CADTH

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SUMMARY WITH CRITICAL APPRAISAL

Gabapentin for Adults with Neuropathic Pain: A Review of the Clinical Effectiveness

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Authors: Tasha Narain, Lorna Adcock

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Context and Policy Issues

Neuropathic pain typically develops as a result of lesions or disease that results in damage to the nervous system including areas such as the peripheral nerve, the dorsal root ganglion or dorsal root, or the central nervous system.[1-3] Neuropathic pain is characterized by pain in the absence of a stimulus, or where minor stimuli result in exaggerated levels of pain.[3] The neuropathic pain experienced by patients is heterogeneous in etiology, pathophysiology, and clinical appearance. Neuropathic pain relates to a complex combination of sensory deficits including partial or complete loss of sensation, and symptoms such as dysaethesia (abnormal sensation, i.e., burning) and paraesthesia (i.e., tingling, prickling).[2] Based on sensory profiles, peripheral neuropathic pain can be grouped into the following three subgroups: sensory loss (small and large fiber function and the presence of paradoxical heat sensation), thermal hyperalgesia (relatively preserved large and small fiber sensory functions in combination with heat and cold hyperalgesia and low-intensity dynamic mechanical allodynia), and mechanical hyperalgesia (predominant loss of cold and heat-sensitive small fiber function in combination with blunt pressure hyperalgesia, pinprick hyperalgesia, and marked and more frequent dynamic mechanical allodynia).[1]

It is estimated that the prevalence of neuropathic pain is between 6.9% and 10% in the general population.[4] Neuropathic pain is associated with a multitude of conditions such as diabetes, shingles, amputation, HIV, and spinal cord injury.[3] While a number of pharmaceutical therapies exist for neuropathic pain treatment, several drawbacks exist. It is known that patients generally do not respond to non-steroidal anti-inflammatory drugs and resistance or insensitivity to opiates is common and thus not recommended.[2,3] Other therapy such as serotonin and norepinephrine uptake inhibitors, antidepressants, and anticonvulsants are associated with negative side-effects and have limited to modest efficacy.[2,3]

Gabapentin (GBP) is a Health Canada approved antiepileptic drug.[5] In the UK, GBP is licensed for the treatment of peripheral and central neuropathic pain in adults and in the US it is marketed for post-herpetic neuralgia (PHN).[3] The mechanism of action for GBP relates to its ability to bind with high-affinity to the alpha-2-delta subunit of voltage-gated calcium channels located throughout the peripheral and central nervous system; thus modifies the release of neurotransmitters and reduces excitability of nerve cells.[3,6] It is this mechanism of action that may produce analgesic effect in patients experiencing neuropathic pain.[3] While there is evidence to support the use of GBP for patients with diabetic peripheral neuropathy (DPN) and PHN the efficacy for the off-label treatment of other conditions requires examination.[7,8]

The purpose of this report is to review the clinical effectiveness of GBP compared to other therapy (tricyclic antidepressants, serotonin–norepinephrine reuptake inhibitors, carbamazepine, topiramate) or placebo in adults with neuropathic pain.

This report serves as an update to CADTH's 2015[8] and 2016[9] Rapid Response reports. These previous reports reviewed studies relating to neuropathic pain (not specific to any conditions) and two studies relating to HIV-associated neuropathic pain, respectively. In the HIV-associated neuropathic pain report,[9] the review suggested that gabapentin may

improve pain and sleep disturbances, however the small sample size of each study and limitations in the analyses conducted prevent strong conclusions. In the 2016 report,[8] most of the available RCT data pertained to DPN and PHN, it was concluded that for DPN there was greater reduction in neuropathic pain and increased risk of adverse events associated with gabapentin compared with placebo. For other conditions there were limited number of RCTs and for some conditions the evidence was from single RCTs.[8]

Research Question

What is the clinical effectiveness of gabapentin for adults with neuropathic pain?

Key Findings

The findings from four systematic reviews and one RCT for gabapentin (GBP) compared to placebo or active comparators is limited by quantity and quality of evidence for studies on neuropathic pain associated with conditions including chronic lower back pain, fibromyalgia, mixed neuropathic pain, and nerve injury pain. While some studies reported little to no difference in pain, the limited data prevent strong conclusions to be drawn for the clinical efficacy of GBP. For patients with trigeminal neuralgia, conclusions about the efficacy of GBP compared to carbamazepine could not be made. Limited evidence suggests that there is no difference between GBP and topiramate for the treatment of neuropathic pain. Common adverse events associated with GBP included somnolence, fatigue, drowsiness, and dizziness.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including Ovid Medline, Ovid Embase, PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases and a focused Internet search. No methodological filters were applied to limit retrieval by publication type. The search was limited to English language documents published between January 1, 2014 and February 9, 2018.

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	Adults with neuropathic pain (other than diabetic peripheral neuropathy [DPN] and post-herpetic neuralgia [PHN]), including: - HIV-associated neuropathic pain - Mixed neuropathic pain - Spinal cord injury - Nerve injury pain - Phantom limb pain - Small fiber sensory neuropathy - Chronic masticatory myalgia

	- Complex regional pain syndrome - Fibromyalgia - Sciatica - Carpal tunnel syndrome
Intervention	Gabapentin
Comparator	Placebo; Alternative drug therapies: - tricyclic antidepressants (e.g., amitriptyline) - serotonin–norepinephrine reuptake inhibitors (e.g., duloxetine) - carbamazepine - topiramate
Outcomes	Clinical benefits and harms (e.g., pain management, symptom relief, quality of life, adverse events)
Study Designs	Heath technology assessments (HTA), systematic reviews (SR), meta-analyses (MA), randomized control trials (RCT), and non-randomized studies

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, they were included in systematic reviews, they were published prior to 2014, or they were included in previous CADTH reports. Articles were excluded if they were solely composed of patients with DPN or PHN.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using AMSTAR 2,[10] and the randomized studies were critically appraised using the Downs and Black Checklist.[11] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 368 citations were identified in the literature search. Following screening of titles and abstracts, 347 citations were excluded and 21 potentially relevant reports from the electronic search were retrieved for full-text review. Nineteen potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 35 publications were excluded for various reasons, while five publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

The details of the individual study characteristics for the included publications are provided in Appendix 2.

Study Design, Aim and Patient Population

Cooper et al. published a Cochrane systematic review to assess the analgesic efficacy of GBP for fibromyalgia pain in adults.[12] This systematic review identified one relevant RCT from 2007 that included 150 patients.

Shanthanna et al. conducted a systematic review to determine the usefulness of either pregabalin or GBP in decreasing pain and improving function in patients with chronic low back pain.[13] This systematic review required patients to have predominant chronic low back pain for three or more months and identified six relevant RCTs (n = 517) with three (n = 185) specifically related to GBP published between 2000 and 2016. One of the included GBP RCTs had a crossover design, while the other two GBP RCTs had a parallel design.

Wiffen et al. published a Cochrane systematic review to assess the analgesic efficacy of GBP for chronic neuropathic pain in adults.[3] This systematic review identified 37 relevant RCTs published between 1998 and 2016 that included 5,914 patients. The majority of the individual trials focused on DPN and PHN. Since this patient population was not included in the present RR, the summary will be on the other patient populations included in the systematic review (i.e., mixed neuropathic pain [1 study], nerve injury pain [1 study]). Other studies focusing on patient populations for radicular leg pain, spinal cord injury, nerve injury pain, phantom limb pain, cancer-related neuropathic pain, and HIV-associated sensory neuropathies were described narratively.

Yuan et al. conducted a systematic review to evaluate the safety and efficacy of GBP compared with carbamazepine for the treatment of trigeminal neuralgia.[14] This systematic review included 16 RCTs published between 2006 and 2014 yielding data from 1,311 patients. The individual trials all originated from China and were published in Chinese.

A RCT by Nazarbaghi et al. published in 2017 followed patients with neuropathic pain attributed to polyneuropathy for 4 weeks.[15] This study was conducted in Iran and included 30 patients. The mean age of patients was 63.6 years, and 40% of patients were female.

Interventions and Comparators

Cooper et al. assessed GBP at any dose, by any route, compared to placebo or any other active comparator.[12] The single RCT that was identified used a placebo control.

Shanthanna et al. assessed the following comparison: GBP versus placebo, and pregabalin versus placebo.[13] A specific dose for GBP was not specified, however across the three included RCTs GBP was administered at 300 mg once a day and increased on a weekly basis to a maximum dose of 1,200 mg per day or 15 mg/kg.

Wiffen et al. assessed GBP at in any dose, by any route compared to placebo or any other active comparator.[3] The majority of studies used oral GBP or GBP encarbil at 1200 mg or higher daily.

Yuan et al. assessed GBP compared to carbamazepine; dosing was not specified.[14]

Nazarbaghi et al. assessed GBP 300 mg/day to a maximum of 900 mg/day compared to topiramate 50 mg/day to a maximum of 100 mg/day.[15]

Outcomes

Across all studies, the outcomes related to pain relief and safety or adverse events. For the systematic reviews by Cooper[12] and Wiffen,[3] pain relief was assessed using the following criteria: 30% pain reduction at 12 weeks, 50% pain reduction at 12 weeks, Patient Global Impression of Change - any category of ''better'' at 12 weeks (for Cooper et al.) or much/very much improved (for Wiffen et al.). Withdraws, serious adverse events, and deaths were also planned outcomes to be assessed. For the Wiffen et al. systematic review, the secondary outcomes were described narratively and not focused on in the

review; thus only studies reporting outcomes relevant to the primary outcomes will be focused on in the CADTH report.

The individual RCTs included in the systematic review by Shanthanna assessed pain relief using a numerical rating scale or visual analogue scale.[13] For consistency, these scales were converted into a common zero to ten numerical rating scale. Safety was assessed using the occurrence of serious adverse events.

The systematic review by Yuan examined the following outcomes: the effective rate of therapy (efficacy assessed via odds ratio), life satisfaction, and adverse reactions.[14]

The RCT by Nazarbaghi evaluated severity of pain using a visual analogue scale with the following specifications: 0 (No Distress), 1 (2 cm, Annoying), 2 (4 cm, Uncomfortable), 3 (6 cm, Dreadful), 4 (8 cm, Horrible) and 5 (10 cm, Agonizing).[15]

Summary of Critical Appraisal

The details of the critical appraisal for the included publications are provided in Appendix 3.

The Cochrane systematic reviews for fibromyalgia by Cooper et al.[12] and neuropathic pain by Wiffen et al.[3] were assessed to be of high quality. Both of these systematic reviews included clear components to the research question (population, intervention, comparator group, outcome) with the exception of the dosages which were unspecified. The systematic reviews used comprehensive literature search strategies and robust methods. The methods for the systematic reviews were pre-determined with a registered protocol in place. Additionally, both systematic reviews selected studies and extracted data in duplicate or triplicate independently. For the individual studies included, each systematic review used the Cochrane risk of bias tool and clearly presented the results pertaining blinding, randomization, and allocation concealment. Where appropriate, publication bias was assessed. The Cooper systematic review did not warrant the use of a meta-analysis due to identifying a single applicable RCT.[12] The included RCT was judged to have low or unclear risk of bias. The Wiffen systematic review used appropriate statistical methods for the meta-analysis including the assessment of heterogeneity, subgroup analysis, and assessment of the certainty of evidence using GRADE (Grading of Recommendations Assessment, Development, and Evaluation).The majority of the individual studies in Wiffen Cochrane systematic review were of moderate quality.

The systematic review for chronic low back pain by [13] was generally of high quality. The research question was clearly described with the exception of the dosages which were unspecified. A comprehensive literature search strategy and robust methods were used. The methods for the systematic review were pre-determined with a registered protocol in place. The studies were screened and the data was extracted in duplicate independently. The RCTs were assessed using the Cochrane risk of bias tool and aspects including blinding, randomization, and allocation concealment were clearly reported. Publication bias due to low sample size was commented on. Appropriate statistical methods were used for the meta-analysis; statistical heterogeneity was assessed using the Cochrane Q-test, extracted results of studies were weighted, and sensitivity analysis based on alternate imputation methods was conducted. The quality of evidence was assessed using GRADE.

The systematic review[14] for GBP compared to carbamazepine for patients with trigeminal neuralgia included a clear research question with the exception of the dosages for both GBP and carbamazepine which were unspecified. A comprehensive literature search strategy was used, and study selection and data extraction were performed in duplicate

independently. Some of the statistical methods for the meta-analysis were appropriate, specifically for the investigation of heterogeneity and the risk of bias. When heterogeneity was present (p-value < 0.10 or I^2 score > 50%), random-effects models were used. Risk of bias was assessed for individual studies using the Cochrane classification to examine aspects including blinding, randomization, and allocation concealment. Risk of bias was assessed for individual studies using the Cochrane classification, and risk of publication bias for the collective studies was assessed using Egger's regression test.

The RCT[15] for GBP compared to topiramate for patients with neuropathic pain attributed to polyneuropathy included a clear research question. The doses were specified, however the details of the associated titration process were not included. The main study outcome to be measured was clearly identified in the methods section and the characteristics of the patients were clearly described. The exact probability values were reported. Validity and reliability of the outcome (visual analogue scale) were not reported. Issues pertaining to external validity were present (i.e., extensive exclusion criteria, recruitment at a single clinic in Iran). The blinding process was not described and a power calculation was not provided.

Summary of Findings

What is the clinical effectiveness of gabapentin for adults with neuropathic pain?

For adults with fibromyalgia pain, a systematic review identified a single RCT which indicated some numerical improvement over placebo for patients on GBP for various pain outcomes: 49% of patients with fibromyalgia on GBP and 31% of patients on placebo achieved 30% or greater reduction in pain over baseline; 91% of patients on GBP and 47% of patients on placebo achieved a patient global impression of change any category of "better".[12] More patients on GBP (16%) discontinued the study due to adverse events compared to placebo (9%). Overall, the sparseness of evidence and methodological limitations in the individual trial contributed to the quality of evidence classified as very low.

For adults with chronic low back pain assessed in the systematic review by Shanthanna et al.,[13] very low quality of evidence indicated minimal improvement of chronic low back pain for GBP compared to placebo (mean difference = 0.22 units, 95% CI: −0.5 to 0.07), where pain was assessed using a 0 to 10 numerical rating scale.[13] Very low quality of evidence indicated increased risk of dizziness or unsteadiness (RR = 1.99, 95% CI: 1.17 to 3.37) and fatigue or lethargy (RR = 1.85, 95% CI: 1.12 to 3.05) for GBP compared to placebo. Moderate quality of evidence indicated increased risk of visual disturbances/blurring of vision (RR = 5.72, 95% CI: 1.94 to 16.91), and low quality of evidence indicated increased risk for difficulty with mentation (RR = 3.34, 95% CI: 1.54 to 7.25).

For adults with mixed neuropathic pain, limited evidence from a single study included in the Wiffen et al. Cochrane systematic review[3] suggested no significant differences between GBP and placebo for at least 50% pain reduction over baseline (Risk ratio = 1.45, 95% CI: 0.88 to 2.37).[3] For patient global impression of change for the combined much improved or very much improved categories, an improvement was noted for GBP compared to placebo (Risk ratio = 2.17, 95% CI: 1.38 to 3.41), but not for much improved (Risk ratio = 1.99, 95% CI: 0.92 to 4.28). For adults with nerve injury pain, limited evidence from a single study suggested no significant differences between GBP and placebo for at least 50% pain reduction over baseline (Risk ratio = 1.44, 95% CI: 0.65 to 3.22).[3] For patient global impression of change for much or very much improved, an improvement was noted for GBP compared to placebo (Risk ratio = 2.21, 95% CI: 1.26 to 3.90), as well as for much improved (Risk ratio = 3.6, 95% CI: 1.39 to 9.31).[3] Other conditions assessed in this

systematic review (radicular leg pain, spinal cord injury, nerve injury pain, phantom limb pain, cancer-related neuropathic pain, HIV-associated sensory neuropathies) were of low quality with a small number of studies, participants, and events. For all conditions combined, adverse event withdrawals were more common with GBP (11%) than with placebo (8.2%) (RR 1.4, (95% CI: 1.1 to 1.7).[3]

For adults with trigeminal neuralgia, low quality evidence indicated that the total effective rate was similar for GBP and carbamazepine (OR = 1.60, 95% CI: 1.18 to 2.16; p = 0.002).[14] Low quality evidence indicated that the life-satisfaction improvement was greater for GBP compared to carbamazepine (SMD = 0.97, 95% CI: 0.58 to 1.35; p < 0.001). Moderate quality of evidence indicated that the adverse reaction rate was lower for GBP compared to carbamazepine (OR = 0.31, 95% CI: 0.24 to 0.41).

For adults with neuropathic pain attributed to polyneuropathy, a single low-quality RCT reported no significant differences between GBP and topiramate in terms of average reduction of neuropathic pain intensity attributed to polyneuropathy (GBP = 59.7% reduction, topiramate = 55.0% reduction, p = 0.48).[15]

Limitations

The systematic reviews were generally well conducted, however all four did not report the specific dose of GBP or route of administration which could have potentially introduced heterogeneity thus limiting the applicability of the results.

With the exception of limited data, no major limitations to the Cochrane systematic reviews for fibromyalgia[12] or neuropathic pain[3] were noted. The systematic review for chronic low back pain[13] did not reveal any major limitations.

Limitations related to the statistical methods used in the meta-analysis were noted for systematic review that compared GBP to carbamazepine for patients with trigeminal neuralgia.[14] Firstly, it is unclear if the methods for the meta-analysis were established prior to the conduct of the study; a pre-published protocol was not referenced. It does not appear that weighting was used to account for differences in sample sizes for the primary outcome of total effective rate. In addition, it is unclear if the risk estimates extracted were based on fully-adjusted models. Sensitivity analyses were not reported or performed to investigate the potential impact of various covariates (i.e., disease severity), or the effect of removing low quality studies (i.e., high risk of bias). The individual studies included in the systematic review were conducted in China and therefore it is unclear if the results are externally valid to the Canadian population. Sources of funding and conflict of interest were not reported for this systematic review.

The RCT comparing GBP to topiramate for patients with polyneuropathy had a number of limitations including a small sample size (n = 30).[15] Firstly, the interventions were not described in adequate detail. A limited description indicated that patients received a specific dose at the beginning of the trial (GBP 300 mg/day, 50 mg/day topiramate) that was titrated to a maximum (GBP 900 mg/day, 100 mg/day topiramate) after a 4-week period. However, the details of the titration (i.e., incremental dose increase, duration between dose increases) were not provided. It is unclear if titration was conducted in the same manner between patients in the same treatment group. The rationale for the dose was not provided, thus it is unclear if the starting and final dosages were equivalent or consistent with the therapeutic norm. The use of a visual analogue scale presents concerns about the validity or reliability as references for its use and design were not provided. The external validity of

the RCT was limited as participants were recruited from a single neurology clinic in Iran. Additionally, patients were excluded if they had taken other medications (tricyclic antidepressants, mexiletine hydrochloride, carbamazepine, phenytoin, valproate sodium and dextromethorphan drugs) within 30 days). This trial stated that it was blinded, but did not provide details of the blinding process and the parties who were blinded. It was unclear if the trial was sufficiently powered as a power calculation was not reported. The numerous limitations reduce the robustness of the findings highlighting the need for caution when interpreting the conclusions.

Conclusions and Implications for Decision or Policy Making

This report serves as an update to CADTH's 2015[8] and 2016[9] Rapid Response reports. These previous reports reviewed neuropathic pain (not specific to any condition) and HIV-associated neuropathic pain, In the HIV-associated neuropathic pain report, the review suggested that gabapentin may improve pain and sleep disturbances, however the small sample size of each study and limitations in the analyses conducted prevented strong conclusions. In the 2016 report, most of the available RCT data pertained to DPN and PHN, and it was concluded that for DPN there was greater reduction in neuropathic pain and increased risk of adverse events associated with gabapentin compared with placebo. For other conditions, there were limited number of RCTs and for some conditions the evidence was from single RCTs thus highlighting the need for a follow-up CADTH report.[8]

In the current CADTH report four systematic reviews and one RCT assessed patients with neuropathic pain associated with a variety of conditions including fibromyalgia, chronic low back pain, mixed neuropathic pain, nerve injury pain, trigeminal neuralgia, and polyneuropathy. Whether compared to placebo or an active comparator the available literature was limited, thus preventing conclusions to be drawn about the clinical effectiveness. The included RCT that assessed patients with polyneuropathy, while having several methodological limitations, reported no difference between GBP and topiramate.

As the focus of this CADTH report was for adults with neuropathic pain for conditions other than DPN and PHN. The findings for the clinical effectiveness of GBP on neuropathic pain attributed to other conditions (i.e., fibromyalgia, chronic low back pain, mixed neuropathic pain, nerve injury pain, and trigeminal neuralgia) were limited by the quantity and quality of individual studies; thus conclusions about the clinical effectiveness cannot be drawn. Further high-quality study is required to draw conclusions pertaining to the clinical benefits and harms for the use of GBP for neuropathic pain related to these conditions.

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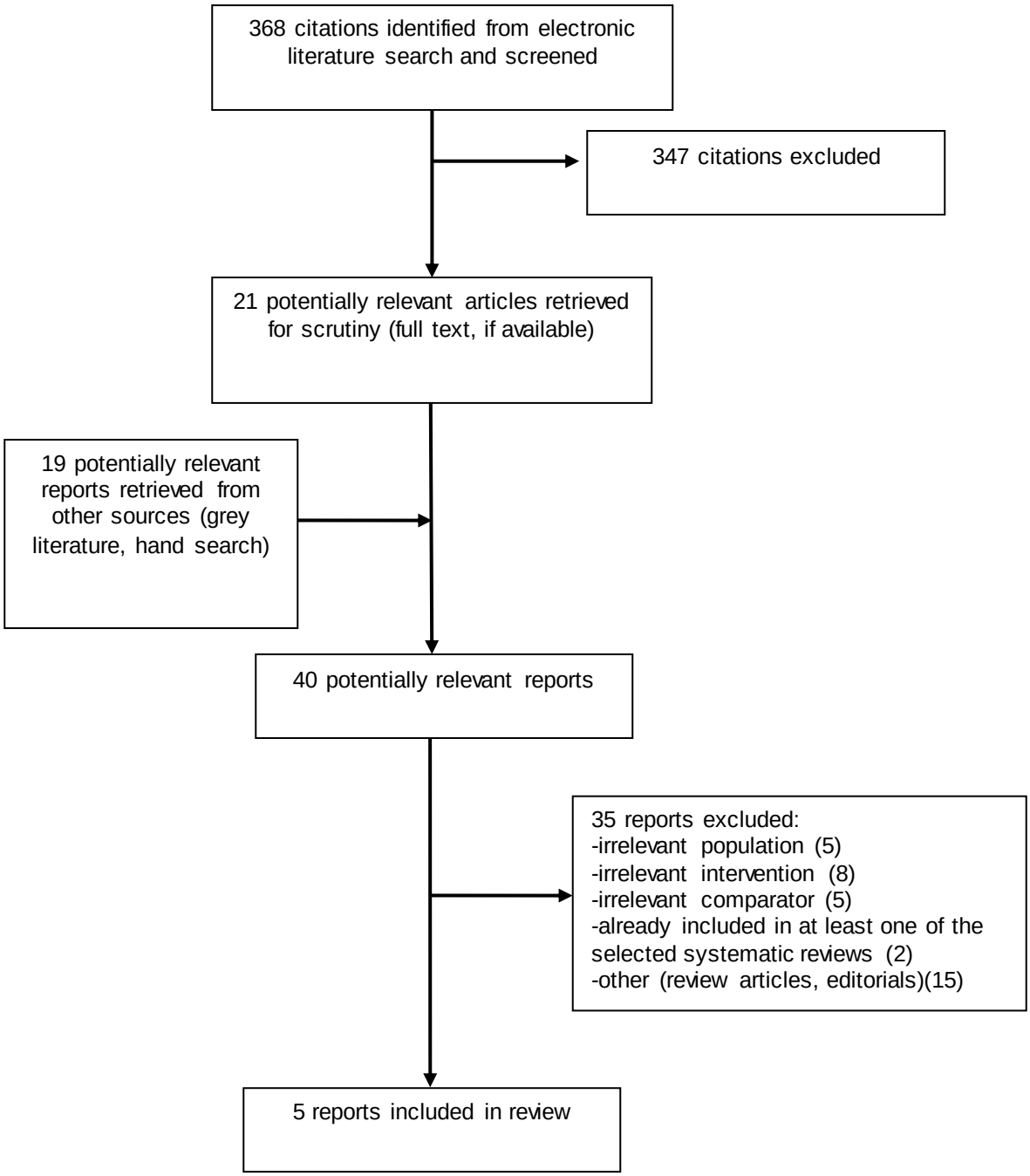
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Type and Number of Primary Studies Included, Aim	Population Characteristics	Comparisons	Outcomes
Cooper,[12] 2017, United Kingdom	1 RCT To assess the analgesic efficacy of gabapentin for fibromyalgia pain in adults and the adverse events associated with its use in clinical trials.	Adults with fibromyalgia pain. n = 150	1. GBP versus placebo 2. GBP versus active comparator	Pain relief (i.e., 30% pain reduction at 12 weeks, 50% pain reduction at 12 weeks, Patient Global Impression of Change any category of "better") Adverse events
Shanthanna,[13] 2017, Canada	6 RCTs (3 related to GBP) To determine the usefulness of either pregabalin or GBP in decreasing pain and improving functions, and the potential adverse effects of pregabalin and GBP, in patients with predominant chronic low back pain	Adult patients with predominant chronic low back pain of 3 months or more. n = 517 (N_{GBP} = 185)	1. GBP versus placebo 2. Pregabalin versus placebo	Pain relief (0 to 10 NRS) Safety (adverse events)
Wiffen,[3] 2017, United Kingdom	37double-blind RCTs To assess the analgesic efficacy and adverse effects of gabapentin in chronic neuropathic pain in adults.	Patients with neuropathic pain. n = 5,914	1. GBP versus placebo 2. GBP versus active comparator	Pain relief (i.e., 30% pain reduction at 12 weeks, 50% pain reduction at 12 weeks, Patient Global Impression of Change – much or very much improved) Adverse events
Yuan,[14] 2016, China	16 RCTs To evaluate the safety and efficacy of GBP in comparison with carbamazepine in the treatment of trigeminal neuralgia.	Patients with trigeminal neuralgia. n = 1,311	1. GBP versus carbamazepine	Effective rate of therapy Life satisfaction Adverse reaction

GBP = gabapentin; NRS = numeric rating scale; RCT = randomized controlled trial.

Table 3: Characteristics of Included Clinical Studies

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)	Clinical Outcomes
Nazarbaghi,[15] 2017, Iran	RCT, 4 weeks	Patients with pain attributed to neuropathy Age, mean = 63.6 Female = 40% N = 30	GBP 300 mg/day to a maximum of 900 mg/day	Topiramate 50 mg/day to a maximum of 100 mg/day	Severity of pain (visual analogue scale)

GBP = gabapentin; RCT = randomized controlled trial.

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2[10]

Strengths	Limitations
Cooper, 2017[12]	
• The research question included the components of PICO (population, intervention, comparator group, outcome) • The methods for the systematic review were established prior to the conduct of the study and the protocol was registered • A comprehensive literature search strategy was used • The study selection and data extraction were performed in duplicate independently • The included study was described in adequate detail • Risk of bias was assessed for individual studies using the Cochrane risk of bias tool, and publication bias was planned to be assessed • Sources of funding were reported, and no conflict of interest was present	• Dose for intervention was not specified
Shanthanna, 2017[13]	
• The research question included the components of PICO (population, intervention, comparator group, outcome) • The methods for the systematic review were established prior to the conduct of the study and the protocol was registered • A comprehensive literature search strategy was used • The study selection and data extraction was performed in duplicate independently • Justification for studies that were excluded was provided • The details of the individual studies were provided • Risk of bias was assessed for individual studies using the Cochrane risk of bias tool • Sources of funding was reported • Generally, appropriate statistical methods were used for the meta-analysis	• Dose for intervention was not specified
Wiffen, 2017[3]	
• The research question included the components of PICO (population, intervention, comparator group, outcome) • The methods for the systematic review were established prior to the conduct of the study and the protocol was registered • A comprehensive literature search strategy was used • The study selection was performed in duplicate and data extraction was performed in triplicate	• Dose for intervention was not specified

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2[10]

Strengths	Limitations
independently • Justification for studies that were excluded was provided • The included studies were described in adequate detail • Risk of bias was assessed for individual studies using the Cochrane risk of bias tool, and publication bias was also assessed • Sources of funding were reported, and no conflict of interest was present • Statistical methods for the meta-analyses were appropriate	
Yuan, 2016[14]	
• The research question included the components of PICO (population, intervention, comparator group, outcome) • A comprehensive literature search strategy was used • The study selection and data extraction was performed in duplicate independently • Justification for studies that were excluded was provided • The details of the individual studies were provided • Risk of bias was assessed for individual studies using the Cochrane classification, and risk of publication bias for the collective studies was assessed using Egger's regression test • Some of the statistical methods for the meta-analysis were appropriate (i.e. investigation of heterogeneity)	• Dose for intervention and comparator were not specified • External validity to Canadian population unclear • Unclear if the methods for the meta-analysis were established prior to the conduct of the study • Sources of funding and conflict of interest were not reported • Some of the common statistical methods used in meta-analyses were referred to but not presented (i.e., sensitivity analyses), or not preformed (i.e., analysis omitting low quality studies)

Table 5: Strengths and Limitations of Randomized Controlled Trials using the Downs and Black Checklist[11]

Strengths	Limitations
Nazarbaghi, 2017[15]	
• The aim of the study was clearly described • The main study outcome to be measured was described in the methods section • The characteristics of the patients included were clearly described • The main findings of the study were clearly described • Probability values were reported	• The intervention was not clearly described (limited description of titration process, unclear rationale for initial and final dose) • No evidence for the validity or reliability of the outcome (visual analogue scale) were provided • External validity was limited as participants were recruited from a single neurology clinic in Iran, and patients were excluded if they had taken other medications (tricyclic antidepressants, mexiletine hydrochloride, carbamazepine, phenytoin, valproate sodium and dextromethorphan drugs) within 30 days • Blinding was stated, but details of the process were not provided • Unclear if the trial was sufficiently powered, power calculation was not reported

Appendix 4: Main Study Findings and Author's Conclusions

Table 6: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusion
Cooper, 2017[12]	
49% of patients with fibromyalgia on GBP and 31% of patients on placebo achieved 30% or greater reduction in pain over baseline. 91% of patients on GBP and 47% of patients on placebo achieved a patient global impression of change any category of "better". 16% of patients on GBP and 9% of patients on placebo discontinued the study because of adverse events.	"We have only very low quality evidence and are very uncertain about estimates of benefit and harm because of a small amount of data from a single trial. There is insufficient evidence to support or refute the suggestion that gabapentin reduces pain in fibromyalgia." P.2[16]
Shanthanna, 2017[13]	
Minimal improvement of chronic low back pain was identified for GBP compared to placebo (mean difference = 0.22 units, 95% CI: −0.5 to 0.07). The most frequently reported adverse events for treatment with GBP were dizziness (RR = 1.99, 95% CI: 1.17 to 3.37), fatigue (RR = 1.85, 95% CI: 1.12 to 3.05), difficulties with mentation (RR = 3.34, 95% CI: 1.54 to 7.25)., and visual disturbances (RR = 5.72, 95% CI: 1.94 to 16.91).	"Existing evidence on the use of gabapentinoids in chronic low back pain is limited and demonstrates significant risk of adverse effects without any demonstrated benefit. Given the lack of efficacy, risks, and costs associated, the use of gabapentinoids for chronic lower back pain merits caution." p.2[15]
Wiffen, 2017[3]	
For mixed neuropathic pain data from one study determined no significant differences between GBP and placebo for at least 50% pain reduction over baseline (Risk ratio = 1.45, 95% CI: 0.88 to 2.37). For patient global impression of change for much or very much improved, an improvement was noted for GBP compared to placebo (Risk ratio = 2.17, 95% CI: 1.38 to 3.41), but not for much improved (Risk ratio = 1.99, 95% CI: 0.92 to 4.28). For nerve injury pain data from one study determined no significant differences between GBP and placebo for at least 50% pain reduction over baseline (Risk ratio = 1.44, 95% CI: 0.65 to 3.22). Other conditions assessed (radicular leg pain, spinal cord injury, nerve injury pain, phantom limb pain, cancer-related neuropathic pain, HIV-associated sensory neuropathies) were of low quality with a small number of studies, participants, and events. For all conditions combined, adverse event withdrawals were more common with GBP (11%) than with placebo (8.2%) (RR 1.4, (95% CI: 1.1 to 1.7). The most frequently reported adverse event for treatment with GBP were dizziness (19%), somnolence (14%), peripheral	"Gabapentin at doses of 1800 mg to 3600 mg daily (1200 mg to 3600 mg gabapentin encarbil) can provide good levels of pain relief to some people with postherpetic neuralgia and peripheral diabetic neuropathy. Evidence for other types of neuropathic pain is very limited." p.2[10]

Table 6: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusion
oedema (7%), and gait disturbance (14%).	
Yuan, 2016[14]	
For patients with trigeminal neuralgia, the total effective rate was similar for GBP and carbamazepine (OR = 1.60, 95% CI 1.18 to 2.16; p = 0.002). The life-satisfaction improvement was greater for GBP compared to carbamazepine (SMD = 0.97, 95% CI: 0.58 to 1.35; p < 0.001). The adverse reaction rate was significantly lower in the GBP group compared to the carbamazepine group (OR = 0.31, 95% CI: 0.24 to 0.41; p < 0.001). The adverse reaction rate was lower for GBP compared to carbamazepine (OR = 0.31, 95% CI: 0.24 to 0.41). The most frequently reported adverse event for treatment with GBP was vertigo, somnolence, fatigue and dizziness; for carbamazepine it was vertigo, somnolence, nausea, and fatigue.	"It is not possible to draw conclusions regarding the efficacy and side effects of gabapentin being superior to carbamazepine." p.1090
Nazarbaghi, 2017[15]	
There were no significant differences between GBP and topiramate in terms of average reduction of neuropathic pain intensity attributed to polyneuropathy (GBP = 59.7% reduction, topiramate = 55.0% reduction, p = 0.48). The most frequently reported complication for treatment with GBP was drowsiness; for CBZ it was topiramate.	"…there was no clear difference between topiramate and gabapentin, and in cases of intolerance to gabapentin and other drugs such as antidepressants, topiramate can be replaced in the treatment of neuropathic pain." p.5621