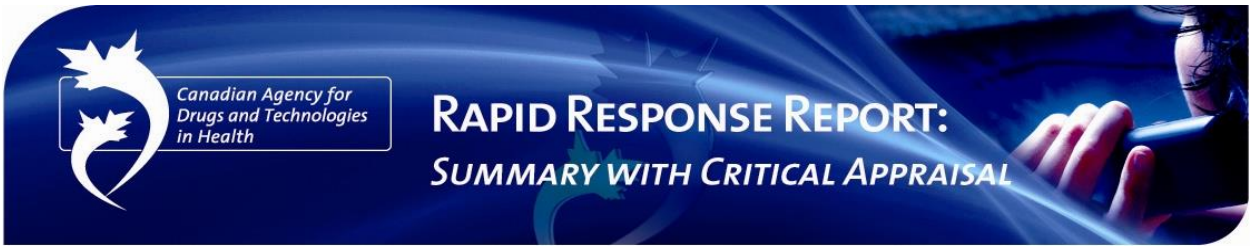

TITLE: Gabapentin for HIV-associated Neuropathic Pain: A Review of the Clinical Effectiveness

DATE: 22 January 2016

CONTEXT AND POLICY ISSUES

Neuropathic pain can be severe and debilitating and results when there is damage to or dysfunction of the central or peripheral nervous system.[1] Sensory neuropathy is a complication of HIV infection, affecting up to 40% of HIV-infected individuals.[2] In 2014, the Public Health Agency of Canada estimated that approximately 75,000 Canadians were living with HIV (including AIDS), with 2,000 to 3,000 new HIV cases reported annually.[3] HIV-associated sensory neuropathy is diagnosed according to a standard definition which includes: distal sensory symptoms (including pain and abnormal sensations such as burning or tingling), abnormal sensory signs (increased sensitivity to pain or higher vibration perception threshold), decreased or lack of ankle reflexes, and no other known causes of neuropathy (such as diabetes or malignancy) as determined by clinical or laboratory investigations.[4,5] Symptoms of HIV-associated sensory neuropathy are observed primarily in the feet, and can interfere with daily activities and sleep.[4]

Pharmacological management of neuropathic pain includes anticonvulsants, antidepressants, serotonin noradrenaline reuptake inhibitors, opioid analgesics, cannabinoids and methadone.[6] The anticonvulsant gabapentin has been used to manage neuropathic pain. However, gabapentin is not without side effects and there is also potential for misuse.[7] Side effects associated with gabapentin include somnolence, dizziness, peripheral edema and gait disturbances.[8] Gabapentinoids (including gabapentin) in high doses may result in sedative and psychedelic effects.[7]

Two previous Rapid Response reports examined the evidence for the use of gabapentin to treat neuropathic pain compared with placebo[9] or active treatments such as tricyclic antidepressants, serotonin noradrenaline reuptake inhibitors, and pregabalin[7] and found that there was evidence of short-term pain relief with gabapentin for patients with painful diabetic neuropathy, postherpetic neuralgia, and fibromyalgia. However evidence for gabapentin for HIV-associated neuropathy was limited.

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The purpose of this report is to examine the evidence for the use of gabapentin for the treatment of adults with HIV-associated neuropathic pain.

RESEARCH QUESTION

What is the clinical effectiveness of gabapentin for the treatment of HIV-associated neuropathic pain?

KEY FINDINGS

There is limited evidence for the use of gabapentin for the treatment of HIV-associated neuropathy. One relevant RCT, included in a systematic review, and one non-randomized study were identified. The studies suggest that gabapentin may improve pain and related sleep disturbances caused by HIV-associated sensory neuropathy; however, due to the limitations of the evidence, the effectiveness of gabapentin for patients with HIV-associated neuropathy is inconclusive.

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, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents. No date limits were used. The search was run on November 17, 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. A second reviewer made the final selection of full-text articles based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults with HIV-associated Neuropathic Pain
Intervention	Gabapentin
Comparator	Placebo, tricyclic antidepressants (TCAs), serotonin–norepinephrine reuptake inhibitors (SNRIs), carbamazepine
Outcomes	Clinical effectiveness (e.g. pain reduction), harms
Study Designs	Heath Technology Assessments, Systematic Reviews/Meta-analyses, Randomized Controlled Trials, Non-randomized studies

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were included in a selected systematic review. Systematic reviews

were excluded if the all relevant studies were captured in a more recent or comprehensive systematic review.

Critical Appraisal of Individual Studies

One reviewer examined the included studies for quality. The included systematic reviews were critically appraised using the AMSTAR checklist[10] and non-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 47 citations were identified in the literature search. Following screening of titles and abstracts, 44 citations were excluded and three potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from other sources. These potentially relevant articles consisted of two systematic reviews,[2,8] one randomized controlled trial,[5] and one non-randomized study.[4] Of these articles, both systematic reviews identified a single randomized trial,[5] which was also identified by the literature search for this report. One systematic review which was superseded by a more recent review[2] and one randomized trial which was included in the selected systematic review[5] were excluded, while one systematic review[8] and one non-randomized study[4] met the selection criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

A summary of the characteristics of the individual studies is provided in Appendix 2.

Study Design

One systematic review[8] and one uncontrolled before-after study[4] were identified. The systematic review included randomized, double-blind studies, with the most recent search conducted January 2011. The systematic review[8] was published in 2014. The uncontrolled before-after study[4] was published in 2001. The systematic review[8] identified one study[5] of HIV-associated neuropathy, published in 2004, relevant to this report.

Country of Origin

The systematic review[8] was conducted by researchers in the United Kingdom, and the relevant RCT it identified was conducted by researchers in Germany. The uncontrolled before-after study was conducted by researchers in Italy.

Patient Population

The systematic review[8] included any double-blind RCT including adult patients receiving gabapentin for neuropathic pain. It identified one RCT[5] on HIV-associated neuropathy which included 26 adults with distal-symmetric polyneuropathy due to HIV itself (n=16) or potentially caused by neurotoxic antiretroviral drugs (n=10). Participants were required to have symptoms

of painful HIV-associated sensory neuropathy diagnosed by a neurologist according to a standard definition.

The uncontrolled before-after study[4] included 19 participants with painful distal sensory neuropathy due to HIV (n=6), neurotoxic HIV therapies (n=9), or both (n=4). Participants were required to be diagnosed according to a standard definition, and a baseline pain or sleep interference score better than 40 mm on a 100 mm visual analogue scale (VAS).

Interventions and Comparators

The RCT[5] identified in the systematic review[8] randomized patients to receive gabapentin or placebo. Gabapentin was initiated at 400 mg/day and titrated over 2 weeks up to 1200 mg/day in three divided doses. If effects were not sufficient, the dosage was increased over a two week period up to 2400 mg/day.

In the uncontrolled before-after study,[4] all patients began at a starting dose of 300 mg/day which was titrated up to a maximum of 3600 mg/day.

Outcomes

The primary outcome of the RCT[5] identified in the systematic review[8] was the difference in the weekly median pain score between the end of treatment (week 4) and baseline. Pain was measured by patients twice daily using a 10 cm VAS (0 = no pain, 10 = maximum pain intensity). The secondary efficacy measure was median sleep interference score measured at the end of treatment on a 10 cm VAS (0 = excellent sleep, 10 = no sleep due to pain). Adverse events were also reported.

The primary outcome of the uncontrolled before-after study[4] change from baseline in pain and sleep interference measured separately on a 100 mm VAS (0 = no pain/no sleep interference, 100 = the worst possible pain/no sleep due to pain. Participants were followed for up to four months. Adverse events were also reported.

Summary of Critical Appraisal

A summary of the critical appraisal of the individual studies is provided in Appendix 3.

The systematic review[8] was well conducted. The objectives, inclusion criteria, and exclusion criteria were clearly stated. A systematic search was conducted on multiple databases, clinical trial registries were searched, and reference lists of relevant articles were manually screened. Article selection and data extraction were conducted by two independent reviewers. Lists of included and excluded studies were provided and quality assessments of the included studies were used to inform conclusions. One study[5] on HIV-associated neuropathy was identified and was deemed by the review authors to be at low risk of bias due to appropriate randomization and allocation concealment, double blinding, and reporting of withdrawals and drop-outs. However the review authors noted that methods for imputation of missing data were not mentioned, the sample size was small (n = 26), and it was unclear whether the 4-week follow-up was a sufficient duration to draw conclusions about effectiveness for a chronic condition.

The uncontrolled before-after study[4] was at risk of bias due to the lack of randomization and lack of blinding. While the study objectives, diagnostic criteria, selection criteria and outcome

measures were clearly described, the study had a limited description of patient characteristics beyond age range, sex, HIV clinical status, and cause of neuropathy (HIV itself, neurotoxic antiretroviral use, or both). Furthermore, only participants with a baseline pain score of 40 mm on a 100 mm VAS were eligible for inclusion. As such, it is unclear whether the study population was representative of the broader population who may be affected. The study had a small sample size (n = 19), and lacked a control group which limits the ability to ascribe and observed response solely to the study drug.

Summary of Findings

Details of the findings of the individual studies are provided in Appendix 4.

One systematic review[8] included one RCT[5] (parallel group, N = 26) comparing the effect of gabapentin with placebo in HIV-associated sensory neuropathy. One patient from the gabapentin group withdrew due to adverse effects, and one patient from the placebo group withdrew for personal reasons. Pain and sleep, on average, were substantially improved with both gabapentin (daily dose 2400 mg) and placebo but the time courses differed. For pain, differences between gabapentin and placebo appeared to diminish after four weeks of follow-up. For sleep scores, differences between gabapentin and placebo appeared to persist at the end of follow-up. For both pain and sleep scores, changes from baseline were statistically significant for gabapentin, but not placebo. The statistical significance of between-group differences was not reported. Adverse events reported included somnolence (12/15 for gabapentin and 2/11 for placebo; $P = 0.006$), dizziness (9/15 for gabapentin and 5/11 for placebo; $P = 0.305$), gait disturbance (7/15 for gabapentin and 3/11 for placebo; $P = 0.357$), and nausea (5/15 for gabapentin and 2/11 for placebo; $P = 0.474$). One patient in each group reported experiencing headache.

Participants in the uncontrolled before-after study[4] received a mean dose of 1480 ± 646 mg/day. At a follow-up of four months, statistically significant improvements from baseline in mean pain score (55.7 ± 19.1 mm versus 14.8 ± 18.6 mm, $P = 0.0001$) and mean sleep interference score (60.4 ± 31.9 mm versus 15.5 ± 27.7 mm, $P = 0.0001$) were observed. The authors reported that mean electrophysiological values did not significantly change, but this data was not provided. One patient reported lower limb edema. No other adverse events were reported.

Limitations

The evidence for the use of gabapentin for the treatment of HIV-associated neuropathic pain is limited. A systematic review, which included one relevant RCT, and one additional non-randomized study were identified. Both studies were based on a small sample size (<30 participants) which may not be generalizable to the broader population experiencing HIV-associated neuropathy. Furthermore limitations in the analyses of the identified studies prevent drawing firm conclusions. The RCT showed differences between gabapentin and placebo in pain scores, however these differences appeared to be diminished at the final time-point (four weeks of treatment), and only changes from baseline for each group were analyzed. No between-group comparison was presented so it is unclear whether gabapentin performed better than placebo with regards to pain relief. Additional, the clinical relevance of a four week trial for a chronic condition is uncertain. The non-randomized study lacked a control group, so improvements in pain and sleep scores may not be attributable to gabapentin alone. Neither study compared gabapentin with other active comparators, so it remains unclear how it may

compare to other treatments currently in use for the management of HIV-associated neuropathy.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Evidence for the effectiveness of gabapentin for patients with HIV-associated neuropathy is limited to one RCT, included in a systematic review, and one non-randomized study. The studies suggest that gabapentin may improve pain and sleep disturbances caused by HIV-associated sensory neuropathy, however the small sample size of each study and limitations in the analyses conducted prevent strong conclusions. Gabapentin appeared to be well-tolerated, with somnolence being the most frequently reported side effect. No serious adverse events were reported.

Two previous Rapid Response reports[7,9] on the use of gabapentin to treat neuropathic pain more generally found that there was evidence of short-term pain relief with gabapentin for patients with painful diabetic neuropathy, postherpetic neuralgia, and fibromyalgia. Evidence for gabapentin for HIV-associated neuropathy remains limited. Larger, well-conducted trials are needed to draw definitive conclusions about the effectiveness of gabapentin for this condition.

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REFERENCES

1. Neuropathic pain – pharmacological management. The pharmacological management of neuropathic pain in adults in non-specialist settings [Internet]. London: National Institute for Health and Care Excellence (NICE); 2013 Nov. 138 p. [cited 2016 Jan 18]. (NICE Clinical Guidelines, no. 173). Available from: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0071628/

2. Phillips TJ, Cherry CL, Cox S, Marshall SJ, Rice AS. Pharmacological treatment of painful HIV-associated sensory neuropathy: a systematic review and meta-analysis of randomised controlled trials. PLoS ONE [Internet]. 2010 [cited 2016 Jan 8];5(12):e14433. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3010990

3. Summary: estimates of HIV incidence, prevalence and proportion undiagnosed in Canada [Internet]. Ottawa: Public Health Agency of Canada; 2015 Nov 27. 13 p. [cited 2016 Jan 18]. Available from: http://healthycanadians.gc.ca/publications/diseases-conditions-maladies-affections/hiv-aids-estimates-2014-vih-sida-estimations/index-eng.php Cat. HP40-147/2015E-PDF.

4. La Spina I, Porazzi D, Maggiolo F, Bottura P, Suter F. Gabapentin in painful HIV-related neuropathy: a report of 19 patients, preliminary observations. Eur J Neurol. 2001 Jan;8(1):71-5.

5. Hahn K, Arendt G, Braun JS, von Giesen HJ, Husstedt IW, Maschke M, et al. A placebo-controlled trial of gabapentin for painful HIV-associated sensory neuropathies. J Neurol. 2004 Oct;251(10):1260-6.

6. Moulin DE, Boulanger A, Clark AJ, Clarke H, Dao T, Finley GA, et al. Pharmacological management of chronic neuropathic pain: Revised consensus statement from the Canadian Pain Society. Pain Res Manag [Internet]. 2014 Nov [cited 2016 Jan 18];19(6):328-35. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4273712/

7. Gabapentin for adults with neuropathic pain: A review of the clinical evidence and guidelines [Internet]. Ottawa: CADTH; 2014 Sep 26. [cited 2016 Jan 7]. (Rapid response report: summary with critical appraisal). Available from: https://www.cadth.ca/sites/default/files/pdf/htis/dec-2014/RC0594%20Gabapentin%20for%20neuropathic%20pain%20Final.pdf

8. Moore RA, Wiffen PJ, Derry S, Toelle T, Rice AS. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev. 2014;4:CD007938.

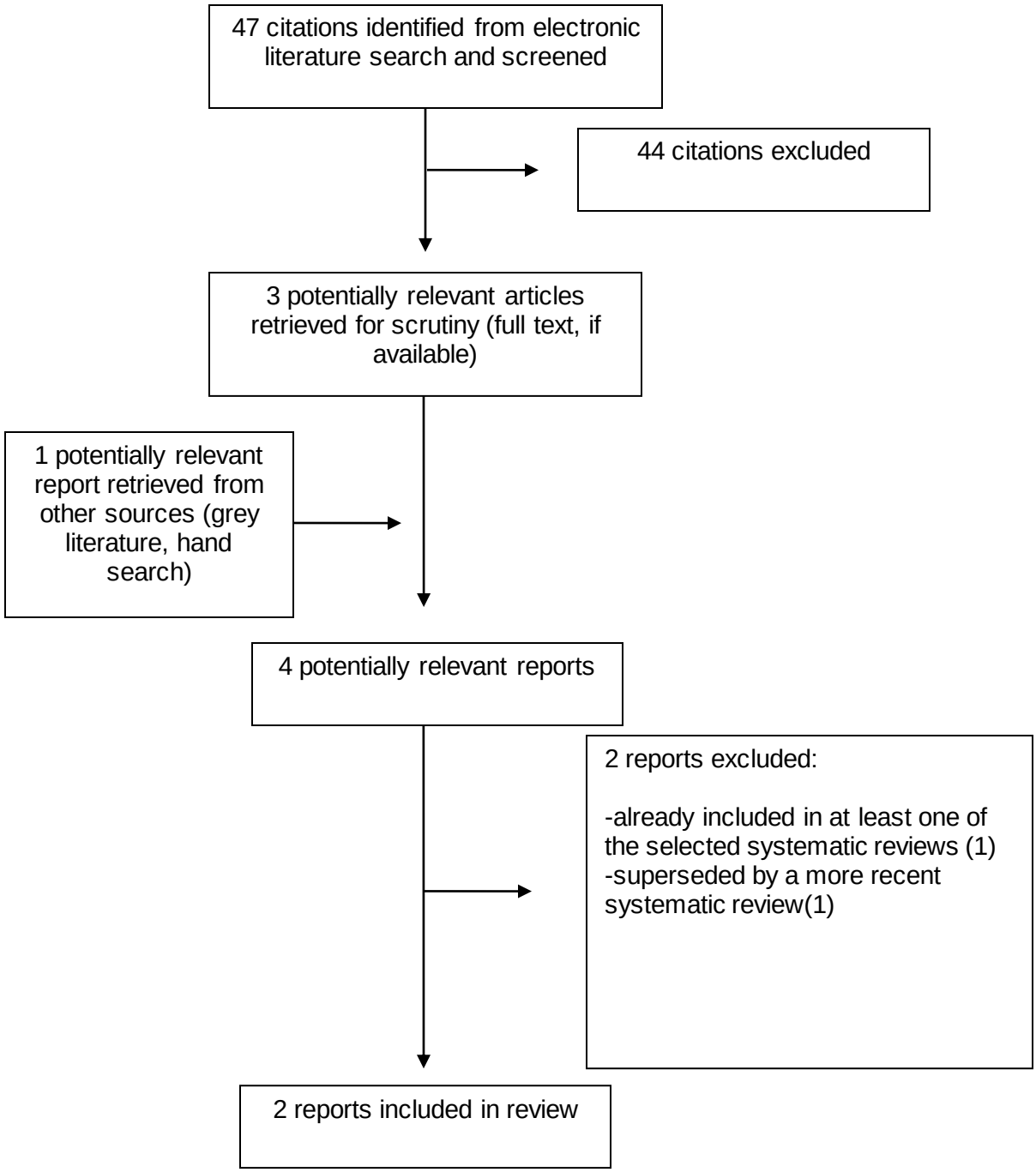
9. Gabapentin for adults with neuropathic pain: A review of the clinical efficacy and safety [Internet]. Ottawa: CADTH; 2015 Apr 14. [cited 2016 Jan 7]. (Rapid response report: summary with critical appraisal). Available from: https://www.cadth.ca/sites/default/files/pdf/htis/apr-2015/RC0637-Gabapentin-NeuropathicPain%20Final.pdf

10. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic

reviews. BMC Med Res Methodol [Internet]. 2007 [cited 2015 Dec 18];7:10. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1810543/pdf/1471-2288-7-10.pdf

11. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health [Internet]. 1998 Jun [cited 2015 Dec 18];52(6):377-84. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Types and numbers of primary studies included	Population	Intervention	Comparator(s)	Clinical Outcomes
Moore,[8] 2014 Germany, UK (Cochrane Collaboration)	Overall: 29 RCTs (n=3571) HIV-SN: 1 RCT (n=26)	Adult participants with any type of chronic neuropathic pain, including HIV-SN	Overall: Gabapentin at any dose by any route of administration HIV-SN: Gabapentin titrated to 2400 mg daily over four weeks (n=15)	Overall: Placebo, no intervention, or any other active comparator HIV-SN: Placebo (n=11)	Pain assessment outcomes on a 10 cm VAS Adverse events

Note: The included systematic review was broad in scope, including a number of neuropathies. The characteristics for the review overall and the studies relevant to this report (HIV-SN) are presented here
HIV-SN = human immunodeficiency virus-associated sensory neuropathy; RCT = randomized controlled trial; UK = United Kingdom
VAS = visual analogue scale

Table A2: Characteristics of Included Clinical Studies

First Author, Publication Year, Country	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
La Spina,[4] 2001, Italy	Uncontrolled before-after study	Patients with HIV and painful distal sensory neuropathy due to the disease or to neurotoxic HIV therapies (n=19) Age range: 30 to 46 years Male/Female: 17/2	Gabapentin 300 mg/day titrated to a maximum of 3600 mg/day (route of administration not specified)	None	Pain and Interference of pain with sleep measure on a 100 mm VAS Adverse events

VAS = visual analogue scale

APPENDIX 3: Critical Appraisal of Included Publications

Table A3: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[10]

Strengths	Limitations
Moore,[8] 2014	
• Objectives, inclusion and exclusion criteria were clearly stated • Multiple databases were searched. Registries and clinical study results websites were searched and reference lists of relevant articles were manually searched • The study selection process was described and presented in a flow chart • Lists of included and excluded studies were provided • Article selection and data extraction were done in duplicate • Quality assessments of the included studies were conducted and used to inform conclusions • An analysis based on the minimum number of unavailable studies required to reduce beneficial effects to a negligible amount indicated that the risk of publication bias was low.	• The analysis of publication bias was based on the full body of literature and may not apply to specific subgroups; one study on HIV-neuropathy was identified.

Table A4: Strengths and Limitations of Non-randomized studies using the Downs and Black checklist[11]

Strengths	Limitations
La Spina,[4] 2001	
• Study objective clearly reported • Outcome measures and diagnostic criteria clearly reported • Main study findings clearly described	• Lack of randomization • Lack of control group • Lack of blinding • Limited description of patient characteristics beyond sex, HIV clinical status, and cause of neuropathy (HIV, use of neurotoxic antiretrovirals, or both) • Small sample size (n=19) • Selection criteria of pain score superior to 40 mm on 100 mm VAS may not be representative of all HIV neuropathy patients

VAS= visual analogue scale

APPENDIX 4: Main Study Findings and Author's Conclusions

Table A5: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
Moore,[8] 2014	
Pain and sleep improved with gabapentin and placebo, though time courses differed. Adverse events: Somnolence Gabapentin: 12/15 Placebo: 2/11 Dizziness Gabapentin: 9/15 Placebo: 5/11 Disturbed Gait Gabapentin: 7/15 Placebo: 3/11 No serious adverse events or deaths reported Additional data from original RCT:[5] Scores measured on a 10cm VAS Placebo Median pain score (baseline): 4.7 Median pain score (4 weeks): 3.3 (P = 0.646) Gabapentin Median pain score (baseline): 5.1 Median pain score (4 weeks): 2.85 (P < 0.05) Placebo Median sleep score (baseline): 5.6 Median sleep score (4 weeks): 4.95 (P = 0.575) Gabapentin Median pain score (baseline): 4.5 Median pain score (4 weeks): 2.3 (P < 0.05)	• "The studies included in this review covered a large number of different painful conditions. For some, like HIV neuropathy for instance, it is unclear whether antiepileptic drugs such as gabapentin are effective in the condition." (p. 23) • "Improvement in pain and sleep interference with gabapentin and placebo, with sustained difference in sleep but not pain." (p. 66)

Table A5: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
La Spina,[4] 2001	
Mean GBP dosage: 1480 ± 646 mg/day Scores measured on a 100 mm VAS Mean pain score (baseline): 55.7 ± 19.1 mm Mean pain score (4 months): 14.8 ± 18.6 mm *P* = 0.0001 Mean sleep interference score (baseline): 60.4 ± 31.9 mm Mean sleep interference score (4 months): 15.5 ± 27.7 mm *P* = 0.0001 Mean electrophysiological values did not significantly change (data not shown) One patient reported lower limb edema; no other adverse events were reported.	• "Gabapentin provided significant pain relief in our patients with HIV-associated painful sensory neuropathy" (p. 71) • "Definitive evidence needs to be obtained from double-blind placebo-controlled trials." (p. 75)

GBP = gabapentin; RCT = randomized controlled trial; VAS = visual analogue scale