentin, amitriptyline, carbamazepine, tramadol, and duloxetine were identified. Of the four included studies, one was a cost-effectiveness and cost-utility analysis, one was a cost-utility analysis, one was a cost-effectiveness analysis, and one was a cost-of-illness analysis. All three pharmacoeconomic studies had methodological flaws. Therefore, firm conclusions cannot be drawn from them.

Canadian Economic Evaluation

Methods: A decision tree was used to model drug use and outcomes for an 18-week period from a Canadian provincial ministry of health and societal perspective. Experts in pain management guided the development of the base-case, treatment pathways, and sensitivity analyses. Three pharmacological treatment groups were ACs, which included carbamazepine, gabapentin, and pregabalin; SNRIs, including duloxetine and venlafaxine; and TCAs, including amitriptyline, clomipramine, nortriptyline, imipramine, and maprotiline. All were administered orally at therapeutic doses for a minimum of four weeks and a maximum of 12 weeks. We conducted an analysis that examined the cost-effectiveness of duloxetine and another analysis that explored the comparison of ACs and SNRIs. Efficacy rates were taken from the meta-analysis and standard price lists were (mainly from Ontario, such as the Ontario Drug Benefit Plan and the Ontario Health Insurance Plan) used to cost resources. The outcomes of interest were full response (50% decrease from baseline to endpoint on visual analogue pain scores) and pain controlled days (PCDs). Two approaches were adopted for the base-case incremental analyses: "from placebo" and "through placebo." One-way sensitivity analyses and Monte-Carlo simulations were performed.

Results: In the first pharmacoeconomic analysis ("from placebo"), TCAs exhibited the highest overall response rate (79.3%), followed by anticonvulsants (77.8%) and SNRIs (76.4%) in managing neuropathic pain patients over the 18-week time horizon. TCAs also produced the most PCDs (average of 49), followed by anticonvulsants (46) and SNRIs (43). Based on the price of duloxetine, the expected cost per patient treated from the ministry of health perspective was lowest with TCAs ($422); ACs were next ($610), and duloxetine was highest ($860). From a societal perspective, TCAs had the lowest expected cost per patient treated of $1,850, ACs were second ($2,112), and duloxetine was the most costly ($2,443). From the ministry of health and societal perspectives, TCAs dominated (were less costly and more effective) duloxetine and ACs for full response and PCDs.

In the second pharmacoeconomic analysis ("through placebo"), TCAs exhibited the highest overall response rate (88.0%), followed by anticonvulsants (84.3%) and SNRIs (80.6%) in managing neuropathic pain patients over the 18-week time horizon. TCAs also produced the most PCDs (average of 60), followed by ACs (54) and SNRIs (41). Based on the price of duloxetine, the expected cost per patient treated from the ministry of health perspective of $355 was lowest with TCAs; ACs were next ($557) and duloxetine was highest ($839). From a societal perspective, TCAs had the lowest expected cost per patient treated of $1,537, ACs were second ($1,906), and SNRIs were the most costly ($2,504). From the ministry of health and societal perspectives, TCAs dominated (were less costly and more effective) duloxetine and ACs for full response and PCDs.

When the price of venlafaxine was used instead of the price of duloxetine for SNRIs, TCAs still represented the most cost-effective option. When TCAs were no longer an option, the results were mixed between SNRIs and ACs.

Budget Impact Analysis

If we assume that the prevalence of those with neuropathic pain is 250,000 adults in Canada and that the government pays for half of them, TCAs represent a $107 million investment. This assumes $331 per patient for the 18 weeks of treatment (from the "through placebo" analysis), or $956 per patient per year, for a total of $214 million for the population (assuming that all patients were covered).

If all patients were switched from TCAs to SNRIs, the average cost to the ministry of health would increase by $128 to $459 per patient or $1,326 per patient per year (an increase of $370 per patient per year). This is an overall increase in cost of $59 million. If only the drug cost of venlafaxine is considered (at minimum titration doses), this is reduced to an additional $17 million. If all patients were switched from TCAs to duloxetine, the daily drug cost per patient would increase by $3.76, and the impact would be $171 million for Canada.

If all patients were switched to ACs, the cost would be $519 per patient for the 18 weeks, or an increase of $543 per year. This represents an extra $68 million per year in drug budget expenditures. Considering the drug cost alone with a minimum standard dose, this estimate is reduced to $36 million.

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 numbers needed to treat 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.

This analysis only examines a treatment decision when all three classes of drugs are equally viable options for an individual patient. The clinical treatment of neuropathic pain needs to consider the needs of the individual and requires balancing optimal pain relief (number needed to treat) with minimizing medication adverse effects (number needed to harm). This analysis does not apply to situations where first-line treatment with any one of these classes of drugs, such as a TCA, is not a realistic approach.

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1 INTRODUCTION

1.1 Background

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, with a higher percentage of females reporting in this category than males (12.7% versus 8.8%).[1]

Chronic pain refers to continuous or intermittent pain that is experienced for longer than three months.[2] The prevalence of chronic pain in Canadian adults ranges from 18% to 29%, with an increased frequency in older age groups and in women.[1,3] Neuropathic pain is started or caused by a primary lesion or dysfunction in the nervous system.[4] Its prevalence increases with age, peaking among those who are older than 65 years of age, when 18.8% of the population are affected. In a 2001 cross-sectional study of 2012 Canadians, the average duration of chronic pain was 10.7 years, and the average intensity was 6.3 on an 11-point scale (0 for no pain and 10 for the worst pain). Chronic pain is negatively associated with household income.[5] The prevalence of depression is twice as high among chronic pain sufferers compared with a population who do not suffer from chronic pain.[5]

No Canadian estimate for the prevalence of neuropathic pain could be found. In the US, the estimated prevalence of neuropathic pain is 1.5%, and in the UK, it is 1%. The US estimate is based on a self-described "conservative" estimate of 0.6% and on an assumption that for at least 1 in 10 sufferers, lower back pain can be attributed to neuropathic pain.[6]

The associated economic burden is high. Patients with painful neuropathic disorders (PND) have a higher level of comorbidities and higher levels of health care use when they are compared with a controlled group without PND.[7,8] An estimated 35% of patients with painful diabetic neuropathy reported a disruption in employment.[8,9] An Australian study estimated that there was an annual reduction in economic productivity of 9.9 million workdays.[10] In 2000, the total US health care charges for patients with neuropathic pain were threefold higher than for matched control subjects (US$17,355 versus US$5,715 respectively).[11]

There is a negative impact on the quality of life of patients. A cross-sectional survey of health state impairment and treatment patterns in patients with neuropathic pain revealed that pain severity was significantly associated with EQ-5D Health State scores and interference with functioning. Patients with mild, moderate, and severe pain scored mean EQ-5D health state valuations of 0.59, 0.43, and 0.20 respectively and mean pain interference scores of 2.5, 4.6, and 6.9 respectively.[8]

1.2 Overview of Technology

1.2.1 Treatment guidelines

The primary goal in managing neuropathic pain is not to eliminate it, but to make it more "bearable" or "tolerable." This realistic approach should incorporate the management of

comorbidities, such as anxiety and depression, and secondary treatment goals such as improving sleep, ability to function, and quality of life. Pharmacological treatment guidelines for neuropathic pain were developed by the Canadian Pain Society (CPS), which used the number of patients who need to be treated (NNT) with a drug to obtain one patient with at least 50% pain relief[12] (Table 1).

Table 1: Pharmacological Management of Chronic Neuropathic Pain[12]

First Line	Second Line	Third Line	Fourth Line

• TCAs
• Anticonvulsants
  • Gabapentin
  • Pregabalin
	• SNRIs
	  • Venlafaxine
	  • Duloxetine*
	• Topical lidocaine
	  • 5% patch†
	  • 5% or 10% gel or cream
		• Tramadol
		• Opioid analgesics
			• Cannabinoids
			• Methadone
			• SSRI
			  • Citalopram
			  • Paroxetine
			• Other anticonvulsants
			  • Lamotrigine
			  • Topiramate
			  • Valproic acid
			• Miscellaneous agents
			  • Mexiletine
			  • Clonidine

SNRI=serotonin noradrenaline 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 pharmacists.

1.2.2 Treatment algorithm

Treatment is usually initiated with tricyclic antidepressants (TCAs) or anticonvulsants (ACs). The failure of TCA treatment leads to a switch to ACs and vice-versa. ACs can be used as adjunctive therapy if TCAs provide partial relief. TCAs are contraindicated in patients with cardiovascular disease. SNRIs are second line to TCAs and ACs because of the low level of available evidence that was identified by the guideline committee and the relative costs. Lidocaine is a practical treatment for elderly persons with focal painful neuropathy. Tramadol or conventional opioid analgesic may be prescribed when first- or second-line therapy has failed. Although the NNT for opioid analgesics is superior or equivalent to some first- and second-line treatments, concerns regarding medication misuse, diversion, addiction, tolerance, and other potential long-term side effects, such as hormonal and sleep disturbance, become an important consideration in some patients.

2 THE ISSUE

Neuropathic pain places a burden on the public-payer health care system, on the economy, and on patients' quality of life. With the continued introduction of new treatments, there is uncertainty about whether currently recommended treatment options are sustainable, given scarce resources. An assessment is needed to identify optimal clinical- and cost-effective treatments of neuropathic pain.

3 OBJECTIVES

The aim of this technology assessment was to assess the clinical and economic impact of first-line drugs in treating 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 tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs), or anticonvulsants (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?

4 CLINICAL REVIEW

4.1 Methods

A protocol was written a priori and followed throughout the review process. Two changes to the protocol occurred during the review phase. First, NNTs were calculated for binary outcomes to aid in clinical decision making and to foster comparisons between this work and previously published work. In addition, a primary meta-analysis used adjusted indirect comparisons through placebo rates.

4.1.1 Selection criteria and method

The criteria (Appendix A) for abstracts that were selected for full-text review included:

- Study design: Double-blinded randomized controlled trial
- Target population: Adults (18 years of age or older) who have been diagnosed with neuropathic pain
- Intervention and comparators: One or more of ACs, SNRIs, and TCAs.

Each abstract was reviewed independently by two of three reviewers [MM, BB, RA]. The selected abstracts were compared, and the differences between reviewers were adjudicated through consensus. Remaining discrepancies were adjudicated by a third person. Full-text articles were retrieved for the selected abstracts.

4.1.2 Literature search strategy

A librarian at the Hospital for Sick Children, Toronto, ON, conducted the literature search on EMBASE, MEDLINE, and The Cochrane Library of Systematic Reviews. The subject headings and keywords included all the available terms for ACs, SNRIs, and botulinum toxin A. The subject headings and selected keywords were used to search pain, musculoskeletal disorders, headaches, and neuropathic disorders that can be associated with chronic pain. All drug terms

were limited to randomized controlled trials using a combination of publication type, MeSH terms, and keywords. The resulting set was limited to human and adult studies.

Appendix B, Appendix C, and Appendix D show the literature search strategy. In addition, the references of key reviews and included articles were hand searched for potential studies that were not captured in the literature search.

Clinical experts discussed a need to retrieve clinical studies that evaluated the use of TCAs for treating patients with neuropathic pain specifically. In this case, we used the literature search results from a Cochrane systematic review of antidepressants for neuropathic pain.[13] In addition, a decision was made to exclude botulinum toxin.

4.1.3 Data extraction strategy

A data extraction sheet was created in Microsoft Excel to record study characteristics, patient characteristics, and clinical outcomes. Data were extracted from each full-text article by two independent reviewers [RA, BB]. Senior researchers [MM, TE] compared and verified the extracted data. In the case of discrepancies between the two reviewers, the senior researcher met with the reviewers and tried to arrive at a consensus. In the case of a lack of consensus, the senior researcher decided which reviewer's opinion prevailed.

4.1.4 Strategy for validity assessment

Jadad et al.'s[14] method was used to assess the internal validity of the articles that were included. Jadad's scale is used to assess the internal validity of randomized controlled trials. It is based on five questions: Is the study randomized? Is the study double blinded? Is there a description of withdrawals? Is the randomization adequately described? Is the blindness adequately described?

The validity of each included study was independently assessed by two raters. Their scores were compared and discussed. Discrepancies that existed in quality ratings were settled by consensus for each item of Jadad's scale. Scores were reported as percentages of the total possible score (5) for each article and for overall results. The scores were used to guide interpretation when conclusions were drawn from the overall results.

4.1.5 Data synthesis method

In a structured review of the quantitative and qualitative data from the selected articles, the data were grouped according to drug class and drug entity. If there were adequate data, then a meta-analysis was performed. We would conduct a meta-analysis when there were three or more studies with the same or similar characteristics:

- Drug or therapeutic class
- Outcomes measured in same fashion on same or comparable scales at approximately the same time
- Duration of use
- Patient populations
- Comparators

If a meta-analytic approach were possible, it could provide quantitative summaries of clinical response rates that could then be used in a decision tree analysis.

The extracted data were combined using a random effects meta-analytic model. That model weights by the inverse of the within-study variance plus the between-study variance. The outcomes of interest were a mean reduction from baseline to endpoint in visual analogue scale (VAS) pain scores of patients with neuropathic pain, the rate of patients achieving 30% and 50% reduction in VAS pain scores from baseline to endpoint, and rates of withdrawals due to adverse drug reactions (ADRs). All outcomes of interest were combined across study arms. The outputs were a set of point estimates and 95% confidence intervals (CIs). Point estimates were used as estimates for success, mean pain reduction, and withdrawals due to ADRs, as required in the pharmacoeconomic model.

No data were found regarding a 50% reduction in VAS pain scores in the TCAs group. For calculating the 50% scores in the TCAs group, we estimated the average ratio of 50% to 30% VAS pain score reduction in the ACs and SNRIs groups (approximately 0.68) and used this as a weighting factor. Thus, TCAs 30% VAS pain reduction rates were weighted by the estimated average ratio to arrive at an estimate for the 50% VAS pain reduction rate in the TCA group.

4.2 Results

4.2.1 Quantity of research available

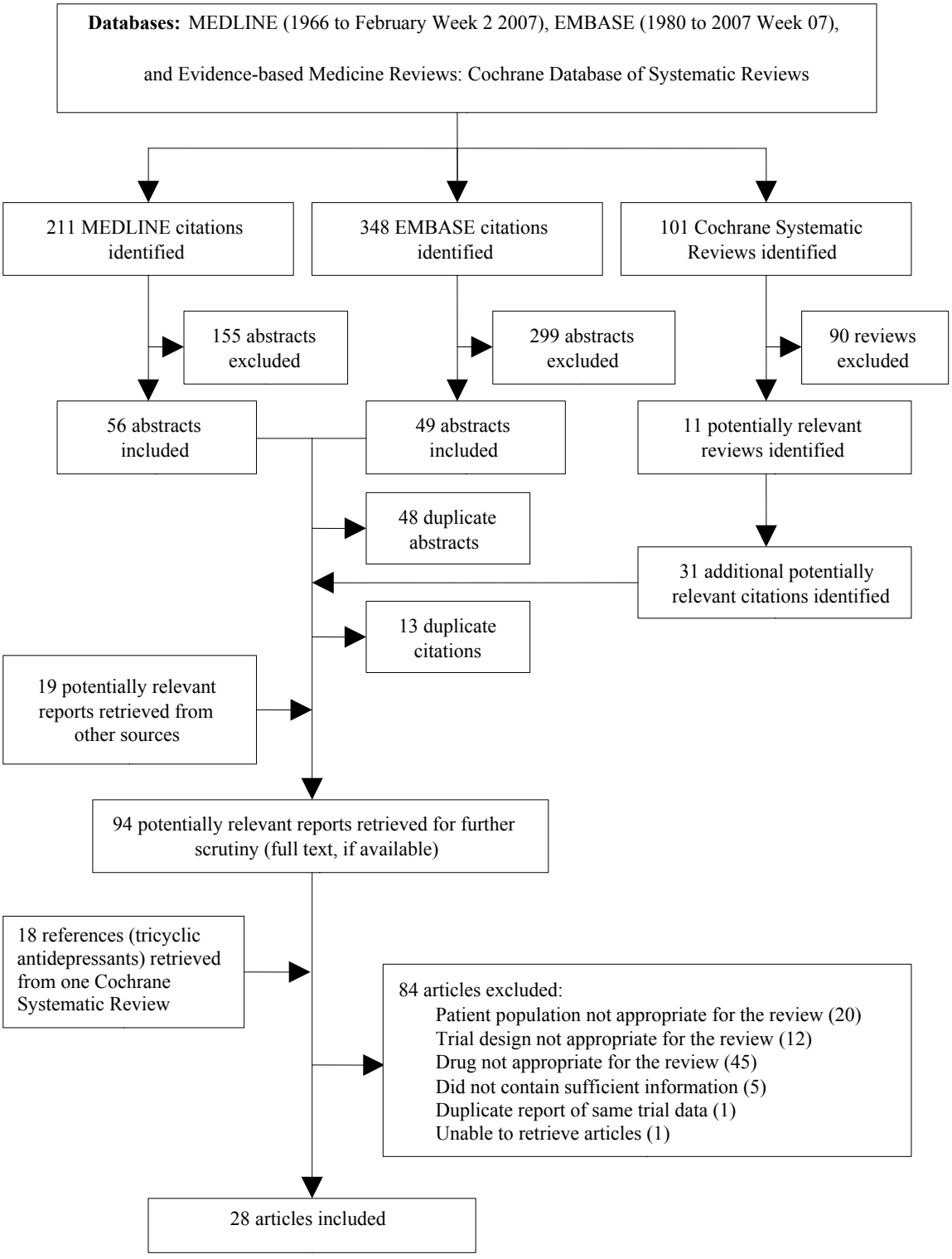
A total of 660 references were identified using the literature search strategy (211 from MEDLINE, 348 from EMBASE, and 101 from Cochrane). After the initial article selection phase (reading abstracts), 105 potentially relevant original articles were retrieved for full-text assessment. An additional 31 references were obtained from the reference lists of 11 review articles that were identified from the Cochrane Systematic Reviews index. After adding more articles from other secondary sources and eliminating duplicates, 112 studies were reviewed, and 84 were excluded (45 did not evaluate the drugs or pharmacological groups of interest,[15-59] 20 evaluated a different patient population,[60-79] 12 reported different study designs,[80-91] five contained insufficient information because the outcomes were not reported,[92-96] one was a duplicate,[97] and one could not be retrieved).[98] Therefore, 28 articles were included in the clinical literature review[99-126] (Figure 1).

4.2.2 Trial characteristics

Among the 28 included studies, 13 evaluated the efficacy and safety of selected ACs (gabapentin and pregabalin), five evaluated SNRIs, and 10 evaluated TCAs. One study evaluated an SNRI and a TCA. Therefore, the study arms from that study appeared in both pharmacological groups (SNRI and TCA).[102] The overall quality of all included studies was 81% [standard deviation (SD)=21%] (Table 2).

The 13 studies describing ACs had a total of 20 active treatment arms of gabapentin (k=5) and pregabalin (k=15) and a total of 1,612 patients (average per study arm of 81, SD=30). Studies were published between 1998 and 2006 and reported an overall quality of 4.2 (SD=0.9).

Figure 1: Clinical Literature Search



The average follow-up (trial length) was 9.1 (SD=3.5) weeks. Gabapentin was evaluated in flexible doses ranging from 900 mg/day to 3,600 mg/day, whereas pregabalin was studied in fixed and flexible dosing schedules ranging from 75 mg/day to 600 mg/day. The average baseline VAS pain score was 6.6 (SD=1.5).

SNRIs were studied in five clinical trials (published from 2003 to 2006) of neuropathic pain patients. There was a total of 10 arms of two active treatments: duloxetine (k=7) and venlafaxine (k=3). The total number of patients was 1,004 with an average baseline VAS pain score of 6.2 (SD=1.5) and an average follow-up of 9.9 (SD=3.5) weeks. Duloxetine was evaluated as fixed doses of 20 mg/day, 60 mg/day, and 120 mg/day, whereas venlafaxine doses were fixed and flexible, and ranged from 75 mg/day to 225 mg/day. The average quality score of all studies that focused on SNRIs was 4.8 (SD=0.5).

The clinical trials that evaluated TCAs (k=11, including one study on SNRIs and TCAs) were published between 1982 and 2004, so they were older studies compared with those for the other two pharmacological groups. The quality scores were lower with an average of 3.6 (SD=1.2). Overall, they were acceptable with one study obtaining a score less than 3. The total number of active treatment arms was 15, which included amitriptyline (k=10), clomipramine (k=1), desipramine (k=1), imipramine (k=1), nortriptyline (k=1), and a study arm with a combination of TCAs. The total number of patients was 305 (average per study arm 20±13). The average baseline VAS pain score was 5.2 (SD=1.8), which was lower at baseline than those from the analyses of the other two drug classes. The average follow-up was less than those of ACs and SNRIs (6.6±3.1 weeks). Drug dose ranges were 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.

4.2.3 Data analyses and syntheses

The primary analyses were the meta-analyses that summarized the rates of success of drug classes when they were compared with placebo in randomized controlled trials. Two measures of success were investigated: proportions of patients who achieved a 30% decrease in pain on a visual analogue scale ("30% response") and proportions achieving a 50% decrease ("50% response"). A random effects model combined data into relative rates (RR), which are also called "rate ratios."

A review of the meta-analytic results revealed that placebo rates varied among the studies. These differences in placebo responses could be due to chance alone. On the other hand, the patients who were recruited into some studies may have had more or less severe disease than those in other studies. Therefore, the response rates were adjusted for placebo effect.

Two approaches were used to adjust for placebo effect. First, we established the weighted overall average difference from the placebo rate for each outcome ("from placebo"). Second, we used Bucher et al.'s[127] method to adjust for placebo response ("through placebo"). We used a random-effects meta-analysis of placebo rates across all studies (Table 3). Individual drug data appear in Appendix E, with the corresponding forest plots.

Table 2: Principal Characteristics of Studies Included in Clinical Review of Anticonvulsants, SNRIs, and TCAs in Managing Neuropathic Pain									
Drug Class	**First Author**	**Year**	**Active Drug Treatment**	**Treatment Duration (Weeks)**	**Patients ITT (n)**	**Patients PP (n)**	**Baseline VAS Pain Score (Mean)**	**Baseline VAS Pain Score (SD)**	**Quality Scores**
ACs	Backonja[108]	1998	gabapentin (900 to 3,600 mg/day)	8	84	70	6.4	1.5	3
	Dworkin[110]	2003	pregabalin (300 to 600 mg/day)	8	89	62	6.3	1.4	4
	Freynhagen[101]	2005	pregabalin (300 mg/day)	12	132	82	7.1	1.7	3
	Freynhagen[101]	2005	pregabalin (150 to 600 mg/day)	12	141	92	7.0	1.5	-
	Lesser[109]	2004	pregabalin (300 mg/day)	5	81	76	6.2	1.4	5
	Lesser[109]	2004	pregabalin (600 mg/day)	5	82	70	6.2	1.5	-
	Lesser[109]	2004	pregabalin (75 mg/day)	5	77	67	6.7	1.3	-
	Levendoglu[100]	2004	gabapentin (900 to 3,600 mg/day)	18	20	20	8.5	0.9	3
	Ritcher[112]	2005	pregabalin (150 mg/day)	6	79	75	6.5	1.3	5
	Ritcher[112]	2005	pregabalin (600 mg/day)	6	82	72	6.7	1.7	
	Rosenstock[113]	2004	pregabalin (300 mg/day)	8	76	65	6.6	1.5	5
	Rowbotham[107]	1998	gabapentin (up to 3,600 mg/day)	8	113	89	6.3	1.6	5
	Sabatowski[114]	2004	pregabalin (150 mg/day)	8	81	71	6.9	1.7	5
	Sabatowski[114]	2004	pregabalin (300 mg/day)	8	76	60	7.0	1.6	-
	Siddal[111]	2006	pregabalin (150 to 600 mg/day)	12	70	49	6.5	1.3	5
	Simpson[106]	2001	gabapentin (300 to 2,700 mg/day)	8	30	30	6.4	1.5	4
	Smith[103]	2005	gabapentin (300 to 3,600 mg/day)	6	24	24	4.4	2.6	4
	van Seventer[117]	2006	pregabalin (150 mg/day)	13	87	61	6.4	1.6	3
	van Seventer[117]	2006	pregabalin (300 mg/day)	13	98	62	6.7	1.4	-
	van Seventer[117]	2006	pregabalin (600 mg/day)	13	90	60	6.7	1.4	-
Overall ACs				**9.1**	**1,612**		**6.6**	**1.5**	**4.2**
SNRIs	Goldstein[104]	2005	duloxetine (120 mg/day)	12	113	80	5.9	1.4	5
	Goldstein[104]	2005	duloxetine (20 mg/day)	12	115	91	5.9	1.6	-
	Goldstein[104]	2005	duloxetine (60 mg/day)	12	114	86	6.0	1.7	-
	Raskin[99]	2005	duloxetine (60 mg twice a day)	12	116	95	5.7	1.3	5
	Raskin[99]	2005	duloxetine (60 mg/day)	12	116	101	5.5	1.1	-

Table 2: Principal Characteristics of Studies Included in Clinical Review of Anticonvulsants, SNRIs, and TCAs in Managing Neuropathic Pain									
Drug Class	**First Author**	**Year**	**Active Drug Treatment**	**Treatment Duration (Weeks)**	**Patients ITT (n)**	**Patients PP (n)**	**Baseline VAS Pain Score (Mean)**	**Baseline VAS Pain Score (SD)**	**Quality Scores**
	Rowbotham[115]	2004	venlafaxine (150 to 225 mg/day)	6	82	64	6.7	1.5	5
	Rowbotham[115]	2004	venlafaxine (75 mg/day)	6	82	69	7.0	1.5	-
	Sindrup[102]	2003	venlafaxine (225 mg/day)	4	40	32	7.0	1.5	5
	Wernicke[116]	2006	duloxetine (120 mg/day)	12	112	78	6.2	1.5	4
	Wernicke[116]	2006	duloxetine (60 mg/day)	12	114	85	6.1	1.6	-
Overall SNRIs				**9.9**	**1,004**		**6.2**	**1.5**	**4.8**
TCAs	Cardenas[118]	2002	amitriptyline (10 to 125 mg/day)	6	44	36	5.5	1.8	4
	Kalso[119]	1995	amitriptyline (100 mg)	10	13	11	5.0	1.8	3
	Kalso[119]	1995	amitriptyline (50 mg)	10	13	13	5.0	1.8	-
	Graff-Radford[105]	2000	amitriptyline (12.5 mg + 25 mg increments each week)	8	11	11	5.6	2.0	4
	Leijon[120]	1989	amitriptyline (12.5 mg + 25 mg increments each week)	4	15	15	4.7	1.3	4
	Panerai[121]	1990	clomipramine (25 mg)	3	8	8	4.9	1.7	1
	Panerai[121]	1990	nortriptyline (25 mg)	3	8	8	4.5	0.8	-
	Pilowsky[122]	1982	amitriptyline (25 mg)	6	18	18	5.5	2.2	4
	Raja[123]	2002	desipramine (average=63 mg) and nortriptyline (average=89 mg)	8	26	16	6.3	2.4	5
	Robinson[124]	2004	amitriptyline (10 to 125 mg/day)	6	20	18	3.9	2.6	4
	Sindrup[102]	2003	imipramine (50 to 150 mg/day)	4	40	29	7.0	1.5	5
	Sharav[125]	1987	amitriptyline (25 to 150 mg/day)	4	11	11	NS	NS	1
	Sharav[125]	1987	amitriptyline (5 to 30 mg/day)	4	8	8	NS	NS	-
	Vrethem[126]	1997	amitriptyline (25 to 75 mg/day)	4	35	33	4.8	1.6	3
	Vrethem[126]	1997	maprotiline (25 to 75 mg/day)	4	35	33	4.8	1.6	-
Overall TCAs				**6.6**	**305**		**5.2**	**1.8**	**3.6**

ACs=anticonvulsants; ITT=intent-to-treat; NS=not significant; PP=per-protocol; SD=standard deviation; SNRIs=serotonin-norepinephrine reuptake inhibitors; TCAs=tricyclic antidepressants; VAS=visual analogue scale.

Under quality scores, the hyphen indicates the score has been reported above for the same study. In secondary analyses, all available data were combined across all randomized controlled trials. These analyses present the rates from all available studies, recognizing that the placebo rates vary between studies and between groups.

a) "From placebo" treatment response adjustment

In the "from placebo" treatment response adjustment, the meta-analytic differences between drug and placebo as the effect of interest were adjusted using the difference of the natural logs. The results were exponentiated to arrive at an adjusted rate ratio for each drug. These ratios were then multiplied by the meta-analytic placebo rate across all placebo trials for each outcome of interest. The placebo rate for 50% response was 20.7%, and the rate for 30% response was 26.1%. These rates were used as the baseline against which we adjusted the drug success rates.

For 30% response, the calculated rates were 54.4% for ACs, 49.7% for SNRIs, and 59.4% for TCAs.

For 50% response, ACs had a success rate that was 21.6% greater than that of placebo. This resulted in an adjusted rate of 42.3%. The success rate for SNRIs was 17.6% greater than placebo, with an adjusted rate of 38.3%. No trials reported 50% response for TCAs, which was estimated by multiplying the 30% rate by the average of the ratio of the 50% to 30% rates for the ACs and SNRIs [0.774=average of 0.777 and 0.771].

Thus, we obtained $0.594 \times 0.774 = 0.460$ (46.0%); $0.424 \times 0.774 = 0.328$ (32.8%); and $0.765 \times 0.774 = 0.592$ (59.2%) for the 50% rate for TCAs and the lower and upper confidence limits respectively.

The results of the analyses appear in Table 3. The forest plots of differences from individual studies are presented for each drug class in Appendix E.

b) "Through placebo" treatment response adjustment

Bucher's approach was used for the "through placebo" treatment response adjustment. The effect size was the rate ratio between the drug effect and the placebo effect. The technique was otherwise the same as that in the "from placebo" approach.

The 30% response for ACs was 2.05 times greater than placebo, 1.56 times greater for SNRIs, and 2.58 times greater for TCAs. Starting with the placebo rate of 26.1%, we calculated the response rate of the next treatment (SNRIs). The SNRI 30% response rate was $1.56 \times 26.1\% = 40.6\%$. Using Bucher's approach, the RR of ACs to SNRIs was 1.32, yielding a 30% response rate for ACs of $1.32 \times 40.6\% = 53.3\%$. TCAs had a RR of 1.70 versus ACs, resulting in a 30% response rate of $1.7 \times 53.5\% = 91.0\%$. (The numbers have been rounded for reporting purposes.)

For 50% response, ACs were 2.50 versus placebo, and SNRIs were 1.62 times placebo. ACs were then 1.55 times SNRIs. Using 20.7% as a baseline for placebo, we get a success rate for SNRIs = $1.62 \times 20.7\% = 33.5\%$; and a success rate for ACs = $1.55 \times 33.5\% = 51.8\%$.

The 50% response for TCAs was estimated using a pro-rate (based on the ratio of TCA:AC for 30% response = 91.0%:53.3%). We would then get a rate of 88.1% for TCAs. By multiplying the

average of the 50% to 30% ratios for TCAs and SNRIs [0.897 = average (0.968, 0.826) by the 30% rate, we obtained 0.674 × 0.897 = 0.604.

The 95% CI limits were obtained by using the adjusted rate ± 1.96 × SE. For the 50% AC interval limits, we used 0.604 ± 1.96 × 0.066, where 0.066 was the standard error of the meta-analytic 30% AC trials. Using 0.066 as the standard error for the 50% rate was appropriate because the standard errors of the SNRI and TCA 30% and 50% trial results were similar. The results of the analyses are presented in Table 3.

c) Alternative analyses ("single arm")

In a separate analysis, the efficacy rates for each drug class and placebo were combined across all trials using Einarson's method.[128] For the 17 study arms (n=1,439), nine involved ACs (n=870), four examined SNRIs (n=458), and four studied TCAs (n=111) (Appendix F).

d) Analyses for estimating number needed to treat

We calculated the NNT for each drug class and each binary outcome (success or fail). In the head-to-head trials against placebo for 50% pain reduction, the NNTs were 5.0 for ACs and 6.0 for SNRIs. In the SNRI group, the NNT was 6.0 for duloxetine and 9.0 for venlafaxine. The placebo rate was 27% across the duloxetine studies and 33.8% across the venlafaxine studies, which accounts for the discrepancy between the NNTs.

For 30% response, NNTs were 3.0 for TCAs, 4.0 for ACs, and 5.0 for SNRIs (NNTs for duloxetine and venlafaxine were both 5.0). When meta-analytic response rates were adjusted through placebo (Appendix Table 0-4), NNTs for 50% pain reduction were 3.9 for TCAs, 4.6 for ACs, and 5.7 for SNRIs. For 30% pain reduction, NNTs were 3.0 for TCAs, 3.5 for ACs, and 4.2 for SNRIs.

Smeeth et al. [129] warned that the results from indirect comparisons were sometimes valid and sometimes not. Nonetheless, their final word was that there was a place for such values. Song et al. and Glenny et al.[130,131,132]reviewed the use of NNT and conclude that the validity of such numbers remain uncertain. Their latest paper suggests that the indirect method may be less biased than the direct method.[131] Thus, our results must be interpreted with caution. We present them only as a guide.

e) Withdrawal due to adverse drug reactions

The rates of dropouts due to adverse drug reactions were reported in 40 study arms of a total of 2,588 patients (n=1,589 for ACs, n=732 for SNRIs, and n=267 for TCAs). ADR dropout rates were similar between pharmacological groups. Meta-analytic dropout rates were 12.3% (SE=1.8%) for ACs, 12.0% (SE=2.3%) for SNRIs, and 11.7% (SE=4.4%) for TCAs. All datasets exhibited heterogeneity of effects ($p<0.05$). Table 4 presents meta-analytic dropout rates due to ADRs by pharmacological group.

Table 3: Meta-analytic Response Rates Adjusted for Placebo Effect									
Adjustment	**Treatment**	**Study Arms (No.)**	**n**	**50% Rate***	**Placebo Rate**	**Difference**	**Adjusted Rate**	**Lower Limit**	**Upper Limit**
From Placebo	AC	14	2,420	0.363	0.133	0.216	0.423	0.383	0.463
	SNRI	9	1,917	0.459	0.280	0.176	0.383	0.331	0.435
	TCA	-	-	-	-	-	0.460†	0.328	0.592
	Placebo	13	1,148	0.207					
	Treatment	**Study Arms (No.)**	**n**	**30% Rate***	**Placebo rate**	**Difference**	**Adjusted Rate**	**Lower Limit**	**Upper Limit**
	AC	9	1,624	0.545	0.252	0.283	0.544	0.499	0.590
	SNRI	4	906	0.660	0.424	0.236	0.497	0.434	0.560
	TCA	4	219	0.492	0.157	0.333	0.594	0.424	0.765
	Placebo	10	703	0.261					
Through Placebo	**Treatment**	**Study Arms (No.)**	**n**	**50% RR**	**Placebo Rate**	**SE**	**Adjusted Rate‡**	**Lower Limit**	**Upper Limit**
	AC	14	2,420	2.50	0.133	0.032	0.518	0.456	0.580
	SNRI	9	1,917	1.62	0.280	0.023	0.335	0.290	0.381
	TCA	-	-	-	-		0.604	0.474	0.734
	Placebo	13	1,148	0.207§					
	Treatment	**Study Arms (No.)**	**n**	**30% RR**	**Placebo Rate**	**SE**	**Adjusted Rate‡**		
	AC	9	1,624	2.05	0.252	0.037	0.535	0.463	0.607
	SNRI	4	906	1.56	0.424	0.022	0.406	0.363	0.449
	TCA	4	219	2.58	0.157	0.066	0.674	0.544	0.803
	Placebo	10	219	0.261					

*Clinical response rate. Proportions reported are for patients attaining the given rate (50% or 30%).
†Because there were no studies of TCAs reporting 50% clinical response rate, this adjusted rate was pro-rated from 30% clinical response rate data.
‡Adjusted rate = meta-analytic placebo rate × RR.
§Meta-analytic placebo rate.
AC=anticonvulsant; n=sample size; RR=rate ratio; SE=standard error; SNRI=serotonin norepinephrine-reuptake inhibitor; TCA=tricyclic antidepressant.

Table 4: Meta-analytic Withdrawal Rates Due to Adverse Drug Reactions by Drug Class									
Drug Class	**Drug**	**Author**	**Year**	**No. of Dropouts**	**No. of Completers**	**Dropout Rates**	**SE**	**$CI_{95\%}$ LL**	**$CI_{95\%}$ UL**
ACs	gabapentin (900 to 3,600 mg/day)	Backonja[108]	1998	7	77	0.083	0.076	0.000	0.233
	pregabalin (300 to 600 mg/day)	Dworkin[110]	2003	28	61	0.315	0.086	0.147	0.482
	pregabalin (300 mg/day)	Freynhagen[101]	2005	24	108	0.182	0.078	0.030	0.334
	pregabalin (150 to 600 mg/day)	Freynhagen[101]	2005	33	108	0.234	0.079	0.080	0.388
	pregabalin (300 mg/day)	Lesser[109]	2004	3	78	0.037	0.073	0.000	0.180
	pregabalin (600 mg/day)	Lesser[109]	2004	12	70	0.146	0.080	0.000	0.303
	pregabalin (75 mg/day)	Lesser[109]	2004	2	75	0.026	0.072	0.000	0.168
	gabapentin (900 to 3,600 mg/day)	Levendoglu[100]	2004	1	20	0.024	0.078	0.000	0.177
	pregabalin (150 mg/day)	Ritcher[112]	2005	2	77	0.025	0.072	0.000	0.167
	pregabalin (600 mg/day)	Ritcher[112]	2005	7	75	0.085	0.076	0.000	0.235
	pregabalin (300 mg/day)	Rosenstock[113]	2004	8	68	0.105	0.078	0.000	0.259
	gabapentin (up to 3,600 mg/day)	Rowbotham[107]	1998	21	92	0.186	0.079	0.031	0.341
	pregabalin (150 mg/day)	Sabatowski[114]	2004	9	72	0.111	0.078	0.000	0.264
	pregabalin (300 mg/day)	Sabatowski[114]	2004	12	64	0.158	0.081	0.000	0.318
	pregabalin (150 to 600 mg/day)	Siddal[111]	2006	15	55	0.214	0.085	0.047	0.382
	gabapentin (300 to 2,700 mg/day)	Simpson[106]	2001	2	28	0.067	0.083	0.000	0.230
	pregabalin (150 mg/day)	van Seventer[117]	2006	7	80	0.080	0.076	0.000	0.229
	pregabalin (300 mg/day)	van Seventer[117]	2006	15	83	0.153	0.079	0.000	0.308
	pregabalin (600 mg/day)	van Seventer[117]	2006	19	71	0.211	0.082	0.050	0.372
Total TCAs				**227**	**1,362**	**0.123**	**0.018**	**0.088**	**0.158**
SNRIs	duloxetine (120 mg/day)	Goldstein[104]	2005	22	91	0.195	0.064	0.070	0.320
	duloxetine (20 mg/day)	Goldstein[104]	2005	5	110	0.043	0.055	0.000	0.151
	duloxetine (60 mg/day)	Goldstein[104]	2005	15	99	0.132	0.061	0.013	0.250
	venlafaxine (150 to 225 mg/day)	Rowbotham[115]	2004	8	74	0.098	0.061	0.000	0.217
	venlafaxine (75 mg/day)	Rowbotham[115]	2004	6	76	0.073	0.059	0.000	0.189

Table 4: Meta-analytic Withdrawal Rates Due to Adverse Drug Reactions by Drug Class									
Drug Class	**Drug**	**Author**	**Year**	**No. of Dropouts**	**No. of Completers**	**Dropout Rates**	**SE**	**$CI_{95\%}$ LL**	**$CI_{95\%}$ UL**
	duloxetine (120 mg/day)	Wernicke[116]	2006	17	95	0.152	0.062	0.031	0.273
	duloxetine (60 mg/day)	Wernicke[116]	2006	20	94	0.175	0.063	0.052	0.298
Total SNRIs				**93**	**639**	**0.120**	**0.023**	**0.075**	**0.164**
TCAs	amitriptyline (10 to 125 mg/day)	Cardenas[118]	2002	8	36	0.182	0.092	0.002	0.362
	amitriptyline (100 mg)	Kalso[119]	1995	4	9	0.308	0.146	0.021	0.595
	amitriptyline (50 mg)	Kalso[119]	1995	4	9	0.308	0.146	0.021	0.595
	amitriptyline (12.5 mg + 25 mg increments each week)	Graff-Radford[105]	2000	1	10	0.091	0.112	0.000	0.311
	amitriptyline (12.5 mg + 25 mg increments each week)	Leijon[120]	1989	1	15	0.032	0.084	0.000	0.197
	clomipramine (25 mg)	Panerai[121]	1990	1	8	0.059	0.108	0.000	0.270
	nortriptyline (25 mg)	Panerai[121]	1990	2	6	0.250	0.169	0.000	0.581
	amitriptyline (25 mg)	Pilowsky[122]	1982	10	8	0.556	0.137	0.287	0.824
	TCAs	Raja[123]	2002	2	24	0.077	0.088	0.000	0.250
	amitriptyline (10 to 125 mg/day)	Robinson[124]	2004	2	18	0.100	0.098	0.000	0.292
	amitriptyline (25 to 150 mg/day)	Sharav[125]	1987	1	11	0.043	0.093	0.000	0.226
	amitriptyline (5 to 30 mg/day)	Sharav[125]	1987	1	8	0.059	0.108	0.000	0.270
	amitriptyline (25 to 75 mg/day)	Vrethem[126]	1997	3	32	0.086	0.085	0.000	0.253
	maprotiline (25 to 75 mg/day)	Vrethem[126]	1997	2	33	0.057	0.081	0.000	0.216
Total TCAs				**40**	**227**	**0.117**	**0.044**	**0.032**	**0.203**

ACs=anticonvulsants; CI=confidence interval; LL=lower limit; SE=standard error; SNRIs=serotonin-norepinephrine reuptake inhibitors; TCAs=tricyclic antidepressants; UL=upper limit.

5 ECONOMIC ANALYSIS

5.1 Review of Economic Studies

5.1.1 Methods

a) Selection criteria and method

The inclusion criteria for economic abstracts to be considered for a full-text review are:

- Study design: Partial or full economic evaluation
- Population: Adults (18 years of age and older) who have been diagnosed with chronic neuropathic pain
- Interventions and comparators: One or more of ACs, SNRIs, TCAs.

Appendix H presents the inclusion and exclusion criteria that were applied.

b) Literature search strategy

A systematic literature search was performed by a librarian at the Hospital for Sick Kids in Toronto, using MEDLINE and EMBASE databases, Evidence-based Medicine reviews (EBM reviews — Cochrane Database of Systematic Reviews and EBM Reviews), and Cochrane Central Register of Controlled Trials.

The search strategy was limited to adult patients with chronic pain (neuropathic, migraine, or musculoskeletal pain), the English language, and articles from 1950 to 2007. The references of review articles were manually searched for additional eligible articles not identified in the primary literature search. Appendix I, Appendix J, and Appendix K show more details about the search strategy.

Two reviewers independently reviewed abstracts for inclusion in the study. Selected abstracts were then compared and assessed for disagreements between the two reviewers. A third reviewer was asked to review the abstract selection with unresolved discrepancies to adjudicate and to reach a final decision between both reviewers.

c) Data extraction strategy

A data extraction sheet was created using Microsoft Excel and validated by a senior researcher and other associates. The data extraction sheet was used to gather demographic information, information about study design, and information about primary and secondary economic outcomes. Data were extracted independently by two extractors. The extracted data were reviewed and verified by a senior researcher. Discrepancies were adjudicated using consensus. When no consensus was reached, discrepancies were adjudicated by a senior member of the team.

d) Strategy for quality assessment

A quality assessment was performed on every selected pharmacoeconomic study. Iskedjian et al.'s validated checklist,[133] which was based on Drummond's[134] approach, was used to distinguish between high versus low quality pharmacoeconomic studies.

e) Data analysis methods

Data were analyzed in a narrative fashion. We included information about patient characteristics, study design, direct and indirect costs related to neuropathic pain, adverse event and complication costs, study limitations, main assumptions, and conclusions. Quality assessment scores were included to rate the strengths and weaknesses of each pharmacoeconomic study. Descriptive statistics were calculated and a summary of studies was provided.

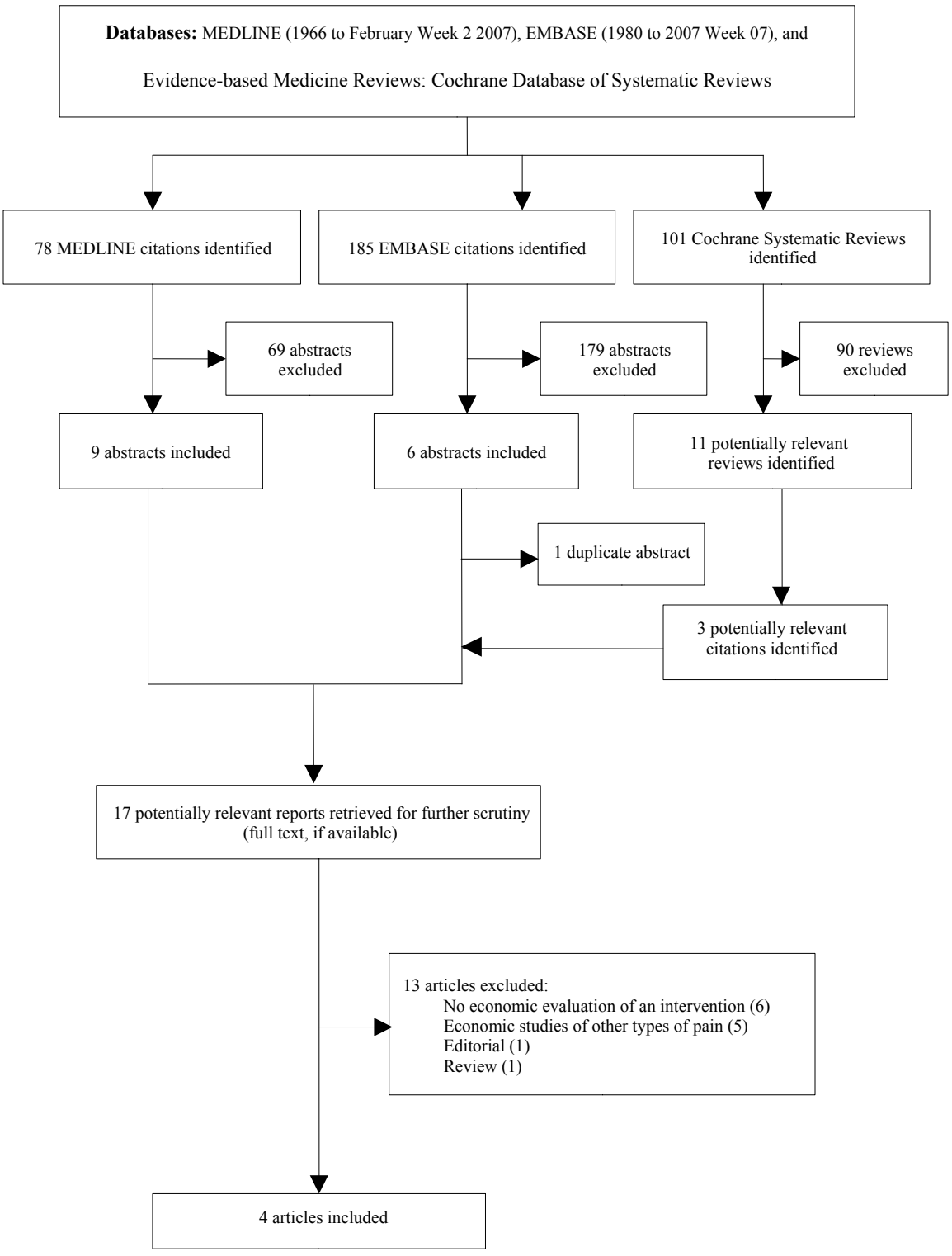
5.1.2 Results

We identified 78 references from MEDLINE, 185 from EMBASE, and 101 systematic reviews from EBM reviews.

Seventeen articles were selected for full-text review. Thirteen were excluded for not being economic or costing studies: six articles did not include an economic evaluation of the intervention of interest, one was an editorial, and one was a review. Five economic articles that did not include neuropathic pain data were excluded.[135-139] Therefore, four articles were included in the economic review[7,140-142] (Figure 2).

Table 5 describes the characteristics of economic studies of selected treatments in neuropathic pain. All four studies evaluated chronic neuropathic pain, particularly Diabetic Peripheral Neuropathy (DPN) and Postherpetic Neuralgia (PHN). The drugs that were evaluated were pregabalin, gabapentin, amitriptyline, carbamazepine, tramadol, and duloxetine. Of the four included studies, one was a cost-effectiveness analysis (CEA) and cost-utility analysis (CUA),[140] one was a CUA,[141] one was a CEA,[142] and one was a cost-of-illness analysis.[7] One study used stochastic Markov modelling,[140] another study used a general decision tree,[141] and another used the mixed modelling approach.[142] LaChaine et al.[7] did not state the type of model that was used in their economic evaluation. The time horizon of the studies ranged from four weeks to 50 weeks. The perspectives that were used were those of the public[7,140] and of private (third-party)[141,142] payers. A description of the analysis and outcomes appears in Table 6 and Table 7 respectively.

Figure 2: Selection and Disposition of Economic Studies of Selected Treatments in Neuropathic Pain



In a CEA-CUA study,[140] pregabalin was evaluated in comparison with gabapentin using the public payer's perspective. The analysis was conducted using a stochastic Markov model in a 12-week time horizon. The estimated average cost per patient with DPN of pregabalin was $818.49, compared with $837.53 for gabapentin. The estimated average cost per patient with PHN of pregabalin was $667.07, compared with $720.61 for gabapentin. Pregabalin provided an additional 0.0047 QALY for DPN and 0.0086 QALY for PHN over gabapentin. In that analysis, pregabalin was a dominant (cost saving with improved health outcomes) treatment of neuropathic pain associated with DPN or PHN.

Another CUA[141] compared amitriptyline, carbamazepine, gabapentin, and tramadol in treating patients with pain arising from PHN or DPN who were free of cardiovascular, hepatic, and renal disease. That study used the perspective of a private (third-party) payer and a probabilistic Monte Carlo Simulation for the analysis within a one-month time horizon. The overall estimated cost of amitriptyline was $29 per patient per month. The estimated costs of carbamazepine, tramadol, and gabapentin were $50, $98, and $270 respectively. Utility was estimated using the Health Utilities Index Mark-3 (HUI-3). Estimated utilities were 0.807 for amitriptyline, 0.807 for carbamazepine, 0.769 for tramadol, and 0.607 for gabapentin. Among all the studied drugs, amitriptyline was considered to be most cost-effective.

Wu et al.[142] determined the cost-effectiveness of duloxetine compared with routine treatment (gabapentin, venlafaxine, and amitriptyline) of pain associated with DPN. The costs were analyzed from the perspectives of a private (third-party) payer, society, and the employer. A mixed modelling approach was used in the analysis within a 50-week time horizon. Duloxetine was cost saving with improved health outcomes in comparison with routine treatment from employer and societal perspectives. The authors suggested that definitive conclusions could not be made from a third-party payer perspective, because of a lack of statistical significance.

A cost-of-illness study[7] assessed the economic burden of PNDs in Canada. The study was performed according to the perspective of the publicly funded health plan of Québec. Resource use was compared between those with PND and control patients without PNDs. The amount reimbursed by the Régie de l'assurance maladie du Québec (RAMQ) was statistically significantly higher in patients with PND ($4,163) compared with those without PND ($1,846). The presence of PND, the level of comorbidities, female gender, and age were significant contributors to the total cost of health care resources, with the presence of PND having the biggest impact.

The quality of all four included pharmacoeconomic studies was assessed using the Iskedjian checklist.[133] The mean quality score for all four included studies was 79%. The study with the highest quality score (91%) was conducted by Wu et al.[142] The study with the lowest quality score (68%) was conducted by Lachaine et al.[7] These scores would be considered to be good to excellent.

Table 5: Characteristics of Pharmacoeconomic Studies of Selected Treatments in Neuropathic Pain							
Author, Year	**Type of Pain**	**Study Drug**	**Objective or Research Question**	**Comparator**	**Funding Source**	**Name of Journal**	**Quality Score (%)**
Tarride, 2006[140]	Neuropathic pain associated with DPN and PHN	Pregabalin	Examine 12-week cost-effectiveness of 2 treatments of neuropathic pain, pregabalin versus gabapentin, in managing DPN and PHN in a Canadian setting	Gabapentin	Contract from Pfizer	*Clinical Therapeutics*	80
Cepeda, 2006[141]	Patients with pain arising from PHN or DPN who were free of cardiovascular, hepatic, and renal disease	• Amitriptyline • Carbamazepine • Gabapentin • Tramadol	Determine most cost-effective treatment of neuropathic pain	• Compared with each other in pharmaco-economic analysis • RCTs of drug versus placebo or active comparator • Meta-analysis summarized data	Grant from Colombian Chapter of International Association for the Study of Pain	*The Journal of Pain*	77
Wu, 2006[142]	Sufferers of neuropathic pain associated with DPN	Duloxetine hydrochloride	Determine cost-effectiveness of duloxetine hydrochloride versus routine treatment in management of DPN	Placebo / routine treatment (gabapentin; venlafaxine hydrochloride; amitriptyline hydrochloride; acetaminophen; trazodone; nortriptyline)	Eli Lilly	*The Journal of Pain*	91
LaChaine, 2007[7]	Peripheral PNDs	N/A	Describe economic characteristics of patients with peripheral PND in 1 of largest Canadian provinces (Québec)	N/A	N/A	*Pain Research and Management*	68

DPN=diabetic peripheral neuropathy; N/A=not applicable; PHN=postherpetic neuralgia; PND=painful neuropathic disorder; RCTs=randomized controlled trials.

Table 6: Designs of Economic Evaluations of Selected Treatments in Neuropathic Pain										
Author, Year	**Type of Economic Evaluation**	**Perspective**	**Country from which Costs were Determined**	**Study Design**	**Analytic Time Horizon**	**Duration of Trial (sourced data)**	**Were results extrapolated? (Yes/No)**	**Primary Outcome Unit**	**Secondary Outcome Unit**	**Other Outcome Unit**
Tarride, 2006[140]	• CUA • CEA	Public Payer	Canada	Stochastic Markov model	12 weeks	N/S	No	QALY (EQ-5D score transformed to QALY score)	Days with no or mild-pain	N/A
Cepeda, 2006[141]	CUA	Private Payer (third-party payer)	US	Decision tree using probabilistic Monte Carlo Simulation	1 month	N/S	N/S	HUI-3 Score	N/A	N/A
Wu, 2006[142]	CEA	• Private Payer (third-party payer) • Societal • Employer	US	Mixed model based on open-label extension study	50 weeks	52 weeks	No	Change in SF-36 BP score	N/A	N/A
LaChaine, 2007[7]	COI	Ministry of health	Canada	Database analysis	N/A	52 weeks	N/A	N/A	N/A	N/A

CEA=cost-effectiveness analysis; COI=cost of illness; CUA=cost-utility analysis; EQ-5D=EuroQol 5D questionnaire; HUI-3=Health Utility Index Mark 3, N/A=not applicable, N/S=not specified, QALY=quality-adjusted life year; SF-36 BP=Medical Outcomes Study Short Form 36 Bodily Pain scale.

Table 7: Primary Outcomes of Pharmacoeconomic Studies of Selected Treatments in Neuropathic Pain			
Author, Year	**Cost**	**Clinical/Patient Outcome**	**Pharmacoeconomic Outcome**
Tarride, 2006[140]	Average cost (SE) DPN: • Pregabalin $818.49 ($36.50) • Gabapentin $837.53 ($37.31) PHN: • Pregabalin $667.07 ($25.33) • Gabapentin $720.61 ($33.70)	QALYs Gained DPN: • Pregabalin provided mean effectiveness of 0.1197 QALYs • Gabapentin provided mean effectiveness of 0.1150 QALYs PHN: • Pregabalin provided mean effectiveness of 0.1211 QALYs • Gabapentin provided mean effectiveness of 0.1125 QALYs	Incremental cost per QALY gained (95% confidence interval) DPN: Pregabalin dominant (Dominant to $15,708/QALY) PHN: Pregabalin dominant (Dominant to $3,325/QALY)
Cepeda, 2006[141]	Average cost per patient per month • Amitriptyline $29.00 • Carbamazepine $50.00 • Tramadol $98.00 • Gabapentin $270.00	HUI-3 score • Amitriptyline 0.807 • Carbamazepine 0.807 • Tramadol 0.769 • Gabapentin 0.697	Average ICER (Cost per HUI-3 utility score increase)* • Amitriptyline dominated all others in ICER values for base-case scenario ($36/HUI-3 increase) • Carbamazepine ($62/HUI-3 increase) • Tramadol ($127/HUI-3 increase) • Gabapentin ($387/HUI-3 increase)
Wu, 2006[142]	50-week cumulative cost difference between duloxetine and routine treatment • Third-party payer — $1,599.84 • Employer — $2,195.86 • Society — $2,753.91	5.61 units increase in SF-36 BP	ICER (Incremental cost per change in SF-36 BP)* Third-party payer — $249/SF-36 BP increase ($p \leq 0.06$) • Employer — $342 ($p \leq 0.03$) • Society — $429 ($p \leq 0.03$)

Table 7: Primary Outcomes of Pharmacoeconomic Studies of Selected Treatments in Neuropathic Pain			
Author, Year	**Cost**	**Clinical/Patient Outcome**	**Pharmacoeconomic Outcome**
Lachaine, 2007[7]	Average cost (SD) • GP visits $164 ($285) • Specialist visits $292 ($462) • GP procedures $137 ($223) • Specialist procedures $416 ($625) • Hospitalization days $1,803 ($5,876) • Medication cost $1,350 ($1,939) • Total $4,163 ($7,536)	N/A	N/A

DPN=Diabetic Peripheral Neuropathy; HUI-3=Health Utilities Index Mark 3; GP=general physician; ICER=incremental cost effectiveness ratio; N/A=not applicable; PHN=postherpetic neuralgia; QALY=quality-adjusted life year; SD=standard deviation; SE=standard error; SF-36 BP=Medical Outcomes Study Short Form 36 Bodily Pain Scale.

*Outcomes reported as they appeared in original analyses. Average cost-effectiveness ratios and negative ICERs largely regarded as informative for decision-making.

5.1.3 Discussion

This economic review included four pharmacoeconomic studies on the treatment of chronic neuropathic pain. The review included CEA, CUA, and cost-of-illness studies.[7,140,141,143]

In one study,[140] pregabalin was cost-effective when compared with other ACs in the treatment of neuropathic pain that was associated with DPN or PHN. In another CUA,[141] amitriptyline was a cost-effective oral treatment in comparison with carbamazepine, gabapentin, and tramadol. Wu et al.[142] found that duloxetine was cost-effective in comparison with routine DPN treatments. A cost-of-illness study[7] that assessed the burden of neuropathic pain in Canada, reported that PND cases are associated with higher medical resource use than non-PND cases.

There are limitations to each study that was included in the review. In Tarride et al.'s study,[140] the efficacy was not derived from a direct head-to-head comparison of drugs. Another possible limitation is the short time horizon, which leads to underestimation of the real economic benefit of the assessed drug. Other limitations included a small sample size and the collection of utility scores that were not directly derived from clinical trials. A major limitation may have been not including all potential comparators, such as amitriptyline. Considering what others have reported,[141] the inclusion of amitriptyline may have altered the conclusions.

Cepeda et al.[141] found that amitriptyline was cost-effective when compared with the other ACs. Carbamazepine seemed to be cost-effective, but not when compared with amitriptyline. That study had the limitation of combining different types of neuropathic pain. Other limitations include the lack of eligible RCTs of carbamazepine in the treatment of neuropathic pain, not accounting for some of the adverse events associated with amitriptyline use, short time horizon, small sample size, and not accounting for unpublished data in the analysis. Another limitation was the inappropriate use of HUI-3 scores as an absolute rather than a relative outcome measure for the cost-outcome analysis, as opposed to deriving an appropriate measure of disease burden, such as a QALY, from those scores.

In Wu et al.'s study,[142] new drugs were introduced. This makes evaluation of the balance between cost and benefit particularly difficult. Those who were included in the study were not typical patients with DPN pain. Another limitation to the study is that the administrative claims database that was used to estimate the costs included only patients with the benefit of medical and prescription coverage. There were reporting of average cost-effectiveness ratios and the inappropriate use of HUI-3 utility scores as an absolute outcome measure. A major limitation was that they did not include the cost of drugs in the analysis. This was noted in a letter to the editor from O'Connor, who stated that the results were probably not valid.[143]Considering the fact that some comparators (for example, amitriptyline) are inexpensive, the outcomes could change when these deficiencies are addressed.

Lachaine et al.'s study[7] included the following limitations: the use of potentially inappropriate pain-related medications, as was common among older adults with PND; it was also assumed that dispensed medications identified in the databases were taken by the patient, although this may not be the case; and the diagnostic information obtained from claims could be prone to coding errors. Based on claims data, it was not possible to associate specific health resources with a specific diagnosis. The sample size was small, and the time horizon was short.

5.2 Primary Economic Evaluation

5.2.1 Methods

a) Perspective

A pharmacoeconomic analysis (PEA) from the ministry of health and societal viewpoints was performed to determine the cost-effectiveness of atypical drugs in the management of chronic neuropathic pain in Canada. Direct costs for drugs, physician visits, and hospitalizations were considered in both viewpoints. The societal perspective also included indirect costs for work loss, leisure, and transportation.

b) Patient population

Patients who were included in the PEA are adults (older than 18 years of age) with diagnosed neuropathic pain (such as diabetic neuropathic pain and postherpetic neuralgia) who were treated in a tertiary setting (pain clinics) for at least 12 weeks. Patients who were evaluated reflected the characteristics of the ones who had been evaluated in the clinical outcomes analysis (meta-analysis). Therefore, patients must have at least a mean pain intensity score of 5 measured on an 11-point (0 to 10) VAS. Only analgesic or anti-inflammatory medications (paracetamol, diclofenac, ketoprofen, or ibuprofen) were allowed as concomitant medications. Patients' comorbidities were directly associated with the characteristics of the neuropathic pain and included diabetes mellitus type I and II, or traumatic injury.

c) Drugs of interest

Three pharmacological treatment groups were compared and were represented by one or more agents in the following drug classes, which are defined as atypical drugs for the treatment of chronic pain:

- ACs
  - gabapentin
  - pregabalin
- SSNRIs
  - duloxetine (only available in Canada in early 2008[144] for treating patients with neuropathic pain and was used in a sensitivity analysis; duloxetine was included for estimating the overall clinical efficacy of SNRIs)
  - venlafaxine
- TCAs
  - amitriptyline
  - clomipramine
  - nortriptyline
  - imipramine
  - maprotiline.

The selected treatment groups would have to be given drugs through an oral administration route and at therapeutic doses for a minimum of four weeks and a maximum of 12 weeks. The selection of the pharmacological classes was based on clinical expert consultation (RJ and DM) and on Canadian clinical practice guidelines for managing neuropathic pain.[12,145]

d) Decision analytic tree

A decision tree analytic model was used to assess the cost-effectiveness of the targeted treatment comparators (as classes). A decision analytic model for assessing the cost-effectiveness of atypical drugs for managing neuropathic pain was appropriate because of the lack of available clinical or observational and naturalistic studies that would replicate clinical practice over a sufficiently long time. The analytical tree pathways were developed using input from clinical experts (RJ and DM) and from clinical practice guidelines.[12,146] The pharmacoeconomic model appears in Figure 3.

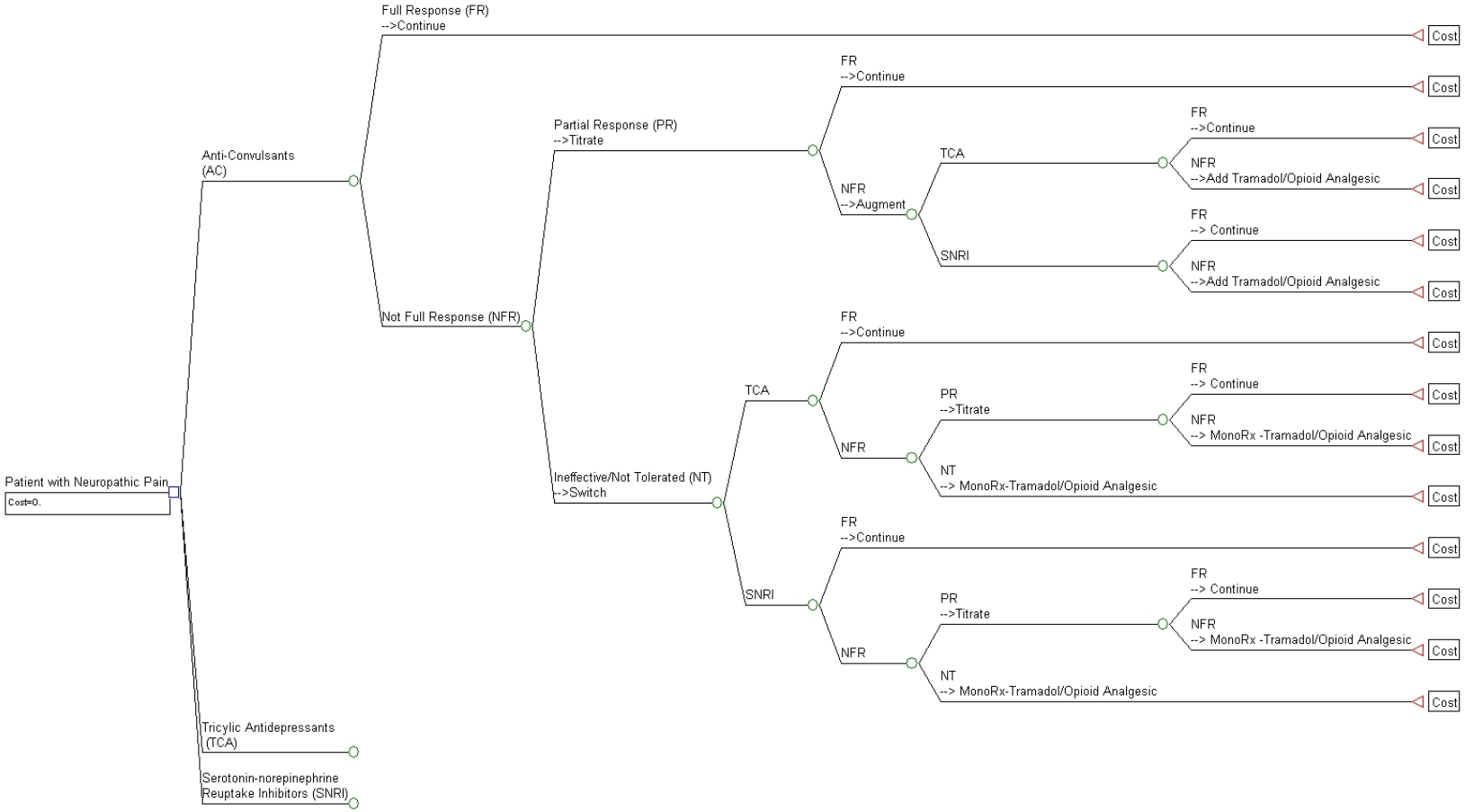
After the failure of conventional therapy for chronic pain (topical anesthetics, non-steroid anti-inflammatories), patients started using one of the three targeted pharmacological groups (ACs, TCAs, or SNRIs) for six weeks. Then, a first clinical assessment of the pharmacotherapy was performed by a clinician to determine whether a patient had full response or did not have full response (in this latter case, there were two possible arms: partial response or ineffective / not tolerated treatment).

Several pathways could be followed by patients depending on the response. If full response was achieved, the patient would continue on the same therapy until the end of the model time horizon, assuming continued effectiveness of the drug.

If full response was not reached, those patients having a partial response were titrated to a higher drug dose, and a switch was made for patients with an ineffective response or who did not tolerate treatment, so that they received another agent from another class. After another six weeks of titration or new drug therapy, a second clinical assessment would be conducted to verify the presence of full response. For those patients achieving full response, the current treatment would be administered until the end of the model evaluation.

For those patients who do not to reach full response after titration, a second agent would be added to the primary drug treatment. For those in whom treatment fails after switching, titration or a second treatment substitution with tramadol or an opioid as monotherapy would occur. After an additional six weeks, a third clinical assessment would be carried out to verify patients' full response to the therapy. In this latter case, patients who were considered to be full responders continued on therapy, and non-responders were automatically switched (after titration).

Figure 3: Management of Neuropathic Pain in Canada



AC=anticonvulsants; FR=full response; NFR=not full response; NT=ineffective/not tolerated; PR=partial response; Rx=pharmacotherapy; SNRI=serotonin-norepinephrine reuptake inhibitor; TCA=tricyclic antidepressant.

e) Time horizon

A time horizon of 18 weeks was applied to the pharmacoeconomic model. Although neuropathic pain is chronic and a longer time horizon is more appropriate, the 18-week time frame was selected because reliable data beyond 18 weeks are unavailable.

f) Outcomes of interest and incremental analyses

The outcomes of primary interest were full and partial response rates, defined as the rates of patients achieving a 50% and 30% reduction respectively in pain scores from baseline to endpoint on an 11-point VAS. A secondary outcome of interest was the number of "pain controlled days," which is the number of days that patients would be in full response within the evaluated model time horizon.

Clinical response (full response), titration, and switching rates were inserted in the decision tree and multiplied together to generate a probability matrix. Then, all costs of the resources that are consumed by patients in any model branch were multiplied by the probability associated for that tree branch. The resulting cumulative sum across all arms represents the overall weighted (expected) cost per patient treated for each tested drug class.

In addition, the probabilities of all branches ending with patients' full response to therapy were summed to arrive at a total overall expected treatment success rate for each pharmacological group. The same was done for the number of "pain controlled days," where the number of days in a full response branch was multiplied by the probability of achieving that endpoint and summed across all full response arms to estimate the number of "pain controlled days" per patient treated.

The expected cost per patient treated for each drug class was divided by its expected success rate and by the number of "pain controlled days" to arrive at the expected cost per outcome (cost-effectiveness measure). Finally, an incremental cost-effectiveness analysis was done for all drug classes by sequentially calculating the incremental cost per outcome.

Clinical data were derived from a meta-analysis of randomized controlled trials evaluating the efficacy of one or more of the drugs. Patient populations included in the pharmacoeconomic model had the same characteristics as those in the meta-analysis.

g) Resource valuation

Because two perspectives were assessed in the pharmacoeconomic model, direct and indirect costs were included in the analysis. We did not consider reduced productivity at work, because we assumed that it would be the same for all drugs. We populated the model with published rates of resource use (Table 8).

Prices for all resources that were consumed at any given model parameter were taken from standard lists such as the ODB formulary,[147] the Ontario Schedule of Benefits,[148] and RAMQ[149] whenever possible. Other sources were used for prices of drugs and interventions that were not covered by provincial health reimbursement schemes. All analyses were performed using 2007 Canadian dollar costs. Discounting was not considered because the model time horizon was less than one year. The costing information appears in Table 9.

The medication costs were determined for the standard doses and the titration doses by following the dosing regimen in Table 1 of Moulin et al.'s report[12] The starting doses that were presented in this paper were used as the starting doses, and the titration doses were the maximum maintenance doses. All medication prices included the 8% markup in addition to the listed formulary prices. A $7.00 per six-week cycle pharmacy fee was added to medication prices in the model. The costing of the starting doses and the titration doses was calculated.

If a tablet of the exact dose was available, then the minimum cost of all the available tablets from different manufacturers was used. We used the ODB formulary costs whenever they were available. If the medication was not covered by the ODB formulary, then the prices were obtained from the RAMQ liste de médicaments. For medications that could not be located from either of these formularies or another provincial formulary, we used the lowest price available online. For medication doses that did not have a corresponding tablet size, we used the smallest number of tablets to produce the number of milligrams of medication needed for the dose, unless a high quantity of tablets of a lower strength was less costly. The cost per milligram was lower for smaller-dose tablets than for larger-dose tablets. It was assumed that unless necessary, tablets of a certain medication strength would not be cut into smaller pieces to provide the necessary medication dose. For pregabalin, the starting dose is listed as 75 mg/day. Because a 75 mg tablet exists, the price of the starting dose was based on the minimum price from the ODB formulary for all 75 mg tablets plus the markup and dispensing fee. The maximum dose for gabapentin is 1,200 mg three times daily. Thus, nine 400 mg tablets were costed.

For the tricyclic antidepressants, the starting dose is 10 mg/day. Several of these medications, however, are unavailable as a 10 mg tablet form. As a result, we costed the 10 mg/day doses based on the next largest tablet's cost per milligram multiplied by 10. For example, if the minimum 20 mg tablet cost $1.00 before markup, the 10 mg/day dosing was costed at $0.50 before markup. For desipramine's titration dose of 150 mg/day, we used three 50 mg tablets for costing because the 50 mg tablet cost less on a per milligram basis than the 75 mg tablet. This costing structure for desipramine seemed to be an exception to the trend where the cost per milligram of medication declined as the tablet size (medication dose) increased.

h) Model assumptions and uncertainty

Because this study adopts a modelling approach that is based on several assumptions and on data from various sources, uncertainty was unavoidable. The following assumptions were made when building the decision analytic tree model and performing the analyses:

- Patients were taking one pain medication unless there was augmentation.
- In the case of switching, patients were taking one new medication, unless they were later augmented with one or more other medications as indicated in the decision analytic tree.
- Adherence to medication was 100%, especially with patients who were responders.
- The response was sustained for the remaining time on the time horizon.
- The cycles where therapy was initiated or changed did not contribute to response days.
- Initial doses and titrations were applied as reported by published treatment guidelines.[12]
- Augmentation was at the average dose for the second medication.
- If a patient's medication was augmented and the patient did not have full response, there was no further titration of the augmented drug, and the patient was considered to be a non-responder.

- All three drug classes were used individually as primary pharmacotherapy. Backup (secondary) or augmentation therapy for ACs was TCAs or SNRIs. Also, ACs served as backup or augmentation therapy for TCAs and SNRIs.
- If one pain therapy was not tolerated or was ineffective and a full response was not seen after switching to another therapy, patients could either have that new therapy titrated or be switched to tramadol or opioid analgesic.
- We assumed that drugs had the same success rate as backup therapy as they did when used as primary therapy.

i) Sensitivity analyses

One-way sensitivity analyses were performed on the effectiveness of comparators. Where ranges of values were available (a statistical analysis of "success" rates), the upper and lower limits of the 95% CIs were used in best case and worst case scenarios. One-way sensitivity analyses were performed on the cost of the medications using dosing regimens that were suggested by Moulin et al.[12] (Table 10). We used the upper starting dose (maximum standard dose) as one sensitivity analysis and the lower maintenance dose (minimum titration dose) as another sensitivity analysis to examine the variability in the medication costs of the three therapies. Combinations of these sensitivities with the baseline costs were performed. In addition, we used placebo-adjusted rates in alternative analyses.

A sensitivity analysis was performed on the SNRIs in the model. Because duloxetine has only recently been approved[150] for neuropathic pain and available for use in Canada,[144] data on the proportion of users given duloxetine for neuropathic pain compared with the proportion of users given venlafaxine for neuropathic pain were unavailable. Therefore, we examined what would happen if all patients who were given SNRIs were prescribed duloxetine rather than venlafaxine as was done in the base case.

Probabilistic sensitivity analysis (PSA) using Monte Carlo simulation is an appropriate method to characterize decision uncertainty as one-way sensitivity analysis cannot reflect the combined uncertainty across all model parameters.[151] PSA has been viewed as a necessary part of informing answers to decision problems,[152,153] Each parameter is assumed to follow a probability distribution. The baseline value and the 95% CI values are used to define the probability distribution. For each simulation, values from the probability distributions are randomly selected and used to populate the model. This is repeated several times, with the mean and standard deviation of the model results over all the simulations being reported. For the 30% and 50% response rates, we assumed that the 95% confidence limits defined the lower and upper bounds of uniform distributions. Uniform distributions were appropriate because a patient may experience any response rate with equal probability between the two bounds. For the therapy costs, discrete distributions (specific values and specific probabilities) were used. It was assumed that because of tablet size and dosing patterns that the lower cost, the upper cost, and the average of these costs were equally likely (each having a probability of 1/3).

A sensitivity analysis was performed for the scenario with 50% response rates, without incorporating TCAs in the decision analytic tree, based on the fact that there was no study reporting 50% response rates for TCAs. Hence, this hypothetical scenario was restricted to ACs and SNRIs, because of the lack of evidence with TCAs for the corresponding outcome.

5.2.2 Results

a) Health outcomes (disaggregated analysis)

Base-case analysis results included two sets of analyses: one set based on response rates from the "from placebo" rates derived in the meta-analysis, and a second set based on the "through placebo" rates.

The "from placebo" model reported that those taking TCAs were the pharmacological group reporting the highest clinical response (79.3%), followed by the group taking ACs (77.8%) and the group taking SNRIs (76.4%) in managing neuropathic pain patients over an 18-week time horizon.

Using the number of days with controlled pain as a health outcome measure, the TCAs group was the best alternative (average of 48 days), followed by the ACs and SNRIs groups with 46 and 43 pain controlled days respectively.

The "through placebo" model reported results that were in line with those of the previous model. The TCAs group reported the highest clinical response (88.0%), followed by the ACs (84.3%) and SNRIs (80.6%) groups.

Using the number of days with controlled pain as a health outcome measure, the TCAs group was the best alternative (average of 60 days), followed by ACs and SNRIs groups with 54 and 41 pain controlled days respectively.

b) Economic outcomes (disaggregated analysis)

For the "from placebo" model, from the MoH perspective (accounting for direct medical costs only), the model estimated that TCAs group was the least costly (total of $380) for managing patients with neuropathic pain over an 18-week time horizon. In the incremental cost analysis, TCAs produced savings of $68 and $181 compared with SNRIs and ACs respectively.

Using the Canadian societal perspective, the least costly alternative ranking was similar, but the magnitude differed. In this scenario, TCAs produced savings of $222 and $255 compared with SNRIs and ACs respectively.

For the "through placebo" model, from the MoH perspective (accounting for direct medical costs only), the model estimated that the TCAs group was the least costly (total of C$331) for managing neuropathic pain patients over an 18-week time horizon. In the incremental cost analysis, TCAs produced savings of $128 and $188 compared with SNRIs and ACs respectively.

Table 8: Rates of Resource Use for Incorporation in Pharmacoeconomic Evaluation of ACs, SNRIs, and TCAs for Management of Neuropathic Pain			
Resource	**Item**	**Rate of Use (%)**	**Source**
Drug therapies	Pregabalin	32	IMS Health Inc., CS, December, 2007
	Gabapentin	68	IMS Health Inc., CS, December, 2007
	Venlafaxine	100	Venlafaxine is the only SNRI available in Canada
	Amitriptyline	50	IMS Health Inc., CS, December, 2007
	Desipramine	18	IMS Health Inc., CS, December, 2007
	Imipramine	8	IMS Health Inc., CS, December, 2007
	Nortriptyline	25	IMS Health Inc., CS, December, 2007
	Morphine	28	IMS Health Inc., CS, December, 2007
	Oxycodone	40	IMS Health Inc., CS, December, 2007
	Fentanyl	20	IMS Health Inc., CS, December, 2007
	Tramadol	13	IMS Health Inc., CS, December, 2007
Dispensing fee	Pharmacist fee	3	According to pharmacoeconomic model
Specialist visits	Initial assessment	1	According to pharmacoeconomic model
	Follow-up visits	3	According to pharmacoeconomic model
Diagnostic tests (specialist referral)	Computed tomography scan	9	Tarride, 2006[140]
	Magnetic resonance imaging	10	Tarride, 2006[140]
	Nerve conduction studies	31	Tarride, 2006[140]
	Quantitative sensory testing	7	Tarride, 2006[140]
	Doppler sonography	5	Tarride, 2006[140]
	Electromyography	23	Tarride, 2006[140]
	Glycosylated hemoglobin	2	Tarride, 2006[140]
	Creatinine	2	Tarride, 2006[140]
	Complete blood count	2	Tarride, 2006[140]
Co-medications (uncontrolled pain)	Anxiolytics	9	Gore, 2006[9]
	Sedatives/hypnotics	6	Gore, 2006[9]
OTC drug use (uncontrolled pain)	Acetaminophen	36	Gore, 2006[9]
	Aspirin	28	Gore, 2006[9]
	Ibuprofen	29	Gore, 2006[9]

Table 8: Rates of Resource Use for Incorporation in Pharmacoeconomic Evaluation of ACs, SNRIs, and TCAs for Management of Neuropathic Pain			
Resource	**Item**	**Rate of Use (%)**	**Source**
	Naproxen	15	Gore, 2006[9]
Procedures (uncontrolled pain)	Physical therapy (15-minute session)	28	Tarride, 2006[140]
	Drug infiltration	13	Tarride, 2006[140]
	Nerve block	22	Tarride, 2006[140]
	Transcutaneous nerve electric stimulator	16	Tarride, 2006[140]
	Implementation of spinal stimulator	1	Tarride, 2006[140]
Hospitalizations (uncontrolled pain)	Average days in hospital per patient (6-week period)	0.363	Lachaine, 2007[7]
	SD =	1.188	
Days lost work (uncontrolled pain)	Absenteeism per patient (6-week period)	1.125	van Leeuwen, 2006[10]
	Loss of productivity per patient (6-week period)	3.019	van Leeuwen, 2006[10]
Adverse drug reactions (ADRs)	Rate of ADRs (ACs)	12.3	Meta-analysis
	Rate of ADRs (SNRIs)	12.0	Meta-analysis
	Rate of ADRs (TCAs)	11.7	Meta-analysis
Days lost work (ADRs)	Absenteeism	3	Assumption

ACs=anticonvulsants; ADRs=adverse drug reactions; OTC=over-the-counter; SD=standard deviation; SNRIs=serotonin-norepinephrine reuptake inhibitors; TCAs=tricyclic antidepressants.

Table 9: Cost Input Estimation for Use in Pharmacoeconomic Evaluation of Anticonvulsants, SNRIs, and TCAs for Management of Neuropathic Pain					
Resource	**Item**	**Unit of Valuation**	**Cost per Unit of Valuation**	**Cost Applied as per Use in Model**	**Source**
Drug therapies*†‡	Pregabalin	Daily cost	$1.64	$0.52	RAMQ, 2007[149]
	Gabapentin	Daily cost	$0.53	$0.36	ODB, 2007[147]
	Anticonvulsants (minimum standard dose, per day)			*$0.87*	
	Pregabalin	Daily cost	$5.02	$1.58	RAMQ, 2007[149]
	Gabapentin	Daily cost	$5.64	$3.83	ODB, 2007[147]
	Anticonvulsants (maximum titration dose, per day)			*$5.41*	
	Venlafaxine	Daily cost	$0.45	$0.45	ODB, 2007[147]
	SNRIs (minimum standard dose, per day)			*$0.45*	
	Duloxetine	Daily cost	$3.84	$3.84	Lauren Fischer, Eli Lilly Canada, Inc., Toronto: personal communication, 2 April 2008.
	SNRIs (minimum standard dose, per day)			*$3.84*	
	Venlafaxine	Daily cost	$1.44	$1.44	ODB, 2007[147]
	SNRIs (maximum titration dose, per day)			*$1.44*	
	Duloxetine	Daily cost	$7.69	$7.69	Lauren Fischer: personal communication, 2 April 2008.
	SNRIs (maximum titration dose, per day)			*$7.69*	
	Amitriptyline	Daily cost	$0.05	$0.02	ODB, 2007[147]
	Desipramine	Daily cost	$0.07	$0.01	ODB, 2007[147]
	Imipramine	Daily cost	$0.09	$0.01	ODB, 2007[147]
	Nortriptyline	Daily cost	$0.14	$0.03	RAMQ, 2007[149]
	TCAs (minimum standard dose, per day)			*$0.08*	
	Amitriptyline	Daily cost	$0.50	$0.25	ODB, 2007[147]

Table 9: Cost Input Estimation for Use in Pharmacoeconomic Evaluation of Anticonvulsants, SNRIs, and TCAs for Management of Neuropathic Pain					
Resource	**Item**	**Unit of Valuation**	**Cost per Unit of Valuation**	**Cost Applied as per Use in Model**	**Source**
	Desipramine	Daily cost	$0.99	$0.17	ODB, 2007[147]
	Imipramine	Daily cost	$0.83	$0.06	ODB, 2007[147]
	Nortriptyline	Daily cost	$1.65	$0.41	RAMQ, 2007[149]
	TCAs (maximum titration dose, per day)			*$0.90*	
	Morphine	Daily cost	$0.52	$0.14	ODB, 2007[147]
	Oxycodone	Daily cost	$1.35	$0.54	ODB, 2007[147]
	Fentanyl	Daily cost	$4.59	$0.92	ODB, 2007[147]
	Tramadol	Daily cost	$0.60	$0.07	JustPills,2007[154]
	Opioids (standard dose, per day)			*$1.68*	
Dispensing fee	Pharmacist fee	Unit cost	$7.00	$21.00	OHIP, 2007[148]
Specialist visits	Initial assessment	Unit cost	$147.80	$147.80	OHIP, 2007[148]
	Follow-up visits	Unit cost	$64.05	$192.15	OHIP, 2007[148]
	Overall			*$339.95*	
Diagnostic tests (specialist referral)[§]	Computed tomography scan	Unit cost	$115.86	$10.43	OHIP, 2007[148]
	Magnetic resonance imaging	Unit cost	$707.00	$70.70	OHIP, 2007[148]
	Nerve conduction studies	Unit cost	n/a	$0.00	
	Quantitative sensory testing	Unit cost	n/a	$0.00	
	Doppler sonography	Unit cost	$31.50	$1.42	OHIP, 2007[148]
	Electromyography	Unit cost	$149.15	$34.30	OHIP, 2007[148]
	Glycosylated hemoglobin	Unit cost	$22.00	$0.33	OHIP, 2007[148]
	Creatinine	Unit cost	$34.00	$0.51	OHIP, 2007[148]
	Complete blood count	Unit cost	$16.00	$0.32	OHIP, 2007[148]
	Overall (per case)			*$118.01*	
Co-medications (uncontrolled pain)[*†‡]	Anxiolytics	Daily cost	$0.27	$0.02	ODB, 2007[147]
	Sedatives/hypnotics	Daily cost	$0.36	$0.02	ODB, 2007[147]
	Overall (per 6-week period)			*$1.91*	

Table 9: Cost Input Estimation for Use in Pharmacoeconomic Evaluation of Anticonvulsants, SNRIs, and TCAs for Management of Neuropathic Pain					
Resource	**Item**	**Unit of Valuation**	**Cost per Unit of Valuation**	**Cost Applied as per Use in Model**	**Source**
OTC drug use (uncontrolled pain)†	Acetaminophen	Daily cost	$0.94	$0.34	ODB, 2007[147]
	Aspirin	Daily cost	$0.13	$0.04	ODB, 2007[147]
	Ibuprofen	Daily cost	$0.11	$0.03	ODB, 2007[147]
	Naproxen	Daily cost	$0.14	$0.02	ODB, 2007[147]
	Overall (per 6-week period)			*$18.03*	
Procedures (uncontrolled pain)§	Physical therapy (15-minute session)	Unit cost	$37.50	$10.31	OHIP, 2007[148]
	Drug infiltration	Unit cost	$10.33	$1.34	OHIP, 2007[148]
	Nerve block	Unit cost	$79.44	$17.48	OHIP, 2007[148]
	Transcutaneous nerve electric stimulator	Unit cost	n/a	$0.00	
	Implementation of spinal stimulator	Unit cost	n/a	$0.00	
	Overall (per case)			*$29.13*	
Hospitalizations (uncontrolled pain)¶	Average days in hospital (6-week period)	6-week period cost	$170.00	$61.71	OHIP, 2007[148]
Days lost work (uncontrolled pain)¶	Absenteeism (6-week period)	6-week period cost	$166.88	$187.74	Statcan: http://www40.statcan.ca/l01/cst01/labr69a.htm
	Loss of productivity (6-week period)	6-week period cost	$166.88	$503.81	Statcan: http://www40.statcan.ca/l01/cst01/labr69a.htm
	Overall (per 6-week period)			*$691.55*	
Adverse drug reactions MOH (per case)**	ADR cost (ACs)	Per event cost	$889.90	$109.46	Dennehy, 1996[155]
	ADR cost (SNRIs)	Per event cost	$889.90	$106.79	Dennehy, 1996[155]
	ADR cost (TCAs)	Per event cost	$889.90	$104.12	Dennehy, 1996[155]
Adverse drug reactions SOC	ADR cost (ACs)	Per event cost	$1.390.54	$171.04	Dennehy, 1996[155]

Table 9: Cost Input Estimation for Use in Pharmacoeconomic Evaluation of Anticonvulsants, SNRIs, and TCAs for Management of Neuropathic Pain					
Resource	**Item**	**Unit of Valuation**	**Cost per Unit of Valuation**	**Cost Applied as per Use in Model**	**Source**
(per case)††	ADR cost (SNRIs)	Per event cost	$1.390.54	$166.86	Dennehy, 1996[155]
	ADR cost (TCAs)	Per event cost	$1.390.54	$162.69	Dennehy, 1996[155]
Days lost work (ADRs)¶	Absenteeism	6-week period cost	$166.88	$500.64	Statcan: http://www40.statcan.ca/l01/cst01/labr69a.htm
	Overall (per case)			*$500.64*	

*All drug costs include an 8% markup paid on eligible ODB formulary claims.

†Cost per unit of valuation was calculated using {[(Drug cost per milligram × prescribed daily dose in mg) + 8% mark-up]}. For example, pregabalin standard daily dose = {[($0.0202 × 75) + 8%]} = $1.64.

‡The cost applied in the model was obtained by summing the proportion of patients taking specific medication in drug therapy class by cost per unit of valuation. For example, for the anticonvulsant drug therapy group, the cost applied was calculated as 0.32 × $1.64 (pregabalin) + 0.68 × $0.53 (gabapentin)=$0.87.

§Diagnostic test and procedure costs were calculated using (unit diagnostic test cost × rate of use). For example, computed tomography scan = ($115.86 × 0.09) = $10.43.

¶Hospitalization and cost of days lost work both due to uncontrolled pain and to adverse drug reactions were calculated using (average days in hospital or work absenteeism or lost of productivity × daily hospital ward cost or average day of work cost). For example, loss of productivity = (3.019 × $166.88) = $503.81.

**Adverse drug reaction (ministry of health) cost was calculated using (average cost of managing ADR × incidence rate of ADR dropout). For example, adverse drug reactions ministry of health cost for anticonvulsants = ($889.90 × 0.123) = $109.46.

††Adverse drug reaction (society) cost was calculated using [(Average cost of managing ADR + cost of days lost work due to ADRs) × incidence rate of ADR dropout]. For example, adverse drug reactions (society) cost for anticonvulsants = [($889.90 + 500.64) × 0.123] = $171.04.

ACs=anticonvulsants; ADRs=adverse drug reactions; MOH=ministry of health; ODB=Ontario Drug Benefit; OHIP=Ontario Health Insurance Plan; OTC=over-the-counter; RAMQ=Régie de l'assurance maladie du Québec, SNRIs=serotonin-norepineprhine reuptake inhibitors; SOC=society; TCAs=tricyclic antidepressants.

Table 10: Maximum Standard Dose and Minimum Titration Dose Medication Cost Adjustments for One-Way Sensitivity Analyses				
Drug Therapy[*†‡]	**Unit of Valuation**	**Cost per Unit of Valuation**	**Cost Applied as per Use in Model**	**Source**
Pregabalin	Daily cost	$2.51	$0.79	RAMQ, 2007[149]
Gabapentin	Daily cost	$0.53	$0.36	ODB, 2007[147]
Anticonvulsants (max standard dose, per day)			*$1.15*	
Pregabalin	Daily cost	$5.02	$1.58	RAMQ, 2007[149]
Gabapentin	Daily cost	$1.58	$1.07	ODB, 2007[147]
Anticonvulsants (min titration dose, per day)			*$2.65*	
Venlafaxine	Daily cost	$0.45	$0.45	ODB, 2007[147]
SNRIs (min standard dose, per day)			*$0.45*	
Venlafaxine	Daily cost	$0.96	$0.96	ODB, 2007[147]
SNRIs (max titration dose, per day)			*$0.96*	
Amitriptyline	Daily cost	$0.09	$0.04	ODB, 2007[147]
Desipramine	Daily cost	$0.19	$0.03	ODB, 2007[147]
Imipramine	Daily cost	$0.15	$0.01	ODB, 2007[147]
Nortriptyline	Daily cost	$0.27	$0.07	RAMQ, 2007[149]
TCAs (max standard dose, per day)			*$0.16*	
Amitriptyline	Daily cost	$0.17	$0.08	ODB, 2007[147]
Desipramine	Daily cost	$0.33	$0.06	ODB, 2007[147]
Imipramine	Daily cost	$0.28	$0.02	ODB, 2007[147]
Nortriptyline	Daily cost	$0.55	$0.14	RAMQ, 2007[149]
TCAs (min titration dose, per day)			*$0.30*	

*All drug costs include an 8% markup paid on eligible ODB formulary claims.
†The cost per unit of valuation was calculated using {[(Drug cost per milligram × prescribed daily dose in mg) + 8% markup]}. For example, pregabalin maximum standard daily dose = {[($0.0155 × 150) + 8%]} = $2.51.
‡The cost applied in the model was obtained by summing proportion of patients taking specific medication in drug therapy class by cost per unit of valuation. For example, for the anticonvulsant drug therapy group, the cost applied for maximum standard daily dose was calculated as 0.32 × $2.51 (pregabalin) + 0.68 × $0.53 (gabapentin) = $1.15.

ODB=Ontario Drug Benefit; RAMQ=Régie de l'assurance maladie du Québec, SNRIs=serotonin-norepinephrine reuptake inhibitors; TCAs=tricyclic antidepressants.

Table 11: Base-Case Cost-Effectiveness Analysis of ACs, SNRIs, and TCAs for Management of Neuropathic Pain for "From Placebo" Approach							
Approach	**Perspective**	**Strategies**	**Cost**	**Incremental Cost**	**Effectiveness**	**Incremental Effectiveness**	**Incremental C/E (ICER)**
Indirect "From Placebo"*							
	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; then, meta-analytic average difference from placebo was calculated for each drug; two were added to give an adjusted rate for each drug.

†Success rates were calculated in same way, but 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.

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

Table 12: 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)**
Indirect "Through Placebo"†							
	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 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 adjusted rate for each drug.
†Success rates were calculated in same way, but 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
C/E=cost-effectiveness ratio; ICER=incremental cost-effectiveness ratio; MOH=ministry of health; PCDs=pain controlled days; SOC=society; SNRIs=serotonin-norepinephrine reuptake inhibitors; TCAs=tricyclic antidepressants.

Using the Canadian societal perspective, the least costly alternative ranking was similar, but the magnitude differed. In this scenario, TCAs produced savings of $355 and $612 compared with SNRIs and ACs respectively.

c) Cost-effectiveness analysis (aggregated analysis)

The base-case cost-effectiveness analyses using the "from placebo" (Table 11) and "through placebo" (Table 12) adjustments for placebo effect were summarized by perspective and outcome measure. From a ministry of health or societal perspective, TCAs were considered to be dominant over both drug classes in terms of producing a 30% or a 50% reduction in pain or producing pain controlled days, and for "from placebo" and "through placebo" analytic models.

d) Alternative cost-effectiveness analysis

An alternative set of results was obtained, based on analyses that applied success rates for all three drug classes that were unadjusted against the placebo response. In this analysis, the response rates were meta-analytic averages across studies and independent from placebo rates (Appendix G).

In all scenarios, TCAs dominated the other two drug classes, with lower costs and higher outcomes (Appendix L).

e) Sensitivity analyses

One-way sensitivity analyses were performed after applying the upper and lower limits of the 95% CIs for each of the three classes of medications as best and worst case scenarios respectively. One-way sensitivities were done on the full response rates of the three drug classes by calculating the full response rates from placebo and through placebo. Finally, medication costs were examined by using different standard doses and titration doses and costing these doses.

For each drug class, analyses were performed for the lower and upper limits of the 95% CI of efficacy results from the meta-analysis. For each of these 95% CI values, two analyses from the ministry of health perspective were conducted: one outcome was clinical response rate and one outcome was pain controlled days (PCDs). These two analyses were repeated for the societal perspective as well. Hence, there were 48 one-way sensitivity analyses (2 Perspectives × 2 Outcomes × 3 Drug Classes × 2 Response Rates (30% and 50%) × 2 limits of upper and lower 95% CI thresholds).

We conducted sensitivities on the medication prices using the dosing regimens from Moulin et al.'s Table 1.[12] We changed the base standard (Minimum Standard) dose to the upper standard dose (Maximum Standard) and the base titration dose (Maximum Titration) to the lower maintenance dose (Minimum Titration). We examined all combinations of the base doses and the other doses. Consequently, we compared base standard and lower titration doses; maximum standard and base titration doses; and maximum standard and minimum standard doses. With these sensitivities, 12 one-way sensitivity analyses were done (2 Perspectives × 2 Outcomes × 3 Price Combinations). When duloxetine was considered to be the SNRI in the model, 4 one-way sensitivity analyses were done (2 Perspectives × 2 Outcomes). Therefore 64 one-way sensitivity analyses were done for the "from placebo" response rates, and 64 one-way sensitivities were done for the "through placebo" response rates. In total, 128 one-way sensitivity analyses were conducted for changes in full response rates, partial response rates, medication prices for the three drug classes, and the use of duloxetine as the SNRI therapy.

All analyses, except three, yielded results in the same direction as that of the base-case analyses (TCAs dominated both other classes) (Table 13 and Table 14 for the "from placebo" and "through placebo" approaches respectively).

Table 13: One-Way Sensitivity Analysis Results for Analyses "From Placebo"							
Sensitivity Variable	**Perspective**	**Strategies**	**Cost**	**Incr Cost**	**Effectiveness**	**Incr Effectiveness**	**Incr C/E (ICER)**
50% Response Rate							
ACs=0.383	MOH	TCAs	$381		78.5% Response rate		
Lower limit		SNRIs	$449	$68	75.4% Response rate	-3.1% Response rate	(Dominated)
		ACs	$577	$196	75.5% Response rate	-3.0% Response rate	(Dominated)
	SOC	TCAs	$1,812		78.5% Response rate		
		SNRIs	$2,036	$224	75.4% Response rate	-3.1% Response rate	(Dominated)
		ACs	$2,145	$333	75.5% Response rate	-3.0% Response rate	(Dominated)
	MOH	TCAs	$381		48 PCDs		
		SNRIs	$449	$68	43 PCDs	-6 PCDs	(Dominated)
		ACs	$577	$196	43 PCDs	-6 PCDs	(Dominated)
	SOC	TCAs	$1,812		48 PCDs		
		SNRIs	$2,036	$224	43 PCDs	-6 PCDs	(Dominated)
		ACs	$2,145	$333	43 PCDs	-6 PCDs	(Dominated)
ACs=0.463	MOH	TCAs	$379		80.1% Response rate		
Upper limit		SNRIs	$446	$68	77.5% Response rate	-2.6% Response rate	(Dominated)
		ACs	$544	$165	80.0% Response rate	-0.1% Response rate	(Dominated)
	SOC	TCAs	$1,803		80.1% Response rate		
		ACs	$1,983	$179	80.0% Response rate	-0.1% Response rate	(Dominated)
		SNRIs	$2,024	$221	77.5% Response rate	-2.6% Response rate	(Dominated)
	MOH	TCAs	$379		49 PCDs		
		SNRIs	$446	$68	43 PCDs	-6 PCDs	(Dominated)
		ACs	$544	$165	49 PCDs	0 PCDs	$941
	SOC	TCAs	$1,803		49 PCDs		
		ACs	$1,983	$179	49 PCDs	0 PCDs	$1,021
		SNRIs	$2,024	$42	43 PCDs	-6 PCDs	(Dominated)
50% Response Rate							
SNRIs=0.331	MOH	TCAs	$381		78.2% Response rate		
Lower limit		SNRIs	$463	$82	73.5% Response rate	-4.7% Response rate	(Dominated)
		ACs	$561	$181	76.5% Response rate	-1.7% Response rate	(Dominated)
	SOC	TCAs	$1,812		78.2% Response rate		
		ACs	$2,069	$256	76.5% Response rate	-1.7% Response rate	(Dominated)
		SNRIs	$2,132	$319	73.5% Response rate	-4.7% Response rate	(Dominated)

Table 13: One-Way Sensitivity Analysis Results for Analyses "From Placebo"							
Sensitivity Variable	**Perspective**	**Strategies**	**Cost**	**Incr Cost**	**Effectiveness**	**Incr Effectiveness**	**Incr C/E (ICER)**
	MOH	TCAs	$381		48 PCDs		
		SNRIs	$463	$82	39 PCDs	-10 PCDs	(Dominated)
		ACs	$561	$181	45 PCDs	-3 PCDs	(Dominated)
	SOC	TCAs	$1,812		48 PCDs		
		ACs	$2,069	$256	45 PCDs	-3 PCDs	(Dominated)
		SNRIs	$2,132	$319	39 PCDs	-10 PCDs	(Dominated)
SNRIs=0.435	MOH	TCAs	$379		80.4% Response rate		
Upper limit		SNRIs	$433	$54	79.3% Response rate	-1.1% Response rate	(Dominated)
		ACs	$559	$180	79.0% Response rate	-1.4% Response rate	(Dominated)
	SOC	TCAs	$1,803		80.4% Response rate		
		SNRIs	$1,930	$128	79.3% Response rate	-1.1% Response rate	(Dominated)
		ACs	$2,057	$255	79.0% Response rate	-1.4% Response rate	(Dominated)
	MOH	TCAs	$379		49 PCDs		
		SNRIs	$433	$54	47 PCDs	-2 PCDs	(Dominated)
		ACs	$559	$180	46 PCDs	-3 PCDs	(Dominated)
	SOC	TCAs	$1,803		49 PCDs		
		SNRIs	$1,930	$128	47 PCDs	-2 PCDs	(Dominated)
		ACs	$2,057	$255	46 PCDs	-3 PCDs	(Dominated)
50% Response Rate							
TCAs=0.328	MOH	TCAs	$420		71.1% Response rate		
Lower limit		SNRIs	$451	$31	72.9% Response rate	1.8% Response rate	$1,741
		ACs	$563	$112	74.6% Response rate	1.7% Response rate	$6,433
	SOC	SNRIs	$2,048		72.9% Response rate		
		TCAs	$2,063	$15	71.1% Response rate	-1.8% Response rate	(Dominated)
		ACs	$2,078	$30	74.6% Response rate	1.7% Response rate	$1,741
	MOH	TCAs	$420		38 PCDs		
		SNRIs	$451	$31	42 PCDs	4 PCDs	$7
		ACs	$563	$112	45 PCDs	3 PCDs	$37
	SOC	SNRIs	$2,048		42 PCDs		
		TCAs	$2,063	$15	38 PCDs	-4 PCDs	(Dominated)
		ACs	$2,078	$30	45 PCDs	3 PCDs	$10
TCAs=0.592	MOH	TCAs	$341		86.3% Response rate		
Upper limit		SNRIs	$444	$103	79.7% Response rate	-6.6% Response rate	(Dominated)
		ACs	$558	$216	80.7% Response rate	-5.6% Response rate	(Dominated)

Table 13: One-Way Sensitivity Analysis Results for Analyses "From Placebo"							
Sensitivity Variable	**Perspective**	**Strategies**	**Cost**	**Incr Cost**	**Effectiveness**	**Incr Effectiveness**	**Incr C/E (ICER)**
	SOC	TCAs	$1,569		86.3% Response rate		
		SNRIs	$2,013	$444	79.7% Response rate	-6.6% Response rate	(Dominated)
		ACs	$2,048	$480	80.7% Response rate	-5.6% Response rate	(Dominated)
	MOH	TCAs	$341		59 PCDs		
		SNRIs	$444	$103	44 PCDs	-15 PCDs	(Dominated)
		ACs	$558	$216	46 PCDs	-12 PCDs	(Dominated)
	SOC	TCAs	$1,569		59 PCDs		
		SNRIs	$2,013	$444	44 PCDs	-15 PCDs	(Dominated)
		ACs	$2,048	$480	46 PCDs	-12 PCDs	(Dominated)
30% Response Rate							
ACs=0.499	MOH	TCAs	$380		79.2% Response rate		
Lower limit		SNRIs	$448	$68	76.3% Response rate	-2.9% Response rate	(Dominated)
		ACs	$554	$175	77.5% Response rate	-1.7% Response rate	(Dominated)
	SOC	TCAs	$1,807		79.2% Response rate		
		SNRIs	$2,030	$222	76.3% Response rate	-2.9% Response rate	(Dominated)
		ACs	$2,074	$267	77.5% Response rate	-1.7% Response rate	(Dominated)
	MOH	TCAs	$380		49 PCDs		
		SNRIs	$448	$68	43 PCDs	-6 PCDs	(Dominated)
		ACs	$554	$175	46 PCDs	-3 PCDs	(Dominated)
	SOC	TCAs	$1,807		49 PCDs		
		SNRIs	$2,030	$222	43 PCDs	-6 PCDs	(Dominated)
		ACs	$2,074	$267	46 PCDs	-3 PCDs	(Dominated)
ACs=0.590	MOH	TCAs	$380		79.4% Response rate		
Upper limit		SNRIs	$448	$68	76.6% Response rate	-2.8% Response rate	(Dominated)
		ACs	$566	$187	78.1% Response rate	-1.4% Response rate	(Dominated)
	SOC	TCAs	$1,808		79.4% Response rate		
		SNRIs	$2,030	$223	76.6% Response rate	-2.8% Response rate	(Dominated)
		ACs	$2,051	$244	78.1% Response rate	-1.4% Response rate	(Dominated)
	MOH	TCAs	$380		49 PCDs		
		SNRIs	$448	$68	43 PCDs	-6 PCDs	(Dominated)
		ACs	$566	$187	46 PCDs	-3 PCDs	(Dominated)
	SOC	TCAs	$1,808		49 PCDs		
		SNRIs	$2,030	$223	43 PCDs	-6 PCDs	(Dominated)
		ACs	$2,051	$244	46 PCDs	-3 PCDs	(Dominated)

Table 13: One-Way Sensitivity Analysis Results for Analyses "From Placebo"							
Sensitivity Variable	**Perspective**	**Strategies**	**Cost**	**Incr Cost**	**Effectiveness**	**Incr Effectiveness**	**Incr C/E (ICER)**
30% Response Rate							
SNRIs=0.434	MOH	TCAs	$380		79.2% Response rate		
Lower limit		SNRIs	$453	$72	76.2% Response rate	-3.0% Response rate	(Dominated)
		ACs	$561	$181	77.6% Response rate	-1.6% Response rate	(Dominated)
	SOC	TCAs	$1,808		79.2% Response rate		
		SNRIs	$2,059	$251	76.2% Response rate	-3.0% Response rate	(Dominated)
		ACs	$2,064	$256	77.6% Response rate	-1.6% Response rate	(Dominated)
	MOH	TCAs	$380		49 PCDs		
		SNRIs	$453	$72	43 PCDs	-6 PCDs	(Dominated)
		ACs	$561	$181	46 PCDs	-3 PCDs	(Dominated)
	SOC	TCAs	$1,808		49 PCDs		
		SNRIs	$2,059	$251	43 PCDs	-6 PCDs	(Dominated)
		ACs	$2,064	$256	46 PCDs	-3 PCDs	(Dominated)
SNRIs=0.560	MOH	TCAs	$379		79.5% Response rate		
Upper limit		SNRIs	$443	$64	76.7% Response rate	-2.7% Response rate	(Dominated)
		ACs	$560	$181	78.0% Response rate	-1.5% Response rate	(Dominated)
	SOC	TCAs	$1,807		79.5% Response rate		
		SNRIs	$2,001	$194	76.7% Response rate	-2.7% Response rate	(Dominated)
		ACs	$2,062	$255	78.0% Response rate	-1.5% Response rate	(Dominated)
	MOH	TCAs	$379		49 PCDs		
		SNRIs	$443	$64	43 PCDs	-6 PCDs	(Dominated)
		ACs	$560	$181	46 PCDs	-3 PCDs	(Dominated)
	SOC	TCAs	$1,807		49 PCDs		
		SNRIs	$2,001	$194	43 PCDs	-6 PCDs	(Dominated)
		ACs	$2,062	$255	46 PCDs	-3 PCDs	(Dominated)
30% Response Rate							
TCAs=0.424	MOH	TCAs	$398		77.9% Response rate		
Lower limit		SNRIs	$450	$52	75.8% Response rate	-2.1% Response rate	(Dominated)
		ACs	$562	$164	77.2% Response rate	-0.7% Response rate	(Dominated)
	SOC	TCAs	$1,891		77.9% Response rate		
		SNRIs	$2,032	$142	75.8% Response rate	-2.1% Response rate	(Dominated)
		ACs	$2,065	$174	77.2% Response rate	-0.7% Response rate	(Dominated)
	MOH	TCAs	$398		48 PCDs		
		SNRIs	$450	$52	43 PCDs	-5 PCDs	(Dominated)
		ACs	$562	$164	46 PCDs	-3 PCDs	(Dominated)

Table 13: One-Way Sensitivity Analysis Results for Analyses "From Placebo"							
Sensitivity Variable	**Perspective**	**Strategies**	**Cost**	**Incr Cost**	**Effectiveness**	**Incr Effectiveness**	**Incr C/E (ICER)**
	SOC	TCAs	$1,891		48 PCDs		
		SNRIs	$2,032	$142	43 PCDs	-5 PCDs	(Dominated)
		ACs	$2,065	$174	46 PCDs	-3 PCDs	(Dominated)
TCAs=0.765	MOH	TCAs	$362		80.7% Response rate		
Upper limit		SNRIs	$446	$84	77.1% Response rate	-3.6% Response rate	(Dominated)
		ACs	$558	$197	78.3% Response rate	-2.3% Response rate	(Dominated)
	SOC	TCAs	$1,724		80.7% Response rate		
		SNRIs	$2,028	$304	77.1% Response rate	-3.6% Response rate	(Dominated)
		ACs	$2,061	$337	78.3% Response rate	-2.3% Response rate	(Dominated)
	MOH	TCAs	$362		49 PCDs		
		SNRIs	$446	$84	43 PCDs	-6 PCDs	(Dominated)
		ACs	$558	$197	46 PCDs	-3 PCDs	(Dominated)
	SOC	TCAs	$1,724		49 PCDs		
		SNRIs	$2,028	$304	43 PCDs	-6 PCDs	(Dominated)
		ACs	$2,061	$337	46 PCDs	-3 PCDs	(Dominated)
Medication Costs							
Maximum standard and maximum titration	MOH	TCAs	$389		79.3% Response rate		
		SNRIs	$452	$64	76.4% Response rate	-2.9% Response rate	(Dominated)
		ACs	$582	$193	77.8% Response rate	-1.5% Response rate	(Dominated)
	SOC	TCAs	$1,817		79.3% Response rate		
		SNRIs	$2,035	$218	76.4% Response rate	-2.9% Response rate	(Dominated)
		ACs	$2,085	$268	77.8% Response rate	-1.5% Response rate	(Dominated)
	MOH	TCAs	$389		49 PCDs		
		SNRIs	$452	$64	43 PCDs	-6 PCDs	(Dominated)
		ACs	$582	$193	46 PCDs	-3 PCDs	(Dominated)
	SOC	TCAs	$1,817		49 PCDs		
		SNRIs	$2,035	$218	43 PCDs	-6 PCDs	(Dominated)
		ACs	$2,085	$268	46 PCDs	-3 PCDs	(Dominated)
Maximum standard and minimum titration	MOH	TCAs	$368		79.3% Response rate		
		SNRIs	$433	$65	76.4% Response rate	-2.9% Response rate	(Dominated)
		ACs	$508	$139	77.8% Response rate	-1.5% Response rate	(Dominated)
	SOC	TCAs	$1,796		79.3% Response rate		
		ACs	$2,010	$214	77.8% Response rate	-1.5% Response rate	(Dominated)
		SNRIs	$2,015	$219	76.4% Response rate	-2.9% Response rate	(Dominated)
	MOH	TCAs	$368		49 PCDs		

Table 13: One-Way Sensitivity Analysis Results for Analyses "From Placebo"							
Sensitivity Variable	**Perspective**	**Strategies**	**Cost**	**Incr Cost**	**Effectiveness**	**Incr Effectiveness**	**Incr C/E (ICER)**
		SNRIs	$433	$65	43 PCDs	-6 PCDs	(Dominated)
		ACs	$508	$139	46 PCDs	-3 PCDs	(Dominated)
	SOC	TCAs	$1,796		49 PCDs		
		ACs	$2,010	$214	46 PCDs	-3 PCDs	(Dominated)
		SNRIs	$2,015	$219	43 PCDs	-6 PCDs	(Dominated)
Medication Costs							
Minimim standard and minimum titration	MOH	TCAs	$359		79.3% Response rate		
		SNRIs	$429	$69	76.4% Response rate	-2.9% Response rate	(Dominated)
		ACs	$486	$127	77.8% Response rate	-1.5% Response rate	(Dominated)
	SOC	TCAs	$1,787		79.3% Response rate		
		ACs	$1,988	$201	77.8% Response rate	-1.5% Response rate	(Dominated)
		SNRIs	$2,011	$224	76.4% Response rate	-2.9% Response rate	(Dominated)
	MOH	TCAs	$359		49 PCDs		
		SNRIs	$429	$69	43 PCDs	-6 PCDs	(Dominated)
		ACs	$486	$127	46 PCDs	-3 PCDs	(Dominated)
	SOC	TCAs	$1,787		49 PCDs		
		ACs	$1,988	$201	46 PCDs	-3 PCDs	(Dominated)
		SNRIs	$2,011	$224	43 PCDs	-6 PCDs	(Dominated)
SNRI Therapy							
Duloxetine costing	MOH	TCAs	$422		79.3% Response rate		
		ACs	$610	$187	77.8% Response rate	-1.5% Response rate	(Dominated)
		SNRIs	$860	$438	76.4% Response rate	-2.9% Response rate	(Dominated)
	SOC	TCAs	$1,850		79.3% Response rate		
		ACs	$2,112	$262	77.8% Response rate	-1.5% Response rate	(Dominated)
		SNRIs	$2,443	$592	76.4% Response rate	-2.9% Response rate	(Dominated)
	MOH	TCAs	$422		49 PCDs		
		ACs	$610	$187	46 PCDs	-3 PCDs	(Dominated)
		SNRIs	$860	$438	43 PCDs	-6 PCDs	(Dominated)
	SOC	TCAs	$1,850		49 PCDs		
		ACs	$2,112	$262	46 PCDs	-3 PCDs	(Dominated)
		SNRIs	$2,443	$592	43 PCDs	-6 PCDs	(Dominated)

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

Table 14: One-Way Sensitivity Results for "Through Placebo" Analyses							
Sensitivity Variable	**Perspective**	**Strategies**	**Cost**	**Incr Cost**	**Effectiveness**	**Incr Effectiveness**	**Incr C/E (ICER)**
50% Response Rate							
ACs=0.456	MOH	TCAs	$332		87.2% Response rate		
Lower limit		SNRIs	$462	$130	78.8% Response rate	-8.4% Response rate	(Dominated)
		ACs	$544	$212	81.4% Response rate	-5.9% Response rate	(Dominated)
	SOC	TCAs	$1,517		87.2% Response rate		
		ACs	$1,989	$472	81.4% Response rate	-5.9% Response rate	(Dominated)
		SNRIs	$2,136	$619	78.8% Response rate	-8.4% Response rate	(Dominated)
	MOH	TCAs	$332		60 PCDs		
		SNRIs	$462	$130	41 PCDs	-19 PCDs	(Dominated)
		ACs	$544	$212	49 PCDs	-11 PCDs	(Dominated)
	SOC	TCAs	$1,517		60 PCDs		
		ACs	$1,989	$472	49 PCDs	-11 PCDs	(Dominated)
		SNRIs	$2,136	$619	41 PCDs	-19 PCDs	(Dominated)
ACs=0.580	MOH	TCAs	$330		88.7% Response rate		
Upper limit		SNRIs	$456	$126	82.3% Response rate	-6.4% Response rate	(Dominated)
		ACs	$495	$165	87.1% Response rate	-1.6% Response rate	(Dominated)
	SOC	TCAs	$1,509		88.7% Response rate		
		ACs	$1,750	$241	87.1% Response rate	-1.6% Response rate	(Dominated)
		SNRIs	$2,113	$604	82.3% Response rate	-6.4% Response rate	(Dominated)
	MOH	TCAs	$330		60 PCDs		
		SNRIs	$456	$126	42 PCDs	-18 PCDs	(Dominated)
		ACs	$495	$165	58 PCDs	-2 PCDs	(Dominated)
	SOC	TCAs	$1,509		60 PCDs		
		ACs	$1,750	$241	58 PCDs	-2 PCDs	(Dominated)
		SNRIs	$2,113	$604	42 PCDs	-18 PCDs	(Dominated)
50% Response Rate							
SNRIs=0.290	MOH	TCAs	$331		87.4% Response rate		
Lower limit		SNRIs	$472	$141	78.7% Response rate	-8.7% Response rate	(Dominated)
		ACs	$520	$189	83.5% Response rate	-3.9% Response rate	(Dominated)
	SOC	TCAs	$1,515		87.4% Response rate		
		ACs	$1,872	$357	83.5% Response rate	-3.9% Response rate	(Dominated)

Table 14: One-Way Sensitivity Results for "Through Placebo" Analyses							
Sensitivity Variable	**Perspective**	**Strategies**	**Cost**	**Incr Cost**	**Effectiveness**	**Incr Effectiveness**	**Incr C/E (ICER)**
		SNRIs	$2,212	$697	78.7% Response rate	-8.7% Response rate	(Dominated)
	MOH	TCAs	$331		60 PCDs		
		SNRIs	$472	$141	38 PCDs	-22 PCDs	(Dominated)
		ACs	$520	$189	53 PCDs	-6 PCDs	(Dominated)
	SOC	TCAs	$1,515		60 PCDs		
		ACs	$1,872	$357	53 PCDs	-6 PCDs	(Dominated)
		SNRIs	$2,212	$697	38 PCDs	-22 PCDs	(Dominated)
SNRIs=0.381	MOH	TCAs	$330		88.6% Response rate		
Upper limit		SNRIs	$446	$116	82.4% Response rate	-6.1% Response rate	(Dominated)
		ACs	$518	$188	85.2% Response rate	-3.4% Response rate	(Dominated)
	SOC	TCAs	$1,510		88.6% Response rate		
		ACs	$1,863	$353	85.2% Response rate	-3.4% Response rate	(Dominated)
		SNRIs	$2,037	$526	82.4% Response rate	-6.1% Response rate	(Dominated)
	MOH	TCAs	$330		60 PCDs		
		SNRIs	$446	$116	45 PCDs	-15 PCDs	(Dominated)
		ACs	$518	$188	54 PCDs	-6 PCDs	(Dominated)
	SOC	TCAs	$1,510		60 PCDs		
		ACs	$1,863	$353	54 PCDs	-6 PCDs	(Dominated)
		SNRIs	$2,037	$526	45 PCDs	-15 PCDs	(Dominated)
50% Response Rate							
TCAs=0.474	MOH	TCAs	$367		81.4% Response rate		
Lower limit		SNRIs	$463	$96	77.0% Response rate	-4.4% Response rate	(Dominated)
		ACs	$521	$155	82.1% Response rate	0.8% Response rate	$20,458
	SOC	TCAs	$1,740		81.4% Response rate		
		ACs	$1,880	$141	82.1% Response rate	0.8% Response rate	$18,582
		SNRIs	$2,146	$266	77.0% Response rate	-5.1% Response rate	(Dominated)
	MOH	TCAs	$367		50 PCDs		
		SNRIs	$463	$96	40 PCDs	-10 PCDs	(Dominated)
		ACs	$521	$155	53 PCDs	3 PCDs	$52
	SOC	TCAs	$1,740		50 PCDs		

Table 14: One-Way Sensitivity Results for "Through Placebo" Analyses							
Sensitivity Variable	**Perspective**	**Strategies**	**Cost**	**Incr Cost**	**Effectiveness**	**Incr Effectiveness**	**Incr C/E (ICER)**
		ACs	$1,880	$141	53 PCDs	3 PCDs	$47
		SNRIs	$2,146	$266	40 PCDs	-13 PCDs	(Dominated)
TCAs=0.734	MOH	TCAs	$298		93.3% Response rate		
Upper limit		SNRIs	$455	$158	83.7% Response rate	-9.5% Response rate	(Dominated)
		ACs	$517	$220	86.3% Response rate	-7.0% Response rate	(Dominated)
	SOC	TCAs	$1,304		93.3% Response rate		
		ACs	$1,856	$551	86.3% Response rate	-7.0% Response rate	(Dominated)
		SNRIs	$2,103	$799	83.7% Response rate	-9.5% Response rate	(Dominated)
	MOH	TCAs	$298		69 PCDs		
		SNRIs	$455	$158	42 PCDs	-26 PCDs	(Dominated)
		ACs	$517	$220	54 PCDs	-15 PCDs	(Dominated)
	SOC	TCAs	$1,304		69 PCDs		
		ACs	$1,856	$551	54 PCDs	-15 PCDs	(Dominated)
		SNRIs	$2,103	$799	42 PCDs	-26 PCDs	(Dominated)
30% Response Rate							
ACs=0.463	MOH	TCAs	$331		87.9% Response rate		
Lower limit		SNRIs	$459	$128	80.2% Response rate	-7.6% Response rate	(Dominated)
		ACs	$511	$180	83.8% Response rate	-4.0% Response rate	(Dominated)
	SOC	TCAs	$1,513		87.9% Response rate		
		ACs	$1,884	$371	83.8% Response rate	-4.0% Response rate	(Dominated)
		SNRIs	$2,124	$612	80.2% Response rate	-7.6% Response rate	(Dominated)
	MOH	TCAs	$331		60 PCDs		
		SNRIs	$459	$128	41 PCDs	-19 PCDs	(Dominated)
		ACs	$511	$180	53 PCDs	-6 PCDs	(Dominated)
	SOC	TCAs	$1,513		60 PCDs		
		ACs	$1,884	$371	53 PCDs	-6 PCDs	(Dominated)
		SNRIs	$2,124	$612	41 PCDs	-19 PCDs	(Dominated)
ACs=0.607	MOH	TCAs	$331		88.1% Response rate		
Upper limit		SNRIs	$459	$128	81.0% Response rate	-7.1% Response rate	(Dominated)
		ACs	$527	$196	84.9% Response rate	-3.2% Response rate	(Dominated)
	SOC	TCAs	$1,513		88.1% Response rate		

Table 14: One-Way Sensitivity Results for "Through Placebo" Analyses							
Sensitivity Variable	**Perspective**	**Strategies**	**Cost**	**Incr Cost**	**Effectiveness**	**Incr Effectiveness**	**Incr C/E (ICER)**
		ACs	$1,852	$338	84.9% Response rate	-3.2% Response rate	(Dominated)
		SNRIs	$2,125	$612	81.0% Response rate	-7.1% Response rate	(Dominated)
	MOH	TCAs	$331		60 PCDs		
		SNRIs	$459	$128	41 PCDs	-19 PCDs	(Dominated)
		ACs	$527	$196	54 PCDs	-6 PCDs	(Dominated)
	SOC	TCAs	$1,513		60 PCDs		
		ACs	$1,852	$338	54 PCDs	-6 PCDs	(Dominated)
		SNRIs	$2,125	$612	41 PCDs	-19 PCDs	(Dominated)
30% Response Rate							
SNRIs=0.363	MOH	TCAs	$331		87.9% Response rate		
Lower limit		SNRIs	$462	$131	80.6% Response rate	-7.3% Response rate	(Dominated)
		ACs	$520	$188	84.2% Response rate	-3.7% Response rate	(Dominated)
	SOC	TCAs	$1,513		87.9% Response rate		
		ACs	$1,868	$355	84.2% Response rate	-3.7% Response rate	(Dominated)
		SNRIs	$2,142	$629	80.6% Response rate	-7.3% Response rate	(Dominated)
	MOH	TCAs	$331		60 PCDs		
		SNRIs	$462	$131	42 PCDs	-18 PCDs	(Dominated)
		ACs	$520	$188	54 PCDs	-6 PCDs	(Dominated)
	SOC	TCAs	$1,513		60 PCDs		
		ACs	$1,868	$355	54 PCDs	-6 PCDs	(Dominated)
		SNRIs	$2,142	$629	42 PCDs	-18 PCDs	(Dominated)
SNRIs=0.449	MOH	TCAs	$331		88.0% Response rate		
Upper limit		SNRIs	$457	$126	80.6% Response rate	-7.4% Response rate	(Dominated)
		ACs	$519	$188	84.4% Response rate	-3.6% Response rate	(Dominated)
	SOC	TCAs	$1,513		88.0% Response rate		
		ACs	$1,867	$355	84.4% Response rate	-3.6% Response rate	(Dominated)
		SNRIs	$2,107	$595	80.6% Response rate	-7.4% Response rate	(Dominated)
	MOH	TCAs	$331		60 PCDs		
		SNRIs	$457	$126	41 PCDs	-19 PCDs	(Dominated)
		ACs	$519	$188	54 PCDs	-6 PCDs	(Dominated)
	SOC	TCAs	$1,513		60 PCDs		

Table 14: One-Way Sensitivity Results for "Through Placebo" Analyses							
Sensitivity Variable	**Perspective**	**Strategies**	**Cost**	**Incr Cost**	**Effectiveness**	**Incr Effectiveness**	**Incr C/E (ICER)**
		ACs	$1,867	$355	54 PCDs	-6 PCDs	(Dominated)
		SNRIs	$2,107	$595	41 PCDs	-19 PCDs	(Dominated)
30% Response Rate							
TCAs=0.544	MOH	TCAs	$342		86.8% Response rate		
Lower limit		SNRIs	$461	$119	80.0% Response rate	-6.8% Response rate	(Dominated)
		ACs	$520	$178	84.0% Response rate	-2.8% Response rate	(Dominated)
	SOC	TCAs	$1,564		86.8% Response rate		
		ACs	$1,869	$304	84.0% Response rate	-2.8% Response rate	(Dominated)
		SNRIs	$2,126	$562	80.0% Response rate	-6.8% Response rate	(Dominated)
	MOH	TCAs	$342		59 PCDs		
		SNRIs	$461	$119	41 PCDs	-18 PCDs	(Dominated)
		ACs	$520	$178	54 PCDs	-6 PCDs	(Dominated)
	SOC	TCAs	$1,564		59 PCDs		
		ACs	$1,869	$304	54 PCDs	-6 PCDs	(Dominated)
		SNRIs	$2,126	$562	41 PCDs	-18 PCDs	(Dominated)
TCAs=0.803	MOH	TCAs	$320		89.2% Response rate		
Upper limit		SNRIs	$458	$137	81.2% Response rate	-8.0% Response rate	(Dominated)
		ACs	$518	$198	84.7% Response rate	-4.5% Response rate	(Dominated)
	SOC	TCAs	$1,462		89.2% Response rate		
		ACs	$1,867	$405	84.7% Response rate	-4.5% Response rate	(Dominated)
		SNRIs	$2,123	$661	81.2% Response rate	-8.0% Response rate	(Dominated)
	MOH	TCAs	$320		60 PCDs		
		SNRIs	$458	$137	41 PCDs	-19 PCDs	(Dominated)
		ACs	$518	$198	54 PCDs	-7 PCDs	(Dominated)
	SOC	TCAs	$1,462		60 PCDs		
		ACs	$1,867	$405	54 PCDs	-7 PCDs	(Dominated)
		SNRIs	$2,123	$661	41 PCDs	-19 PCDs	(Dominated)
Medication Costs							
Maximum standard and maximum	MOH	TCAs	$340		88.0% Response rate		
		SNRIs	$465	$125	80.6% Response rate	-7.4% Response rate	(Dominated)
		ACs	$543	$203	84.3% Response rate	-3.6% Response rate	(Dominated)

Table 14: One-Way Sensitivity Results for "Through Placebo" Analyses							
Sensitivity Variable	**Perspective**	**Strategies**	**Cost**	**Incr Cost**	**Effectiveness**	**Incr Effectiveness**	**Incr C/E (ICER)**
titration	SOC	TCAs	$1,522		88.0% Response rate		
		ACs	$1,892	$370	84.3% Response rate	-3.6% Response rate	(Dominated)
		SNRIs	$2,131	$608	80.6% Response rate	-7.4% Response rate	(Dominated)
	MOH	TCAs	$340		60 PCDs		
		SNRIs	$465	$125	41 PCDs	-19 PCDs	(Dominated)
		ACs	$543	$203	54 PCDs	-6 PCDs	(Dominated)
	SOC	TCAs	$1,522		60 PCDs		
		ACs	$1,892	$370	54 PCDs	-6 PCDs	(Dominated)
		SNRIs	$2,131	$608	41 PCDs	-19 PCDs	(Dominated)
Maximum standard and minimum titration	MOH	TCAs	$325		88.0% Response rate		
		SNRIs	$447	$122	80.6% Response rate	-7.4% Response rate	(Dominated)
		ACs	$482	$157	84.3% Response rate	-3.6% Response rate	(Dominated)
	SOC	TCAs	$1,507		88.0% Response rate		
		ACs	$1,831	$324	84.3% Response rate	-3.6% Response rate	(Dominated)
		SNRIs	$2,112	$606	80.6% Response rate	-7.4% Response rate	(Dominated)
	MOH	TCAs	$325		60 PCDs		
		SNRIs	$447	$122	41 PCDs	-19 PCDs	(Dominated)
		ACs	$482	$157	54 PCDs	-6 PCDs	(Dominated)
	SOC	TCAs	$1,507		60 PCDs		
		ACs	$1,831	$324	54 PCDs	-6 PCDs	(Dominated)
		SNRIs	$2,112	$606	41 PCDs	-19 PCDs	(Dominated)
Medication Costs							
Minimum standard and minimum titration	MOH	TCAs	$315		88.0% Response rate		
		SNRIs	$441	$126	80.6% Response rate	-7.4% Response rate	(Dominated)
		ACs	$458	$143	84.3% Response rate	-3.6% Response rate	(Dominated)
	SOC	TCAs	$1,497		88.0% Response rate		
		ACs	$1,807	$309	84.3% Response rate	-3.6% Response rate	(Dominated)
		SNRIs	$2,107	$609	80.6% Response rate	-7.4% Response rate	(Dominated)
	MOH	TCAs	$315		60 PCDs		
		SNRIs	$441	$126	41 PCDs	-19 PCDs	(Dominated)
		ACs	$458	$143	54 PCDs	-6 PCDs	(Dominated)

Table 14: One-Way Sensitivity Results for "Through Placebo" Analyses							
Sensitivity Variable	**Perspective**	**Strategies**	**Cost**	**Incr Cost**	**Effectiveness**	**Incr Effectiveness**	**Incr C/E (ICER)**
	SOC	TCAs	$1,497		60 PCDs		
		ACs	$1,807	$309	54 PCDs	-6 PCDs	(Dominated)
		SNRIs	$2,107	$609	41 PCDs	-19 PCDs	(Dominated)
SNRI Therapy							
Duloxetine costing	MOH	TCAs	$355		88.0% Response rate		
		ACs	$557	$202	84.3% Response rate	-3.6% Response rate	(Dominated)
		SNRIs	$839	$484	80.6% Response rate	-7.4% Response rate	(Dominated)
	SOC	TCAs	$1,537		88.0% Response rate		
		ACs	$1,906	$369	84.3% Response rate	-3.6% Response rate	(Dominated)
		SNRIs	$2,504	$967	80.6% Response rate	-7.4% Response rate	(Dominated)
	MOH	TCAs	$355		60 PCDs		
		ACs	$557	$202	54 PCDs	-6 PCDs	(Dominated)
		SNRIs	$839	$484	41 PCDs	-19 PCDs	(Dominated)
	SOC	TCAs	$1,537		60 PCDs		
		ACs	$1,906	$369	54 PCDs	-6 PCDs	(Dominated)
		SNRIs	$2,504	$967	41 PCDs	-19 PCDs	(Dominated)

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

Table 15: Parameters for Monte Carlo Simulations for Base-Case Analyses (adjusted for placebo response) and Alternative Analyses ("single arm")					
Parameter	**Variable**	**Distribution**	**Value (Probability)**		
			Value 1	**Value 2**	**Value 3**
Drug Cost					
Standard Dose	ACs	Discrete	$1.04 (1/3)	$1.18 (1/3)	$1.31 (1/3)
	SNRIs	Discrete	$0.62 (1/3)	$0.62 (1/3)	$0.62 (1/3)
	TCAs	Discrete	$0.24 (1/3)	$0.28 (1/3)	$0.32 (1/3)
Titration Dose	ACs	Discrete	$2.82 (1/3)	$4.20 (1/3)	$5.58 (1/3)
	SNRIs	Discrete	$1.12 (1/3)	$1.36 (1/3)	$1.60 (1/3)
	TCAs	Discrete	$0.47 (1/3)	$0.76 (1/3)	$1.06 (1/3)
Response Rate					
"From Placebo"			Minimum	Midpoint	Maximum
Full Response	ACs	Uniform	0.383	0.423	0.463
	SNRIs	Uniform	0.331	0.383	0.435
	TCAs	Uniform	0.328	0.460	0.592
Partial Response	ACs	Uniform	0.499	0.544	0.590
	SNRIs	Uniform	0.434	0.497	0.560
	TCAs	Uniform	0.424	0.594	0.765
Response Rate					
"Through Placebo"			Minimum	Midpoint	Maximum
Full Response	ACs	Uniform	0.456	0.518	0.580
	SNRIs	Uniform	0.290	0.335	0.381
	TCAs	Uniform	0.474	0.604	0.734
Partial Response	ACs	Uniform	0.463	0.535	0.607
	SNRIs	Uniform	0.363	0.406	0.449
	TCAs	Uniform	0.544	0.674	0.803
Response Rate					
"Single Arm" (unadjusted)			Minimum	Midpoint	Maximum
Full Response	ACs	Uniform	0.301	0.363	0.425
	SNRIs	Uniform	0.413	0.459	0.504
	TCAs	Uniform	0.237	0.323	0.408
Partial Response	ACs	Uniform	0.473	0.545	0.617
	SNRIs	Uniform	0.617	0.660	0.704
	TCAs	Uniform	0.363	0.492	0.622

ACs=anticonvulsants; SNRIs=serotonin-norepinephrine reuptake inhibitors; TCAs=tricyclic antidepressants.

In three scenarios, the model was sensitive to changes in parameter values. First in the "from placebo" analyses, when the upper level of the 95% CI was applied to the efficacy of ACs, this class of medications ceased being dominated. Instead, it displayed incremental cost-effectiveness ratios of $941 per 1% response in the ministry of health perspective and $1,021 in the societal perspective. SNRIs remained dominated by the TCAs. Second, in the "from placebo" analyses,

when the lower level of the 95% CI was applied to the efficacy of TCAs, they ceased being dominant over the other two classes while remaining the alternative with the lowest cost and lowest efficacy from the ministry of health perspective. They were dominated by the SNRIs in the societal perspective. The results changed in the third scenario when the lower level of the 95% CI was applied to the efficacy of TCAs in the "through placebo" analysis. In this sensitivity analysis, TCAs remained dominant over SNRIs but no longer over ACs, which displayed incremental cost-effectiveness ratios in the range of $18,000 to $21,000 per 1% response and per pain controlled year.

Three Monte Carlo simulation probability sensitivity analyses were conducted. A total of 10,000 iterations were done to ensure that an adequate testing of the parameters was achieved. The variables tested, the presumed shape of their distributions, and the range of values over which they were tested were described (Table 15). Two simulations were adjusted for the placebo effect, using "from placebo" and "through placebo" corrections. The third simulation used absolute "single arm" response rates across drug classes that were unadjusted for placebo effect.

Using the "from placebo" adjustment, TCAs dominated SNRIs and ACs (Table 16). Similar results were observed using the "through placebo" adjustment (Table 17).

Table 16: Monte Carlo Simulation Results for "From Placebo" Response Rate Adjustment

Perspective	Strategy	Mean Cost (SD)	Mean Outcome (SD)	Incr C/E (ICER)
MOH	TCAs	$374 ($25)	79.1% (4.5%) Response rate	
	SNRIs	$441 ($11)	76.4% (2.7%) response rate	(Dominated)
	ACs	$534 ($32)	77.7% (2.3%) Response rate	(Dominated)
SOC	TCAs	$1,806 ($150)	79.1% (4.5%) Response rate	
	SNRIs	$2,023 ($62)	76.4% (2.7%) Response rate	(Dominated)
	ACs	$2,036 ($56)	77.7% (2.3%) Response rate	(Dominated)
MOH	TCAs	$374 ($25)	48 (6) PCDs	
	SNRIs	$441 ($11)	43 (2) PCDs	(Dominated)
	ACs	$534 ($32)	46 (2) PCDs	(Dominated)
SOC	TCAs	$1,806 ($150)	48 (6) PCDs	
	SNRIs	$2,023 ($62)	43 (2) PCDs	(Dominated)
	ACs	$2,036 ($56)	46 (2) PCDs	(Dominated)

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

Table 17: Monte Carlo Simulation Results for "Through Placebo" Response Rate Adjustment				
Perspective	**Strategy**	**Mean Cost (SD)**	**Mean Outcome (SD)**	**Incr C/E (ICER)**
MOH	TCAs	$328 ($21)	87.7% (3.5%) Response rate	
	SNRIs	$453 ($10)	80.5% (2.5%) Response rate	(Dominated)
	ACs	$500 ($29)	84.3% (2.1%) Response rate	(Dominated)
SOC	TCAs	$1,515 ($128)	87.7% (3.5%) Response rate	
	ACs	$1,849 ($73)	84.3% (2.1%) Response rate	(Dominated)
	SNRIs	$2,118 ($54)	80.5% (2.5%) Response rate	(Dominated)
MOH	TCAs	$328 ($21)	60 (5) PCDs	
	SNRIs	$453 ($10)	41 (2) PCDs	(Dominated)
	ACs	$500 ($29)	54 (3) PCDs	(Dominated)
SOC	TCAs	$1,515 ($128)	60 (5) PCDs	
	ACs	$1,849 ($73)	54 (3) PCDs	(Dominated)
	SNRIs	$2,118 ($54)	41 (2) PCDs	(Dominated)

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

The results of the Monte Carlo analysis for the alternative analyses ("single arm" non-adjusted response rates) are presented in Table 0-5 in Appendix L. SNRIs were dominant over TCAs and ACs in all analyses.

The last sensitivity analysis examined the hypothetical scenario without the availability of TCAs (based on the lack of trials reporting 50% response) (Table 18).

In the "from placebo" analyses, SNRIs were less costly and less effective than ACs, yielding incremental cost-effectiveness ratios for ACs (over the SNRIs) of about $6,000 per 1% response from the societal perspective to about $26,000 from the ministry of health perspective, and from about $3,000 per pain controlled year (societal perspective) to about $13,000 per pain controlled year (ministry of health perspective).

In the "through placebo" analyses, the results were mixed with the SNRIs being dominated in analyses from the societal perspective.

f) Subgroup analysis

No subgroup analyses were performed, because there was insufficient information in the literature.

Table 18: Sensitivity Analyses: ACs and SNRIs as Therapies without TCAs as Backup Treatment							
Calculation	**Perspective**	**Strategies**	**Cost**	**Incremental Cost**	**Effectiveness**	**Incremental Effectiveness**	**Incremental C/E (ICER)**
Indirect from placebo*	MOH	SNRIs	$469		75.3% Response rate		
		ACs	$568	$99	75.7% Response rate	0.4% Response rate	$25,770
	SOC	SNRIs	$2,055		75.3% Response rate		
		ACs	$2,078	$23	75.7% Response rate	0.4% Response rate	$5,883
	MOH	SNRIs	$469		43 PCDs		
		ACs	$568	$99	45 PCDs	3 PCDs	$36
	SOC	SNRIs	$2,055		43 PCDs		
		ACs	$2,078	$23	45 PCDs	3 PCDs	$8
Indirect through placebo†	MOH	SNRIs	$487		77.6% Response rate		
		ACs	$531	$44	78.9% Response rate	1.3% Response rate	$3,473
	SOC	ACs	$1,900		78.9% Response rate		
		SNRIs	$2,164	$263	77.6% Response rate	-1.3% Response rate	(Dominated)
	MOH	SNRIs	$487		41 PCDs		
		ACs	$531	$44	52 PCDs	12 PCDs	$4
	SOC	ACs	$1,900		52 PCDs		
		SNRIs	$2,164	$263	41 PCDs	-12 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 adjusted rate for each drug.
†Success rates were calculated in same way, but 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; SOC=society; SNRIs=serotonin-norepinephrine reuptake inhibitors; TCAs=tricyclic antidepressants.

5.2.3 Discussion

a) Clinical review

In our clinical review, TCAs had the highest success rates for both outcomes in all analyses. SNRIs were always lowest. In the analyses through placebo (using rate differences), all the 95% CIs overlapped, suggesting that there was no difference between groups. In the analyses through placebos (using rate ratios), the 95% CIs for SNRIs were below the lower limits of other drugs, suggesting that those differences may be significant. The data were sparse for TCAs, so firm conclusions could not be drawn at this time.

We calculated the NNT for each drug class and each binary outcome (success or fail). In the head-to-head trials against placebo for 50% pain reduction, the NNTs were 5.0 for ACs and 6.0 for SNRIs. In the SNRI group, the NNT was 6.0 for duloxetine and 9.0 for venlafaxine. The placebo rate was 27% across the duloxetine studies and 33.8% across the venlafaxine studies, which accounts for the discrepancy between the NNTs. For 30% pain reduction, NNTs were 3.0 for TCAs, 4.0 for ACs, and 5.0 for SNRIs (duloxetine and venlafaxine were equal; both NNTs were 5.0). When the rates were adjusted through placebo (Appendix Table 0-4), NNTs for 50% pain reduction were 3.9 for TCAs, 4.6 for ACs, and 5.7 for SNRIs. For 30% pain reduction, NNTs were 3.0 for TCAs, 3.5 for ACs, and 4.2 for SNRIs.

The clinical review is consistent with current guidelines that suggest the lowest NNT across drug classes can be achieved with the use of TCAs, and the highest NNT with SNRIs. Although the mechanism of TCAs in managing pain is unknown, this class of drugs exhibits analgesic properties that are independent of the antidepressant effects. The magnitude of the estimates in our review differ from those presented in previous guidelines, because different trials were considered.[12]

Our clinical review has several limitations. One limitation is the range of therapies that was reviewed, mainly due to the limited evidence in the literature for some medications. Our review did not examine the evidence for topical lidocaine, tramadol, or other opioid analgesics, which are recommended in current guidance. Lidocaine is recommended as second-line therapy and is most useful for patients with localized peripheral neuropathic pain. The 5% lidocaine patch has an NNT of 4.4.[12] The guidelines suggest that high quality evidence exists to support the claim that tramadol is beneficial in managing painful diabetic neuropathy. It has an estimated NNT of 3.9 and has been recommended as a third-line therapy. Tramadol exhibits similar properties to those of the TCAs, it but produces less constipation and nausea than other weak opioid analgesics. The NNT for morphine and oxycodone was approximately 2.5.[12]

Other drugs that are not considered in this review include fourth-line treatments such as cannabinoids, methadone, selected SSRIs (citalopram and paroxetine), lamotrigine, mexiletine, and clonidine. The evidence for managing neuropathic pain, however, is not considered to be robust. Some evidence exists for botulinum toxin.

Another limitation of this study is the inconsistency of the meta-analysis results depending on the analytic approach that was adopted. In conducting this evidence synthesis, we used a comparison method based on adjustment “from placebo” (differences from placebo), a method based on

adjustment "through placebo" (relative to the placebo response), and an unadjusted indirect comparison method.

b) Economic evaluation

The base-case analyses included those based on the "from placebo" and "through placebo" approaches, from the ministry of health and societal perspectives. In the "from placebo" analysis, the TCAs group had the highest expected overall 50% clinical response (79.3%), followed by the ACs (77.8%) and SNRIs (76.4%) groups. These average expected clinical response rates were similar, possibly because of the backup therapies that were used. Therefore, results reflect a treatment strategy that starts with each of the three drug classes, but does not exclude the other drugs from being used as backup treatments. TCAs also produced the most PCDs (49), followed by ACs (46) and SNRIs (43).

The expected cost per patient treated from the ministry of health perspective of $380 was lowest with TCAs, whereas SNRIs were next with a cost of $448 and ACs were highest at $560. From the societal perspective, TCAs had the lowest expected cost per patient treated of $1,808, SNRIs were second at $2,030, and ACs were most costly at $2,063. In all "from placebo" analyses, TCAs were dominant over the ACs and the SNRIs.

In the "through placebo" analysis, the TCAs group had the highest expected overall 50% clinical response (88.0%), followed by the ACs (84.3%) and SNRIs (90.6%) groups. These average expected clinical response rates were similar, possibly because of the backup therapies that were used. Therefore, the results reflect a treatment strategy that starts with each of the three drug classes but does not exclude the other drugs from being used as backup treatments. TCAs also produced the most PCDs (60), followed by ACs (54) and SNRIs (41).

When costs were considered, the expected cost per patient treated from the ministry of health perspective of $331 was lowest with TCAs, whereas SNRIs were next with a cost of $459 and ACs were highest at $519. From the societal perspective, TCAs had the lowest expected cost per patient treated of $1,513, SNRIs were second at $1,868, and ACs were most costly at $2,125. In all "through placebo" analyses, TCAs were dominant over the ACs and the SNRIs.

In the analyses that used unadjusted "single arm" rates, SNRIs displayed the lowest cost and the highest effectiveness, resulting in dominance over the other two classes (ACs and TCAs). ACs had the highest costs in most of the analyses, whereas TCAs had the lowest costs in most analyses.

The robustness of the results was confirmed in one-way sensitivity analyses. There were few changes from the corresponding base-case results (relative to the approach adopted). This indicated that, based on the assumptions of the model, there was confidence in the findings. Monte Carlo simulation results confirmed the direction of the base-case results, with TCAs dominating over SNRIs and ACs in analyses adopting adjusted efficacy rates relative to placebo, and SNRIs being dominant in analyses using unadjusted rates.

In the sensitivity analysis based on the model structure (elimination of TCAs from the analysis), SNRIs displayed the lowest cost and lowest efficacy from most analyses, except in the "through placebo" analyses from the societal perspective, in which SNRIs were dominated by ACs.

c) Research design

This analysis may be called a cost-efficacy study, because we used efficacy rates from randomized controlled clinical trials. We assumed full compliance, which may not be reasonable in several cases, considering the problem being studied. We did not try to model effectiveness, mainly because of the lack of reliable data. More research on a linked database to track actual patients in real life could be done to determine how accurately we reflected the everyday treatment of patients.

We used a time horizon of 18 weeks, which was common to the clinical trials, and then projected it to a year. Events could change from that point, but this would not create a selective bias for or against any class of drugs.

d) Limitations

One limitation is the less than ideal outcomes that were used. A 50% reduction in pain is less than complete, so eliminating pain would require interventions in addition to the classes of drugs being studied in this report. Thus, our results underestimate the cost of eliminating chronic pain (if that were possible). We did not account for the costs incurred by those patients who remained unsuccessfully treated at the end of the time horizon. They seem to constitute a small proportion of the population.

Another limitation is that the literature is limited on this topic. Although the number of patients was high for ACs and SNRIs, the sample for TCAs was only 305. Such values give wide CIs. This imprecision introduces doubt into the validity of sensitivity analyses that use the 95% CI.

Few studies examine the effect of drugs that are used as second- or third-line treatments. In the absence of data, we assumed that the success rates for drugs was the same when used as backup as when they were used as primary therapy. This may have produced an overestimation for all clinical response rates, because it is unknown whether resistance to treatment is shared across drug classes. If so, then success rates have been overestimated and costs have been underestimated. On the other hand, the average quality score was 81% (SD=21%). Nonetheless, more high-quality studies are needed.

The use of a class approach could be misleading. The combination of data increases the sample size, and hence, the power. It assumes, however, that all drugs in a class are comparable with respect to efficacy and safety. This may be true, depending on the drugs. In this study, most of the anticonvulsant data were obtained from studies of pregabalin, with some from studies of gabapentin. On the other hand, it may not be possible to extrapolate these results to other (untested) anticonvulsants. In the case of SNRIs, duloxetine and venlafaxine had an identical success rate of 66% for 30% pain reduction and varied by 1% (46.1% versus 45.1%) for 50% pain reduction. Therefore, the results of this study should be interpreted cautiously.

Another issue is the different designs that may be used in primary research. For example, Siddall et al.[111] allowed patients to remain on their current treatment regimen, which included SNRIs, TCAs, or opioids. Thus, it was different from other studies. One might have expected its success rates to have been higher because of possible potentiation, but it had a lower success rate. When it was removed for the meta-analysis, the overall rate increased from 36.3% to 37.5%.

There was a lack of data in the literature. We assumed that patients having a partial response would be titrated to a higher drug dose, and patients with an ineffective response or who did not tolerate treatment were switched to another agent from another class. Then, another six weeks of titration or new drug therapy and a second clinical assessment would be conducted to verify the presence of a full response. Some drugs, such as duloxetine, however, may not generate further successes after a dose increase. According to the Canadian monograph for Cymbalta,[156] it has not been established that there would be additional benefit above 60 mg/day. There is evidence that some people may benefit from higher doses. The product monograph for duloxetine that has been made available by the Veterans Affairs system in the US lists the results of three randomized controlled trials done on patients with neuropathic pain.[157] The controlled clinical trial results (response rates, decreases in VAS scores) for 120 mg of duloxetine were numerically superior to those of 60 mg duloxetine. Therefore, improvements may occur. To assess this uncertainty, we conducted a sensitivity analysis. No changes occurred.

Since this project began, other (possibly relevant) publications have been brought to our attention. Because they were identified so late in the process, they could not be included.[158] Nonetheless, they may contain valuable information.

6 BUDGET IMPACT ANALYSIS

In this pharmacoeconomic analysis, TCAs dominated the SNRIs and the ACs from the ministry of health perspective. Thus, the base assumption is that patients should be started on TCAs. If we were to use the other classes of drugs, there would be an increase in expenditure for the ministry of health and society.

If we consider that the population of Canada is 25.3 million adults (StatCan) and the prevalence of neuropathic pain sufferers is 1% as in the UK, then there are approximately 250,000 adults in Canada who experience neuropathic pain.

For the ministry of health, TCAs would cost $331 per patient for the 18 weeks of treatment (from the "through placebo" analysis) or $956 per patient per year, for a total of $214 million for the population (assuming that all patients were covered). If the government pays for half of the patients (a realistic estimate in Canada), it would cost approximately $107 million overall.

If all patients were switched from TCAs to SNRIs, the cost per patient to the ministry of health would increase by $128 to $459 per patient or $1,326 per patient per year (an increase of $370 per patient per year). It would then cost $332 million in total or an overall increase in cost of $118 million. If the ministry of health pays half of this amount, then the ministry of health would pay $56 million more.

If only the drug cost of venlafaxine is considered (at minimum titration doses), it would increase by $135 per patient per year, for a total increase of $34 million. If the ministry of health paid for half of this amount, it would be about $17 million. If all patients were switched from TCAs to duloxetine, the daily drug cost per patient would increase by $3.76 or annually by more than

$343 million for Canada. If the ministry of health pays half, then the impact would be $171 million for Canada.

If all patients were switched to ACs, the cost would be $519 per patient over the 18 weeks or an increase of $188 ($1,499 per year per patient or an increase of $543 per year). The total cost would be $375 million or an increase of $136 million over TCAs. If the ministry of health share were 50%, they would incur an extra $69 million per year in costs. Considering the dug cost alone with a minimum standard dose, the increase would amount to $289 per patient per year or $72 million ($36 million for a 50% share by the ministry of health).

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 NNTs 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.

This analysis only examines a treatment decision when all three classes of drugs are equally viable options for an individual patient. The clinical treatment of neuropathic pain needs to consider the needs of the individual and requires balancing optimal pain relief (number needed to treat) with minimizing medication adverse effects (number needed to harm). This analysis does not apply to situations where first-line treatment with any one of these classes of drugs, such as a TCA, is not a realistic approach.

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Appendix A: Inclusion/exclusion criteria for clinical abstracts

Ref#: **Reviewer's Initials:** **Accept / Reject**

Exclusion criteria for clinical study abstracts:

1. **Is the study designed as a double-blinded randomized clinical trial?**
   - ☐ YES
   - ☐ NO (if not – the study is excluded)

2. **Is the population included in the study 18 years of age and/or older?**
   - ☐ YES
   - ☐ NO (if not – the study is excluded)

3. **Is one or more of the included drugs mentioned in the abstract?**
   - ☐ YES (if yes, please indicate which one by checking the box beside each mentioned drug)
   - ☐ NO (if not – the study is exclude)

   ☐ **Anticonvulsant drugs**
   - ☐ pregabalin
   - ☐ gabapentin

   ☐ **SNRI**
   - ☐ venlafaxine
   - ☐ milnacipran
   - ☐ duloxetine

   ☐ **Tricyclic antidepressants**
   - ☐ amitriptyline
   - ☐ clomipramine
   - ☐ nortriptyline
   - ☐ imipramine
   - ☐ maprotiline

4. **Is the following indication mentioned in the abstract?**
   - ☐ YES (if yes, please indicate which one by checking the box beside the mentioned indication)
   - ☐ NO (if not – the study is excluded)

     ☐ **Neuropathic pain**

Appendix B: EMBASE literature search strategy

Database: EMBASE <1980 to 2007 Week 07>
Search Strategy:
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1 anticonvulsive agent/ or carbamazepine/ or 298-46-4.rn. or 8047-84-5.rn. or (carbamazepin: or Amizepin: or Atretol or Biston or Calepsin or Carbategral or Carbatrol or Convuline or Epimax or Epitol or Equetro or Finlepsin or "G 32883" or G32883 or Lexin or Mazepine or Neurotol or Neurotop or Servimazepin or Sirtal or Tegral or Tegretal or Tegretol or Tegrital or Telesmin or Teril or Timonil).mp. (48485)
2 gabapentin/ or 60142-96-3.rn. or (gabapentin: or "Ci 945" or Ci945 or "Go 3450" or Go3450 or "Goe 3450" or Goe3450 or Neurontin:).mp. (8591)
3 Lamotrigine/ or 84057-84-1.rn. or (Lamotrigine or "Bw 430c:" or Bw430c: or Labileno or Lamictal).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (7472)
4 etiracetam/ or 102767-28-2.rn. or 33996-58-6.rn. or (Etiracetam or Levetiracetam or Etirazetam or Keppra or "Lo 59" or Lo59 or "Ucb 6474" or Ucb6474 or "Ucb L059" or "ucb l 059" or ucbl059).mp. (2049)
5 oxcarbazepine/ or 28721-07-5.rn. or (oxcarbazepine or Apydan or "GP 47680" or GP47680 or Oxocarbazepine or Timox or Trileptal).mp. (2787)
6 pregabalin/ or 148553-50-8.rn. or (pregabalin or "Ci 1008" or Ci1008 or Lyrica or "Pd 144723" or Pd144723).mp. (844)
7 topiramate/ or 97240-79-4.rn. or (topiramate or Epitomax or "MCN 4853" or MCN4853 or "Rwj 17021:" or Rwj17021: or Topamax or Topimax).mp. (5261)
8 Harkoseride/ or 175481-36-4.rn. or (Harkoseride or Lacosamide or "Add 234037" or Add234037 or Erlosamide or "Spm 927" or Spm927).mp. (55)
9 valproic acid/ or valproic acid derivative/ or 1069-66-5.rn. or 99-66-1.rn. or ((valproic adj2 acid) or "Abbott 44090" or Abbott44090 or (Alpha adj2 Propylvalerate) or (Alpha adj2 Propylvaleric) or Apilepsin or Convulex or Depacon or Depakene or Depakin: or Deprakine or "Di N Propylacet:" or DiNPropylacet: or Dipropylacetate or Dipropylacetatic or (Dipropyl adj2 Acetic) or Dipropylacetic or Diprosin or Epilim or Epival or Ergenyl or Everiden or Goilim or "Kw 6066 N" or Kw6066N or Labazene or Leptilan or Leptilanil or Mylproin or (Myproic adj2 Acid) or "N Dipropylacetic Acid" or (Dipropylacetic adj2 Acid) or Orfiril or Orlept or "2 Propylpentanoate" or 2Propylpentanoate or "2 Propylpentanoic Acid" or "2 Propylvalerate Sodium" or "2 Propylvaleric Acid" or Propymal or (Sodium adj2 Valproate) or Valerin or Valparin or Valpro or Valproate or Vupral).mp. (25610)
10 or/1-9 (64697)
11 serotonin uptake inhibitors/ or citalopram/ or 59729-33-8.rn. or (Citalopram or Celexa or Cipramil or Cytalopram or Elopram or "Lu 10 171" or "Lu 10171" or Lu10171 or Nitalapram or Sepram or Seropram or "Zd 211" or Zd211).mp. (23182)
12 escitalopram/ or (escitalopram or Cipralex or Lexapro or "Lu 26054 0" or "Lu 260540" or Lu260540).mp. (1077)
13 fluoxetine/ or 54910-89-3.rn. or (fluoxetine or "Compound 110140" or Compound110140 or Fluctin: or Flunirin or Fluoxifar or "Lilly 110140" or Lilly110140 or Lovan or "Ly 110140" or Ly110140 or Prosac or Prozac or Prozamin or Sarafem).mp. (21457)

14 fluvoxamine/ or 54739-18-3.rn. or (fluvoxamine or "Du 23000" or Du23000 or Dumirox or Fluroxamine).mp. (7550)
15 paroxetine/ or 61869-08-7.rn. or (paroxetine or Aropax or "Brl 29060:" or Brl29060: or Deroxat or Dexorat or "Fg 7051" or Fg7051 or Motivan or Paroxetine or Paxil or Pexeva or Seroxat or "Si 211103" or Si211103 or Tagonis).mp. (12376)
16 sertraline/ or 79617-96-2.rn. or (sertraline or altruline or aremis or besitran or gladem or lustral or sealdin or zoloft or "Cp 51974:" or Cp51974: or Serad or Serlain or Tresleen).mp. (10018)
17 venlafaxine/ or 93413-69-5.rn. or (Venlafaxine or Efexor or Effexor or "Wy 45030" or Wy45030).mp. (6746)
18 Duloxetine/ or 116539-58-3.rn. or (duloxetine or Ariclaim or Cymbalta or "Ly 248686" or Ly248686 or Xeristar or Yentreve).mp. (1147)
19 Milnacipran/ or 92623-85-3.rn. or (milnacipran or Dalcipran or "F 2207" or F2207 or Ixel or Midalcipran or "Tn 912" or Tn912 or Toledomin).mp. (621)
20 or/11-19 (43723)
21 tricyclic antidepressant agent/ or adinazolam mesilate/ or amineptine/ or amitriptyline/ or amitriptyline plus perphenazine/ or amitriptylinoxide/ or amoxapine/ or butriptyline/ or cianopramine/ or clomipramine/ or danitracen/ or demexiptiline/ or desipramine/ or dibenzepin/ or dimetacrin/ or dosulepin/ or doxepin/ or etizolam/ or 2 hydroxydesipramine/ or 10 hydroxynortriptyline/ or imipramine/ or imipraminoxide/ or iprindole/ or limbitrol/ or lofepramine/ or melitracen/ or metapramine/ or nitroxazepine/ or norclomipramine/ or nordoxepin/ or nortrimipramine/ or nortriptyline/ or noxiptiline/ or opipramol/ or propizepine/ or protriptyline/ or quinupramine/ or s 3344/ or tampramine/ or tandamine/ or tianeptine/ or trimipramine/ or trimipramine maleate/ (58448)
22 or/11-20 (43723)
23 Botulinum Toxin A/ or 93384-43-1.rn. or botulinum toxin b/ or botulinum toxin e/ or (botulinum: or botulinium: or botox or dysport or oculinum).mp. (10568)
24 or/10,22-23 (110354)
25 randomized controlled trial/ or randomization/ or double blind procedure/ or single blind procedure/ or triple blind procedure/ or Placebo/ or (((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)) or (placebo$ or random$)).mp. or ((random: adj10 control: adj 5 trial:) or (rct or rcts) or (double adj5 blind:) or (tripl: adj5 blind:) or randomiz: or randomis:).mp. (451051)
26 24 and 25 (13042)
27 anticonvulsive agent/ct or carbamazepine/ct or gabapentin/ct or Lamotrigine/ct or etiracetam/ct or oxcarbazepine/ct or pregabalin/ct or Harkoseride/ct or valproic acid/ct or valproic acid derivative/ct or serotonin uptake inhibitors/ct or citalopram/ct or escitalopram/ct or fluoxetine/ct or fluvoxamine/ct or paroxetine/ct or sertraline/ct or venlafaxine/ct or Duloxetine/ct or Milnacipran/ct or tricyclic antidepressant agent/ct or adinazolam mesilate/ct or amineptine/ct or amitriptyline/ct or amitriptyline plus perphenazine/ct or amitriptylinoxide/ct or amoxapine/ct or butriptyline/ct or cianopramine/ct or clomipramine/ct or danitracen/ct or demexiptiline/ct or desipramine/ct or dibenzepin/ct or dimetacrin/ct or dosulepin/ct or doxepin/ct or etizolam/ct or 2 hydroxydesipramine/ct or 10 hydroxynortriptyline/ct or imipramine/ct or imipraminoxide/ct or iprindole/ct or limbitrol/ct or lofepramine/ct or melitracen/ct or metapramine/ct or nitroxazepine/ct or norclomipramine/ct or nordoxepin/ct or nortrimipramine/ct or nortriptyline/ct or noxiptiline/ct or opipramol/ct or propizepine/ct or protriptyline/ct or quinupramine/ct or s 3344/ct or tampramine/ct or tandamine/ct or tianeptine/ct or trimipramine/ct or trimipramine

maleate/ct or botulinum toxin/ct or botulinum toxin a/ct or botulinum toxin b/ct or botulinum toxin e/ct (12581)
28 26 or 27 (19521)
29 chronic:.mp. (466223)
30 chronic pain/ or (((chronic: or constant) adj5 pain:) or (pain adj2 pathway:) or (pain adj2 path) or (pain adj2 paths)).ti,ab. (24671)
31 musculoskeletal disease/ or morning stiffness/ or musculoskeletal pain/ or musculoskeletal stiffness/ or arthropathy/ or ankle instability/ or arthralgia/ or ehlers danlos syndrome/ or hemarthrosis/ or joint contracture/ or joint degeneration/ or joint destruction/ or joint effusion/ or joint hypermobility/ or joint instability/ or joint laxity/ or joint limitation/ or joint necrosis/ or joint stiffness/ or joint swelling/ or nail patella syndrome/ or neuropathic joint disease/ or patellofemoral pain syndrome/ or spondyloarthropathy/ or synovial cyst/ or temporomandibular joint disorder/ or vibration disease/ or ankylosis/ or ankylosing spondylitis/ or temporomandibular ankylosis/ or arthritis/ or adjuvant arthritis/ or antisynthetase syndrome/ or behcet disease/ or blau syndrome/ or chronic arthritis/ or gout/ or hemorrhagic arthritis/ or papa syndrome/ or pigmented villonodular synovitis/ or polyarthritis/ or pseudogout/ or psoriatic arthritis/ or reactive arthritis/ or reiter syndrome/ or infectious arthritis/ or bacterial arthritis/ or gonococcal arthritis/ or lyme disease/ or tuberculous arthritis/ or monarthritis/ or coxitis/ or knee arthritis/ or sacroiliitis/ or osteoarthritis/ or hip osteoarthritis/ or knee osteoarthritis/ or spondylosis/ or cervical spondylosis/ or rheumatoid arthritis/ or adult onset still disease/ or felty syndrome/ or juvenile rheumatoid arthritis/ or rheumatoid nodule/ or spondylitis/ or spondylarthritis/ or tuberculous spondylitis/ or joint malformation/ or arthrogryposis/ or congenital hip dislocation/ or congenital pseudarthrosis/ or coxa vara/ or hip dysplasia/ or hip malformation/ or larsen syndrome/ or osteoarthropathy/ or hypertrophic osteoarthropathy/ or periarticular joint disease/ or bursitis/ or carpal tunnel syndrome/ or cubital tunnel syndrome/ or farber disease/ or shoulder hand syndrome/ or tarsal tunnel syndrome/ or periarthritis/ or humeroscapular periarthritis/ or tendinitis/ or achilles tendinitis/ or tenosynovitis/ or synovitis/ or sapho syndrome/ (170160)
32 pain/ or allodynia/ or cystalgia/ or dysmenorrhea/ or dyspareunia/ or dysuria/ or eyelid pain/ or eye pain/ or female genital pain/ or flank pain/ or genital pain/ or hyperalgesia/ or hypoalgesia/ or intractable pain/ or limb pain/ or musculoskeletal chest pain/ or musculoskeletal pain/ or neck pain/ or noncardiac chest pain/ or odynophagia/ or pelvis pain syndrome/ or phantom pain/ or posttraumatic pain/ or precordial pain/ or psychogenic pain/ or retrosternal pain/ or shoulder pain/ or sinus pain/ or skin pain/ or spinal pain/ or substernal pain/ or thorax pain/ or urethral pain/ or vagina pain/ or vein pain/ or vulvodynia/ or abdominal pain/ or abdominal angina/ or lower abdominal pain/ or upper abdominal pain/ or backache/ or low back pain/ or bone pain/ or metatarsalgia/ or schnitzler syndrome/ or burning sensation/ or epigastric burning/ or skin burning sensation/ or vaginal burning sensation/ or "headache and facial pain"/ or chronic paroxysmal hemicrania/ or cluster headache/ or face pain/ or headache/ or heavy-headedness/ or hypnic headache/ or postdural puncture headache/ or sinus headache/ or sunct syndrome/ or temporal arteritis/ or trigeminus neuralgia/ or vascular headache/ or chronic daily headache/ or chronic tension headache/ or hemicrania continua/ or new daily persistent headache/ or transformed migraine/ or migraine/ or familial hemiplegic migraine/ or migraine aura/ or migraine with aura/ or migraine without aura/ or tension headache/ or episodic tension headache/ or leg pain/ or ankle pain/ or erythromelalgia/ or foot pain/ or heel pain/ or knee pain/ or patellofemoral pain syndrome/ or myalgia/ or compartment syndrome/ or eosinophilia myalgia

syndrome/ or fibromyalgia/ or intermittent claudication/ or myofascial pain/ or neuralgia/ or burning feet syndrome/ or cauda equina syndrome/ or cervicobrachial neuralgia/ or cubital tunnel syndrome/ or deafferentation pain/ or glossopharyngeal neuralgia/ or herpes zoster oticus/ or ischialgia/ or meralgia paresthetica/ or neuropathic pain/ or otalgia/ or postherpetic neuralgia/ or proctalgia/ or radicular pain/ or tarsal tunnel syndrome/ or thorax outlet syndrome/ or complex regional pain syndrome/ or complex regional pain syndrome type i/ or algodystrophy/ or posttraumatic osteoporosis/ or shoulder hand syndrome/ or sympathetic dystrophy/ or complex regional pain syndrome type ii/ or causalgia/ or scrotal pain/ or acute scrotum/ or chronic scrotal pain/ or visceral pain/ or biliary colic/ or biliary tract pain/ or colic/ or esophagus pain/ or gastrointestinal pain/ or kidney colic/ or kidney pain/ or liver pain/ or pleural pain/ or stomach pain/ or urinary tract pain/ or epigastric pain/ or epigastric discomfort/ or epigastric fullness/ (262954)

33 demyelinating disease/ or alpers disease/ or chronic inflammatory demyelinating polyneuropathy/ or demyelination/ or marchiafava bignami disease/ or multiple sclerosis/ or schilder disease/ (33700)

34 neuromuscular junction disorder/ or congenital myasthenic syndrome/ or eaton lambert syndrome/ or myasthenia/ or myasthenia gravis/ or myasthenia like syndrome/ (8752)

35 neuropathy/ or allergic neuropathy/ or demyelinating neuropathy/ or mononeuropathy multiplex/ or motor neuropathy/ or narp syndrome/ or nerve conduction disorder/ or nerve degeneration/ or nerve lesion/ or sensorimotor neuropathy/ or sensory neuropathy/ or autonomic neuropathy/ or aganglionosis/ or autonomic dysreflexia/ or colon aganglionosis/ or frey syndrome/ or horner syndrome/ or plexus paresis/ or cranial neuropathy/ or accessory nerve disease/ or garcin syndrome/ or hypoglossal nerve disease/ or oculomotor nerve disease/ or trochlear nerve disease/ or abducens nerve disease/ or abducens nerve injury/ or abducens nerve paralysis/ or cranial nerve injury/ or facial nerve injury/ or optic nerve injury/ or cranial nerve paralysis/ or bulbar paralysis/ or progressive bulbar palsy/ or facial nerve paralysis/ or bell palsy/ or herpes zoster oticus/ or melkersson rosenthal syndrome/ or moebius syndrome/ or burning feet syndrome/ (50807)

36 lupus erythematosus/ or lupus erythematosus nephritis/ or lupus like syndrome/ or systemic lupus erythematosus/ or systemic lupus erythematosus rash/ or skin lupus erythematosus/ or discoid lupus erythematosus/ or scleroderma/ or localized scleroderma/ or linear scleroderma/ or morphea/ or systemic sclerosis/ or diffuse scleroderma/ or limited scleroderma/ or syndrome crest/ (40922)

37 paralysis/ or amyotrophic lateral sclerosis/ or centronuclear myopathy/ or cerebral palsy/ or diaphragm paralysis/ or familial hemiplegic migraine/ or flaccid paralysis/ or hemiparesis/ or hemiplegia/ or kugelberg welander disease/ or locked in syndrome/ or mitochondrial myopathy/ or monoplegia/ or myasthenia gravis/ or myotonic dystrophy/ or nemaline myopathy/ or paraplegia/ or paresis/ or periodic paralysis/ or peripheral paralysis/ or pseudobulbar palsy/ or quadriplegia/ or spastic paraplegia/ or spastic paresis/ or spinal paralysis/ or tongue paralysis/ or vocal cord paralysis/ or wallenberg syndrome/ or werdnig hoffmann disease/ (60916)

38 myelitis/ or allergic encephalomyelitis/ or chronic fatigue syndrome/ or encephalomyelitis/ or poliomyelitis/ or postpoliomyelitis syndrome/ (16678)

39 muscular dystrophy/ or becker muscular dystrophy/ or duchenne muscular dystrophy/ or emery dreifuss muscular dystrophy/ or facioscapulohumeral muscular dystrophy/ or fukuyama congenital muscular dystrophy/ or limb girdle muscular dystrophy/ or miyoshi myopathy/ or

muscle eye brain disease/ or myotonic dystrophy/ or oculopharyngeal muscular dystrophy/ or progressive muscular dystrophy/ or walker warburg syndrome/ (13826)
40 or/31-39 (581135)
41 28 and 29 and 40 (1129)
42 28 and 30 (609)
43 41 or 42 (1209)
44 limit 43 to human (1206)
45 limit 44 to (adult <18 to 64 years> or aged <65+ years>) (360)
46 exp Neoplasm/ (1289875)
47 44 not 46 (1135)
48 limit 47 to (adult <18 to 64 years> or aged <65+ years>) (348)
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Appendix C: MEDLINE® literature search strategy

Database: Ovid MEDLINE(R) <1950 to February Week 2 2007>
Search Strategy:
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1 anticonvulsants/ or carbamazepine/ or (carbamazepin: or Amizepin: or Atretol or Biston or Calepsin or Carbategral or Carbatrol or Convuline or Epimax or Epitol or Equetro or Finlepsin or "G 32883" or G32883 or Lexin or Mazepine or Neurotol or Neurotop or Servimazepin or Sirtal or Tegral or Tegretal or Tegretol or Tegrital or Telesmin or Teril or Timonil).mp. (34477)
2 gabapentin/ or (gabapentin: or "Ci 945" or Ci945 or "Go 3450" or Go3450 or "Goe 3450" or Goe3450 or Neurontin:).mp. (2174)
3 Lamotrigine/ or (Lamotrigine or "Bw 430c:" or Bw430c: or Labileno or Lamictal).mp. (2128)
4 (Etiracetam or Levetiracetam or Etirazetam or Keppra or "Lo 59" or Lo59 or "Ucb 6474" or Ucb6474 or "Ucb L059" or "ucb l 059" or ucbl059).mp. (594)
5 oxcarbazepine/ or (oxcarbazepine or Apydan or "GP 47680" or GP47680 or Oxocarbazepine or Timox or Trileptal).mp. (701)
6 pregabalin/ or (pregabalin or "Ci 1008" or Ci1008 or Lyrica or "Pd 144723" or Pd144723).mp. (270)
7 topiramate/ or (topiramate or Epitomax or "MCN 4853" or MCN4853 or "Rwj 17021:" or Rwj17021: or Topamax or Topimax).mp. (1451)
8 (Harkoseride or Lacosamide or "Add 234037" or Add234037 or Erlosamide or "Spm 927" or Spm927).mp. (24)
9 valproic acid/ or valproic acid derivative/ or ((valproic adj2 acid) or "Abbott 44090" or Abbott44090 or (Alpha adj2 Propylvalerate) or (Alpha adj2 Propylvaleric) or Apilepsin or Convulex or Depacon or Depakene or Depakin: or Deprakine or "Di N Propylacet:" or DiNPropylacet: or Dipropylacetate or Dipropylacetatic or (Dipropyl adj2 Acetic) or Dipropylacetic or Diprosin or Epilim or Epival or Ergenyl or Everiden or Goilim or "Kw 6066 N" or Kw6066N or Labazene or Leptilan or Leptilanil or Mylproin or (Myproic adj2 Acid) or "N Dipropylacetic Acid" or (Dipropylacetic adj2 Acid) or Orfiril or Orlept or "2 Propylpentanoate" or 2Propylpentanoate or "2 Propylpentanoic Acid" or "2 Propylvalerate Sodium" or "2 Propylvaleric Acid" or Propymal or (Sodium adj2 Valproate) or Valerin or Valparin or Valpro or Valproate or Vupral).mp. (9468)
10 or/1-9 (40728)
11 serotonin uptake inhibitors/ or citalopram/ or (Citalopram or Celexa or Cipramil or Cytalopram or Elopram or "Lu 10 171" or "Lu 10171" or Lu10171 or Nitalapram or Sepram or Seropram or "Zd 211" or Zd211).mp. (10716)
12 (escitalopram or Cipralex or Lexapro or "Lu 26054 0" or "Lu 260540" or Lu260540).mp. (218)
13 fluoxetine/ or (fluoxetine or "Compound 110140" or Compound110140 or Fluctin: or Flunirin or Fluoxifar or "Lilly 110140" or Lilly110140 or Lovan or "Ly 110140" or Ly110140 or Prosac or Prozac or Prozamin or Sarafem).mp. (7129)
14 fluvoxamine/ or (fluvoxamine or "Du 23000" or Du23000 or Dumirox or Fluroxamine).mp. (1881)

15 paroxetine/ or (paroxetine or Aropax or "Brl 29060:" or Brl29060: or Deroxat or Dexorat or "Fg 7051" or Fg7051 or Motivan or Paroxetine or Paxil or Pexeva or Seroxat or "Si 211103" or Si211103 or Tagonis).mp. (3386)
16 sertraline/ or sertraline (nm) or (sertraline or altruline or aremis or besitran or gladem or lustral or sealdin or zoloft or "Cp 51974:" or Cp51974: or Serad or Serlain or Tresleen).mp. (2171)
17 (Venlafaxine or Efexor or Effexor or "Wy 45030" or Wy45030).mp. (1478)
18 (duloxetine or Ariclaim or Cymbalta or "Ly 248686" or Ly248686 or Xeristar or Yentreve).mp. (356)
19 (milnacipran or Dalcipran or "F 2207" or F2207 or Ixel or Midalcipran or "Tn 912" or Tn912 or Toledomin).mp. (208)
20 or/11-19 (18672)
21 antidepressive agents, tricyclic/ or Dibenzazepines/ or AZEPINES/ or BENZAZEPINES/ (17899)
22 amitriptyline/ or (amitriptylin: or amitrol or anapsique or damilen or domical or elavil or endep or laroxyl or lentizol or novoprotect or saroten or sarotex or syneudon or triptafen or tryptanol or tryptine or tryptizol).mp. (6555)
23 clomipramine/ or (Clomipramine or chlomipramine or anafranil or hydiphen).mp. (3132)
24 desipramine/ or desipramine:.mp. (6611)
25 dothiepin/ or (dosulepin or dothiepin or prothiaden).mp. (345)
26 doxepin/ or (doxepin?? or aponal or deptran or desidox or doneurin or doxepia or espadox or mareen or prudoxin or quitaxon or sin?quan or xepin or zonalon).mp. (1104)
27 imipramine/ or (imipramine or imidobenzyle or imizin or janimine or melipramine or norchlorimipramine or pryleugan or tofranil).mp. (10845)
28 Lofepramine/ or (Lofepramine or lopramine or deftan or feprapax or gam?nil or (leo adj2 "640") or leo640 or (lofepramine adj2 hydrochloride) or lomont).mp. (160)
29 Iprindole/ or (Antidepressive Agents/ and Indoles/) or iprindole:.mp. (492)
30 nortriptyline/ or (desitriptyline or desmethylamitriptylin or allegron or aventyl or norfenazin or nortrilen or pamelor or paxtibi).mp. (1726)
31 Opipramol/ or (Opipramol or insidon).mp. (234)
32 Protriptyline/ or (Protriptyline or vivactil).mp. (361)
33 Trimipramine/ or (Trim?pramine or stangyl or surmontil).mp. (428)
34 or/21-33 (39006)
35 botulinum toxins/ or botulinum toxin type a/ or (botulinum: or botox or dysport or oculinum).mp. (9443)
36 or/10,20,34-35 (101874)
37 randomized control trials/ or ((random: adj10 control: adj 5 trial:) or (rct or rcts) or (double adj5 blind:) or (tripl: adj5 blind:) or randomiz: or randomis:).mp. (346824)
38 36 and 37 (10017)
39 limit 36 to randomized controlled trial (6101)
40 38 or 39 (10017)
41 limit 40 to humans (9886)
42 joint diseases/ or ankylosis/ or spondylitis, ankylosing/ or arthralgia/ or shoulder pain/ or arthritis/ or arthritis, experimental/ or arthritis, infectious/ or arthritis, reactive/ or arthritis, psoriatic/ or arthritis, rheumatoid/ or arthritis, juvenile rheumatoid/ or caplan's syndrome/ or felty's syndrome/ or rheumatoid nodule/ or sjogren's syndrome/ or still's disease, adult-onset/ or

chondrocalcinosis/ or gout/ or arthritis, gouty/ or osteoarthritis/ or osteoarthritis, hip/ or osteoarthritis, knee/ or spinal osteophytosis/ or periarthritis/ or reiter syndrome/ or rheumatic fever/ or rheumatic nodule/ or wissler's syndrome/ or spondylarthritis/ or spondylarthropathies/ or arthrogryposis/ or arthropathy, neurogenic/ or bursitis/ or chondromatosis, synovial/ or contracture/ or hip contracture/ or hallux limitus/ or hallux rigidus/ or hemarthrosis/ or hip dislocation, congenital/ or hydrarthrosis/ or joint deformities, acquired/ or joint instability/ or joint loose bodies/ or metatarsalgia/ or nail-patella syndrome/ or osteoarthropathy, primary hypertrophic/ or osteoarthropathy, secondary hypertrophic/ or patellofemoral pain syndrome/ or shoulder impingement syndrome/ or synovitis/ or synovitis, pigmented villonodular/ or temporomandibular joint disorders/ or temporomandibular joint dysfunction syndrome/ or fibromyalgia/ or hyperostosis, sternocostoclavicular/ or polymyalgia rheumatica/ or tennis elbow/ or digestive system diseases/ or stomatognathic diseases/ or arthrit:.ti,ab. (225891)
43 headache disorders/ or headache disorders, primary/ or migraine disorders/ or migraine with aura/ or migraine without aura/ or tension-type headache/ or trigeminal autonomic cephalalgias/ or cluster headache/ or paroxysmal hemicrania/ or sunct syndrome/ or headache disorders, secondary/ or post-dural puncture headache/ or post-traumatic headache/ or vascular headaches/ or (headache: or migrain:).ti,ab. (45684)
44 demyelinating autoimmune diseases, cns/ or "diffuse cerebral sclerosis of schilder"/ or encephalomyelitis, acute disseminated/ or leukoencephalitis, acute hemorrhagic/ or multiple sclerosis/ or multiple sclerosis, chronic progressive/ or multiple sclerosis, relapsing-remitting/ or neuromyelitis optica/ or myelitis, transverse/ or lambert-eaton myasthenic syndrome/ or myasthenia gravis/ or myasthenia gravis, autoimmune, experimental/ or myasthenia gravis, neonatal/ or polyradiculoneuropathy/ or guillain-barre syndrome/ or miller fisher syndrome/ or "hereditary sensory and autonomic neuropathies"/ or dysautonomia, familial/ or polyradiculoneuropathy, chronic inflammatory demyelinating/ or stiff-person syndrome/ or uveomeningoencephalitic syndrome/ or vasculitis, central nervous system/ or aids arteritis, central nervous system/ or lupus vasculitis, central nervous system/ or temporal arteritis/ (54815)
45 lupus erythematosus, cutaneous/ or lupus erythematosus, discoid/ or panniculitis, lupus erythematosus/ or lupus erythematosus, systemic/ or lupus nephritis/ or lupus vasculitis, central nervous system/ or lupus.ti,ab. (46880)
46 pain:.mp. or pain/ or back pain/ or low back pain/ or facial pain/ or headache/ or labor pain/ or metatarsalgia/ or neck pain/ or neuralgia/ or neuralgia, postherpetic/ or sciatica/ or pain, intractable/ or pain, referred/ or paralysis/ or facial paralysis/ or hemiplegia/ or ophthalmoplegia/ or ophthalmoplegia, chronic progressive external/ or supranuclear palsy, progressive/ or paraplegia/ or brown-sequard syndrome/ or pseudobulbar palsy/ or quadriplegia/ or respiratory paralysis/ or vocal cord paralysis/ or paresis/ or paraparesis/ or paraparesis, spastic/ (376250)
47 neuromuscular diseases/ or fatigue syndrome, chronic/ or isaacs syndrome/ or motor neuron disease/ or amyotrophic lateral sclerosis/ or bulbar palsy, progressive/ or muscular atrophy, spinal/ or "spinal muscular atrophies of childhood"/ or poliomyelitis/ or postpoliomyelitis syndrome/ or muscular diseases/ or muscular disorders, atrophic/ or muscular dystrophies/ or distal myopathies/ or muscular dystrophies, limb-girdle/ or muscular dystrophy, duchenne/ or muscular dystrophy, emery-dreifuss/ or muscular dystrophy, facioscapulohumeral/ or muscular dystrophy, oculopharyngeal/ or myotonic dystrophy/ or eosinophilia-myalgia syndrome/ or fibromyalgia/ or mitochondrial myopathies/ or mitochondrial encephalomyopathies/ or melas syndrome/ or merrf syndrome/ or ophthalmoplegia, chronic progressive external/ or kearns-sayer syndrome/ or myopathies, structural, congenital/ or

myopathies, nemaline/ or myopathy, central core/ or myositis/ or dermatomyositis/ or myositis, inclusion body/ or polymyositis/ or pyomyositis/ or myotonic disorders/ or myotonia congenita/ or paralyses, familial periodic/ or hypokalemic periodic paralysis/ or paralysis, hyperkalemic periodic/ or neuromuscular junction diseases/ or botulism/ or lambert-eaton myasthenic syndrome/ or myasthenia gravis/ or myasthenia gravis, autoimmune, experimental/ or myasthenia gravis, neonatal/ or myasthenic syndromes, congenital/ or peripheral nervous system diseases/ or acrodynia/ or amyloid neuropathies/ or amyloid neuropathies, familial/ or brachial plexus neuropathies/ or brachial plexus neuritis/ or complex regional pain syndromes/ or causalgia/ or reflex sympathetic dystrophy/ or diabetic neuropathies/ or guillain-barre syndrome/ or miller fisher syndrome/ or hand-arm vibration syndrome/ or mononeuropathies/ or femoral neuropathy/ or median neuropathy/ or carpal tunnel syndrome/ or peroneal neuropathies/ or radial neuropathy/ or sciatic neuropathy/ or sciatica/ or tibial neuropathy/ or tarsal tunnel syndrome/ or ulnar neuropathies/ or cubital tunnel syndrome/ or ulnar nerve compression syndromes/ or nerve compression syndromes/ or thoracic outlet syndrome/ or cervical rib syndrome/ or neuralgia/ or neuralgia, postherpetic/ or neuritis/ or neuritis, autoimmune, experimental/ or neurofibromatosis 1/ or pain insensitivity, congenital/ or peripheral nervous system neoplasms/ or nerve sheath neoplasms/ or neurilemmoma/ or neurofibroma/ or neurofibroma, plexiform/ or neurofibrosarcoma/ or polyneuropathies/ or tarlov cysts/ or stiff-person syndrome/ or neuropath:.ti,ab. (205087)
48 or/42-47 (833309)
49 Chronic Disease/ or chronic:.mp. (626318)
50 41 and 48 and 49 (317)
51 (((chronic: or constant) adj5 pain:) or (pain adj2 pathway:) or (pain adj2 path) or (pain adj2 paths)).ti,ab. (20065)
52 41 and 51 (152)
53 50 or 52 (322)
54 limit 53 to "all adult (19 plus years)" (211)
****

Appendix D: EBM Reviews – Cochrane Database of Systematic Reviews literature search strategy

Database: EBM Reviews - Cochrane Database of Systematic Reviews <1st Quarter 2007>
Search Strategy:

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35 ((atypical or chronic) adj5 pain:).mp. [mp=title, short title, abstract, full text, keywords, caption text] (215)
36 (ssri: or antidepressant: or botox or botulinum or (selective adj2 serotonin)).mp. [mp=title, short title, abstract, full text, keywords, caption text] (314)
37 35 and 36 (35)
38 (neuropath: or musculoskelet: or headache: or migraine: or joint: or arthrit: or lupus or spondylitis or neurologi: or neuromuscul: or parapleg: or quadripleg: or hemipleg: or paresis or dystrophy or sclerosis).mp. [mp=title, short title, abstract, full text, keywords, caption text] (2024)
39 36 and 38 (168)
40 pain:.mp. [mp=title, short title, abstract, full text, keywords, caption text] (1783)
41 39 and 40 (95)
42 37 or 41 (101)
43 from 42 keep 1-101 (101)

****

Appendix E: Forest plots for each class for "From Placebo" analyses.

NB: Result to the left of 0 favour placebo and to the right favours the drug.

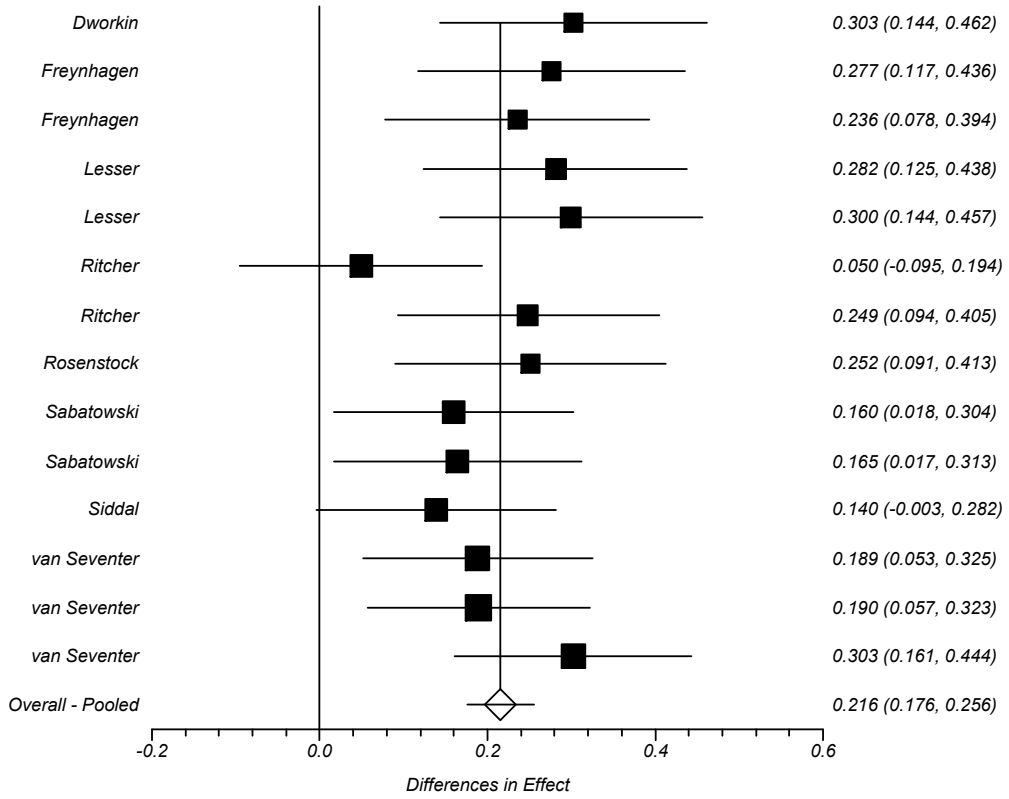


Figure A-1. Outcome: 50% decrease in pain scores for anticonvulsants

NB: A result to the left of 0 favours placebo and to the right favours the drug.

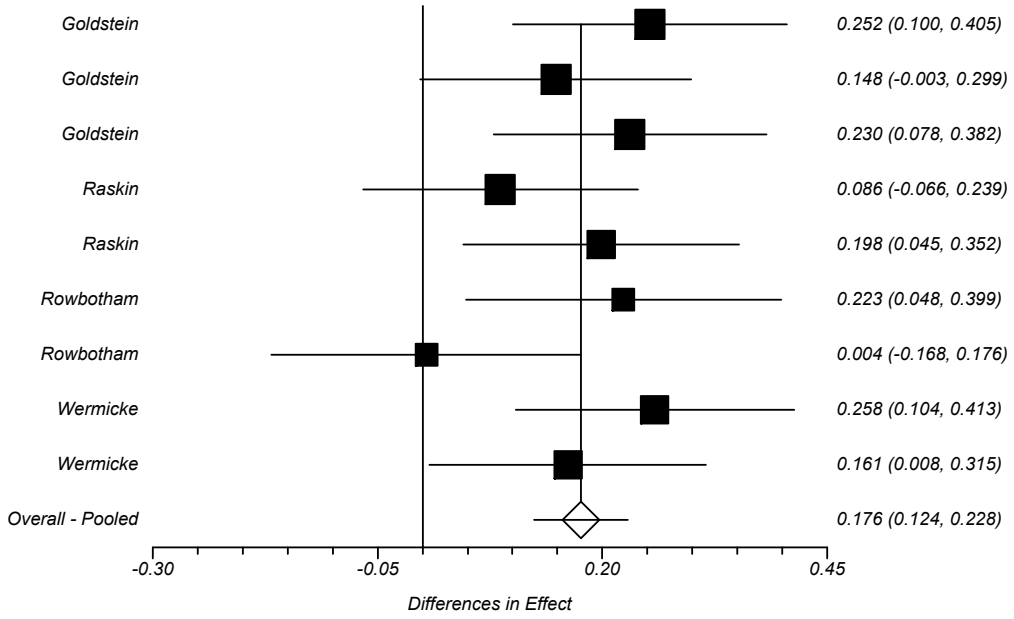


Figure A-2. Outcome: 50% decrease in pain scores for SNRIs.

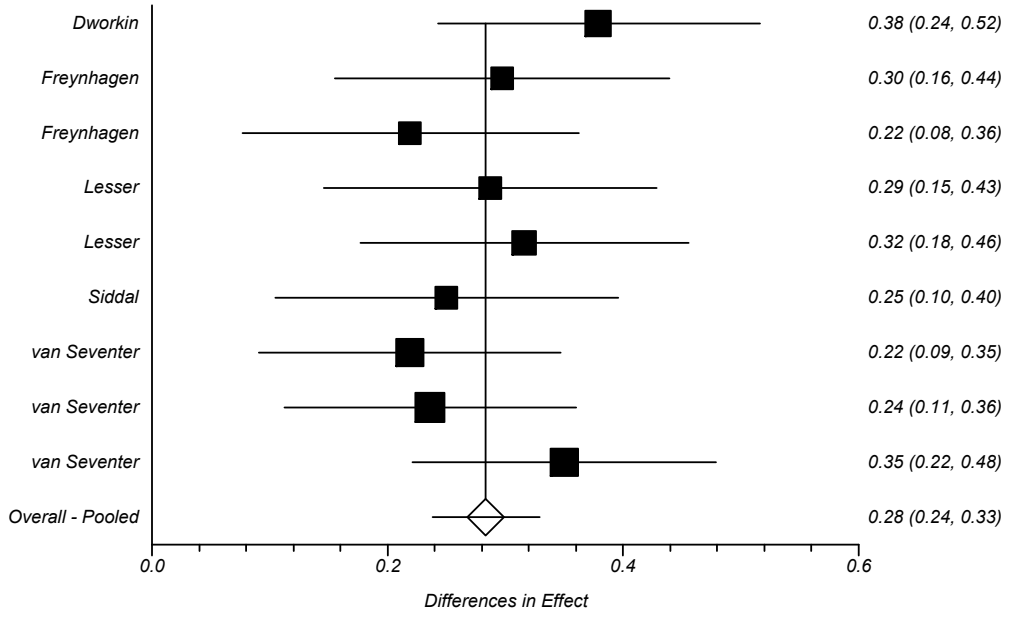


Figure A-3. Outcome: 30% decrease in pain scores for anticonvulsants.

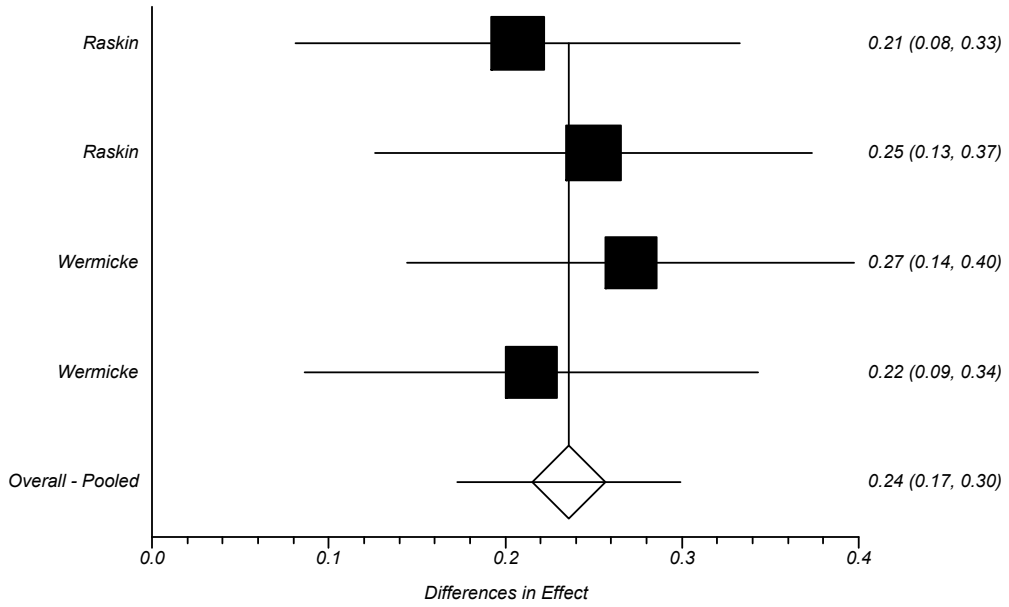


Figure A-4. Outcome: 30% decrease in pain scores for SNRIs.

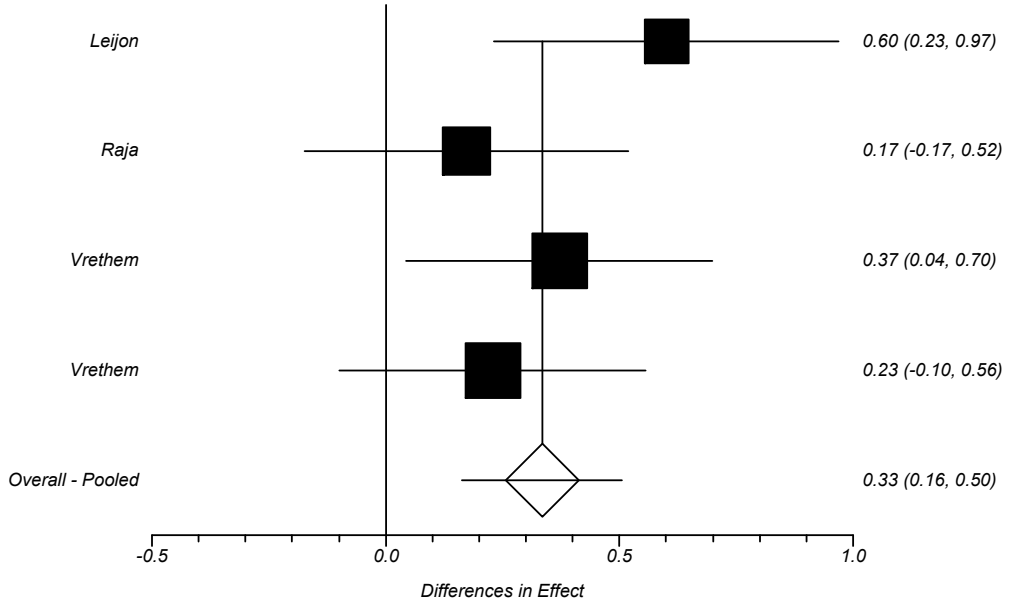


Figure A-5. Outcome: 30% decrease in pain scores for TCAs

Appendix F

Table A-1 presents the meta-analytic weighted average partial clinical response rates (defined as a 30% reduction in VAS pain scores from baseline to endpoint) across study arms using the intent-to-treat model. The SNRIs had the highest partial weighted average clinical response rate of 66.0% (SE=2.2%), followed by ACs with 54.5% (SE=3.7%), and by TCAs with 49.2% (SE=6.6%). Heterogeneity was found in the ACs dataset (Chi-squared=39.19, df=8, $p<0.001$; $I^2 = 79.6\%$). Chi-squared values were non-significant ($p>0.05$) in the datasets of the SNRIs and the TCAs. The 95% confidence intervals of the TCAs overlapped with those of the ACs (almost completely) and the SNRIs. The SNRIs and ACs did not overlap, suggesting a possible superiority for SNRIs. However, when we compared the rates across the three groups using a Kruskal-Wallis test, there was no measurable difference using from a standpoint of statistical significance (chi-squared=5.21, P=0.074).

Table A-2 describes the meta-analytic weighted average full clinical response rates (defined as a 50% reduction in VAS pain scores from baseline to endpoint). Heterogeneity was found in ACs (chi-squared=75.06, df=13, $p<0.001$; I-squared=82.7%) and SNRIs (chi-squared=17.05, df=8, p=0.030, I-squared=53.1%) datasets. TCAs displayed no significant heterogeneity (chi-squared=2.94, df=3, p=0.400). In this analysis, 23 study arms were summarized. In the intent-to-treat analysis, the SNRIs had higher clinical response rates compared to ACs; meta-analytic weighted average full clinical response rates were 45.9% (SE=2.3%) and 36.3% (SE=3.2%), respectively. The confidence intervals overlapped, suggesting no significant difference between drugs. A Mann-Whitney test contrasting rates between studies was not significant (Z = 1.953, P=0.053). It appears quite possible that additional studies could change these results.

Table A-1. Meta-analytic partial clinical response rates (30% reduction in VAS pain scores from baseline to endpoint) across study arms using an intent-to-treat model.

Drug Class	Drug	Author	Year	No. of Responders	No. of Non-responders	Clinical Response Rate	SE	$CI_{95\%}$ LL	$CI_{95\%}$ UL
ACs	pregabalin (300-600 mg/day)	Dworkin[110]	2003	56	33	0.629	0.111	0.412	0.846
	pregabalin (300 mg/day)	Freynhagen[101]	2006	88	44	0.667	0.106	0.458	0.875
	pregabalin (150-600 mg/day)	Freynhagen[101]	2005	83	58	0.589	0.106	0.380	0.797
	pregabalin (300 mg/day)	Lesser[109]	2004	50	31	0.617	0.112	0.398	0.837
	pregabalin (600 mg/day)	Lesser[109]	2004	53	29	0.646	0.111	0.428	0.865
	pregabalin (150-600 mg/day)	Siddal[111]	2006	29	41	0.414	0.114	0.190	0.638
	pregabalin (150 mg/day)	van Seventer[117]	2006	34	53	0.391	0.111	0.173	0.609
	pregabalin (300 mg/day)	van Seventer[117]	2006	40	58	0.408	0.110	0.193	0.624
	pregabalin (600 mg/day)	van Seventer[30]	2006	47	43	0.522	0.111	0.304	0.740
Total ACs				**480**	**390**	**0.545**	**0.037**	**0.473**	**0.617**
SNRIs	duloxetine (60 mg BID)	Raskin[99]	2005	74	42	0.638	0.045	0.550	0.725
	duloxetine (60 mg QD)	Raskin[99]	2005	79	37	0.681	0.043	0.596	0.766
	duloxetine (120 mg/day)	Wernicke[116]	2006	77	35	0.688	0.044	0.602	0.773
	duloxetine (60 mg/day)	Wernicke[116]	2006	72	42	0.632	0.045	0.543	0.720
Total SNRIs				**302**	**156**	**0.660**	**0.022**	**0.617**	**0.704**
TCAs	amitriptyline (12.5 mg + 25 mg increments each week)	Leijon[120]	1989	10	5	0.667	0.153	0.366	0.967
	TCAs	Raja[123]	2002	9	17	0.346	0.132	0.088	0.604
	amitriptyline (25-75 mg/day)	Vrethem[126]	1997	20	15	0.571	0.125	0.326	0.817
	maprotiline (25-75 mg/day)	Vrethem[126]	1997	15	20	0.429	0.125	0.183	0.674
Total TCAs				**54**	**57**	**0.492**	**0.066**	**0.363**	**0.622**

ACs = Anticonvulsants; BID = Twice in a day; CI = Confidence interval; LL = Lower limit; QD = Once a day; SE = Standard error; SNRIs = Serotonin-norepinephrine reuptake inhibitors ; TCAs = Tricyclic antidepressants ; UL = Upper limit.

Table A-2. Meta-analytic full clinical response rates (50% reduction in VAS pain scores from baseline to endpoint) across study arms using an intent-to-treat model.[*]

Drug Class	Drug	Author	Year	No. of Responders	No. of Non-responders	Clinical Response Rate	SE	$CI_{95\%}$ LL	$CI_{95\%}$ UL
ACs	pregabalin (300-600 mg/day)	Dworkin[110]	2003	45	44	0.506	0.120	0.271	0.740
	pregabalin (300 mg/day)	Freynhagen[101]	2006	69	63	0.523	0.116	0.296	0.750
	pregabalin (150-600 mg/day)	Freynhagen[101]	2005	68	73	0.482	0.115	0.256	0.708
	pregabalin (300 mg/day)	Lesser[109]	2004	37	44	0.457	0.121	0.220	0.694
	pregabalin (600 mg/day)	Lesser[109]	2004	39	43	0.476	0.121	0.239	0.712
	pregabalin (150 mg/day)	Ritcher[112]	2005	16	63	0.203	0.117	0.000	0.431
	pregabalin (600 mg/day)	Ritcher[112]	2005	33	49	0.402	0.120	0.167	0.638
	pregabalin (300 mg/day)	Rosenstock[113]	2004	30	46	0.395	0.121	0.157	0.632
	pregabalin (150 mg/day)	Sabatowski[114]	2004	21	60	0.259	0.118	0.028	0.490
	pregabalin (300 mg/day)	Sabatowski[114]	2004	21	55	0.276	0.119	0.043	0.510
	pregabalin (150-600 mg/day)	Siddal[111]	2006	15	55	0.214	0.118	0.000	0.446
	pregabalin (150 mg/day)	van Seventer[117]	2006	23	64	0.264	0.117	0.034	0.494
	pregabalin (300 mg/day)	van Seventer[117]	2006	26	72	0.265	0.116	0.037	0.493
	pregabalin (600 mg/day)	van Seventer[117]	2006	34	56	0.378	0.119	0.145	0.611
Total ACs				**477**	**787**	**0.363**	**0.032**	**0.301**	**0.425**
SNRIs	duloxetine (120 mg/day)	Goldstein[104]	2005	57	56	0.504	0.069	0.369	0.640
	duloxetine (20 mg/day)	Goldstein[104]	2005	46	69	0.400	0.068	0.266	0.534
	duloxetine (60 mg/day)	Goldstein[104]	2005	55	59	0.482	0.069	0.347	0.618
	duloxetine (60 mg BID)	Raskin[99]	2005	45	71	0.388	0.068	0.255	0.521
	duloxetine (60 mg QD)	Raskin[99]	2005	58	58	0.500	0.069	0.365	0.635
	venlafaxine (150-225 mg/day)	Rowbotham[115]	2004	46	36	0.561	0.075	0.415	0.707
	venlafaxine (75	Rowbotha	2004	28	54	0.341	0.073	0.198	0.484

Drug Class	Drug	Author	Year	No. of Responders	No. of Non-responders	Clinical Response Rate	SE	$CI_{95\%}$ LL	$CI_{95\%}$ UL
	mg/day)	m[115]							
	duloxetine (120 mg/day)	Wernicke[116]	2006	59	53	0.527	0.069	0.391	0.663
	duloxetine (60 mg/day)	Wernicke[116]	2006	49	65	0.430	0.069	0.295	0.565
Total SNRIs				**443**	**521**	**0.459**	**0.023**	**0.413**	**0.504**

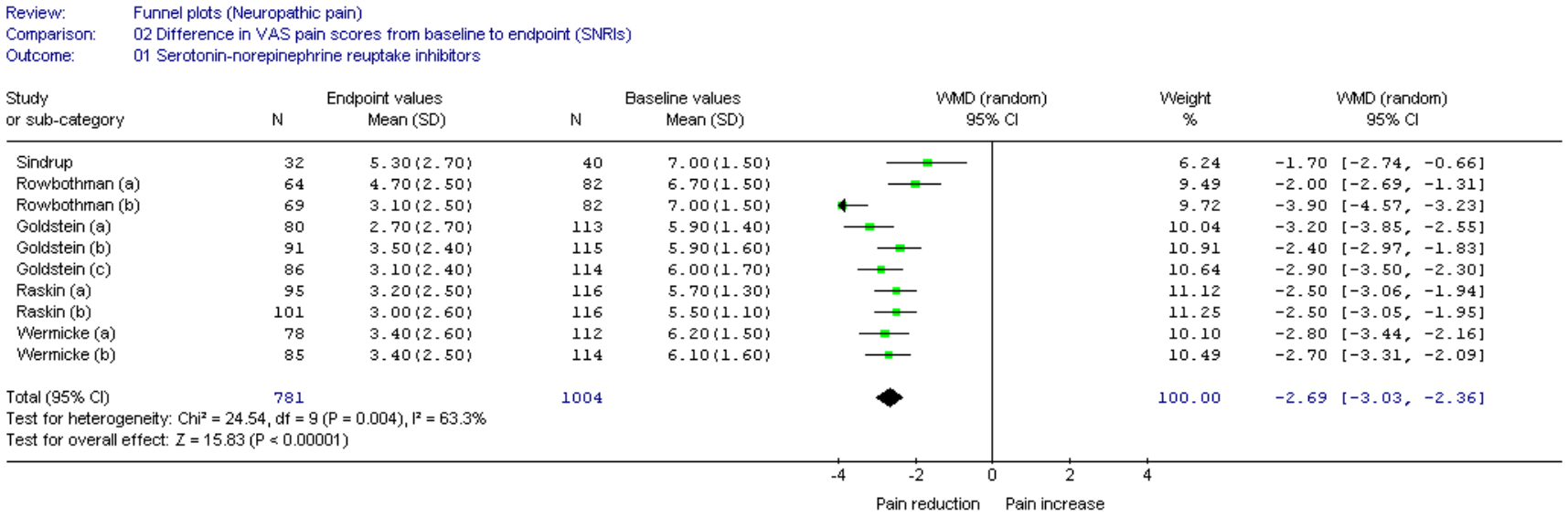
*No data were available for the TCAs for 50% reduction in VAS.
ACs = Anticonvulsants; BID = Twice in a day; CI = Confidence interval; LL = Lower limit; SE = Standard error; SNRIs = Serotonin-norepinephrine reuptake inhibitors; QD = Once a day; TCAs = Tricyclic antidepressants ; UL = Upper limit.

Appendix G

The ACs pharmacological group had the largest sample size (n=1612) and number of studies (k=13). The meta-analytic weighted average baseline pain (VAS) scores from all included studies was 6.8 ($CI_{95\%}$=6.2, 7.4). The endpoint VAS score reached a meta-analytic value of 4.1 ($CI_{95\%}$=3.3, 5.0). The estimated meta-analytic difference between baseline and endpoint VAS pain scores was -2.4 ($CI_{95\%}$=-2.8,-2.0; $p<0.001$). Figure A-6 depicts the forest plot of the studies evaluating neuropathic pain patients under gabapentin or pregabalin therapy.

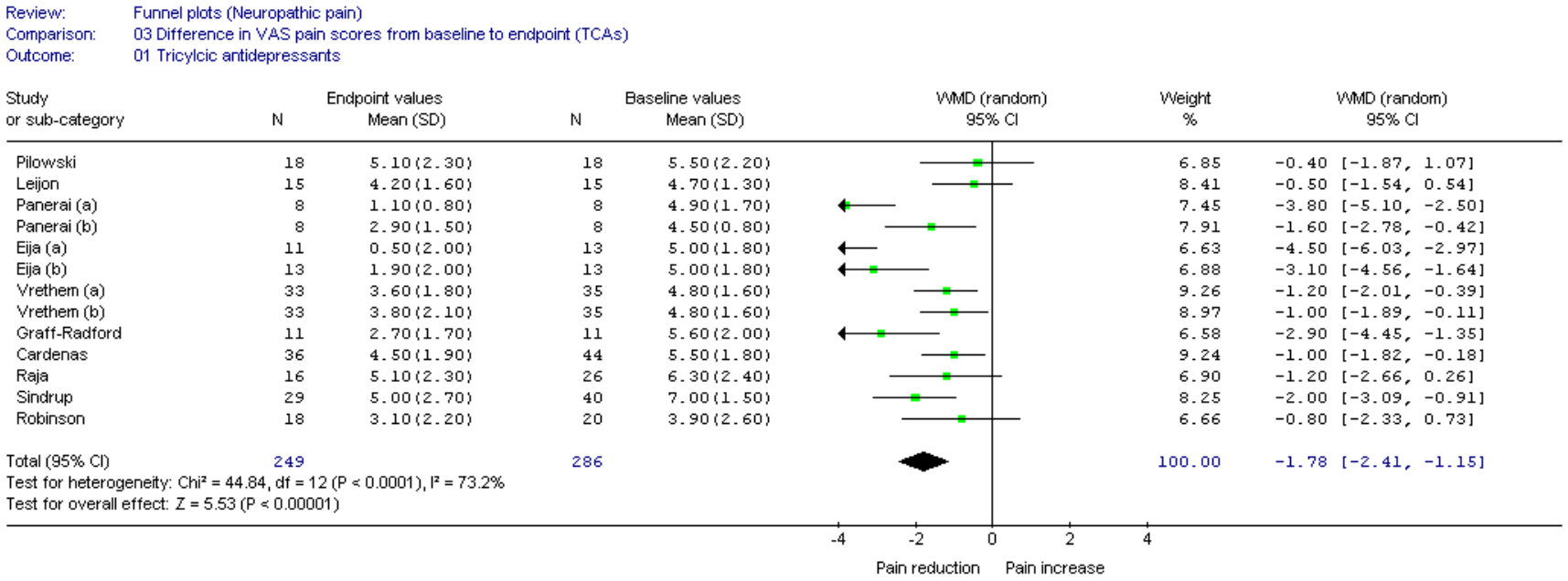
Figure A-7 presents the distribution of SNRI studies with their results reported and the estimated weighted average meta-analytic difference in VAS pain scores from baseline to endpoint. The total number of patients diagnosed with neuropathic pain in the trials evaluating the efficacy of SNRIs was 1004. The SNRIs were also able to reduce VAS pain scores significantly from baseline (6.1, $CI_{95\%}$= 5.2, 7.0) to endpoint (3.5, $CI_{95\%}$=2.0, 5.1). The estimated weighted average meta-analytic reduction in VAS pain scores was -2.7 ($CI_{95\%}$=-3.0, -2.4; $p<0.001$).

TCAs comprised the pharmacological group reporting the lowest weighted average reduction (-1.8, $CI_{95\%}$= -2.4, -1.15) in VAS pain scores from baseline (5.0, $CI_{95\%}$=4.2, 5.9) to endpoint (2.6, $CI_{95\%}$=1.8, 3.5). However, the weighted average meta-analytic difference between baseline and endpoint VAS pain scores within the TCA group was statistically significant ($p<0.001$). Additionally, there was a notable difference in baseline VAS pain scores between TCAs and the other two targeted pharmacological groups (>1.1 points), which could partially explain the lowest observed impact by this therapeutic group. Figure A-8 depicts all studies evaluating TCAs in patients with neuropathic pain and meta-analytic results.



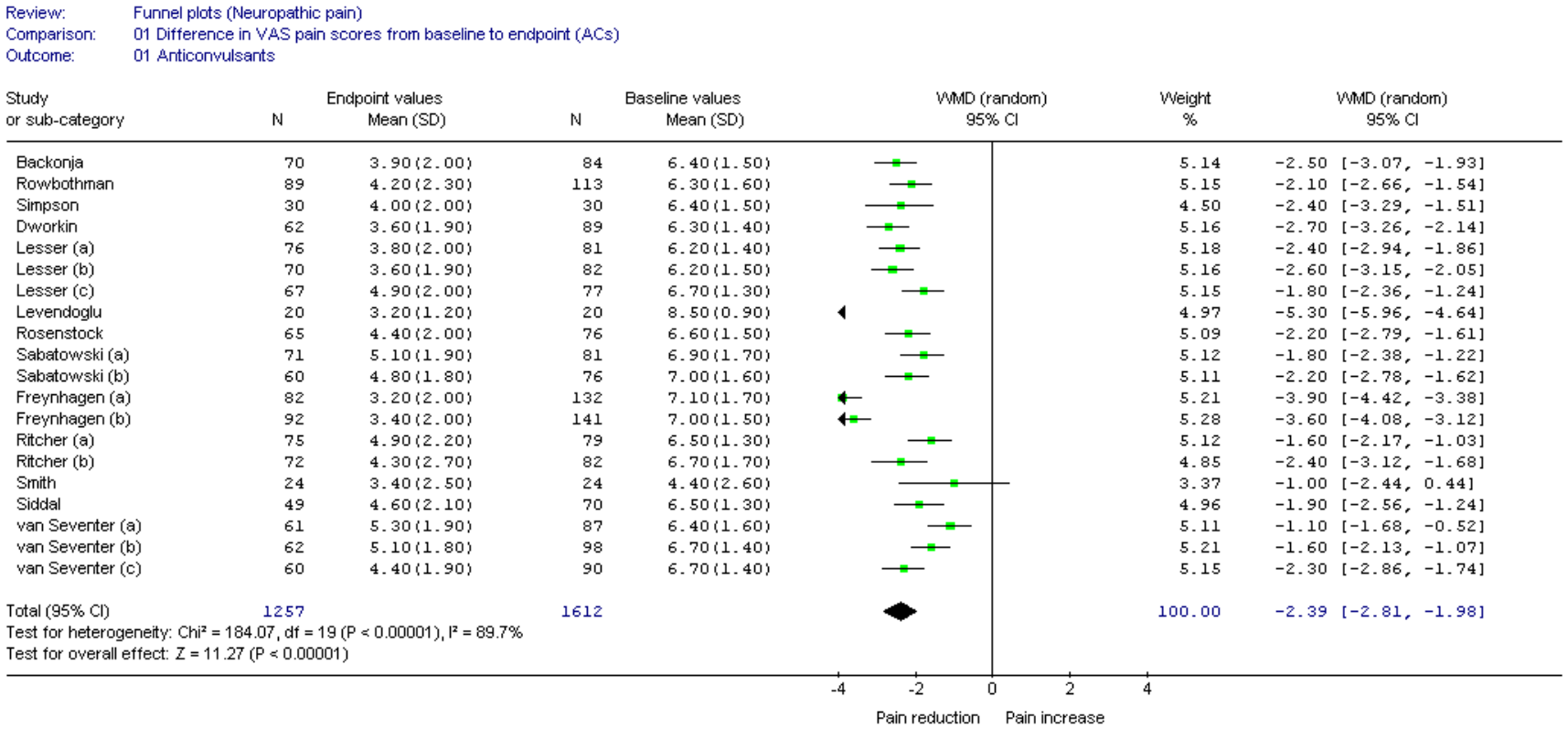
CI = Confidence intervals; SD = Standard deviation; SNRIs = Serotonin-norepinephrine reuptake inhibitors; VAS = Visual analog scale; WMD = Weighted mean difference.

Figure A-6. Forest plot of the studies evaluating patients with neuropathic pain using anticonvulsant therapy ("Single Arm" results).



CI = Confidence intervals; SD = Standard deviation; TCAs = Tricyclic antidepressants; VAS = Visual analog scale; WMD = Weighted mean difference.

FigureA-7. Forest plot of the studies evaluating patients with neuropathic pain using serotonin-norepinephrine reuptake inhibitor therapy ("Single Arm" results).



CI = Confidence intervals; SD = Standard deviation; ACs = Anticonvulsants; VAS = Visual analog scale; WMD = Weighted mean difference.

Figure A-8. Forest plot of the studies evaluating patients with neuropathic pain using tricyclic antidepressant therapy("Single Arm" results).

Appendix H

Inclusion/exclusion criteria for economic abstracts

Ref#: Reviewer's Initials: Accept / Reject

Exclusion criteria for clinical study abstracts:

1. **Study design:**
   - ☐ Cost analysis
   - ☐ Full economic evaluation
     - ☐ Cost consequence analysis
     - ☐ Cost minimization analysis
     - ☐ Cost-effectiveness analysis
     - ☐ Cost-utility analysis
     - ☐ Cost-benefit analysis
   - ☐ None of the above (if none of the above – the study is excluded)

2. **Is the population included in the study 18 years of age and/or older?**
   - ☐ YES
   - ☐ NO (if not – the study is excluded)

3. **Is one or more of the included drugs mentioned in the abstract?**
   - ☐ YES (if yes, please indicate which one by checking the box beside each mentioned drug)
   - ☐ NO (if not – the study is exclude)

   ☐ **Anticonvulsant drugs**
   - ☐ pregabalin
   - ☐ gabapentin

   ☐ **SNRI**
   - ☐ venlafaxine
   - ☐ milnacipran
   - ☐ duloxetine

   ☐ **Tricyclic antidepressants**
   - ☐ amitryptiline
   - ☐ clomipramine
   - ☐ nortriptyline
   - ☐ imipramine
   - ☐ maprotiline

4. **Is the following indication mentioned in the abstract?**
   - ☐ YES (if yes, please indicate which one by checking the box beside the mentioned indication)
   - ☐ NO (if not – the study is excluded)

     ☐ **Neuropathic pain**

Appendix I

Database: EMBASE <1980 to 2007 Week 07>
Search Strategy:
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1 anticonvulsive agent/ or carbamazepine/ or 298-46-4.rn. or 8047-84-5.rn. or (carbamazepin: or Amizepin: or Atretol or Biston or Calepsin or Carbategral or Carbatrol or Convuline or Epimax or Epitol or Equetro or Finlepsin or "G 32883" or G32883 or Lexin or Mazepine or Neurotol or Neurotop or Servimazepin or Sirtal or Tegral or Tegretal or Tegretol or Tegrital or Telesmin or Teril or Timonil).mp. (48485)
2 gabapentin/ or 60142-96-3.rn. or (gabapentin: or "Ci 945" or Ci945 or "Go 3450" or Go3450 or "Goe 3450" or Goe3450 or Neurontin:).mp. (8591)
3 Lamotrigine/ or 84057-84-1.rn. or (Lamotrigine or "Bw 430c:" or Bw430c: or Labileno or Lamictal).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (7472)
4 etiracetam/ or 102767-28-2.rn. or 33996-58-6.rn. or (Etiracetam or Levetiracetam or Etirazetam or Keppra or "Lo 59" or Lo59 or "Ucb 6474" or Ucb6474 or "Ucb L059" or "ucb l 059" or ucbl059).mp. (2049)
5 oxcarbazepine/ or 28721-07-5.rn. or (oxcarbazepine or Apydan or "GP 47680" or GP47680 or Oxocarbazepine or Timox or Trileptal).mp. (2787)
6 pregabalin/ or 148553-50-8.rn. or (pregabalin or "Ci 1008" or Ci1008 or Lyrica or "Pd 144723" or Pd144723).mp. (844)
7 topiramate/ or 97240-79-4.rn. or (topiramate or Epitomax or "MCN 4853" or MCN4853 or "Rwj 17021:" or Rwj17021: or Topamax or Topimax).mp. (5261)
8 Harkoseride/ or 175481-36-4.rn. or (Harkoseride or Lacosamide or "Add 234037" or Add234037 or Erlosamide or "Spm 927" or Spm927).mp. (55)
9 valproic acid/ or valproic acid derivative/ or 1069-66-5.rn. or 99-66-1.rn. or ((valproic adj2 acid) or "Abbott 44090" or Abbott44090 or (Alpha adj2 Propylvalerate) or (Alpha adj2 Propylvaleric) or Apilepsin or Convulex or Depacon or Depakene or Depakin: or Deprakine or "Di N Propylacet:" or DiNPropylacet: or Dipropylacetate or Dipropylacetatic or (Dipropyl adj2 Acetic) or Dipropylacetic or Diprosin or Epilim or Epival or Ergenyl or Everiden or Goilim or "Kw 6066 N" or Kw6066N or Labazene or Leptilan or Leptilanil or Mylproin or (Myproic adj2 Acid) or "N Dipropylacetic Acid" or (Dipropylacetic adj2 Acid) or Orfiril or Orlept or "2 Propylpentanoate" or 2Propylpentanoate or "2 Propylpentanoic Acid" or "2 Propylvalerate Sodium" or "2 Propylvaleric Acid" or Propymal or (Sodium adj2 Valproate) or Valerin or Valparin or Valpro or Valproate or Vupral).mp. (25610)
10 or/1-9 (64697)
11 serotonin uptake inhibitors/ or citalopram/ or 59729-33-8.rn. or (Citalopram or Celexa or Cipramil or Cytalopram or Elopram or "Lu 10 171" or "Lu 10171" or Lu10171 or Nitalapram or Sepram or Seropram or "Zd 211" or Zd211).mp. (23182)
12 escitalopram/ or (escitalopram or Cipralex or Lexapro or "Lu 26054 0" or "Lu 260540" or Lu260540).mp. (1077)
13 fluoxetine/ or 54910-89-3.rn. or (fluoxetine or "Compound 110140" or Compound110140 or Fluctin: or Flunirin or Fluoxifar or "Lilly 110140" or Lilly110140 or Lovan or "Ly 110140" or Ly110140 or Prosac or Prozac or Prozamin or Sarafem).mp. (21457)

14 fluvoxamine/ or 54739-18-3.rn. or (fluvoxamine or "Du 23000" or Du23000 or Dumirox or Fluroxamine).mp. (7550)
15 paroxetine/ or 61869-08-7.rn. or (paroxetine or Aropax or "Brl 29060:" or Brl29060: or Deroxat or Dexorat or "Fg 7051" or Fg7051 or Motivan or Paroxetine or Paxil or Pexeva or Seroxat or "Si 211103" or Si211103 or Tagonis).mp. (12376)
16 sertraline/ or 79617-96-2.rn. or (sertraline or altruline or aremis or besitran or gladem or lustral or sealdin or zoloft or "Cp 51974:" or Cp51974: or Serad or Serlain or Tresleen).mp. (10018)
17 venlafaxine/ or 93413-69-5.rn. or (Venlafaxine or Efexor or Effexor or "Wy 45030" or Wy45030).mp. (6746)
18 Duloxetine/ or 116539-58-3.rn. or (duloxetine or Ariclaim or Cymbalta or "Ly 248686" or Ly248686 or Xeristar or Yentreve).mp. (1147)
19 Milnacipran/ or 92623-85-3.rn. or (milnacipran or Dalcipran or "F 2207" or F2207 or Ixel or Midalcipran or "Tn 912" or Tn912 or Toledomin).mp. (621)
20 or/11-19 (43723)
21 tricyclic antidepressant agent/ or adinazolam mesilate/ or amineptine/ or amitriptyline/ or amitriptyline plus perphenazine/ or amitriptylinoxide/ or amoxapine/ or butriptyline/ or cianopramine/ or clomipramine/ or danitracen/ or demexiptiline/ or desipramine/ or dibenzepin/ or dimetacrin/ or dosulepin/ or doxepin/ or etizolam/ or 2 hydroxydesipramine/ or 10 hydroxynortriptyline/ or imipramine/ or imipraminoxide/ or iprindole/ or limbitrol/ or lofepramine/ or melitracen/ or metapramine/ or nitroxazepine/ or norclomipramine/ or nordoxepin/ or nortrimipramine/ or nortriptyline/ or noxiptiline/ or opipramol/ or propizepine/ or protriptyline/ or quinupramine/ or s 3344/ or tampramine/ or tandamine/ or tianeptine/ or trimipramine/ or trimipramine maleate/ (58448)
22 or/11-20 (43723)
23 Botulinum Toxin A/ or 93384-43-1.rn. or botulinum toxin b/ or botulinum toxin e/ or (botulinum: or botulinium: or botox or dysport or oculinum).mp. (10568)
24 or/10,22-23 (110354)
25 randomized controlled trial/ or randomization/ or double blind procedure/ or single blind procedure/ or triple blind procedure/ or Placebo/ or (((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)) or (placebo$ or random$)).mp. or ((random: adj10 control: adj 5 trial:) or (rct or rcts) or (double adj5 blind:) or (tripl: adj5 blind:) or randomiz: or randomis:).mp. (451051)
26 24 and 25 (13042)
27 anticonvulsive agent/ct or carbamazepine/ct or gabapentin/ct or Lamotrigine/ct or etiracetam/ct or oxcarbazepine/ct or pregabalin/ct or Harkoseride/ct or valproic acid/ct or valproic acid derivative/ct or serotonin uptake inhibitors/ct or citalopram/ct or escitalopram/ct or fluoxetine/ct or fluvoxamine/ct or paroxetine/ct or sertraline/ct or venlafaxine/ct or Duloxetine/ct or Milnacipran/ct or tricyclic antidepressant agent/ct or adinazolam mesilate/ct or amineptine/ct or amitriptyline/ct or amitriptyline plus perphenazine/ct or amitriptylinoxide/ct or amoxapine/ct or butriptyline/ct or cianopramine/ct or clomipramine/ct or danitracen/ct or demexiptiline/ct or desipramine/ct or dibenzepin/ct or dimetacrin/ct or dosulepin/ct or doxepin/ct or etizolam/ct or 2 hydroxydesipramine/ct or 10 hydroxynortriptyline/ct or imipramine/ct or imipraminoxide/ct or iprindole/ct or limbitrol/ct or lofepramine/ct or melitracen/ct or metapramine/ct or nitroxazepine/ct or norclomipramine/ct or nordoxepin/ct or nortrimipramine/ct or nortriptyline/ct or noxiptiline/ct or opipramol/ct or propizepine/ct or protriptyline/ct or quinupramine/ct or s 3344/ct or tampramine/ct or tandamine/ct or tianeptine/ct or trimipramine/ct or trimipramine

maleate/ct or botulinum toxin/ct or botulinum toxin a/ct or botulinum toxin b/ct or botulinum toxin e/ct (12581)
28 26 or 27 (19521)
29 chronic:.mp. (466223)
30 chronic pain/ or (((chronic: or constant) adj5 pain:) or (pain adj2 pathway:) or (pain adj2 path) or (pain adj2 paths)).ti,ab. (24671)
31 musculoskeletal disease/ or morning stiffness/ or musculoskeletal pain/ or musculoskeletal stiffness/ or arthropathy/ or ankle instability/ or arthralgia/ or ehlers danlos syndrome/ or hemarthrosis/ or joint contracture/ or joint degeneration/ or joint destruction/ or joint effusion/ or joint hypermobility/ or joint instability/ or joint laxity/ or joint limitation/ or joint necrosis/ or joint stiffness/ or joint swelling/ or nail patella syndrome/ or neuropathic joint disease/ or patellofemoral pain syndrome/ or spondyloarthropathy/ or synovial cyst/ or temporomandibular joint disorder/ or vibration disease/ or ankylosis/ or ankylosing spondylitis/ or temporomandibular ankylosis/ or arthritis/ or adjuvant arthritis/ or antisynthetase syndrome/ or behcet disease/ or blau syndrome/ or chronic arthritis/ or gout/ or hemorrhagic arthritis/ or papa syndrome/ or pigmented villonodular synovitis/ or polyarthritis/ or pseudogout/ or psoriatic arthritis/ or reactive arthritis/ or reiter syndrome/ or infectious arthritis/ or bacterial arthritis/ or gonococcal arthritis/ or lyme disease/ or tuberculous arthritis/ or monarthritis/ or coxitis/ or knee arthritis/ or sacroiliitis/ or osteoarthritis/ or hip osteoarthritis/ or knee osteoarthritis/ or spondylosis/ or cervical spondylosis/ or rheumatoid arthritis/ or adult onset still disease/ or felty syndrome/ or juvenile rheumatoid arthritis/ or rheumatoid nodule/ or spondylitis/ or spondylarthritis/ or tuberculous spondylitis/ or joint malformation/ or arthrogryposis/ or congenital hip dislocation/ or congenital pseudarthrosis/ or coxa vara/ or hip dysplasia/ or hip malformation/ or larsen syndrome/ or osteoarthropathy/ or hypertrophic osteoarthropathy/ or periarticular joint disease/ or bursitis/ or carpal tunnel syndrome/ or cubital tunnel syndrome/ or farber disease/ or shoulder hand syndrome/ or tarsal tunnel syndrome/ or periarthritis/ or humeroscapular periarthritis/ or tendinitis/ or achilles tendinitis/ or tenosynovitis/ or synovitis/ or sapho syndrome/ (170160)
32 pain/ or allodynia/ or cystalgia/ or dysmenorrhea/ or dyspareunia/ or dysuria/ or eyelid pain/ or eye pain/ or female genital pain/ or flank pain/ or genital pain/ or hyperalgesia/ or hypoalgesia/ or intractable pain/ or limb pain/ or musculoskeletal chest pain/ or musculoskeletal pain/ or neck pain/ or noncardiac chest pain/ or odynophagia/ or pelvis pain syndrome/ or phantom pain/ or posttraumatic pain/ or precordial pain/ or psychogenic pain/ or retrosternal pain/ or shoulder pain/ or sinus pain/ or skin pain/ or spinal pain/ or substernal pain/ or thorax pain/ or urethral pain/ or vagina pain/ or vein pain/ or vulvodynia/ or abdominal pain/ or abdominal angina/ or lower abdominal pain/ or upper abdominal pain/ or backache/ or low back pain/ or bone pain/ or metatarsalgia/ or schnitzler syndrome/ or burning sensation/ or epigastric burning/ or skin burning sensation/ or vaginal burning sensation/ or "headache and facial pain"/ or chronic paroxysmal hemicrania/ or cluster headache/ or face pain/ or headache/ or heavy-headedness/ or hypnic headache/ or postdural puncture headache/ or sinus headache/ or sunct syndrome/ or temporal arteritis/ or trigeminus neuralgia/ or vascular headache/ or chronic daily headache/ or chronic tension headache/ or hemicrania continua/ or new daily persistent headache/ or transformed migraine/ or migraine/ or familial hemiplegic migraine/ or migraine aura/ or migraine with aura/ or migraine without aura/ or tension headache/ or episodic tension headache/ or leg pain/ or ankle pain/ or erythromelalgia/ or foot pain/ or heel pain/ or knee pain/ or patellofemoral pain syndrome/ or myalgia/ or compartment syndrome/ or eosinophilia myalgia

syndrome/ or fibromyalgia/ or intermittent claudication/ or myofascial pain/ or neuralgia/ or burning feet syndrome/ or cauda equina syndrome/ or cervicobrachial neuralgia/ or cubital tunnel syndrome/ or deafferentation pain/ or glossopharyngeal neuralgia/ or herpes zoster oticus/ or ischialgia/ or meralgia paresthetica/ or neuropathic pain/ or otalgia/ or postherpetic neuralgia/ or proctalgia/ or radicular pain/ or tarsal tunnel syndrome/ or thorax outlet syndrome/ or complex regional pain syndrome/ or complex regional pain syndrome type i/ or algodystrophy/ or posttraumatic osteoporosis/ or shoulder hand syndrome/ or sympathetic dystrophy/ or complex regional pain syndrome type ii/ or causalgia/ or scrotal pain/ or acute scrotum/ or chronic scrotal pain/ or visceral pain/ or biliary colic/ or biliary tract pain/ or colic/ or esophagus pain/ or gastrointestinal pain/ or kidney colic/ or kidney pain/ or liver pain/ or pleural pain/ or stomach pain/ or urinary tract pain/ or epigastric pain/ or epigastric discomfort/ or epigastric fullness/ (262954)

33 demyelinating disease/ or alpers disease/ or chronic inflammatory demyelinating polyneuropathy/ or demyelination/ or marchiafava bignami disease/ or multiple sclerosis/ or schilder disease/ (33700)

34 neuromuscular junction disorder/ or congenital myasthenic syndrome/ or eaton lambert syndrome/ or myasthenia/ or myasthenia gravis/ or myasthenia like syndrome/ (8752)

35 neuropathy/ or allergic neuropathy/ or demyelinating neuropathy/ or mononeuropathy multiplex/ or motor neuropathy/ or narp syndrome/ or nerve conduction disorder/ or nerve degeneration/ or nerve lesion/ or sensorimotor neuropathy/ or sensory neuropathy/ or autonomic neuropathy/ or aganglionosis/ or autonomic dysreflexia/ or colon aganglionosis/ or frey syndrome/ or horner syndrome/ or plexus paresis/ or cranial neuropathy/ or accessory nerve disease/ or garcin syndrome/ or hypoglossal nerve disease/ or oculomotor nerve disease/ or trochlear nerve disease/ or abducens nerve disease/ or abducens nerve injury/ or abducens nerve paralysis/ or cranial nerve injury/ or facial nerve injury/ or optic nerve injury/ or cranial nerve paralysis/ or bulbar paralysis/ or progressive bulbar palsy/ or facial nerve paralysis/ or bell palsy/ or herpes zoster oticus/ or melkersson rosenthal syndrome/ or moebius syndrome/ or burning feet syndrome/ (50807)

36 lupus erythematosus/ or lupus erythematosus nephritis/ or lupus like syndrome/ or systemic lupus erythematosus/ or systemic lupus erythematosus rash/ or skin lupus erythematosus/ or discoid lupus erythematosus/ or scleroderma/ or localized scleroderma/ or linear scleroderma/ or morphea/ or systemic sclerosis/ or diffuse scleroderma/ or limited scleroderma/ or syndrome crest/ (40922)

37 paralysis/ or amyotrophic lateral sclerosis/ or centronuclear myopathy/ or cerebral palsy/ or diaphragm paralysis/ or familial hemiplegic migraine/ or flaccid paralysis/ or hemiparesis/ or hemiplegia/ or kugelberg welander disease/ or locked in syndrome/ or mitochondrial myopathy/ or monoplegia/ or myasthenia gravis/ or myotonic dystrophy/ or nemaline myopathy/ or paraplegia/ or paresis/ or periodic paralysis/ or peripheral paralysis/ or pseudobulbar palsy/ or quadriplegia/ or spastic paraplegia/ or spastic paresis/ or spinal paralysis/ or tongue paralysis/ or vocal cord paralysis/ or wallenberg syndrome/ or werdnig hoffmann disease/ (60916)

38 myelitis/ or allergic encephalomyelitis/ or chronic fatigue syndrome/ or encephalomyelitis/ or poliomyelitis/ or postpoliomyelitis syndrome/ (16678)

39 muscular dystrophy/ or becker muscular dystrophy/ or duchenne muscular dystrophy/ or emery dreifuss muscular dystrophy/ or facioscapulohumeral muscular dystrophy/ or fukuyama congenital muscular dystrophy/ or limb girdle muscular dystrophy/ or miyoshi myopathy/ or

muscle eye brain disease/ or myotonic dystrophy/ or oculopharyngeal muscular dystrophy/ or progressive muscular dystrophy/ or walker warburg syndrome/ (13826)
40 or/31-39 (581135)
41 28 and 29 and 40 (1129)
42 28 and 30 (609)
43 41 or 42 (1209)
44 limit 43 to human (1206)
45 limit 44 to (adult <18 to 64 years> or aged <65+ years>) (360)
46 exp Neoplasm/ (1289875)
47 44 not 46 (1135)
48 limit 47 to (adult <18 to 64 years> or aged <65+ years>) (348)
49 from 48 keep 1-199 (199)
50 from 48 keep 200-348 (149)
51 47 not 48 (787)
52 from 51 keep 1-199 (199)
53 from 51 keep 200-399 (200)
54 from 51 keep 400-599 (200)
55 from 51 keep 600-787 (188)
56 economic aspect/ or "cost"/ or "health care cost"/ or "drug cost"/ or health care financing/ or "nursing cost"/ or "hospital cost"/ or economics/ or finance/ or health economics/ or economic evaluation/ or "cost benefit analysis"/ or "cost control"/ or "cost effectiveness analysis"/ or "cost minimization analysis"/ or "cost of illness"/ or "cost utility analysis"/ or fee/ or hospital billing/ or hospital charge/ or medical fee/ or health insurance/ or "health plan employer data and information set"/ or medicaid/ or medicare/ or national health insurance/ or private health insurance/ or prospective payment/ or prospective pricing/ or public health insurance/ or reimbursement/ or research utilization group/ or pharmacoeconomics/ or drug approval/ or drug formulary/ or drug utilization/ or "utilization review"/ (255098)
57 24 and 29 and 40 and 56 (334)
58 57 not 47 (185)
59 from 58 keep 1-185 (185)

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Appendix J

Database: Ovid MEDLINE(R) <1950 to February Week 2 2007>
Search Strategy:
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1 anticonvulsants/ or carbamazepine/ or (carbamazepin: or Amizepin: or Atretol or Biston or Calepsin or Carbategral or Carbatrol or Convuline or Epimax or Epitol or Equetro or Finlepsin or "G 32883" or G32883 or Lexin or Mazepine or Neurotol or Neurotop or Servimazepin or Sirtal or Tegral or Tegretal or Tegretol or Tegrital or Telesmin or Teril or Timonil).mp. (34477)
2 gabapentin/ or (gabapentin: or "Ci 945" or Ci945 or "Go 3450" or Go3450 or "Goe 3450" or Goe3450 or Neurontin:).mp. (2174)
3 Lamotrigine/ or (Lamotrigine or "Bw 430c:" or Bw430c: or Labileno or Lamictal).mp. (2128)
4 (Etiracetam or Levetiracetam or Etirazetam or Keppra or "Lo 59" or Lo59 or "Ucb 6474" or Ucb6474 or "Ucb L059" or "ucb l 059" or ucbl059).mp. (594)
5 oxcarbazepine/ or (oxcarbazepine or Apydan or "GP 47680" or GP47680 or Oxocarbazepine or Timox or Trileptal).mp. (701)
6 pregabalin/ or (pregabalin or "Ci 1008" or Ci1008 or Lyrica or "Pd 144723" or Pd144723).mp. (270)
7 topiramate/ or (topiramate or Epitomax or "MCN 4853" or MCN4853 or "Rwj 17021:" or Rwj17021: or Topamax or Topimax).mp. (1451)
8 (Harkoseride or Lacosamide or "Add 234037" or Add234037 or Erlosamide or "Spm 927" or Spm927).mp. (24)
9 valproic acid/ or valproic acid derivative/ or ((valproic adj2 acid) or "Abbott 44090" or Abbott44090 or (Alpha adj2 Propylvalerate) or (Alpha adj2 Propylvaleric) or Apilepsin or Convulex or Depacon or Depakene or Depakin: or Deprakine or "Di N Propylacet:" or DiNPropylacet: or Dipropylacetate or Dipropylacetatic or (Dipropyl adj2 Acetic) or Dipropylacetic or Diprosin or Epilim or Epival or Ergenyl or Everiden or Goilim or "Kw 6066 N" or Kw6066N or Labazene or Leptilan or Leptilanil or Mylproin or (Myproic adj2 Acid) or "N Dipropylacetic Acid" or (Dipropylacetic adj2 Acid) or Orfiril or Orlept or "2 Propylpentanoate" or 2Propylpentanoate or "2 Propylpentanoic Acid" or "2 Propylvalerate Sodium" or "2 Propylvaleric Acid" or Propymal or (Sodium adj2 Valproate) or Valerin or Valparin or Valpro or Valproate or Vupral).mp. (9468)
10 or/1-9 (40728)
11 serotonin uptake inhibitors/ or citalopram/ or (Citalopram or Celexa or Cipramil or Cytalopram or Elopram or "Lu 10 171" or "Lu 10171" or Lu10171 or Nitalapram or Sepram or Seropram or "Zd 211" or Zd211).mp. (10716)
12 (escitalopram or Cipralex or Lexapro or "Lu 26054 0" or "Lu 260540" or Lu260540).mp. (218)
13 fluoxetine/ or (fluoxetine or "Compound 110140" or Compound110140 or Fluctin: or Flunirin or Fluoxifar or "Lilly 110140" or Lilly110140 or Lovan or "Ly 110140" or Ly110140 or Prosac or Prozac or Prozamin or Sarafem).mp. (7129)
14 fluvoxamine/ or (fluvoxamine or "Du 23000" or Du23000 or Dumirox or Fluroxamine).mp. (1881)

15 paroxetine/ or (paroxetine or Aropax or "Brl 29060:" or Brl29060: or Deroxat or Dexorat or "Fg 7051" or Fg7051 or Motivan or Paroxetine or Paxil or Pexeva or Seroxat or "Si 211103" or Si211103 or Tagonis).mp. (3386)
16 sertraline/ or sertraline (nm) or (sertraline or altruline or aremis or besitran or gladem or lustral or sealdin or zoloft or "Cp 51974:" or Cp51974: or Serad or Serlain or Tresleen).mp. (2171)
17 (Venlafaxine or Efexor or Effexor or "Wy 45030" or Wy45030).mp. (1478)
18 (duloxetine or Ariclaim or Cymbalta or "Ly 248686" or Ly248686 or Xeristar or Yentreve).mp. (356)
19 (milnacipran or Dalcipran or "F 2207" or F2207 or Ixel or Midalcipran or "Tn 912" or Tn912 or Toledomin).mp. (208)
20 or/11-19 (18672)
21 antidepressive agents, tricyclic/ or Dibenzazepines/ or AZEPINES/ or BENZAZEPINES/ (17899)
22 amitriptyline/ or (amitriptylin: or amitrol or anapsique or damilen or domical or elavil or endep or laroxyl or lentizol or novoprotect or saroten or sarotex or syneudon or triptafen or tryptanol or tryptine or tryptizol).mp. (6555)
23 clomipramine/ or (Clomipramine or chlomipramine or anafranil or hydiphen).mp. (3132)
24 desipramine/ or desipramine:.mp. (6611)
25 dothiepin/ or (dosulepin or dothiepin or prothiaden).mp. (345)
26 doxepin/ or (doxepin?? or aponal or deptran or desidox or doneurin or doxepia or espadox or mareen or prudoxin or quitaxon or sin?quan or xepin or zonalon).mp. (1104)
27 imipramine/ or (imipramine or imidobenzyle or imizin or janimine or melipramine or norchlorimipramine or pryleugan or tofranil).mp. (10845)
28 Lofepramine/ or (Lofepramine or lopramine or deftan or feprapax or gam?nil or (leo adj2 "640") or leo640 or (lofepramine adj2 hydrochloride) or lomont).mp. (160)
29 Iprindole/ or (Antidepressive Agents/ and Indoles/) or iprindole:.mp. (492)
30 nortriptyline/ or (desitriptyline or desmethylamitriptylin or allegron or aventyl or norfenazin or nortrilen or pamelor or paxtibi).mp. (1726)
31 Opipramol/ or (Opipramol or insidon).mp. (234)
32 Protriptyline/ or (Protriptyline or vivactil).mp. (361)
33 Trimipramine/ or (Trim?pramine or stangyl or surmontil).mp. (428)
34 or/21-33 (39006)
35 botulinum toxins/ or botulinum toxin type a/ or (botulinum: or botox or dysport or oculinum).mp. (9443)
36 or/10,20,34-35 (101874)
37 randomized control trials/ or ((random: adj10 control: adj 5 trial:) or (rct or rcts) or (double adj5 blind:) or (tripl: adj5 blind:) or randomiz: or randomis:).mp. (346824)
38 36 and 37 (10017)
39 limit 36 to randomized controlled trial (6101)
40 38 or 39 (10017)
41 limit 40 to humans (9886)
42 joint diseases/ or ankylosis/ or spondylitis, ankylosing/ or arthralgia/ or shoulder pain/ or arthritis/ or arthritis, experimental/ or arthritis, infectious/ or arthritis, reactive/ or arthritis, psoriatic/ or arthritis, rheumatoid/ or arthritis, juvenile rheumatoid/ or caplan's syndrome/ or felty's syndrome/ or rheumatoid nodule/ or sjogren's syndrome/ or still's disease, adult-onset/ or

chondrocalcinosis/ or gout/ or arthritis, gouty/ or osteoarthritis/ or osteoarthritis, hip/ or osteoarthritis, knee/ or spinal osteophytosis/ or periarthritis/ or reiter syndrome/ or rheumatic fever/ or rheumatic nodule/ or wissler's syndrome/ or spondylarthritis/ or spondylarthropathies/ or arthrogryposis/ or arthropathy, neurogenic/ or bursitis/ or chondromatosis, synovial/ or contracture/ or hip contracture/ or hallux limitus/ or hallux rigidus/ or hemarthrosis/ or hip dislocation, congenital/ or hydrarthrosis/ or joint deformities, acquired/ or joint instability/ or joint loose bodies/ or metatarsalgia/ or nail-patella syndrome/ or osteoarthropathy, primary hypertrophic/ or osteoarthropathy, secondary hypertrophic/ or patellofemoral pain syndrome/ or shoulder impingement syndrome/ or synovitis/ or synovitis, pigmented villonodular/ or temporomandibular joint disorders/ or temporomandibular joint dysfunction syndrome/ or fibromyalgia/ or hyperostosis, sternocostoclavicular/ or polymyalgia rheumatica/ or tennis elbow/ or digestive system diseases/ or stomatognathic diseases/ or arthrit:.ti,ab. (225891)
43 headache disorders/ or headache disorders, primary/ or migraine disorders/ or migraine with aura/ or migraine without aura/ or tension-type headache/ or trigeminal autonomic cephalalgias/ or cluster headache/ or paroxysmal hemicrania/ or sunct syndrome/ or headache disorders, secondary/ or post-dural puncture headache/ or post-traumatic headache/ or vascular headaches/ or (headache: or migrain:).ti,ab. (45684)
44 demyelinating autoimmune diseases, cns/ or "diffuse cerebral sclerosis of schilder"/ or encephalomyelitis, acute disseminated/ or leukoencephalitis, acute hemorrhagic/ or multiple sclerosis/ or multiple sclerosis, chronic progressive/ or multiple sclerosis, relapsing-remitting/ or neuromyelitis optica/ or myelitis, transverse/ or lambert-eaton myasthenic syndrome/ or myasthenia gravis/ or myasthenia gravis, autoimmune, experimental/ or myasthenia gravis, neonatal/ or polyradiculoneuropathy/ or guillain-barre syndrome/ or miller fisher syndrome/ or "hereditary sensory and autonomic neuropathies"/ or dysautonomia, familial/ or polyradiculoneuropathy, chronic inflammatory demyelinating/ or stiff-person syndrome/ or uveomeningoencephalitic syndrome/ or vasculitis, central nervous system/ or aids arteritis, central nervous system/ or lupus vasculitis, central nervous system/ or temporal arteritis/ (54815)
45 lupus erythematosus, cutaneous/ or lupus erythematosus, discoid/ or panniculitis, lupus erythematosus/ or lupus erythematosus, systemic/ or lupus nephritis/ or lupus vasculitis, central nervous system/ or lupus.ti,ab. (46880)
46 pain:.mp. or pain/ or back pain/ or low back pain/ or facial pain/ or headache/ or labor pain/ or metatarsalgia/ or neck pain/ or neuralgia/ or neuralgia, postherpetic/ or sciatica/ or pain, intractable/ or pain, referred/ or paralysis/ or facial paralysis/ or hemiplegia/ or ophthalmoplegia/ or ophthalmoplegia, chronic progressive external/ or supranuclear palsy, progressive/ or paraplegia/ or brown-sequard syndrome/ or pseudobulbar palsy/ or quadriplegia/ or respiratory paralysis/ or vocal cord paralysis/ or paresis/ or paraparesis/ or paraparesis, spastic/ (376250)
47 neuromuscular diseases/ or fatigue syndrome, chronic/ or isaacs syndrome/ or motor neuron disease/ or amyotrophic lateral sclerosis/ or bulbar palsy, progressive/ or muscular atrophy, spinal/ or "spinal muscular atrophies of childhood"/ or poliomyelitis/ or postpoliomyelitis syndrome/ or muscular diseases/ or muscular disorders, atrophic/ or muscular dystrophies/ or distal myopathies/ or muscular dystrophies, limb-girdle/ or muscular dystrophy, duchenne/ or muscular dystrophy, emery-dreifuss/ or muscular dystrophy, facioscapulohumeral/ or muscular dystrophy, oculopharyngeal/ or myotonic dystrophy/ or eosinophilia-myalgia syndrome/ or fibromyalgia/ or mitochondrial myopathies/ or mitochondrial encephalomyopathies/ or melas syndrome/ or merrf syndrome/ or ophthalmoplegia, chronic progressive external/ or kearns-sayer syndrome/ or myopathies, structural, congenital/ or

myopathies, nemaline/ or myopathy, central core/ or myositis/ or dermatomyositis/ or myositis, inclusion body/ or polymyositis/ or pyomyositis/ or myotonic disorders/ or myotonia congenita/ or paralyses, familial periodic/ or hypokalemic periodic paralysis/ or paralysis, hyperkalemic periodic/ or neuromuscular junction diseases/ or botulism/ or lambert-eaton myasthenic syndrome/ or myasthenia gravis/ or myasthenia gravis, autoimmune, experimental/ or myasthenia gravis, neonatal/ or myasthenic syndromes, congenital/ or peripheral nervous system diseases/ or acrodynia/ or amyloid neuropathies/ or amyloid neuropathies, familial/ or brachial plexus neuropathies/ or brachial plexus neuritis/ or complex regional pain syndromes/ or causalgia/ or reflex sympathetic dystrophy/ or diabetic neuropathies/ or guillain-barre syndrome/ or miller fisher syndrome/ or hand-arm vibration syndrome/ or mononeuropathies/ or femoral neuropathy/ or median neuropathy/ or carpal tunnel syndrome/ or peroneal neuropathies/ or radial neuropathy/ or sciatic neuropathy/ or sciatica/ or tibial neuropathy/ or tarsal tunnel syndrome/ or ulnar neuropathies/ or cubital tunnel syndrome/ or ulnar nerve compression syndromes/ or nerve compression syndromes/ or thoracic outlet syndrome/ or cervical rib syndrome/ or neuralgia/ or neuralgia, postherpetic/ or neuritis/ or neuritis, autoimmune, experimental/ or neurofibromatosis 1/ or pain insensitivity, congenital/ or peripheral nervous system neoplasms/ or nerve sheath neoplasms/ or neurilemmoma/ or neurofibroma/ or neurofibroma, plexiform/ or neurofibrosarcoma/ or polyneuropathies/ or tarlov cysts/ or stiff-person syndrome/ or neuropath:.ti,ab. (205087)
48 or/42-47 (833309)
49 Chronic Disease/ or chronic:.mp. (626318)
50 41 and 48 and 49 (317)
51 (((chronic: or constant) adj5 pain:) or (pain adj2 pathway:) or (pain adj2 path) or (pain adj2 paths)).ti,ab. (20065)
52 41 and 51 (152)
53 50 or 52 (322)
54 limit 53 to "all adult (19 plus years)" (211)
55 53 not 54 (111)
56 economics/ or "costs and cost analysis"/ or "cost allocation"/ or cost-benefit analysis/ or "cost control"/ or "cost savings"/ or "cost of illness"/ or "cost sharing"/ or "deductibles and coinsurance"/ or medical savings accounts/ or health care costs/ or direct service costs/ or drug costs/ or employer health costs/ or hospital costs/ or health expenditures/ or economics, hospital/ or hospital charges/ or economics, medical/ or fees, medical/ or economics, pharmaceutical/ or "fees and charges"/ or capitation fee/ or fee-for-service plans/ or fees, pharmaceutical/ or prescription fees/ or "rate setting and review"/ (174577)
57 (36 and 48 and 49 and 56) or (36 and 51 and 56) (5)
58 36 and 48 and 56 (51)
59 36 and 48 and ec.fs. (67)
60 58 or 59 (78)
61 from 60 keep 1-78 (78)

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Appendix K

Database: EBM Reviews - Cochrane Database of Systematic Reviews <1st Quarter 2007>
Search Strategy:
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35 ((atypical or chronic) adj5 pain:).mp. [mp=title, short title, abstract, full text, keywords, caption text] (215)
36 (ssri: or antidepressant: or botox or botulinum or (selective adj2 serotonin)).mp. [mp=title, short title, abstract, full text, keywords, caption text] (314)
37 35 and 36 (35)
38 (neuropath: or musculoskelet: or headache: or migraine: or joint: or arthrit: or lupus or spondylitis or neurologi: or neuromuscul: or parapleg: or quadripleg: or hemipleg: or paresis or dystrophy or sclerosis).mp. [mp=title, short title, abstract, full text, keywords, caption text] (2024)
39 36 and 38 (168)
40 pain:.mp. [mp=title, short title, abstract, full text, keywords, caption text] (1783)
41 39 and 40 (95)
42 37 or 41 (101)
43 from 42 keep 1-101 (101)

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Appendix L

Table A-3. Alternate cost-effectiveness analysis of ACs, SNRIs, and TCAs for the management of neuropathic pain by type of perspective using "Single Arm" response rates: Primary anlyses.

Perspective	Strategies	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Incremental C/E (ICER)
MOH	SNRIs	$418		77.4% Response rate		
	TCAs	$432	$14	71.4% Response rate	-5.9% Response rate	(Dominated)
	ACs	$587	$168	72.8% Response rate	-4.6% Response rate	(Dominated)
SOC	SNRIs	$1,830		77.4% Response rate		
	TCAs	$2,124	$294	71.4% Response rate	-5.9% Response rate	(Dominated)
	ACs	$2,193	$363	72.8% Response rate	-4.6% Response rate	(Dominated)
MOH	SNRIs	$418		48 PCDs		
	TCAs	$432	$14	38 PCDs	-11 PCDs	(Dominated)
	ACs	$587	$168	41 PCDs	-8 PCDs	(Dominated)
SOC	SNRIs	$1,830		48 PCDs		
	TCAs	$2,124	$294	38 PCDs	-11 PCDs	(Dominated)
	ACs	$2,193	$363	41 PCDs	-8 PCDs	(Dominated)

ACs = Anticonvulsants; C/E = Cost-effectiveness ratio; ICER = Incremental cost-effectiveness ratio; MOH = Ministry of Health; PCD= Pain controlled days; SOC = Society; SNRIs = Serotonin-norepinephrine reuptake inhibitors; TCAs = Tricyclic antidepressants.

Table A-4. One-way sensitivity results of alternate analyses ("single arm" response rates).

Sensitivity Variable	Perspective	Strategies	Cost	Incr Cost	Effectiveness	Incr Effectiveness	Incr C/E (ICER)
50% Response Rate							
ACs=0.301	MOH	SNRI	$420		76.1% Response rate		
lower limit		TCAs	$435	$15	69.5% Response rate	-6.6% Response rate	(Dominated)
		ACs	$613	$193	68.7% Response rate	-7.4% Response rate	(Dominated)
	SOC	SNRIs	$1,835		76.1% Response rate		
		TCAs	$2,134	$299	69.5% Response rate	-6.6% Response rate	(Dominated)
		ACs	$2,324	$489	68.7% Response rate	-7.4% Response rate	(Dominated)
	MOH	SNRIs	$420		48 PCDs		
		TCAs	$435	$15	37 PCDs	-11 PCDs	(Dominated)
		ACs	$613	$193	35 PCDs	-13 PCDs	(Dominated)
	SOC	SNRIs	$1,835		48 PCDs		
		TCAs	$2,134	$299	37 PCDs	-11 PCDs	(Dominated)
		ACs	$2,324	$489	35 PCDs	-13 PCDs	(Dominated)
ACs=0.425	MOH	SNRIs	$417		78.6% Response rate		
upper limit		TCAs	$430	$13	73.3% Response rate	-5.3% Response rate	(Dominated)
		ACs	$561	$144	76.6% Response rate	-2.0% Response rate	(Dominated)
	SOC	SNRIs	$1,825		78.6% Response rate		
		ACs	$2,065	$241	76.6% Response rate	-2.0% Response rate	(Dominated)
		TCAs	$2,114	$289	73.3% Response rate	-5.3% Response rate	(Dominated)
	MOH	SNRIs	$417		48 PCDs		
		TCAs	$430	$13	38 PCDs	-10 PCDs	(Dominated)
		ACs	$561	$144	46 PCDs	-3 PCDs	(Dominated)
	SOC	SNRIs	$1,825		48 PCDs		
		ACs	$2,065	$241	46 PCDs	-3 PCDs	(Dominated)
		TCAs	$2,114	$289	38 PCDs	-10 PCDs	(Dominated)

Sensitivity Variable	Perspective	Strategies	Cost	Incr Cost	Effectiveness	Incr Effectiveness	Incr C/E (ICER)
50% Response Rate	MOH	SNRIs	$431		74.3% Response rate		
SNRIs=0.413		TCAs	$434	$2	70.1% Response rate	-4.2% Response rate	(Dominated)
lower limit		ACs	$588	$156	71.6% Response rate	-2.7% Response rate	(Dominated)
	SOC	SNRIs	$1,916		74.3% Response rate		
		TCAs	$2,131	$215	70.1% Response rate	-4.2% Response rate	(Dominated)
		ACs	$2,199	$283	71.6% Response rate	-2.7% Response rate	(Dominated)
	MOH	SNRIs	$431		44 PCDs		
		TCAs	$434	$2	37 PCDs	-7 PCDs	(Dominated)
		ACs	$588	$156	40 PCDs	-4 PCDs	(Dominated)
	SOC	SNRIs	$1,916		44 PCDs		
		TCAs	$2,131	$215	37 PCDs	-7 PCDs	(Dominated)
		ACs	$2,199	$283	40 PCDs	-4 PCDs	(Dominated)
SNRIs=0.504	MOH	SNRIs	$406		80.2% Response rate		
upper limit		TCAs	$431	$25	72.7% Response rate	-7.5% Response rate	(Dominated)
		ACs	$586	$180	74.0% Response rate	-6.2% Response rate	(Dominated)
	SOC	SNRIs	$1,748		80.2% Response rate		
		TCAs	$2,118	$370	72.7% Response rate	-7.5% Response rate	(Dominated)
		ACs	$2,188	$440	74.0% Response rate	-6.2% Response rate	(Dominated)
	MOH	SNRIs	$406		52 PCDs		
		TCAs	$431	$25	38 PCDs	-14 PCDs	(Dominated)
		ACs	$586	$180	41 PCDs	-11 PCDs	(Dominated)
	SOC	SNRIs	$1,748		52 PCDs		
		TCAs	$2,118	$370	38 PCDs	-14 PCDs	(Dominated)
		ACs	$2,188	$440	41 PCDs	-11 PCDs	(Dominated)

Sensitivity Variable	Perspective	Strategies	Cost	Incr Cost	Effectiveness	Incr Effectiveness	Incr C/E (ICER)
50% Response Rate	MOH	SNRIs	$420		75.6% Response rate		
TCAs= 0.237		TCAs	$461	$41	65.9% Response rate	-9.7% Response rate	(Dominated)
lower limit		ACs	$589	$169	70.3% Response rate	-5.2% Response rate	(Dominated)
	SOC	SNRIs	$1,837		75.6% Response rate		
		ACs	$2,204	$367	70.3% Response rate	-5.2% Response rate	(Dominated)
		TCAs	$2,301	$464	65.9% Response rate	-9.7% Response rate	(Dominated)
	MOH	SNRIs	$420		48 PCDs		
		TCAs	$461	$41	30 PCDs	-17 PCDs	(Dominated)
		ACs	$589	$169	40 PCDs	-8 PCDs	(Dominated)
	SOC	SNRIs	$1,837		48 PCDs		
		TCAs	$2,204	$367	40 PCDs	-8 PCDs	(Dominated)
		ACs	$2,301	$464	30 PCDs	-17 PCDs	(Dominated)
TCAs= 0.408	MOH	TCAs	$405		76.5% Response rate		
upper limit		SNRIs	$417	$12	79.1% Response rate	2.6% Response rate	$451
		ACs	$584	$167	75.2% Response rate	-3.9% Response rate	(Dominated)
	SOC	SNRIs	$1,823		79.1% Response rate		
		TCAs	$1,955	$132	76.5% Response rate	-2.6% Response rate	(Dominated)
		ACs	$2,182	$359	75.2% Response rate	-3.9% Response rate	(Dominated)
	MOH	TCAs	$405		44 PCDs		
		SNRIs	$417	$12	48 PCDs	4 PCDs	$3
		ACs	$584	$167	41 PCDs	-7 PCDs	(Dominated)
	SOC	SNRIs	$1,823		48 PCDs		
		TCAs	$1,955	$132	44 PCDs	-4 PCDs	(Dominated)
		ACs	$2,182	$359	41 PCDs	-7 PCDs	(Dominated)

Sensitivity Variable	Perspective	Strategies	Cost	Incr Cost	Effectiveness	Incr Effectiveness	Incr C/E (ICER)
30% Response Rate							
ACs=0.473	MOH	SNRIs	$418		77.2% Response rate		
lower limit		TCAs	$432	$14	71.2% Response rate	-6.1% Response rate	(Dominated)
		ACs	$576	$158	72.4% Response rate	-4.8% Response rate	(Dominated)
	SOC	SNRIs	$1,830		77.2% Response rate		
		TCAs	$2,124	$294	71.2% Response rate	-6.1% Response rate	(Dominated)
		ACs	$2,212	$382	72.4%Response rate	-4.8% Response rate	(Dominated)
	MOH	SNRIs	$418		48 PCDs		
		TCAs	$432	$14	38 PCDs	-11 PCDs	(Dominated)
		ACs	$576	$158	41 PCDs	-7 PCDs	(Dominated)
	SOC	SNRIs	$1,830		48 PCDs		
		TCAs	$2,124	$294	38 PCDs	-11 PCDs	(Dominated)
		ACs	$2,212	$382	41 PCDs	-7 PCDs	(Dominated)
ACs=0.617	MOH	SNRIs	$419		77.5% Response rate		
upper limit		TCAs	$433	$14	71.7% Response rate	-5.8% Response rate	(Dominated)
		ACs	$597	$179	73.2% Response rate	-4.3% Response rate	(Dominated)
	SOC	SNRIs	$1,830		77.5% Response rate		
		TCAs	$2,124	$294	71.7% Response rate	-5.8% Response rate	(Dominated)
		ACs	$2,174	$344	73.2% Response rate	-4.3% Response rate	(Dominated)
	MOH	SNRIs	$419		48 PCDs		
		TCAs	$433	$14	38 PCDs	-11 PCDs	(Dominated)
		ACs	$597	$179	40 PCDs	-8 PCDs	(Dominated)
	SOC	SNRIs	$1,830		48 PCDs		
		TCAs	$2,124	$294	38 PCDs	-11 PCDs	(Dominated)
		ACs	$2,174	$344	40 PCDs	-8 PCDs	(Dominated)

Sensitivity Variable	Perspective	Strategies	Cost	Incr Cost	Effectiveness	Incr Effectiveness	Incr C/E (ICER)
30% Response Rate							
SNRIs=0.617	MOH	SNRIs	$422		76.9% Response rate		
lower limit		TCAs	$433	$11	71.3% Response rate	-5.7% Response rate	(Dominated)
		ACs	$587	$165	72.7% Response rate	-4.3% Response rate	(Dominated)
	SOC	SNRIs	$1,851		76.9% Response rate		
		TCAs	$2,125	$274	71.3% Response rate	-5.7% Response rate	(Dominated)
		ACs	$2,194	$342	72.7% Response rate	-4.3% Response rate	(Dominated)
	MOH	SNRIs	$422		48 PCDs		
		TCAs	$433	$11	38 PCDs	-10 PCDs	(Dominated)
		ACs	$587	$165	41 PCDs	-7 PCDs	(Dominated)
	SOC	SNRIs	$1,851		48 PCDs		
		TCAs	$2,125	$274	38 PCDs	-10 PCDs	(Dominated)
		ACs	$2,194	$342	41 PCDs	-7 PCDs	(Dominated)
SNRIs=0.704	MOH	SNRIs	$415		77.8% Response rate		
upper limit		TCAs	$432	$17	71.6% Response rate	-6.2% Response rate	(Dominated)
		ACs	$586	$171	73.0% Response rate	-4.8% Response rate	(Dominated)
	SOC	SNRIs	$1,809		77.8% Response rate		
		TCAs	$2,124	$315	71.6% Response rate	-6.2% Response rate	(Dominated)
		ACs	$2,193	$384	73.0% Response rate	-4.8% Response rate	(Dominated)
	MOH	SNRIs	$415		48 PCDs		
		TCAs	$432	$17	38 PCDs	-11 PCDs	(Dominated)
		ACs	$586	$171	41 PCDs	-8 PCDs	(Dominated)
	SOC	SNRIs	$1,809		48 PCDs		
		TCAs	$2,124	$315	38 PCDs	-11 PCDs	(Dominated)
		ACs	$2,193	$384	41 PCDs	-8 PCDs	(Dominated)

Sensitivity Variable	Perspective	Strategies	Cost	Incr Cost	Effectiveness	Incr Effectiveness	Incr C/E (ICER)
30% Response Rate							
TCAs=0.363	MOH	SNRIs	$420		77.1% Response rate		
lower limit		TCAs	$448	$28	71.1% Response rate	-6.1% Response rate	(Dominated)
		ACs	$589	$169	72.4% Response Rate	-4.7% Response rate	(Dominated)
	SOC	SNRIs	$1,831		77.1% Response rate		
		TCAs	$2,193	$361	71.1% Response rate	-6.1% Response rate	(Dominated)
		ACs	$2,195	$364	72.4% Response rate	-4.7% Response rate	(Dominated)
	MOH	SNRIs	$420		48 PCDs		
		TCAs	$448	$28	38 PCDs	-10 PCDs	(Dominated)
		ACs	$589	$169	41 PCDs	-8 PCDs	(Dominated)
	SOC	SNRIs	$1,831		48 PCDs		
		TCAs	$2,193	$361	38 PCDs	-10 PCDs	(Dominated)
		ACs	$2,195	$364	41 PCDs	-8 PCDs	(Dominated)
TCAs=0.622	MOH	TCAs	$417		71.8% Response rate		
upper limit		SNRIs	$417	$0	77.6% Response rate	5.8% Response rate	$6
		ACs	$585	$168	73.2% Response rate	-4.4% Response rate	(Dominated)
	SOC	SNRIs	$1,829		77.6% Response rate		
		TCAs	$2,055	$226	71.8% Response rate	-5.8% Response rate	(Dominated)
		ACs	$2,191	$362	73.2% Response rate	-4.4% Response rate	(Dominated)
	MOH	TCAs	$417		37 PCDs		
		SNRIs	$417	$0	48 PCDs	11 PCDs	$0
		ACs	$585	$168	41 PCDs	-8 PCDs	(Dominated)
	SOC	SNRIs	$1,829		48 PCDs		
		TCAs	$2,055	$226	37 PCDs	-11 PCDs	(Dominated)
		ACs	$2,191	$362	41 PCDs	-8 PCDs	(Dominated)

Sensitivity Variable	Perspective	Strategies	Cost	Incr Cost	Effectiveness	Incr Effectiveness	Incr C/E (ICER)
Medication Costs							
Max Standard	MOH	SNRIs	$422		77.4% Response rate		
&		TCAs	$442	$20	71.4% Response rate	-5.9% Response rate	(Dominated)
Max Titration		ACs	$607	$186	72.8% Response rate	-4.6% Response rate	(Dominated)
	SOC	SNRIs	$1,833		77.4% Response rate		
		TCAs	$2,134	$300	71.4% Response rate	-5.9% Response rate	(Dominated)
		ACs	$2,214	$380	72.8% Response rate	-4.6% Response rate	(Dominated)
	MOH	SNRIs	$422		48 PCDs		
		TCAs	$442	$20	38 PCDs	-11 PCDs	(Dominated)
		ACs	$607	$186	41 PCDs	-8 PCDs	(Dominated)
	SOC	SNRIs	$1,833		48 PCDs		
		TCAs	$2,134	$300	38 PCDs	-11 PCDs	(Dominated)
		ACs	$2,214	$380	41 PCDs	-8 PCDs	(Dominated)
Max Standard	MOH	SNRIs	$403		77.4% Response rate		
&		TCAs	$417	$14	71.4% Response rate	-5.9% Response rate	(Dominated)
Min Titration		ACs	$524	$122	72.8% Response rate	-4.6% Response rate	(Dominated)
	SOC	SNRIs	$1,814		77.4% Response rate		
		TCAs	$2,109	$294	71.4% Response rate	-5.9% Response rate	(Dominated)
		ACs	$2,131	$317	72.8% Response rate	-4.6% Response rate	(Dominated)
	MOH	SNRIs	$403		48 PCDs		
		TCAs	$417	$14	38 PCDs	-11 PCDs	(Dominated)
		ACs	$524	$122	41 PCDs	-8 PCDs	(Dominated)
	SOC	SNRIs	$1,814		48 PCDs		
		TCAs	$2,109	$294	38 PCDs	-11 PCDs	(Dominated)
		ACs	$2,131	$317	41 PCDs	-8 PCDs	(Dominated)

Sensitivity Variable	Perspective	Strategies	Cost	Incr Cost	Effectiveness	Incr Effectiveness	Incr C/E (ICER)
Medication Costs							
Min Standard	MOH	SNRIs	$400		77.4% Response rate		
&		TCAs	$408	$8	71.4% Response rate	-5.9% Response rate	(Dominated)
Min Titration		ACs	$504	$104	72.8% Response rate	-4.6% Response rate	(Dominated)
	SOC	SNRIs	$1,811		77.4% Response rate		
		TCAs	$2,100	$288	71.4% Response rate	-5.9% Response rate	(Dominated)
		ACs	$2,110	$299	72.8% Response rate	-4.6% Response rate	(Dominated)
	MOH	SNRIs	$400		48 PCDs		
		TCAs	$408	$8	38 PCDs	-11 PCDs	(Dominated)
		ACs	$504	$104	41 PCDs	-8 PCDs	(Dominated)
	SOC	SNRIs	$1,811		48 PCDs		
		TCAs	$2,100	$288	38 PCDs	-11 PCDs	(Dominated)
		ACs	$2,110	$299	41 PCDs	-8 PCDs	(Dominated)
SNRI Therapy – Duloxetine costing							
Duloxetine	MOH	TCAs	$500		71.4% Response rate		
		ACs	$646	$146	72.8% Response rate	1.4% Response rate	$10,645 (ExD)
		SNRIs	$879	$379	77.4% Response rate	6.0% Response rate	$6,317*
	SOC	TCAs	$2,192		71.4% Response rate		
		ACs	$2,253	$61	72.8% Response rate	1.4% Response rate	$4,420 (ExD)
		SNRIs	$2,291	$99	77.4% Response rate	4.6% Response rate	$1,650*
	MOH	TCAs	$500		38 PCDs		
		ACs	$646	$146	41 PCDs	3 PCDs	$49 (ExD)
		SNRIs	$879	$369	48 PCDs	8 PCDs	$38*
	SOC	TCAs	$2,192		38 PCDs		
		ACs	$2,253	$61	41 PCDs	3 PCDs	$20 (ExD)
		SNRIs	$2,291	$99	48 PCDs	8 PCDs	$10*

ACs = Anticonvulsants; C/E = Cost-effectiveness ratio; ExD = Extended dominance; Exp = expected; ICER = Incremental cost-effectiveness ratio; incr = incremental; MOH = Ministry of Health; PCDs = Pain controlled days; SOC = Society; SNRIs = Serotonin-norepinephrine reuptake inhibitors; TCAs = Tricyclic antidepressants
*ICER against TCAs, after removal of the dominated ACs

Table A-5. Monte Carlo simulation results for "Single Arm" unadjusted response rates.

Perspective	Strategy	Mean Cost (SD)	Mean Outcome (SD)	Incr C/E (ICER)
MOH	SNRIs	$411 ($10)	77.3.% (2.1%) Response rate	
	TCAs	$425 ($20)	71.3% (3.4%) Response rate	(Dominated)
	ACs	$555 ($37)	72.7% (2.8%) Response rate	(Dominated)
SOC	SNRIs	$1,823 ($50)	77.3.% (2.1%) Response rate	
	TCAs	$2,119 ($108)	71.3% (3.4%) Response rate	(Dominated)
	ACs	$2,162 ($81)	72.7% (2.8%) Response rate	(Dominated)
MOH	SNRIs	$411 ($10)	48 (2) PCDs	
	TCAs	$425 ($20)	37 (4) PCDs	(Dominated)
	ACs	$555 ($37)	41 (3) PCDs	(Dominated)
SOC	SNRIs	$1,823 ($50)	48 (2) PCDs	
	TCAs	$2,119 ($108)	37 (4) PCDs	(Dominated)
	ACs	$2,162 ($81)	41 (3) PCDs	(Dominated)

ACs = Anticonvulsants; ICER = Incremental cost-effectiveness ratio; Incr = Incremental; MOH=Ministry of Health; PCDs=Pain Controlled Days; SD=Standard Deviation; SNRIs = Serotonin-norepinephrine reuptake inhibitors; SOC=Society; TCAs = Tricyclic antidepressants