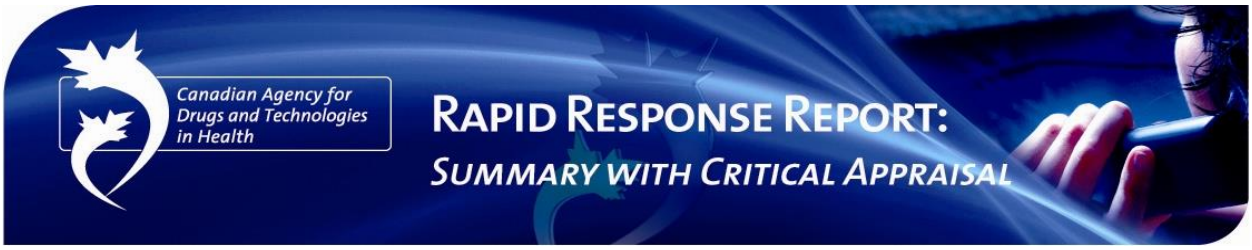

TITLE: Gabapentin for Adults with Neuropathic Pain: A Review of the Clinical Efficacy and Safety

DATE: 14 April 2015

CONTEXT AND POLICY ISSUES

Neuropathic pain (NP) can be severe and debilitating. It can significantly impact one's quality of life, general health, psychological health, and social and emotional well-being.[1] NP results when there is damage to or dysfunction of the central or peripheral nervous system.[2] The peripheral nervous system is the communications network that enables transmission of signals from the central nervous system (the brain and spinal cord) to other parts of the body. The terminology peripheral neuropathy is used when peripheral nerve dysfunction or damage is involved. Examples of peripheral neuropathy include diabetic peripheral neuropathy (DPN), and postherpetic neuralgia (PHN).[1] Central neuropathic pain can occur in conditions such as spinal cord injury (SCI) and multiple sclerosis.[1] NP can be complex and difficult to manage as etiology varies and there is heterogeneity with respect to symptoms and underlying mechanisms.[1,3]

The prevalence of neuropathic pain in developed countries is between 4% to 8% of the population, as estimated using population-based questionnaires.[4] Painful diabetic neuropathy is estimated to affect 16% to 26% of individuals with diabetes.[1] Estimates of prevalence of postherpetic neuropathic pain ranges between 8% and 19% in individuals who have had herpes zoster infection.[1]

Pharmacological management of NP includes medications such as anticonvulsants, antidepressants, serotonin noradrenaline reuptake inhibitors, opioid analgesics, cannabinoids and methadone.[4] Gabapentin is an anticonvulsant and has been used to manage neuropathic pain. Gabapentin is not without side effects and there is also potential for misuse.[5] Side effects associated with gabapentin include somnolence, dizziness, peripheral edema and gait disturbances.[6] Gabapentinoids (including gabapentin) in high doses may result in sedative and psychedelic effects.[5] Gabapentin is structurally related to the neurotransmitter gamma aminobutyric acid (GABA) but does not bind to the GABA receptors.[3] Its mechanism of action is through binding to calcium channels and modulating the influx of calcium and thereby bestowing antiepileptic, analgesic and sedative effects.[6] Recent research also suggests that gabapentin

acts by blocking new synapse formation.[6] Gabapentin is available in various dosages and formulations.[3,6] Besides the immediate release gabapentin there is an extended release, gastro-retentive formulation and an extended release gabapentin prodrug (enacarbil) that rapidly hydrolyses to gabapentin.[6]

The purpose of this report is to review the clinical efficacy and safety of gabapentin compared with placebo in adults with neuropathic pain.

RESEARCH QUESTIONS

1. What is the clinical efficacy and safety of gabapentin compared with placebo for adults with neuropathic pain?

2. What is the clinical efficacy and safety of gabapentin compared with placebo in a subset of adults with diabetic peripheral neuropathy?

KEY FINDINGS

Overall there is a suggestion that there is greater reduction in neuropathic pain with gabapentin compared with placebo in adults with a variety of conditions including diabetic peripheral neuropathy. Generally, adverse events were numerically higher with gabapentin compared with placebo.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2015, Issue 3), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and March 6, 2015.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria	
Population	Q1. Adult patients with neuropathic pain Q2. Adult patients with diabetic peripheral neuropathy
Intervention	Gabapentin
Comparator	Placebo
Outcomes	Clinical outcomes (including pain management, symptom relief, etc), patient reported outcomes (including quality of life, etc) and safety and harms (including adverse events, etc.)
Study Designs	Health technology assessment (HTA), systematic review (SR), meta-analysis (MA), and randomized controlled trial (RCT)

Exclusion Criteria

Studies were excluded if they did not satisfy the selection criteria, if they were duplicate publications, or were published prior to 2010. Studies on perioperative gabapentin use for pain prevention and studies on cancer pain were excluded. Systematic reviews which included studies which were included in a more recent or comprehensive review were excluded. RCTs which were included in a selected systematic review were excluded.

Critical Appraisal of Individual Studies

Critical appraisal of a study was conducted based on an assessment tool appropriate for the particular study design. The AMSTAR checklist[7] was used for systematic reviews and the Downs and Black checklist[8] was used for RCTs.

For the critical appraisal, a numeric score was not calculated. Instead, the strength and limitations of the study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 527 citations were identified in the literature search. Following screening of titles and abstracts, 474 citations were excluded and 53 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publication was retrieved from the grey literature search. Of these potentially relevant articles, 46 publications were excluded for various reasons, while seven publications[6,9-14] met the inclusion criteria and were included in this report. These seven publications comprised of six systematic reviews[6,9-13] and one RCT.[14] Appendix 1 describes the PRISMA flowchart of the study selection.

One systematic review[6] assessed the role of gabapentin in several disease conditions. Although, four systematic reviews[9-12] included relevant studies which were already included in this comprehensive systematic review,[6] they have been retained for additional information presented. As such for the purposes of this report, the comprehensive systematic review[6] is discussed in depth and only additional information from the other four systematic reviews are presented here and details are provided in the appendices.

Summary of Study Characteristics

Characteristics of the included systematic reviews (SRs) and randomized controlled trials (RCTs) are summarized below and details are provided in Appendix 2.

Systematic reviews

Six relevant systematic reviews[6,9-13] were identified. In five SRs.[6,9-12] there was overlap in the included studies. Of these five SRs, one SR[6] captured all studies that were included in the other four SRs.[9-12] Hence, most of the information presented here was taken from this comprehensive SR.[6] Additional information that was not presented in this SR[6] was taken from these other four SRs.[9-12] One SR[9] was published in 2015 from Europe, one SR[6] was published in 2014 by the Cochrane Collaboration, one SR[11] was published in 2014 from Canada, two SRs[10,12] were published in 2014 from China, and one SR[13] was published in 2012 from Australia. One SR[6] assessed the effect of gabapentin for treating neuropathic pain in a variety of conditions and included 28 RCTs comparing gabapentin with placebo in 4608 patients. One SR[9] assessed several drugs for treating neuropathic pain in a variety of conditions and included 20 RCTs comparing gabapentin with placebo in 3623 patients. One SR[11] assessed gabapentin for treating SCI and included three RCTs comparing gabapentin with placebo in 72 patients. One SR[10] assessed gabapentin for treating PHN and included six RCTs comparing gabapentin with placebo in 1633 patients. One SR[12] assessed gabapentin for treating PHN and included seven RCTs comparing gabapentin with placebo in 2039 patients. One SR[13] assessed several drugs for treating sciatica pain and include one RCT comparing gabapentin with placebo in 50 patients. All SRs included adult patients. Treatment duration in the RCTs that were included in the SRs varied between two and 15 weeks and various doses of gabapentin were used. All the SRs[6,9-13] reported on pain reduction and four SRs[6,10-13] also reported on adverse events.

Randomized controlled trial

One relevant RCT[14] comparing gabapentin (daily dose of 300 mg titrated to target 900 mg) with placebo in 140 adults with carpal tunnel syndrome (CTS) was identified. The RCT was published in 2011 from Hong Kong. Treatment duration was 8 weeks. Pain reduction and adverse events were reported.

Summary of Critical Appraisal

Critical appraisal of the included SRs, and RCTs are summarized below and additional details for the SRs and RCTs are provided in Appendix 3.

Systematic reviews

All the included SRs[6,9-13] stated objectives, inclusion and exclusion criteria, searched multiple databases, described study selection, conducted article selection in duplicate, provided lists of included studies, described characteristics of individual included studies, conducted quality assessment of the studies and stated conflict of interest of the authors. In addition, two SRs[6,9] included a grey literature search and one SR[6] provided substantial details of the individual included study characteristics and a list of excluded studies. Four SRs[6,9,10,12] conducted meta-analyses and they appeared to be appropriate. A random effects model was used when heterogeneity was present. Data extraction was done in duplicate in five SRs[6,9-11,13] and unclear in one SR.[12] Publication bias was explored in two SRs[6,9] and not explored in four SRs.[10-13]

Randomized controlled trial

In the included RCT,[14] the objective, inclusion and exclusion criteria, description of patient characteristics, intervention and outcomes, and sample size calculation were provided. The sample size used in this RCT was expected to have 80% power to detect a difference of 30%. Randomization was done by computer generated numbers and the RCT was stated to be double blind. The analysis was stated to be intention-to-treat, with the intention-to-treat population defined as all patients who were randomized and received at least one dose of the study medication. No patients were lost to follow up but there were some withdrawals and the numbers of withdrawals in each group were comparable. The study was partly funded by industry. The authors stated there was no conflict of interest. Generalizability was limited as the study was conducted at a single centre.

Summary of Findings

The overall findings are summarized below and details of the findings of the systematic reviews and RCT are provided in Appendix 4.

What is the clinical efficacy and safety of gabapentin compared with placebo for adults with neuropathic pain?

Six[6,9-13] relevant systematic reviews and one[14] relevant RCT were identified.

One systematic review[6] assessed the effect of gabapentin on neuropathic pain and included a variety of conditions. The level of evidence (first tier, second tier, and third tier) varied for the different conditions and descriptions of the different tiers are provided in Appendix 4. No first tier evidence was available. Second tier evidence was available for PHN, DPN and mixed NP and third tier evidence was available for the other conditions. Summary estimates were calculated by the authors when pooling was possible. Summary estimates are presented in Table 2. The relative risk (RR) and 95% confidence interval (CI) indicate that there is greater proportion of patients with ≥50% pain reduction with gabapentin compared with placebo, however the difference is statistically significant for PHN and DPN and not statistically significant for mixed NP, nerve injury pain (NIP), or small fibre sensory neuropathy.

Table 2: Assessment of substantial benefit (defined as at least 50% pain intensity reduction) with gabapentin compared to placebo

Condition	No. of RCTs	No. of patients	Patients with substantial benefit (%) G vs plb	RR (95% CI)	NNT (95% CI)
PHN	6	1816	34 vs 21	1.6 (1.3 to 1.9)	8.0 (6.0 to 12)
DPN	6	1277	38 vs 21	1.9 (1.5 to 2.3)	5.9 (4.6 to 8.3)
Mixed NP	1	305	21 vs 14	1.5 (0.9 to 2.4)	NC
NIP	1	98	13 vs 9	1.4 (0.7 to 3.2)	NC
Small fibre sensory neuropathy	1	18	22 vs 6	5 (0.65 to 38.65)	NC

CI = confidence interval, DPN = diabetic peripheral neuropathy, G = gabapentin, NC = not calculated, NIP = nerve injury pain, NNT = number needed to treat to benefit, NP = neuropathic pain, PHN = postherpetic neuralgia, plb = placebo, RCT = randomized controlled trial, RR = risk ratio, vs = versus

This systematic review[6] showed that withdrawals due to adverse events (AEs) were statistically significantly higher and withdrawals due lack of efficacy was statistically significantly lower with gabapentin compared to placebo for the various conditions considered together (RR [95% CI] 1.4 [1.1 to 1.7] for withdrawal due to AEs and 0.5 [0.3 to 0.8] for withdrawal due to lack of efficacy). Also, considering the various conditions together, the adverse events experienced with gabapentin were statistically significantly higher than with placebo (RR [95% CI] 1.25 [1.2 to 1.3]). Examples of adverse events include somnolence, dizziness, peripheral edema and ataxia or gait disturbance. Serious adverse events were not significantly different between the gabapentin and placebo groups.

One systematic review[9] pooled 14 RCTs comparing gabapentin (including extended release gabapentin [G-ER] and gabapentin enacarbil [G-En]) with placebo in a variety of conditions (such as PHN, DPN, SCI, and peripheral nerve injury [PNI]) and showed that the number needed to treat to benefit (NNT) was 7.2 and the corresponding 95% CI was 5.9 to 9.1. Safety was expressed in terms of the number needed to be treated to harm (NNH). The NNH and corresponding 95% CI was 25.6 (15.3 to 78.6) for gabapentin and 31.9 (17.1 to 230.0) for G-ER and G-En.

Postherpetic pain (PHN)

One systematic review[6] included seven RCTs (six parallel group and one crossover) comparing gabapentin with placebo in patients with PHN. In this set of RCTs, the numbers of patients ranged between 102 and 452 and treatment duration ranged between two and 14 weeks. The systematic review showed that for PHN, gabapentin at daily doses of 1800 mg or more or G-En at a daily dose of 1200 mg was more effective than placebo with respect to various pain measures, such as ≥50% reduction in pain, Patient Global Impression of Change (PGIC) of much or very much improved. Results are shown in Table 2 and Appendix 4.

One systematic review[10] showed that for PHN, gabapentin at daily doses of 1800 mg was statistically significantly more effective than placebo with respect to various pain measures, such as ≥50% reduction in pain, PGIC, and Clinician Global Impression of Change. The RR (95% CI) for patients having ≥50% reduction in pain was 1.88 (1.35 to 2.61) favoring gabapentin. Gabapentin was also found to be statistically significantly more effective than placebo in a number of subgroups (duration >10 weeks or ≤10 weeks, gabapentin- immediate release [GR-IR] or G-ER). The adverse events experienced with gabapentin were statistically significantly higher than with placebo (RR [95% CI] 1.28 [1.16 to 1.42]). Examples of adverse events included somnolence, dizziness, peripheral edema, and fatigue. Withdrawals due to adverse events were statistically significantly higher with gabapentin than with placebo (RR [95% CI] 1.51 [1.06 to 2.16]).

One systematic review[12] showed that for PHN, gabapentin (G-En or non-G-En) was statistically significantly more effective than placebo with respect to various pain measures, such as ≥50% reduction in pain, PGIC, and average daily pain score. Only the results for the subgroup treated with G-En are presented here, as additional information. Summary estimates were derived by pooling two RCTs comparing G-En with placebo. There was a statistically significantly greater proportion of patients with ≥50% pain reduction with G-En compared with placebo (RR [95% CI] 1.66 [1.17 to 2.35]). Adverse events with G-En compared with placebo were greater (RR [95% CI]: 1.15 [0.99 to 1.33]), but did not achieve statistical significance. Other results are similar to

the results presented in the systematic review[6] described above and are available in Appendix 4.

Mixed neuropathic pain (mixed NP)

One systematic review[6] included three RCTs (crossover) comparing effect of gabapentin with placebo in mixed neuropathic pain. In this set of RCTs, the numbers of patients ranged between 56 and 305 and treatment duration ranged between 22 days and five weeks. One RCT (including mostly patients with PHN and complex regional pain syndrome [CRPS]) showed ≥ 50% pain reduction was not statistically significantly different in the two groups (Table 2) but moderate benefit (PGIC much or very much improved) was statistically significantly greater with gabapentin (daily dose 2400 mg) compared to placebo (RR [95% CI] 2.2 [1.4 to 3.4]). This RCT also showed that adverse events were greater with gabapentin compared to placebo. The second RCT (including mostly patients with PHN and DPN) showed that moderate pain relief was statistically significantly greater with gabapentin (daily dose 3200 mg) compared to placebo (RR [95% CI] 2.5 [1.5 to 4.2]). The third RCT (including patients with pain below the neck classified as neuropathic or mixed) investigated the effects of intrathecal gabapentin of various doses (1 mg, 6 mg, and 30 mg daily) and placebo over 22 days and showed there was no significant reduction in pain scores.

Spinal cord injury (SCI)

One systematic review[11] included three RCTs (crossover) comparing the effect of gabapentin with placebo in pain resulting from SCI. In this set of RCTs, the numbers of patients ranged between 14 and 38 and treatment duration ranged between four and eight weeks. Standardized mean differences (SMDs) and 95% CIs indicated greater pain relief with gabapentin compared to placebo but the difference was statistically significant in two RCTs and not significant in one RCT (Appendix 4). Adverse events (dizziness, edema, headache, sedation, and weakness) were reported for one RCT and were greater with gabapentin compared to placebo but not statistically significant as indicated by odds ratios and 95% CIs (Appendix 4). These three RCTs were also included in another systematic review[6] but as dichotomous data was not available for these RCTs, this systematic review did not further analyze these RCTs.

Nerve injury pain (NIP)

One systematic review[6] included one RCT (crossover, N = 120) comparing the effect of gabapentin with placebo in nerve injury pain. Greater pain relief was obtained with gabapentin compared to placebo but was not statistically significant (Table 2). Dizziness was found to be higher with gabapentin compared to placebo (39/120 for gabapentin and 9/120 for placebo).

Phantom limb pain (PLP)

One systematic review[6] included two RCTs (crossover) comparing effect of gabapentin with placebo in PLP. One RCT(N= 19) showed that greater pain relief was achieved with gabapentin (daily dose 2400 mg) compared to placebo at 6 weeks using the visual analog scale (VAS) but not at any other time point or with other pain measures. Adverse events reported were somnolence (7/19 for gabapentin and 2/19 for placebo) and dizziness (2/19 for gabapentin and 1/19 for placebo).The second RCT (N= 24) showed that statistically significantly greater pain relief (using a 5-point scale) was achieved with gabapentin (daily dose 3600 mg) compared to placebo (RR [95% CI] 2.6 [1.1 to 6.2]).

Human immune deficiency virus associated neuropathic pain (HIV-NP)

One systematic review[6] included one RCT (parallel group, N = 24) comparing effect of gabapentin with placebo in HIV-NP. Pain and sleep, on average, were substantially improved with both gabapentin (daily dose 2400 mg) and placebo but the time courses differed. Adverse events reported included somnolence (12/15 for gabapentin and 2/11 for placebo), dizziness (9/15 for gabapentin and 5/11 for placebo), and gait disturbance (7/15 for gabapentin and 3/11 for placebo).

Small fiber sensory neuropathy

One systematic review[6] included one RCT (crossover, N = 18) comparing the effect of gabapentin with placebo in patients with small fiber sensory neuropathies. Greater pain relief was achieved with gabapentin (daily dose 4800 mg) compared to placebo over two weeks but was not statistically significant (Table 2).

Chronic masticatory myalgia

One systematic review[6] included one RCT (parallel group, N = 50) comparing the effect of gabapentin with placebo in patients with chronic masticatory myalgia. Gabapentin was stated to be significantly better than placebo over 12 weeks, based on VAS, but details were not available. The NNT reported for gabapentin compared to placebo for ≥ 30% pain reduction was 3.4. Adverse events reported included drowsiness (7/25 for gabapentin and 5/25 for placebo), dizziness (7/25 for gabapentin and 2/25 for placebo), and ataxia (1/25 for gabapentin and 0/25 for placebo).

Complex regional pain syndrome (CRPS)

One systematic review[6] included one RCT (crossover, N = 58) comparing the effect of gabapentin with placebo in patients with CRPS. Greater pain relief was achieved with gabapentin (daily dose 1800 mg) compared to placebo over three weeks but was not statistically significant; relative benefit of 4.0 (0.9 to 18). RR (95% CI) for one or more adverse events was 1.64 (1.15 to 2.32), favoring placebo.

Fibromyalgia (FBM)

One systematic review[6] included one RCT (parallel group, N = 150) comparing the effect of gabapentin (2400 mg) with active placebo (diphenhydramine) in patients with FBM. Statistically significant pain relief (assessed as ≥ 30% pain reduction over baseline) was achieved with gabapentin (daily dose 2400 mg) compared to placebo over 12 weeks with RR (95% CI) of 1.6 (1.1 to 2.4) and corresponding NNT (95% CI) of 5.4 (2.9 to 31). Adverse events reported included somnolence (14/75 for gabapentin and 6/75 for placebo), dizziness (19/75 for gabapentin and 7/75 for placebo), aesthenia (6/75 for gabapentin and 5/75 for placebo) and peripheral edema (12/75 for gabapentin and 6/75 for placebo).

Sciatica

One systematic review[13] included one RCT (N = 50) comparing the effect of gabapentin with placebo in patients with sciatica. Statistically significant pain reduction was achieved with

gabapentin (daily dose 900 to 3600 mg) compared to placebo over eight weeks with a mean difference of -26.6; *P* < 0.001. Details were not available. Adverse events were 8% in the gabapentin group and 0% in the placebo group.

Carpal tunnel syndrome (CTS)

One RCT[14] (parallel group, N =140) comparing the effect of gabapentin (daily dose 300 mg titrated to target 900 mg) with placebo in patients with CTS showed that the decrease in global symptom score (GSS) from baseline values was not statistically significantly different (*P* = 0.39) between the two groups, over an eight week period. Adverse events included somnolence, dizziness and fatigue and were numerically higher in the gabapentin group.

What is the clinical efficacy and safety of gabapentin compared with placebo in a subset of adults with diabetic peripheral neuropathy (DPN)?

One systematic review[6] included eight RCTs (seven parallel group and one crossover) comparing gabapentin with placebo in patients with DPN. Seven RCTs with gabapentin daily doses in the range of 1200 to 3600 mg were included in the meta-analysis. In this set of RCTs, the numbers of patients ranged between 60 to 389 and treatment duration ranged between four and 15 weeks. For DPN, gabapentin (including G-ER and G-En) was more effective than placebo as assessed by pain measures, such as ≥50% reduction in pain, PGIC (much or very much improved). Results are shown in Tables 2 and 3 and Appendix 4. The RR (95% CI) values indicate statistically significant benefit with gabapentin compared with placebo. The crossover RCT (N = 40) which was not included in the meta-analysis, showed that moderate or excellent pain reduction was achieved by 43% of patients receiving gabapentin (daily dose of 900 mg) compared with 23% on placebo.

Table 3: Assessment of benefit with gabapentin compared to placebo in DPN

Outcome	No. of RCTs	No. of patients	Patients with benefit (%) G vs plb	RR (95% CI)	NNT (95% CI)
Substantial benefit (≥50% pain reduction or PGIC very much improved)	6	1277	38 vs 21	1.9 (1.5 to 2.3)	5.9 (4.6 to 8.3)
PGIC very much improved	2	408	24 vs 14	1.9 (1.3 to 3.0)	9.6 (5.5 to 35)
Moderate benefit (≥30% pain reduction or PGIC much or very much improved)	7	1439	52 vs 37	1.4 (1.3 to 1.6)	6.6 (4.9 to 9.9)
PGIC much or very much improved	5	695	50 vs 30	1.7 (1.4 to 2.0)	4.9 (3.6 to 7.6)

CI = confidence interval, DPN = diabetic peripheral neuropathy, G = gabaplentin, NNT = number needed to treat to benefit, PGIC = Patient Global Impression of Change, plb = placebo, RCT = randomized controlled trial, RR = risk ratio, vs = versus

The systematic review[6] did not present pooled summary estimates for adverse events experienced by patients with DPN separately. In the individual RCTs, generally greater proportions of patients experienced adverse events with gabapentin compared with placebo but

the results varied across the studies and were not always statistically significant (Appendix 4). Examples of adverse events included somnolence, dizziness, peripheral edema, and ataxia.

Limitations

There was overlap in the studies included in the SRs.[6,9-12] However, only additional information from SRs[9-12] that was not already presented in the comprehensive SR[6] were included in this report.

Various doses and formulations of gabapentin were used in the RCTs included in the SRs but there was not enough information to determine a dose-effect relationship. Use of rescue medication was reported in some RCTs but not in some RCTs hence there was potential for confounding. Reporting of age of the patients varied among studies hence comparability of studies was difficult. Age was reported as mean, median, or as a range. In some systematic reviews details of the age of the patients were not reported. In some cases where age was reported, the range was wide (e.g. 18 to 92 years in one SR). This could confound results.

Efficacy and safety outcomes were not reported consistently across studies. Different approaches and methods were used for assessment of pain in the different studies hence comparability of results across studies was difficult. Because of the subjectivity of the sensation of pain, and the lack of widely approved standardized tools for identifying neuropathic pain, the evaluation of neuropathic pain and interpretation of results were difficult. Though in many instances statistically significant differences were observed with gabapentin compared to placebo, the clinical significance of the findings is unclear. There was lack of evidence on the long term effects of gabapentin. The duration of treatment in the included studies ranged between two and 15 weeks. A placebo effect was seen in some studies and may impact results. One systematic review presented results of subgroup analyses but it was not clear if the subgroups had been determined a priori.

Most of the RCTs included in the SRs were on PHN or DPN. There were limited numbers of RCTs on the other conditions and in some conditions the evidence was from single studies. No systematic review specifically on DPN was identified.

Details regarding the countries where the RCTs were conducted were not reported in the SRs hence it is unclear to what extent the results were relevant to a Canadian setting.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Seven relevant SRs and one relevant RCT were identified. Most of the information reported in this report is from the systematic review[6] evaluating the effect of gabapentin for treating neuopathic pain in a variety of conditions, with additional relevant information from the other included SRs and one RCT. Overall there is a suggestion that for DPN as well as for several other conditions there is greater reduction in neuropathic pain with gabapentin compared with placebo. However, the proportion of patients experiencing substantial pain relief (assessed as ≥ 50% reduction in pain intensity) was moderate ranging between 13% and 38%. Generally adverse events were numerically higher with gabapentin compared with placebo and serious adverse events were few and comparable between the two groups. Adverse events included somnolence, dizziness, peripheral edema and gait disturbances. Specifics of serious adverse events were not available. However, results need to be interpreted with caution, considering the limitations associated with the included SRs and RCT. As evident from the included SRs, most

of the available RCTs were on PHN and DPN. However, no SR specifically assessing the effect of gabapentin on neuropathic pain in DPN was identified. For the other conditions there were limited number of RCTs and for some conditions the evidence was from single RCTs.

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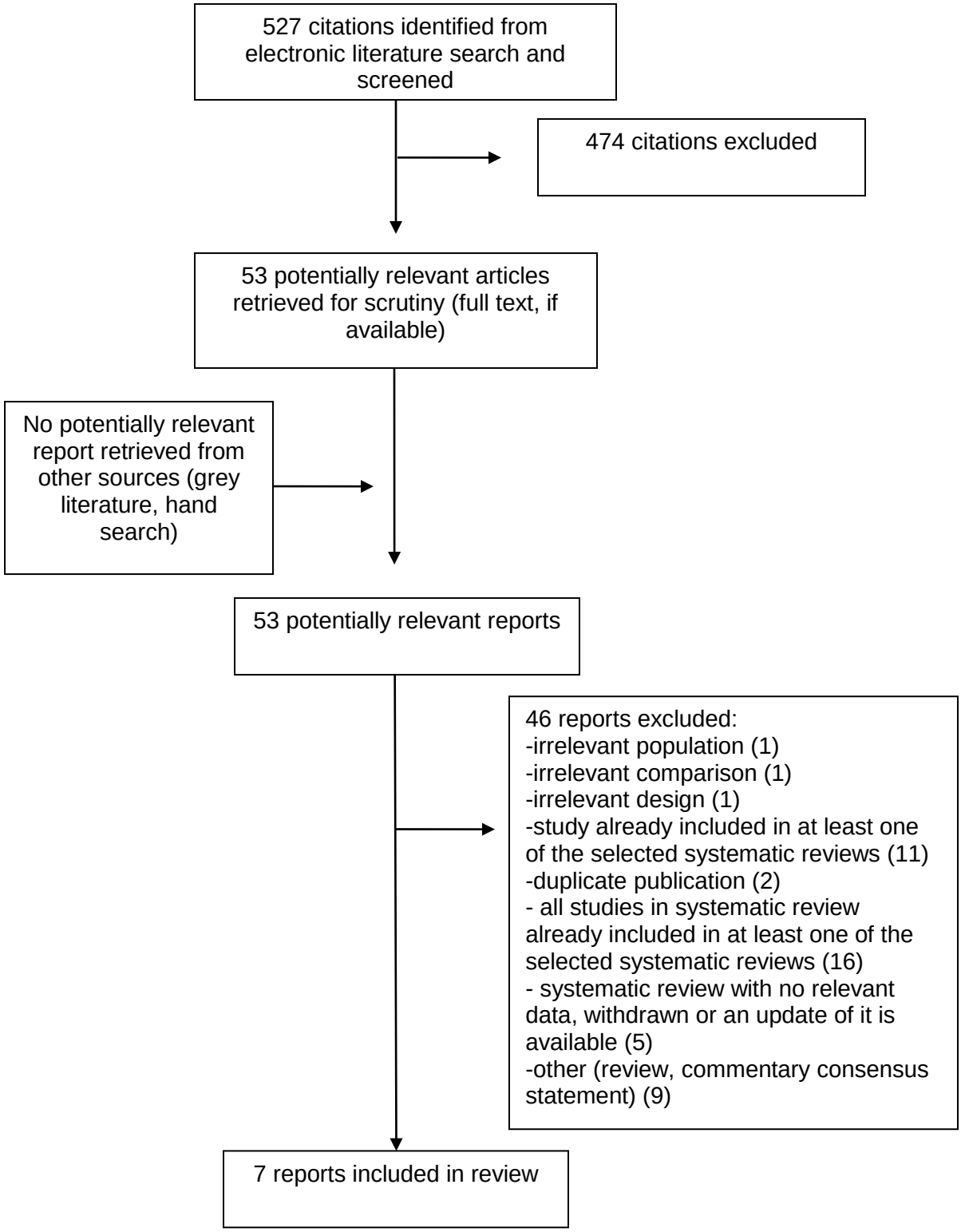
14. Hui AC, Wong SM, Leung HW, Man BL, Yu E, Wong LK. Gabapentin for the treatment of carpal tunnel syndrome: a randomized controlled trial. Eur J Neurol. 2011 May;18(5):726-30.

ABBREVIATIONS

AE	adverse event
CGIC	clinician global impression of change
CRPS	complex regional pain syndrome
FU	follow up
G	gabapentin
G-ER	gabapentin extended release
G-IR	gabapentin immediate release
GSS	global symptom score
HRQoL	health related quality of life
IMMPACT	Initiative on Methods, Measurement and Pain Assessment in Clinical Trials
MA	meta-analysis
MD	mean difference
mg	milligram
NC	not calculated
NIP	nerve injury pain
NNH	number needed to treat to harm
NNT	number needed to treat to benefit
NP	neuropathic pain
NR	not reported
NRS	numerical rating scale
NS	not significant
OR	odds ratio
P	pregabalin
PGIC	patient global impression of change
PHN	postherpetic neuralgia
plb	placebo
PLP	phantom limb pain
PNI	peripheral nerve injury
RCT	randomized controlled trial
RR	relative risk, risk ratio
SAE	serious adverse event
SD	standard deviation
SMD	standardized mean difference
SR	systematic review
VAS	visual analog scale

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Studies

First Author, Publication Year, Country	Study Design, Duration	Patient Characteristics, Sample Size[a] (N)	Comparison[a]	Outcomes[a] Measured
Systematic review				
Finnerup,[9] 2015, Europe and USA	SR including MA (To assess drugs for treating neuropathic pain) SR included 20 RCTs on G vs plb FU: 4 to 13 weeks	Adults with neuropathic pain (PHN, DPN, NP-HIV, SCI, PNI, PLP, post amputation pain) N = 3623 (in 20 RCTs) Age: NR	G including G-ER and enacarbil (prodrug for G) versus plb Max daily dose for G: 1800 mg to 3600 mg (900 mg for one study not included in meta-analysis), G-ER: 1800 mg to 3000 mg, Enacarbil: 1200 mg to 3600 mg	Pain reduction
Fan,[10] 2014, China	SR including MA (To assess efficacy and safety of G [1800 mg] for PHN) SR included 6 RCTs on G vs plb FU: 4 to 14 weeks	Adults with neuropathic pain (PHN) N = 1633 Age (years): 18 to 92 (from 2 RCTs,. Mean age (years): 65 to 76 (from 4 RCTs)	G including G-ER and enacarbil (prodrug for G) versus plb Max daily dose for G: 1800 mg, Enacarbil: 1200 mg to 3600 mg	Pain reduction, AE, withdrawal
Guy,[11] 2014, Canada	SR including MA (To assess efficacy and safety of gabapentinoids (G, P) for SCI SR included 3 RCTs on G vs plb FU: 4 to 8 weeks	Adults with SCI N = 72 Age: NR	G Daily dose: 600 mg to 3600 mg	Pain reduction, AE
Meng,[12] 2014, China	SR including MA (To assess efficacy and safety of G for PHN) SR included 7 RCTs FU: 4 to 14 weeks	Adults with neuropathic pain (PHN) N = 2039 Age: NR	G including gastric-retentive G and enacarbil (prodrug for G) versus plb G dose1800 mg to 2400 mg, Gastric-retentive G dose: 1800 mg, Enacarbil dose: 1200 mg to 3600 mg	Pain reduction, AE
Moore,[6] 2014, Germany, UK (Cochrane	SR including MA (To assess efficacy and safety of G for	Adults with chronic neuropathic pain (PHN, DPN, mixed	G including G-ER and enacarbil (prodrug for G)	Pain reduction, AE, withdrawal

First Author, Publication Year, Country	Study Design, Duration	Patient Characteristics, Sample Size[a] (N)	Comparison[a]	Outcomes[a] Measured
Collaboration)	neuropathic pain and fibromyalgia) SR included 28 RCTs (relevant for this report) but fewer studies included in the meta-analyses as data presentation was not always complete. FU: 2 to 15 weeks	NP, NP-HIV, SCI, NIP, PLP,cancer related pain, small fibre sensory neuropathy) or fibromyalgia N = 4609 (for 28 studies considered) Age (years): 27 to 48 (1 RCT), Mean age (years): 34 to 70 (22 RCTs), Median age (years): 48 to 73 (5 RCTs)	versus plb Max daily dose for G: 1800 mg to 3600 mg (900 mg for one study not included in meta-analysis), G-ER: 1800 mg to 3000 mg, Enacarbil: 1200 mg to 3600 mg	
Pinto,[13] 2012, Australia, Netherlands	SR including MA (To assess efficacy and safety of drugs for pain relief in patients with sciatica) SR included 1 RCT with G vs plb FU: 8 weeks	Adults with sciatica N = 50 (25 in G, 25 in plb) Age (years) (mean ± SD): 38 ± 7 in G, 41 ± 11 in plb	G versus plb G daily dose: 900 to 3600 mg	Pain reduction, AE
Randomized controlled trial				
Hui,[14] 2011, Hong Kong	Double-blind, single centre RCT FU = 8 weeks	Adults with CTS N = 140 (71 in G and 69 in plb) Age (mean ± SD) (years): 52.3 ± 10.6 in G, 51.0 ± 8.3 in plb Female/Male: 59/12 in G, 55/14 in plb Baseline GSS (mean ± SD): 23.8 ± 9.6 in G, 21.2 ± 8.6 in plb	G vs plb Daily dose: Starting dose of 300 mg to a target dose of 900 mg	Pain reduction, AE

CTS = carpal tunnel syndrome, FBM = fibromyalgia, FU = follow up, G = gabapentin, G-ER = gabapentin extended release, GSS = global symptom score, HRQoL = health related quality of life, MA = metaanalysis, NIP = nerve injury pain, NNH = number needed to harm, NNT = number needed to treat, NP = neuropathic pain, NR = not reported, NRS = numerical rating scale, P = pregabalin, PHN = postherpetic neuralgia, plb = placebo, PLP = phantom leg pain, PNI = peripheral nerve injury, RCT = randomized controlled trial, SCI = spinal cord injury, VAS = visual analog scale

[a]In case of reports with multiple comparisons only comparisons of relevance for this report and the corresponding characteristics, sample size and outcomes are mentioned in the table.

APPENDIX 3: Summary of Study Strengths and Limitations

First Author, Publication Year, Country	Strengths	Limitations
Systematic review (SR)		
Finnerup,[9] 2015, Europe and USA	• The objective was clearly stated. • The inclusion and exclusion criteria were stated. • Multiple databases were searched, Jan 1966 to April 2013. Registries and, clinical study results websites were searched. Also reference list of the relevant articles were manually searched. • Study selection was described and flow chart was presented • List of included studies was provided • Article selection and data extraction were done in duplicate • Quality assessments of studies were conducted using the 5-point Oxford quality scale and were mostly found to be high • Publication bias was explored using Funnel plots considering all drugs not just each drug (e.g. gabapentin) as authors considered there were not enough studies for each separate drug. Trim and Fill approach was also used and for gabapentin susceptibility to bias was considered to be low • Authors declared their conflict of interest	• List of excluded studies was not provided • Characteristics of the individual studies were provided but lacked details • In some instances it was unclear which studies were pooled for the summary estimates
Fan,[10] 2014, China	• The objective was clearly stated. • The inclusion and exclusion criteria were stated. • Multiple databases were searched, up to June 2013. Also reference list of the relevant articles were manually searched. • Study selection was described and flow chart was presented • Lists of included studies was provided • Article selection and data extraction were done in duplicate • Characteristics of the individual studies were provided • Quality assessments of studies	• Lists of excluded studies was not provided • Publication bias was not explored as the number of included studies was less than 10 (the recommended arbitrary minimum number)

First Author, Publication Year, Country	Strengths	Limitations
	were conducted using the Cochrane risk of bias tool and were mostly found to be of good quality • Authors stated there was no conflict of interest	
Guy,[11] 2014, Canada)	• The objective was clearly stated. • The inclusion and exclusion criteria were stated. • Multiple databases were searched, up to June 2013. Also reference list of the relevant articles were manually searched. • Study selection was described and flow chart was presented • Lists of included studies was provided • Article selection and data extraction were done in duplicate • Characteristics of the individual studies were provided • Quality assessments of studies were conducted using the Jadad scale or the Downs and Black scale and were mostly found to be of good quality • Authors stated there was no conflict of interest	• Lists of excluded studies was not provided • Publication bias was not explored
Meng,[12] 2014, China	• The objective was clearly stated. • The inclusion and exclusion criteria were stated. • Multiple databases were searched, up to August 2013. Also reference list of the relevant articles were manually searched. • Study selection was described and flow chart was presented • Lists of included studies was provided • Article selection was done in duplicate • Characteristics of the individual studies were provided • Quality assessments of studies were conducted using the Jadad scale and were mostly found to be of good quality • Authors stated there was no conflict of interest	• Lists of excluded studies was not provided • Unclear if data extraction was done in duplicate • Publication bias was not explored

First Author, Publication Year, Country	Strengths	Limitations
Moore,[6] 2014, Germany, UK (Cochrane Collaboration)	• The objective was clearly stated. • The inclusion and exclusion criteria were stated. • Multiple databases were searched, up to March 2014. Registries and, clinical study results websites were searched. Also reference list of the relevant articles were manually searched. • Study selection was described and flow chart was presented • Lists of included and excluded were provided • Article selection and data extraction were done in duplicate • Characteristics of the individual studies were provided • Quality assessments of studies were conducted using the 5-point Oxford quality scale and Cochrane risk of bias tool and were mostly found to be good. • No statistical assessment of publication bias was undertaken however the number of patients in zero effect studies that could impact results was determined and was 1390 patients. With a median of 220 patients in studies, this would need a minimum of 6 or 7 unavailable studies • Authors declared their conflict of interest	• No major limitations
Pinto,[13] 2012, Australia, The Netherlands	• The objective was clearly stated. • The inclusion and exclusion criteria were stated. • Multiple databases were searched, up to March 2010. Also reference list of the relevant articles were manually searched. • Study selection was described and flow chart was presented • Lists of included studies was provided • First level article selection was conducted by one reviewer. Second level article selection and data extraction were done in duplicate • Characteristics of the individual	• Lists of excluded studies was not provided • Publication bias was not assessed as there were too few studies

First Author, Publication Year, Country	Strengths	Limitations
	studies were provided • Quality assessment was conducted using the criteria advocated by Cochrane back review group. Also the GRADE approach was used • Authors declared their conflict of interest and stated there was no conflict of interest	
Randomized controlled trial (RCT)		
Hui,[14] 2011, Hong Kong	• Objectives were clearly stated. • Inclusion and exclusion criteria were stated. • Patient characteristics, interventions, and outcomes were described. • Randomized using computer generated numbers. Stated as double blind but specifics were not provided except that the assessor was blinded and the placebo tablets were identical to gabapentin tablets. • Sample size calculations described • The authors stated that no patients were lost to follow up, but 9 from the gabapentin group and 8 from the placebo group withdrew by completion. • Intention-to-treat analysis, with intention-to-treat population defined as patients who were randomized and who received at least one dose of treatment. • *P*-values provided in some cases • The authors stated that there was no conflict of interest.	• Generalizability limited as a single center study; uncertain as to whether study patients were representative of all patients. • The study was partially funded by industry

APPENDIX 4: Main Study Findings and Authors' Conclusions

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td colspan="2">Systematic review</td></tr>
<tr><td rowspan="2">Finnerup,[9] 2015, Europe and USA</td><td>Main Findings:

<table>
<tr><th>Drug</th><th>No. of RCTs</th><th>No. of patients</th><th>NNT (95% CI)</th><th>NNH (95% CI)</th></tr>
<tr><td>G</td><td>NR</td><td>NR</td><td>6.3 (5.0 to 8.4)</td><td>25.6 (15 to 79)</td></tr>
<tr><td>G-ER or Enacarbil</td><td>NR</td><td>NR</td><td>8.3 (6.2 to 13)</td><td>31.9 (17 to 230)</td></tr>
<tr><td>G, G-ER or Enacarbil</td><td>14</td><td>3503</td><td>7.2 (5.9 to 9.1)</td><td>NR</td></tr>
</table></td></tr>
<tr><td>Authors' Conclusion:
"These findings permitted a strong recommendation for use and proposal as first-line treatment in neuropathic pain for tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitors, pregabalin, and gabapentin; a weak recommendation for use and proposal as second line for lidocaine patches, capsaicin high-concentration patches, and tramadol; and a weak recommendation for use and proposal as third line for strong opioids and botulinum toxin A. Topical agents and botulinum toxin A are recommended for peripheral neuropathic pain only." P. 162</td></tr>
<tr><td>Fan,[10] 2014, China</td><td>Main Findings:

Efficacy with gabapentin compared with placebo for PHN
<table>
<tr><th>Outcome</th><th>No. of RCTs</th><th>No. of patients</th><th>RR (95% CI)</th><th>Heterogeneity I^2 (%)</th></tr>
<tr><td>50% reduction in pain intensity</td><td>6</td><td>1633</td><td>1.88 (1.35 to 2.61)</td><td>65</td></tr>
<tr><td>30% reduction in pain intensity</td><td>2</td><td>340</td><td>1.43 (1.12 to 1.83)</td><td>0</td></tr>
<tr><td>PGIC</td><td>5</td><td>1339</td><td>1.49 (1.28 to 1.74)</td><td>0</td></tr>
<tr><td>CGIC</td><td>5</td><td>1320</td><td>1.58 (1.29 to 1.92)</td><td>31</td></tr>
</table>

Efficacy (50% reduction in pain intensity) with gabapentin compared with placebo in various subgroups of PHN patients
<table>
<tr><th>Grouping by</th><th>Subgroup</th><th>No. of RCTs</th><th>No. of patients</th><th>RR (95% CI)</th></tr>
<tr><td rowspan="2">Duration of treatment</td><td>>10 weeks</td><td>3</td><td>650</td><td>1.45 (1.20 to 1.75)</td></tr>
<tr><td>≤ 10 weeks</td><td>3</td><td>1165</td><td>3.04 (1.56 to 5.91)</td></tr>
<tr><td rowspan="2">Type of gabapentin</td><td>G-IR</td><td>2</td><td>441</td><td>3.74 (1.14 to 12.23)</td></tr>
<tr><td>G-ER</td><td>4</td><td>1374</td><td>1.48 (1.23 to 1.78)</td></tr>
<tr><td rowspan="2">Administration method</td><td>Divided dose</td><td>2</td><td>372</td><td>1.41 (0.89 to 2.25)</td></tr>
<tr><td>Once daily</td><td>2</td><td>368</td><td>1.59 (0.92 to 2.74)</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td></td><td>
Adverse events with gabapentin compared with placebo for PHN
<table>
<tr><th>Outcome</th><th>No. of RCTs</th><th>No. of patients</th><th>RR (95% CI)</th><th>Heterogeneity I^2 (%)</th></tr>
<tr><td>Any AE</td><td>4</td><td>1265</td><td>1.28 !1.16 to 1.42)</td><td>0</td></tr>
<tr><td>Somnolence</td><td>6</td><td>1638</td><td>2.13 (1.39 to 3.27)</td><td>10</td></tr>
<tr><td>Dizziness</td><td>6</td><td>1638</td><td>2.69 (1.90 to 3.80)</td><td>19</td></tr>
<tr><td>Peripheral edema</td><td>5</td><td>1423</td><td>9.16 (2.82 to 29.78)</td><td>0</td></tr>
<tr><td>Nausea</td><td>4</td><td>1007</td><td>1.17 (0.68 to 2.00)</td><td>0</td></tr>
<tr><td>Blurred vision</td><td>2</td><td>397</td><td>1.58 (0.76 to3.28)</td><td>0</td></tr>
<tr><td>Tremor</td><td>2</td><td>397</td><td>7.01 (0.86 to 57.00)</td><td>0</td></tr>
<tr><td>Headache</td><td>4</td><td>1197</td><td>0.93 (0.57 to 1.53)</td><td>0</td></tr>
<tr><td>Fatigue</td><td>2</td><td>340</td><td>9.23 (1.76 to 48.47)</td><td>0</td></tr>
<tr><td>Dry mouth</td><td>2</td><td>408</td><td>3.40 (0.92 to 12.53)</td><td>0</td></tr>
<tr><td>Nasopharyngitis</td><td>2</td><td>634</td><td>0.97 (0.42 to 2.25)</td><td>0</td></tr>
<tr><td>Diarrhea</td><td>2</td><td>408</td><td>2.37 (0.49 to 11 62)</td><td>48</td></tr>
<tr><td>Withdrawal due to AE</td><td>6</td><td>1423</td><td>1.51 (1.06 to 2.16)</td><td>6</td></tr>
</table>
Authors' Conclusion:
"Treatment with gabapentin 1800 mg/day yielded a significant reduction in PHN up to 14 weeks. Gabapentin 1800 mg appeared safe in treating PHN for up to 24 weeks." P. 334
</td></tr>
<tr><td>Guy,[11] 2014, Canada)</td><td>
Main Findings:
Efficacy with gabapentin compared with placebo for SCI
<table>
<tr><th>Outcome</th><th>No. of RCTs</th><th>No. of patients in each RCT</th><th>SMD (95% CI)[a]</th></tr>
<tr><td rowspan="3">Pain reduction</td><td rowspan="3">3</td><td>20</td><td>4.38 (3.24 to 5.19</td></tr>
<tr><td>38</td><td>0.10 (-0.50 to 0.69)[b]</td></tr>
<tr><td>14</td><td>1.27 (0.12 to 2.42</td></tr>
<tr><td colspan="4">[a] Results are reported for each individual RCT
[b] In this RCT the placebo was an active placebo (diphenhydramine)</td></tr>
</table>
Adverse events with gabapentin compared with placebo for SCI (results from I RCT with 20 patients)
<table>
<tr><th>Outcome</th><th>OR (95% CI)</th></tr>
<tr><td>Dizziness</td><td>3.35 (0.32 to 35.36</td></tr>
<tr><td>Edema</td><td>8.20 (0.40 to 169.90)</td></tr>
<tr><td>Headache</td><td>1.00 (0.06 to17.18)</td></tr>
<tr><td>Sedation</td><td>8.20 (0.40 to 169.90</td></tr>
<tr><td>Weakness</td><td>3.00 (0.51 to 17.74)</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td></td><td>Authors' Conclusion:
"Gabapentin and pregabalin are the two anticonvulsants which have been shown to have some benefit in reducing neuropathic pain." P. 89</td></tr>
<tr><td>Meng,[12] 2014, China</td><td>Main Findings:
Efficacy with gabapentin compared with placebo for PHN
<table>
<tr><th>Outcome</th><th>Gabapentin type</th><th>No. of RCTs</th><th>No. of patients</th><th>RR (95% CI)[a]</th><th>Heterogeneity I^2 (%)</th></tr>
<tr><td rowspan="3">≥50% reduction in pain intensity</td><td>Enacarbil (G-En)</td><td>2</td><td>472</td><td>1.66 (1.17 to 2.35)</td><td>0</td></tr>
<tr><td>Non G-En</td><td>4</td><td>1342</td><td>1.57 (1.30 to 1.90)</td><td>41</td></tr>
<tr><td>G-En and non G-En</td><td>6</td><td>1814</td><td>1.59 (1.35 to 1.88)</td><td>6</td></tr>
<tr><td rowspan="3">Much or very much improved (PGIC)</td><td>G-En</td><td>2</td><td>472</td><td>2.16 (1.17 to 4.01)</td><td>56</td></tr>
<tr><td>Non G-En</td><td>5</td><td>1567</td><td>1.75 (1.28 to 2.38)</td><td>69</td></tr>
<tr><td>G-En and non G-En</td><td>7</td><td>2039</td><td>1.82 (1.41 to 2.35)</td><td>63</td></tr>
<tr><td rowspan="3">Change in average daily pain score</td><td>G-En</td><td>2</td><td>472</td><td>–0.83 (–1.20 to –0.47)[b]</td><td>0</td></tr>
<tr><td>Non G-En</td><td>3</td><td>783</td><td>–0.94 (–1.69 to –0.20)[b]</td><td>90</td></tr>
<tr><td>G-En and non G-En</td><td>5</td><td>1255</td><td>–0.89 (–1.32 to –0.45)[b]</td><td>83</td></tr>
<tr><td colspan="6">[a]Unless otherwise stated
[b]SMD (95% CI)</td></tr>
</table>
Adverse events (AEs) with gabapentin compared with placebo for PHN
<table>
<tr><th>Outcome</th><th>Gabapentin type</th><th>No. of RCTs</th><th>No. of patients</th><th>RR (95% CI)[a]</th><th>Heterogeneity I^2 (%)</th></tr>
<tr><td rowspan="3">≥ 1 AE</td><td>Enacarbil (G-En)</td><td>2</td><td>472</td><td>1.15 (0.99 to 1.33)</td><td>0</td></tr>
<tr><td>Non G-En</td><td>4</td><td>1420</td><td>1.41 (1.19 to 1.67)</td><td>54</td></tr>
<tr><td>G-En and non G-En</td><td>6</td><td>1892</td><td>1.32 (1.15 to 1.51)</td><td>53</td></tr>
<tr><td rowspan="3">SAE</td><td>G-En</td><td>2</td><td>NR</td><td>0.85 (P = 0.78)</td><td>NR</td></tr>
<tr><td>Non G-En</td><td>4</td><td>NR</td><td>1.28 (P = 0.50)</td><td>NR</td></tr>
<tr><td>G-En and non G-En</td><td>6</td><td>NR</td><td>1.12 (0.59 to 2.10)</td><td>0</td></tr>
<tr><td rowspan="3">Withdrawal due to AE</td><td>G-En</td><td>2</td><td>472</td><td>0.87 (0.48 to 1.60)</td><td>52</td></tr>
<tr><td>Non G-En</td><td>5</td><td>1578</td><td>1.72 (1.23 to 2.39)</td><td>31</td></tr>
<tr><td>G-En and non G-En</td><td>7</td><td>2050</td><td>1.48 (1.11 to 1.97)</td><td>39</td></tr>
<tr><td colspan="6">[a]Unless otherwise stated</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td></td><td>
Specific adverse events with gabapentin (G-En and non G-En) compared with placebo for PHN
<table>
<tr><th>Adverse event</th><th>No. of RCTs</th><th>RR (95% CI)[a]</th><th>Heterogeneity I^2 (%)</th></tr>
<tr><td>Somnolence</td><td>6</td><td>2.19 (1.36 to 3.53)</td><td>39</td></tr>
<tr><td>Dizziness</td><td>7</td><td>3.03 (2.00 to 4.58)</td><td>43</td></tr>
<tr><td>Ataxia or gait disturbance</td><td>2</td><td>10.48 (1.40 to 78.58)</td><td>0</td></tr>
<tr><td>Asthenia</td><td>4</td><td>1.98 (P = 0.22)</td><td>37</td></tr>
<tr><td>Dry mouth</td><td>3</td><td>2.25 (0.88 to 5.81)</td><td>0</td></tr>
<tr><td>Nausea</td><td>4</td><td>1.15 (0.68 to 1.92)</td><td>0</td></tr>
<tr><td>Headache</td><td>5</td><td>1.00 (0.66 to 1.54)</td><td>0</td></tr>
<tr><td>Diarrhea</td><td>3</td><td>2.02 (0.59 to 6.50)</td><td>39</td></tr>
<tr><td colspan="4">[a]Unless otherwise stated</td></tr>
</table>
Authors' Conclusion:
"This meta-analysis indicates that gabapentin is an effective and well-tolerated treatment for patients with PHN." P. 556
</td></tr>
<tr><td>Moore,[b] 2014, Germany, UK (Cochrane Collaboration)</td><td>
Main Findings:

Assessment of substantial benefit (defined as at least 50% pain intensity reduction) of gabapentin compared to placebo
<table>
<tr><th>Condition</th><th>No. of RCTs</th><th>No. of patients</th><th>Patients with substantial benefit (%) G vs plb</th><th>RR (95% CI)</th><th>NNT (95% CI)</th></tr>
<tr><td>PHN</td><td>6</td><td>1816</td><td>34 vs 21</td><td>1.6 (1.3 to 1.9)</td><td>8.0 (6.0 to 12)</td></tr>
<tr><td>DPN</td><td>6</td><td>1277</td><td>38 vs 21</td><td>1.9 (1.5 to 2.3)</td><td>5.9 (4.6 to 8.3)</td></tr>
<tr><td>Mixed NP</td><td>1</td><td>305</td><td>21 vs 14</td><td>1.5 (0.9 to 2.4)</td><td>NC</td></tr>
<tr><td>NIP</td><td>1</td><td>92</td><td>13 vs 9</td><td>1.4 (0.7 to 3.2)</td><td>NC</td></tr>
<tr><td>Small fibre sensory neuropathy</td><td>1</td><td>36</td><td></td><td>5 (0.65 to 38.65)</td><td>NC</td></tr>
</table>
</td></tr>
</table>

First Author, Publication Year, Country	Main Findings and Authors' Conclusion

Efficacy assessment of gabapentin compared to placebo

Outcome	Condition	No. of RCTs	No. of patients	RR (95% CI)
Very much improved	PHN	2	563	2.70 (1.51 to 4.82)
	DPN	2	408	1.94 (1.26 to 2.99)
	Mixed NP	1	305	1.99 (0.92 to 4.28)
	Complex regional pain syndrome 1	1	92	4.0 (0.90 to 17.83)
	NIP	1	196	3.6 (1.39 to 9.31)
	Small fibre sensory neuropathy	1	36	5.0 (0.65 to 38.65)
Much or very much improved	PHN	7	2013	1.32 (1.16 to 1.50)
	DPN	5	695	1.66 (1.36 to 2.03)
	Mixed NP	1	305	2.17 (1.38, 3.41)
	NIP	1	196	2.21 (1.26 to 3.90)
	Small fibre sensory neuropathy	1	36	1.5 (0.67 to 3.34)
IMMPACT outcome of substantial improvement	PHN	7	2045	1.63 (1.37 to 1.93)
	DPN	6	1277	1.86 (1.53 to 2.27)
	Mixed NP	1	305	1.45 (0.88 to 2.37)
	Complex regional pain syndrome 1	1	92	4.0 (0.90 to 17.83)
	NIP	1	196	1.44 (0.65 to 3.22)
	PLP	1	48	2.6 (1.10 to 6.16)
	Small fibre sensory neuropathy	1	36	5.0 (0.65 to 38.65)
IMMPACT outcome of at least moderate improvement	PHN	7	2045	1.59 (1.40 to 1.82)
	DPN	7	1439	1.41 (1.24 to 1.59)
	Mixed NP	2	391	2.10 (1.49 to 2.95)
	Fibromyalgia	1	150	1.61 (1.07 to 2.42)
	NIP	1	196	1.53 (0.92 to 2.53)
	Small fibre sensory neuropathy	1	36	2.25 (0.84 to 5.99)

Patient withdrawal for treatment with gabapentin compared with placebo in various conditions

Reason for withdrawal	No. of RCTs	No. of patients	Withdrawal (%) G vs plb	RR (95% CI)	NNH (95% CI)
All cause	23	4709	20 vs 18	1.04 (0.90 to 1.2)	NC
Adverse events	22	4448	11 vs 7.9	1.4 (1.1 to 1.7)	31 (20 to 66)
Lack of efficacy	16	3693	1.6 vs 3.1	0.5 (0.3 to 0.8)	67 (40 to 205)
Note: All studies which reported on withdrawals were pooled to derive summary estimates, irrespective of the patient condition					

First Author, Publication Year, Country	Main Findings and Authors' Conclusion

Adverse events experienced with gabapentin compared with placebo in various conditions

Adverse event (AE)	No. of RCTs	No. of patients	Patients with AE (%) G vs plb	RR (95% CI)	NNH (95% CI)
SAE	19	3952	3.2 vs 2.8	1.2 (0.8 to 1.7)	NC
≥ 1 AE	17	4002	62 vs 50	1.25 (1.2 to 1.3)	8.6 (6.8 to 12)
Somnolence or drowsiness	20	4125	14 vs 5	2.9 (2.3 to 3.6)	11 (9.4 to 14)
Dizziness	22	4576	19 vs 6.1	3.1 (2.6 to 3.8)	7.6 (6.6 to 8.8)
Peripheral edema	12	3220	7.0 vs 2.2	3.3 (2.2 to 4.9)	21 (16 to 30)
Ataxia or gait disturbance	5	544	8.8 vs 1.2	4.5 (1.9 to 11)	13 (9 to 24)
Note: All studies which reported on the specific adverse event were pooled to derive summary estimates, irrespective of the patient condition					

Adverse events experienced with gabapentin (daily dose 1200 mg to 3600 mg) compared with placebo in DPN

Outcome	No. of RCTs	RCTs with significant results/ not significant results	Range[a] for RR (95% CI)
SAE	4	0/4	(0.18 [0.01 to 4.31]) to (0.45 [0.25 to 8.43])
≥ 1 AE	5	2/3	(1.03 [0.77 to 1.37]) to (1.33 [0.90 to 1.97])
Somnolence or drowsiness	6	3/3	(2.55 [1.00 to 6.50]) (9.11 [0.54 to 54.77])
Dizziness	6	3/3	(2.32 [0.52 to 10.33]) to (15.55 [0.95 to 255.40])
Peripheral edema	3	1/2	(0.70 [0.12 to 4.08]) to (4.46 [2.02 to 9.81])
Withdrawal due to AE	6	0/6	(0.81 [0.36 to 1.85]) to (1.76 [0.94 to 3.33])
Withdrawal due to lack of efficacy	4	0/4	(0.19 [0.02 to 1.62]) to (1.00 [0.07 to 15.26])
[a] Range indicates the minimum and maximum value for the set of RCTs for which RR [95% CI] were calculated			

Death

Overall, three deaths occurred in 3603 patients exposed to gabapentin and five deaths in 2377 patients exposed to placebo.

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td></td><td>Authors' Conclusion:
"There was no top tier evidence that was unequivocally unbiased. Second tier evidence, with potentially important residual biases, showed that gabapentin at doses of 1200 mg or more was effective for some people with some painful neuropathic pain conditions. The outcome of at least 50% pain intensity reduction is regarded as a useful outcome of treatment by patients, and the achievement of this degree of pain relief is associated with important beneficial effects on sleep interference, fatigue, and depression, as well as quality of life, function, and work. About 35% achieved this degree of pain relief with gabapentin, compared with 21%for placebo. Over half of those treated with gabapentin will not have worthwhile pain relief. Results might vary between different neuropathic pain conditions, and the amount of evidence for gabapentin in neuropathic pain conditions except postherpetic neuralgia and painful diabetic neuropathy, and in fibromyalgia, is very limited. The levels of efficacy found for gabapentin are consistent with those found for other drug therapies in postherpetic neuralgia and painful diabetic neuropathy." P. 2

(Levels of evidence [first tier, second tier, and third tier]:
"First tier evidence derived from data meeting current best standards and subject to minimal risk of bias (outcome equivalent to substantial pain intensity reduction, intention-to-treat analysis without imputation for dropouts; at least 200 participants in the comparison, 8 to 12 weeks duration, parallel design), second tier from data that failed to meet one or more of these criteria and were considered at some risk of bias but with adequate numbers in the comparison, and third tier from data involving small numbers of participants that were considered very likely to be biased or used outcomes of limited clinical utility, or both" P. 1).</td></tr>
<tr><td rowspan="2">Pinto,[13] 2012, Australia, Netherlands</td><td>Main Findings:
Pain relieving effect of gabapentin compared with placebo for sciatica:
Mean difference (95% CI) = -26.6 (-38.3 to -14.9), P<0.001

Adverse events with gabapentin compared with placebo for sciatica:
G: 8%, placebo 0%</td></tr>
<tr><td>Authors' Conclusion:
"As the existing evidence from clinical trials is of low quality, the efficacy and tolerability of drugs commonly prescribed for the management of sciatica in primary care is unclear." P. 1 of 15
".....In one small sample trial there was also limited support ("low quality" evidence) for the short term relief of pain in chronic sciatica
with an anticonvulsant drug....." P 4 of 15</td></tr>
<tr><td colspan="2">Randomized controlled trial (RCT)</td></tr>
<tr><td>Hui,[14] 2011, Hong Kong</td><td>Main Findings:

Change in Global symptom score (GSS) from baseline values for CTS
<table>
<tr><th rowspan="2">Time period</th><th colspan="2">Reduction in GSS, mean ± SD</th><th rowspan="2">P value</th></tr>
<tr><th>Gabapentin group</th><th>Placebo group</th></tr>
<tr><td>2 weeks</td><td>–7.4 ± 10.0</td><td>–6.3 ± 7.6</td><td>0.51</td></tr>
<tr><td>8 weeks</td><td>–10.4 ±10.8</td><td>–8.7 ± 8.1</td><td>0.39</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td></td><td>
Adverse events with gabapentin compared with placebo for CTS
<table>
<tr><th rowspan="2">Adverse event</th><th colspan="2">Number patients experiencing adverse events</th></tr>
<tr><th>Gabapentin</th><th>Placebo</th></tr>
<tr><td>Dizziness</td><td>28</td><td>19</td></tr>
<tr><td>Somnolence</td><td>15</td><td>12</td></tr>
<tr><td>Fatigue</td><td>10</td><td>8</td></tr>
<tr><td>Parasthesia</td><td>8</td><td>4</td></tr>
<tr><td>Headache</td><td>8</td><td>7</td></tr>
<tr><td>Nausea</td><td>7</td><td>4</td></tr>
<tr><td>Anorexia</td><td>5</td><td>2</td></tr>
</table>
Authors' Conclusion:
"Gabapentin did not produce a significant reduction in symptom severity compared with placebo over an eight-week period." P. 726
</td></tr>
<tr><td colspan="2">AE = adverse event, CGIC = clinician global impression of change, CI = confidence interval, DPN = diabetic peripheral neuropathy, G-ER = gabapentin extended release, G-IR = gabapentin immediate release, IMMPACT = Initiative on Methods, Measurement and Pain Assessment in Clinical Trials, NC = not calculated, NIP = nerve injury pain, NNH = number needed to treat to harm, NNT = number needed to treat to benefit, NP = neuropathic pain, OR = odds ratio, PGIC = patient global impression of change, PHN = postherpetic neuralgia, PLP = phantom leg pain, PNI = peripheral nerve injury, RR = risk ratio, SAE = serious adverse event, SCI = spinal cord injury, SD = standard deviation, SMD = standardized mean difference</td></tr>
</table>