Methods Research Report

Supplemental Project To Assess the Transparency of Reporting Requirements for Studies Evaluating the Effectiveness of Treatment Options for Symptoms of Diabetic Peripheral Neuropathy

Methods Research Report

Supplemental Project To Assess the Transparency of Reporting Requirements for Studies Evaluating the Effectiveness of Treatment Options for Symptoms of Diabetic Peripheral Neuropathy

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857
www.ahrq.gov

Contract No. 290-2015-00006-I

Prepared by:
Johns Hopkins University Evidence-based Practice Center
Baltimore, MD

Investigators:
Lisa M. Wilson, Sc.M.
Ritu Sharma, B.Sc.
Sydney M. Dy, M.D., M.Sc.
Karen A. Robinson, Ph.D.

AHRQ Publication 17-EHC006-EF
July 2017

This report is based on research conducted by the Johns Hopkins University Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No.290-2015-00006-I). The findings and conclusions in this document are those of the author(s), who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

Persons using assistive technology may not be able to fully access information in this report. For assistance, contact EffectiveHealthCare@ahrq.hhs.gov

Suggested citation: Wilson LM, Sharma R, Dy SM, Robinson KA. Supplemental Project to Assess the Transparency of Reporting Requirements for Studies Evaluating the Effectiveness of Treatment Options for Symptoms of Diabetic Peripheral Neuropathy. Methods Research Report. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No.290-2015-00006-I). AHRQ Publication No. 17-EHC006-EF. Rockville, MD: Agency for Healthcare Research and Quality. July 2017. www.effectivehealthcare.ahrq.gov/reports/final.cfm. doi: https://doi.org/10.23970/AHRQEPCMETH1.

Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To improve the scientific rigor of these evidence reports, AHRQ supports empiric research by the EPCs to help understand or improve complex methodologic issues in systematic reviews. These methods research projects are intended to contribute to the research base in and be used to improve the science of systematic reviews. They are not intended to be guidance to the EPC program, although may be considered by EPCs along with other scientific research when determining EPC program methods guidance.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality. The reports undergo peer review prior to their release as a final report.

We welcome comments on this Methods Research Project. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by e-mail to epc@ahrq.hhs.gov.

Gopal Khanna, M.B.A.
Director
Agency for Healthcare Research and Quality

Arlene S. Bierman, M.D., M.S.
Director
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director, Evidence-based Practice Center Program
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Elise Berliner
TOO, Evidence-based Practice Center Program
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Acknowledgments

We would like to thank the other authors of the "Effectiveness and Treatment Options for the Prevention of Complications and Treatments of Symptoms of Diabetic Peripheral Neuropathy," including Wendy L. Bennett, MD, MPH, Allen Zhang, BS, Suzanne Amato Nesbit, PharmD, BCPS, CPE, Hsin-Chieh Yeh, PhD, Yohalakshmi Chelladurai, MD, MPH, Dorianne Feldman, MD, MSPT and Julie M. Waldfogel, PharmD, CPE for sharing the results of their systematic review.

Supplemental Project To Assess the Transparency of Reporting Requirements for Studies Evaluating the Effectiveness of Treatment Options for Symptoms of Diabetic Peripheral Neuropathy

Structured Abstract

Objectives. To assess the impact of including studies identified from ClinicalTrials.gov on the conclusions and strength of evidence (SOE) grading from an ongoing systematic review of treatments for diabetic peripheral neuropathy symptoms.

Data sources. We searched ClinicalTrials.gov through March 2016 to identify trial records. Peer-reviewed publications were identified from an ongoing systematic review of treatments for diabetic peripheral neuropathy symptoms.

Review methods. Two independent reviewers screened ClinicalTrials.gov records for randomized controlled trials evaluating treatments for diabetic peripheral neuropathy symptoms. We matched ClinicalTrials.gov records to publications. Two reviewers extracted data from ClinicalTrials.gov records. We compared conclusions and SOE grade with and without ClinicalTrials.gov records for pain and quality of life, conducting sensitivity analyses where possible.

Results. We identified 53 studies from ClinicalTrials.gov (46 completed, 3 recruiting, 2 withdrawn, 2 with unknown status). 37% of the completed trials posted results. We compared 25 ClinicalTrials.gov records with 25 matched publications. These differed in the number enrolled (8 studies, 32%), the primary outcome (14 studies, 56%), and adverse event reporting (2 of 10 studies with posted results, 20%). Pooled results of published trials showed greater effectiveness of pregabalin than placebo at reducing pain, but pooled results of unpublished trials were not statistically significant. Otherwise, ClinicalTrials.gov was mostly useful in confirming suspected reporting biases and did not meaningfully change either the overall conclusions or the SOE grading.

Conclusions. Researchers conducting systematic reviews should account for reporting bias in their analyses. But, until outcomes data are more consistently reported, the usefulness of searching ClinicalTrials.gov is limited.

Contents

Background and Objectives **1**
Objectives 1
Methods **3**
Datasources and Searching Methods 3
Study Selection and Matching with Peer-Reviewed Publications 3
Data Extraction 3
Assessment of Risk of Bias 4
Data Synthesis 4
Question 1. Description of the Identified Studies 4
Question 2. Comparison of Data Elements and Results from ClinicalTrials.gov and Matched Publications 4
Question 3. Description of Incomplete or Discontinued Trials 5
Question 4. Incorporating the ClinicalTrials.gov Findings into the Review 5
Results **7**
Question 1. Description of the Identified Studies 7
Question 2. Comparison of Data Elements and Results from ClinicalTrials.gov and Matched Publications 8
Question 3. Description of Incomplete or Discontinued Trials 10
Question 4. Incorporating the ClinicalTrials.gov Findings Into the Review 10
Placebo-Controlled Comparisons 14
Drug-Drug Comparisons 50
Discussion **54**
Key Findings 54
Question 1. Description of the Identified Studies 54
Question 2. Comparison of Data Elements and Results from ClinicalTrials.gov and Matched Publications 54
Question 3. Description of Incomplete or Discontinued Trials 54
Question 4. Incorporating the ClinicalTrials.gov Findings into the Review 54
Limitations 55
Next Steps 56
References **57**

Tables

Table 1. Data extraction elements 3
Table 2. Status of the 53 studies found in ClinicalTrials.gov 7
Table 3. Comparison of the sample size, primary outcome, and withdrawals due to adverse events reported in the earliest version of the ClinicalTrials.gov record with the corresponding publication 9
Table 4. Effect of searching ClinicalTrials.gov on the overall conclusion and strength of evidence grade for key comparisons and outcomes 12
Table 5. Studies comparing gabapentin with placebo identified through ClinicalTrials.gov, published literature, or both 15
Table 6. Comparison of the pain and quality of life results reported in the publication and the ClinicalTrials.gov record and/or additional results reported only in ClinicalTrials.gov 15

Table 7. Studies comparing pregabalin with placebo identified through ClinicalTrials.gov, published literature, or both 18
Table 8. Comparison of the pain and quality of life results reported in the publication and the ClinicalTrials.gov record and/or additional results reported only in ClinicalTrials.gov 19
Table 9. Univariate meta-regression results of year of publication/completion date on the standardized mean difference in pain scores comparing pregabalin with placebo 23
Table 10. Strength of evidence domains for studies comparing pregabalin with placebo in terms of pain and quality of life among adults with diabetic peripheral neuropathy 24
Table 11. Studies comparing topiramate with placebo identified through ClinicalTrials.gov, published literature, or both 25
Table 12. Studies comparing lacosamide with placebo identified through ClinicalTrials.gov, published literature, or both 27
Table 13. Strength of evidence domains for studies comparing lacosamide with placebo in terms of quality of life among adults with diabetic peripheral neuropathy 27
Table 14. Studies comparing duloxetine with placebo identified through ClinicalTrials.gov, published literature, or both 29
Table 15. Comparison of the pain and quality of life results reported in the publication and the ClinicalTrials.gov record and/or additional results reported only in ClinicalTrials.gov 29
Table 16. Studies comparing milnacipran with placebo identified through ClinicalTrials.gov, published literature, or both 30
Table 17. Studies comparing oxycodone with placebo identified through ClinicalTrials.gov, published literature, or both 32
Table 18. Comparison of the pain and quality of life results reported in the publication and the ClinicalTrials.gov record and/or additional results reported only in ClinicalTrials.gov 32
Table 19. Strength of evidence domains for studies comparing oxycodone with placebo in terms of pain among adults with diabetic peripheral neuropathy 34
Table 20. Studies comparing atypical opioids with placebo identified through ClinicalTrials.gov, published literature, or both 36
Table 21. Comparison of the pain and quality of life results reported in the publication and the ClinicalTrials.gov record and/or additional results reported only in ClinicalTrials.gov 36
Table 22. Studies comparing capsaicin with placebo identified through ClinicalTrials.gov, published literature, or both 39
Table 23. Comparison of the pain and quality of life results reported in the publication and the ClinicalTrials.gov record and/or additional results reported only in ClinicalTrials.gov 39
Table 24. Strength of evidence domains for studies comparing 8% capsaicin patch with placebo in terms of pain and quality of life among adults with diabetic peripheral neuropathy 40
Table 25. Studies comparing clonidine with placebo identified through ClinicalTrials.gov, published literature, or both 42
Table 26. Strength of evidence domains for studies comparing clonidine with placebo in terms of pain among adults with diabetic peripheral neuropathy 42
Table 27. Studies comparing lidocaine with placebo identified through ClinicalTrials.gov, published literature, or both 43
Table 28. Studies comparing dextromethorphan with placebo identified through ClinicalTrials.gov, published literature, or both 44
Table 29. Studies comparing mexiletine with placebo identified through ClinicalTrials.gov, published literature, or both 45

Table 30. Studies comparing botulinum toxin with placebo identified through ClinicalTrials.gov, published literature, or both 46
Table 31. Studies comparing cannabinoids with placebo identified through ClinicalTrials.gov, published literature, or both 48
Table 32. Comparison of the pain and quality of life results reported in the publication and the ClinicalTrials.gov record and/or additional results reported only in ClinicalTrials.gov 48
Table 33. Strength of evidence domains for studies comparing nabiximol with placebo in terms of pain among adults with diabetic peripheral neuropathy 49
Table 34. Studies comparing an anticonvulsant with a serotonin-noradrenaline reuptake inhibitor identified through ClinicalTrials.gov, published literature, or both 51
Table 35. Comparison of the pain and quality of life results reported in the publication and the ClinicalTrials.gov record and/or additional results reported only in ClinicalTrials.gov 51
Table 36. Studies comparing an anticonvulsant with a tricyclic antidepressant identified through ClinicalTrials.gov, published literature, or both 52
Table 37. Studies comparing an anticonvulsant with a topical agent identified through ClinicalTrials.gov, published literature, or both 53
Table 38. Studies comparing two antidepressants identified through ClinicalTrials.gov, published literature, or both 53

Figures

Figure 1. Standardized mean difference in pain scores comparing pregabalin with placebo stratified by studies found in the published literature versus those found only in ClinicalTrials.gov 21
Figure 2. Meta-regression of year of publication/completion date on the standardized mean difference in pain scores comparing pregabalin with placebo 22
Figure 3. Standardized mean difference in pain scores comparing oxycodone with placebo stratified by studies found in the published literature versus those found only in ClinicalTrials.gov 33

Background and Objectives

The underlying principle of systematic reviews is a consideration of all relevant available evidence. As standards have developed on how to conduct and report systematic reviews, an Achilles heel has remained: are we really considering all available evidence? Missing relevant information in systematic reviews, because of reporting bias such as publication bias and outcome reporting bias, may lead to biased and flat out wrong conclusions. Mandating that information about trials be reported through registries, such as ClinicalTrials.gov, has been proposed as a way to assess and possibly ameliorate the effects of reporting bias.

ClinicalTrials.gov is administered by the National Library of Medicine. In 2007, the legal requirements were expanded to ensure registration of all trials and to enable public searching of the database. As of 2008, basic summaries of trial results must be submitted for certain applicable trials, including phase 2-4 drug, biologic, or device trials. ClinicalTrials.gov captures several data elements including number of enrolled and completed trial participants, participant characteristics, summary results for pre-specified primary and secondary outcome measures, and adverse events by organ system.

Objectives

The purpose of this study was to address questions about how to access and integrate information from ClinicalTrials.gov into systematic reviews, as well as the impact of such inclusion on the conclusions of the reviews. Using a systematic review on the effectiveness of treatment options for symptoms of diabetic peripheral neuropathy, we addressed the following questions:

1. Which studies were in the published literature alone, ClinicalTrials.gov alone, or in both?
2. For the completed studies which were in both:
    a. What were the differences, if any, in pre-specified outcome measures, statistical plan and size of the study reported in the peer reviewed literature vs. ClinicalTrials.gov?
    b. Were results reported in ClinicalTrials.gov for any of the studies? If they were, what were the differences, if any, in the results reported in the peer reviewed literature vs. ClinicalTrials.gov?
3. For studies in ClinicalTrials.gov that were not completed or discontinued:
    a. For the discontinued studies, were there reasons given for discontinuation? If so, what were they?
    b. For studies that are ongoing but not completed, what was the date of initiation of the studies? Are the studies proceeding according to the original schedule or is there information in ClinicalTrials.gov indicating a delay in completion? If there is a delay in completion, what is the reason given?
4. What is the impact on the conclusions of the EPC report with and without the information from ClinicalTrials.gov? What is the impact on the strength of evidence (including impact of knowledge of outcomes measured in studies but not reported in the peer reviewed literature)?

We conducted this study in our review “Effectiveness of Treatments Options for the Prevention of Complications and Treatment of Symptoms of Diabetic Peripheral Neuropathy on Diabetic Peripheral Neuropathy,” which began at the end of September 2015. The Diabetic

Peripheral Neuropathy review sought to address two key questions with sub-questions. For this project we focused on the following sub-question:

> *Key Question 2a: What is the safety and effectiveness of pharmacologic treatment options (antidepressants, antiepileptics, and topical and subcutaneous treatments) to improve the symptoms of diabetic peripheral neuropathy and health-related quality of life among adults age 18 or older with type 1 or type 2 diabetes mellitus?*

Methods

Datasources and Searching Methods

To identify studies in the published literature, we searched MEDLINE®, and the Cochrane Central Register of Controlled Trials (CENTRAL) from January 1, 2012 through May 25, 2016. We selected the January 2012 date restriction to overlap with the search dates of a relevant, high-quality systematic review.[1]

We used a broad search to identify records in ClinicalTrials.gov. We used the advanced search function and entered the following terms: diabetic peripheral neuropathy [DISEASE] AND "Interventional" [STUDY-TYPES] AND NOT ("not yet recruiting" OR "terminated") [OVERALL-STATUS]. We ran the search on March 9, 2016. We downloaded all study fields for the search results as a comma-separated values file.

Study Selection and Matching with Peer-Reviewed Publications

Two reviewers independently assessed each ClinicalTrials.gov record for eligibility. We used the same eligibility criteria as the Diabetic Peripheral Neuropathy systematic review. We reviewed the ClinicalTrials.gov records using Microsoft Excel 2013 (Microsoft Corporation, Redmond, WA).

We matched ClinicalTrials.gov records to their published papers using their embedded PubMed citations and the National Library of Medicine's National Clinical Trial Identifier (NCT) listed in published articles. Where we did not identify a match using the NCT identifier, we manually searched Medline using terms for the interventions and principal investigator as search criteria.[2] Based on methods developed by Hartung and colleagues, we considered a PubMed publication to match a ClinicalTrials.gov registered trial if the intervention was the same AND 1 or more groups in the trial had an identical number of study participants.[2] We used all publications that matched each trial.

Data Extraction

Two team members extracted data from ClinicalTrials.gov and matched publications. We extracted the following elements into pre-designed data extraction forms (Table 1) in Microsoft Excel 2013 (Microsoft Corporation, Redmond, WA). We developed two sets of evidence tables: the first set included only data from ClinicalTrials.gov, and the second set also had the data from the matched publications, if available.

Table 1. Data extraction elements

Trial design	Design (parallel or crossover)
	Number of groups
	Trial start date, trial end date
Trial discontinuation	Early discontinuation? Reason for discontinuation.
Ongoing trial	Any delays? Reasons for delays (if any)
Population	Total enrollment, sample size in each arm, drop-outs
	Participants included in analysis for each outcome
Intervention and comparator	Description of the intervention and comparator
Outcomes	Description of pre-specified primary outcomes, number of primary outcomes

	Description of secondary outcome
Analysis	Description of the pre-specified statistical analysis plan
Results of primary and secondary outcomes	Results, direction and magnitude, if any were reported
Adverse outcomes	
Funding	Funding source and role
History of Changes	Summary of changes

Assessment of Risk of Bias

We completed risk of bias assessment for any studies uniquely identified from ClinicalTrials.gov. We used the same tools as used for the published studies in our Diabetic Peripheral Neuropathy project (i.e., Cochrane Risk of Bias tool).

Data Synthesis

Question 1. Description of the Identified Studies

For the first question, we described all studies we identified in ClinicalTrials.gov. We reported *"Which studies were in the EPC report alone, ClinicalTrials.gov alone or in both?"* We described which studies are ongoing and which have been completed and trial completion dates (since it may take 1 year or longer for trial results to appear in peer reviewed literature).

Question 2. Comparison of Data Elements and Results from ClinicalTrials.gov and Matched Publications

Next, we addressed the second question, "*For the completed studies which were in both:*

What were the differences, if any, in pre-specified outcome measures, statistical plan and size of the study reported in the peer reviewed literature vs. ClinicalTrials.gov?

Were results reported in ClinicalTrials.gov for any of the studies? If they were, what were the differences, if any, in the results reported in the peer reviewed literature vs. ClinicalTrials.gov?"

Two reviewers compared the planned sample size, the primary outcome, and the analysis plan specified in the earliest version of the ClinicalTrials.gov record with what is reported in the corresponding publication. The earliest version of the ClinicalTrials.gov record was found under the History of Changes. Investigators independently assessed for discrepancies and then discussed these comparisons. Where discrepancies existed, we also reviewed the summary of changes from the ClinicalTrials.gov records to describe a rationale for the different results or plans.

We classified discrepancies between the elements extracted from ClinicalTrials.gov and the matched publications.

- **Identification of the primary outcome**. For assessing consistency of the pre-specified primary outcome (s), we used a framework developed by Zarin and colleagues.[3] Applying this tool, the primary outcome could differ in the following ways: description of outcome (i.e. different "primary outcome" reported), different domain used, different measurement or diagnostic test used, different reporting of the same measure (e.g. change in pain scale or percentage from baseline), different results of the same reported measure. For trials with multiple publications and outcomes, we assessed each outcome separately, but designated one as the "main" primary.

- **Adverse event and deaths**. ClinicalTrials.gov began to mandate reporting of adverse events in September 2009 as serious adverse events and non-serious adverse events. We compared the total adverse events reported in ClinicalTrials.gov with the total reported in the matched publications.
- **Comparison of prespecified statistical plan**
- **Sample sizes, total.**

To determine if studies were changing the primary outcomes to report more favorable results, we conducted a post-hoc analysis among the studies identified in ClinicalTrials.gov and the peer-reviewed literature. We created a binary variable for the studies that changed their pre-specified primary outcome in any way. We regressed this variable on the standardized mean difference in pain scores.

Question 3. Description of Incomplete or Discontinued Trials

We created separate tables for those studies that are incomplete or discontinued to address Question 3: *"For studies in ClinicalTrials.gov that were not completed or discontinued:*

For the discontinued studies, were there reasons given for discontinuation? If so, what were they?

For studies that are ongoing but not completed, what was the date of initiation of the studies? Are the studies proceeding according to the original schedule or is there information in ClinicalTrials.gov indicating a delay in completion? If there is a delay in completion, what is the reason given?"

These data were extracted as above to address this question.

Question 4. Incorporating the ClinicalTrials.gov Findings into the Review

The Diabetic Peripheral Neuropathy systematic review team graded the strength of evidence only for the outcomes identified as important and critical. They specified *a priori* that pain and quality of life were the most important and critical outcomes for assessing treatment options for symptoms of diabetic peripheral neuropathy. Therefore, we focus our assessment of the effects of searching ClinicalTrials.gov on these two outcomes.

We organized the results by comparison. For each outcome and comparator, we synthesized the body of evidence obtained with and without ClinicalTrials.gov. We highlighted discrepant outcomes and results between the published and unpublished results, based on our review, described above.

We conducted the following for each outcome by drug comparison:

- Describe the source of each study (published literature only, ClinicalTrials.gov only, or both)
    - For studies found in the published literature only, we noted those that were published prior to 2008, when Congress expanded the requirements of ClinicalTrials.gov.
    - For studies found in both the published literature and ClinicalTrials.gov, we compared the results for pain and quality of life that were reported in each source. We noted any additional or different outcomes and/or different or additional results.
    - For studies found in ClinicalTrials.gov only, we summarized the results for pain and quality of life.

- We qualitatively described the discordance (within an outcome and drug comparison) between results from ClinicalTrials.gov and published literature, in terms of direction of conclusions.
- Where ClinicalTrials.gov provided results, and we were able to conduct meta-analyses, we conducted sensitivity analyses, with and without the additional data from ClinicalTrials.gov.
- We considered if the final conclusions were influenced by any indication of reporting bias based on what was reported in ClinicalTrials.gov versus in the peer-reviewed literature.
- We graded the level evidence with and without the ClinicalTrials.gov results.

Throughout the process we logged challenges and issues, as well as tracked the time and effort to complete this work.

Results

Question 1. Description of the Identified Studies

In the systematic review, we included one high-quality, relevant systematic review[1] (65 studies) and 27 additional studies that evaluated the effectiveness of treatment options for symptoms of diabetic peripheral neuropathy.

Our search of ClinicalTrials.gov yielded 266 records. Of these, 53 met the inclusion criteria for our review. We matched 28 ClinicalTrials.gov records to 28 publications (Table 2). Three ClinicalTrials.gov records (NCT00553475, NCT00143156, NCT00156078) were matched to a pooled analysis of 11 trials.[4] One of these records also had a separate publication.[5] The pooled analysis (Parsons 2016) was excluded from the systematic review because not all of the included studies were eligible. We identified the pooled analysis by searching for the NCT number in PubMed. Two ClinicalTrials.gov records (NCT01041859 and NCT00455520) were matched to a pooled analysis[6] plus to separate publications.[7, 8] We matched 17 (61%) records using the NCT number, 7 (25%) through the publication link in ClinicalTrials.gov, and 4 (14%) by using search terms in PubMed. Of these 28 records, 16 (57%) were completed during or prior to 2008, 6 (21%) in 2009, 0 in 2010, 4 (14%) in 2011, 1 (4%) in 2012, and 1 (4%) in 2013. Less than half (10 of 28 records, 36%) reported results in ClinicalTrials.gov.

We found an additional 25 records in ClinicalTrials.gov for which we were unable to identify a publication. Of these, 18 are completed, two are withdrawn, three are recruiting, and two have an unknown status (Table 2). For the 18 completed studies without publications, five (28%) were completed during or prior to 2008, three (17%) were completed in 2010, four (22%) were completed in 2013, three (17%) were completed in 2014, and three (17%) were completed in 2015. Less than half (39%) of the completed trials reported results in ClinicalTrials.gov.

We provide the completion dates for the studies that were withdrawn, recruiting, or unknown status in Table 2. None of these records had posted results.

Table 2. Status of the 53 studies found in ClinicalTrials.gov

Status	ClinicalTrials.gov Records	Range in Completion Dates	n / N (%) with Results in ClinicalTrials.gov
Completed with publication	NCT00643760,[9] NCT00712439,[10] NCT00159679,[11] NCT01345045,[12] NCT00573261,[13] NCT01057693,[14] NCT00553475,[4, 5] NCT00143156,[4] NCT00156078,[4] NCT00861445,[15] NCT00235469,[16] NCT00135109,[17] NCT00238524,[18] NCT01179672,[19] NCT00408993,[20] NCT00552175,[21] NCT00507936,[22] NCT01041859,[6, 7] NCT00455520,[6, 8] NCT00210847,[23] NCT00993070,[24] NCT00695565,[25] NCT00113620,[26] NCT00004647,[27] NCT00336349,[28] NCT01035281,[29] NCT01089556,[30] NCT00370656[31]	Feb 1999 to Aug 2013	10 / 28 (36%)
Completed, but no publication	NCT00231673, NCT00238550, NCT00350103, NCT00710424, NCT00785577, NCT00838799, NCT00904202, NCT00944697, NCT01125215, NCT01332149, NCT01455415, NCT01474772, NCT01478607, NCT01504412, NCT01533428, NCT01928381, NCT01939366, NCT02068027	Jan 2000 to May 2015	7 / 18 (39%)
Withdrawn	NCT00837941, NCT01116531	Sep 2009 to Dec 2012	0 / 2 (0%)

Recruiting	NCT02363803, NCT02372578,[a] NCT02460107	Oct 2015 to Mar 2018	0 / 3 (0%)
Unknown	NCT01288937, NCT01770964	Jul 2013 to Oct 2014	0 / 2 (0%)

[a] The status of this study was changed to terminated in June 2016.

Question 2. Comparison of Data Elements and Results from ClinicalTrials.gov and Matched Publications

We matched 28 ClinicalTrials.gov to 28 publications (Table 2). We did not include the two pooled analyses[4, 6] in the analysis for Question 2. We also were not able to include one study (NCT00004647)[27] in this analysis because we were unable to retrieve the publication. Therefore, we compared 25 ClinicalTrials.gov records with 25 publications.

Table 3 shows the comparison of the planned and actual number of participants enrolled. Two studies enrolled a greater number (over 10% more) of participants than originally planned.[14, 21] One of these studies reported in the publication that they needed to enroll more participants because fewer than expected participants from the single-blind treatment phase qualified for randomization.[14] The other study did not provide an explanation.[21] Six studies reported enrolling fewer (at least 10% fewer) participants than anticipated.[8, 19, 24, 26, 28, 29] One study reported needing to stop the recruitment early because the hospital unexpectedly closed for a prolonged period due to severe flooding.[24] Another study reported terminating the study early due to insufficient funding.[29] The remaining studies did not report an explanation for the lower enrollment.

Table 3 also describes how the primary outcome differed, if at all, between the earliest version of the ClinicalTrials.gov record and the publication. Fourteen (56%) of the 25 studies reported similar primary outcomes in the ClinicalTrials.gov record and the publication. Seven studies reported different specific measurements of the primary outcome.[11, 15-18, 28, 29] In all of these seven studies, the ClinicalTrials.gov record did not report a specific measurement of pain (e.g., 11-point numerical rating scale), whereas the publication did report which measurement was used. Four studies had different reporting of the same measure.[5, 12, 14, 20] In all four of these studies, the ClinicalTrials.gov record did not report which specific metric (e.g., final values, change from baseline) would be used. None of the studies changed a primary outcome to a secondary outcome. We compared the studies that changed their primary outcome to the studies that did not change their primary outcome, and we did not find any significant differences in the standardized mean difference in pain scores (p=0.287). The tables in Question 4 provide a detailed description of how the results for pain and quality of life differed between the ClinicalTrials.gov record and the publication.

Ten of these 25 studies reported results in ClinicalTrials.gov; for these studies, we also compared the reported number of participants withdrawn due to adverse events (Table 3). Eight of the ten studies reported the same number of participants that withdrew due to adverse events in the publication and in the ClinicalTrials.gov record. One study[21] reported fewer participants withdrawn due to adverse events in ClinicalTrials.gov and another study[7] reported more participants withdrawn due to adverse events in the ClinicalTrials.gov record.

Only one study pre-specified an analysis plan in ClinicalTrials.gov (NCT00336349).[28] The pre-specified analysis plan was also reported in the publication.

Table 3. Comparison of the sample size, primary outcome, and withdrawals due to adverse events reported in the earliest version of the ClinicalTrials.gov record with the corresponding publication

Publication Author, Year NCT Number	Planned Enrollment / Enrollment Reported in Publication	Comparison of Primary Outcomes[a]	Comparison of Adverse Event Reporting
Rauck, 2012[9] NCT00643760	392 / 420	No difference	Similar number withdrawn for adverse events
Sandercock, 2012[10] NCT00712439	NR / 147	No difference	Not reported in CT.gov
Arrezzo, 2008[11] NCT00159679	160 / 167	Different specific measurement used	Not reported in CT.gov
Ziegler, 2015[12] NCT01345045	180 / 194	Different reporting of the same measure	Not reported in CT.gov
Jiang, 2011[13] NCT00573261	40 / 40	No difference	Similar number withdrawn for adverse events
Raskin, 2014[14] NCT01057693	564 / 665	Different reporting of the same measure	Similar number withdrawn for adverse events
Satoh, 2010[5] NCT00553475	308 / 317	Different reporting of the same measure	Similar number withdrawn for adverse events
Rauck, 2007[15] NCT00861445	NR / 119	Different specific measurement used	Not reported in CT.gov
Wymer, 2009[16] NCT00235469	360 / 495	Different specific measurement used	Not reported in CT.gov
Shaibani, 2009[17] NCT00135109	NR / 654	Different specific measurement used	Not reported in CT.gov
Ziegler, 2010[18] NCT00238524	NR / 357	Different specific measurement used	Not reported in CT.gov
Gao, 2015[19] NCT01179672	480 / 405	No difference	Similar number withdrawn for adverse events
Gao, 2010[20] NCT00408993	208 / 215	Different reporting of the same measure	Similar number withdrawn for adverse events
Yasuda, 2011[21] NCT00552175	300 / 339	No difference	CT.gov reported fewer patients withdrawn due to adverse events for the duloxetine 60mg group than the publication (10 vs. 12).
Rowbotham, 2012[22] NCT00507936	275 / 280	No difference	Not reported in CT.gov
Vinik, 2014[7] NCT01041859	455 / 459	No difference	There were some discrepancies in the number withdrawn due to adverse events for the open label period, but not for the double-blind period. CT.gov reported more adverse events.
Schwartz, 2011[8] NCT00455520	760 / 591	No difference	Similar number withdrawn for adverse events
Freeman, 2007[23] NCT00210847	300 / 313	No difference	Not reported in CT.gov
Kulkantrakorn, 2013[24] NCT00993070	40 / 33	No difference	Not reported in CT.gov
Campbell, 2012[25] NCT00695565	170 / 182	No difference	Not reported in CT.gov
Shaibani, 2012[26] NCT00113620	450 / 379	No difference	Not reported in CT.gov
Yuan, 2009[28] NCT00336349	30 / 20	Different specific measurement used	Not reported in CT.gov
Toth, 2012[29] NCT01035281	60 / 37	Different specific measurement used	Not reported in CT.gov

Tesfaye, 2013[30] NCT01089556	800 / 811	No difference	Similar number withdrawn for adverse events
Boyle, 2012[31] NCT00370656	90 / 83	No difference	Not reported in CT.gov

CT.gov = ClinicalTrials.gov

[a] Using the framework developed by Zarin et al.[3]

Question 3. Description of Incomplete or Discontinued Trials

We found two studies that were withdrawn (NCT00837941, NCT01116531). Both of these studies were withdrawn prior to enrollment. Neither study provided reasons for withdrawal in ClinicalTrials.gov.

We found three studies with a "Recruiting" status (NCT02363803, NCT02372578, NCT02460107). One study (NCT02363803), which is currently recruiting 35 participants, had a start date of February 2015, a primary completion date of March 2017, and a study completion date of March 2018. This study was last verified in June 2016. Another study (NCT02460107), which is currently recruiting 81 patients, had a start date of May 2015, a primary completion date of March 2016, and a study completion date of September 2016. This study was last verified in October 2015. There is no indication of any delays from either study.

One study (NCT02372578) had a start date of May 2015 and a completion date of October 2015. During the writing of this report, the study status changed to "Terminated" due to futility analysis.

Question 4. Incorporating the ClinicalTrials.gov Findings Into the Review

Table 4 provides an overview of how the results from ClinicalTrials.gov influenced the overall conclusion and the strength of evidence grading for each comparison in terms of pain and quality of life. We included 53 ClinicalTrials.gov records that evaluated 21 different comparisons. A new study (i.e., a study that was not identified in the published literature) was found in ClinicalTrials.gov for 15 comparisons (71%). For six comparisons, we identified only ClinicalTrials.gov records with corresponding publications.

Based on the results of studies found in ClinicalTrials.gov, we changed the estimate for the effect of pregabalin compared with placebo in terms of reducing pain. The pooled results from ClinicalTrials.gov were not as favorable for pregabalin as the pooled results from the published literature. We did not downgrade the strength of evidence for this comparison for pain because the systematic review team had already considered the inconsistent results and suspected reporting bias in the evidence grade.

For the remaining comparisons, the effect of searching ClinicalTrials.gov on the overall conclusions and the strength of evidence grading was trivial at best. Searching ClinicalTrials.gov yielded the only studies evaluating two comparisons (8% capsaicin patch versus placebo and nabiximol versus placebo). However, the strength of evidence grade for both of these comparisons remained "Insufficient." For another two comparisons (lacosamide versus placebo and atypical opioids versus placebo), we found evidence of potential selective outcomes reporting for quality of life. For these two comparisons, we found ClinicalTrials.gov records that noted quality of life as an outcome but we did not find quality of life results in the corresponding publications. This did not change our strength of evidence grading, but rather provided further support for suspecting reporting bias.

For two different comparisons (oxycodone versus placebo and clonidine versus placebo) for pain, we downgraded the reporting bias domain to “Suspected” based on the ClinicalTrials.gov results. The overall strength of evidence remained the same.

For all other comparisons, searching ClinicalTrials.gov did not affect either the overall conclusion or the strength of evidence grading for both pain and quality of life. None of the ClinicalTrials.gov records for these comparisons posted any results for pain or quality of life.

Details of the ClinicalTrials.gov search by comparison is provided below.

Table 4. Effect of searching ClinicalTrials.gov on the overall conclusion and strength of evidence grade for key comparisons and outcomes

Comparison	Studies Identified in CT.gov Only / Studies with Pain Results / Studies with QOL Results	Effect on Overall Conclusion for Pain	Effect on Strength of Evidence Grading for Pain	Effect on Overall Conclusion for QOL	Effect on Strength of Evidence Grading for QOL
Gabapentin vs. placebo	1 / 0 / 0	No effect	No effect	No effect	No effect
Pregabalin vs. placebo	10 / 4 / 3	Estimated effect size is less favorable for pregabalin.	No effect	No effect	No effect
Topiramate vs. placebo	1 / 0 / 0	No effect	No effect	No effect	No effect
Lacosamide vs. placebo	1 / 0 / 0	No effect	No effect	No effect	No effect on evidence grade, but there is a suggestion of selective outcomes reporting
Duloxetine vs. placebo	0 / 0 / 0	No effect	No effect	No effect	No effect
Milnacipran vs. placebo	1 / 0 / 0	No effect	No effect	No effect	No effect
Oxycodone vs. placebo	1 / 1 / 0	No effect	No effect on overall strength of evidence grade, but the Reporting Bias domain was downgraded to “Suspected.”	No effect	No effect
Atypical opioids vs. placebo	0 / 0 / 0	No effect	No effect	No effect	No effect on evidence grade, but there is a suggestion of selective outcomes reporting
0.75% capsaicin topical cream vs. placebo	1 / 0 / 0	No effect	No effect	No effect	No effect
8% capsaicin patch vs. placebo	2 / 1 / 1	No effect	Although we now have a body of evidence to grade, the overall evidence grade remained “Insufficient.”	No effect	Although we now have a body of evidence to grade, the overall evidence grade remained “Insufficient.”
Clonidine vs. placebo	1 / 0 / 0	No effect	No effect on overall strength of evidence grade, but the Reporting Bias domain was downgraded to “Suspected.”	No effect	No effect
Lidocaine vs. placebo	2 / 0 / 0	No effect	No effect	No effect	No effect
Dextromethorphan vs. placebo	0 / 0 / 0	No effect	No effect	No effect	No effect
Mexiletine vs. placebo	0 / 0 / 0	No effect	No effect	No effect	No effect
Botulinum toxin vs. placebo	1 / 0 / 0	No effect	No effect	No effect	No effect

Comparison	Studies Identified in CT.gov Only / Studies with Pain Results / Studies with QOL Results	Effect on Overall Conclusion for Pain	Effect on Strength of Evidence Grading for Pain	Effect on Overall Conclusion for QOL	Effect on Strength of Evidence Grading for QOL
Cannabinoids (nabilone, cannabis-based medicine extract) vs. placebo	1 / 0 / 0	No effect	No effect	No effect	No effect
Cannabinoids (nabiximol) vs. placebo	1 / 1 / 1	No effect	Although we now have a body of evidence to grade, the overall evidence grade remained “Insufficient.”	No effect	Although we now have a body of evidence to grade, the overall evidence grade remained “Insufficient.”
Anticonvulsants vs. serotonin-noradrenaline reuptake inhibitors	2 / 0 / 0	No effect	No effect	No effect	No effect
Anticonvulsants vs. tricyclic antidepressants	0 / / 0 / 0	No effect	No effect	No effect	No effect
Anticonvulsants vs. topical agents	1 / 0 / 0	No effect	No effect	No effect	No effect
Antidepressants vs. antidepressants	0 / 0 / 0	No effect	No effect	No effect	No effect

CT.gov = ClinicalTrials.gov; QOL = quality of life; vs = versus

Placebo-Controlled Comparisons

Anticonvulsants

Gabapentin Versus Placebo

Detailed Results

We identified six studies (five with available data) that compared gabapentin with placebo among patients with diabetic peripheral neuropathy (Table 5).

Three studies, all published before 2008, were identified in the published literature only.[32-34]

Two studies were identified in both the published literature and in ClinicalTrials.gov.[9, 10] Only one study reported results in ClinicalTrials.gov for pain and quality of life (Table 6).[9] For pain, we compared the results for the Average Pain Intensity Numerical Rating Scale between the publication and the ClinicalTrials.gov record. The ClinicalTrials.gov record did not report baseline values. Although the analyses appeared to be the same, the publication and the record reported different values for the change from baseline. However, the mean between-group differences were the same. For quality of life, we compared the results for the 36-Item Short Form Health Survey (SF-36) Physical Component Score (PCS) between the publication and the ClinicalTrials.gov record. The ClinicalTrials.gov record reported change from baseline values, but the publication reported between-group differences in the change score. Using the data reported in ClinicalTrials.gov, we derived the between-group differences and obtained similar, but different, results.

One study (NCT00904202), which was completed in June 2003, was identified only in ClinicalTrials.gov (Table 5). We were unable to find any publication for this trial. This study also did not post any results in ClinicalTrials.gov.

Did Searching ClinicalTrials.gov Change the Overall Conclusion for this Comparison for Either Pain or Quality of Life

The overall conclusions for pain and for quality of life would not have changed based on the results found in ClinicalTrials.gov. While searching ClinicalTrials.gov yielded an additional study, the study did not provide any results. Additionally, for the two publications that were matched to a ClinicalTrials.gov record, neither entry provided additional results that would have changed the overall conclusion.

Did Searching ClinicalTrials.gov Change the Strength of Evidence for this Comparison for Either Pain or Quality of Life

The evidence grading domains and the strength of the evidence comparing gabapentin with placebo for pain and for quality of life would not change based on the results found in ClinicalTrials.gov.

Table 5. Studies comparing gabapentin with placebo identified through ClinicalTrials.gov, published literature, or both

Source	Publication Author, Year	NCT Number	Matched by	Study Completion Date In CT.gov	Reported Results in CT.gov?	Sample Size	Followup
Published literature only	Gorson, 1999[32a]	Not found	NA	NA	NA	40	6 weeks
	Backonja, 1998[33a]	Not found	NA	NA	NA	165	8 weeks
	Simpson, 2001[34a]	Not found	NA	NA	NA	60	8 weeks
Both published literature and CT.gov	Rauck, 2013[9]	NCT00643760	NCT number abstracted from publication	Feb 2009	Yes	354	13 weeks
	Sandercock, 2012[10]	NCT00712439	Publication found in CT.gov	Dec 2006	No	147	4 weeks
CT.gov only	None identified	NCT00904202	NA	Jun 2003	No	62	5 weeks

[a] Study was identified in a systematic review by Griebeler, 2014.[1]
CT.gov = ClinicalTrials.gov; NA = not applicable

Table 6. Comparison of the pain and quality of life results reported in the publication and the ClinicalTrials.gov record[a] and/or additional results reported only in ClinicalTrials.gov

Publication Author, Year	NCT Number	Pain Scale	Did Pain Results Differ?	Describe How Pain Results Differed	QOL Scale	Did QOL Results Differ?	Describe How QOL Results Differed
Rauck, 2013[9]	NCT00643760	PI-NRS	Yes	Although the analysis was the same, the change from baseline values for all intervention groups differed between the publication and CT.gov registry. However, the mean between-group differences with placebo were identical. Baseline values were not reported in CT.gov. The overall conclusions did not change.	SF-36 PCS	Yes	CT.gov record reported the change from baseline in each arm, but the publication reported the between-group difference in the change. Deriving the between-group difference using the data reported in CT.gov yielded similar, but slightly different, results.

[a] For studies that reported results in ClinicalTrials.gov.
CT.gov = ClinicalTrials.gov; PI-NRS = Pain Intensity Numerical Rating Scale; SF-36 PCS = 36-Item Short Form Health Survey Physical Component Score; QOL = quality of life

Pregabalin Versus Placebo

Detailed Results

We identified 24 studies (15 with available data) that compared pregabalin with placebo among patients with diabetic peripheral neuropathy (Table 7).

Six studies were identified in the published literature only.[35-40] Five of these studies were published either prior to or during 2008.[36-40] The other study was a small, single-center, crossover trial conducted in Canada.[35] It is unclear from the publication if this trial is registered in any clinical trials registry.

Eight studies (in seven publications) were identified in both the published literature and in ClinicalTrials.gov.[4, 5, 9, 11-14] Four studies reported pain results and three reported quality of life results in ClinicalTrials.gov (Table 8). Among the four studies reporting pain results in ClinicalTrials.gov, three had similar results to those reported in their respective publications.[5, 13, 14] The fourth study[9] had slightly different values for the change from baseline values, but the mean between-group differences were the same as those reported in the publication. The differences in values did not change the overall conclusions. Results for quality of life differed between the ClinicalTrials.gov records and the publications for all three studies (Table 8).[5, 9, 14] For two studies,[9, 14] the ClinicalTrials.gov record and the publication reported different measures for quality of life, making comparisons between the two difficult. The third publication[5] only reported significant results and omitted the nonsignificant results. Additionally, we matched three ClinicalTrials.gov records to a published pooled analysis by Parsons et al.[4] The pooled analysis was not included in the systematic review because it pooled both published and unpublished studies. We are unable to compare results because two of the three studies did not post results in ClinicalTrials.gov. The study with posted results was also published as Satoh 2010.[5]

Ten studies (NCT00838799, NCT01504412, NCT01770964, NCT01928381, NCT01939366, NCT02372578, NCT00785577, NCT01332149, NCT01455415, NCT01474772) were identified only in ClinicalTrials.gov (Table 7). Eight studies were completed within the last 3 years and two were completed in 2010. One study had an unknown status (NCT01770964) and another indicated that it was recruiting (NCT02372578). Four studies (N=1422), with 5 to 9 weeks of followup, posted results on pain (Table 8). None of these studies reported a statistically significant difference in pain between placebo and pregabalin. Three studies (N=796) reported on quality of life. None of the studies found a statistically significant difference between placebo and pregabalin in terms of quality of life.

Did Searching ClinicalTrials.gov Change the Overall Conclusion for this Comparison for Either Pain or Quality of Life

Figure 1 shows the standardized mean differences in pain scores for studies found in the published literature versus those found only in ClinicalTrials.gov. The studies found in the published literature favored pregabalin over placebo (SMD, -0.44; 95% CI, -0.65 to -0.22), but the studies found only in ClinicalTrials.gov were not statistically significant (SMD, -0.09; 95% CI, -0.19 to 0.01). The overall pooled results still favored pregabalin over placebo (SMD, -0.34; 95% CI, -0.50 to -0.18), but there was significant heterogeneity in the findings (I-squared, 80%). Because there seemed to be a temporal trend, we regressed the SMD pain scores on the year of publication or the year of study completion. More recent studies showed a smaller difference in pain relief with pregabalin than placebo (P<0.0001; **Table 9** and **Figure 2**). We also regressed

publication status on the SMD pain scores, but publication status was not significant (*P*=0.813; Table 9).

We did not conduct a meta-analysis for quality of life because so many studies reported insufficient data for pooling; many reported only statistical significance. Generally, it was difficult to compare results posted in both the published literature and in ClinicalTrials.gov because different metrics were reported, as in Rauck 2013 and Raskin 2014 (Table 8), or the publication reported only the components of the quality of life assessment tool that were statistically significant, as in Satoh 2010. Generally, the results from the studies identified only in ClinicalTrials.gov were less favorable towards pregabalin than those found in the published literature.

Did Searching ClinicalTrials.gov Change the Strength of Evidence for this Comparison for Either Pain or Quality of Life

The evidence grading domains and the strength of the evidence comparing pregabalin with placebo for pain and for quality of life would not change based on the results found in ClinicalTrials.gov (Table 10).

Table 7. Studies comparing pregabalin with placebo identified through ClinicalTrials.gov, published literature, or both

Source	Publication Author, Year	NCT Number	Matched by	Study Completion Date In CT.gov	Reported Results in CT.gov?	Sample Size	Followup
Published literature only	Karmakar, 2014[35]	Not found	NA	NA	NA	28	6 weeks
	Rosenstock, 2004[36a]	Not found	NA	NA	NA	146	8 weeks
	Lesser, 2004[37a]	Not found	NA	NA	NA	337	5 weeks
	Freynhagen, 2005[38a]	Not found	NA	NA	NA	338	12 weeks
	Richter, 2005[39a]	Not found	NA	NA	NA	246	6 weeks
	Tolle, 2008[40a]	Not found	NA	NA	NA	395	12 weeks
Both published literature and CT.gov	Arrezzo, 2008[11]	NCT00159679	NCT number abstracted from publication	Oct 2005	No	167	13 weeks
	Ziegler, 2015[12]	NCT01345045	NCT number abstracted from publication	Oct 2011	No	193	6 weeks
	Rauck, 2013[9]	NCT00643760	NCT number abstracted from publication	Feb 2009	Yes	421	16 weeks
	Jiang, 2011[13]	NCT00573261	Publication found in CT.gov	May 2008	Yes	40	4 weeks
	Raskin, 2014[14]	NCT01057693	Found by using search terms in PubMed	Jan 2012	Yes	665	13 weeks
	Satoh, 2010[5a]	NCT00553475	NCT number abstracted from publication	Mar 2009	Yes	314	13 weeks
	Parsons, 2016[4]	NCT00553475 NCT00143156 NCT00156078	Searched NCT number in PubMed	May 2007 to Mar 2009	No[b]	1208	Up to 13 weeks
CT.gov only	None identified	NCT00838799	NA	Apr 2010	No	458	14 weeks
	None identified	NCT01504412	NA	Jun 2013	No	450	7 weeks
	None identified	NCT01770964	NA	Jul 2013	No	90[c]	3 weeks
	None identified	NCT01928381	NA	May 2015	No	46	6 weeks
	None identified	NCT01939366	NA	Jan 2015	No	699	6 weeks
	None identified	NCT02372578	NA	Oct 2015	No	250§	6 weeks
	None identified	NCT00785577	NA	Jun 2010	Yes	273	5 weeks
	None identified	NCT01332149	NA	Jun 2014	Yes	626	9 weeks
	None identified	NCT01455415	NA	Nov 2013	Yes	306	6 weeks
	None identified	NCT01474772	NA	Jul 2013	Yes	217	6 weeks

[a] Study was identified in a systematic review by Griebeler, 2014.[1]
[b] Only two of the three studies reported results in ClinicalTrials.gov.
[c] Planned enrollment. The study status was unknown.
§Planned enrollment. The study status is still recruiting.
CT.gov = ClinicalTrials.gov; NA = not applicable

Table 8. Comparison of the pain and quality of life results reported in the publication and the ClinicalTrials.gov record[a] and/or additional results reported only in ClinicalTrials.gov

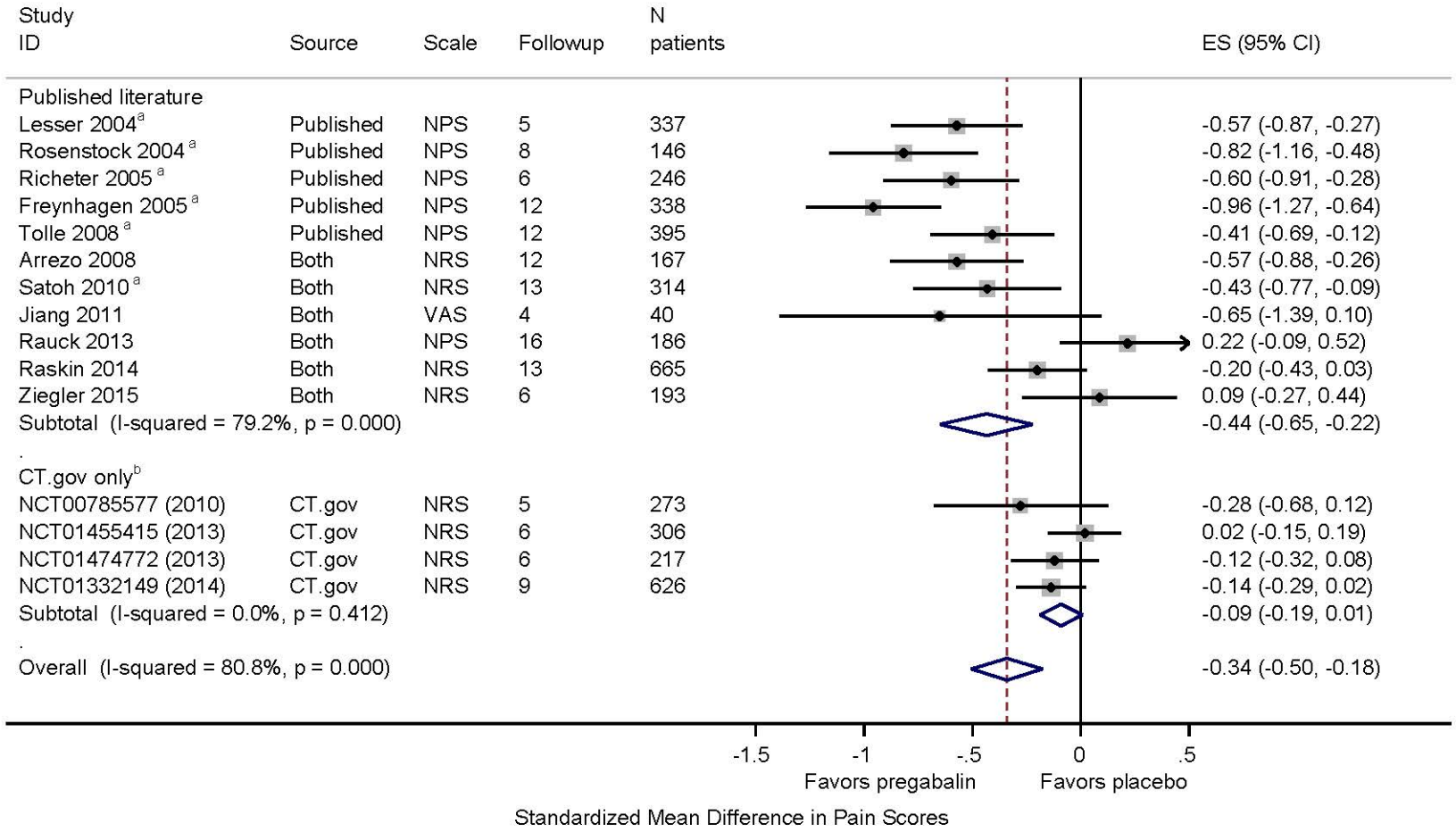
Publication Author, Year	NCT Number	Pain Scale	Did Pain Results Differ?	Describe How Pain Results Differed	QOL Scale	Did QOL Results Differ?	Describe How QOL Results Differed
Rauck, 2013[9]	NCT00643760	PI-NRS	Yes	Although the analysis was the same, the change from baseline values for all intervention groups differed between the publication and CT.gov registry. However, the mean between-group differences with placebo were identical. Baseline values were not reported in CT.gov. The overall conclusions would not change.	SF-36 PCS	Yes	The CT.gov record reported the change from baseline in each arm, but the publication reported the between-group difference in the change. Deriving the between-group difference using the data reported in CT.gov yields similar, but slightly different, results.
Jiang, 2011[13]	NCT00573261	VAS	No	The CT.gov record reported only the mean change in the visual analog pain rating.	NE	NE	NE
Raskin, 2014[14]	NCT01057693	NRS	No	The CT.gov record reported the baseline from the start of the run-in period (separately for each group) and the change scores. These values match what is reported in the publication.	QOL-DN	Yes	Both the CT.gov record and the publication reported the same baseline and final values for the run-in period. For the 13-week followup after randomization, CT.gov reported only final values, but the publication reported the change from the run-in baseline. We derived final values using the run-in baseline and change scores reported in the publication. The derived final values do not match the final values reported in CT.gov.
Satoh, 2010[5]	NCT00553475	NRS	No	Both the CT.gov record and the publication reported the same values for the change from baseline in each arm and the mean between-group difference in pain scores.	SF-36 PF	Yes	The CT.gov record reported the change from baseline and the mean between-group difference for each component of the SF-36. However, the publication only reported a p-value for the two components of the SF-36 which were statistically significant.
None identified	NCT00785577	NRS	NA	The weekly mean worst daily pain severity score as measured on an 11-pt numerical rating scale decreased by 2.27 pts (SE 0.25) in the placebo arm and by 2.87 pts (SE 0.35) in the pregabalin arm. The standardized mean difference was not significant (-0.28; 95% CI, -0.68 to 0.12).	EQ-5D	NA	The EQ-5D score improved by 0.09 pts (SE 0.02) in both the placebo and pregabalin arms. The standardized mean difference was not significant (0; 95% CI, -0.36 to 0.36).

None identified	NCT01332149	NRS	NA	The daily pain rating score as measured on an 11-pt numerical rating scale decreased by -1.86 pts (SE 0.12) in the placebo arm and by 2.14 (SE 0.12) in the pregabalin arm. The standardized mean difference was not significant (-0.14; 95% CI, -0.30 to 0.02).	NE	NE	NE
None identified	NCT01455415	NRS	NA	Only final values were reported on CT.gov, so we could not derive a change from baseline. The final daily pain score as measured by an 11-pt numerical rating scale was 5.0 (SE 0.13) in the placebo group and 5.0 (SE 0.13) in the pregabalin group. The standardized mean difference in final values was not significant (0.02, 95% CI, -0.15 to 0.19).	EQ-5D Dolan 2002 Index	NA	The EQ-5D scores after 6 weeks of treatment were 0.64 pts (SE 0.01) in the placebo arm and by 0.63 pts (SE 0.01) in the pregabalin arm. The standardized mean difference was not significant (-0.06; 95% CI, -0.23 to 0.11).
None identified	NCT01474772	NRS	NA	Only final values were reported on CT.gov, so we could not derive a change from baseline. The final daily pain score as measured by an 11-pt numerical rating scale was 5.0 (SE 0.14) in the placebo group and 4.7 (SE 0.14) in the pregabalin group. The standardized mean difference in final values was not significant (-0.01, 95% CI, -0.21 to 0.19).	EQ-5D Dolan 2001 Index	NA	The EQ-5D scores after 6 weeks of treatment were 0.64 pts (SE 0.01) in the placebo arm and by 0.65 pts (SE 0.01) in the pregabalin arm. The standardized mean difference was not significant (0.05; 95% CI, -0.15 to 0.25).

[a] For studies that reported results in ClinicalTrials.gov.

CI = confidence interval; CT.gov = ClinicalTrials.gov; EQ-5D = European Quality of Life Scale – 5 Dimensions; NA = not applicable; NA = not applicable; NE = not evaluated; NRS = Numerical Rating Scale; PI-NRS = Pain Intensity Numerical Rating Scale; pts = points; QOL-DN = Quality of Life Questionnaire – Diabetic Neuropathy; SE = standard error; SF-36 PCS = 36-Item Short Form Health Survey Physical Component Score; SF-36 PF = 36-Item Short Form Health Survey Physical Functioning; VAS = Visual Analog Scale

Figure 1. Standardized mean difference in pain scores comparing pregabalin with placebo stratified by studies found in the published literature versus those found only in ClinicalTrials.gov

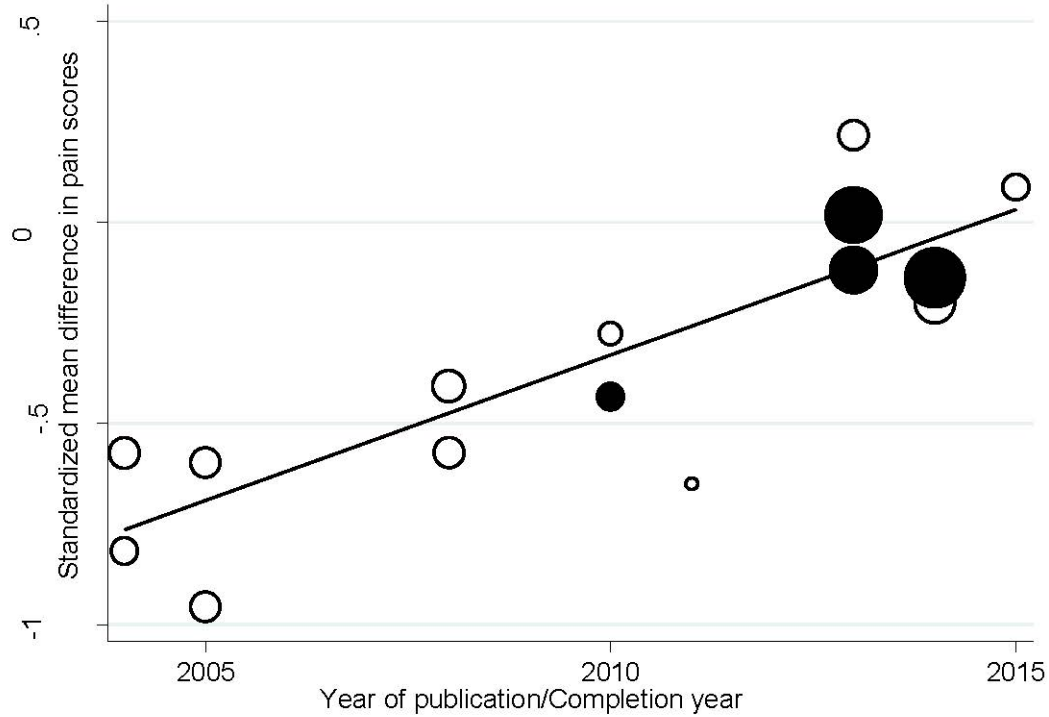


CI = confidence interval; CT.gov = ClinicalTrials.gov; ES = effect size; NPS = Numeric Pain Scale; NRS = Numeric Rating Scale; VAS = Visual Analog Scale

[a] Study was identified in a systematic review by Griebeler, 2014.[1]

[b] Dates for the ClinicalTrials.gov studies are the study completion dates.

Figure 2. Meta-regression of year of publication/completion date on the standardized mean difference in pain scores comparing pregabalin with placebo



Circles represent individual studies. Filled circles represent unpublished studies and are plotted by their study completion dates reported in ClinicalTrials.gov. Open circles represent published studies and are plotted by their publication dates.

Table 9. Univariate meta-regression results of year of publication/completion date on the standardized mean difference in pain scores comparing pregabalin with placebo

Covariate	Coefficient (95% CI)	Residual I^2	Adjusted R^2
Publication status	-0.32 (-0.70 to 0.07)	75%	19%
Year of publication/ completion date	0.07 (0.04 to 0.10)	24%	93%

Table 10. Strength of evidence domains for studies comparing pregabalin with placebo in terms of pain and quality of life among adults with diabetic peripheral neuropathy

Source	Outcome	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Other Issues	Strength of Evidence	Conclusions
Published literature	Pain	12 RCTs (3290)	Unclear	Inconsistent	Direct	Precise	Suspected	Studies were short-term; newer studies did not find evidence of effectiveness	Low	Pregabalin is more effective than placebo for reducing pain.
Published literature + CT.gov	Pain	16 RCTs (4712)	Unclear	Inconsistent	Direct	Precise	Suspected		Low	Pregabalin is more effective than placebo for reducing pain. However, effect size is small and pregabalin may be less effective than what would be estimated from the published literature alone.
Published literature	QOL	7 RCTs (2052)	Unclear	Inconsistent	Direct	Could not be evaluated	Unsuspected	Studies were short-term.	Insufficient	We are unable to draw a conclusion.
Published literature + CT.gov	QOL	11 RCTs (3513)	Unclear	Inconsistent	Direct	Could not be evaluated	Suspected		Insufficient	We are unable to draw a conclusion.

CT.gov = ClinicalTrials.gov; QOL = quality of life; RCT = randomized controlled trial

Topiramate Versus Placebo

Detailed Results

We identified four studies (three with available data) that compared topiramate with placebo among patients with diabetic peripheral neuropathy (Table 11).

Three studies, published before 2008, were identified in the published literature only.[41-43]

We did not identify any studies in both the published literature and in ClinicalTrials.gov

One study (NCT00231673), which was completed in January 2003, was identified only in ClinicalTrials.gov (Table 11). We were unable to find any publication for this trial. This study also did not post any results in ClinicalTrials.gov. This study, if ever published, would be unlikely to add to the body of evidence because none of the primary or secondary outcomes listed in ClinicalTrials.gov mentioned either pain or quality of life.

Did Searching ClinicalTrials.gov Change the Overall Conclusion for this Comparison for Either Pain or Quality of Life

While searching ClinicalTrials.gov yielded an additional study, the study did not provide any results. Furthermore, the study did not list either pain or quality of life as an outcome. We did not find any ClinicalTrials.gov entries for the three published studies.

Did Searching ClinicalTrials.gov Change the Strength of Evidence for this Comparison for Either Pain or Quality of Life

The additional trial identified in ClinicalTrials.gov is unlikely to affect the evidence grading for either pain or quality of life. The entry does not list pain and quality of life as outcomes.

Table 11. Studies comparing topiramate with placebo identified through ClinicalTrials.gov, published literature, or both

Source	Publication Author, Year	NCT Number	Matched by	Study Completion Date In CT.gov	Reported Results In CT.gov?	Sample Size	Followup
Published literature only	Thienel, 2004[41a]	Not found	NA	NA	NA	1269	18 to 22 weeks
	Raskin, 2004[42a]	Not found	NA	NA	NA	317	12 weeks
	Freeman, 2007[43]	Not found	NA	NA	NA	65	9 weeks
CT.gov only	None identified	NCT00231673	NA	Jan 2003	No	72	18 weeks

[a] Study was identified in a systematic review by Griebeler, 2014.[1]

CT.gov = ClinicalTrials.gov; NA = not applicable

Lacosamide Versus Placebo

Detailed Results

We identified five studies (four with available data) that compared lacosamide with placebo among patients with diabetic peripheral neuropathy (Table 12). All of the studies were listed in ClinicalTrials.gov.

Four studies were identified in both the published literature and in ClinicalTrials.gov.[15-18] None of these studies provided results in ClinicalTrials.gov. We noted that all of these studies

listed quality of life as an outcome in ClinicalTrials.gov, but only one reported on quality of life in their publication.[15]

One study (NCT00350103), which was completed in June 2007, was identified only in ClinicalTrials.gov (Table 12). We were unable to find any publication for this trial. This study also did not post any results in ClinicalTrials.gov.

Did Searching ClinicalTrials.gov Change the Overall Conclusion for this Comparison for Either Pain or Quality of Life

While searching ClinicalTrials.gov yielded an additional study, the study did not provide any results. Additionally, the four ClinicalTrials.gov records with publications did not provide any results for either pain or quality of life.

Did Searching ClinicalTrials.gov Change the Strength of Evidence for this Comparison for Either Pain or Quality of Life

The evidence grading domains and the strength of the evidence comparing lacosamide with placebo for pain would not change based on the results found in ClinicalTrials.gov.

For quality of life, evidence grading domains and the strength of the evidence did not change based on the ClinicalTrials.gov results (Table 13). However, in addition to suspecting reporting bias, there is now a suggestion of selective outcome reporting bias. All five of the studies listed quality of life as an outcome measure. Four of the studies had publications, but only one of these publications reported on quality of life. The overall evidence grade would remain "Insufficient."

Other Anticonvulsants Versus Placebo

We did not identify any ClinicalTrials.gov record for any of the other anticonvulsants included in the review (zonisamide, valproic acid, oxcarbazepine, carbamazepine, and lamotrigine). The conclusions and strength of evidence would not change from what is posted in the evidence report.

Table 12. Studies comparing lacosamide with placebo identified through ClinicalTrials.gov, published literature, or both

Source	Publication Author, Year	NCT Number	Matched by	Study Completion Date In CT.gov	Reported Results in CT.gov?	Sample Size	Followup
Both published literature and CT.gov	Rauck, 2007[15a]	NCT00861445	Publication found in CT.gov	Feb 2003	No	119	10 weeks
	Wymer, 2009[16a]	NCT00235469	Publication found in CT.gov	Jun 2005	No	496	18 weeks
	Shaibani, 2009[17a]	NCT00135109	NCT number abstracted from publication	Dec 2005	No	654	18 weeks
	Ziegler, 2010[18a]	NCT00238524	NCT number abstracted from publication	Jan 2005	No	357	18 weeks
CT.gov only	None identified	NCT00350103	NA	Jun 2007	No	537	12 weeks

[a] Study was identified in a systematic review by Griebeler, 2014.[1]
CT.gov = ClinicalTrials.gov; NA = not applicable

Table 13. Strength of evidence domains for studies comparing lacosamide with placebo in terms of quality of life among adults with diabetic peripheral neuropathy

Source	Outcome	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Other Issues	Strength of Evidence	Conclusions
Published literature	QOL	1 RCT (119)	Unclear	NA	Direct	Unable to evaluate	Suspected		Insufficient	We are unable to draw a conclusion.
Published literature + CT.gov	QOL	1 RCT (119)	Unclear	NA	Direct	Unable to evaluate	Suspected, with additional suggestion of selective outcome reporting[a]		Insufficient	We are unable to draw a conclusion.

[a] All four of the studies identified in both the published literature and ClinicalTrials.gov listed quality of life as an outcome. However, only one study included quality of life in their publication.
CT.gov = ClinicalTrials.gov; QOL = quality of life; RCT = randomized controlled trial

Antidepressants

Serotonin-Noradrenaline Reuptake Inhibitors Versus Placebo

Duloxetine Versus Placebo

Detailed Results

We identified seven studies (all with available data) that compared duloxetine with placebo among patients with diabetic peripheral neuropathy (Table 14).

Three studies, all published before 2008, were identified in the published literature only.[44-46]

Four studies were identified in both the published literature and in ClinicalTrials.gov.[19-22] Three studies[19-21] reported pain results and one[20] reported quality of life results in ClinicalTrials.gov (Table 15). With the exception of the pain results from one study,[20] the results reported in the ClinicalTrials.gov record and the publication were similar. In the one study with non-matching results, only the p-values for the mean between-group difference were different, although both the p-values were non-significant.

Did Searching ClinicalTrials.gov Change the Overall Conclusion for this Comparison/Outcome

ClinicalTrials.gov did not yield any new data for the included publications nor did it yield any new studies. Therefore, the overall conclusion (i.e., duloxetine reduced pain more than placebo in the short term) did not change.

Did Searching ClinicalTrials.gov Change the Strength of Evidence for this Comparison/Outcome

Searching ClinicalTrials.gov did not yield any new data that influenced the strength of evidence grading for the outcomes of pain and quality of life.

Table 14. Studies comparing duloxetine with placebo identified through ClinicalTrials.gov, published literature, or both

Source	Publication Author, Year	NCT Number	Matched by	Study Completion Date In CT.gov	Reported Results in CT.gov?	Sample Size	Followup
Published literature only	Raskin, 2005[44a]	Not found	NA	NA	NA	348	12 weeks
	Goldstein, 2005[45a]	Not found	NA	NA	NA	457	12 weeks
	Wernicke, 2006[46a]	Not found	NA	NA	NA	334	13 weeks
Both published literature and CT.gov	Gao, 2015[19]	NCT01179672	NCT number abstracted from publication	Aug 2013	Yes	405	12 weeks
	Gao, 2010[20a]	NCT00408993	NCT number abstracted from publication	Dec 2006	Yes	215	12 weeks
	Yasuda, 2011[21a]	NCT00552175	NCT number abstracted from publication	Mar 2009	Yes	339	12 weeks
	Rowbotham, 2012[22]	NCT00507936	Found by using search terms in PubMed	Oct 2008	No	280	8 weeks

[a] Study was identified in a systematic review by Griebeler, 2014.[1]
CT.gov = ClinicalTrials.gov; NA = not applicable

Table 15. Comparison of the pain and quality of life results reported in the publication and the ClinicalTrials.gov record[a] and/or additional results reported only in ClinicalTrials.gov

Publication Author, Year	NCT Number	Pain Scale	Did Pain Results Differ?	Describe How Pain Results Differed	QOL Scale	Did QOL Results Differ?	Describe How QOL Results Differed
Gao, 2015[19]	NCT01179672	PSS	No	The baseline, change from baseline, and the mean between-group difference in the change in pain scores for the 24-hour average pain score were identical between the CT.gov record and the publication.	NE	NE	NE
Gao, 2010[20]	NCT00408993	BPI	Yes	The baseline and change from baseline values for the 24-hour average pain score were similar between the CT.gov record and the publication. Both reported non-significant p-values for the mean between-group difference, but the values were different.	EQ-5D	No	The change from baseline values and the p-value for the mean between-group difference were identical between the CT.gov record and the publication.
Yasuda, 2011[21]	NCT00552175	NRS	No	The baseline and change from baseline for the average pain severity was identical between the CT.gov record and the publication.	NE	NE	NE

[a] For studies that reported results in ClinicalTrials.gov.
BPI = Brief Pain Inventory; CT.gov = ClinicalTrials.gov; EQ-5D = European Quality of Life Scale – 5 Dimensions; NE = not evaluated; NRS = Numerical Rating Scale; PSS = Pain Severity Score; QOL = quality of life

Milnacipran Versus Placebo

Detailed Results

We identified one study that compared milnacipran with placebo among patients with diabetic peripheral neuropathy (Table 16). This study (NCT01288937), which was completed in October 2014, was identified only in ClinicalTrials.gov. This study did not post any results in ClinicalTrials.gov. The status of the study was "unknown."

Did Searching ClinicalTrials.gov Change the Overall Conclusion for this Comparison/Outcome

Although we identified a new study, the study did not provide any results. Therefore, the overall conclusion did not change.

Did Searching ClinicalTrials.gov Change the Strength of Evidence for this Comparison/Outcome

Although we identified a new study, the study did not provide any results. Therefore, the strength of evidence grade remained as "Insufficient."

Table 16. Studies comparing milnacipran with placebo identified through ClinicalTrials.gov, published literature, or both

Source	Publication Author, Year	NCT Number	Matched by	Study Completion Date In CT.gov	Reported Results In CT.gov?	Sample Size	Followup
CT.gov only	None identified	NCT01288937	NA	Oct 2014	No	52	9 weeks

CT.gov = ClinicalTrials.gov; NA = not applicable

Other Serotonin-Noradrenaline Reuptake Inhibitors and Antidepressants Versus Placebo

We did not identify any ClinicalTrials.gov record for any of the other serotonin-noradrenaline reuptake inhibitors (desvenlafaxine, levomilnacipran, and venlafaxine) or other antidepressants (tricyclic antidepressants) included in the review. The conclusions and strength of evidence did not change from what is posted in the evidence report.

Analgesics

Oxycodone Versus Placebo

Detailed Results

We identified four studies (five publications; all with available data) that compared oxycodone with placebo among patients with diabetic peripheral neuropathy (Table 17).

Three of these studies, all published either during or prior to 2008, were found in the published literature only.[47-49]

One study (NCT00944697) was identified only in ClinicalTrials.gov. Although this study was completed in 2010, we were unable to find a publication. This study randomized 98 patients to a combination of oxycodone and naloxone or placebo. This study reported pain results in ClinicalTrials.gov, but the results were limited to the final values (Table 18). The standardized

mean difference in the final Short-Form McGill Pain Score was not significant (-0.06; 95% CI, -0.46 to 0.34). This study did not evaluate quality of life.

Did Searching ClinicalTrials.gov Change the Overall Conclusion for this Comparison/Outcome

Figure 3 shows the standardized mean differences in pain scores for studies found in the published literature versus those found only in ClinicalTrials.gov. We decided not to pool these studies due to high statistical heterogeneity (I-squared = 79% and 75% for the published studies and the overall results, respectively). The results from the published literature displayed in the figure would suggest that oxycodone was more effective than placebo at reducing pain. However, the systematic review concluded that oxycodone was not more effective than placebo. This conclusion was based on the results of a network meta-analysis,[1] which combines both direct and indirect comparisons, and one additional study (Hanna 2008).[47] The study found in ClinicalTrials.gov supports the conclusion of the systematic review (i.e., oxycodone is not more effective than placebo at reducing pain).

There were no additional results for quality of life. Therefore, the conclusions did not change.

Did Searching ClinicalTrials.gov Change the Strength of Evidence for this Comparison/Outcome

We downgraded the Reporting Bias domain to "Suspected" because we are aware of at least one 12-week study with 96 participants that was not published in the peer-reviewed literature. Since the results found in ClinicalTrials.gov support the conclusion from the systematic review, we did not downgrade the overall strength of evidence grade.

We did not change the strength of evidence grading for quality of life because we did not find any new data on quality of life.

Table 17. Studies comparing oxycodone with placebo identified through ClinicalTrials.gov, published literature, or both

Source	Publication Author, Year	NCT Number	Matched by	Study Completion Date In CT.gov	Reported Results in CT.gov?	Sample Size	Followup
Published literature only	Hanna, 2008[47]	Not found	NA	NA	NA	338	12 weeks
	Gimbel, 2003[48, 50a]	Not found	NA	NA	NA	159	6 weeks
	Watson, 2003[49a]	Not found	NA	NA	NA	45	4 weeks
CT.gov only	None identified	NCT00944697	NA	Apr 2010	Yes	98	12 weeks

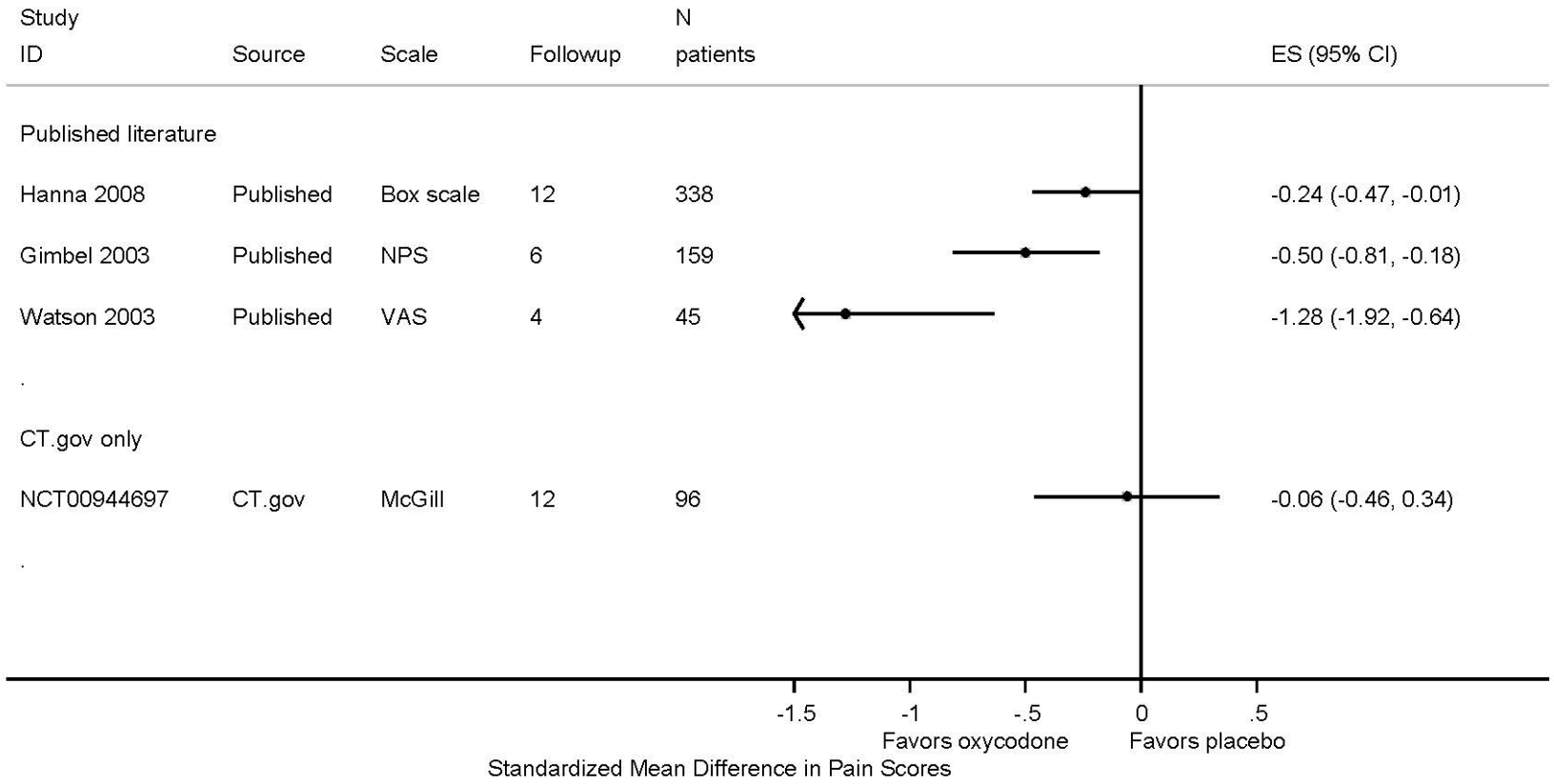
[a] Study was identified in a systematic review by Griebeler, 2014.[1]
CT.gov = ClinicalTrials.gov; NA = not applicable

Table 18. Comparison of the pain and quality of life results reported in the publication and the ClinicalTrials.gov record[a] and/or additional results reported only in ClinicalTrials.gov

Publication Author, Year	NCT Number	Pain Scale	Did Pain Results Differ?	Describe How Pain Results Differed	QOL Scale	Did QOL Results Differ?	Describe How QOL Results Differed
None identified	NCT00944697	McGill	NA	Only final values were reported on CT.gov, so we could not derive a change from baseline. The final McGill pain score was 49.6 (SD 29.6) in the placebo group and 47.7 (SD 30.3) in the oxycodone group. The standardized mean difference in final values was not significant (-0.06, 95% CI, -0.46 to 0.34).	NE	NE	NE

[a] For studies that reported results in ClinicalTrials.gov.
CI = confidence interval; CT.gov = ClinicalTrials.gov; McGill = Short-Form McGill Pain Score; NA = not applicable; NE = not evaluated; SD = standard deviation

Figure 3. Standardized mean difference in pain scores comparing oxycodone with placebo stratified by studies found in the published literature versus those found only in ClinicalTrials.gov



CI = confidence interval; CT.gov = ClinicalTrials.gov; ES = effect size; McGill = Short-form McGill Pain Score; NPS = Numeric Pain Scale; VAS = Visual Analog Scale

Table 19. Strength of evidence domains for studies comparing oxycodone with placebo in terms of pain among adults with diabetic peripheral neuropathy

Source	Outcome	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Other Issues	Strength of Evidence	Conclusions
Published literature	Pain	3 RCTs (542)	Unclear	Inconsistent	Direct	Imprecise	Unsuspected	Studies were short-term	Low	Opioids are not more effective than placebo for reducing pain.
Published literature + CT.gov	Pain	4 RCTs (638)	Unclear	Inconsistent	Direct	Imprecise	Suspected		Low	Opioids are not more effective than placebo for reducing pain.

CT.gov = ClinicalTrials.gov; RCT = randomized controlled trial

Atypical Opioids Versus Placebo

Detailed Results

We identified five studies (all with available data) that compared an atypical opioid with placebo among patients with diabetic peripheral neuropathy (Table 20).

Two of these studies were found in the published literature only.[51, 52] One of these studies was published prior to 2008.[52] The other study was conducted in The Netherlands, and was registered in the Nederlands Trial Register.[51]

The other three trials were identified in both the published literature and in ClinicalTrials.gov.[7, 8, 23] Two studies reported results in ClinicalTrials.gov (Table 21).[7, 8] For both of these studies, we compared the results for the Average Pain Intensity Numerical Rating Scale between the publication and the ClinicalTrials.gov record. The ClinicalTrials.gov record did not report baseline values for either study. The mean change from baseline and the mean between-group differences were similar between the publication and the ClinicalTrials.gov record. Both of these studies evaluated quality of life using the European Quality of Life Scale-5 Dimensions. In one study,[7] the change from baseline values posted in the ClinicalTrials.gov record matched what was reported in the publication. In the other study,[8] the quality of life scores were only reported in ClinicalTrials.gov. However, this study was also included in a pooled analysis (Schwartz, 2015),[6] which reported on quality of life. Because the analysis was pooled, it is unclear whether or not the results differed.

Did Searching ClinicalTrials.gov Change the Overall Conclusion for this Comparison/Outcome

For pain, searching ClinicalTrials.gov did not yield any new data for the included publications nor did it yield any new studies. For quality of life, searching ClinicalTrials.gov provided separate data for the two studies that were included in the pooled analysis. Therefore, the conclusions for pain and quality of life did not change.

Did Searching ClinicalTrials.gov Change the Strength of Evidence for this Comparison/Outcome

Searching ClinicalTrials.gov did not yield any new data that influenced the strength of evidence grading for the outcomes of pain and quality of life. Although we already suspected reporting bias for quality of life, there is now a suggestion of selective outcome reporting bias as well.

Table 20. Studies comparing atypical opioids with placebo identified through ClinicalTrials.gov, published literature, or both

Source	Publication Author, Year	NCT Number	Matched by	Study Completion Date In CT.gov	Reported Results in CT.gov?	Sample Size	Followup
Published literature only	Niesters, 2014[51]	Not found	NA	NA	NA	24	4 weeks
	Harati, 1998[52]	Not found	NA	NA	NA	131	6 weeks
Both published literature and CT.gov	Vinik, 2014[7]	NCT01041859	NCT number	Mar 2011	Yes	459	12 weeks
	Schwartz, 2011[8a]	NCT00455520	NCT number	Aug 2008	Yes	395	12 weeks
	Freeman, 2007[23a]	NCT00210847	Publication found in CT.gov	May 2005	No	313	9 weeks
	Schwartz, 2015[6]	NCT01041859 NCT00455520	NCT number	Mar 2011	Yes		12 weeks

[a] Study was identified in a systematic review by Griebeler, 2014.[1]
CT.gov = ClinicalTrials.gov; NA = not applicable

Table 21. Comparison of the pain and quality of life results reported in the publication and the ClinicalTrials.gov record[a] and/or additional results reported only in ClinicalTrials.gov

Publication Author, Year	NCT Number	Pain Scale	Did Pain Results Differ?	Describe How Pain Results Differed	QOL Scale	Did QOL Results Differ?	Describe How QOL Results Differed
Vinik, 2014[7]	NCT01041859	NRS	No	The CT.gov record reported only the mean change from baseline and the mean between-group difference in the NRS score. Baseline values were not reported.	EQ-5D	No	The CT.gov record reported the mean change from baseline. These values match what is reported in the publication.
Schwartz, 2011[8]	NCT00455520	NRS	No	The CT.gov record reported only the mean change from baseline and the mean between-group difference in the NRS score. Baseline values were not reported.	EQ-5D	Yes	This publication did not report on quality of life, but quality of life was reported in CT.gov. However, this study was also included in a pooled analysis (Schwartz, 2015[b]), which reported on quality of life. Because the analysis was pooled, it is unclear whether or not the results differed.

[a] For studies that reported results in ClinicalTrials.gov.
[b] The Schwartz 2015 publication was a pooled analysis of two studies: NCT01041859 and NCT00455520. Because the results were pooled in the publication, it was impossible to determine if the results differed between the publication and the ClinicalTrials.gov record.
NRS = Numerical Rating Scale;

Topical Agents

Capsaicin Versus Placebo

Detailed Results

We identified eight studies (six with available data) that compared capsaicin with placebo among patients with diabetic peripheral neuropathy (Table 22). Six studies evaluated 0.75% capsaicin topic cream and two studies evaluated 8% capsaicin patch. We considered the different formulations of capsaicin separately.

0.75% Capsaicin Topical Cream

Four studies, all published prior to 2008, were found in the published literature only and evaluated 0.75% capsaicin topical cream.[53-56]

One study was identified in both the published literature and in ClinicalTrials.gov.[24] This study did not post results in ClinicalTrials.gov.

One study was identified in ClinicalTrials.gov only (NCT01125215). This study was completed in December 2013 and has not posted results.

8% Capsaicin Patch

Two studies were identified only in ClinicalTrials.gov (NCT01533428 and NCT01478607). We were unable to find any publications for these trials. Considering these studies were completed within the last 3 years, it is possible that the authors will be publishing results soon. One of these studies (NCT01533428) posted results in ClinicalTrials.gov (Table 23). This study reported the percentage change in the average daily pain score as measured by the Brief Pain Inventory. The mean between-group difference in the percentage change in average daily pain score significantly favored capsaicin (-7.1%; 95% CI, -12.9% to -1.2%; $P = 0.018$). This study also evaluated quality of life using the EQ-5D. Quality of life improved both in the placebo and capsaicin arms, but the standardized mean difference was not significant (0.005; 95% CI, -0.20 to 0.21).

Did Searching ClinicalTrials.gov Change the Overall Conclusion for this Comparison/Outcome

0.75% Capsaicin Topical Cream

Although searching ClinicalTrials.gov yielded one additional study that evaluated 0.75% capsaicin topical cream, the study did not post any results for pain and did not list quality of life as an outcome. Therefore, we did not change our conclusions for pain or quality of life.

8% Capsaicin Patch

Searching ClinicalTrials.gov yielded the only two studies that evaluated the 8% capsaicin patch in terms of pain or quality of life. One of these studies had posted results. This study followed 369 patients for up to 12 weeks, and measured pain on the Brief Pain Inventory and quality of life using the European Quality of Life Scale – 5 Dimensions. However, the overall strength of evidence is still “Insufficient” and we are still unable to draw a conclusion.

Did Searching ClinicalTrials.gov Change the Strength of Evidence for this Comparison/Outcome

0.75% Capsaicin Topical Cream

Searching ClinicalTrials.gov did not yield any new data that could have influenced the strength of evidence grading comparing 0.75% capsaicin topical cream with placebo for the outcomes of pain and quality of life.

8% Capsaicin Patch

There were no published studies comparing the 8% capsaicin patch with placebo in terms of pain or quality of life among patients with diabetic peripheral neuropathy. By searching ClinicalTrials.gov, we identified one unpublished, 12-week study with 369 participants (Table 24). Considering the unclear study limitations, the imprecise results, and the suspected reporting bias, we kept the overall strength of evidence as "Insufficient."

Table 22. Studies comparing capsaicin with placebo identified through ClinicalTrials.gov, published literature, or both

Source	Publication Author, Year	NCT Number	Matched by	Formulation	Study Completion Date In CT.gov	Reported Results in CT.gov?	Sample Size	Followup
Published literature only	Capsaicin group, 1991[53a]	Not found	NA	0.75% topical cream	NA	NA	277	8 weeks
	Scheffler, 1991[54a]	Not found	NA	0.75% topical cream	NA	NA	54	8 weeks
	Tandan, 1992[55a]	Not found	NA	0.75% topical cream	NA	NA	22	8 weeks
	Chad, 1990[56]	Not found	NA	0.75% topical cream	NA	NA	58	4 weeks
Both published literature and CT.gov	Kulkantrakorn, 2013[24]	NCT00993070	Found by using search terms in PubMed	0.75% topical cream	Dec 2011	No	33	20 weeks
CT.gov only	None identified	NCT01125215	NA	0.75% topical cream	Dec 2013	No	60[b]	12 weeks
	None identified	NCT01533428	NA	8% patch	Feb 2014	Yes	369	12 weeks
	None identified	NCT01478607	NA	8% patch	Feb 2014	No	468	64 weeks

[a] Study was identified in a systematic review by Griebeler, 2014.[1]
[b] Planned enrollment. The study status was unknown.
CT.gov = ClinicalTrials.gov; NA = not applicable

Table 23. Comparison of the pain and quality of life results reported in the publication and the ClinicalTrials.gov record[a] and/or additional results reported only in ClinicalTrials.gov

Publication Author, Year	NCT Number	Pain Scale	Did Pain Results Differ?	Describe How Pain Results Differed	QOL Scale	Did QOL Results Differ?	Describe How QOL Results Differed
None identified	NCT01533428	BPI	NA	The average daily pain score as measured by the BPI decreased by 21% in the placebo arm and by 28.0% in the 8% capsaicin patch arm. The mean between-group difference in the percentage change significantly favored 8% capsaicin patch (-7.1%; 95% CI, -12.9% to -1.2%; *P* = 0.018).	EQ-5D	NA	Quality of life improved by 3.7 pts (SD 19.08) in the placebo arm and by 3.8 pts (SD 17.94) in the 8% capsaicin patch arm. The standardized mean difference was not significant (0.005; 95% CI, -0.20 to 0.21).

[a] For studies that reported results in ClinicalTrials.gov.
BPI = Brief Pain Inventory; CI = confidence interval; EQ-5D = European Quality of Life Scale – 5 Dimensions; NA = not applicable; pts = points; QOL = quality of life; SD = standard deviation

Table 24. Strength of evidence domains for studies comparing 8% capsaicin patch with placebo in terms of pain and quality of life among adults with diabetic peripheral neuropathy

Source	Outcome	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Other Issues	Strength of Evidence	Conclusions
Published literature	Pain	0 RCTs								
Published literature + CT.gov	Pain	1 RCT (369)	Unclear	NA	Direct	Imprecise	Suspected		Insufficient	We are unable to draw a conclusion.
Published literature	QOL	0 RCTs								
Published literature + CT.gov	QOL	1 RCT (369)	Unclear	NA	Direct	Imprecise	Suspected		Insufficient	We are unable to draw a conclusion.

CT.gov = ClinicalTrials.gov; NA = not applicable; QOL = quality of life; RCT = randomized controlled trial

Clonidine Versus Placebo

Detailed Results

We identified two studies (one with available data) that compared clonidine with placebo among patients with diabetic peripheral neuropathy (Table 25).

One study was identified in both the published literature and in ClinicalTrials.gov.[25] This study did not post results in ClinicalTrials.gov.

One study (NCT02068027) was identified only in ClinicalTrials.gov. We were unable to find any publications for this trial. This study was completed in 2015, so it is possible that the authors will be publishing results soon. This study did not post results in ClinicalTrials.gov.

Did Searching ClinicalTrials.gov Change the Overall Conclusion for this Comparison/Outcome

Although we found a new study, the study has not yet posted any results. However, this study is relatively large, and if ever published, could influence the overall conclusions for the effect of clonidine on pain. Therefore, we lowered the evidence grade to "Insufficient" and consequently, we are now unable to draw a conclusion.

This new study did not list quality of life as an outcome in ClincalTrials.gov. Therefore, we did not change the conclusions for quality of life.

Did Searching ClinicalTrials.gov Change the Strength of Evidence for this Comparison/Outcome

For pain, the reporting bias domain would change from "Unsuspected" to "Suspected" based on the ClinicalTrials.gov results (Table 26). By searching ClinicalTrials.gov, we identified one additional study with 260 participants that evaluated pain. The strength of the evidence would remain "Insufficient."

Since quality of life was not listed as an outcome in the ClinicalTrials.gov record, we did not change the evidence grading for quality of life.

Table 25. Studies comparing clonidine with placebo identified through ClinicalTrials.gov, published literature, or both

Source	Publication Author, Year	NCT Number	Matched by	Study Completion Date In CT.gov	Reported Results in CT.gov?	Sample Size	Followup
Both published literature and CT.gov	Campbell, 2012[25]	NCT00695565	NCT number	Dec 2009	No	182	16 weeks
CT.gov only	None identified	NCT02068027	NA	Mar 2015	No	260	12 weeks

CT.gov = ClinicalTrials.gov; NA = not applicable

Table 26. Strength of evidence domains for studies comparing clonidine with placebo in terms of pain among adults with diabetic peripheral neuropathy

Source	Outcome	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Other Issues	Strength of Evidence	Conclusions
Published literature	Pain	1 RCT (182)	Unclear	Unknown	Direct	Imprecise	Unsuspected	Studies were short-term	Insufficient	We are unable to draw a conclusion.
Published literature + CT.gov	Pain	1 RCT (182)	Unclear	Unknown	Direct	Imprecise	Suspected		Insufficient	We are unable to draw a conclusion.

CT.gov = ClinicalTrials.gov; RCT = randomized controlled trial

Lidocaine Versus Placebo

Detailed Results

We identified two studies (neither with available data) that compared lidocaine with placebo among patients with diabetic peripheral neuropathy (Table 27).

Both studies (NCT02363803 and NCT00904202) were identified only in ClinicalTrials.gov and neither posted results. One of the studies (NCT02363803) is currently recruiting and is not expected to complete until 2018.

Did Searching ClinicalTrials.gov Change the Overall Conclusion for this Comparison/Outcome

None of the included studies comparing lidocaine with placebo have posted or published any results. Therefore, we are still unable to draw any conclusions for pain and quality of life.

Did Searching ClinicalTrials.gov Change the Strength of Evidence for this Comparison/Outcome

We are unable to grade the evidence for this comparison for pain and for quality of life because there is no available evidence.

Table 27. Studies comparing lidocaine with placebo identified through ClinicalTrials.gov, published literature, or both

Source	Publication Author, Year	NCT Number	Matched by	Study Completion Date In CT.gov	Reported Results in CT.gov?	Sample Size	Followup
CT.gov only	None identified	NCT02363803	NA	Mar 2018	No	35[a]	NA
	None identified	NCT00904202	NA	Jun 2003	No	62	5 weeks

a Planned enrollment. The study status was recruiting.
CT.gov = ClinicalTrials.gov; NA = not applicable

Other Agents

Dextromethorphan Versus Placebo

Detailed Results

We identified three studies (all with available data) that compared dextromethorphan with placebo among patients with diabetic peripheral neuropathy (Table 28).

Two studies, both published prior to 2008, were found in the published literature only.[57, 58]

One study was identified in both the published literature and in ClinicalTrials.gov.[26] This study did not post results in ClinicalTrials.gov.

Did Searching ClinicalTrials.gov Change the Overall Conclusion for this Comparison/Outcome

Searching ClinicalTrials.gov did not yield any new data for the included publications nor did it yield any new studies. Therefore, the conclusions did not change for the outcomes of pain and quality of life.

Did Searching ClinicalTrials.gov Change the Strength of Evidence for this Comparison/Outcome

Searching ClinicalTrials.gov did not yield any new data for the included publications nor did it yield any new studies that could have affected the strength of evidence grading. Therefore, we did not change the strength of evidence grading for the outcomes of pain and quality of life.

Table 28. Studies comparing dextromethorphan with placebo identified through ClinicalTrials.gov, published literature, or both

Source	Publication Author, Year	NCT Number	Matched by	Study Completion Date in CT.gov	Reported Results in CT.gov?	Sample Size	Followup
Published literature only	Nelson, 1997[57a]	Not found	NA	NA	NA	14	6 weeks
	Sang, 2002[58a]	Not found	NA	NA	NA	23	9 weeks
Both published literature and CT.gov	Shaibani, 2012[26]	NCT00113620	Publication found in CT.gov	Dec 2006	No	450	13 weeks

[a] Study was identified in a systematic review by Griebeler, 2014.[1]
CT.gov = ClinicalTrials.gov; NA = not applicable

Mexiletine Versus Placebo

Detailed Results

We identified six studies (all with available data) that compared mexiletine with placebo among patients with diabetic peripheral neuropathy (Table 29).

Five studies, all published prior to 2008, were found in the published literature only.[59-63]

One study was identified in both the published literature and in ClinicalTrials.gov.[27] This study did not post results in ClinicalTrials.gov. We also did not include this study in the systematic review because we were unable to retrieve the publication.

Did Searching ClinicalTrials.gov Change the Overall Conclusion for this Comparison/Outcome

Searching ClinicalTrials.gov did not yield any new data for the included publications nor did it yield any new studies. Therefore, we did not change the conclusions for the outcomes of pain and quality of life.

Did Searching ClinicalTrials.gov Change the Strength of Evidence for this Comparison/Outcome

Searching ClinicalTrials.gov did not yield any new data for the included publications nor did it yield any new studies that could have affected the strength of evidence grading. Therefore, we did not change the strength of evidence grading for the outcomes of pain and quality of life.

Table 29. Studies comparing mexiletine with placebo identified through ClinicalTrials.gov, published literature, or both

Source	Publication Author, Year	NCT Number	Matched by	Study Completion Date in CT.gov	Reported Results in CT.gov?	Sample Size	Followup
Published literature only	Dejgard, 1988[59a]	Not found	NA	NA	NA	19	26 weeks
	Stracke, 1992[60a]	Not found	NA	NA	NA	95	6 weeks
	Matsuoka, 1997[61a]	Not found	NA	NA	NA	118	2 weeks
	Oskarsson, 1997[62a]	Not found	NA	NA	NA	126	3 weeks
	Wright, 1997[63a]	Not found	NA	NA	NA	31	3 weeks
Both published literature and CT.gov	Bertorini, 1998[27b]	NCT00004647	Publication found in CT.gov	Feb 1999	No	40	6 weeks

[a] Study was identified in a systematic review by Griebeler, 2014.[1]
[b] We did not include this study in the systematic review because we were unable to retrieve the publication.
CT.gov = ClinicalTrials.gov; NA = not applicable

Botulinum Toxin Versus Placebo

Detailed Results

We identified three studies (two with available data) that compared botulinum toxin with placebo among patients with diabetic peripheral neuropathy (Table 30).

One study was found in the published literature only.[64] This study was conducted in Iran. The publication does not indicate if the protocol was ever registered in any clinical trials registry.

One study was identified in both the published literature and in ClinicalTrials.gov.[28] This study did not post results in ClinicalTrials.gov.

One study (NCT02460107) was identified only in ClinicalTrials.gov. This study is currently recruiting, and is scheduled to be completed in September 2016.

Did Searching ClinicalTrials.gov Change the Overall Conclusion for this Comparison/Outcome

Searching ClinicalTrials.gov did not yield any new data for the included publications. Therefore, the conclusions did not change for the outcomes of pain and quality of life. However, we did identify a new study that is currently ongoing. This small (N = 81), 24-week study could add to the body of evidence once it is completed. The investigators are evaluating pain using a numeric rating scale and quality of life using the World Health Organization Quality of Life assessment tool.

Did Searching ClinicalTrials.gov Change the Strength of Evidence for this Comparison/Outcome

Searching ClinicalTrials.gov did not yield any new data for the included publications. Therefore, the strength of evidence grading would not change for the outcomes of pain and quality of life. However, we did identify a new study that is currently ongoing. This small (N = 81), 24-week study could add to the body of evidence once it is completed.

Table 30. Studies comparing botulinum toxin with placebo identified through ClinicalTrials.gov, published literature, or both

Source	Publication Author, Year	NCT Number	Matched by	Study Completion Date In CT.gov	Reported Results in CT.gov?	Sample Size	Followup
Published literature only	Ghasemi, 2014[64]	Not found	NA	NA	NA	40	3 weeks
Both published literature and CT.gov	Yuan, 2009[28]	NCT00336349	Found by using search terms in PubMed	Dec 2007	No	30	12 weeks
CT.gov only	Not identified	NCT02460107	NA	Sep 2016	No	81[a]	24 weeks

[a] Planned enrollment. The study status was recruiting.
CT.gov = ClinicalTrials.gov; NA = not applicable

Cannabinoids Versus Placebo

Detailed Results

We identified three studies (two with available data) that compared a cannabinoid with placebo among patients with diabetic peripheral neuropathy (Table 31). One study each evaluated nabilone,[29] a nabiximol (NCT00710424), and a cannabis-based medicine extract (NCT00238550). We analyzed each of these different cannabinoids separately.

One study was identified in both the published literature and in ClinicalTrials.gov.[29] This study, which evaluated nabilone, did not post results in ClinicalTrials.gov.

Two studies (NCT00238550 and NCT00710424) were identified only in ClinicalTrials.gov. One study (NCT00710424), which evaluated nabiximol, posted results in ClinicalTrials.gov for both pain and quality of life. This study, which followed 297 patients for 14 weeks, reported non-significant differences in the effects of cannabinoids on pain and quality of life (Table 32).

Did Searching ClinicalTrials.gov Change the Overall Conclusion for this Comparison/Outcome

Searching ClinicalTrials.gov did not yield any new studies nor any new data for the comparison of nabilone with placebo for either pain or quality of life. Therefore, we did not change the overall conclusions.

By searching ClinicalTrials.gov, we identified the only studies that evaluated nabiximol or a cannabis-based medicine extract. Although the nabiximol study posted results, we still are unable to draw a conclusion.

The cannabis-based medicine extract study did not post any results, so we are unable to draw a conclusion.

Did Searching ClinicalTrials.gov Change the Strength of Evidence for this Comparison/Outcome

Searching ClinicalTrials.gov did not yield any new studies nor any new data for the comparison of nabilone with placebo for either pain or quality of life. Therefore, we did not change the strength of evidence grading.

By searching ClinicalTrials.gov, we identified the only studies that evaluated nabiximol or a cannabis-based medicine extract. Although the nabiximol study posted results, we still graded

the overall strength of evidence as “Insufficient,” considering the unclear study limitations, the imprecise results, and the suspected reporting bias (Table 33).

The study evaluating cannabis-based medicine extract did not post any results. The overall evidence grade is “Insufficient.”

Table 31. Studies comparing cannabinoids with placebo identified through ClinicalTrials.gov, published literature, or both

Source	Publication Author, Year	NCT Number	Matched by	Type of Cannabinoid	Study Completion Date In CT.gov	Reported Results in CT.gov?	Sample Size	Followup
Both published literature and CT.gov	Toth, 2012[29]	NCT01035281	NCT number	Nabilone	Apr 2011	No	60	4 weeks
CT.gov only	None identified	NCT00238550	NA	Cannabis-based medicine extract	Mar 2006	No	36	12 weeks
	None identified	NCT00710424	NA	Nabiximol	Jun 2006	Yes	297	14 weeks

CT.gov = ClinicalTrials.gov; NA = not applicable

Table 32. Comparison of the pain and quality of life results reported in the publication and the ClinicalTrials.gov record[a] and/or additional results reported only in ClinicalTrials.gov

Publication Author, Year	NCT number	Pain Scale	Did Pain Results Differ?	Describe How Pain Results Differed	QOL Scale	Did QOL Results Differ?	Describe How QOL Results Differed
None identified	NCT00710424	NPS	NA	NPS score, measured on a scale of 0 to 100, decreased by 14.2 pts (SD 17.4) in the placebo arm and by 13.7 pts (SD 19.9) in the cannabinoids arm. The standardized mean difference was not significant (0.02; 95% CI, -0.21 to 0.26).	EQ-5D VAS	NA	Quality of life, as measured by the EQ-5D VAS, increased by 7.8 pts (SD 22.9) in the placebo arm and by 3.3 pts (SD 22.3) in the cannabinoids arm. The standardized mean difference was not significant (-0.20; 95% CI, -0.44 to 0.04).

[a] For studies that reported results in ClinicalTrials.gov.

CI = confidence interval; EQ-5D VAS = European Quality of Life Scale – 5 Dimensions, Visual Analog Scale; NA = not applicable; NPSS = Neuropathic Pain Scale; pts = points; QOL = quality of life; SD = standard deviation

Table 33. Strength of evidence domains for studies comparing nabiximol with placebo in terms of pain among adults with diabetic peripheral neuropathy

Source	Outcome	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Other Issues	Strength of Evidence	Conclusions
Published literature	Pain	0 RCTs								
Published literature + CT.gov	Pain	1 RCT (297)	Unclear	NA	Direct	Imprecise	Suspected		Insufficient	We are unable to draw a conclusion.
Published literature	QOL	0 RCTs								
Published literature + CT.gov	QOL	1 RCT (297)	Unclear	NA	Direct	Imprecise	Suspected		Insufficient	We are unable to draw a conclusion.

CT.gov = ClinicalTrials.gov; QOL = quality of life; RCT = randomized controlled trial

Drug-Drug Comparisons

Anticonvulsants Versus Antidepressants

Anticonvulsants Versus Serotonin-Noradrenaline Reuptake Inhibitors

Detailed Results

We identified five studies (three with available data) that compared an anticonvulsant with a serotonin-noradrenaline reuptake inhibitor among patients with diabetic peripheral neuropathy (Table 34). One study compared carbamazepine with venlafaxine[65] and the others compared pregabalin with duloxetine.

One study, which was published prior to 2008, was found in the published literature only.[65]

Two studies were found in both the published literature and in ClinicaTrials.gov.[30, 31] One of these studies posted pain results on ClinicalTrials.gov.[30] The study evaluated pain using the Brief Pain Inventory – Modified Short Form and the results were similar between the publication and the ClinicalTrials.gov record (Table 35). The study did not evaluate quality of life.

Two studies were found only in ClinicalTrials.gov (NCT00837941 and NCT01116531). Both of these trials were withdrawn prior to enrollment. Neither ClinicalTrials.gov record provided a reason for withdrawal.

Did Searching ClinicalTrials.gov Change the Overall Conclusion for this Comparison for Either Pain or Quality of Life

ClinicalTrials.gov did not yield any new data for the included publications nor did it yield any new studies. Therefore, the overall conclusion (i.e., serotonin-noradrenaline reuptake inhibitors reduced pain more than anticonvulsants) did not change.

Did Searching ClinicalTrials.gov Change the Strength of Evidence for this Comparison for Either Pain or Quality of Life

Searching ClinicalTrials.gov did not yield any new data that influenced the strength of evidence grading for the outcomes of pain and quality of life.

Table 34. Studies comparing an anticonvulsant with a serotonin-noradrenaline reuptake inhibitor identified through ClinicalTrials.gov, published literature, or both

Source	Publication Author, Year	NCT Number	Matched by	Study Completion Date in CT.gov	Reported Results in CT.gov?	Sample Size	Followup
Published literature only	Jia, 2006[65a]	Not found	NA	NA	NA	132	2 weeks
Both published literature and CT.gov	Tesfaye, 2013[30]	NCT01089556	NCT number	Nov 2011	Yes	811	8 weeks
	Boyle, 2012[31a]	NCT00370656	NCT number	May 2009	No	90	5 weeks
CT.gov only	None identified	NCT00837941	NA	Sep 2009	No	30[b]	NA
	None identified	NCT01116531	NA	Dec 2012	No	40[b]	NA

[a] Study was identified in a systematic review by Griebeler, 2014.[1]
[b] Planned enrollment. Study was withdrawn prior to enrollment.
CT.gov = ClinicalTrials.gov; NA = not applicable

Table 35. Comparison of the pain and quality of life results reported in the publication and the ClinicalTrials.gov record[a] and/or additional results reported only in ClinicalTrials.gov

Publication Author, Year	NCT Number	Pain Scale	Did Pain Results Differ?	Describe How Pain Results Differed	QOL Scale	Did QOL Results Differ?	Describe How QOL Results Differed
Tesfaye, 2013[30]	NCT01089556	BPI-MSF	No	Both the CT.gov record and the publication reported the same change from baseline and mean between-group difference for the BPI-MSF 24-hour average pain score.	NE	NE	NE

[a] For studies that reported results in ClinicalTrials.gov.
BPI-MSF = Brief Pain Inventory – Modified Short Form; CT.gov = ClinicalTrials.gov; NE = not evaluated; QOL = quality of life

Anticonvulsants Versus Tricyclic Antidepressants

Detailed Results

We identified four studies (all with available data) that compared an anticonvulsant with a tricyclic antidepressant among patients with diabetic peripheral neuropathy (Table 36). Two studies compared pregabalin with amitriptyline,[31, 66] one compared gabapentin with amitriptyline,[67] and one compared lamotrigine with amitriptyline.[68]

Three studies were found in the published literature only.[66-68] Two were published prior to 2008.[67, 68] The other study was conducted in India, and does not appear to have been registered in any clinical trials registry.[66]

One study was found in both the published literature and in ClinicaTrials.gov.[31] This study did not post any results in ClinicalTrials.gov.

Did Searching ClinicalTrials.gov Change the Overall Conclusion for this Comparison for Either Pain or Quality of Life

ClinicalTrials.gov did not yield any new data for the included publications nor did it yield any new studies. Therefore, the overall conclusion (i.e., tricyclic antidepressants reduced pain more than anticonvulsants in the short term) did not change.

Did Searching ClinicalTrials.gov Change the Strength of Evidence for this Comparison for Either Pain or Quality of Life

Searching ClinicalTrials.gov did not yield any new data that influenced the strength of evidence grading for the outcomes of pain and quality of life.

Table 36. Studies comparing an anticonvulsant with a tricyclic antidepressant identified through ClinicalTrials.gov, published literature, or both

Source	Publication Author, Year	NCT Number	Matched by	Study Completion Date In CT.gov	Reported Results in CT.gov?	Sample Size	Followup
Published literature only	Bansal, 2009[66a]	Not found	NA	NA	NA	51	5 weeks
	Morello, 1999[67a]	Not found	NA	NA	NA	25	6 weeks
	Jose, 2007[68a]	Not found	NA	NA	NA	53	14 weeks
Both published literature and CT.gov	Boyle, 2012[31a]	NCT00370656	NCT number	May 2009	No	90	5 weeks

[a] Study was identified in a systematic review by Griebeler, 2014.[1]
CT.gov = ClinicalTrials.gov; NA = not applicable

Anticonvulsants Versus Topical Agents

Detailed Results

We identified one study that compared an anticonvulsant (gabapentin) with a topical agent (lidocaine) among patients with diabetic peripheral neuropathy (Table 37). This study was found only in ClinicaTrials.gov (NCT00904202) and did not post any results in ClinicalTrials.gov.

Did Searching ClinicalTrials.gov Change the Overall Conclusion for this Comparison for Either Pain or Quality of Life

ClinicalTrials.gov did not yield any new data for the included publications nor did it yield any new studies with results. Therefore, we are still unable to draw a conclusion about the comparative effectiveness of anticonvulsants and topical agents on pain and quality of life.

Did Searching ClinicalTrials.gov Change the Strength of Evidence for this Comparison for Either Pain or Quality of Life

Searching ClinicalTrials.gov did not yield any new data that influenced the strength of evidence grading for the outcomes of pain and quality of life.

Table 37. Studies comparing an anticonvulsant with a topical agent identified through ClinicalTrials.gov, published literature, or both

Source	Publication Author, Year	NCT Number	Matched by	Study Completion Date In CT.gov	Reported Results in CT.gov?	Sample Size	Followup
CT.gov only	None identified	NCT00904202	NA	Jun 2003	No	62	5 weeks

CT.gov = ClinicalTrials.gov; NA = not applicable

Antidepressants Versus Antidepressants

Detailed Results

We identified one study that compared two different antidepressants (amitriptyline versus a duloxetine) among patients with diabetic peripheral neuropathy (Table 38). This study was found in the published literature and in ClinicalTrials.gov,[31] but did not report results in ClinicalTrials.gov.

Did Searching ClinicalTrials.gov Change the Overall Conclusion for this Comparison for Either Pain or Quality of Life

ClinicalTrials.gov did not yield any new data for the included publications nor did it yield any new studies. Therefore, we did not change the overall conclusions for pain or quality of life.

Did Searching ClinicalTrials.gov Change the Strength of Evidence for this Comparison for Either Pain or Quality of Life

Searching ClinicalTrials.gov did not yield any new data that influenced the strength of evidence grading for the outcomes of pain and quality of life.

Table 38. Studies comparing two antidepressants identified through ClinicalTrials.gov, published literature, or both

Source	Publication Author, Year	NCT Number	Matched by	Study Completion Date in CT.gov	Reported Results in CT.gov?	Sample Size	Followup
Both published literature and CT.gov	Boyle, 2012[31a]	NCT00370656	NCT number	May 2009	No	90	5 weeks

[a] Study was identified in a systematic review by Griebeler, 2014.[1]

CT.gov = ClinicalTrials.gov; NA = not applicable

Discussion

Key Findings

Question 1. Description of the Identified Studies

We identified 53 studies comparing the effectiveness of treatment options for symptoms of diabetic peripheral neuropathy by searching ClinicalTrials.gov. We matched 28 of the studies to 28 publications. These studies were completed between 1999 and 2013. We matched 17 (61%) records using the NCT number, 7 (25%) through the publication link in ClinicalTrials.gov, and 4 (14%) by using search terms in PubMed.

We were unable to identify a publication for 25 ClinicalTrials.gov records. Of these 25 records, 18 were completed, two were withdrawn, three were recruiting, and two have an unknown status. Seven of the 18 (39%) completed studies had posted results in ClinicalTrials.gov. Of the 18 completed studies, 10 (55%) were completed within the last 4 years.

About one-third (18 out of 53 records; 34%) of the ClinicalTrials.gov records posted results.

Question 2. Comparison of Data Elements and Results from ClinicalTrials.gov and Matched Publications

We were able to compare 25 ClinicalTrials.gov records with 25 publications. We noted discrepancies between the ClinicalTrials.gov record and the publication in terms of the number enrolled (8 studies, 32%) and adverse event reporting (2 of 10 studies with posted results, 20%). Similar to another review,[69] discrepancies were rarely explained.

We also noted that the primary outcome changed from the ClinicalTrials.gov record to the publication in 14 of the 25 studies (56%). The changes to the primary outcomes included specifying the measure (e.g., 11-point numerical rating scale) and/or the metric (e.g., change from baseline) used to evaluate pain. In contrast to other studies that evaluated selective reporting outcome bias,[70] we did not find evidence that studies were selecting outcomes based on statistical significance.

Question 3. Description of Incomplete or Discontinued Trials

We found two studies (NCT00837941 and NCT01116531) that were withdrawn prior to enrollment. Neither study provided a rationale for withdrawal. Three studies were recruiting (NCT02363803, NCT02372578, NCT02460107). Two studies had an estimated completion date in the future. During the writing of this report, the status of third study (NCT02372578) changed to terminated due to futility analysis.

Question 4. Incorporating the ClinicalTrials.gov Findings into the Review

Our analysis comparing the effectiveness of pregabalin with placebo for reducing pain showed different results by publication status. Pooled results from the published studies showed that pregabalin was more effective than placebo at reducing pain, but the unpublished studies did not indicate a statistically significant difference. However, it is not clear if this reflects

publication bias or a temporal trend. One study has suggested that the effectiveness of placebo at reducing neuropathic pain has increased over time,[71] which could partially explain the temporal trend of relative decreasing pregabalin effectiveness we observed. Additionally, we found in ClinicalTrials.gov six other studies without results (NCT00838799, NCT01504412, NCT01770964, NCT01928381, NCT01939366, and NCT02372578). Most of these studies were completed within the last 3 years. The publication of the results of these studies may or may not lead to different conclusions about the effectiveness of pregabalin in reducing pain among patients with diabetic peripheral neuropathy. We were unable to pool the quality of life results comparing pregabalin with placebo because of the limited outcomes reporting. However, the quality of life results may also suffer from publication bias.

With the exception of the pregabalin versus placebo comparison, our search of ClinicalTrials.gov had little to no effect on the overall conclusions and strength of evidence grading.

For two comparisons, we found selective outcomes reporting for quality of life (i.e., quality of life was listed as an outcome in the ClinicalTrials.gov record but not reported on in the publication). However, we had already suspected reporting bias because many studies that did report on quality of life did so insufficiently. Therefore, the evidence for selective outcomes reporting did not change our strength of evidence grading.

We suspected publication bias for the following comparisons: (1) oxycodone versus placebo in terms of pain and (2) clonidine versus placebo in terms of pain. For both of these comparisons, we found unpublished studies on ClinicalTrials.gov. We downgraded the reporting bias domain to "Suspected," but otherwise the overall strength of evidence remained the same.

Our search of ClinicalTrials.gov did not change the overall conclusions and the overall evidence grade for the remaining comparisons. For these comparisons, searching ClinicalTrials.gov did not provide any additional information that would make us change our conclusions.

We found 10 studies with a publication and posted results on ClinicalTrials.gov. Although different metrics were reported in the publication and ClinicalTrials.gov, we were usually able to derive similar conclusions.

Our search of ClinicalTrials.gov never strengthened the conclusions or evidence grades.

Limitations

There are several limitations to using the ClinicalTrials.gov registry. First, it can be time consuming to match ClinicalTrials.gov records with publications when the NCT number is not included in the publication. In a study by Zarin and colleagues in 2011, of the 2324 ClinicalTrials.gov results entries, only 14% were linked to a PubMed citation through the NCT number.[3] In our study, we were able to match 28 ClinicalTrials.gov records to 28 publications. Most of our matches were made through the NCT number or the publication link in ClinicalTrials.gov, but some were made by searching PubMed. Using search terms in PubMed to identify a matching publication can be problematic. Not all ClinicalTrials.gov records list a person as the principal investigator. Therefore, the investigator's name cannot always be used to limit the search for a publication on Medline. Sometimes, not enough information is reported either in the publication or in the ClinicalTrials.gov record to confidently decide if there is a match or not. Because of these issues, we could have missed some studies and misclassified the records as "unmatched."

Secondly, there is limited reporting in ClinicalTrials.gov. The limited reporting complicates all steps of this process, including screening, matching, data abstracting, assessing the risk of bias, and synthesizing the results. In particular, the limited reporting of results in ClinicalTrials.gov hindered our ability to use the data collected from ClinicalTrials.gov. Seventeen of the 46 (37%) completed studies identified in ClinicalTrials.gov had posted results. We were often able to identify unpublished studies, but had no results to inform our conclusions and/or evidence grades.

Thirdly, comparing results reported in a publication with results posted on ClinicalTrials.gov was hampered by the use of different metrics (baseline, final, change from baseline) and limited reporting in both sources.

Lastly, not all trials are registered in ClinicalTrials.gov. In our review, we found 36 studies in the published literature that were not registered in ClinicalTrials.gov. Most of these studies were older (prior to 2008), but four were more recent. These four studies were all conducted outside the U.S.

Next Steps

Reporting bias continues to be a problem for systematic reviews. In its current state, ClinicalTrials.gov does not help to ameliorate the problem of reporting bias. In our review of randomized controlled trials of treatment options for symptoms of diabetic peripheral neuropathy, our search of ClinicalTrials.gov was mostly useful in confirming suspected reporting biases and did not meaningfully change either the overall conclusions or the strength of evidence grading.

There are several limitations to searching ClinicalTrials.gov. First, including a search of ClinicalTrials.gov takes additional time to screen and abstract data, as well as to match records to published articles. The total time is dependent on the specific questions being addressed. In this project, we estimate that it took 10 to 45 minutes per additional eligible study identified. Some tasks, such as matching ClinicalTrials.gov registries with publications, can be time consuming. More consistent reporting of the NCT number in the peer-reviewed publication will help with reducing the time needed to complete this task.

Second, most of the studies registered in ClinicalTrials.gov are clinical trials. Therefore, searching ClinicalTrials.gov may not be as useful for systematic reviews of non-interventional studies.

Third, the usefulness of searching ClinicalTrials.gov is reduced by the limited reporting of outcomes data. Although we were able to identify unpublished studies, these studies often did not provide outcomes data we could use in our systematic review. In November 2014, the U.S. Department of Health and Human Services issued a Notice of Proposed Rulemaking that could affect results reporting in ClinicalTrials.gov.[72] The final rule became available on September 16, 2016.[73] When implemented, this new rule will require results reporting for any applicable clinical trial, regardless of the intervention's status with the Food and Drug Administration. Results should consist of demographic and baseline characteristics, primary and secondary outcomes, including appropriate statistical tests, and adverse events. More complete results reporting in ClinicalTrials.gov could expand the utility of the registry.

Researchers conducting systematic reviews of interventional studies should account for reporting bias in their analyses. But, until outcomes data are more consistently being reported, the usefulness of searching ClinicalTrials.gov will be limited. We are optimistic of the future of ClinicalTrials.gov and look forward to the implementation of the final rule.

References

1. Griebeler ML, Morey-Vargas OL, Brito JP, et al. Pharmacologic interventions for painful diabetic neuropathy: An umbrella systematic review and comparative effectiveness network meta-analysis. Ann Intern Med. 2014 Nov 4;161(9):639-49. doi: 10.7326/m14-0511. PMID: 25364885.
2. Hartung DM, Zarin DA, Guise JM, et al. Reporting discrepancies between the ClinicalTrials.gov results database and peer-reviewed publications. Ann Intern Med. 2014 Apr 1;160(7):477-83. doi: 10.7326/m13-0480. PMID: 24687070.
3. Zarin DA, Tse T, Williams RJ, et al. The ClinicalTrials.gov results database--update and key issues. N Engl J Med. 2011 Mar 3;364(9):852-60. doi: 10.1056/NEJMsa1012065. PMID: 21366476.
4. Parsons B, Li C. The efficacy of pregabalin in patients with moderate and severe pain due to diabetic peripheral neuropathy. Curr Med Res Opin. 2016 May;32(5):929-37. doi: 10.1185/03007995.2016.1151776. PMID: 26854578.
5. Satoh J, Yagihashi S, Baba M, et al. Efficacy and safety of pregabalin for treating neuropathic pain associated with diabetic peripheral neuropathy: a 14 week, randomized, double-blind, placebo-controlled trial. Diabet Med. 2011 Jan;28(1):109-16. doi: 10.1111/j.1464-5491.2010.03152.x. PMID: 21166852.
6. Schwartz S, Etropolski MS, Shapiro DY, et al. A pooled analysis evaluating the efficacy and tolerability of tapentadol extended release for chronic, painful diabetic peripheral neuropathy. Clin Drug Investig. 2015 Feb;35(2):95-108. doi: 10.1007/s40261-014-0249-3. PMID: 25503082.
7. Vinik AI, Shapiro DY, Rauschkolb C, et al. A randomized withdrawal, placebo-controlled study evaluating the efficacy and tolerability of tapentadol extended release in patients with chronic painful diabetic peripheral neuropathy. Diabetes Care. 2014 Aug;37(8):2302-9. doi: 10.2337/dc13-2291. PMID: 24848284.
8. Schwartz S, Etropolski M, Shapiro DY, et al. Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results of a randomized-withdrawal, placebo-controlled trial. Curr Med Res Opin. 2011 Jan;27(1):151-62. doi: 10.1185/03007995.2010.537589. PMID: 21162697.
9. Rauck R, Makumi CW, Schwartz S, et al. A randomized, controlled trial of gabapentin enacarbil in subjects with neuropathic pain associated with diabetic peripheral neuropathy. Pain Pract. 2013 Jul;13(6):485-96. doi: 10.1111/papr.12014. PMID: 23186035.
10. Sandercock D, Cramer M, Biton V, et al. A gastroretentive gabapentin formulation for the treatment of painful diabetic peripheral neuropathy: efficacy and tolerability in a double-blind, randomized, controlled clinical trial. Diabetes Res Clin Pract. 2012 Sep;97(3):438-45. doi: 10.1016/j.diabres.2012.03.010. PMID: 22497967.
11. Arezzo JC, Rosenstock J, Lamoreaux L, et al. Efficacy and safety of pregabalin 600 mg/d for treating painful diabetic peripheral neuropathy: a double-blind placebo-controlled trial. BMC Neurol. 2008;8:33. doi: 10.1186/1471-2377-8-33. PMID: 18796160.
12. Ziegler D, Duan WR, An G, et al. A randomized double-blind, placebo-, and active-controlled study of T-type calcium channel blocker ABT-639 in patients with diabetic peripheral neuropathic pain. Pain. 2015 Oct;156(10):2013-20. doi: 10.1097/j.pain.0000000000000263. PMID: 26067585.

13. Jiang W, Ladd S, Martsberger C, et al. Effects of pregabalin on heart rate variability in patients with painful diabetic neuropathy. J Clin Psychopharmacol. 2011 Apr;31(2):207-13. doi: 10.1097/JCP.0b013e31820f4f57. PMID: 21346609.

14. Raskin P, Huffman C, Toth C, et al. Pregabalin in patients with inadequately treated painful diabetic peripheral neuropathy: a randomized withdrawal trial. Clin J Pain. 2014 May;30(5):379-90. doi: 10.1097/AJP.0b013e31829ea1a1. PMID: 23887339.

15. Rauck RL, Shaibani A, Biton V, et al. Lacosamide in painful diabetic peripheral neuropathy: a phase 2 double-blind placebo-controlled study. Clin J Pain. 2007 Feb;23(2):150-8. doi: 10.1097/01.ajp.0000210957.39621.b2. PMID: 17237664.

16. Wymer JP, Simpson J, Sen D, et al. Efficacy and safety of lacosamide in diabetic neuropathic pain: an 18-week double-blind placebo-controlled trial of fixed-dose regimens. Clin J Pain. 2009 Jun;25(5):376-85. doi: 10.1097/AJP.0b013e318196d2b6. PMID: 19454870.

17. Shaibani A, Fares S, Selam JL, et al. Lacosamide in painful diabetic neuropathy: an 18-week double-blind placebo-controlled trial. J Pain. 2009 Aug;10(8):818-28. doi: 10.1016/j.jpain.2009.01.322. PMID: 19409861.

18. Ziegler D, Hidvegi T, Gurieva I, et al. Efficacy and safety of lacosamide in painful diabetic neuropathy. Diabetes Care. 2010 Apr;33(4):839-41. doi: 10.2337/dc09-1578. PMID: 20067958.

19. Gao Y, Guo X, Han P, et al. Treatment of patients with diabetic peripheral neuropathic pain in China: a double-blind randomised trial of duloxetine vs. placebo. Int J Clin Pract. 2015 Sep;69(9):957-66. doi: 10.1111/ijcp.12641. PMID: 25939897.

20. Gao Y, Ning G, Jia WP, et al. Duloxetine versus placebo in the treatment of patients with diabetic neuropathic pain in China. Chin Med J (Engl). 2010 Nov;123(22):3184-92. PMID: 21163113.

21. Yasuda H, Hotta N, Nakao K, et al. Superiority of duloxetine to placebo in improving diabetic neuropathic pain: Results of a randomized controlled trial in Japan. J Diabetes Investig. 2011 Apr 7;2(2):132-9. doi: 10.1111/j.2040-1124.2010.00073.x. PMID: 24843472.

22. Rowbotham MC, Arslanian A, Nothaft W, et al. Efficacy and safety of the alpha4beta2 neuronal nicotinic receptor agonist ABT-894 in patients with diabetic peripheral neuropathic pain. Pain. 2012 Apr;153(4):862-8. doi: 10.1016/j.pain.2012.01.009. PMID: 22386472.

23. Freeman R, Raskin P, Hewitt DJ, et al. Randomized study of tramadol/acetaminophen versus placebo in painful diabetic peripheral neuropathy. Curr Med Res Opin. 2007 Jan;23(1):147-61. doi: 10.1185/030079906x162674. PMID: 17257476.

24. Kulkantrakorn K, Lorsuwansiri C, Meesawatsom P. 0.025% capsaicin gel for the treatment of painful diabetic neuropathy: a randomized, double-blind, crossover, placebo-controlled trial. Pain Pract. 2013 Jul;13(6):497-503. doi: 10.1111/papr.12013. PMID: 23228119.

25. Campbell CM, Kipnes MS, Stouch BC, et al. Randomized control trial of topical clonidine for treatment of painful diabetic neuropathy. Pain. 2012 Sep;153(9):1815-23. doi: 10.1016/j.pain.2012.04.014. PMID: 22683276.

26. Shaibani AI, Pope LE, Thisted R, et al. Efficacy and safety of dextromethorphan/quinidine at two dosage levels for diabetic neuropathic pain: a double-blind, placebo-controlled, multicenter study. Pain Med. 2012 Feb;13(2):243-54. doi: 10.1111/j.1526-4637.2011.01316.x. PMID: 22314263.

27. Bertorini TE, Alzagatiti BI, Horner LH. Electrophysiological effects of mexiletine in painful neuropathy. Nerve. 1998;21(11):1576.

28. Yuan RY, Sheu JJ, Yu JM, et al. Botulinum toxin for diabetic neuropathic pain: a randomized double-blind crossover trial. Neurology. 2009 Apr 28;72(17):1473-8. doi: 10.1212/01.wnl.0000345968.05959.cf. PMID: 19246421.

29. Toth C, Mawani S, Brady S, et al. An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic peripheral neuropathic pain. Pain. 2012 Oct;153(10):2073-82. doi: 10.1016/j.pain.2012.06.024. PMID: 22921260.

30. Tesfaye S, Wilhelm S, Lledo A, et al. Duloxetine and pregabalin: high-dose monotherapy or their combination? The "COMBO-DN study"--a multinational, randomized, double-blind, parallel-group study in patients with diabetic peripheral neuropathic pain. Pain. 2013 Dec;154(12):2616-25. doi: 10.1016/j.pain.2013.05.043. PMID: 23732189.

31. Boyle J, Eriksson ME, Gribble L, et al. Randomized, placebo-controlled comparison of amitriptyline, duloxetine, and pregabalin in patients with chronic diabetic peripheral neuropathic pain: impact on pain, polysomnographic sleep, daytime functioning, and quality of life. Diabetes Care. 2012 Dec;35(12):2451-8. doi: 10.2337/dc12-0656. PMID: 22991449.

32. Gorson KC, Schott C, Herman R, et al. Gabapentin in the treatment of painful diabetic neuropathy: a placebo controlled, double blind, crossover trial. J Neurol Neurosurg Psychiatry. 1999 Feb;66(2):251-2. PMID: 10071116.

33. Backonja M, Beydoun A, Edwards KR, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. JAMA. 1998 Dec 2;280(21):1831-6. PMID: 9846777.

34. Simpson DA. Gabapentin and venlafaxine for the treatment of painful diabetic neuropathy. J Clin Neuromuscul Dis. 2001 Dec;3(2):53-62. PMID: 19078655.

35. Karmakar S, Rashidian H, Chan C, et al. Investigating the role of neuropathic pain relief in decreasing gait variability in diabetes mellitus patients with neuropathic pain: a randomized, double-blind crossover trial. J Neuroeng Rehabil. 2014;11:125. doi: 10.1186/1743-0003-11-125. PMID: 25139539.

36. Rosenstock J, Tuchman M, LaMoreaux L, et al. Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. Pain. 2004 Aug;110(3):628-38. doi: 10.1016/j.pain.2004.05.001. PMID: 15288403.

37. Lesser H, Sharma U, LaMoreaux L, et al. Pregabalin relieves symptoms of painful diabetic neuropathy: a randomized controlled trial. Neurology. 2004 Dec 14;63(11):2104-10. PMID: 15596757.

38. Freynhagen R, Strojek K, Griesing T, et al. Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial of flexible- and fixed-dose regimens. Pain. 2005 Jun;115(3):254-63. doi: 10.1016/j.pain.2005.02.032. PMID: 15911152.

39. Richter RW, Portenoy R, Sharma U, et al. Relief of painful diabetic peripheral neuropathy with pregabalin: a randomized, placebo-controlled trial. J Pain. 2005 Apr;6(4):253-60. doi: 10.1016/j.jpain.2004.12.007. PMID: 15820913.

40. Tolle T, Freynhagen R, Versavel M, et al. Pregabalin for relief of neuropathic pain associated with diabetic neuropathy: a randomized, double-blind study. Eur J Pain. 2008 Feb;12(2):203-13. doi: 10.1016/j.ejpain.2007.05.003. PMID: 17631400.

41. Thienel U, Neto W, Schwabe SK, et al. Topiramate in painful diabetic polyneuropathy: findings from three double-blind placebo-controlled trials. Acta Neurol Scand. 2004 Oct;110(4):221-31. doi: 10.1111/j.1600-0404.2004.00338.x. PMID: 15355485.

42. Raskin P, Donofrio PD, Rosenthal NR, et al. Topiramate vs placebo in painful diabetic neuropathy: analgesic and metabolic effects. Neurology. 2004 Sep 14;63(5):865-73. PMID: 15365138.

43. Freeman R, McIntosh KA, Vijapurkar U, et al. Topiramate and physiologic measures of nerve function in polyneuropathy. Acta Neurol Scand. 2007 Apr;115(4):222-31. doi: 10.1111/j.1600-0404.2006.00789.x. PMID: 17376119.

44. Raskin J, Pritchett YL, Wang F, et al. A double-blind, randomized multicenter trial comparing duloxetine with placebo in the management of diabetic peripheral neuropathic pain. Pain Med. 2005 Sep-Oct;6(5):346-56. doi: 10.1111/j.1526-4637.2005.00061.x. PMID: 16266355.

45. Goldstein DJ, Lu Y, Detke MJ, et al. Duloxetine vs. placebo in patients with painful diabetic neuropathy. Pain. 2005 Jul;116(1-2):109-18. doi: 10.1016/j.pain.2005.03.029. PMID: 15927394.

46. Wernicke JF, Pritchett YL, D'Souza DN, et al. A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. Neurology. 2006 Oct 24;67(8):1411-20. doi: 10.1212/01.wnl.0000240225.04000.1a. PMID: 17060567.

47. Hanna M, O'Brien C, Wilson MC. Prolonged-release oxycodone enhances the effects of existing gabapentin therapy in painful diabetic neuropathy patients. Eur J Pain. 2008 Aug;12(6):804-13. doi: 10.1016/j.ejpain.2007.12.010. PMID: 18262450.

48. Gimbel JS, Richards P, Portenoy RK. Controlled-release oxycodone for pain in diabetic neuropathy: a randomized controlled trial. Neurology. 2003 Mar 25;60(6):927-34. PMID: 12654955.

49. Watson CP, Moulin D, Watt-Watson J, et al. Controlled-release oxycodone relieves neuropathic pain: a randomized controlled trial in painful diabetic neuropathy. Pain. 2003 Sep;105(1-2):71-8. PMID: 14499422.

50. Jensen MP, Friedman M, Bonzo D, et al. The validity of the neuropathic pain scale for assessing diabetic neuropathic pain in a clinical trial. Clin J Pain. 2006 Jan;22(1):97-103. PMID: 16340598.

51. Niesters M, Proto PL, Aarts L, et al. Tapentadol potentiates descending pain inhibition in chronic pain patients with diabetic polyneuropathy. Br J Anaesth. 2014 Jul;113(1):148-56. doi: 10.1093/bja/aeu056. PMID: 24713310.

52. Harati Y, Gooch C, Swenson M, et al. Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy. Neurology. 1998 Jun;50(6):1842-6. PMID: 9633738.

53. . Treatment of painful diabetic neuropathy with topical capsaicin. A multicenter, double-blind, vehicle-controlled study. The Capsaicin Study Group. Arch Intern Med. 1991 Nov;151(11):2225-9. PMID: 1953227.

54. Scheffler NM, Sheitel PL, Lipton MN. Treatment of painful diabetic neuropathy with capsaicin 0.075%. J Am Podiatr Med Assoc. 1991 Jun;81(6):288-93. doi: 10.7547/87507315-81-6-288. PMID: 1920093.

55. Tandan R, Lewis GA, Krusinski PB, et al. Topical capsaicin in painful diabetic neuropathy. Controlled study with long-term follow-up. Diabetes Care. 1992 Jan;15(1):8-14. PMID: 1737545.

56. Chad DA, Aronin N, Lundstrom R, et al. Does capsaicin relieve the pain of diabetic neuropathy? Pain. 1990 Sep;42(3):387-8. PMID: 1701234.

57. Nelson KA, Park KM, Robinovitz E, et al. High-dose oral dextromethorphan versus placebo in painful diabetic neuropathy and postherpetic neuralgia. Neurology. 1997 May;48(5):1212-8. PMID: 9153445.

58. Sang CN, Booher S, Gilron I, et al. Dextromethorphan and memantine in painful diabetic neuropathy and postherpetic neuralgia: efficacy and dose-response trials. Anesthesiology. 2002 May;96(5):1053-61. PMID: 11981142.

59. Dejgard A, Petersen P, Kastrup J. Mexiletine for treatment of chronic painful diabetic neuropathy. Lancet. 1988 Jan 2-9;1(8575-6):9-11. PMID: 2891940.

60. Stracke H, Meyer UE, Schumacher HE, et al. Mexiletine in the treatment of diabetic neuropathy. Diabetes Care. 1992 Nov;15(11):1550-5. PMID: 1468285.

61. Matsuoka K, Kanazawa Y, Ohtake M, et al. Double blind trial of mexiletine on painful diabetic polyneuropathy. Diabetologia. 1997 1997;40:A559.

62. Oskarsson P, Ljunggren JG, Lins PE. Efficacy and safety of mexiletine in the treatment of painful diabetic neuropathy. The Mexiletine Study Group. Diabetes Care. 1997 Oct;20(10):1594-7. PMID: 9314641.

63. Wright JM, Oki JC, Graves L, 3rd. Mexiletine in the symptomatic treatment of diabetic peripheral neuropathy. Ann Pharmacother. 1997 Jan;31(1):29-34. PMID: 8997461.

64. Ghasemi M, Ansari M, Basiri K, et al. The effects of intradermal botulinum toxin type a injections on pain symptoms of patients with diabetic neuropathy. J Res Med Sci. 2014 Feb;19(2):106-11. PMID: 24778662.

65. Jia H, Li Q, Song D, et al. Effects of venlafaxine and carbamazepine for painful peripheral diabetic neuropathy: a randomized double blind and double dummy controlled multicenter trial. Chinese Journal of Evidence-Based Medicine. 2006;6:321-7.

66. Bansal D, Bhansali A, Hota D, et al. Amitriptyline vs. pregabalin in painful diabetic neuropathy: a randomized double blind clinical trial. Diabet Med. 2009 Oct;26(10):1019-26. doi: 10.1111/j.1464-5491.2009.02806.x. PMID: 19900234.

67. Morello CM, Leckband SG, Stoner CP, et al. Randomized double-blind study comparing the efficacy of gabapentin with amitriptyline on diabetic peripheral neuropathy pain. Arch Intern Med. 1999 Sep 13;159(16):1931-7. PMID: 10493324.

68. Jose VM, Bhansali A, Hota D, et al. Randomized double-blind study comparing the efficacy and safety of lamotrigine and amitriptyline in painful diabetic neuropathy. Diabet Med. 2007 Apr;24(4):377-83. doi: 10.1111/j.1464-5491.2007.02093.x. PMID: 17335465.

69. Dwan K, Altman DG, Cresswell L, et al. Comparison of protocols and registry entries to published reports for randomised controlled trials. Cochrane Database Syst Rev. 2011(1):MR000031. doi: 10.1002/14651858.MR000031.pub2. PMID: 21249714.

70. Mathieu S, Boutron I, Moher D, et al. Comparison of registered and published primary outcomes in randomized controlled trials. JAMA. 2009 Sep 2;302(9):977-84. doi: 10.1001/jama.2009.1242. PMID: 19724045.

71. Tuttle AH, Tohyama S, Ramsay T, et al. Increasing placebo responses over time in U.S. clinical trials of neuropathic pain. Pain. 2015 Dec;156(12):2616-26. doi: 10.1097/j.pain.0000000000000333. PMID: 26307858.

72. National Institutes of Health. HHS and NIH take steps to enhance transparency of clinical trial results. 2014. https://www.nih.gov/news-events/news-releases/hhs-nih-take-steps-enhance-transparency-clinical-trial-results. Accessed on July 20 2016.

73. Zarin DA, Tse T, Williams RJ, et al. Trial Reporting in ClinicalTrials.gov - The Final Rule. N Engl J Med. 2016 Sep 16doi: 10.1056/NEJMsr1611785. PMID: 27635471.