Comparative Effectiveness Review
Number 187

Preventing Complications and Treating Symptoms of Diabetic Peripheral Neuropathy

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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.

This report may periodically be assessed for the currency of conclusions. If an assessment is done, the resulting surveillance report describing the methodology and findings will be found on the Effective Health Care Program Web site at www.effectivehealthcare.ahrq.gov. Search on the title of the report.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

If you have comments on this systematic review, 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 email to epc@ahrq.hhs.gov.

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Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest identified.

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Preventing Complications and Treating Symptoms of Diabetic Peripheral Neuropathy

Structured Abstract

Objectives. To assess benefits and harms of interventions for preventing diabetic peripheral neuropathy (DPN) complications and treatment of DPN symptoms.

Data sources. We searched PubMed® and the Cochrane Database of Systematic Reviews for systematic reviews from January 1, 2011, to October 12, 2015. For questions for which we did not identify high-quality relevant systematic reviews, we searched for primary studies using PubMed®, Embase®, and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to May 24, 2016. We searched ClinicalTrials.gov for pharmacologic treatment of DPN symptoms.

Review methods. For the prevention of DPN complications, we included a systematic review of primary randomized controlled trials and nonrandomized studies with a concurrent comparison group. For the treatment of DPN symptoms, we included a systematic review of primary parallel or crossover randomized controlled trials that were blinded for interventions where blinding was possible from the published literature and ClinicalTrials.gov. Two reviewers evaluated studies for eligibility, serially abstracted data using standardized forms, independently evaluated the risk of bias of the reviews and studies, and graded the strength of evidence (SOE) for critical outcomes (foot ulcers, amputations, falls, pain, and quality of life).

Results. We included 62 studies (30 studies from an existing systematic review and 32 newly identified studies reported in 37 articles) for prevention of DPN complications and 129 studies (57 studies from an existing systematic review, 47 newly identified additional studies reported in 48 articles, and 25 studies from ClinicalTrials.gov) for treatment of DPN symptoms. For prevention of DPN complications, although intensive glycemic control (as defined by each individual study) does not prevent foot ulcers more than standard control for type 2 diabetes, it prevents lower extremity amputations (moderate SOE). Intensive glycemic control had higher rates of hypoglycemia than standard treatment. For nonpharmacologic treatment options, specific types of therapeutic footwear (moderate SOE), integrated foot care (low SOE), home monitoring of foot skin temperature (moderate SOE), and specific types of surgical interventions (low SOE) are effective for lowering incidence and/or recurrence of foot ulcers. There is insufficient evidence to evaluate whether physical therapy, exercise, or balance training reduces falls. For treatment of DPN pain symptoms, the serotonin-noradrenaline reuptake inhibitors duloxetine and venlafaxine (moderate SOE), the anticonvulsants pregabalin and oxcarbazepine (low SOE), the drug classes of tricyclic antidepressants (low SOE) and atypical opioids (tramadol and tapentadol) (low SOE), and the injectable neurotoxin botulinum toxin (low SOE) are more effective than placebo for reducing pain in short-term followup. For harms, all effective oral drugs had more than 9 percent dropouts due to adverse effects. For nonpharmacologic treatments, alpha-lipoic acid is more effective than placebo (low SOE) and spinal cord stimulation is more effective than usual care for pain (low SOE), but spinal cord stimulation had risks of serious complications. We were unable to draw conclusions about quality of life for any of the treatments due to incomplete reporting (insufficient SOE).

Conclusions. For prevention of complications, intensive glycemic control is more effective than standard control for prevention of amputation, and home monitoring of foot skin temperature, therapeutic footwear, and integrated interventions are effective for preventing incidence and/or recurrence of foot ulcers. For reducing pain, the only class with moderate strength of evidence was serotonin-noradrenaline reuptake inhibitors; pregabalin and oxcarbazepine, atypical opioids, botulinum toxin, alpha-lipoic acid and spinal cord stimulation are more effective than placebo but with low SOE. However, studies were generally short term with unclear risk of bias, we could not draw conclusions for quality of life, all oral drugs had significant side effects, opioids have significant long-term risks including abuse, and spinal cord stimulation has risks of serious complications.

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Introduction

Background

Diabetic Peripheral Neuropathy

According to an estimate from the Centers for Disease Control (CDC), 29.1 million people, or 9.3 percent of the U.S. population, have diabetes.[1] Thirty to 50 percent of patients with diabetes will eventually develop nerve damage called neuropathy.[2] Clinical diabetic neuropathy has been categorized into distinct syndromes according to the neurologic distribution, but many overlapping syndromes occur. Feldman et al.[3] classified diabetic neuropathy into several categories:

1) Distal symmetric sensorimotor polyneuropathy [4]
2) Autonomic neuropathy
3) Thoracic and lumbar polyradiculopathies due to nerve root disease
4) Individual cranial and peripheral nerve involvement causing focal mononeuropathies
5) Asymmetric involvement of multiple peripheral nerves, resulting in a mononeuropathy multiplex

Studies have found that peripheral neuropathy (which includes any disorder of the peripheral nervous system, including polyneuropathy, polyradiculopathies, and mononeuropathy, as listed above) occurs in up to half of the population with diabetes. In one study of patients with diabetic neuropathy, more than 50 percent had distal symmetric sensorimotor polyneuropathy, and other neuropathies included median mononeuropathies (25%), autonomic neuropathy (7%), thoracic and lumbar polyradiculopathy and cranial mononeuropathies (3%).[5] A recent expert panel report from the Diabetic Neuropathy Study Group of the European Association for the Study of Diabetes (NEURODIAB) defined diabetic polyneuropathy as a "symmetrical, length-dependent sensorimotor polyneuropathy attributable to metabolic and microvessel alterations as a result of chronic hyperglycemia exposure (diabetes) and cardiovascular risk covariates".[6] For the purposes of this review, we use the term *diabetic peripheral neuropathy* as the *symmetrical sensorimotor polyneuropathy* of the hands and feet.

The earliest signs of diabetic peripheral neuropathy are loss of vibratory sensation and altered proprioception caused by large-fiber loss and impairment of pain, light touch, and temperature caused by loss of small nerve fibers.[3] Diabetic peripheral neuropathy is usually described as glove-stocking distribution of numbness, sensory loss, paresthesia (abnormal sensation) and/or pain (shooting or stabbing). Sensory loss from neuropathy increases risk for foot injury, delayed treatment (since injuries are not noticed by the patient immediately), and foot and leg ulceration and infections. Recurrent ulcers and infections may eventually lead to amputation of the lower extremities. Altered proprioception causes imbalance and increased risk for falls. Painful neuropathy may lead to reduced ability to perform daily activities and a decrease in quality of life.[7] Complications of diabetic peripheral neuropathy include secondary diseases or conditions that develop in the course of diabetic peripheral neuropathy, such as foot ulcers. Symptoms are defined as the subjective experience of diabetic peripheral neuropathy and include numbness and pain.

Interventions

Pharmacologic Treatment Options To Prevent Complications

The cornerstone of pharmacologic interventions to prevent complications of diabetic peripheral neuropathy is medications and strategies that improve glucose control.[8] Key pharmacologic interventions that address comorbid conditions in patients with diabetes are statins and antihypertensives. These agents may also contribute to preventing *diabetic peripheral neuropathy* complications,[9] since co-existing peripheral vascular disease can contribute to long-term diabetic complications, such as foot ulcerations.[10] Although *diabetic peripheral neuropathy* is not an outcome in studies addressing these comorbid conditions, they may be described as important comorbidities in studies of glucose control that report on diabetic neuropathy outcomes.

Nonpharmacologic Treatment Options To Prevent Complications

These interventions include non-pharmacologic glucose control interventions, such as diet and exercise, and interventions to prevent specific complications, such as foot care for prevention of foot ulcers, as well as exercise and balance training for the prevention of falls.

Pharmacologic Treatment Options To Improve Symptoms

A variety of pharmacological approaches has been evaluated to reduce pain and improve health-related quality of life through a number of mechanisms. These include drugs with direct impact on neurotransmitters and inhibitory pathways or drugs that bind to opioid receptors. Several medications are Food And Drug Administration (FDA) approved for diabetic peripheral neuropathy (e.g., pregabalin) or other types of neuropathy (e.g., gabapentin, lidocaine patches for herpes zoster), but most are approved for other indications (e.g., depression, seizure disorders) and evaluated and used off-label for painful diabetic peripheral neuropathy. For diabetic peripheral neuropathy, pain is the most commonly studied symptom in the literature, although other symptoms, such as paresthesia, that are less commonly addressed in trials are also important to patients.

Nonpharmacologic Treatment Options To Improve Symptoms

These interventions also focus mainly on treating pain. Although there is less evidence in this area, modalities that have been evaluated specifically for diabetic peripheral neuropathy and addressed in previous, reviews include acupuncture, physical therapy and exercise, electrical stimulation, and surgical decompression.

Available Evidence and Shortcomings

Prevention of Complications (Foot Ulcers, Falls, and Perceived Fall Risk)

For pharmacologic and lifestyle interventions, prior reviews have mainly addressed medications for glucose control [which have been evaluated in multiple reviews, including recent and ongoing Evidence-based Practice Center (EPC) reviews on oral diabetes medications which have generally not evaluated neuropathy as an outcome], [11-13] lifestyle interventions, and a variety of quality improvement strategies (such as care management) previously included in the

EPC review Closing the Quality Gap Series.[14] A recent Cochrane review focused on the prevention of diabetic peripheral neuropathy included 17 randomized controlled trials.[15] The review reported a significantly reduced risk of developing clinical polyneuropathy among patients with type 1 diabetes with intensive glucose control after five years of followup (annualized risk difference -1.84%), but a non-significantly reduced risk of -0.58 percent (95% confidence interval [CI], 0.01 to -1.17) in patients with type 2 diabetes and intensive glucose control. This review is currently being updated.

For nonpharmacologic interventions, some systematic reviews have addressed specific interventions, such as exercise training or improving footwear.[16, 17] The International Working Group on the Diabetic Foot (IWGDF) conducted a systematic review to investigate the effectiveness of interventions (i.e., care intervention, self-management intervention, medical intervention) to prevent first and recurrent foot ulcers or amputation in persons with diabetes who are at-risk for complications.[18] This review found moderate evidence supporting the home-monitoring of foot skin temperatures with subsequent preventative actions and the use of therapeutic footwear with a demonstrated pressure-relieving effect consistently worn by the patient. There was some evidence to suggest that prevention of a recurrent foot ulcer by integrated foot care is effective. Surgical interventions can be effective in selected patients, but the evidence is limited.

A variety of pharmacological and non-pharmacological approaches have been evaluated for preventing complications of diabetic peripheral neuropathy. However, complications other than foot ulcers and amputations have not been comprehensively addressed in recent reviews or guidelines.

Treatment of Symptoms (Pain, Paresthesia, Numbness)

Treatments for diabetic peripheral neuropathy symptoms were last reviewed comprehensively by an American Association of Neuromuscular and Electrodiagnostic Medicine, American Academy of Neurology, and American Academy of Physical Medicine & Rehabilitation systematic review and guideline, published in 2011, that reviewed literature through 2008. This review addressed a variety of issues with treatment but focused mainly on pharmacotherapy and the outcome of pain. The guideline recommended only pregabalin as an effective treatment and recommended several other antidepressants and anticonvulsants, tramadol, and capsaicin, as well as opioids, as probably effective. For non-pharmacological interventions, only percutaneous electrical nerve stimulation was recommended as “should be considered”.

Since the completion of this review and guideline, new trials have been conducted on the drugs evaluated in this review and related medications. One additional agent has been FDA-approved for treatment of painful neuropathy: the high-dose capsaicin patch.

Many newer reviews focusing on pharmacologic treatment of painful neuropathy have reported on effectiveness for a number of agents, but not for diabetic peripheral neuropathy specifically, or addressed only certain drug classes or specific drugs.[19-24] The most recently published review (published in February 2015), developed by the NeuPSIG (Special Interest Group on Neuropathic Pain of the International Association for the Study of Pain) to update their clinical recommendations, addressed all causes of peripheral neuropathy and recommended a number of agents.[22] The review assessed a broad range of interventions as moderate- to high-quality evidence, including serotonin-norepinephrine reuptake inhibitors (specifically, duloxetine) and gabapentin. Two comprehensive systematic reviews focusing solely on

pharmacologic interventions for painful diabetic peripheral neuropathy were published in 2014,[2,,25] but these reviews focused only on pain, did not synthesize evidence on other symptoms (numbness and paresthesia), health-related quality of life or dropouts due to adverse effects, and did not search for unpublished studies, which are common in this area. No recent reviews have comprehensively covered nonpharmacologic interventions.

Scope and Key Questions

We conducted a systematic review on pharmacological and non-pharmacological interventions for the prevention of diabetic peripheral neuropathy complications and treatment of diabetic peripheral neuropathy symptoms. We developed an analytic framework to illustrate the different questions and outcomes we considered (Figure 1), and we sought to address the following Key Questions:

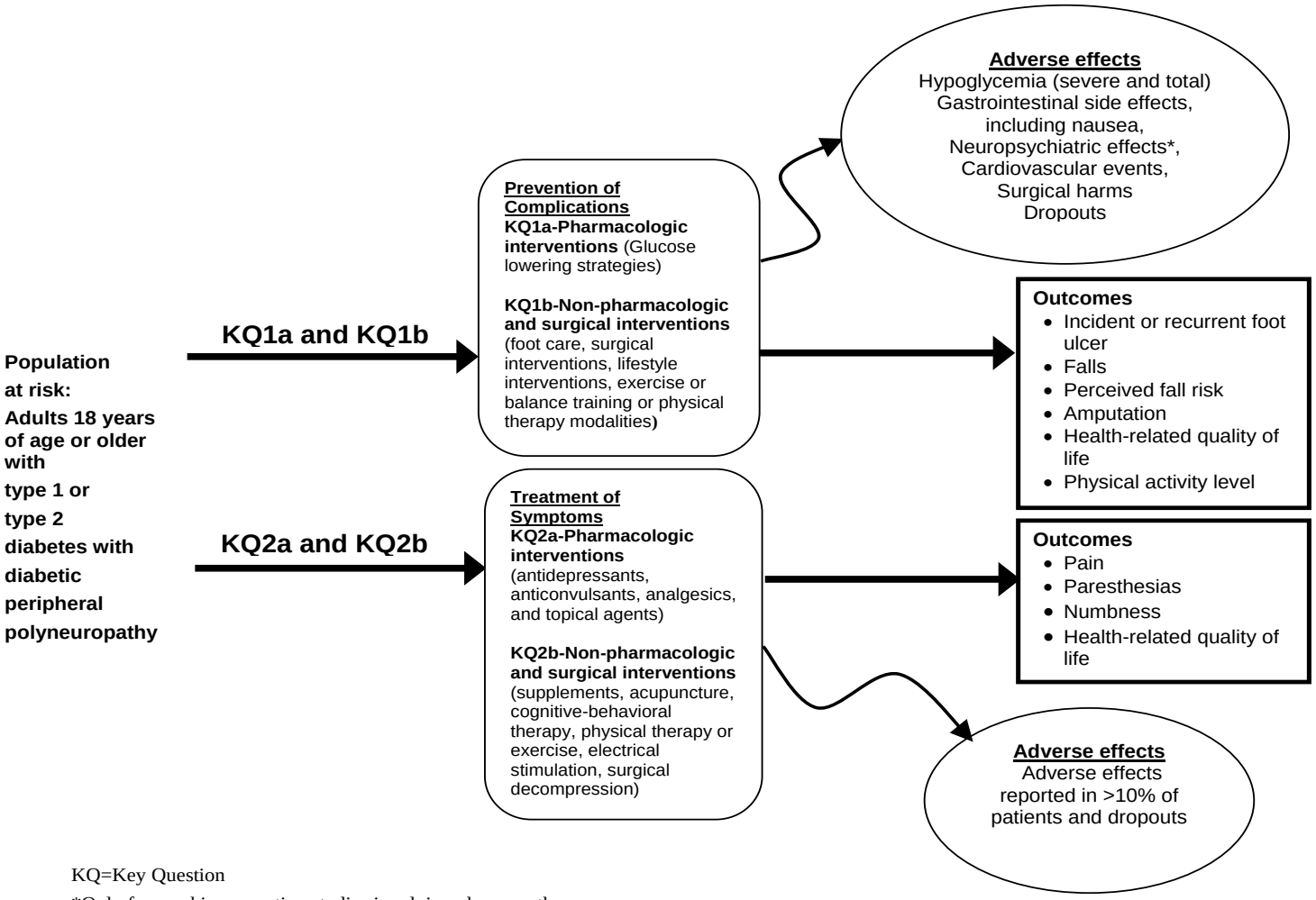
Key Question 1a: What are the benefits and harms of pharmacologic treatment options focused on glucose lowering to prevent the complications of diabetic peripheral neuropathy among adults age 18 or older with type 1 or type 2 diabetes mellitus?

Key Question 1b: What are the benefits and harms of non-pharmacologic treatment options (foot care, surgical interventions, dietary strategies, lifestyle interventions, exercise, and balance training) to prevent complications of diabetic peripheral neuropathy among adults age 18 or older with type 1 or type 2 diabetes mellitus?

Key Question 2a: What are the benefits and harms of pharmacologic treatment options 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?

Key Question 2b: What are the benefits and harms of non-pharmacologic treatment options (alpha-lipoic acid, acetyl-L-carnitine, acupuncture, physical therapy and exercise, cognitive behavioral therapy, electrical stimulation, surgical decompression) 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?

Figure 1. Analytic framework for effectiveness of treatments for diabetic peripheral neuropathy



KQ=Key Question

*Only for smoking cessation studies involving pharmacotherapy

Methods

The methods for this review follow the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[26]

Protocol Development

With input from AHRQ representatives, our panel of technical experts and key informants, we developed a protocol for this systematic review. The final protocol is posted on the AHRQ Effective Health Care Web site: www.effectivehealthcare.ahrq.gov/.

Data Source and Search Strategy

Systematic Reviews

We searched PubMed and the Cochrane Database of Systematic Reviews for systematic reviews. We searched for recent reviews from January 1st, 2011 to October 12th, 2015.

Primary Studies

For questions where we identified systematic reviews to incorporate, we updated the searches of those reviews by using their search strategy, including the year before the end date of their search. For Key Question (KQ)1b (foot ulcer) and KQ2a, we thus searched for new study publications from January 1st, 2013 to May 24, 2016.

For questions where we did not identify high quality relevant systematic reviews, we searched for primary studies using PubMed, Embase®, and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to May 24, 2016. We developed a search strategy for PubMed based on medical subject headings (MeSH®) terms and text words of relevant reviews and primary studies identified *a priori* (Appendix B). We limited our search to studies published in English.

As part of a related methods project, we searched the U.S. clinical trials registry (ClinicalTrials.gov) for KQ2a. 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" OR "with-drawn") [OVERALL-STATUS] [Search Date –March 9th, 2016].

Study Selection

Systematic Reviews

When available, topically relevant and recent reviews were included to answer one or more of the Key Questions. As per the Cochrane Collaboration definition, a systematic review includes a specific research question, a search strategy (e.g., sources such as electronic databases, period covered by the search), and methods used to assess the risk of bias of studies included in the review. Narrative reviews were excluded. We limited our review to those systematic reviews judged to be of *low risk of bias* (see below for information about how we assessed this for each review).

For additional primary studies we identified that were not included in systematic reviews, two reviewers independently screened the studies based on the PICOTS (populations,

interventions, comparators, outcomes, timing, and settings) detailed in Table 1. The studies were excluded if both reviewers agreed that one or more of the exclusion criteria was met. Differences between reviewers regarding abstract eligibility were resolved through consensus.

Primary Studies

We included studies based on the PICOTS (populations, interventions, comparators, outcomes, timing, and settings) detailed in Table 1. For KQ1 we sought randomized controlled trials and non-randomized studies with concurrent comparison groups. For KQ2, we sought randomized controlled trials. Two reviewers independently screened abstracts and, if deemed potentially eligible, full-text versions of the citations. Studies were excluded if both reviewers agreed that one or more of the exclusion criteria was met. Differences between reviewers regarding eligibility were resolved through consensus. We used DistillerSR (Evidence Partners, 2010) to manage the screening process.

Two reviewers independently assessed each ClinicalTrials.gov record for eligibility applying the same eligibility criteria as for the published reports. We screened the ClinicalTrials.gov records using Microsoft Excel 2013 (Microsoft Corporation, Redmond, WA).

Table 1. PICOTS (population, interventions, comparators, outcomes, timing, and setting) for the Key Questions

	KQ1a and KQ1b: Preventing Complications of Diabetic Peripheral Neuropathy	KQ2a and KQ2b: Treating Symptoms of Diabetic Peripheral Neuropathy
Population(s)	Adults 18 years of age or older with type 1 or type 2 diabetes **at risk for peripheral polyneuropathy**	Adults 18 years of age or older with type 1 or type 2 diabetes **with peripheral polyneuropathy**
Interventions	**Pharmacologic treatments focused on glucose control (KQ1a):** - Glucose-lowering strategies (single or combination agents or an intensive control approach using multiple medications): Studies with the goal of glucose control generally include multiple agents and combinations and substitutions and specific agents are not specified. We therefore are not listing the agents here because we are not evaluating specific agents but all glucose-lowering strategies. **Non-pharmacologic and surgical interventions (KQ1b):** - Foot care (daily foot skin temperature measurements and consequent preventative actions, therapeutic footwear, integrated foot care, patient education, self-management) - Surgical interventions for foot ulcers - Lifestyle interventions (carbohydrate-controlled diet aimed at glucose reduction, weight loss, smoking cessation) - Exercise or balance training or physical therapy modalities	**Pharmacologic interventions focused on diabetic peripheral neuropathy (KQ2a):** **Antidepressants**: Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protiptyline, trimipramine), serotonin-noradrenaline reuptake inhibitor antidepressants (desvenlafaxine, duloxetine, levomilnacipran, milnacipran, venlafaxine) **Anticonvulsants:** pregabalin, gabapentin or gabapentin extended release and enacarbil, other antiepileptics (carbamazepine, lacosamide, lamotrigine, levitiracetam, oxcarbazepine, sodium valproate, tiagabine, topiramate, zonisamide) **Analgesics:** Opioids (morphine, oxycodone, fentanyl, hydromorphone, methadone, oxymorphone), tramadol, tapentadol **Topical Agents:** lidocaine, capsaicin, other topical treatments (clonidine, , pentoxyifylline) **Other:** N-methyl-D-aspartate (NMDA) antagonists (ketamine, dextromethorphan), mexiletine, botulinum toxin A, cannabinoids **Combinations of any of the above treatments** **Non-pharmacologic and surgical interventions (KQ2b):** - Supplements: alpha-lipoic acid, acetyl-L-carnitine - Acupuncture - Cognitive-behavioral therapy - Physical therapy or exercise - Electrical stimulation (transcutaneous (or percutaneous) electrical nerve stimulation (TENS) or spinal cord stimulator, frequency-modulated electromagnetic neural stimulation, patient-specific electrocutaneous nerve stimulation (Scrambler) - Surgical decompression
Comparators	Active interventions as well as usual care/placebo	Active interventions as well as treatment/placebo

Outcomes*	**Benefits (KQ1a and KQ1b):** - Incident or recurrent foot ulcer (excluding healing of ulcer as the outcome) - Falls - Perceived fall risk - Amputation - Health-related quality of life - Physical activity level **Harms (KQ1a and KQ1b):** - Hypoglycemia (severe and total) - Gastrointestinal side effects, including nausea - Neuropsychiatric effects (ONLY for smoking cessation studies involving pharmacotherapy) - Cardiovascular events - Surgical harms - Dropouts	**Benefits (KQ2a and KQ2b):** - Pain - Paresthesia - Numbness - Health-related quality of life (Health-related quality of life is defined using measurement with instruments designed for this topic) **Harms (KQ2a and KQ2b):** - Adverse effects reported in >10% of patients and dropouts
Type of Study	Randomized controlled trials, non-randomized studies with a concurrent comparison group	Parallel or crossover randomized controlled trials [must be double-blind (patient and researcher assessing the outcomes) for pharmacologic and others where blinding is possible, such as acupuncture]
Timing and Setting	At least 3 months of followup for pharmacologic interventions and any followup for non-pharmacologic interventions Ambulatory care for all the interventions except surgical interventions	3 weeks or more of followup Ambulatory care
Language	Study must be published in English	

KQ = Key Question

*Outcomes were included that were patient-centered and addressed more than just pain, based on discussion with the Technical Expert Panel.

Health-related quality of life may include areas such as physical health and function, mental health, social and role function, and physical and psychological symptoms

Table 2. List of exclusion criteria applied during abstract and full-text screening

Exclusion criteria at abstract screening	• Not evaluating people with type 1 or type 2 diabetes with peripheral neuropathy • No original data (editorial, commentary) • No full report • Case series or case reports • Not in English • Not conducted in humans • Study of children only • Address KQ1a &b but not a RCT or non-randomized with a concurrent comparison group • Address KQ2a &b but not a parallel or crossover randomized controlled trials • Drug is not available in the U.S./ non-approved(e.g. Investigational)/Not included in the protocol =57 • Not relevant to Key Questions
Additional exclusion criteria at full-text screening	• Not all patients have diabetes in both group • Addresses KQ1a (pharmacologic intervention) but follow-up less than 3 months • Addresses KQ2 but follow-up less than 3 weeks • Study with less than ten patients • No outcome of interest • Does not evaluate an intervention of interest

KQ = Key Question, RCT = randomized controlled trial

Data Extraction and Data Management

We created and pilot tested data extraction forms in Excel (Microsoft, Redmond, WA). Reviewers extracted information on general study characteristics (e.g., study design, study period, followup); eligibility criteria; study participants (e.g., age, gender, race/ethnicity, body mass index, comorbidities, etc.); interventions (including adherence by study participants); outcome measures and the method of ascertainment; and the results of each outcome (continuous and dichotomous data), including measures of variability. We also collected data on outcomes for the subgroups of interest, including age, sex, race/ethnicity, and body mass index.

For pain, paresthesia, numbness outcomes, and neuropathy composite scores, we followed the methods described in the identified review by Griebeler et. al.[2] Results from one numerical pain score (both continuous and categorical, if reported) were extracted using the following tools hierarchy (see Table 3).

Table 3. Tools hierarchy for numerical pain score

Pain, paresthesia, numbness	Neuropathy composite score
VAS (Visual Analog Scale)	TSS (Total Symptom Score)
NPS (Neuropathic Pain Scale)	NSC (Neuropathy Symptom Change Score) – severity score; LL (lower leg) if both reported
NRS (Numerical Rating Scale)	NTSS (Neuropathy Total Symptom Score)
BPI (Brief Pain Inventory (BPI severity))	mTCNS (modified Toronto clinical neuropathy score)
McGill	NPSI (neuropathic pain symptom inventory)
SF-MPQ	
Other score or numerical scale or Likert	

One reviewer completed the data extraction, and a second reviewer checked the first reviewer's extraction for completeness and accuracy. We resolved differences through discussion and, as needed, through consensus among our team.

We used the data extraction results from the systematic reviews for the included studies and supplemented these with additional data extraction for any outcomes not included in the systematic reviews.

Risk of Bias Assessment

Systematic Reviews

Two reviewers assessed risk of bias of relevant systematic reviews using the ROBIS tool. This tool uses categories of yes, probably yes, probably no, no, no information across four domains (study eligibility criteria; identification and selection of studies; data collection and study appraisal; and synthesis and findings).[27] The overall assessment for each systematic review is based on a reviewer's overall judgement given their response to the individual ROBIS items, and has three overall ratings: *Low*, *High*, and *Unclear*. An independent reviewer resolved any discrepancies regarding the ROBIS tool assessment between the reviewers.

Primary Studies

For primary studies included in systematic reviews, we relied on the risk of bias assessments as performed in the systematic reviews. For newly identified studies, two reviewers independently assessed risk of bias. We used the Cochrane Collaboration Tool for assessing the risk of bias of controlled studies.[28] For non-randomized studies of treatment interventions, we used the Cochrane Risk of Bias Assessment Tool for Non-Randomized Studies of Interventions (ACROBAT-NRSI).[29] We completed risk of bias assessment for any studies uniquely identified from ClinicalTrials.gov using the same tools (i.e., Cochrane Risk of Bias tool). Differences between reviewers were resolved through consensus.

Data Synthesis

For each Key Question, we created a detailed set of evidence tables containing all of the information abstracted from the newly identified studies. All studies were summarized qualitatively. We did not abstract data for primary studies included in systematic reviews; we relied on the information provided in the review. We conducted meta-analyses for an outcome when there were sufficient data (at least three studies of the same design) and studies were sufficiently homogenous with respect to key variables (population characteristics, intervention, and outcome measurement) using a profile likelihood estimate for a random effects model. All meta-analyses were conducted using STATA 12.1 (College Station, TX). Pain scales reported in the included studies were standardized by estimating the standardized mean difference using the Cohen d method. When possible, for studies that did not include variability measures, the standard deviation of change in mean was calculated using a correlation coefficient of 0.5, in accordance with methods provided in Fu et al (2013). [30]

Strength of the Body of Evidence

After synthesizing the evidence, two reviewers graded the body of evidence for each KQ using the evidence grading scheme recommended in the Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[26] In assigning evidence grades, we considered the five

recommended domains, including study limitation in the included studies, directness of the evidence, consistency across studies, precision, and reporting bias. We assessed the aggregate risk of bias of individual studies and integrated these assessments into a qualitative summary risk of bias rating across studies of similar interventions for each outcome.

We classified the strength of evidence pertaining to the KQs and critical outcomes into four basic categories or grades: *high*, *moderate*, *low*, and *insufficient* (see Table 4). The strength of evidence was based on the totality of evidence (i.e., evidence in prior reviews as well as new evidence) where we included an existing systematic review.

We graded the strength of evidence for the outcomes we classified as most important or critical during protocol development: pain, health-related quality of life, falls, foot ulcers, and amputation. The investigators writing each section completed the strength of evidence grading. Throughout the report writing process, team members reviewed the grading and discussed the process used to grade the evidence.

Table 4. Strength of evidence grades and definitions

Grade	Definition
High	We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable.
Moderate	We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. The body of evidence may have unacceptable deficiencies, precluding judgment.

Applicability

Applicability was assessed separately for the different outcomes and was guided by the PICOTS framework as recommended in the Methods Guide for Comparative Effectiveness Reviews of Interventions.[26] We considered important population characteristics (age, gender, race, ethnicity, duration and severity of diabetes) and intervention features that may cause heterogeneity of treatment effects, and issues such as length of followup that may affect generalizability of the findings.

Peer Review and Public Comment

A full draft report was reviewed by experts and posted for public commentary from June 8th, 2016, through July 7th, 2016. Comments received from invited reviewers and through the public comment website were compiled and addressed. A disposition of comments will be posted on the Effective Health Care Program Web site 3 months after the release of the evidence report.

Results for Key Questions (KQs) 1a and b

Results of the Search

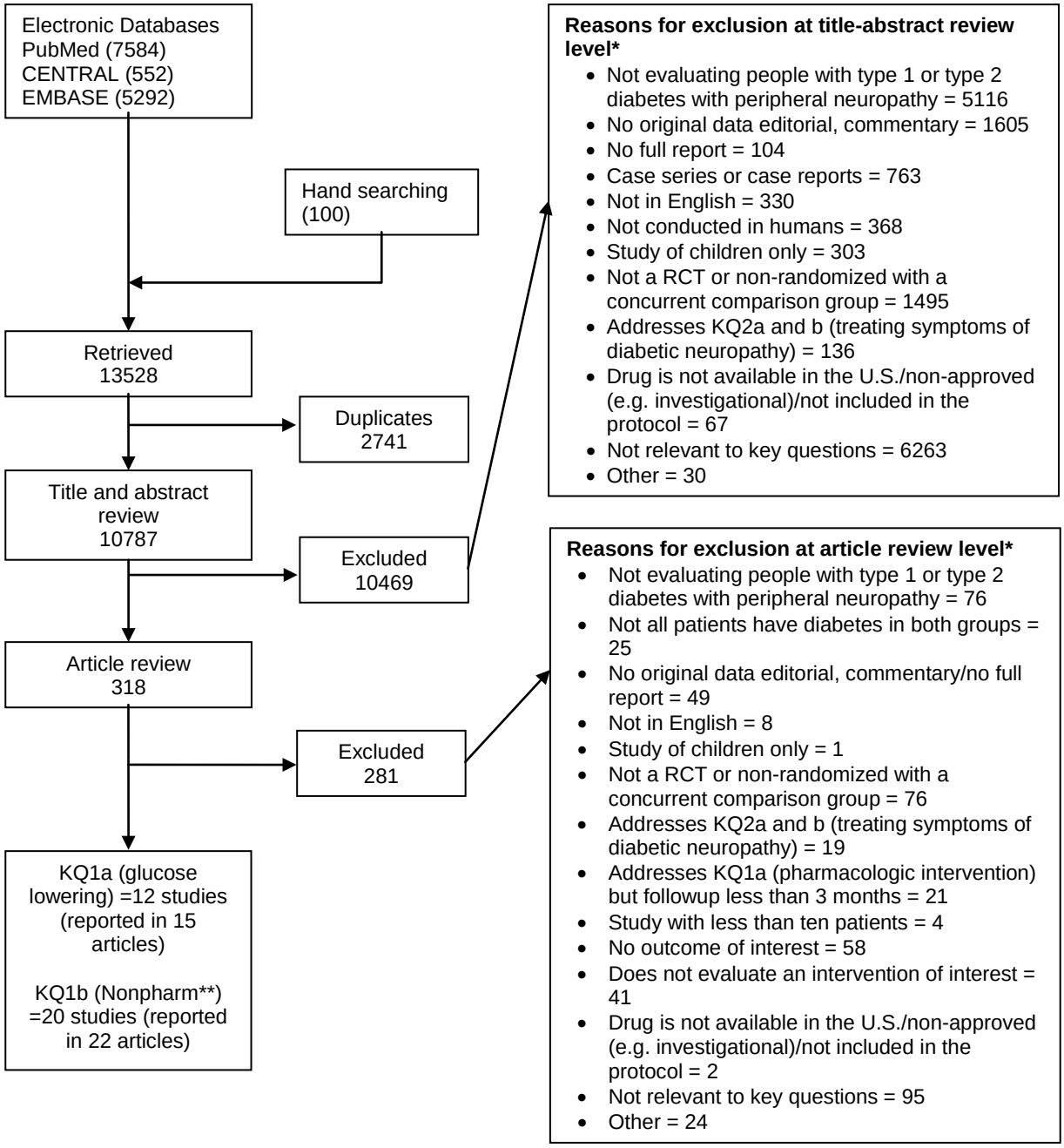
We included 62 studies (30 studies from an existing review and 32 newly identified studies reported in 37 articles. Figure 2 summarizes the search and selection of primary studies. (See Appendix C for list of citations excluded at full-text level, with reasons for exclusion.).

The breakdown of the included studies for KQ1a and b by study design is:

- KQ1a -12 studies (11 randomized controlled trials [RCTs] and 1 cohort study);
- KQ1b - Foot care interventions – 35 studies (20 RCTs and 10 cohort studies from an existing review and five newly identified studies (2 RCTs and 3 cohort studies);
- KQ1b - Lifestyle interventions - 1 RCT;
- KQ1b - Balance interventions - 6 RCTs and 1 cohort study;
- KQ1b - Exercise training interventions - 4 RCTs and 1 cohort study;
- KQ1b - Physical therapy interventions - 2 RCTs

.The findings are summarized in Tables 5 to 11

Figure 2. Summary of the literature search for primary studies: preventing complications



* Reviewers did not need to agree on reason for exclusion.
** Non-pharmacologic treatment options: foot care, surgical interventions, dietary strategies, lifestyle interventions, exercise and balance training
KQ = Key Question, RCT = Randomized Controlled Trial

KQ1a: Benefits and Harms of -Pharmacologic Treatment Options Focused on Glucose Lowering To Prevent Complications

Key Points

- Glucose lowering strategies or specific glucose lowering medications did not prevent foot ulcers in patients with type 1 or type 2 diabetes (low or insufficient strength of evidence).
- Intensive glycemic control prevented lower extremity amputations more than standard glycemic control in patients with type 2 diabetes (moderate strength of evidence).
- Intensive glycemic control had higher rates of hypoglycemia than standard treatment.
- There was insufficient evidence to assess the effect of glucose lowering strategies on quality of life.

Table 5. Summary of findings for pharmacologic treatment options

Outcome	Comparison	Number of Studies (N)	Findings	Strength of Evidence*
Foot ulcer	Intensive vs. standard glycemic control	Type 1 diabetes 2 RCTs (N=1329)	There was no significant difference between intensive vs standard glycemic control for prevention of foot ulcers (RR 0.32, 95% CI, 0.10 to 1.06 and 0.37, 95% CI 0.12 to 1.15)	Low
		Type 2 diabetes 2 RCTs (N=1326)	There was no significant difference between intensive and standard glycemic control.	Low
	Comparisons of individual medications either as monotherapy or in combination, to each other or to placebo	Type 1 diabetes None	NA	Insufficient
		Type 2 diabetes 1 cohort study (N=23,395)	We could not draw conclusions based on insufficient evidence for prevention of foot ulcers between glargine insulin versus NPH insulin.	Insufficient
Lower extremity amputations	Intensive vs. standard glycemic control	Type 1 diabetes 1 RCT (N=1257)	There was no statistically significant difference between risk of lower extremity amputations in the intensive vs. standard glycemic control arms.	Low
		Type 2 diabetes 5 RCTs (N=9348)	There was a decreased risk of lower extremity amputations in the intensive vs. standard glycemic control arms. (Pooled RR 0.63, 95% CI 0.40 to 0.96).	Moderate
	Comparisons of individual medications either as monotherapy or in combination, to each other or to placebo	Type 1 diabetes None	NA	Insufficient
		Type 2 diabetes 1 RCT (N=5238)	There was no effect of pioglitazone on risk of amputations compared to placebo.	Low
Quality of life	Comparisons of individual	Type 1 diabetes None	NA	Insufficient

	medications either as monotherapy or in combination, to each other or to placebo	Type 2 diabetes 1 RCT (N=46)	We could not draw conclusions based on insufficient evidence on quality of life scores between exenatide and glargine.	Insufficient

*we graded only the key outcomes (falls, foot ulcer, amputation, and quality of life)
CI= confidence interval, RR = risk ratio, RCT = Randomized Controlled Trial, NA =Not applicable
. Please see Appendix table E-1 -Strength of evidence table for domains

Description of Included Studies

Twelve studies, reported in 15 articles, assessed the effectiveness of glycemic control and hypoglycemic medications to prevent the complications of diabetic peripheral neuropathy. Two studies, reported in three articles, included patients with type 1 diabetes,[31-33] and 10 studies, reported in 12 articles, included patients with type 2 diabetes. [34-45]

Of the 12 included studies, eleven were parallel arm RCTs[31, 32, 34, 35, 37, 39-45] and one was a retrospective observational cohort study.[38] The treatment duration of the RCTs ranged from 18 months to 12 years. The number of participants in the seven RCTs ranged from 46 to 5238 (with a median of 1173) and the observational study included 23,395 participants. Among the eleven RCTs, nine compared an intensive glycemic control strategy with standard care and did not describe the outcomes by specific medications.[31, 32, 34, 35, 40-45] The two other RCTs included head-to-head medication comparisons. [37, 39] The seven RCTs [35, 39, 40, 43, 45-47] comparing intensive with standard glycemic control in patients with type 2 diabetes had similar populations, with mean age ranges between 50 and 60 years, except for the Japanese Elderly Diabetes Intervention Trial (J-EDIT) with a mean age of 72 years.[43] These trials also differed in their glycemic control targets for the intensive treatment arms, with older trials having more modest targets (Hemoglobin A1c less than 7.5% in the 1997 Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes [VACSDM][41, 42]) and more recent trials being more intensive (Hemoglobin A1c less than 7.0% in the 2011 ADDITION study and less than 6.5% in the 2009 VADT). [40, 45] In addition, Steno-2 investigated blood pressure and lipid lowering along with tight glycemic control in the same arm, making it unclear which component led to the effect. [36]

Four of the 11 RCTs comparing treatment strategies included post-trial observational followup, with durations ranging from 5.5 to 28 years, allowing for the ascertainment of long-term clinical outcomes, such as amputations and diabetic foot ulcers.[31, 32, 34, 35] The Steno-2 trial reported amputation outcomes at two time points, at the end of the trial [35] and again after additional observational followup.[36] The two RCTs that included comparisons of individual drugs were pioglitazone versus placebo[39] and exenatide versus glargine insulin.[37] The retrospective observational cohort study of over 23,000 participants compared glargine insulin versus NPH insulin.[38]

The overall risk of bias for these studies was low for seven trials, unclear for four trials and high for one cohort study. The trials had generally low risk of bias regarding the allocation concealment, random sequence generation, assessment of blinding by the outcome, selective outcome reporting, other sources of bias, and incomplete outcome data. The primary sources of bias in the cohort study were in the selection of participants, bias due to confounding, due to missing data, due to measurement of outcomes, and due to departures from intended interventions.

Outcomes

Foot Ulcer

Five studies (4 RCTs and 1 cohort study) assessed foot ulcer.[31, 33, 38, 41, 43] Two RCTs included patients with type 1 diabetes[31, 32] and two included patients with type 2 diabetes,[41, 43] comparing intensive with standard glycemic control strategies. One retrospective observational cohort study compared glargine insulin versus NPH insulin for the outcome of foot ulcer.[38]

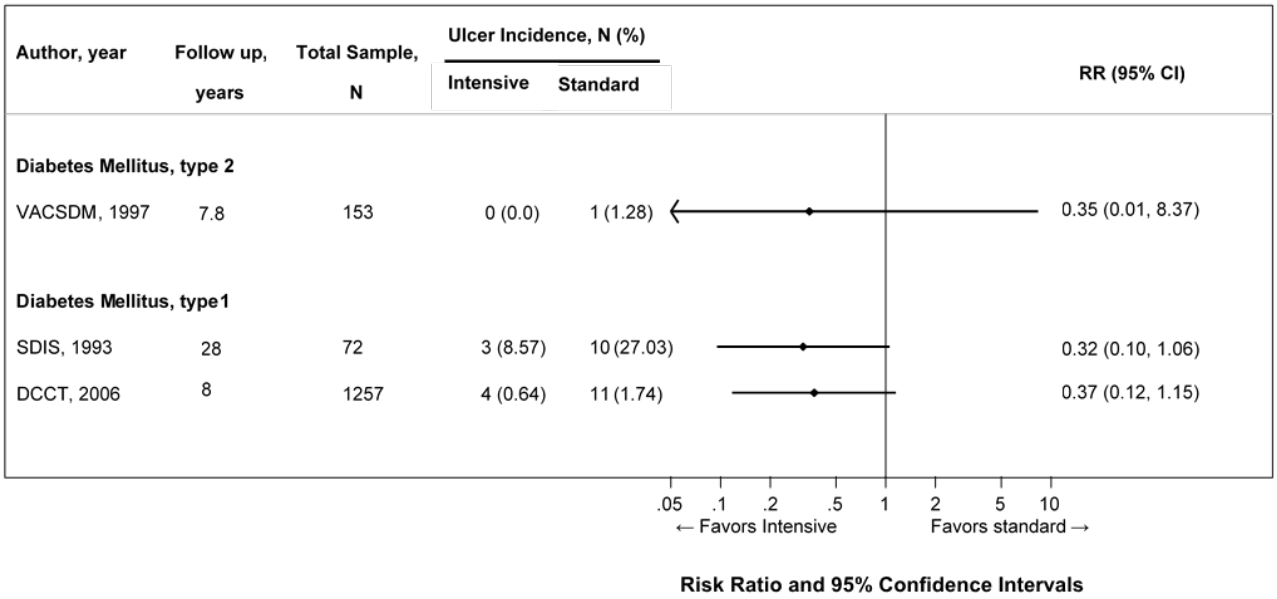
For type 1 diabetes, the Stockholm Diabetes Intervention Study (SDIS) RCT reported 13 foot ulcers over 28 years of followup, three (8.6%) in the intensive glycemic control treatment arm and 10 (27%) in the standard treatment group arm. The calculated risk ratio for foot ulcers in the intensive versus standard glycemic control was 0.32 (95% CI, 0.10 to 1.06).[33] The Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) trial had 8 years of followup, with four (0.6%) foot ulcers in the intensive glycemic control treatment arm compared with 11 (1.7%) in the standard treatment arm.[31] The calculated risk ratio for intensive versus standard glycemic control was 0.37 (95% CI, 0.12 to 1.15). The Stockholm Diabetes Intervention Study (SDIS) and DCCT/EDIC trials both had continued observational followup and consistently reported decreased odds of foot ulcers in intensive versus standard glycemic control. The differences between intensive and standard care for the prevention of foot ulcers were not statistically significant, likely because the number of events was low despite long followup periods. We were unable to pool these results owing to the limited number of studies in patients with type 1 diabetes and similar interventions (Figure 3). We graded the strength of evidence as low for comparisons of intensive vs. standard glycemic control for the outcome of foot ulcer in patients with type 1 diabetes.

For type 2 diabetes, the Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes (VACSDM) and the Japanese Elderly Diabetes Intervention Trial (J-EDIT) RCTs reported foot ulcers.[41, 43] In the VACSDM, one ulcer occurred (in the intensive treatment arm) in the total population of 153 over 7.8 years of treatment.[41] The 3-year J-EDIT RCT reported a total of 12 foot ulcers or gangrene and that the between-arm difference was not statistically significant (p=0.56), but the event rates were not reported by arm[43]. We were unable to pool these results owing to the limited number of studies in patients with type 2 diabetes and because the J-EDIT study did not report foot ulcer rates by arm.

One cohort study including patients with type 2 diabetes reported a reduced hazard ratio (HR) for foot ulcers for patients taking glargine insulin versus NPH insulin (HR 0.61; 95% CI, 0.38 to 0.98).[38] In this cohort study, the main outcome was diabetic foot ulcer and post-treatment between group glycemic control was not described. At baseline, the HbA1c was 8.0% in both groups.

We graded the strength of evidence as low for comparisons of intensive vs. standard glycemic control for the outcome of foot ulcer in patients with type 2 diabetes, because few included studies addressed the outcome of ulcers and the estimates were imprecise due to low event rates (Table 5).

Figure 3. Calculated risk ratio for foot ulcers in the intensive versus standard glycemic control



%=percent; CI=confidence interval; N=sample size; p=p-value; RR=risk ratio

Lower Extremity Amputation

Eight RCTs reported lower extremity amputations as an outcome.[31, 35, 39-41, 44, 45, 47] The DCCT/EDIC RCT [31] included patients with type 1 diabetes and the seven other RCTs included patients with type 2 diabetes.[35, 39-41, 44, 45, 47] Six RCTs reported lower extremity amputation in patients with type 2 diabetes comparing intensive versus standard glycemic control strategies[31, 35, 40, 41, 44, 45, 47] and one trial, the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) trial compared pioglitazone vs. placebo.[39] Steno-2 reported amputations at two time points, at trial end (7.8 years) [35] and after an additional mean of 5.5 years.[36]

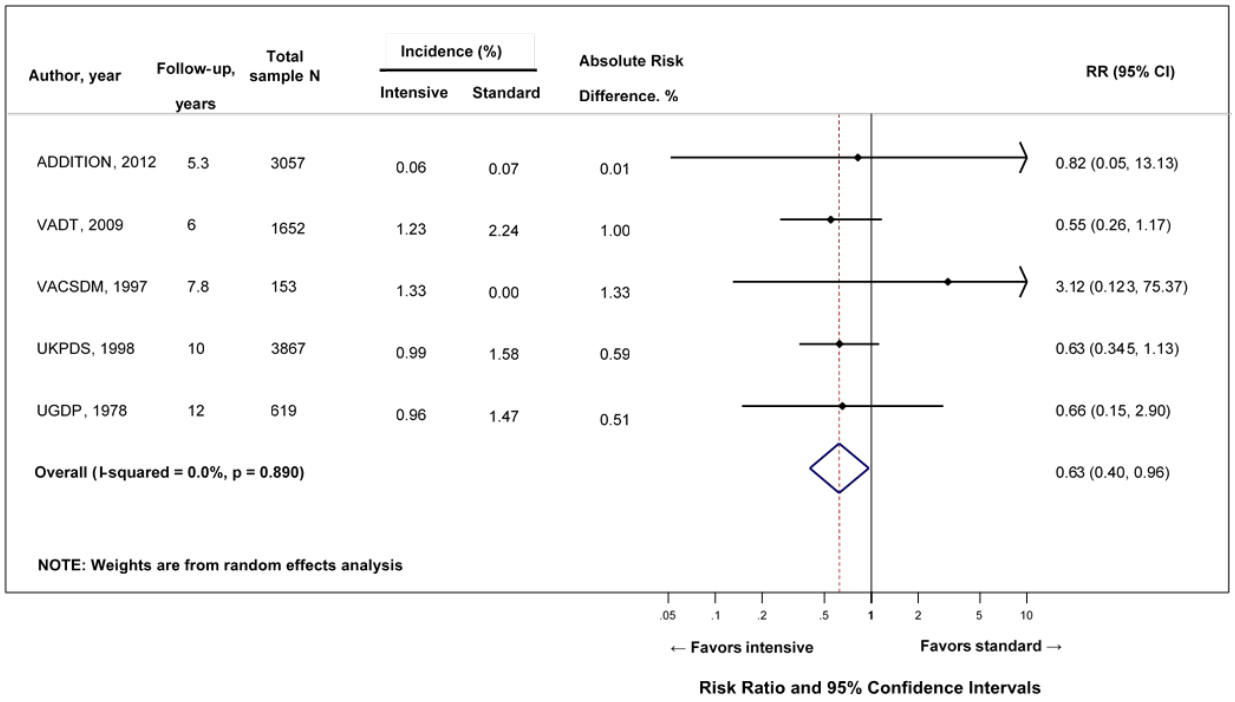
Figure 4 includes the five trials comparing intensive versus standard glycemic control. We excluded the Steno-2 from the meta-analysis because it had a mixed intervention approach[36]. The calculated risk ratios for amputations ranged from 0.55 to 3.12 and were not statistically significant (Figure 4). The five trials comparing the effectiveness of intensive glycemic control versus standard treatment indicated a decreased risk of lower extremity amputations in patients with type 2 diabetes (pooled RR 0.63 [95% CI, 0.40 to 0.96]) (Figure 4). Results from the five trials comparing the effectiveness of intensive glycemic control versus standard treatment indicate the clinical benefit of decreased risk of lower extremity amputations in patients with type 2 diabetes, with moderate strength of evidence. However, the total number of events, event rates and absolute risk differences were low despite long followup periods.

The DCCT/EDIC trial reported lower extremity amputation in patients with type 1 diabetes who received intensive glycemic control versus standard treatment with a calculated odds ratio of 0.40 (95% CI, 0.08 to 2.09), which was not statistically significant. We graded the strength of evidence as low for a lack of benefit of intensive vs. standard glycemic control, because only one trial assessed amputations in patients with type 1 diabetes and the point estimate was imprecise.

The PROactive trial compared pioglitazone (added to background medications) versus placebo in patients with type 2 diabetes and reported no difference in risk of amputations between the two arms [Hazard Ratio1.01 (95% CI, 0·58 to 1·73)].[39]

We graded the strength of evidence as low for comparison of pioglitazone vs. placebo, given that PROactive was a large trial (> 5000 participants) and it showed a lack of benefit for reducing lower extremity amputations due to diabetic peripheral neuropathy, although this was not the main objective of the study.

Figure 4. Calculated risk ratio for lower extremity amputations in the intensive versus standard glycemic control in patients with type 2 diabetes with diabetic peripheral neuropathy



%=percent; CI=confidence interval; N=sample size; p=p-value; RR=risk ratio

Quality of Life

One trial assessed the quality of life using global-neuropathy-specific quality of life (NeuroQOL).[37] The RCT reported no difference in scores between the exenatide (change from baseline to 18 months -0.16±1.0) and glargine arms (change from baseline to 18 months 0.40±0.9) among patients with type 2 diabetes and diabetic peripheral neuropathy.

Harms

Six studies (reported in 7 articles) evaluated the risk of hypoglycemia.[35, 37, 39-42, 47] RCTs evaluating intensive glycemic control versus standard treatment had greater event rates of hypoglycemia (range 0.6% to 6% in standard vs. 9% to 15% in intensive arms). The RCT comparing exenatide versus insulin glargine reported greater gastrointestinal problems in the exenatide group (27% vs. 17%) (Table 6).[37]

Table 6. Studies reporting harms of glucose lowering treatments in patients with type 1 and 2 diabetes at risk for diabetic peripheral neuropathy

Author, Year	Arm	Harm	N for Analysis	Time Point (s)	N of Patients with Harms	% of Patients with Harms
Jaiswal, 2015 [37]	Exenatide	Severe hypoglycemia	22	18 months	0	0%
	Insulin glargine	Severe hypoglycemia	24	18 months	1	4%
	Exenatide	Gastrointestinal problems	22	18 months	6	27%
	Insulin glargine	Gastrointestinal problems	24	18 months	4	17%
UKPDS*, 1998 [47]	Intensive glycemic control	Severe hypoglycemia	2,729	10.7 years	NR	1-2%
	Conventional treatment	Severe hypoglycemia	1,138	10.7 years	NR	0.7%
Steno-2, 2003 [35]	Intensive glycemic control	Severe hypoglycemia	80	7.8 years	12	15%
	Conventional treatment	Severe hypoglycemia	80	7.8 years	5	6%
PROactive [39]	Pioglitazone	Hypoglycemia	2,605	34.5 months	728	28%
	Placebo	Hypoglycemia	2,633	34.5 months	528	20%
VADT 2009 [40]	Intensive glycemic control	Hypoglycemia	892	6 years	76	9%
	Standard treatment	Hypoglycemia	760	6 years	28	5%
VACSDM 1995 [41, 42]	Intensive glycemic control	Severe hypoglycemia	75	7.8 years	5	6%
	Standard treatment	Severe hypoglycemia	78	7.8 years	2	2.5%

* Trial reported the harms by drug class under intensive glycemic control arm instead of overall

KQ1b: Benefits and Harms of Nonpharmacologic Treatment Options (Foot Care, Surgical Interventions, Lifestyle Interventions, Exercise, and Balance Training) To Prevent Complications

Foot Care and Surgical Interventions

Key Points

- Patient education programs are not effective for reducing the incidence of foot ulcer with low strength of evidence.
- Integrated foot care (care given by one or multiple collaborating professionals treating patients at multiple occasions with multiple interventions) is effective in reducing foot ulcer incidence and/or recurrence with low strength of evidence.
- Home monitoring of foot skin temperature is effective for reducing foot ulcer incidence and recurrence with moderate strength of evidence.
- Specific modalities of therapeutic footwear are effective in prevention of recurrent plantar foot ulcers compared with standard-of-care therapeutic footwear with moderate strength of evidence.
- In patients with initially non-healing ulcers, Achilles tendon lengthening, single- or pan-metatarsal head resection and metatarsophalangeal joint arthroplasty are effective for reducing ulcer recurrence risk when compared with non-surgical treatment with low strength of evidence. However, Achilles tendon lengthening appeared to worsen physical functioning based on limited evidence.
- There was insufficient evidence to assess the effect of foot care and surgical interventions on quality of life.
- Adverse effects were not systematically assessed in studies.

Table 7. Summary of findings for foot care and surgical interventions for foot ulcers, amputation and quality of life

Outcome	Intervention	Number of Studies (N)	Findings	Strength of Evidence*
Foot ulcer	Integrated foot care	**4 Studies** Previous SR: 3 RCTs and 1 cohort Newly identified study: None (N =350)	The previous review concluded that integrated foot care reduced foot ulcer incidence or recurrence. The reduction was ~20% across studies as compared to standard care or no podiatrist involvement. We did not identify new studies in our updated search	Low
	Self-management – Home-monitoring of foot temperature	**4 Studies** Previous SR: 3 RCTs Newly identified studies: 1 RCT (N=583)	The previous review concluded that home monitoring of foot temperature reduced incidence and recurrence of foot ulcers compared with standard of care. The new study did not report statistically significant benefit but did not change the conclusion.	Moderate

Outcome	Intervention	Number of Studies (N)	Findings	Strength of Evidence*
	Self-management – Self-inspection and topical treatment on foot	**2 Studies** Previous SR: 1 RCT Newly identified studies: 1 cohort study (N=360)	The previous review concluded that there was insufficient evidence to determine effectiveness of use of foot topical treatments on foot ulcers. The new study did not change the conclusion.	Insufficient
	Patient education	**4 Studies** Previous SR: 2 RCTs Newly identified studies: 1 RCT and 1 cohort study (N=16943)	The previous review concluded that there was no reduction in ulcer recurrence from one time educational programs. The new studies did not change the conclusion.	Low
	Therapeutic footwear	**10 Studies** Previous SR: 7 RCTs and 3 cohort studies Newly identified study: None (N=1913)	The previous review concluded that specific modalities of therapeutic footwear were effective in the prevention of a recurrent plantar foot ulcer compared with more standard-of-care therapeutic footwear. The risk reduction ranged from 4% to 45% across studies. We did not identify new studies.	Moderate
	Surgical interventions	**9 Studies** Previous SR: 3 RCTs and 6 cohort studies Newly identified study: None (N=744)	The previous review concluded that surgical interventions (Achilles tendon lengthening, single or pan-metatarsal head resection and metatarsophalangeal joint arthroplasty) reduce ulcer recurrence risk in a range from 24% to 43% in some patients with initially non-healing ulcers when compared with non-surgical treatment. We did not identify new studies.	Low
Netten et al. did not assess amputation and quality of life				
Amputation	Integrated foot care	**4 Studies** 2 RCTs and 2 Cohort studies (n=27840)	We could not draw conclusions due to inconsistency of results between RCTs and cohort studies.	Insufficient
	Self-management	1 RCT (N=85)	We could not draw conclusions due to insufficient evidence from one study.	Insufficient
	Patient education	**3 Studies** 2 RCTs and 1 cohort study (N=16812)	The education programs did not change the occurrence of amputation in patients who received education program vs patients who did not receive education program.	Low
	Therapeutic footwear	1 Cohort study (N=46)	We could not draw conclusions based on insufficient evidence from one study.	Insufficient
	Surgical interventions	2 Cohort studies (N=168)	We could not draw conclusions due to inconsistent findings from a limited number of studies.	Insufficient
Quality of	Home-	1 RCT	We could not draw conclusions	Insufficient

Outcome	Intervention	Number of Studies (N)	Findings	Strength of Evidence*
Life	monitoring of foot temperature	(N=85)	based on insufficient evidence from one study.	
	Surgical interventions	1 RCT (N=28)	We could not draw conclusions based on insufficient evidence from one study.	Insufficient

*we graded only the key outcomes (falls, foot ulcer, amputation, and quality of life)
Please see Appendix table E-2 -Strength of evidence table for domains
N= number of patients, NA = not applicable, RCT = Randomized controlled trial, SR: Systematic review,

Description of Included Studies

Summary of Studies Included in Existing Systematic Review

Netten and colleagues (2016) conducted a systematic review of interventions aimed specifically at the prevention of foot ulcers in at-risk patients with diabetes and included 74 studies (30 controlled studies and 44 non-controlled studies).We included 30 controlled studies (19 RCTs and 11 cohort studies) for this review from the Netten's SR. Eligible studies included patients with diabetes mellitus type 1 or 2 at risk for foot ulceration, as defined in the International Working Group on the Diabetic Foot (IWGDF) guidance documents. Integrated foot care, self-management, patient education, therapeutic footwear, and surgical interventions were included and compared either with standard care plus other interventions or standard care alone. The primary outcomes of interest were first diabetic foot ulcer and recurrent diabetic foot ulcer. The secondary outcomes were amputation, A1c, ulcer incidence, ulcer severity, mortality, and hyperkeratosis. Thirty of the included controlled studies addressed outcomes of interest in our review (foot ulcer or amputation outcomes). The review authors used scoring sheets developed by the Dutch Cochrane Centre (www.cochrane.nl) to assess the risk of bias of included studies and assessed the quality of evidence for each question based on the risk of bias of included studies, effect sizes, and expert opinion. They rated the quality of evidence as 'high', 'moderate' or 'low'.

The review authors concluded that the evidence base to support the use of specific self-management and footwear interventions for the prevention of recurrent plantar foot ulcers is consistent, but the evidence base is small for the use of other, sometimes widely applied, interventions and is practically nonexistent for the prevention of a first foot ulcer and non-plantar foot ulcer.

We assessed methodological quality of the Netten et al. review using the ROBIS tool.[27] Overall risk of bias for this review was low. There were no concerns with the review process. The review conclusions appropriately reflect the results of the review.

Description of Newly Identified Studies

We updated the review by Netten et al. conducting a search for additional primary studies, as described in the Methods section. We identified five new studies: two parallel-arm RCTs[48, 49] and three cohort studies.[50-52] The cohort studies[50-52] included patients with type 2 diabetes exclusively, while one RCT[48] included patients with both type 1 and type 2 diabetes and the other RCT did not specify diabetes status of patients.[51]

Outcomes

We found studies evaluating incident or recurrent foot ulcer, amputation, and adverse events (e.g., dropouts, hypoglycemia, and cardiovascular events). We did not find any studies evaluating falls or perceived fall risk. The outcomes are presented by interventions. The results for the outcomes are summarized by foot care intervention (Table 7).

Foot Ulcer

We identified 34 studies that reported non-pharmacologic interventions and prevention of foot ulcers, including 26 RCTs and 8 cohort studies.

Integrated Foot Care

The review by Netten et al. defined integrated foot care as care given by one or multiple collaborating professionals treating patients at multiple occasions with multiple interventions. The authors identified three RCTs, one cohort, and one unpublished RCT.[53-56]. Integrated foot care provided by an endocrinologist and diabetes nurse,[53] chiropody treatment [55], or multidisciplinary foot care given at least once every three months[56] showed significant reductions in foot ulcer incidence or recurrence. The review by Netten et al. rated the strength of evidence as low.

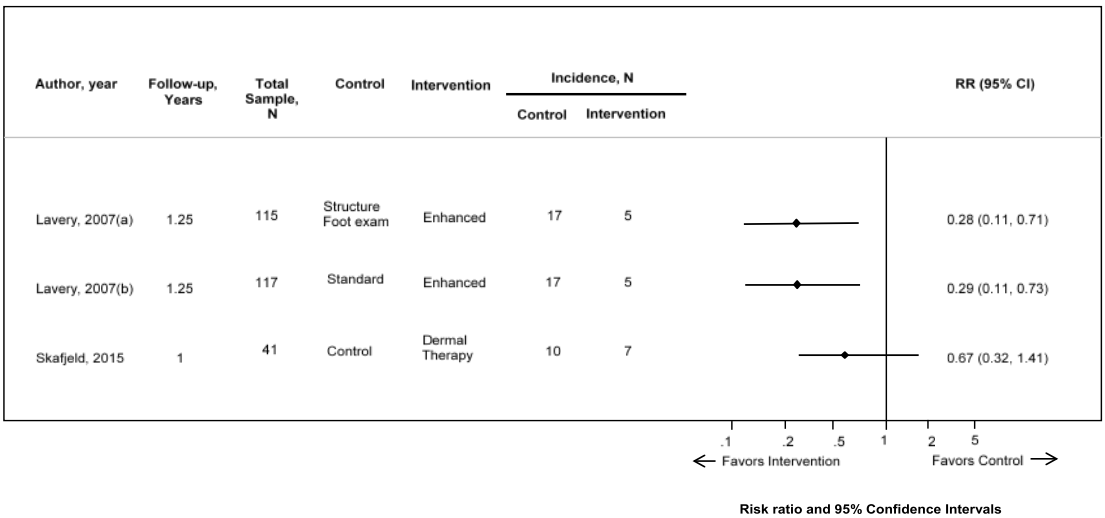
In our updated search, we did not identify any new studies that evaluated the effectiveness of integrated care for foot ulcers.

Self-Management

Four studies, three RCTs from the Netten review and one newly identified RCT, evaluated the effectiveness of home monitoring of foot temperature on the incidence or recurrence of foot ulcers. Areas on foot that are likely to ulcerate have been associated with increased local skin temperatures due to inflammation. An infrared skin temperature device was used to provide objective information to patients to identify an early warning sign of inflammation and tissue injury.[57] The review by Netten et al. found a significant reduction in foot ulcer incidence based on two studies with low risk of bias with moderate strength of evidence.[58, 59] One RCT reported 12.2% patients ulcerated in the standard care group compared with 4.7% in the dermal thermometry group (OR 3.0; 95% CI, 1.0 to 8.5; P=.038)[59] Another RCT reported the foot temperature monitoring group had significantly fewer incident diabetic foot ulcer (2.4% vs. standard therapy group 16%, P<0.05).

In addition, one RCT with low risk of bias included in the Netten review [60] reported a significant reduction in foot ulcer recurrence with instructions to perform structured foot inspection daily and to use an infrared skin thermometer after 15 months (8.5%), compared with either standard care plus instructions to perform daily foot inspection (30.4%, p=0.006) or with standard care alone (29.3%, p=0.008). One newly identified RCT with unclear risk of bias reported no statistically significant benefit from home-monitoring foot temperature on foot ulcer recurrence (7 ulcer recurrences out of 21 patients vs. 10 recurrences out of 20 patients).[60] Figure 5 summarizes results from those studies.

Figure 5. Studies showing reduction in recurrence of foot ulcers in patients using home monitoring of foot temperature*



* The figure shows results from 2 RCTs on recurrence. The study by Lavery et al., consisted of 3 study groups, including 2 separate comparisons.
CI=confidence interval; N=sample size; RR=risk ratio

Two studies evaluated the effectiveness of improving self-inspection of the feet through use of foot topical treatments on the outcome of foot ulcers. The Netten et al. review included one low risk of bias RCT of applying topical antifungal nail lacquer on a daily basis and found no benefit after 12 months as compared with standard care (5.9% vs. 5.6% ulcer incidence, p=0.9).[61]

In our updated search, we identified a retrospective cohort study[52] that explored the predictors of diabetic foot ulcers among diabetic neuropathy patients. With moderate risk of bias, this study showed that application of moisturizing lotion to the feet was associated with higher incidence of subsequent foot ulcer (HR, 1.19; 95% CI, 1.04 to 1.36). This result may reflect the severity of disease of the patients who engaged in more foot lotion application. The study also reported no benefit from examining the bottom of feet or examining between toes on foot ulcer prevention.

A variety of foot care self-management programs have been evaluated showing heterogeneous effects. Use of home monitoring of the temperature of the feet was effective in lowering foot ulcer incidence. Improving self-inspections through topical application did not seem to be effective. We graded the strength of evidence as moderate for use of home monitoring of the temperature for foot ulcer incidence and insufficient for topical application.

Patient Education

Four studies evaluated the effectiveness of educational programs on diabetic foot ulcer and its complications. The Netten et al. review concluded that there was no reduction in ulcer recurrence from one-time single educational programs, based on two RCTs: one with high risk of bias[62] and one with low risk of bias,[63] and a low overall strength of evidence.

One newly identified RCT with high risk of bias[49] reported no cases (0%) of foot ulcer in the group receiving the education program versus six cases (10%) in the standard care group which was not receiving the education program (p=0.012). A newly identified cohort study with low risk of bias showed a hazard ratio of 1.16 (95% CI, 0.95 to 1.41, p=0.055) comparing patients who did not attend an education program to those who did attend an education program.[50] Results are thus inconsistent on the effect of education programs on foot ulcer prevention. We

concluded that education programs were not effective for foot ulcer prevention based on the overall evidence.

Therapeutic Footwear

The Netten review included seven RCTs and three cohort studies on a variety of therapeutic footwear in preventing a first foot ulcer in at-risk patients with diabetes. Among those studies, RCTs reported custom-made digital silicon orthoses,[64] intensive footwear therapy based on a prescription algorithm,[65] shape or barefoot pressure-based custom-made insoles,[66] or therapeutic shoes[67] were effective in lowering the foot ulcer incidence. Cohort studies also reported decreased ulcer recurrence in patients wearing therapeutic sandals,[68], and in patients who were beneficiaries of prescribed diabetic footwear compared to those wore their own footwear.[69.] However, selection bias cannot be ruled out and may be an important determinant of outcome. We did not find new studies in our updated search.

The review rated the strength of evidence as moderate for the use of various therapeutic footwear.

Surgical Interventions

The review by Netten et al.[18] included three RCTs and six cohorts, evaluating a variety of surgical procedures to decrease foot ulcer recurrence risk in patients with diabetes with non-healing foot ulcers. The review authors concluded based on low strength of evidence that Achilles tendon lengthening, single- or pan-metatarsal head resection, and metatarsophalangeal joint arthroplasty appear to reduce foot ulcer recurrence in some patients with initially non-healing foot ulcers when compared with non-surgical treatment. Achilles tendon lengthening allows a patient to walk flat-footed without a bend in the knee. Single- or pan-metatarsal head resection includes either removing bone segments underlying the lesion or conservative treatment (i.e. relief of weight-bearing and regular dressing). Metatarsophalangeal joint arthroplasty prevents the surfaces of the joint toe from rubbing together. It is noted that surgical interventions are often performed in selected patients who did not respond well in previous treatments. Those patients may be at high risk of foot ulcer recurrence.[18]

Lower Extremity Amputation

Eleven studies, five RCTs and six cohorts, reported non-pharmacologic interventions and prevention of amputation outcomes. The Netten et al. systematic review did not grade the strength of evidence for amputation outcomes.

Integrated Foot Care

Four studies (2 RCTs and 1 cohort study from Netten et al. review and 1 newly identified cohort study) evaluated the effect of integrated foot care on amputation outcomes. One RCT with high risk of bias[53] reported no amputation (0%) in patients who received standard care plus a foot care kit, were asked to perform daily foot care, had the involvement of a family member, attended hands-on workshops, received re-education every 3 to 6 months, and had monthly foot exams by an endocrinologist and a diabetes nurse versus two minor amputations (6.9%, p=0.46) in patients who received standard care plus foot assessment and 2 hours of diabetes education, including tips on foot care. Another RCT with low risk of bias[55] reported two minor amputations (4%) in patients who received free chiropodist service versus one minor amputation (2%) in patients who received chiropodist service, if requested, but not free-of-charge. One cohort with

high risk of bias reported 7 percent amputation with multidisciplinary foot care; podiatry every 3 months, or more often, if needed; re-education; and extra depth shoes versus 13.7 percent with education provided by the local endocrinologist or nurse and followup review examinations from local physicians every 3 months.[56] One newly identified cohort study with low risk of bias[51] reported a significant 20 to 25 percent reduction in lower extremity amputations and 30 to 35 percent reduction in major amputations if patients had prior podiatrist visits. We cannot draw conclusions about the effects of integrated foot care on amputation outcomes owing to the limited number of amputation cases and inconsistency of results between RCTs and cohort studies.

Self-Management

One RCT in the Netten et al. review with low risk of bias reported no cases of amputation in patients who received instruction to perform structured foot inspection daily plus infrared skin thermometer versus one case of amputation in patients who received instruction to perform structured foot inspection daily only.[59]. In our updated search, we did not identify any studies of self-management on amputation outcomes.

Patient Education

We identified three studies (1 RCT from Netten et al. review and 2 newly identified studies) evaluating effectiveness of education programs regarding diabetic foot disease and its complications. One RCT with low risk of bias in the Netten review reported no benefit from a single educational session about amputation (RR 1.0; 95% CI, 0.91 to 1.11). One newly identified RCT with high risk of bias did not report any amputations in either group.[49] A cohort study[50] with low risk of bias did not find a significant difference between patients who attended an education program and those who did not attend an education program about amputation. Results from all three studies suggested that education programs did not change the occurrence of amputation.

Therapeutic Footwear

One cohort study of therapeutic footwear with high risk of bias in the Netten et al. review reported no cases of amputation in 24 patients who accepted a prescription of orthopedic footwear and wore the footwear while being active versus two cases of amputation in 22 patients who did not ask for such a prescription.[70] (p=0.13). In our updated search, we did not identify any studies of therapeutic footwear. We graded the strength of evidence as insufficient.

Surgical Interventions

The Netten et al. review identified two cohort studies evaluating surgical interventions on amputation outcomes. One cohort with low risk of bias reported no difference among patients who received multiple metatarsal head resections for multiple metatarsal head ulcers versus moisture-retentive dressing.[71]. Another cohort[72] reported significant reduction in amputation rate in patients who received subtraction osteotomy ahead of metatarsal head ulcer to redress bone axis plus arthrodesis with staples versus conservative treatment (2.5% vs. 14.9%, p=0.04). We did not identify new studies in the updated search. We graded the strength of evidence as low.

Quality of Life

Home Monitoring of Foot Temperature

An RCT by Lavery et al [57] compared standard therapy with enhanced therapy that included a handheld infrared skin thermometer to measure temperatures on the foot. The investigators used the SF-36 to evaluate functional status and found no statistical differences in the SF-36 scores (total or subcategory scores) either between groups or, in the pre- and post- study evaluations, within groups. We graded the strength of evidence as insufficient.

Surgical Interventions

In our updated search, we identified one 8-month RCT[73] with high risk of bias that evaluated Achilles tendon lengthening (ATL) after total contact casting (TCC) on foot ulcer recurrence, quality of life using SF-36, and perceived disability. Achilles tendon lengthening is performed in high-risk patients with diabetes, peripheral neuropathy, and a history of recurrent ulcers. The study reported a worse score in SF-36 physical summary after Achilles tendon lengthening as compared with- TCC only (p=0.035), while no difference between the interventions in other physical performance outcomes was found. There was insufficient evidence to address the effectiveness of Achilles tendon lengthening for quality of life after total contact casting.

Harms

The prior review[18] did not assess adverse effects. Two of the five newly identified studies reported adverse effects.[48, 50] One high risk of bias study[48] reported no dropouts in the control group and three dropouts in the intervention group. Statistical testing was not reported. Another study[50] with low risk of bias reported glycemia-related emergency department visits and found no difference between the two groups [n=43 (0.5%) in attendees vs. n= 44 (0.6%) in non-attendees; RR 1.02; 95% CI, 0.58 to 1.77]. The same study also reported a significantly increased risk of cardiovascular events in patients who attended an education program versus patients who did not attend an education program (16.66 per 1000 person-year vs. 15.14 per 1000 person-year; 99% CI, 0.9 to 1.31; p=0.036). Adverse effects were not systematically documented in clinical trials. We were unable to draw conclusions, as most studies did not report harms.

Lifestyle Intervention

Key Point

- There was insufficient evidence from one study on lifestyle intervention and any of the diabetic peripheral neuropathy complications.(Insufficient strength of evidence)

Table 8. Summary of findings for lifestyle intervention

Outcomes	Comparison	Number of Studies (N)	Findings	Strength of Evidence
Quality of Life	Dietary Intervention: vitamin B12 alone vs. education on plant-based diet plus Vitamin B12	1 RCT (N=34)	We could not draw conclusions based on insufficient evidence from one study.	Insufficient

RCT =Randomized Controlled Trial

Description of Included Studies

Only one 20-week pilot randomized trial assessed the effectiveness of dietary interventions using a plant-based diet and Vitamin B12 to improve quality of life with diabetic peripheral neuropathy. [74] This was a single-center study conducted in the United States. The trial included 34 patients with type 2 diabetes. The risk of bias was high. The main potential cause of bias was lack of allocation concealment and blinding; details of allocation and blinding were not reported.

Outcomes

Quality of Life

One trial assessed the benefit of a plant-based diet on health-related quality of life using the Norfolk Quality of Life Questionnaire.[74] The trial reported no significant difference in total score (difference of mean change: -4.0; 95% CI, -15.1 to 7.1) of the Norfolk Quality of Life Questionnaire between the intervention arm that received nutrition education about a plant-based diet plus a B12 supplement and the comparison arm that received B12 only. We could not draw conclusions due to insufficient evidence from one study (Table 8).

Harms

No harms data were reported.

Balance Training and Whole Body Vibration Interventions

Definition: In this review, we used the term *balance training* to refer to exercises designed to improve balance, with better control of movement of center of mass and improved coordination of lower extremities.[75-77] measured with and without quantitative devices, force plates, or platform systems (Biodex); using established balance scales (TUG, Berg balance, FRT); and under static and dynamic conditions. Computerized balance devices enable computation of anterior-posterior stability, medio-lateral stability, and overall stability.

Key Points

- Balance training did not improve the outcomes of physical activity or perceived fall risk.
- Evidence was inconsistent for the effect of balance training on balance outcomes.
- There was insufficient evidence to assess the effect of balance training and whole body vibration interventions on quality of life.

Table 9. Summary of findings for balance training and whole body vibration

Outcome	Comparison	Number of Studies (N)	Findings	Strength of Evidence*
Falls	Balance training vs control group	1 RCTs (reported in 2 articles)	We could not draw conclusions based on	Insufficient

Outcome	Comparison	Number of Studies (N)	Findings	Strength of Evidence*
		(N=79)	insufficient evidence from one study.	
	Whole body vibration	None	NA	Insufficient
Foot ulcer	Balance training	None	NA	Insufficient
	Whole body vibration	None	NA	Insufficient
Quality of life	Balance training vs control group	1 RCT (N=39)	We could not draw conclusions based on insufficient evidence from one study.	Insufficient
	Whole body vibration	None	NA	Insufficient

*we graded only the key outcomes (falls, foot ulcer, amputation, and quality of life)
Please see Appendix table E-3 -Strength of evidence table for domains
NA = not applicable, RCT =Randomized Controlled Trial

Description of Included Studies

We identified seven studies (reported in 8 articles) that assessed the effect of balance training and/or whole body vibration on balance outcomes, physical activity, perceived fall risk, falls, and quality of life. Balance interventions include static, dynamic, and progressive balance exercises, generally supervised by a physical therapist, and may include simulation training. Whole body vibration applies vibratory stimuli with the aim of activating leg musculature and improving balance; whole body vibration was conducted in these studies with an applied frequency of 30 Hz and an amplitude of one to three millimeters.

Five RCTs (reported in 6 articles) and one non-randomized study compared balance training with a control group (no intervention) [75-81] (one trial also included simulation as part of the training[78]). One RCT compared whole body vibration therapy with a control group[82] and one RCT included combined whole body vibration and balance training, balance training alone, and control arms.[76]

The number of participants in the included studies ranged from 20 to 79, with a total of 320 participants in all studies. Duration of followup ranged from 3 weeks to 12 months. The average age of the participants ranged from 57 to 77 years and most studies included a percentage of female participants at more than 50 percent. Three RCTs studied patients with type 2 diabetes[75, 78, 82] and one RCT studied patients with both type 1 and 2 diabetes[79, 80] The remaining two RCTs and the non-randomized trial did not specify the type of diabetes patients.[76, 77, 81]

The overall risk of bias for most of the studies was low. Bias was unclear in some studies owing to poor reporting regarding allocation concealment, random sequence generation, assessing blinding by the outcome, and other sources of bias. Studies generally had a low risk of bias regarding incomplete outcome data and selective outcome reporting.

One trial also included exercise training components and, therefore, physical activity outcomes for this study are included in the exercise training section.[79, 80]

Outcomes

Dynamic Balance and Stability

Five trials (reported in six articles) and one non-randomized study assessed dynamic balance and stability outcomes, measured using the Berg Balance Scale (BBS), Timed Up and Go Test (TUG) and Functional Reach Test (FRT). Five studies evaluated the effects of balance training[76-

[82] one trial evaluated whole body vibration with balance training [76] and one trial evaluated whole body vibration alone.[82]

For balance training, standardized mean difference could not be calculated for many of the studies due to incomplete data, so results from the scales are provided. Four of the trials, reported in five articles, reported effects on the BBS.[76-80] The difference between the balance training group and the control group for the mean change from baseline ranged from 0.2 to 2.0 on a 0-56 scale, with the direction of effect favoring the intervention group.

Five of the balance training trials, reported in six articles, reported effects on the TUG.[76-80, 82] Four trials, reported in five articles, compared TUG outcomes in balance training and control groups.[76-80] The mean difference between the balance training group and the control group for the mean change from baseline ranged from –2.12 to 0.1, (the minimal clinically important difference is 1-2 seconds), with the direction of effect favoring the intervention group.

Three of these balance training studies (2 RCTs and one non-randomized study) also reported effects on the Functional Reach Test (FRT).[76, 77, 81] The difference between the balance training group and the control group ranged from 0.4 to 8.97, with the direction of effect favoring the intervention group. Evidence was imprecise and inconsistent for the effect of balance training on balance outcomes.

For whole body vibration, results are presented as standardized mean difference. The study combining balance training with whole body vibration reported effects on the Berg Balance Scale (BBS) with a standardized mean difference of 1.77 (95% CI, 1.01 to 2.53), Timed Up and Go Test (TUG) with an standardized mean difference of -1.95 (95% CI, -2.74 to -1.17) and Functional Reach Test (FRT) with an standardized mean difference of 1.72 (95% CI, 0.967 to 2.48), all with the direction of effect favoring the intervention group.[76] The study of whole body vibration alone reported effects on the Timed Up and Go Test (TUG) [82]; with an standardized mean difference of -2.47 (95% CI, -3.63 to -1.31), with direction of effect favoring the intervention group (negative standardized mean difference denotes less time required to complete task). One of the studies also reported effects on the, with the direction of effect favoring the intervention group. Given the heterogeneity of interventions (whole body vibration alone vs combined with balance training), we were unable to draw any conclusions.

Physical Activity

For balance training, three trials (reported in four articles) assessed physical activity outcomes such as 6-minute walk test; 10-meter walk test; total daily steps; and time spent sitting, standing, and walking.[75, 77, 79, 80]

A RCT of balance training (reported in two articles) assessed 6-minute walk outcomes in balance training and control groups.[79, 80] The effect size was -0.04 (95% CI, -0.52 to 0.43) in the direction favoring the control group.

Another RCT of balance training assessed a 10-meter walk test.[77] The standardized mean difference was -0.51 (95% CI, -1.16 to 0.13), direction of effect favoring the intervention group.

Two of these trials of balance training, reported in three articles, also assessed the effect on total daily steps.[75, 79, 80] The effect size for the difference between groups in change in activity from baseline at 12 months ranged from 0.15 to 0.16 in the direction favoring the intervention group, with similar results at earlier timepoints.

One of these RCTs of balance training also assessed the effect on time spent sitting, standing, or walking during a 48-hour period.[75] The effect size was 0.01 for sitting, 0.04 for standing, and 0.14 for walking (95% CI not given, but not statistically significant).

Based on the lack of findings of effectiveness, we concluded that balance training did not improve physical activity.

Studies of whole body vibration did not evaluate physical activity.

Perceived Fall Risk

Three RCTs (reported in four articles) and one non-randomized study[75, 78-81] assessed perceived fall risk among participants, each study using a different scale of assessment. The heterogeneity in assessment outcomes precluded pooling of data.

Two RCTs, reported in three articles, evaluated the effect on the Falls Efficacy Scale (FES)[79, 80] or FES-I (international version, modified to be more culturally and socially sensitive)[75] score between balance training and control groups.[75, 79, 80] The standardized mean difference for FES/FES-I ranged from -0.13 to zero.

Another RCT of balance training reported the effect on the Fall Risk Index, with a standardized mean difference of -1.21 (95% CI -1.94 to -0.48), in the direction favoring the intervention group.[78]

A non-randomized study assessed the effect on the Activities-specific Balance and Confidence (ABC) scale.[81] The standardized mean difference was 0.42 (95% CI, -0.58 to 1.41) in the direction favoring the intervention group.[81] Based on the lack of findings of effectiveness, we concluded that balance training did not improve perceived fall risk.

Studies of whole body vibration did not evaluate perceived fall risk.

Falls

For balance training, one RCT, reported in two articles, assessed falls per 1000 person-days of follow at 12-month followup.[79, 80] There was no statistically significant difference in falls between the balance training group and the control group (2.06 versus 2.02 falls/1000 person-days, respectively). We could not draw conclusions due to insufficient evidence from one study.

No studies of whole body vibration evaluated falls (Table 9).

Quality of Life

For balance training, one RCT reported the outcome of quality of life.[75] It reported the SF-12 physical component score; standardized mean difference was 0.012 (95% CI, -0.65 to 0.68), in the direction favoring the intervention group. We could not draw conclusions due to insufficient evidence from one study.

No studies of whole body vibration evaluated quality of life (Table 9).

Harms

For balance training, one study reported no dropouts owing to adverse effects in either group.[75] In another study, one of the participants in the intervention group dropped out owing to ankle pain.[81]

Exercise Training Interventions

Definition: Exercise training is defined as maintaining or increasing physical activity for the purpose of fitness and can be done solo or in a group. For this review, fitness activities which did not include supervision by physical therapists were classified in the exercise category.

Key Points

- Exercise training did not improve the outcomes of physical activity or perceived risk of fall.
- There was insufficient evidence to assess the effect of exercise training on falls, foot ulcer, amputation, and quality of life.

Table 10. Summary of findings for exercise training interventions by outcome

Outcome	Number of Studies (N)	Findings	Strength of Evidence*
Falls	1 RCT (reported in 2 articles) (N=79)	We could not draw conclusions based on insufficient evidence from one study.	Insufficient
Foot ulcer	1 RCT (reported in 2 articles) 1 prospective cohort study (N=469)	We could not draw conclusions based on inconsistent findings from a limited number of studies.	Insufficient
Quality of life	1 RCT (N=87)	We could not draw conclusions based on insufficient evidence from one study.	Insufficient

Note that table is organized by outcome, so some trials are listed more than once
*we graded only the key outcomes (falls, foot ulcer, amputation, and quality of life)
Please see Appendix table E-3 -Strength of evidence table for domains
RCT = Randomized Controlled Trial

Description of Included Studies

Five studies, reported in six articles, assessed the effect of exercise training.[79, 80, 83-86]

Exercise training interventions included treadmill training[83, 85] and/or muscle strengthening,[79, 83, 84] with sessions ranging from two to six times per week and up to 360 minutes total time per week.[85]

Four studies, reported in five articles, were parallel arm RCTs comparing exercise training interventions with a control condition.[79, 80, 83-85]One study was a prospective cohort comparing three study groups classified by self-reported physical activity level (number of self-reported hours per day of any weight-bearing activity, including standing, walking, or more active).[86]

The number of participants in the five studies ranged from 27 to 390, with a total of 638. Duration of followup ranged from 4 weeks to 2 years. All studies except one included patients with type 2 diabetes mellitus, but the diabetes type was not specified in the cohort study.[86] The average age of the participants ranged from 54 to 73 years of age. Two trials included participants with a mean BMI in the obese category.[79, 80, 83]

The overall risk of bias for trials was low. These trials had generally low risk of bias regarding random sequence generation, blinding of outcome assessors, and selective outcome reporting. However, the risk of bias was unclear regarding the allocation concealment, incomplete outcome data, and other source of bias. The overall risk of bias for the cohort study was graded as moderate. The primary sources of bias were in the selection of participants and bias due to confounding.

We also included one of the RCTs, reported in two articles, in the balance training section, as the study intervention also aimed to improve balance.[79, 80] Another RCT included exercise and physical therapy components but is only described in this section given overlap in outcomes.[84]

Outcomes

Physical Activity

Two RCTs, reported in three articles, assessed the effect of exercise training on the physical activity outcome using the distance traveled in the 6-minute walk test and total daily steps.[79, 80, 83]

For the 6-minute walk test, the mean difference from baseline between groups ranged from -0.04 meters (95% CI, -0.52 to 0.43)[80] to 0.35 meters (95% CI not reported, but was not statistically significant).[83]

For total daily step counts, the effect size for the difference between groups in change in daily steps from baseline to 12 months was 0.16 (95% CI, -0.31 to 0.63), with similar results at earlier time points.[79, 80] Based on the lack of effect, we concluded that exercise did not improve physical activity outcomes.

Perceived Fall Risk

Two studies, reported in three articles, used different scales to assess perceived fall risk among participants.

One RCT, reported in two articles, evaluated the difference in the Falls Efficacy Scale (FES) score between exercise training and control groups.[79, 80] Standardized mean difference was 0 (95% CI, -0.44 to 0.44).

Another RCT used the ABC scale to assess an exercise training group versus a control group.[84] The reported intervention effect size was 0.5 (95% CI not reported, $p<0.05$) in the direction favoring the intervention group.

Based on the lack of consistent findings, we were unable to draw any conclusions on the effect of exercise training on perceived fall risk.

Falls

One RCT(reported in two articles) assessed falls per 1000 person-days after 12 months of followup.[79, 80] The difference in falls between the exercise training group and the control group was 2.06 versus 2.02 falls/1000 person-days, respectively, and was not statistically significantly different. We could not draw conclusions due to insufficient evidence from one study (Table 10).

Foot Ulcer

One RCT (reported in 2 articles) and one prospective cohort study assessed outcomes of foot ulceration.[79, 80, 86]

The RCT evaluated the effect of exercise training on foot ulcers.[79, 80] At the end of 12 months, the incidence rate of all foot ulcers, defined as any disruption of skin surface at or below malleolus, was not statistically different in the intervention group when compared to the control group (0.63 versus 0.51 lesions/person-year at risk; rate ratio 1.24; 95% CI, 0.70 to 2.19). The incidence rate of full thickness ulcers was similar in both groups (0.21 versus 0.22 lesions/person-year at risk; rate ratio 0.96; 95% CI, 0.38 to 2.42).

One prospective cohort study evaluated outcomes of foot ulceration in three participant groups based on their daily physical activity: least active (less than 4.5 active hours/day), moderately active (4.5 to 7.5 active hours/day), and most active (more than 7.5 active hours/day). The incidence rate of re-ulceration at 2 years followup was statistically significantly higher in the least active group when compared to the two other groups [16.5% in the least active group with OR 1 (95% CI not reported), 13.4% in the moderately active group with OR 0.66 (95% CI, 0.36 to 1.19), and 13% in the most active group with OR 0.36 (95% CI, 0.16 to 0.82)].[86] We graded the strength of evidence as insufficient (Table 10).

Quality of Life

One RCT assessed the outcome of quality of life between exercise and control groups. [85] Standardized mean difference was -4.9 (95% CI, -5.74 to -4.06), in the direction of effect favoring the intervention group. We could not draw conclusions due to insufficient evidence from one study (Table 10).

Harms

Only one RCT reported on harms and only for risk of severe hypoglycemia: 23.4 percent of participants in the control arm experienced severe hypoglycemia compared to 5 percent in the exercise training arm. The hypoglycemic events in the control group were insulin/oral hypoglycemic agent-related and in the intervention group, the events were exercise-related. [85]

Physical Therapy Interventions

Definition: Physical therapy was defined as any physical and therapeutic activity performed under the guidance of a physical therapist.

Key Points

- No physical therapy intervention studies evaluated the outcomes of perceived fall risk, falls or quality of life.

Table 11. Summary of findings for physical therapy interventions

Outcome	Number of Studies (N)	Findings	Strength of Evidence*
Falls	None	NA	Insufficient
Foot ulcer	1 RCT of weight-bearing vs non-weight-bearing activity (N=29)	We could not draw conclusions based on insufficient evidence from one study.	Insufficient
Quality of life	None	NA	Insufficient

*we graded only the key outcomes (falls, foot ulcer, amputation, and quality of life)
Please see Appendix table E-3 -Strength of evidence table for domains
RCT = Randomized Controlled Trial, NA = not applicable

Description of Included Studies

Two RCTs assessed the effect of physical therapy interventions in diabetic peripheral neuropathy.[87, 88] One RCT compared two types of physical therapy exercises to improve physical activity: weight bearing (n=15) versus non-weight bearing (n=14), each conducted in-group exercise sessions supervised by a physical therapist.[87] The other RCT assessed Thai foot massage to improve balance, modified foot massage performed by traditional Thai massage therapist, (n=30) compared to a non-massage control intervention (n=30).[88] One trial reported followup of 12 weeks[87], and the other trial reported a mean followup of 2 weeks[88] The average age of the participants was 64 years in one trial,[87] and 58 years in the other trial.[88] One trial included participants with mean BMI in the obese category[87] and one included participants with mean BMI in the overweight category.[88] Overall risk of bias in these trials was low.

Outcomes

Balance

The RCT comparing Thai foot massage to control used the TUG instrument to assess the impact on balance.[88] The standardized mean difference was -0.46 (95% CI, -0.46 to -0.82), with the direction of effect favoring the intervention group[88].

Physical Activity

One trial reported data on physical activity. The RCT comparing weight bearing to non-weight bearing physical activity measured outcomes with average daily steps and the 6-minute walk test.[87] The standardized mean difference was 0.66 (95% CI, -0.09 to 1.41) with the direction of effect favoring the weight-bearing group. The standardized mean difference for the 6-minute walk test was 0.28 (95% CI, -0.45 to 1.01) with the direction of effect favoring the weight-bearing group.[87]

Given the limited number and heterogeneity of studies and interventions, we were unable to draw any conclusions.

Falls/Perceived Fall Risk

No studies reported data on falls or perceived fall risk.

Foot Ulcer

One RCT assessed outcomes of foot ulceration.[87] There was one ulcer in the weight-bearing exercise group compared with three ulcers in two participants in the non-weight-bearing exercise group. We could not draw conclusions due to insufficient evidence from one study (Table 11).

Quality of Life

No studies reported quality of life.

Harms

No harms data were reported.

Discussion

Key Findings and Implications

We identified 62 studies (30 studies from a prior systematic review, and 32 newly identified studies) that addressed the benefits and harms of pharmacologic and non-pharmacologic treatment options to prevent the complications of diabetic peripheral neuropathy in patients with type 1 and type 2 diabetes. We assessed glycemic control (including individual hypoglycemic medications and the effect of lowering blood glucose), foot care, surgical interventions, lifestyle interventions, balance training, exercise training, and physical therapy. Our review focuses on complications of diabetic peripheral neuropathy, specifically diabetic foot ulcers, lower extremity amputations, falls, physical activity level, perceived risk of falling, and quality of life.

Our review showed the benefit of intensive versus standard glycemic control for preventing lower extremity amputations in patients with type 2 diabetes. However, amputation was not the primary outcome in any of the included studies and the event rates were very low. We identified only one large RCT conducted in type 1 diabetic patients and this study reported no difference for intensive compared to standard glycemic control for the prevention of lower extremity amputations.[89]

There was no benefit for diabetic foot ulcers for glycemic control versus standard control for patients with either type 1 or type 2 diabetes, although the number of events were low. Only one RCT assessed the effectiveness of one glucose-lowering medication compared to another glucose-lowering medication for prevention of diabetic foot ulcers and lower extremity amputations and this study found no difference in benefit. Intensive glycemic control had higher rates of hypoglycemia than standard treatment.

For foot care interventions aimed at the prevention of foot ulcers and amputations, moderate strength of evidence supported home monitoring of foot skin temperature for the reduction of recurrence of diabetic foot ulcers. However, three out of the four studies were done by the same investigators; additional studies by different investigative teams are needed to confirm reproducibility. Integrated foot care interventions were also shown to prevent ulcer recurrence, but the assessment of the effect of patient education about foot care on foot ulcer prevention was inconclusive. The review we updated concluded that specific modalities of therapeutic footwear are effective in the prevention of a recurrent plantar foot ulcer compared with more standard-of-care therapeutic footwear. For amputation outcomes, evidence was not consistent regarding benefit from integrated foot care, as the review by Netten et al. did not show significant difference while one newly identified study reported significant reduction. The previous systematic review [18] reported no benefit from an education session and the findings from newly identified studies were consistent with this previous conclusion.

Results were inconsistent for the effect of balance training on specific balance measures. Balance training did not improve outcomes of physical activity or perceived risk of falling. Exercise also did not improve physical activity or perceived risk of falling. Data were insufficient to assess the effect of physical therapy alone on physical activity levels. No physical therapy intervention studies evaluated the outcome of perceived risk of falling. The strength of evidence for physical therapy, exercise, or balance training was insufficient for falls outcome.

We found few studies that assessed the benefits of glycemic control or foot care for improving quality of life. The strength of evidence was insufficient to provide conclusions favoring one treatment over another for improving quality of life for patients with diabetic peripheral neuropathy.

Findings in Relationship to What Is Already Known

Our review confirms the conclusions from three recent systematic reviews that addressed intensive versus standard glycemic control for the prevention of lower extremity amputations in patients with type 1 and type 2 diabetes. [89-91] In contrast with these reviews, our review also assessed the prevention of foot ulcers when reported in the included studies. However, diabetic foot ulcers are likely under-reported owing to the possibility of limited outcome ascertainment if the ulcer had healed prior to the data collection visit and because it was not a primary or adjudicated outcome in any studies. Because diabetic foot ulcer is often in the causal pathway leading toward gangrene and the indication for lower extremity amputation, the reduction in ulcer rates was consistent with the direction for the prevention of lower extremity amputation, a more distal outcome. Overall, the preponderance of evidence supports intensive glycemic control in patients with type 2 diabetes to prevent lower extremity amputations. Few studies had evidence supporting intensive glycemic control for ulcer prevention in patients with type 1 and type 2 diabetes. The recent guidelines from the Society for Vascular Surgery and collaborative professional organizations included foot ulcer prevention in its recommendations for the prevention of amputation, and recommended achieving a hemoglobin A1c of seven percent or

lower (intensive control) to reduce foot ulcer incidence. [92] Although our review was unable to quantify the long-term risks associated with intensive glycemic control, the ACCORD trial has raised significant concerns about very intensive glycemic control (hemoglobin A1c goal less than 6%) strategies and increased cardiovascular disease mortality.[93]

We updated a recent systematic review by Netten et al. on foot care interventions to prevent ulcers and lower extremity amputations.[18] Evidence from this previous systematic review supports an integrated foot care program that involves podiatrist care for reducing foot ulcer recurrence.[18] This is consistent with the recommendation from the Society for Vascular Surgery that patients with diabetes should undergo annual interval foot inspections by physicians, podiatrists or advanced practice providers with training in foot care. Regarding foot care, home-monitoring of foot skin temperature also reduces foot ulcer recurrence based on 2 RCTs. [48, 60] There was no benefit from patient education on foot ulcer prevention, similar to other reviews. The previous systematic review by Netten et al. also concluded that specific modalities of therapeutic footwear could be effective in the prevention of a recurrent plantar foot ulcer at selected high risk patients; we did not identify any new studies for these interventions. However, the Society for Vascular Surgery recommended against the routine use of specialized therapeutic footwear in average-risk diabetic patients, while it did recommend using custom therapeutic footwear in high-risk diabetic patients, including those with significant neuropathy, foot deformities, or previous amputation.[92] Finally, Netten et al. reported that Achilles tendon lengthening, single- or pan-metatarsal head resection, and metatarsophalangeal joint arthroplasty appear to reduce ulcer recurrence risk in selected patients with initially non-healing ulcers.[18] In our updated search, one new study reported statistically significantly worsened quality of life (as measured using the SF-36 physical function summary score) after Achilles tendon lengthening versus total contact casting and no difference in ulcers. [56, 94] The report from the Society for Vascular Surgery did not address Achilles tendon lengthening, single- or pan-metatarsal head resection, or metatarsophalangeal joint arthroplasty for ulcer prevention. [92]

Finally, our review is the first of which we are aware to assess the outcomes of falls and perceived risk of falling in patients with type 1 and 2 diabetes and diabetic peripheral neuropathy.

Applicability

Our results are highly applicable to patients with type 2 diabetes and with diabetic peripheral neuropathy. For the complications of diabetic peripheral neuropathy, we graded the body of evidence for outcomes (ulcers, amputations, falls and quality of life) which are clinically important as well as important to patients. Diabetic foot ulcers are likely under-reported in these studies and few studies assessed perceived risk of falling, an outcome important to patients. The studied populations were typically those with type 2 diabetes older than 50 years of age, so the findings may not apply to younger patients or those with type 1 diabetes. Several trials comparing intensive versus standard glycemic control followed the study population with observational followup, enabling ascertainment of longer-term outcomes, such as amputation and ulcers, in patients with longstanding diabetes.

Limitations of the Review Process

We did not include non-English studies. However, we did not limit our searching by language and, where possible, screened non-English language articles for eligibility. We do not feel that the exclusion of the non-English studies influenced our conclusions or ability to draw

conclusions. We excluded studies of mixed populations with diabetic peripheral neuropathy and other types of neuropathy that did not report outcomes separately for diabetic peripheral neuropathy. This may have excluded some relevant data.

For foot care, we identified a relevant high-quality review meaning that we did not have to complete a systematic review de novo. However, there are challenges in using a prior review. For instance, there are some areas where we do not have the same level of detail as we would if we had completed the assessment and abstraction of all of the primary studies.

Finally, our review questions focused on patients with a diagnosis of type 1 or type 2 diabetes and so we make no conclusions about the prevention of neuropathy, progression to more severe neuropathy or neuropathic complications (e.g., foot ulcers and amputations) in patients with impaired glucose tolerance.

Strengths and Limitations of the Evidence Base

Despite the clinical importance and importance to patients of falls, we identified few studies that assessed the effect of pharmacologic and non-pharmacologic interventions on falls and perceived risk of falling in patients with diabetic peripheral neuropathy.

The major strength of the evidence base is the availability of long-term followup in RCTs assessing diabetic foot complications in patients with type 1 and 2 diabetes. Because foot ulcer and amputations were secondary outcomes in these studies, the limitation of the evidence is that many ulcers, and possibly amputations, were missed owing to the need to review medical records and a lack of standard outcome ascertainment protocols. Foot ulcer and amputation event rates were low resulting in small absolute risk differences between groups. Despite these small absolute differences, foot ulcers and amputation are clinically relevant and patient-important outcomes, and despite lack of statistical significance, could be clinically significant. We identified few studies of individual glucose lowering medications that reported the outcomes of foot ulcer or amputation. In addition, few studies assessing glycemic control reported on other patient reported outcomes, such as quality of life.

For foot care and surgical interventions, the major limitation is that the types of therapeutic footwear and surgical interventions varied across studies. It is difficult to make conclusions about the effectiveness of a specific intervention based on a few number of studies. In addition, surgery is sometimes a last-resort approach. Patients with diabetes who receive surgeries are often selected because of previously failed conservative treatment and therefore at high risk of foot ulcer recurrence. Furthermore, most of the cohort studies were considered high risk of bias due to unblinded outcome assessment by investigators.[18]

The limitations for the evidence base on balance, exercise, and physical therapy interventions were the reliance on intermediate measures of balance, falls, and function. It was not clear how well these measures correlate with long-term benefits and with the patient-important outcomes of falls and the ability to perform activities of daily living.

The included studies were heterogeneous in study design, population, intervention, outcomes reported and length of follow up limiting our ability to synthesize results. The studies addressing pharmacologic treatment did not systematically report harms of treatment, or provide references to publications where harms were described. For foot care, because the studies evaluated multiple types of interventions (e.g., type of therapeutic footwear; surgical procedures) and the number of studies per comparison was limited, we were unable to make conclusions about the risks or benefits of specific interventions and conduct rigorous comparative effectiveness evaluations. Balance training exercises adopted in these studies were diverse ranging from

physical therapist guided training to computerized systems, which limited our ability to draw conclusions by intervention type.

Implications for Clinical and Policy Decisionmaking

Our results have implications for the clinical management of patients with diabetic peripheral neuropathy. The strongest evidence favors a more intensive glycemic control approach for patients with type 2 diabetes, but potential benefits need to be balanced with known harms of intensive treatment, such as hypoglycemia and the potential for increased cardiovascular events and mortality with very intensive control,[95, 96] a concern identified in other reviews and meta-analyses specifically addressing this topic. Our review confirms existing practice for more intensive approaches to glycemic control in patients with diabetes to prevent complications associated with diabetic peripheral neuropathy, although the target A1c is not clear. Evidence supporting referrals for particular foot care programs, physical therapy modalities, or balance training is limited due to concerns about intermediate measures as outcomes, lower study quality and few studies per intervention.

Future Research Needs

We identified the need for future research in several areas. Because few studies focused on diabetic peripheral neuropathy in patients with type 1 diabetes, we suggest future research in this unique population.

Regarding interventions, we identified a need for studies to test physical therapy modalities and balance training programs appropriately tailored to the needs of patients with diabetic peripheral neuropathy to prevent falls and improve mobility, function, and quality of life. In addition, future research is needed on low-cost interventions, such as home monitoring of foot skin temperature, as well as health services programs that incorporate a multidisciplinary foot care model for patients with diabetic peripheral neuropathy.

Long-duration studies that assess the effects of glucose lowering medications on a variety of long-term complications of diabetes also need to develop protocols to include diabetic peripheral neuropathy-related complications (ulcers, amputations, and falls). Protocols that systematically assess these patient-important diabetic foot complications, using periodic prospective data collection with foot exams, surveys and medical record review, are needed to capture these outcomes. Even among the few studies that reported on these outcomes, event rates were low, in part due to their lack of systematic ascertainment. Having consistent outcome ascertainment methods across multiple studies would strengthen our ability to combine studies and make accurate estimates of benefits. Nonetheless, although observational studies can provide additional data, cohort studies are still limited due to unobserved confounding factors and selection bias, e.g. why certain patients receive therapy vs. those without intervention. In addition to the collection of data on diabetic peripheral neuropathy related ulcers and amputations, future research needs to evaluate the outcomes of falls and perceived fall risk. Because altered proprioception due to diabetic peripheral neuropathy can also increase risk of falling and fear of falling, these are important clinical and patient-oriented outcomes that should be addressed in future studies.

Conclusions

We confirmed results from prior reviews in type 2 diabetes that more intensive glycemic control is associated with reduced lower extremity amputations compared with standard glycemic control. However, event rates in the studies were very low. For foot ulcers, we found no effect of intensive glycemic control compared with standard glycemic control. We identified few studies in type 1 diabetes.

For foot care, a previous review found that home monitoring of foot skin temperatures, the use of therapeutic footwear, or integrated foot care may be effective in preventing ulcer incidence or recurrence. Our new search identified only a few new studies and these did not change the conclusions. For falls, neither balance training nor exercise improved outcomes of physical activity or perceived risk of falling. Exercise also did not improve physical activity or perceived risk of falling, and only one study evaluated falls as an outcome.

We recommend that future studies comparing monotherapy and combination pharmacotherapies in patients with type 1 and type 2 diabetes include the complications of diabetic peripheral neuropathy as outcomes, specifically assessing foot ulcers, amputations, falls, and perceived risk of falling. Additional studies evaluating balance, exercise and physical therapy interventions for diabetic peripheral neuropathy are also needed, and should evaluate the patient-relevant outcomes of perceived risk of falling and falls.

Results for Key Questions (KQs) 2a and 2b

Results of the Search

We included 129 studies (57 studies from an existing review, 47 newly identified additional studies reported in 48 articles, and 25 studies from ClinicalTrials.gov). Figure 6 summarizes the search and selection of the primary studies. (See Appendix C for list of citations excluded at full-text level, with reasons for exclusion)

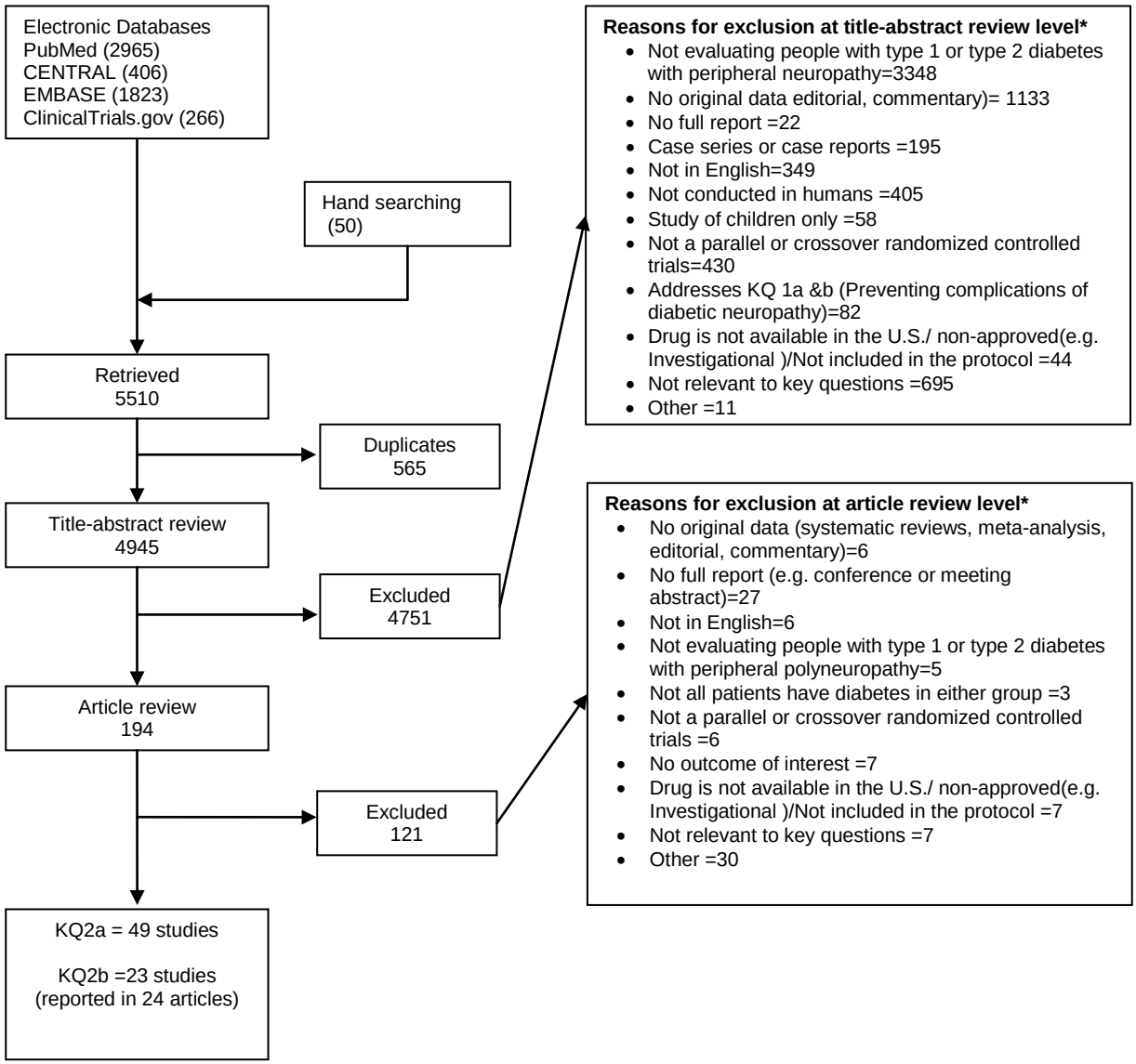
The breakdown of the included studies for KQ2a and b by study design is:

- KQ2a -106 randomized controlled trials (RCTs) (57 RCTs from existing systematic review, 24 additional RCTs and 25 from ClinicalTrials.gov);

- KQ2b - Supplements (alpha-lipoic acid, acetyl-L-carnitine)- 7 RCTs;
- KQ2b - Acupuncture - 1 RCT;
- KQ2b - Cognitive behavioral therapy -1 RCT;
- KQ2b - Electrical Stimulation- 7 RCTs;
- KQ2b - Electromagnetic Stimulation- 4 RCTs;
- KQ2b - Spinal Cord Stimulation - 2 RCTs;
- KQ2b - Surgical Decompression - 1 RCT (reported in 2 articles)

The findings are summarized in Tables 12 to 17.

Figure 6. Summary of the literature search for primary studies: treating symptoms



* Reviewers did not need to agree on reason for exclusion
KQ = Key Question, RCT = Randomized controlled trial

KQ2a: Benefits and Harms of Pharmacologic Treatment Options To Improve Symptoms

Key Points

- The anticonvulsants pregabalin and oxcarbazepine (low strength of evidence), the serotonin-noradrenaline reuptake inhibitors duloxetine and venlafaxine (moderate strength of evidence), the drug classes of tricyclic antidepressants (low strength of evidence) and atypical opioids (tramadol and tapentadol) (low strength of evidence), and the intradermal neurotoxin botulinum toxin (low strength of evidence) were more effective than placebo for reducing pain in diabetic peripheral neuropathy.
- We were unable to draw conclusions for quality of life with pharmacologic treatments due to incomplete reporting across studies (insufficient strength of evidence).
- All oral treatments had substantial rates of adverse effects, with dropout rates due to adverse effects of greater than 9 percent for all effective treatments.

Table 12. Summary of key effectiveness results on pain and quality of life

Outcomes* Comparison	Number of Studies Reporting Outcome (N)	Findings	Strength of Evidence**
Pain intensity **Placebo-controlled comparisons**			
Key anticonvulsants			
Pregabalin vs placebo	**16 studies** Previous SR: 6 RCTs Additional identified studies: 6 RCTs ClinicalTrials.gov: 4 RCTs (N=4017)	The previous review concluded that pregabalin was more effective than placebo for reducing pain (Standardized mean difference, -0.55 [95% CrI -0.94 to -0.15]) For an updated meta-analysis of 15 RCTs, the Standardized mean difference was -0.34 (95% CI, -0.50 to -0.18). The new studies did not change the conclusion.	Low
Gabapentin vs placebo	**5 studies** Previous SR: 3 RCTs Additional identified studies: 2 RCTs, one with 2 different arms at maximum dose (N=766)	The previous review concluded that there was no difference in effectiveness of gabapentin compared to placebo for reducing pain (Standardized mean difference -0.73 [95% CrI, -1.54 to 0.09]). Additional identified RCTs at maximum dose were consistent with this finding (Standardized mean difference -0.65 [95% CI, -1.1 to -0.23], -0.27 [95% CI, -0.7 to 0.14]) and -0.20 ([95% CI, -0.46 to 0.06]). The new studies did not change the conclusion.	Low

Outcomes* Comparison	Number of Studies Reporting Outcome (N)	Findings	Strength of Evidence**
Oxcarbazepine vs placebo	**3 studies** Previous SR: 3 RCTs Additional identified studies: None (N=634)	The previous review concluded that oxcarbazepine was more effective than placebo for reducing pain (Standardized mean difference -0.45 [CrI,-0.68 to -0.21]). We did not identify new studies.	Low
Key serotonin- noradrenaline reuptake inhibitors			
Duloxetine vs placebo	**7 studies** Previous SR: 5 RCTs Additional identified studies: 2 RCTs (N=2203)	The previous review concluded that duloxetine was more effective than placebo for reducing pain (Standardized mean difference -1.33 [CrI, -1.82 to -0.86]). Additional identified RCTs were consistent with this finding (Standardized mean difference -0.33 [95% CI, -0.54 to -0.12] for the one study where this could be calculated). The new studies did not change the conclusion.	Moderate
Venlafaxine vs placebo	**2 studies** Previous SR: 2 RCTs Additional identified studies: None (N=304)	The previous review concluded that venlafaxine was more effective than placebo for reducing pain (Standardized mean difference, -1.53 [CrI, -2.41 to -0.65]) We did not identify new studies.	Moderate
Tricyclic antidepressants			
Tricyclic antidepressants (TCAs) vs placebo	**4 studies** Previous SR: 4 RCTs Additional identified studies: None (N=81)	The previous review concluded that TCAs were more effective than placebo for reducing pain (Standardized mean difference -0.78 [CrI, -1.24 to -0.33]). We did not identify new studies.	Low
Opioids			
Oxycodone vs. placebo	**4 studies** Previous SR: 2 RCTs Additional identified studies: 1 RCT ClinicalTrials.gov: 1 RCT (N = 583)	The previous review concluded that opioids (all studies of oxycodone) were not more effective than placebo for reducing pain [Standardized mean difference -0.58 (95% CrI, -1.53 to 0.36)]. For two additional identified RCTs, one published trial reported a standardized mean difference of -0.24 [95% CI, -0.47 to -0.01] and one trial from clinicaltrials.gov found a standardized mean difference of -0.06 (95% CI, -0.46	Low

Outcomes* Comparison	Number of Studies Reporting Outcome (N)	Findings	Strength of Evidence**
		to 0.34) The new studies did not change the conclusion.	
Atypical opioids (tramadol and tapentadol) vs. placebo	**5 studies** Previous SR: 2 RCTs Additional identified studies: 3 RCTs (N=1177)	The previous review did not report on atypical opioids separately. We conducted a new meta-analysis. Meta-analysis – Standardized mean difference -0.68 (95% CI, -.80 to -0.56). Atypical opioids are more effective than placebo for reducing pain.	Low
Topical capsaicin			
Topical capsaicin 0.075% vs placebo	**5 studies** Previous SR: 3 RCTs Additional identified studies: 2 RCTs (N=432)	The previous review concluded that capsaicin 0.075% was more effective than placebo for reducing pain (Standardized mean difference -0.91 [CrI, -1.18 to -0.08]). The pooled Standardized mean difference from a meta-analysis of 3 studies (2 from previous review and 1 new study) where a Standardized mean difference could be calculated was -0.46; 95% CI, -0.95 to 0.03) Capsaicin is not more effective than placebo for reducing pain.	Low
Topical capsaicin patch 8% vs placebo	**1 study** Previous SR: None Additional identified studies: None Clinicaltrials.gov: 1 RCT (N=369)	We could not draw conclusions based on insufficient evidence from one study.	Insufficient
Dextromethorphan			
Dextromethorphan vs placebo	**3 studies** Previous SR: 2 RCTs Additional identified study: 1 RCT (N =416)	The previous review concluded that dextromethorphan was not more effective than placebo for reducing pain (Standardized mean difference -0.28 [95% CrI, -1.49 to 0.92]). We could not calculate a Standardized mean difference for the newly identified study. The new study did not change the conclusion	Low
Mexiletine vs placebo	**5 studies**	The previous review concluded that mexiletine was not more	Low

Outcomes* Comparison	Number of Studies Reporting Outcome (N)	Findings	Strength of Evidence**
	Previous SR: 5 RCTs Additional identified studies: None (N=389)	effective than placebo for reducing pain (Standardized mean difference, -0.29 [95% CrI, -0.91 to 0.33]). We did not identify new studies.	
Botulinum toxin vs placebo	**2 studies** Previous SR: None Additional identified studies: 2 RCTs (N=60)	The previous review did not include this drug. Botulinum toxin is more effective than placebo for reducing pain. The Standardized mean difference ranged from -0.96 to -0.79	Low
Key drug-drug comparisons			
Duloxetine vs. pregabalin	**2 studies** Previous SR: 1 RCT Additional identified study: 1 RCT (N =411)	We could not draw conclusions due to insufficient evidence.	Insufficient
Quality of life* - Griebeler et al did not assess this outcome**			
Key anticonvulsants			
Gabapentin vs placebo	**3 RCTs** Additional identified studies: 3 RCTs (N =646)	We could not draw conclusions due to incomplete reporting of results and inconsistent results.	Insufficient
Pregabalin vs placebo	**10 RCTs** Additional identified studies: 7 RCTs (N =1746)	We could not draw conclusions due to incomplete reporting of results and inconsistent results.	Insufficient
Key serotonin-noradrenaline reuptake inhibitors			
Duloxetine vs placebo	**3 RCTs** (N=1006)	We could not draw conclusions due to incomplete reporting of results and inconsistent results.	Insufficient
Opioids			
Atypical opioids vs placebo	**4 RCTs** (N =1157)	We could not draw conclusions due to incomplete reporting of results and inconsistent results	Insufficient

* Only key comparison and outcomes are included in the table.

**we graded only the key outcomes (pain and quality of life)

Since this is an update of a prior systematic review, for the pain outcome the results are generally reported as (1) results from the Griebeler et al. network meta-analysis, (2) whether results from additional identified studies are consistent or inconsistent with Griebeler et al., and (3) specific results from these additional studies.

Anticonvulsants are not summarized as a drug category overall, given divergent results among drugs. A new meta-analysis was conducted for pregabalin and atypical opioids, given a significant number of new studies with potentially inconsistent results with Griebeler et al.

** Griebeler et al. did not abstract results for quality of life outcome; we abstracted these results from the studies. Since many studies did not report actual values for quality of life, but only statistical significance, results could only be summarized as the number of studies reporting statistical significance.

Please see Appendix table E-4 and E-5 -Strength of evidence table for domains

RCT= randomized clinical trial; SR= systematic review; SMD= standardized mean difference; CrI=credible interval; SNRIs = Serotonin–norepinephrine reuptake inhibitors

Description of Included Studies for Treatment of Pain

Summary of Studies Included in Systematic Review

Griebeler et al. conducted a systematic review, identifying RCTs through April 2014, to evaluate the comparative effectiveness of oral and topical analgesics for the outcome of pain for painful diabetic peripheral neuropathy. The investigators included 65 RCTs (57 RCTs eligible for our review that included 10,639 patients and compared 21 medications). Included trials were mostly short-term (less than three months) (mean followup: 14 weeks for all short- and long-term studies); very few extended beyond 3 months, and these studies of longer duration (which were all less than 5 months in length) were not included in their main analyses. The review authors evaluated the efficacy of one outcome, pain, by standardizing the results from pain intensity scales to estimated standard mean difference. The review authors included studies reporting less than 3 months of followup in a network meta-analysis to compare drug classes and individual drugs to placebo and to each other. Key findings from their network meta-analysis of short-term studies are shown in Appendix D. The review authors concluded that the evidence is scant and often derived from trials of less than five months in duration, the majority of which had an unclear or high risk of bias.

Summary of Studies Identified From Updated Search and ClinicalTrials.gov

Our literature search identified 25 comparisons (24 RCTs) not included in the Griebeler et al. review. (One RCT[97] included two drugs (pregabalin and gabapentin in separate arms, both compared to placebo.) Followup ranged from three to 18 weeks (we included all additional studies in the update and did not separate out studies by length of followup), with a median of 12 weeks of duration. Seventeen trials were multicenter studies. Four trials had academic funding and two did not report a funding source; the remaining twenty-one were industry funded. All of the trials were published between 1987 and 2015. The number of participants ranged from 20 to 804. All trials were placebo-controlled except for one trial comparing duloxetine, pregabalin, and combination therapy, (only the duloxetine and pregabalin comparison was abstractable and reported here.)[98]

We found an additional 25 trials in ClinicalTrials.gov for which we were unable to identify a publication. Of these, 18 trials are completed, two are withdrawn, three are recruiting, and two have an unknown status. 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%) reported results in ClinicalTrials.gov (Table 13).

Table 13. Number of studies addressing pain symptoms of diabetic peripheral neuropathy

Drug class	N of studies included from Griebeler et al.	N of studies in updated search	N of completed studies identified in ClinicalTrials.gov only (N of studies with reported results)
Placebo comparisons			
Anticonvulsants			
Carbamazepine	1	0	0
Gabapentin	3	2	1(0)
Lacosamide	4	0	1(0)
Lamotrigine	3	0	0
Oxcarbazepine	3	0	0
Pregabalin	6	6	10(4)
Topiramate	2	1	1(0)
Valproic acid	2	0	0
Zonisamide	0	1	0
Serotonin-Noradrenaline Reuptake Inhibitors (SNRIs)			
Desvenlafaxine	0	1	0
Duloxetine	5	2	0
Milnacipran	0	0	1(0)
Venlafaxine	2	0	0
Tricyclic antidepressants (TCAs)			
Amitriptyline	1	0	0
Desipramine	1	0	0
Imipramine	2	0	0
Opiates			
Oxycodone	2	1	1(1)
Tapentadol ER	1	2	0
Tramadol/Acetaminophen	1	1	0
Topical Agents			
Capsaicin 0.075%	3	2	1(0)
Capsaicin 8% patch	0	0	2(1)
Clonidine	0	1	1(0)
Lidocaine	0	0	2 (0)
N-methyl-D-aspartate receptor antagonists			
Dextromethorphan	2	1	0
Class IB antiarrhythmic			
Mexiletine	5	0	0
Botulinum Toxin	0	2	1 (0)
Cannabinoids			
Nabilone	0	1	1 (0)
Nabiximols	0	0	1 (1)
Trials Comparing Medications of Different Classes			
Amitriptyline vs. Duloxetine vs. Pregabalin	1	0	0
Amitriptyline vs. Lamotrigine	1	0	0
Amitriptyline vs. Maprotiline vs. Placebo	1	0	0

Drug class	N of studies included from Griebeler et al.	N of studies in updated search	N of completed studies identified in ClinicalTrials.gov only (N of studies with reported results)
Amitriptyline vs. Topical Capsaicin 0.075%	1	0	0
Duloxetine vs. Pregabalin*	0	1	2 (0)
Gabapentin vs. Amitriptyline	1	0	0
Gabapentin vs. Topical lidocaine	0	0	1 (0)
Pregabalin vs. Amitriptyline	1	0	0
Imipramine vs. Paroxetine	1	0	0
Venlafaxine vs. Carbamazepine	1	0	0

*1 study listed above compared these two drugs in a three-armed trial
TCAs -Tricyclic antidepressants, SNRIs- Serotonin-Noradrenaline Reuptake Inhibitors

Outcomes

Pain

Placebo-Controlled Comparisons

Anticonvulsants

Forty-two RCTs assessed the effect of anticonvulsants compared with placebo on pain (20 RCTs from the Griebeler et al. review, 10 RCTs from an updated search, and 13 RCTs from ClinicalTrials.gov). We analyzed each anticonvulsant separately, given heterogeneity in effectiveness.

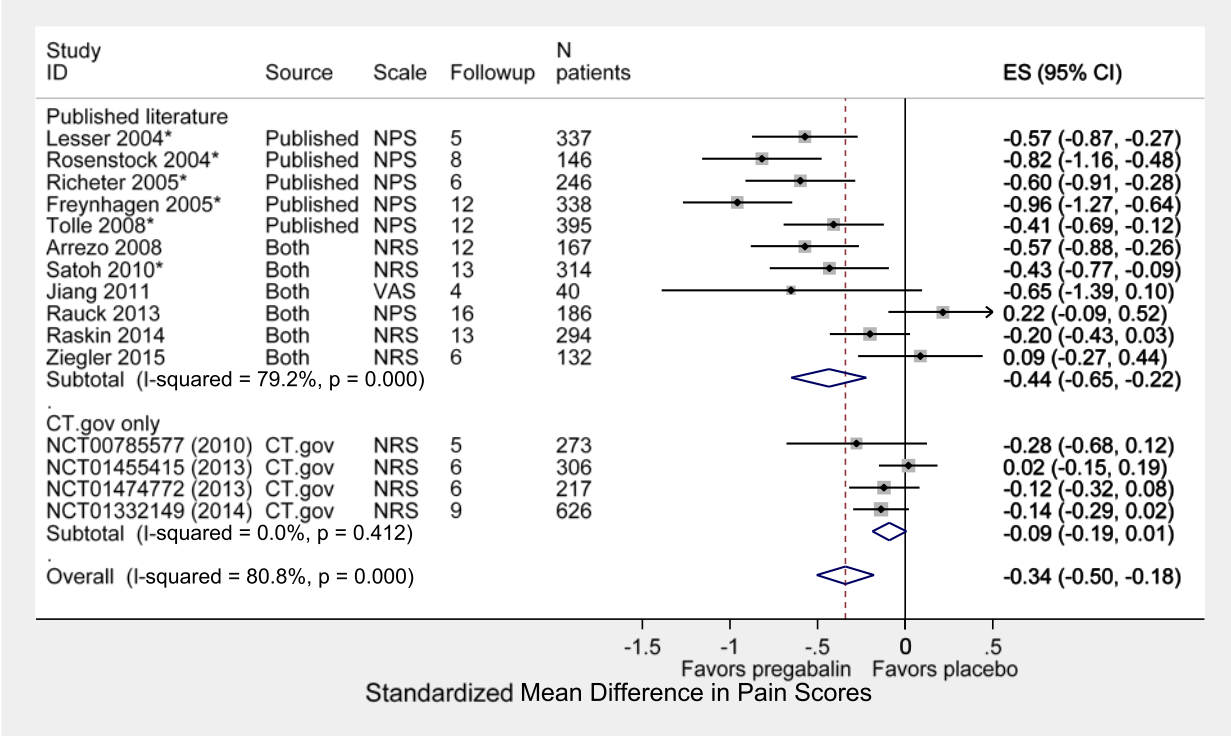
Pregabalin Versus Placebo

Twenty-two RCTs (6 RCTs from the Griebeler et al. review, 6 RCTs from an updated search, and 10 RCTs from ClinicalTrials.gov, 4 of which had available data) assessed the effect of pregabalin compared with placebo on pain.

We conducted a new meta-analysis for pregabalin, given the additional studies with inconsistent findings. (A meta-analysis limited to the five RCTs published since Griebeler et al. where a standardized mean difference could be calculated, and all four unpublished RCTs, did not show that pregabalin was more effective than placebo for reducing pain (Standardized mean difference, -0.13; 95% CI, -0.27 to 0.01) (data not shown). In addition, we identified six RCTs in ClinicalTrials.gov with no available results.

In the overall pooled results from the full meta-analysis, based on the 15 (out of 16) trials where a standardized mean difference could be calculated from Griebeler et al., the updated search, and RCTs from ClinicalTrials.gov with available data, pregabalin is more effective than placebo for reducing pain (Standardized mean difference, -0.34; 95% CI, -0.50 to -0.18). (Figure 7). (Standardized mean difference could not be calculated due to incomplete crossover trial data for one additional study,[99] but this study reported statistically insignificant findings.) However, we found no trials longer than 3 months, this is a small effect size, and there was significant heterogeneity in the findings (I-squared, 80%) (Figure 7). We considered the strength of evidence low due to inconsistency across the studies, as well as because of suspected reporting bias.

Figure 7. 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

Gabapentin Versus Placebo

Six RCTs (3 RCTs from the Griebeler et al. review, 2 RCTs from an updated search, and 1 RCT from ClinicalTrials.gov) assessed the effect of gabapentin compared with placebo on pain.

Griebeler et al. (based on three short-term RCTs) concluded that gabapentin was not more effective than placebo (Standardized mean difference, -0.73 [95% CrI, -1.54 to 0.09]). Two RCTs from the updated search were consistent with this finding, with an Standardized mean difference of -0.65 [95% CI, -1.1 to -0.23], -0.27 [95% CI, -0.7 to 0.14] and -0.20 [95% CI, -0.46 to 0.06]) (including results from two different doses for gabapentin in one study).[97, 100] All the trials were of gabapentin encarbil (which is a long-acting bioequivalent) and short-term in duration. One RCT (NCT00904202) from ClinicalTrials.gov was completed in June 2003 but did not report any results. Since results of new studies were consistent with Griebeler et al., we did not conduct a new meta-analysis.

Overall, based on the available data, gabapentin is no more effective than placebo for reducing pain. We considered the strength of evidence low due to inconsistency across the studies, suspected reporting bias, and unclear risk of bias.

Oxcarbazepine Versus Placebo

Three RCTs from the Griebeler et al. review assessed the effect of oxcarbazepine compared with placebo on pain.

Griebeler et al. concluded (based on three 16 week studies), that oxcarbazepine was more effective than placebo (Standardized mean difference from long-term network, -0.45 [95% CrI, -0.68 to -0.21]) (small effect size). Oxcarbazepine is more effective than placebo for reducing pain. We considered the strength of evidence low due to inconsistency among the studies, incomplete reporting and unclear risk of bias.

Topiramate Versus Placebo

Four RCTs (2 RCTs from the Griebeler et al. review, 1 RCT from the updated search, and 1 RCT from ClinicalTrials.gov) assessed the effect of topiramate compared with placebo on pain.

Griebeler et al. concluded (based on one RCT) that topiramate was not more effective than placebo (Standardized mean difference was -0.45 [95% CrI, -1.98 to 1.08]) in short-term studies. In long-term studies, Griebeler et al. also concluded that topiramate was not more effective than placebo for reducing pain based on one RCT. One additional identified RCT of topiramate was consistent with this finding, with a standardized mean difference of -0.14 (95% CI, -0.62 to 0.34).[101] One RCT (NCT00231673) from ClinicalTrials.gov was completed in January 2003 but did not report any results.

Overall, based on the available data, topiramate is no more effective than placebo. We considered the strength of evidence low due to consistency across the studies, imprecise findings and unclear risk of bias.

Zonisamide Versus Placebo

We identified one RCT of zonisamide with an standardized mean difference of -0.63 (95% CI, -1.47 to 0.21).[102] Griebeler et al. did not include zonisamide. We were unable to draw a conclusion about zonisamide. We considered the strength of evidence as insufficient given only one study.

Other Anticonvulsants (Valproic Acid, Lacosamide, Carbamazepine, Lamotrigine) Versus Placebo

Griebeler et al. found that all other anticonvulsants evaluated (valproic acid, lacosamide, carbamazepine, lamotrigine) were not more effective than placebo in short-term studies (see Appendix D for details), and we identified no additional RCTs. We considered the strength of evidence low for all of these anticonvulsants, due to inconsistency across the studies, except for carbamazepine, where we could not draw conclusions due to insufficient evidence from one study.

Antidepressants

Serotonin-Noradrenaline Reuptake Inhibitors Versus Placebo

Ten studies assessed the effect of serotonin-noradrenaline reuptake inhibitor antidepressants compared with placebo on pain [7 RCTs from the Griebeler et al. review (all short-term RCTs) and 3 RCTs from an updated search (2 for duloxetine[103, 104] and 1 for desvenlafaxine[105])].

Greibeler at al. concluded that serotonin-noradrenaline reuptake inhibitor antidepressants overall were more effective for the outcome of pain compared with placebo [Standardized mean difference, -1.36 (95% CrI, -1.77 to -0.95)] (large effect size). In additional identified studies, standardized mean difference ranged from -0.33 to -0.11 for serotonin-noradrenaline reuptake inhibitors [-0.33 (95% CI, -0.54 to -0.12) and -0.11 (95% CI, -0.42 to 0.21)].

We did not redo the Griebeler et al. meta-analysis for the outcome of pain for serotonin-noradrenaline reuptake inhibitors because the evidence both overall for this drug class and for

duloxetine specifically was consistent with the results of Griebeler et al. and the conclusions are therefore not changed.

Individual Serotonin-Noradrenaline Reuptake Inhibitors

Duloxetine Versus Placebo. Seven studies (5 RCTs from the Griebeler et al. review and 2 RCTs from an updated search) assessed the effect of duloxetine compared with placebo on pain.

Griebeler et al. (based on 5 RCTs) concluded that duloxetine was more effective than placebo (Standardized mean difference, -1.33 [95% Crl, -1.82 to -0.86]) (large effect size). Findings from two RCTs from an updated search were consistent with this finding. Standardized mean difference was -0.33 [95% CI, -0.54 to -0.12]) although standardized mean difference could be calculated only for one study.[103]. For other RCT of duloxetine, [104] standardized mean difference could not be calculated, but the least squares mean change from baseline was -2.8 in the duloxetine arm and -2.1 in the placebo arm (p=0.03 in the direction favoring effectiveness of duloxetine). Since results of additional identified studies were consistent with Griebeler et al., we did not conduct a new meta-analysis.

Overall, based on the available data, duloxetine is more effective than placebo. We considered the strength of evidence moderate due to consistency across the studies, precise findings and unclear risk of bias.

Venlafaxine Versus Placebo. Two RCTs (2 RCTs from Griebeler et al. and 0 RCT from updated search) assessed the effect of venlafaxine compared with placebo on pain.

Griebeler et al. concluded (based on two RCTs) that venlafaxine was more effective than placebo (Standardized mean difference, -1.53 [95% Crl, -2.41 to -0.65]) (large effect size). We considered the strength of evidence moderate due to consistency across the studies, precise findings and unclear risk of bias.

Desvenlafaxine Versus Placebo. One RCT (Griebeler et al. did not include desvenlafaxine) identified from the updated search assessed the effect of desvenlafaxine compared with placebo on pain.

Standardized mean difference was -0.11 (95% CI, -0.42 to 0.21).[105] We could not draw conclusions due to insufficient evidence from one study.

Milnacipran Versus Placebo. One RCT (NCT01288937) identified in ClinicalTrials.gov completed in October 2014 did not report any results.

Tricyclic Antidepressants

Four RCTs from the Griebeler et al. review reported in five articles assessed the effect of tricyclic antidepressants compared with placebo on pain. All four RCTs were short-term. We identified no new studies.

Griebeler et al. concluded that tricyclic antidepressants were more effective than placebo in reducing pain (Standardized mean difference, -0.78 [95% Crl, -1.24 to -0.33]) and that one specific drug, amitriptyline, was more effective than placebo (Standardized mean difference, -0.72 [95% Crl, -1.35 to -0.08]) (moderate effect size).

We considered the strength of evidence low for the effectiveness of tricyclic antidepressants overall in reducing pain due to imprecision and inconsistency across the studies, low for the individual drug imipramine due to imprecision, inconsistency across the studies, and high risk of bias, and insufficient for desipramine and amitriptyline.

Analgesics

Opioids (Oxycodone) Versus Placebo

Four RCTs (2 RCTs from the Griebeler et al. review described in three articles, one RCT from an updated search, and one RCT from ClinicalTrials.gov) assessed the effect of opioids (all on oxycodone controlled-release) compared with placebo on pain.

Griebeler et al. concluded, based on network meta-analysis of the three articles, that oxycodone was not more effective than placebo [Standardized mean difference, -0.58 (95% CrI, -1.53 to 0.36)]. The individual standardized mean differences for the 2 RCTs were -0.50 (95% CI, -0.81 to -0.18) and -1.28 (-1.92 to -0.64). The additional identified published trial [106] found a Standardized mean difference, -0.24 (95% CI, -0.47 to -0.01). One RCT (NCT00944697) from ClinicalTrials.gov reported pain results but the results were limited to the final values. The standardized mean difference was -0.06 (95% CI, -0.46 to 0.34). We did not pool these studies due to high statistical heterogeneity (I-squared = 79% and 75% for the published studies and the overall results, respectively).

Overall, based on the available data, opioids are not more effective than placebo for reducing pain. We considered the strength of evidence low due to inconsistency across the studies, suspected reporting bias, and unclear risk of bias.

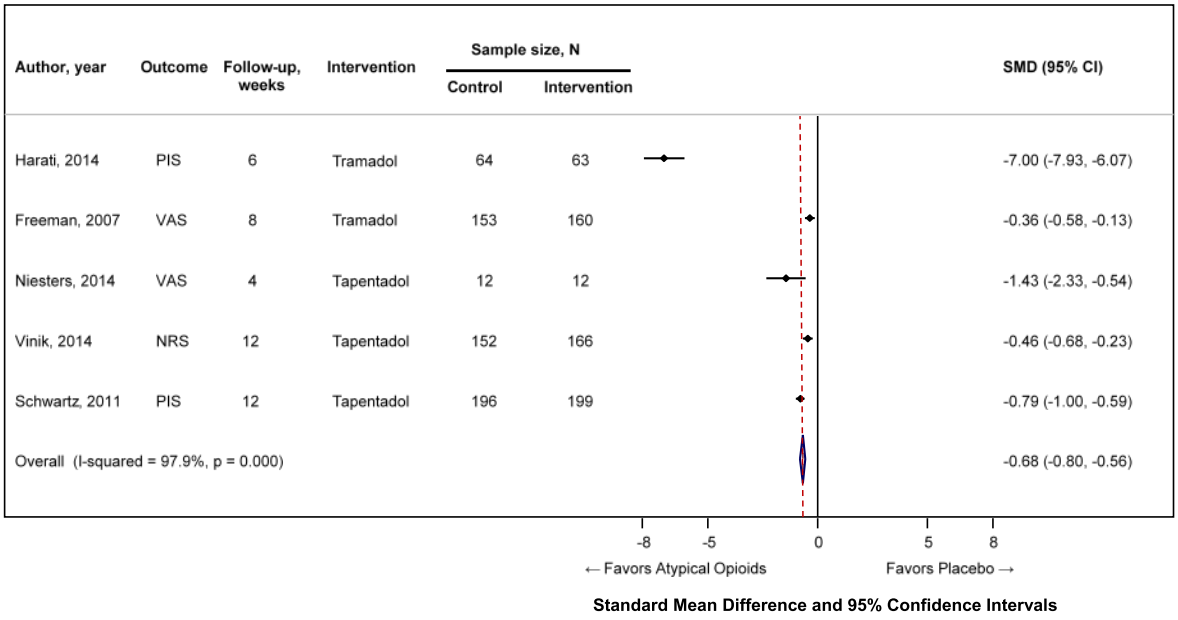
Atypical Opioids (Tapentadol, Tramadol) Versus Placebo

Five RCTs assessed the effect of atypical opioids compared with placebo on pain, two from Griebeler et al. (one each with tramadol/acetaminophen and tapentadol extended-release) and three additional identified studies (two with tapentadol[107, 108] and one with tramadol[109]).

Griebeler et al. did not report on atypical opioids separately. Given different mechanisms of action and the number of new studies, we reanalyzed these separately from other opioids and conducted a new meta-analysis in this drug class. Standardized mean difference ranged from -7.0 to -0.36 (from -1.43 to -0.46 for tapentadol and from -7.0 to -0.36 for tramadol). Excluding the outlier,[109] the standardized mean difference for the meta-analysis of all five studies was -0.57 (95% CI, -0.69 to -0.44), and including the outlier, was -0.68 (95% CI, -0.80 to -0.56) (Figure 8) (moderate effect size).

Overall, based on the available data, atypical opioids are more effective than placebo for reducing pain.We considered the strength of evidence low for atypical opioids overall due to precise but inconsistent findings across the studies, as well as concerns about study methodology. There were particular concerns for the tapentadol studies as they were inconsistent with standards for pain trials, including using nonstandard primary pain outcomes and withdrawal study methodology (of concern for studies of opioids, where withdrawal causes additional symptoms). For individual drugs, we considered the strength of evidence low for use of tapentadol to reduce pain due to these issues, and low for tramadol due to inconsistency across the studies and unclear risk of bias.

Figure 8. Meta-analysis of calculated standardized mean differences for studies comparing an atypical opioid with placebo for pain outcome



CI=confidence interval; N=sample size; SMD=standardized mean difference

Topical Agents

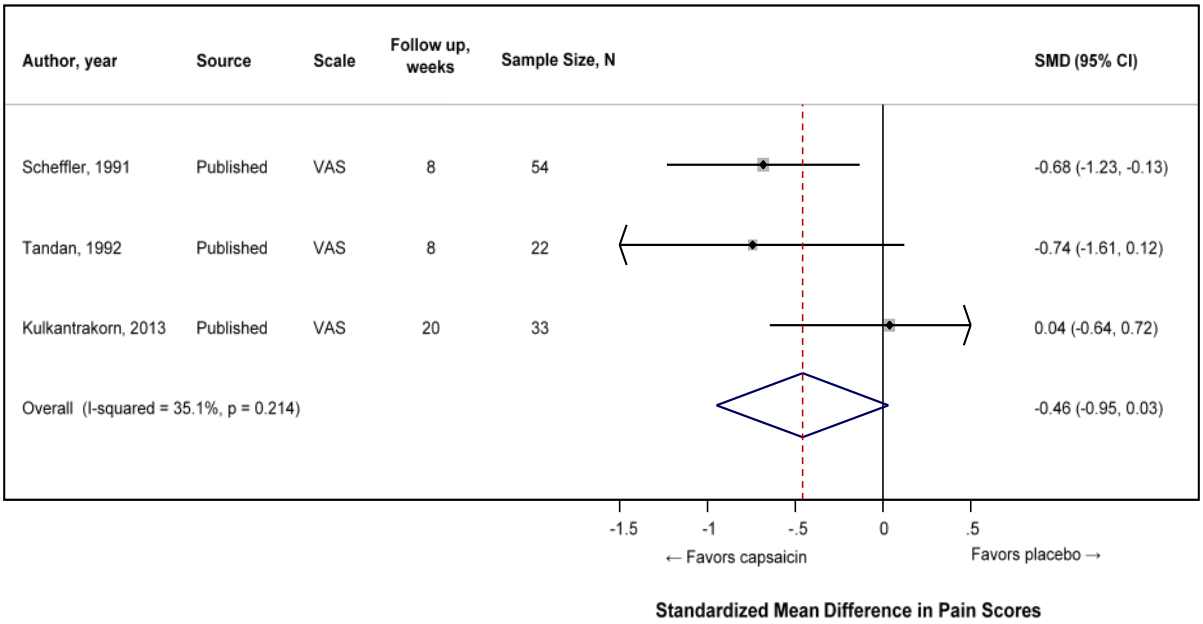
Capsaicin Versus Placebo

We summarized results separately for the 0.075% capsaicin cream and 8% capsaicin topical patch, given different use and potential heterogeneity in effectiveness. Eight RCTs (3 RCTs from Griebeler et al. review and 2 from an updated search, all of 0.075% capsaicin, and 3 from ClinicalTrials.gov (1 of 0.075% and 2 of the 8% patch, only the trial on the 8% patch had results available) assessed the effect of capsaicin compared with placebo on pain.

For 0.075% capsaicin, three RCTs from Griebeler et al. and two RCTs from an updated search[110, 111] assessed topical capsaicin for pain. Griebeler et al. concluded that capsaicin was more effective than placebo (Standardized mean difference, -0.91 [95% Crl, -1.18 to -0.08]). For the one additional RCT identified where standardized mean difference could be calculated, standardized mean difference was -0.04 (95% CI: -0.65 to 0.72). [110] The other RCT [111] only reported the percentage of patients with more than 20 percent improvement for pain severity, which was 71 percent in the capsaicin group compared to 46 percent in the placebo group and was not statistically significant. The results from these two studies were not consistent with the results of Griebeler et al. In a pooled meta-analysis of the three studies where a SMD could be calculated (including 1 new study), topical capsaicin 0.075% was ineffective (SMD, -0.46; 95% CI, -0.95 to 0.03) (Figure 9). Overall, based on the available data, capsaicin 0.075% is no more effective than placebo for reducing pain. We considered the strength of evidence low for capsaicin in reducing pain, due to inconsistency across the studies, imprecision and unclear risk of bias.

For the 8% patch, one trial (NCT01533428) from ClinicalTrials.gov found that the mean between-group difference in the average daily pain score was (in the direction favoring capsaicin) -7.1% (95% CI, -12.9% to -1.2%). We were unable to draw a conclusion on the capsaicin 8% patch, given insufficient evidence from one study.

Figure 9. Meta-analysis of calculated standardized mean differences for studies comparing topical capsaicin 0.075 percent with placebo for pain outcome



CI=confidence interval; SMD=standardized mean difference, VAS =visual analogue scale

Clonidine Versus Placebo

Two RCTs (1 from an updated search and 1 from ClinicalTrials.gov) assessed the effect of the topical version of the alpha-agonist clonidine compared with placebo on pain (this drug was not included in Griebeler et al. review). For the RCT from an updated search, standardized mean difference was -0.50 (95% CI, -1.0 to 0.004). [112] One RCT (NCT02068027) from ClinicalTrials.gov was completed in 2015 but did not report the results. We considered the strength of evidence insufficient for clonidine based on insufficient evidence from one study.

Lidocaine Versus Placebo

We did not identify any studies of topical lidocaine that met inclusion criteria. Two RCTs from ClinicalTrials.gov that addressed this treatment did not report the results (NCT02363803 and NCT00904202). One of the trial (NCT02363803) is currently recruiting and is not expected to complete until 2018.

Other Agents

Dextromethorphan Versus Placebo

Three RCTs (2 from Griebeler et al. review and 1 from an updated search) assessed the effect of dextromethorphan compared with placebo on pain.

Griebeler et al. concluded that dextromethorphan was not more effective than placebo (Standardized mean difference, -0.28 [95% CrI, -1.49 to 0.92]). For the RCT identified from an updated search [113], standardized mean difference could not be calculated, but the mean difference in pain scores between baseline and followup was -2.6 in the dextromethorphan and -2.0 in the placebo group (in the direction favoring effectiveness of dextromethorphan, $p<0.0001$). These

results were inconsistent with the findings of Griebeler et al. However, we could not update the meta-analysis for dextromethorphan versus placebo for pain because the study reported insufficient data for pooling.

Overall, based on the findings of Griebler et al., dextromethorphan is not more effective than placebo for reducing pain. We considered the strength of evidence low for dextromethorphan due to imprecision and inconsistency of results.

Cannabinoids (Nabilone and Nabiximols) Versus Placebo

Three RCTs (1 from an updated search and 2 from ClinicalTrials.gov, 1 of which had available data) assessed the effect of different cannabinoids (nabilone and nabiximols) compared with placebo on pain. The Griebeler et al. review did not include this drug class.

For one RCT of the synthetic cannabinoid nabilone, the standardized mean difference for pain was -1.02 (95% CI, -1.82 to -0.21). [114] We could not draw conclusions for nabilone due to insufficient evidence from one study.

One RCT (NCT00710424) from ClinicalTrials.gov reported results for pain for the oromucosal spray cannabinoid extract nabiximols. The standardized mean difference for pain was 0.02 (95% CI, -0.21 to 0.26).

We could not draw conclusions for nabiximols due to insufficient evidence from one study.

Botulinum Toxin Versus Placebo

Three RCTs (2 RCTs from an updated search and 1 RCT from ClinicalTrials.gov) assessed the effect of botulinum toxin compared with placebo on pain. Griebeler et al. did not include this drug.

The standardized mean difference for pain for botulinum toxin ranged from -0.96 [115] to -0.79 [116] (moderate to large effect size). One RCT from ClinicalTrials.gov did not report the results. This trial is currently recruiting, and is scheduled to be completed in September 2016.

We considered the strength of evidence as low for botulinum toxin in reducing pain due to imprecise but consistent findings across the studies.

Mexiletine Versus Placebo

We did not identify additional studies for the Class IB antiarrhythmic mexiletine. Griebeler et al. concluded (based on 5 RCTs) that mexiletine was not more effective than placebo in reducing pain (Standardized mean difference, -0.29 [95% CrI, -0.91 to 0.33]). Strength of evidence for this conclusion was low , given imprecision, inconsistency across the studies, and unclear risk of bias.

Ketamine Versus Placebo

We did not identify any eligible studies of the N-methyl-D-aspartate receptor antagonist ketamine.

Drug-Drug Comparisons

Three RCTs reported pain as an outcome in comparing two different anticonvulsants to two different serotonin-noradrenaline reuptake inhibitors [2 RCTs from the Griebeler et al. review (1 of carbamazepine vs. venlafaxine and 1 of pregabalin vs. duloxetine) and one newly identified RCT of pregabalin and duloxetine]. Given differences in effectiveness, we analyzed anticonvulsants separately. The additional identified study included a comparison phase of pregabalin compared with duloxetine, which was consistent with the findings from Griebeler et

al. (Standardized mean difference could not be calculated given insufficient data, but 40.9 percent of those treated with duloxetine had more than 30 percent improvement in pain compared to 28.8 percent for pregabalin, $p<0.001$).[98]

Given the lack of complete data in one of the studies, we considered the strength of evidence insufficient for pregabalin compared to duloxetine in reducing pain, and insufficient for carbamazepine compared to venlafaxine.

Griebeler et al. found no other drug-drug or drug class-drug class comparisons that were significantly different based on more than one study (see Appendix D for details). We considered the strength of evidence insufficient for all other individual drug-drug comparisons.

Composite Neuropathic Symptoms Score

The Griebeler et al. review did not address composite neuropathic symptom scores. Three RCTs, all studies that were included in Griebeler et al., evaluated composite scores [2 addressing tricyclic antidepressants, both with imipramine,[117, 118] with a 6-item scale including pain, paresthesia, and numbness, and 1 with mexilitine[119] with a 4-item scale including pain and paresthesia.

For tricyclic antidepressants, neither study reported sufficient data for mean differences between intervention and control arms to be calculated; one study reported a statistically significant difference ($p<0.01$) and one study reported a statistically insignificant difference ($p<0.10$). For mexilitine, the mean difference between the study arms in the change between baseline and followup scores was zero (exactly the same in both arms).

Numbness

The Griebeler et al. systematic review did not address numbness. Three RCTs, all studies that were included in Griebeler et al., evaluated numbness as an outcome[120-122], all assessing anticonvulsants. Of the three studies, two used a 10-point visual analog scale and reported a mean difference in the change between baseline and followup scores between arms ranging from -1.47 to 0.12 (negative value is in the direction favoring the intervention arm). One study (of pregabalin) reported the percentage of patients rating themselves as improved from baseline to followup, with a difference between arms ranging from 10-15%, depending on the dose (statistically significant at $p<0.01$ for the 300 mg dose but not the 600 mg dose; 95% CI could not be calculated given the data reported.)

Paresthesia

The Griebeler et al. systematic review did not address paresthesia. Three studies [2 from the Griebeler et al. review (1 addressing mexilitine[123] and 1 of the anticonvulsant pregabalin)[121] and 1 additional identified study on the atypical opioid tapentadol ER[108]] reported paresthesia as an outcome.

The study of mexilitine reported a mean difference from baseline to followup between the intervention and control arms of -0.9 on a 0-3 scale, with the direction of effect favoring the intervention group ($p<0.03$).

The anticonvulsant study reported the percentage of patients rating themselves as improved, with a difference between arms ranging from ten to twenty percent, depending on the dose (statistically significant at $p<0.01$ for the 600 mg dose but not the 300 mg dose; 95% CI could not be calculated given the data reported).

The additional identified withdrawal RCT of tapentadol used the paresthesia/dysesthesia subscale of the Neuropathic Pain Symptom Inventory (NPSI)[108] and found a mean difference from baseline to followup between the intervention and control arms of -1.3 between groups (95% CI, -1.42 to -1.20), with the direction of effect favoring the intervention group.

Quality of Life

The Griebeler et al. systematic review did not assess quality of life. Many studies did not report values for quality of life scores, instead only describing whether the results were statistically significantly different between the study arms. The results are summarized in table 13.

We abstracted the most relevant quality of life subscale using the following hierarchy for the highest therapeutic dose in each RCT: SF-36 physical function, then VAS quality of life score, then EQ-5D overall, then other quality of life score, then SF-36 bodily pain. Comparisons not reported in the table had no studies reporting quality of life. Given that many studies did not report values, but only whether or not results were statistically significant, we could not quantitatively report or synthesize the results.

We considered the strength of evidence insufficient for all classes (serotonin-noradrenaline reuptake inhibitors and atypical opioids) and individual drugs that reported more than one study, due to incomplete reporting of results, inconsistent results, and unclear risk of bias (with suspected reporting bias) (Table 14).

Table 14. Number of studies reporting quality of life as an outcome

Number of studies reporting quality of life	Number of studies with statistically significant results favoring treatment over placebo	Number of studies with non-statistically significant results
Anticonvulsants vs. placebo		
Pregabalin (10 studies)	4[121, 124-126]	6[97, 127, 128]; 3(NCT01474772, NCT01455415; NCT00785577)
Gabapentin (3 studies)	1[129]	2[97, 130]
Oxcarbazepine (3 studies)	1[131]	2[132, 133]
Topiramate (1 study)	0	1[134]
Lacosamide (1 study)	1[135]	0
Serotonin-noradrenaline reuptake inhibitors vs. placebo		
Duloxetine (3 studies)	1[136]	2[104, 137, 138]
Desvenlafaxine (1 study)	0	1[105]
Typical opioids vs. placebo		
Typical opioids (1 study)	0	1[139]
Atypical opioids vs. placebo		
Tramadol (2 studies)	1[109]	1[140]
Tapentadol (2 studies)	2[108,141]	0
Topical drugs vs. placebo		

Capsaicin 8% patch (1 study)	0	1 (NCT01533428)
Other drugs vs. placebo		
Dextromethorphan (1 study)	1[142]	0
Botulinum toxin (1 study)	0	1[115]
Nabilone (1 study)	1[114]	0
Nabiximols (1 study)	0	1 (NCT00710424)
Drug vs. drug comparisons study		
Anticonvulsant vs. Serotonin–norepinephrine reuptake inhibitors vs. tricyclic antidepressant (1 study)	1[143]	0

Studies that did not report statistics are not shown in the table

Harms

The harms results are summarized in Table 15. For drugs not reported in the table, the Griebeler et al. review did not summarize harms for the drug and we did not identify additional identified studies reporting harms in >10%. Types of harms reported in greater than 10% of participants varied by drug class. Studies of serotonin-norepinephrine reuptake inhibitors and anticonvulsants most commonly reported dizziness, nausea and somnolence while studies of tricyclic antidepressants reported xerostomia, somnolence and insomnia. For both opioids and atypical opioids, the most common adverse effects were constipation, nausea and somnolence. Dropout rates due to adverse effects varied widely from 2.5% up to 70% for oral agents. For non-oral agents, dropouts were less frequent, ranging from 0% to 8.6%.

Table 15. Summary of findings of harms reported in pharmacological studies

Adverse effects	Intervention	Comparison (Placebo -/Drug)
Anticonvulsants		
anorexia	10.9 - 20%	0 – 0.9%
back pain	9 -11%	2.8 -6%
Cardiovascular	25%	8.3%
dermatological	8 - 33.3%	9 – 25%
diarrhea	10.7 -12.3%	3.7% to 8.6%
dizziness	2.5% to 52.5%	0% to 18%
Fatigue	4-16%	2-11%
headache	4.4% to 36.6%	3.7% to 38
nausea	2.4% to 41	0% 16%
paresthesia	12 -20%	5 -9%
Peripheral edema	8 – 17%	0 – 31.8%
respiratory	33.3%,	25%
restlessness/insomnia	25%	0%
somnolence	3% to 40%	0 – 16.7%
taste perversion	14%	0%
urinary	25%	0%
weight change	25%	8.3%
weight gain	14.6%	1.2%
weight loss	14%	6%
Serotonin-noradrenaline reuptake inhibitors (SNRIs)		
Constipation	7% to 19%	2% to 8%
Dizziness	1.6% to 26.1%	6% to 11%
Dry mouth	3.2% to 13%	2.2%
Dyspepsia	9% to 10%	1%
Nausea	10% to 32%	2% to 12%
Somnolence	8% to 28%	1% to 8%
Vomiting	2.9% to 10.1%	2.2%
Tricyclic antidepressants (TCAs)		
Dizziness	8 -16%	3%
Insomnia	35%	15%
Somnolence	4% to 69%	12 – 40%
Xerostomia	26% to 89%	8% to 45%
Topical capsaicin		
Burning pain at the application site	13.98 - 63%	2.7% to 19%
Opioids- oxycodone		
Constipation	45 – 59%	14 – 17%
Fatigue	18%	8%
Nausea	36 – 73%	8 – 36%
Somnolence	40 – 41%	1 – 47%
Atypical opioids		
Constipation	6 -22%	1-5%
Dizziness	6.3 – 7.2%	1.3 – 2%
Headache	2.4 -5%	5-5.3%
Nausea	11.9 to 23%	3-9.9%
Somnolence	6 -12%	0.7 -6%
Vomiting	12.7%	4.6%

Griebeler et al. did not summarize dropouts due to adverse effects. We abstracted the data from the studies included in that review as well as from newly identified published studies. The dropout results are summarized in Table 16.

Table 16. Dropouts due to adverse effects reported in all the studies

Drug Class	Intervention	Dropouts Due to Adverse Effects (%)
Anticonvulsants	Carbamazepine	3
	Gabapentin	8 - 21
	Lacosamide	8.3 - 42.3
	Lamotrigine	7.4 – 21.1
	Oxcarbazepine	10.8 – 40.9
	Pregabalin	2.5 – 25.6
	Topiramate	12 – 30.4
	Valproic Acid	3.4 – 4.8
	Zonisamide	38.5
Serotonin-noradrenaline reuptake inhibitors (SNRIs)	Desvenlafaxine	8 - 30.4
	Duloxetine	4.3 – 19.3
	Venlafaxine	6 – 9.8
Tricyclic antidepressants (TCAs)	Amitriptyline	3.6 - 38.6
	Desipramine	10 - 13
	Imipramine	Not reported
Opiates and Atypical Opiates	Oxycodone	3 – 70
	Tapentadol	8.1 – 16.3
	Tramadol	8.1 - 13.8
Topical Agents	Capsaicin	0 – 8.6
	Clonidine	3
N-methyl-D-aspartate Receptor Antagonists	Dextromethorphan	20.2-25.2
Class IB Antiarrhythmics	Mexiletine	13.3
Botulinum Toxin	Botulinum Toxin	0
Cannabinoids	Nabilone	Not reported

KQ2b: Benefits and Harms of Nonpharmacologic Treatment Options (Alpha-Lipoic Acid, Acetyl-L-Carnitine, Acupuncture, Physical Therapy and Exercise, Cognitive Behavioral Therapy, Electrical Stimulation, Surgical Decompression) To Improve Symptoms

Key Points

- Alpha-lipoic acid was more effective than placebo for reducing pain, although studies were short-term (<3 months) (low strength of evidence).
- Spinal cord stimulation was more effective than usual care for the outcome of pain (low strength of evidence), but the procedure has risks of severe complications.
- Transcutaneous electrical nerve stimulation (TENS) was not more effective than sham for reducing pain (low strength of evidence).
- Frequency-modulated electromagnetic stimulation was more effective than sham for reducing pain short-term, but not long-term (low strength of evidence).
- We could not draw conclusions for quality of life (insufficient strength of evidence).
- Adverse effects were not systematically assessed in studies.

Table 17. Summary of key findings of nonpharmacologic interventions for symptoms and quality of life

Outcomes	Comparison	Number of studies reporting outcome (N)	Findings	Strength of Evidence*
Pain	Supplements: Alpha-lipoic acid vs placebo	5 RCTs (N =984)	Alpha-lipoic acid is more effective than placebo for reducing pain in short-term studies Standardized mean difference for pain ranged from -2.64 to -0.54 for the two studies where this could be calculated	Low
Pain	Electrical stimulation: Transcutaneous electrical nerve stimulation vs sham	4 RCTs (N =118)	Transcutaneous electrical nerve stimulation is not more effective than sham therapy for reducing pain in short-term studies. Standardized mean difference ranged from -5.4 to -0.19 for the three studies where this could be calculated	Low
Pain	Electromagnetic stimulation: Frequency-modulated electromagnetic neural stimulation vs sham	2 RCTs (N =132)	Frequency-modulated electromagnetic neural stimulation is more effective than sham for reducing pain short-term, but not long-term. Standardized mean difference ranged from -2.62 to -1.31 for short-term (<12 week) outcomes.	Low

Outcomes	Comparison	Number of studies reporting outcome (N)	Findings	Strength of Evidence*
Pain	Spinal cord stimulation vs usual care	2 RCTs (N =96)	Spinal cord stimulation is more effective than usual care for reducing pain. Standardized mean difference ranged from -1.83 to -1.57.	Low
Quality of life	Spinal cord stimulation vs usual care	2 RCTs (N =96)	We could not draw conclusions due to incomplete reporting of results.	Insufficient

RCT = Randomized Controlled Trial
*we graded only the key outcomes (pain and quality of life)
Please see Appendix table E-6-Strength of evidence table for domains

Supplements (Alpha-Lipoic Acid, Acetyl-L-Carnitine)

Description of Included Studies

Seven RCTs addressed the benefits and/or harms of supplements. Six RCTs evaluated alpha-lipoic acid (ALA) [144-149] and one assessed acetyl-l-carnitine.[150]

Doses of alpha-lipoic acid considered to be therapeutic ranged from 600 mg to 1800 mg daily. The dose of acetyl-l-carnitine was 2000 mg/day. Followup ranged from three weeks to four years, with four of the studies five weeks or less in duration. Five studies were multicenter studies. Five studies took place in Europe. All trials were funded by industry. All alpha-lipoic acid studies had the same investigator as the first or last author. Trials were published from 1995 to 2011. The number of participants in the included studies ranged from four to 503 (with a total 1,614 participants for alpha-lipoic acid and 333 participants for acetyl-l-carnitine). All trials were placebo-controlled.

The overall risk of bias for trials was unclear due to poor reporting regarding allocation concealment, random sequence generation, assessing blinding by the outcome, incomplete outcome data, and selective outcome reporting.

Outcomes

We did not conduct meta-analyses for any of the outcomes for supplements owing to heterogeneity in study design and length, drug dosing, and outcome measurement and reporting.

Pain

Five RCTs reported pain as an outcome (other studies reported only a composite score that included pain),[145, 147-150] four of which studied alpha-lipoic acid with a study duration of 3 to 5 weeks (the long-term study of alpha-lipoic acid did not report pain separately). Three out of four RCTs of alpha-lipoid acid reported the total symptom score (TSS) subscale for lancinating pain. Standardized mean difference between the intervention group and the control group of the difference from baseline to followup on the total symptom score pain subscale ranged from -2.64 to -0.54, with the direction of effect favoring the intervention group for the two studies in which this could be calculated (Figure 10).

One study reported categorical outcomes only and therefore is not shown in Figure 9. In that study, the percentage of participants with a greater than 30 percent reduction in pain ranged from 70.8 percent to 82.5 percent in the study groups receiving alpha-lipoic acid, compared with 57.6 percent in the placebo group ($p<0.05$ for only one study group).[147]

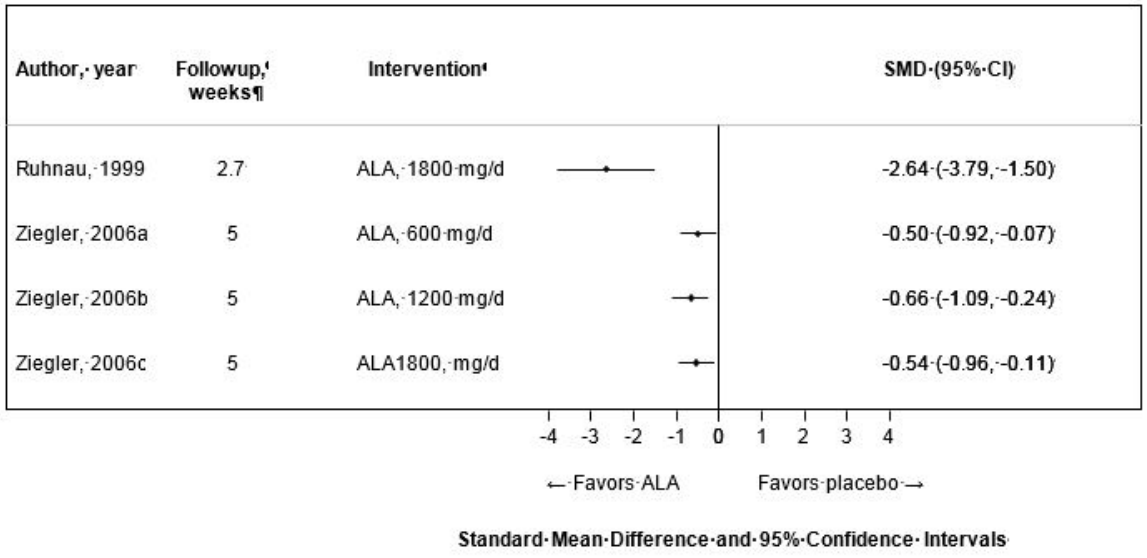
One study of alpha-lipoic acid reported the Neuropathy Symptom Change Score – Lower Legs (NSC[LL]) pain severity score, with a mean change in baseline of -7.3 in the treatment group compared with -4.6 in the placebo group ($p<0.0001$) (neither the standardized mean difference nor 95% CI could be calculated, as standard deviation was not reported).

Alpha-lipoic acid was effective for reducing pain compared to placebo in short-term studies (moderate to large effect size). We considered the strength of evidence low for alpha-lipoic acid in reducing pain, due to inconsistency across the studies and unclear risk of bias, including suspected reporting bias. In particular, only four of the six studies reported pain separately; studies were five weeks or less (the only long-term study did not report pain separately); and standardized mean difference could only be calculated for half the studies where pain outcomes were reported given incomplete data. In addition, we were unable to find any published psychometric evaluation of the total symptom score tool used in most of these studies.

The RCT of acetyl-L-carnitine had a standardized mean difference between the intervention and the control group of the difference from baseline to followup of -3.6, in the direction favoring the intervention group (95% CI, -3.99 to -3.29).[150]

We could not draw conclusions for acetyl-L-carnitine due to insufficient evidence from one study.

Figure 10. Calculated standardized mean difference between alpha-lipoic acid (ALA) and placebo on change in the total symptom score (TSS) pain subscale



ALA=alpha lipoic acid; CI=confidence interval; Mg/d=milligram per day; SMD=standardized mean difference

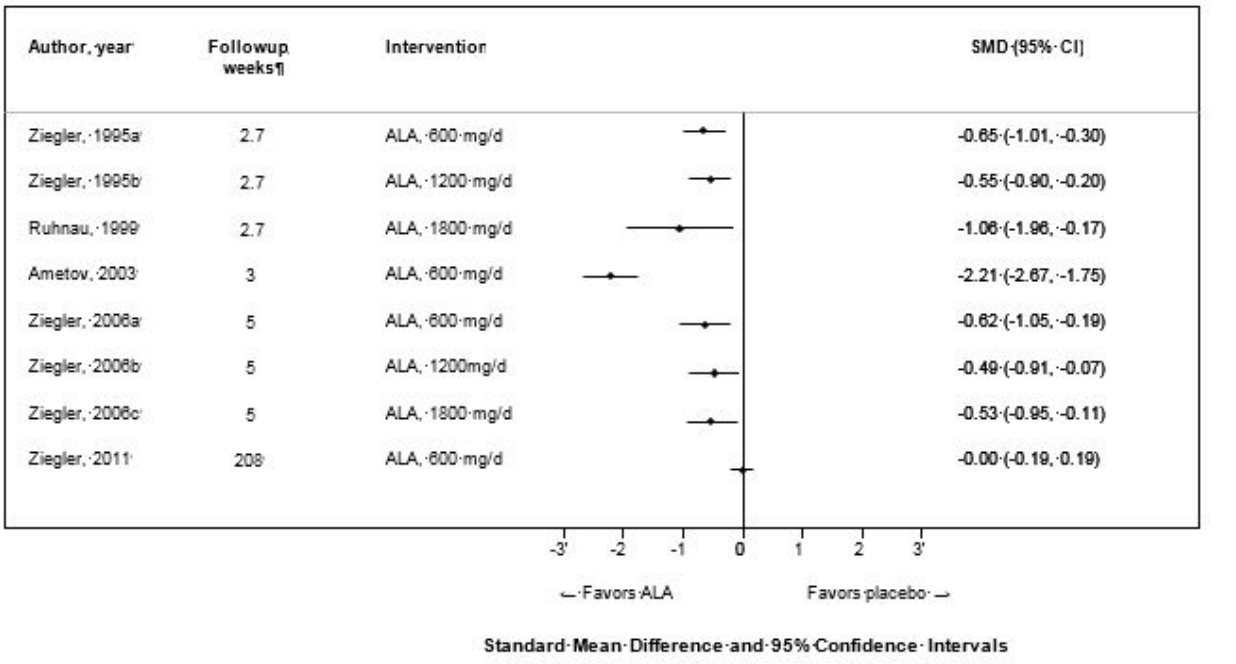
Composite Outcome

All six RCTs of alpha-lipoic acid reported the Total Symptom Score (TSS) composite scale. The total symptom score is a summary score of the presence, severity and duration of lancinating pain, burning pain, prickling (paresthesia), and numbness, with a range of possible scores from 0 to 14.64.[146] Some of the studies also reported the individual subscales (described separately in the pain, paresthesia, and numbness sections). Calculated standardized mean differences between the intervention group and the control group of the difference from baseline to followup on the total total symptom score ranged from -2.21 (95% CI, -2.67 to -1.75) to 0.00 (95% CI, -0.19 to

0.19) (for the only long-term study), with the direction of effect favoring the intervention group in the five studies in which the standardized mean difference could be calculated (Figure 9).

One study reported only the median change from baseline, so standardized mean difference could not be calculated (-3.7 in the alpha-lipoic acid group compared with -3 in the placebo group, p=0.447).[146]

Figure 11. Calculated standardized mean difference between alpha-lipoic acid (ALA) and placebo on change in the total symptom score composite scale



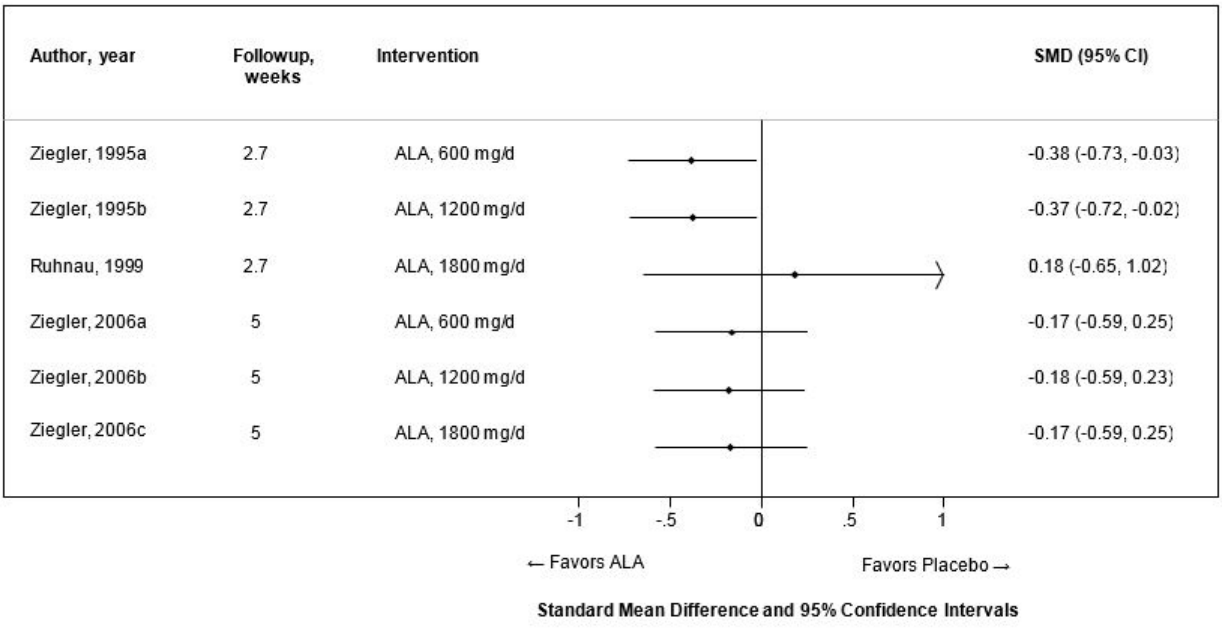
ALA=alpha lipoic acid; CI=confidence interval; Mg/d=milligram per day; SMD=standardized mean difference

Numbness

Four RCTs reported numbness as an outcome, all of which used alpha-lipoic acid and had a study duration of 3 to 5 weeks.[145, 147-149] Three trials reported the Total Symptom Score (TSS) numbness subscale. Standardized mean differences between the intervention group and the control group of the difference from baseline to followup on the total symptom score numbness subscale could be calculated for three studies. These ranged from -0.38 (95% CI, -0.73 to -0.03), with the direction of effect favoring the intervention group, to 0.17 (95% CI, -0.59 to 0.25) (Figure 12).[145, 147, 149]

One trial reported the Neuropathic Symptom Change Score – Lower Legs (NSC[LL]) negative sensation severity subscale (mean change from baseline of –1.2 in alpha-lipoic acid group compared with -0.7 in the placebo group, p=0.043) (neither the standardized mean difference nor 95% CI was calculated as standard deviation was not reported).[148]

Figure 12. Calculated standardized mean difference for numbness between alpha-lipoic acid (ALA) and placebo on change in the total symptom score (TSS) numbness subscale

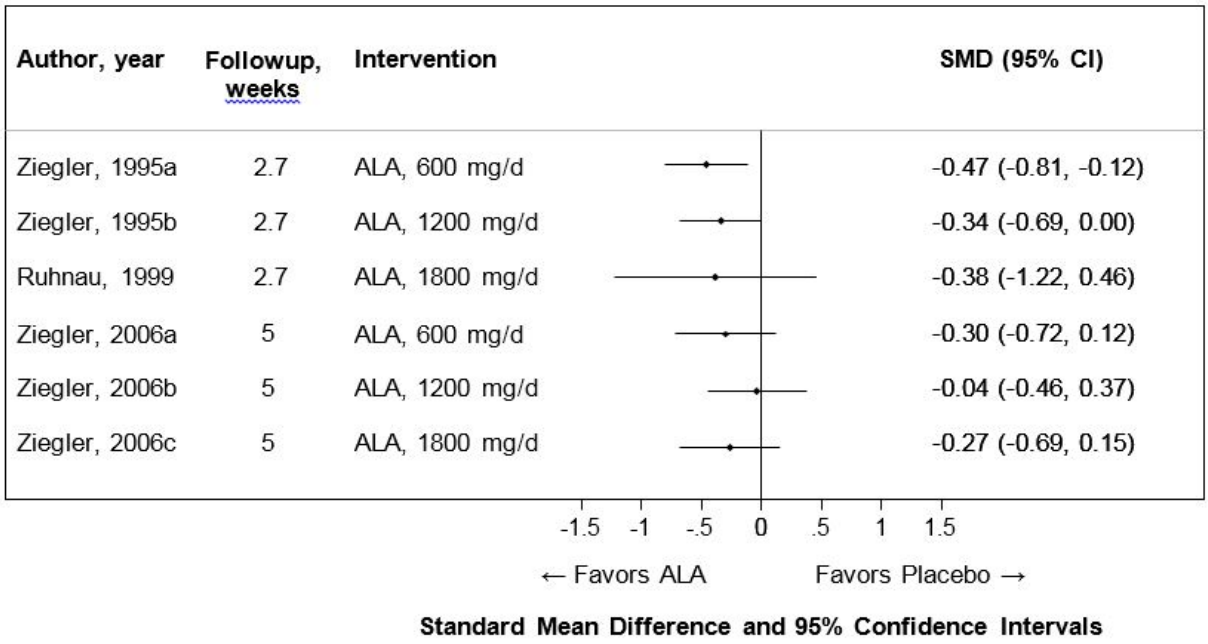


ALA=alpha lipoic acid; CI=confidence interval; Mg/d=milligram per day; SMD=standardized mean difference

Paresthesia

Four RCTs reported paresthesia as an outcome, all of which used alpha-lipoic acid and had a study duration of 3 to 5 weeks.[145, 147-149] Three trials reported the total symptom score (TSS) paresthesia subscale. Standardized mean difference between the intervention group and the control group of the difference from baseline to followup on the total symptom score numbness subscale could be calculated for three studies, ranging from -0.47 (95% CI, -0.81 to -0.12) to -0.04 (95% CI, -0.46 to 0.37), with the direction of effect favoring the intervention group (Figure 13). One RCT reported the NSC[LL] positive sensation severity subscale (neither standardized mean difference nor 95% CI was calculated as standard deviation was not reported) (mean change from baseline of -8.3 in alpha-lipoic acid group compared with -5.0 in the placebo group, $p<0.001$). [148]

Figure 13. Calculated standardized mean difference between alpha-lipoic acid (ALA) and placebo on change in the total symptom score (TSS) paresthesia score



ALA=alpha lipoic acid; CI=confidence interval; Mg/d=milligram per day; SMD=standardized mean difference

Harms

Three RCTs, all of which used alpha-lipoic acid, reported adverse effects[145-147]. Rates of specific adverse effects occurring in more than 10 percent of patients in at least one study arm receiving alpha-lipoic acid included nausea, ranging from 1 to 25 percent; vomiting, ranging from 0 to 26 percent; and vertigo, ranging from 4 to 11 percent of participants. Rates were dose-dependent, with the highest rates in the 1800 mg group.[145]

All studies reported dropouts due to adverse effects, ranging from zero percent for 600 mg[145] to 13 percent for 1800 mg[145] in study arms. The dropout rate due to adverse effects for acetyl-L-carnitine was 6.3 percent.

Acupuncture

Description of Included Studies

Only one RCT with a sham arm assessed the benefits and/or harms of acupuncture to improve the symptoms of diabetic peripheral neuropathy.[151] Five acupuncture points on the lower limb of each leg were used in the study in weekly sessions: Liver 3 Taichong, Spleen 6 Sanyinjiao, Spleen 10 Xuehai, Stomach 36 Zusanli and Kidney 3 Taixi. This was a single center study conducted in Europe with government funding. The trial included 45 patients. The study followup was 10 weeks. Overall risk of bias was low.

Outcomes

Pain

The trial reported pain as an outcome using a visual analog scale. The calculated standardized mean difference between the intervention arm and the control arm of the difference

from baseline to followup on numerical pain scales was -0.43 (95% CI, -1.02 to 0.16) in the direction favoring the intervention arm. We could not draw conclusions due to insufficient evidence from one study.

Quality of Life

The trial reported quality of life using the Short Form (SF-36) physical component [difference in the mean difference from baseline between the intervention arm and the control arm of -2.2 (95% CI, -5.2, 0.77), in the direction favoring the intervention arm]. We could not draw conclusions due to insufficient evidence from one study.

Harms

There were no adverse effects occurring in more than ten percent of patients. The trial reported three dropouts (one from the sham group and two from the intervention group) owing to adverse events.

Cognitive Behavioral Therapy

Description of Included Studies

Only one RCT of 20 patients assessed the benefits and/or harms of cognitive behavioral therapy to improve the symptoms of diabetic peripheral neuropathy.[152] The intervention included eleven sessions of weekly cognitive behavioral therapy, with a chronic pain management treatment protocol using a therapist manual and corresponding patient workbook and homework. The study followup was four months. This was a single center study conducted in North America using government funding. Overall risk of bias was unclear.

Outcomes

Pain

Pain was the only outcome reported in this study.[152] The study used the West Haven Yale Multidimensional Pain Inventory (WHYMPI) pain severity subscale to assess pain severity. Calculated standardized mean difference between the cognitive behavioral therapy arm and the usual care arm of the difference from baseline to followup was -0.87 in the direction favoring the intervention group ($p<0.05$ with hierarchical linear modeling for longitudinal data). We could not draw conclusions due to insufficient evidence from one study.

Harms

The study did not report adverse effects or dropouts due to adverse effects.

Electrical Stimulation

Description of Included Studies

Seven RCTs addressed the benefits and/or harms of electrical stimulation. Four trials evaluated transcutaneous electrical nerve stimulation (TENS), during which electrodes are applied to the skin in affected areas[153-156] [of these, three used 5-70 milliamperes (mA) and one used microcurrent (30-40 microamperes)][153]. One trial used percutaneous electrical nerve stimulation (PENS), during which needles are used to deliver the electrical stimulation to affected areas (25 mA).[157] One trial used stockings with electrodes (50 microamperes)[158] and one

trial used mesodiencephalic modulation, or transcranial stimulation (4-10 mA).[159] Followup ranged from 3 to 12 weeks, with a median of 8 weeks.

Four of the seven RCTs were parallel trials and three were crossover trials. All were either single center or not reported (presumably single center). Four studies took place in Europe and the remainder in North America. Three had reported industry funding. The number of participants in the included studies ranged from 19 to 100 (with a total of 118 for transcutaneous electrical nerve stimulation (TENS), 50 for percutaneous electrical nerve stimulation (PENS), 30 for stocking electrodes, and 22 for mesodiencephalic). All included a sham arm as the control. The overall risk of bias was unclear for four trials and low for three trials. There was generally unclear bias due to poor reporting regarding the allocation concealment, random sequence generation, assessing blinding by the outcome, and other sources of bias including incomplete outcome data and selective outcome reporting.

Outcomes

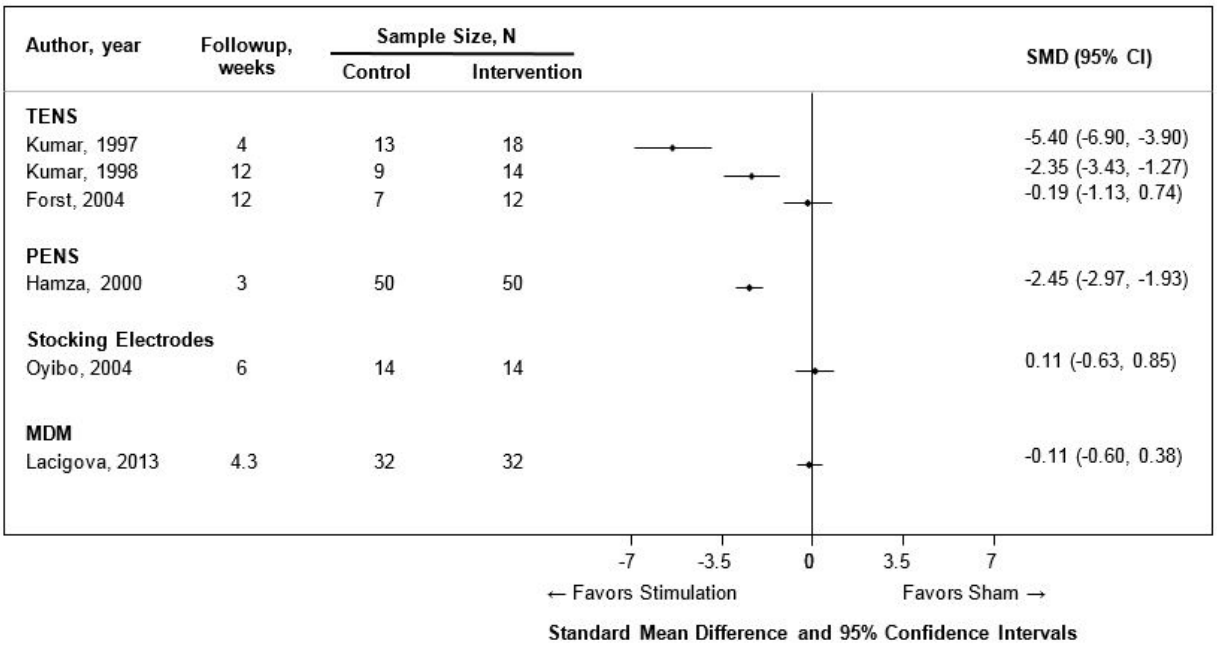
Pain

All seven RCTs of all types of electrical stimulation reported pain as an outcome. Six out of the seven RCTs reported a numerical pain or visual analog scale, while one study (of micro-transcutaneous electrical nerve stimulation) used the Neuropathic Pain Score.[153] Among the four studies of transcutaneous electrical nerve stimulation specifically, standardized mean differences between the intervention group and the control group on numerical pain scales ranged from -5.4 to -0.19, in the direction favoring the intervention group, in the three studies that used a numerical pain scale (Figure 13). For the study of microTENS that reported the Neuropathic Pain Score, the mean difference in the change from baseline between the groups was 3.73, in the direction favoring the sham arm (not statistically significant). We did not perform a meta-analysis for transcutaneous electrical nerve stimulation owing to study heterogeneity in intervention (micro-TENS versus Transcutaneous electrical nerve stimulation and modes of delivery of the electrical stimulation), outcome measures, and design (different types of run-in periods, including one with amitriptyline).

Standardized mean differences for the other trials were as follows: percutaneous electrical nerve stimulation (PENS), -2.5 (95% CI, -3.0 to -1.9), in the direction favoring the intervention arm; stockings with electrodes, 0.11 (95% CI, -0.63 to 0.85), in the direction favoring the sham arm; and mesodiencephalic stimulation, -0.11 (95% CI, -0.60 to 0.38), in the direction favoring the intervention arm (Figure 14).

Transcutaneous electrical nerve stimulation is not more effective than placebo for reducing pain, and studies were all short-term. We considered the strength of evidence as low for transcutaneous electrical nerve stimulation due to inconsistency across studies and unclear risk of bias. We could not draw conclusions for other methods of electrical stimulation due to insufficient evidence from one study each.

Figure 14. Calculated standardized mean difference for reducing pain between electrical stimulation and sham group on numeric pain scale



CI=confidence interval; MDM=mesodiencephalic modulation; N=sample size; PENS=percutaneous electric nerve stimulation; SMD=standardized mean difference; TENS=transcutaneous electric nerve stimulation.
Note that for one study of micro-TENS, standardized mean difference could not be calculated but results were not statistically significant

Composite Neuropathic Symptoms Score

One RCT of mesodiencephalic modulation reported a composite neuropathic symptoms outcome: the Total Symptom Score (TSS)[159]. Standardized mean difference between the intervention arm and the control arm was -0.28, in the direction favoring the intervention arm (95% CI, -0.77 to 0.21).

Numbness

One RCT of transcutaneous electrical nerve stimulation [154] reported on the outcome of numbness on the New Total Symptom Score (NTSS-6). Standardized mean difference between the intervention arm and the control arm was 0.05 (95% CI, -0.88 to 0.98), in the direction not favoring the intervention arm.

Paresthesia

One RCT of transcutaneous electrical nerve reported on the outcome of paresthesia on the NTSS-6. Standardized mean difference between the intervention arm and the control arm was -0.21 (95% CI, -1.14 to 0.72), in the direction favoring the intervention arm.

Quality of Life

Two RCTs reported on the outcome of quality of life using the Short Form (SF-36) physical component. One study of mesodiencephalic stimulation[159] reported a mean difference in the change from baseline between arms of 4.5, in the direction favoring the intervention arm (SDs were not reported, so 95% CIs could not be calculated) ($p<0.01$). One study of percutaneous electrical nerve stimulation (PENS) reported a mean difference in the change from baseline between arms of 4.2, in the direction favoring of the intervention arm (95% CI, 3.82 to 4.98).[157]

We did not perform meta-analysis as there were only two studies and these assessed different interventions. We considered the strength of evidence as insufficient for either of these methods of electrical stimulation because of insufficient evidence from one study.

Harms

No studies reported adverse effects or dropouts due to adverse effects.

Electromagnetic Stimulation

Description of Included Studies

Four RCTs addressed the benefits and/or harms of electromagnetic stimulation. Two trials evaluated frequency-modulated electromagnetic neural stimulation,[160, 161] one trial evaluated pulsed electromagnetic fields,[162] and one trial evaluated repetitive transcranial magnetic stimulation [163]. Followup ranged from three to 51 weeks (two of the studies were 9 weeks or less). Studies were published between 2005 and 2013. Two of the studies were parallel trials and two were crossover trials. One study was single center and three were multicenter. Three studies took place in Europe and one in North America. Two studies had reported industry funding. The number of participants ranged from 23 to 225 (with totals of 132 participants for frequency-modulated electromagnetic neural stimulation, 225 participants for pulsed electromagnetic fields, and 23 for repetitive transcranial magnetic stimulation). All included a sham arm as the control. The overall risk of bias for trials was low. There was generally low to unclear bias, due to poor reporting regarding the allocation concealment, random sequence generation, and selective outcome reporting. These trials generally had a low risk of bias regarding incomplete outcome data, assessing blinding by the outcome and other sources of bias.

Outcomes

Pain

All four RCTs reported pain as an outcome on a visual analog scale. For frequency-modulated electromagnetic stimulation, the standardized mean difference between the intervention arm and the control arm for the difference between baseline and followup for the shorter-term outcomes reported in the studies (<12 week outcomes, if reported) ranged from -2.62 to -1.31, in the direction favoring the intervention arm. Bosi et al.[160] also reported longer-term outcomes, and the difference at the 51-week followup was no longer statistically significant.

For the study of pulsed electromagnetic fields,[162] the standardized mean difference between the intervention arm and the control arm for the difference between baseline and followup was -0.09 in the direction favoring the intervention group (95% CI, -0.37 to 0.19) (Figure 15).

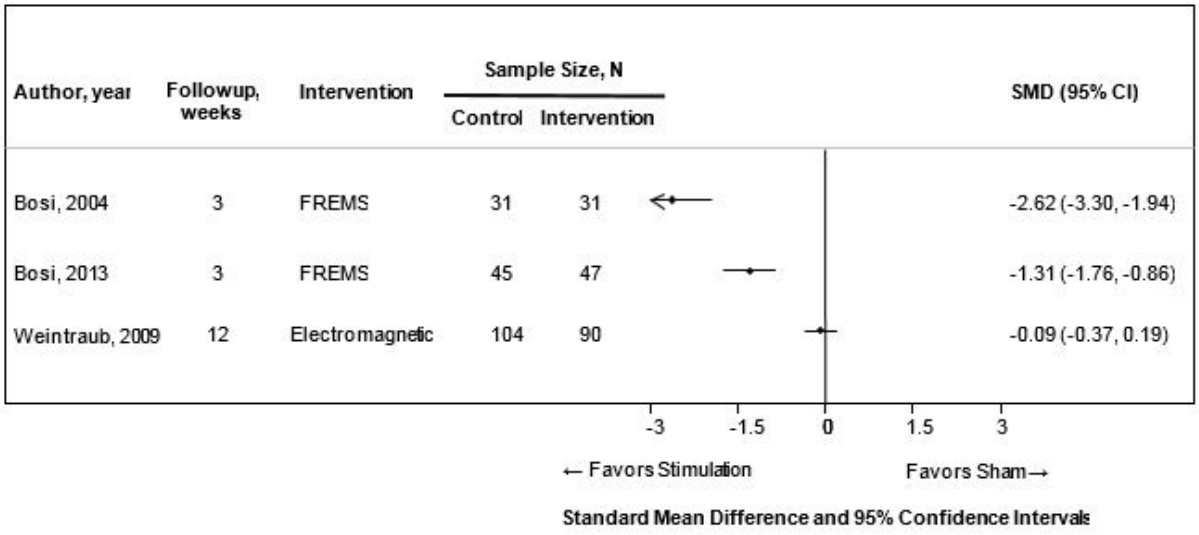
The study of repetitive transcranial magnetic stimulation [163] did not report standard deviation for the followup and, therefore, standardized mean difference could not be calculated; the time by group effect at the end of the first study period was statistically significant in the direction favoring the intervention group (mean difference between the intervention group and the sham group difference from baseline to followup on a presumed 0-100 VAS of -16.41, p=0.005).

We did not perform meta-analysis given only two studies with the same intervention (frequency-modulated electromagnetic neural stimulation).

Frequency-modulated electromagnetic stimulation is not effective for reducing pain (effective in short term but not in long-term studies). We considered the strength of evidence low due to inconsistency across the studies and unclear risk of bias; in particular, Bosi et al. [160]

reported immediate relief of pain after each treatment session, but this was not sustained longer-term. We could not draw conclusions for the other methods of electromagnetic stimulation due to insufficient evidence from one study each.

Figure 15. Calculated standardized mean difference for pain outcome between electromagnetic stimulation and sham group of the difference from baseline to followup



CI=confidence interval; FREMS=frequency modulated electromagnetic neural stimulation; N=sample size; SMD=standardized mean difference

Quality of Life

Only one study reported on the outcome of quality of life as a result of frequency-modulated electromagnetic neural stimulation and using the SF-36 total score.[161] The mean difference between followup and baseline between the intervention arm and the control arm was 0.4, in the direction favoring the intervention arm (not statistically significant). We could not draw conclusions due to insufficient evidence from one study.

Harms

No studies reported on adverse effects. Three studies reported dropouts due to adverse effects, two reported no dropouts[160, 161], and one reported dropouts due to adverse effects of 2.2 percent in the intervention arm and 1.9 percent in the sham arm.

Spinal Cord Stimulation

Description of Included Studies

Two RCTs addressed the benefits and harms of spinal cord stimulation (implanted lead that electrically stimulates the spinal cord dorsal columns).[164, 165] Followup was 6 months in both studies. Both studies were parallel trials, multicenter, took place in Europe, and were funded by industry. The studies were conducted between 2008 and 2013. The number of participants in the included studies ranged from 36-60 (with a total of 96 participants in both studies). Both studies included a trial phase to determine whether patients responded and used best conventional practice as the control arm. The overall risk of bias was unclear for one trial and low for another

trial, with issues of poor reporting regarding the allocation concealment, random sequence generation, and assessing blinding by the outcome.

Outcomes

Pain

Both RCTs reported pain as an outcome; one used a visual analog scale[164] and the other the modified Brief Pain Inventory Pain Severity Index.[165] Standardized mean differences between the intervention arm and the control arm on numerical pain scales ranged from -1.83 to -1.57 (large effect size), in the direction favoring the intervention arm. We did not perform meta-analysis because there were only two studies. Spinal cord compression was effective for reducing pain compared to usual care. We considered the strength of evidence low due to consistency across the studies, imprecision, and low risk of bias. Other concerns included the use of a run-in period to identify responders before implantation and the lack of a sham arm due to the need to implant the device.

Quality of Life

Two RCTs reported this outcome, one using the McGill Pain Questionnaire Quality of Life scale [difference in the mean difference from baseline between the intervention arm and the control arm of 7 (95% CI, 5.08 to 8.92)][164] and one using the Short Form (SF-36) physical component [difference in the mean difference from baseline between the intervention arm and the control arm of 5.6 (not statistically significant), both in the direction favoring the intervention arm].[165] We did not perform meta-analysis, as there were only two studies. We were unable to draw a conclusion given incomplete reporting of data. We considered the strength of evidence as insufficient given incomplete data.

Harms

There were no adverse effects occurring in >10% of patients. One study reported no dropouts due to adverse effects, one study reported one death (4.5%) and one dropout owing to severe infection (4.5%).

Surgical Decompression

Description of Included Studies

One RCT, randomized by leg and described in two articles, addressed the benefits of surgical decompression (a decompression procedure of the lower extremity nerves according to Dellon in one limb: the common peroneal, deep peroneal, or superficial peroneal nerve).[166, 167] This trial was a parallel trial, in a single center in Europe, with nonprofit funding. The study was conducted between 2010 and 2013 with 42 patients. Followup was 1 year. Overall risk of bias was unclear, due to poor reporting of methods.

Outcomes

Pain

The RCT reported pain on a visual analog scale (specifics not reported). The standardized mean difference between the intervention arm and the control arm could not be calculated as standardized difference was not reported; the difference in the mean difference from baseline between the intervention arm and the control arm was -1.8 ($p<0.001$), in the direction favoring

the intervention arm. We could not draw conclusions due to insufficient evidence from one study.

Quality of Life

Quality of life scores were the same in both study arms, as people served as their own controls (randomization was by leg).

Harms

Neither adverse effects nor dropouts due to adverse effects were reported.

Discussion

Key Findings and Implications

We identified a substantial literature on the effectiveness of both pharmacologic (106 studies) and non-pharmacologic (23 studies) approaches to improve the symptoms of diabetic peripheral neuropathy, mostly focusing on the outcome of pain.

The following drug classes were more effective than placebo in reducing pain: serotonin-noradrenaline reuptake inhibitors (moderate strength of evidence), tricyclic antidepressants (low strength of evidence), and atypical opioids (low strength of evidence). Opioids were not more effective for the outcome of pain (low strength of evidence).

For specific drugs within larger classes, we found the following effects for the outcome of pain: for anticonvulsants, only pregabalin and oxcarbazepine were more effective than placebo (low strength of evidence) (although in newer studies and unpublished trials, pregabalin was not more effective than placebo, and oxcarbazepine studies were inconsistent); and for serotonin-noradrenaline reuptake inhibitors, only duloxetine and venlafaxine (moderate strength of evidence). Of note, while most effect sizes were moderate (Cohen's d >0.5) or large (>0.8),[168] the effect sizes for pregabalin and oxcarbazepine were small (<0.5). Gabapentin was not effective for the outcome of pain, consistent with the findings of the previous systematic review and consistent with two newly identified studies. The anticonvulsants topiramate or lacosamide were also not more effective in reducing pain compared to placebo. Botulinum toxin was effective for the outcome of pain (low strength of evidence). Dextromethorphan, mexilitine and topical capsaicin 0.075% were not effective, and most other individual drugs had insufficient evidence to draw conclusions. We were unable to draw conclusions for any drug-drug comparisons due to insufficient evidence.

Since values for quality of life were often not reported (only whether results were statistically significant), we were limited to counting the number of statistically significant studies for the most relevant quality of life measures; no drug classes had more than half of studies showing statistically significant results (insufficient strength of evidence). Few studies evaluated paresthesia or numbness, so we could not draw conclusions.

For non-pharmacologic treatments, we found the following effects: for supplements, alpha-lipoic acid (with a moderate effect size) was more effective than placebo for the outcome of pain (low strength of evidence with incomplete reporting of outcomes). For other interventions with more than one study, spinal cord stimulation (although there were not sham arms and there is a risk of serious complications) was more effective than usual care, with a large effect size, and frequency-modulated electrical stimulation was more effective than sham in short-term but not

long-term followup; transcutaneous electrical nerve stimulation was not more effective than sham for the outcome of pain (low strength of evidence for all). Supplements were not more effective than placebo for the outcomes of paresthesia or numbness. Quality of life was rarely reported in studies of non-pharmacologic treatments, and where it was reported, for spinal cord stimulation, results were inconsistent and we could not draw a conclusion (low strength of evidence).

Harms reported in greater than 10% of participants varied by drug class. Studies of serotonin-noradrenaline reuptake inhibitors and anticonvulsants reported dizziness, nausea and somnolence most frequently while studies of tricyclic antidepressants reported xerostomia, somnolence and insomnia. For both opioids and atypical opioids, adverse effects were most frequently constipation, nausea and somnolence. It should be noted that comparison data for these studies not only includes placebo but "active controls" to mimic some of the known side effects of medications and thus preserve blinding. Dropout rates due to adverse effects varied widely from 2.5% up to 70% for oral agents. For non-oral agents, dropouts were less frequent, ranging from 0% to 8.6%.

We found no studies for exercise or physical therapy for the outcomes of pain, paresthesia or numbness, nor studies comparing different treatments or combining treatments, and, for quality of life, evidence was either insufficient or there were no studies for all nonpharmacologic treatments. Most trials included were of relatively short duration (<3 months, with many <1 month). In this limited timeframe, investigators are unlikely to capture progression of neuropathic symptoms or long-term dropout rates or side effects.

Findings in Relationship to What Is Already Known

For pharmacotherapy, we updated the network meta-analysis by Griebeler et al.[169] which searched through April 2014, and we identified 24 additional published studies and 25 unpublished studies from ClinicalTrials.gov. The Griebeler et al. review addressed only the outcome of pain and concluded that serotonin-noradrenaline reuptake inhibitors (specifically venlafaxine and duloxetine), tricyclic antidepressants (specifically amitriptyline), anticonvulsants (specifically carbamazepine and pregabalin), and topical capsaicin were better than placebo for short-term pain control. In adding additional studies to the body of evidence, our findings were consistent for the drug categories of serotonin-noradrenaline reuptake inhibitors and the anticonvulsants gabapentin and pregabalin, and we did not identify additional studies for tricyclic antidepressants. Given that carbamazepine and amitriptyline had only one study with high risk of bias, we concluded that strength of evidence was insufficient for either of these individual drugs. Since we identified three new studies of atypical opioids in addition to the two described in Griebeler et al., and given the differences in mechanism of action from other opioids, we reanalyzed these studies separately, and found that this drug class was effective for the outcome of pain, but studies had many limitations (low strength of evidence). Another, more recent systematic review of pharmacologic treatments included open-label studies and concluded that many more drugs were effective for pain.[170] Finally, the most recent comprehensive systematic review of pharmacologic treatments for all types of neuropathic pain (including other etiologies such as chemotherapy and trigeminal neuralgia[171]) included only blinded studies and had a few different conclusions, with a strong recommendation for gabapentin (in contrast to our findings that gabapentin had no effect) and a weak recommendation for lidocaine patches, where we identified no blinded studies for diabetic peripheral neuropathy. Adding to the Griebeler et al. review, we also synthesized data for paresthesia and numbness, but found that few studies

addressed these outcomes. Griebeler et al. did not address quality of life, and we found insufficient strength of evidence across drug classes due to incomplete reporting. We also synthesized data on dropouts due to adverse effects and found that all drug classes of oral agents had at least some study arms with a >10% dropout rate due to adverse effects.

For nonpharmacologic approaches, the last comprehensive review including non-pharmacologic treatments [172] for diabetic peripheral neuropathy addressed literature through August 2008 and concluded that there were no effective treatments. Specifically, the review concluded that evidence was insufficient for alpha-lipoic acid or other supplements, that percutaneous electrical nerve stimulation should be considered, and that other methods should not be considered or had insufficient evidence. Our review found a number of new studies for non-pharmacologic approaches for the treatments addressed in Bril et al., as well as studies of new treatments. We concluded that spinal cord stimulation (although this has a risk of serious complications) and alpha-lipoic acid were effective for the outcome of pain (low strength of evidence), and transcutaneous electrical nerve stimulation and frequency-modulated electromagnetic stimulation were not effective (low strength of evidence); other treatments had insufficient evidence and require more research.

Applicability

Trials were generally in populations of younger diabetic patients, with a mean age generally in the mid-50s, and results may not be applicable to populations of older diabetic patients who may be more susceptible to side effects, such as somnolence and dizziness. No studies reported subgroup analyses; patients with significant comorbidities may also have other sources of pain, in addition to diabetic peripheral neuropathy, and/or be more susceptible to side effects and drug interactions.

Few nonpharmacologic pain interventions were studied specifically for diabetic peripheral neuropathy, and evidence from treatments that are effective for other types of peripheral neuropathy or other chronic pain conditions (e.g., exercise, physical therapy) could also be relevant. Comparators were mostly limited to placebo or sham, limiting our ability to compare effectiveness among treatments or appropriateness for patient selection. Outcome synthesis was limited mainly to pain severity scores assessed at a single time point, which do not reflect the dynamic nature of pain; impact of pain on function; other symptoms of neuropathy, such as numbness and paresthesia; or overall impact of both benefits and side effects on patients' quality of life. Lack of long-term outcomes and long-term adverse effect data is a particular limitation in this condition in a population with long-term, chronic issues.

Limitations of the Review Process

This review updated a previous network meta-analysis by Griebeler et al., which had a number of limitations. Given the small number of head-to-head comparisons, some conclusions from the network meta-analysis were of questionable validity, particularly comparisons with only one study or from studies with high risk of bias. We did not update the network meta-analysis, given these issues, but rather conducted new meta-analyses where we identified additional studies with results that were not consistent with the network meta-analysis and had data that could be pooled. Given different findings from the direct and network meta-analysis from Griebeler et al. for opioids, the different mechanism of action of atypical opioids, and identification of three additional studies in this drug class, we separated out studies for atypical opioids and reanalyzed those data. Griebeler et al. also used standardized mean differences rather

than a more clinically meaningful approach, and although these can be interpreted as small, moderate or large, they do not correlate with recommendations for interpretation of relative or absolute decreases in pain[173] as clinically meaningful; findings may have been different with a different analytical method.

There are also a number of limitations of our review. We excluded studies including mixed populations of those with diabetic peripheral neuropathy and other types of neuropathy that did not report outcomes separately for diabetic peripheral neuropathy, which may have excluded some relevant data. In addition, given the heterogeneity of outcomes reported, we focused only on pain scales to synthesize results for pharmacologic agents, as done in previous systematic reviews. However, pain scales have many limitations as outcomes, as they evaluate pain only at one point in time and do not address other important aspects of pain treatment, such as improvement in function. In addition, some studies, particularly for non-pharmacologic treatments, had unusually high calculated effect sizes, potentially based on limitations of the reported data; we included these studies in our review but also evaluated results without them as a sensitivity analysis. We limited the review to pharmacologic and non-pharmacologic treatments evaluated in prior reviews or guidelines and available in the United States, to studies with at least 3 weeks of followup, and to studies with sham or placebo arms, wherever appropriate. This excluded some types of alternative treatments, very short-term studies, and studies where sham was possible but not used (especially for acupuncture). We also excluded non-English language publications and this limited our scope for acupuncture. Since we addressed the effectiveness of these interventions for diabetic peripheral neuropathy specifically, this review does not address the broader literature describing harms of these interventions in different conditions. This broader safety data, such as overall mortality from spinal cord stimulation,[174] is therefore not included in this report.

Strengths and Limitations of the Evidence Base

The strength of evidence was insufficient for many comparisons and outcomes owing to a paucity of studies, particularly for non-pharmacologic treatments. The lack of head-to-head comparisons for drugs limits comparative conclusions.[175] Although drugs are often prescribed in combination with other drugs or in combination with non-pharmacologic treatments, we identified no studies on combinations of treatments. Trials were frequently downgraded in risk of bias assessment for not reporting blinding by participant and study personnel (performance bias) or outcome assessors (detection bias), and for incomplete outcome reporting. In addition, larger, higher-quality studies have almost all been conducted with new drugs with pharmaceutical company funding, and these were the only drugs with moderate strength of evidence: duloxetine and venlafaxine. For nonpharmacologic treatments, invasive procedures involving devices (i.e, spinal cord stimulators) are also more likely to have device manufacturer-sponsored trials.

The newest studies of pregabalin did not show effectiveness for pain compared to placebo. This may have been partly because these studies did not have a primary objective of evaluating the effectiveness of pregabalin for the outcome of pain, but there was also concern about reporting bias, given that none of the four studies found on Clinicaltrials.gov with results showed effectiveness for pain, and six additional studies from clinicaltrials.gov had not results. In addition, drugs with very large numbers of studies and enrolled patients (e.g., pregabalin) and pharmaceutical company funding would have greater power to show a statistically significant effect despite a small effect size than older drugs with few, small studies. For many of the studies and tapentadol in particular, there were concerns about study methodology inconsistent with

standards for pain trials,[176] including using nonstandard primary pain outcomes and withdrawal study methodology (of concern for studies of opioids, where withdrawal causes additional symptoms).

Studies often reported multiple assessment tools for a given outcome, which sometimes had conflicting results; the specific tools used and how they were reported was often inconsistent across studies. For pain, many different types of scales and composite tools were used, and pain severity was sometimes not reported separately. Other important issues, such as the impact of pain on function or quality of life (which includes patient-reported function), were inconsistently measured or reported; we analyzed data on quality of life, but were unable to draw conclusions due to incomplete reporting. All of these factors limited our ability to conduct meta-analyses in some cases or fully evaluate the impact of interventions.

Many studies were underpowered or did not recruit sufficient patients for the intended sample size, and withdrawal rates were often high, particularly in the few longer-term studies. The evidence base was also limited owing to the short duration of most studies. Most trials we identified were less than three months in duration and many were less than one month, despite the fact that these medications are used in clinical practice as chronic, long-term medications. Many studies were of insufficient duration to adequately assess long-term clinical outcomes, including continued effectiveness with progression of diabetic peripheral neuropathy; long-term side effects, such as weight gain; or long-term impact on function or diabetic complications. Adverse effects were often not reported for non-pharmacologic treatments and were often reported inconsistently for drugs, making synthesis difficult. Information from the broader literature on long-term use of these medications, particularly evolving data on the long-term harms of opioids[177] in addition to the high dropout rates identified in our review, is needed for clinical decision making on benefit/harm ratios.

Implications for Clinical and Policy Decisionmaking

Given that comparative effectiveness of pharmacologic options to each other and to non-pharmacologic options is very limited, and recent evidence focuses mainly on newly approved agents, clinical decisions regarding approach should take into consideration adverse effect profiles and patient preferences. Our findings generally support the effectiveness for the outcome of pain of the three drugs approved by the Food and Drug Administration for the symptom of pain in diabetic peripheral neuropathy: the serotonin-noradrenaline reuptake inhibitor duloxetine, the anticonvulsant pregabalin and the atypical opioid tapentadol. However, the effect size was small for pregabalin, new and unpublished studies did not show effectiveness for pain, and strength of evidence was low due to concerns about reporting bias. All these treatments also have substantial risks of adverse effects, which may be of particular concern for older patients with diabetes. Duloxetine had high rates of dropouts due to adverse effects, with rates of 17 to 20 percent in most study arms. In addition, pregabalin has a similar mechanism of action to gabapentin, and the two agents are often used interchangeably in clinical care, but Griebeler et al. and our updated review found that gabapentin was not more effective than placebo for the outcome of pain.

Few long-term studies exist for diabetic peripheral neuropathy. This is particularly important for the atypical opioids, which we found were more effective than placebo for the outcome of pain in short-term studies. However, these studies had significant methodological limitations. New guidelines and position papers now recommend against the use of opioids for chronic pain

conditions, such as fibromyalgia and low back pain, given lack of evidence for long-term benefit and increasing evidence of serious risks, particularly abuse, misuse and overdose.[178]

Given the limitations of pharmacologic approaches, nonpharmacologic treatments could be of particular value. We found that the supplement alpha-lipoic acid was effective for pain (low strength of evidence), and there were few adverse effects. However, these studies were all conducted by the same investigator and had methodologic and reporting limitations. The only long-term study had a high dropout rate. Alpha-lipoic acid was not effective for numbness and paresthesia.

We also found that spinal cord stimulation was effective, but assessed strength of evidence as low, and it should be noted that this treatment has a risk of serious complications. Evidence on non-pharmacologic approaches all had methodologic limitations or a limited number of studies, with small sample sizes and inconsistent results for transcutaneous electrical nerve stimulation, lack of long-term effects for frequency-modulated electromagnetic stimulation, only one small study on cognitive behavioral therapy and no studies of exercise or physical therapy for pain.

Future Research Needs

Many comparisons and outcomes that have low or insufficient evidence are future research needs. In particular, more studies are needed on lower-risk approaches, such as topical medications, and non-pharmacologic approaches, such as cognitive-behavioral therapy and exercise or physical therapy; for acupuncture, studies with sham arms are needed.

Larger studies with sufficient sample size and longer-term studies are also critical for future research. Followup of several weeks is insufficient for treatments that are often burdensome (e.g., electrical stimulation interventions that require frequent visits) or have significant adverse effects and dropout rates. The few longer-term studies often had very high dropout rates over time (e.g., for alpha-lipoic acid) and lower efficacy (e.g., for frequency-modulated electromagnetic stimulation).

We identified no studies that compared or combined pharmacologic and non-pharmacologic approaches; combinations of therapies would be critical to study further, as these approaches are often used together in clinical practice. Better assessment of adverse effects would also allow better evaluation of the benefit-risk balance, rather than just evaluation of effectiveness. Studies should also follow guidelines for pain intervention studies and evaluation of outcomes.[176]

Conclusions

The anticonvulsants pregabalin and oxcarbazepine (low strength of evidence), the serotonin-noradrenaline reuptake inhibitors duloxetine and venlafaxine (moderate strength of evidence), the drug classes of tricyclic antidepressants (low strength of evidence) and atypical opioids (tramadol and tapentadol) (low strength of evidence), and the intradermal neurotoxin botulinum toxin (low strength of evidence) were more effective than placebo for reducing pain in diabetic peripheral neuropathy, although all oral drug classes had >10% dropout rates due to adverse effects. For nonpharmacologic treatments, we found no interventions with greater than low strength of evidence. Alpha-lipoic acid and spinal cord stimulation had low strength of evidence for the reduction of pain compared to placebo, but the latter has risk of serious adverse effects. Magnitudes of effect were generally moderate and all studies had deficits in quality. There were few studies evaluating non-pharmacologic interventions, such as exercise or cognitive therapy, for pain.

Additional studies evaluating longer-term outcomes, and those combining pharmacologic and non-pharmacologic approaches to maximize function, are needed to better inform clinical decisionmaking, patient choice, and clinical practice guidelines.

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Appendix A. List of Acronyms

%	percent
ABC	Activities-specific Balance and Confidence scale
ACROBAT-NRSI	Cochrane Risk of Bias Assessment Tool for Non-Randomized Studies of Interventions
AHRQ	Agency for Healthcare Research and Quality
ALA	Alpha-lipoic Acid
ALADIN	Alpha-Lipoic Acid in Diabetic Neuropathy Trial
ATL	Achilels tendon lengthening
BBS	Berg Balance Scale
BMI	Body Mass Index
BMT	Best Medical Treatment
CBT	Cognitive Behavioral Therapy
CDC	Centers for Disease Control
CI	Confidence interval
DCCT	Diabetic Control and Complications Trial
DPN	Diabetic Peripheral Neuropathy
EDIC	Epidemiology of Diabetes Interventions and Complications
EPC	Evidence-based practice center
FDA	Food and Drug Administration
FES	Falls Efficacy Scale
FES-I	Falls Efficacy Scale – Internation version
FRT	Functional Reach Test
HbA1c	Glycated Haemoglobin
HR	Hazard Ratio
IWGDF	International Working Group on the Diabetic Foot
J-EDIT	Japanese Elderly Diabetes Intervention Trial
KQ	Key Question
LAC	Levacecarnine
MDM	Mesodiencephalic moedulation
MPQ-QOL	McGill Pain Questionnaire – Quality of Life
NEURODIAB	Diabetic Neuropathy Study Group of the European Association for the Study of Diabetes
NMDA	N-methyl-D-aspartate
NPSI	Neuropathic Pain Symptom Inventory
NQOL	Neuropathic Quality of Life
NR	Not reported
NS	Not significant
NSC(LL)	Neuropathy Symptom Change Score – Lower Legs
OR	odds ratio
ORPIL	Oral Pilot Trial
PEMF	Pulsed electromagnetic fields
PENS	Percutaneous Electrical Nerve Stimulation
PICOTS	Populations, interventions, comparators, outcomes, timing, setting
QOL	Quality of Life
RCT	Randomized controlled trial
RR	Relative risk
rTMS	repetitive transcranial magnetic stimulation
SCS	Spinal Cord Stimulation
SD	Standard deviation
SDIS	Stockholm Diabetes Intervention Study
SF-36	36 item Short Form Survey
SMD	Standardized Mean Difference
SNRI	Serotonin-Norepinephrine Reuptake Inhibitors
SOE	Strenght of Evidence
SYDNEY2	Sumptomatic Diabetic Neuropathy Trial
T2DM	Type 2 diabetes mellitus
TCA	Tricyclic antidepressants
TCC	Total Contact Casting

TENS	Transcutaneous Electrical Nerve Stimulation
TOO	Task Order Officer
TUG	Timed Up and Go Test
VACSDM	Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes
VAS	Pain Visual Analogue Scale
WHYMPI	West Haven Yale Multidimensional Pain Inventory

Appendix B. Detailed Search Strategy

PubMed

A (diabetes neuropathy)	B (Interventions for KQ1 and 2)
diabetes mellitus[mh] OR diabetes [tiab] AND peripheral nervous system diseases [mh] OR “Peripheral Nerve Diseases”[tiab] OR “Peripheral Nerve Diseases”[tiab] OR neuropathy[tiab] OR Polyneuropathy[tiab] OR “Peripheral Nerve Disease”[tiab] OR neuropathies[tiab] OR Polyneuropathies[tiab] OR "PNS disease"[tiab] OR "PNS diseases"[tiab] OR “Diabetic Neuropathies” [MH] OR neuropathy[tiab] OR “diabetic polyneuropathy" [tiab] .	"hypoglycemic agents"[mh] OR Hypoglycemic[tiab] OR hypoglycaemic [tiab] OR antidiabetic[tiab] OR Antihyperglycemic[tiab] OR "insulin infusion systems"[MeSH Terms] OR insulin [tiab] OR “glycemic control”[tiab] OR “glycaemic control”[tiab] OR “metformin”[mh] or “thiazolidinediones”[mh] or “glipizide”[mh] or “glyburide”[mh] OR “Dipeptidyl-Peptidase IV Inhibitors”[mh] OR “Glucagon-Like Peptide 1”[mh] OR biguanide*[tiab] OR metformin[tiab] OR thiazolidinedione*[tiab] or pioglitazone[tiab] OR rosiglitazone[tiab] OR sulfonylurea*[tiab] or sulphonylurea*[tiab] OR glipizide[tiab] OR glyburide[tiab] OR glimepiride[tiab] OR glibenclamide[tiab] OR “insulin secretagogues”[tiab] OR sitagliptin*[tiab] OR saxagliptin*[tiab] OR dpp-4[tiab] OR(exercise [mh]) OR ((exercise[tiab] or exercises[tiab]) AND (program[tiab] OR programs[tiab] OR intervention [tiab] OR interventions [tiab] OR balance [tiab] OR coordination[tiab] OR coordinations[tiab] OR aerobic[tiab] OR isometric[tiab] OR therapy OR strength[tiab] OR endurance[tiab] OR endurances[tiab] OR running[tiab] OR walking [tiab] OR cycle[tiab] OR treadmill[tiab] OR stair[tiab]))) OR physical exertion[mh] OR ((physical [tiab]) AND (activity[tiab] OR activities[tiab] OR fitness [tiab] OR therapy[tiab] OR exercise[tiab] OR education[tiab] OR training[tiab] OR exertion[tiab] OR exertions[tiab] OR effort[tiab] OR efforts[tiab])) OR Rehabilitation[mh] OR Rehabilitation[tiab] OR (training [tiab] AND (aerobic [tiab] OR resistance[tiab] OR strength [tiab] OR balance [tiab] OR endurance[tiab] OR endurances[tiab] OR weight[tiab])) Sports[mh] OR ((therapy[tiab] OR therapies[tiab]) AND (moving[tiab] OR sports[tiab]))) OR “Stair Navigation”[tiab] OR postural balance[mh] OR “postural stability”[tiab] OR posture[mh] or posture[tiab] OR postures[tiab] or “postural control” [tiab] OR muscle strength[mh] OR muscle strength[tiab] OR proprioception[mh] OR Proprioception[tiab] OR)) OR Weight-Bearing[mh] OR WeightBearing[tiab] OR “weight loss”[mh] OR “weight loss”[tiab] OR “Diet, Carbohydrate-Restricted”[mh] OR diet[tiab] OR “smoking cessation”[mh] OR “smoking cessation”[tiab] OR “lifestyle intervention”[tiab] OR “physical therapy”[tiab] OR” Physical Therapy Modalities”[mh] OR Rehabilitation[mh] OR Rehabilitation[tiab] OR (Acupuncture [MH])) OR ((acupuncture[tiab]) AND (injection[tiab] OR therapy [tiab] points[tiab] OR therapy[tiab]))) OR ("decompression, surgical"[mh] OR "surgical decompression"[tiab])) OR "electric stimulation therapy"[mh]) OR (((neural [tiab] OR nerve[tiab] OR therapy[tiab])) AND stimulation[tiab])) OR “TENS”[tiab]) OR (Cognitive therapy [mh] OR “Cognitive therapy” [tiab] OR “Cognitive behavioral”[tiab] or “cognition therapy”[tiab] OR “cognitive Psychotherapy”[tiab] OR “behavioral therapy”[tiab] OR “behavioral therapies”[tiab] OR “thioctic acid”[mh] OR “lipoid acid”[tiab] OR “thioctic acid”[tiab] OR acetylcarnitine[mh] OR Acetylcarnitine [tiab] OR “Acetyl-L-Carnitine”[tiab] OR carnitine[tiab])) OR ((((((((((diabetes mellitus[mh] OR diabetes [tiab])) AND (peripheral nervous system diseases [mh] OR “Peripheral Nerve Diseases”[tiab] OR “Peripheral Nerve Diseases”[tiab] OR neuropathy[tiab] OR Polyneuropathy[tiab] OR “Peripheral Nerve Disease”[tiab] OR neuropathies[tiab] OR Polyneuropathies[tiab] OR "PNS disease"[tiab] OR "PNS diseases"[tiab]))) OR (“Diabetic Neuropathies” [MH] OR neuropathy[tiab] OR “diabetic polyneuropathy" [tiab]))) AND (((("Neuralgia"[Mesh] OR neuralgia [tiab]OR "Neuropathic pain"[tiab] OR “Trigeminal neuralgia”[tiab])) AND ("therapy"[Subheading] OR "therapy"[tiab] OR "treatment"[tiab] OR "Therapeutic Uses"[mh] OR "therapeutics"[MeSH Terms] OR "therapeutics"[tiab]))))

Appendix C. Excluded Articles

KQ1 Excluded Articles

No full report/ original data

Induration of the diabetic foot pad: another risk factor for recurrent neuropathic plantar ulcers. T. Brink. Biomed Tech (Berl) 1995: 205-9

Effect of near normoglycaemia for two years on progression of early diabetic retinopathy, nephropathy, and neuropathy: the Oslo study. K. Dahl-Jorgensen, O. Brinchmann-Hansen, K. F. Hanssen, T. Ganes, P. Kierulf, E. Smeland, L. Sandvik and O. Aagenaes. Br Med J (Clin Res Ed) 1986: 1195-9

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Capsaicin 8% patch repeat treatment versus standard of care in painful diabetic peripheral neuropathy: A randomised, open-label, 52-week study. A. I. Vinik, S. Perrot, E. J. Vinik, L. Pazdera, H. Jacobs, M. Stoker, S. Long, R. Snijder, M. Van Der Stoep, E. Ortega and N. Katz. Diabetologia 2015: S514-S515

Incidence of microvascular outcomes in type 2 diabetes patients treated with vildagliptin vs sulphonylurea: A retrospective study using German electronic medical records. W. M. Kolaczynski, M. Hankins, S. H. Ong, H. Richter, A. Clemens and M. Toussi. Diabetologia 2015: S394

Pregabalin positively affects subjective pain, falls risk, and gait in persons with diabetic peripheral neuropathy. S. Morrison, H. Parson and A. I. Vinik. Diabetes 2015: A164

Incidence of microvascular outcomes among type 2 diabetes patients treated with vildagliptin vs. Sulfonylurea: A retrospective cohort study using german electronic medical records. M. Hankins, S. H. Ong, H. Richter, W. M. Kolaczynski, A. Clemens, G. Machnicki, M. Toussi and J. Vora. Diabetes 2015: A4

Effect of intensive weight reduction on neuropathy progression in patients with diabetes: A 1-year controlled clinical trial. A. Mottalib, A. Morsi, M. Shehabeldin, M. Sakr and O. Hamdy. Diabetes 2015: A51-A52

The effects of treatment modalities on outcome in diabetic foot patients and retrospective evaluation of comorbidities. E. Ozay, O. Ersen, S. Bilgic and O. Rodop. European Surgical Research 2015: 163

Incidence and impact of hypoglycemia in diabetic patients with intensified glycaemic control in clinical practice-results of DiaRegis. A. K. Gitt, P. Bramlage, S. Schneider, C. Binz, M. Krekler and D. Tschoepe. European Heart Journal 2014: 1020-1021

Regular exercise improves metabolic control and reduces chronic complications in patients with type 2 diabetes. J. Tang, X. Li, Y. Yang, L. Yuan, J. Han, C. Ju, L. Shen, Q. Lou, F. Zhao, Z. Sun and X. Guo. Diabetologia 2014: S434

Game-based guided exercise: Using an avatar with real-time feed back to improve postural stability in diabetic peripheral neuro pathy. B. Najafi, G. Grewal, J. Lee-Eng, T. K. Talal, R. A. Menzies and D. G. Armstrong. Diabetes 2014: A186

Effect of roux-en-y gastric bypass surgery on microvascular complications of type 2 diabetes mellitus. L. L. Chuah, A. D. Miras, D. Papamargaritis, A. Vusiri Kala, S. N. Jackson, N. Oliver, T. Olbers and C. W. Le Roux. Diabetes 2014: A525

Nutrition intervention for diabetic neuropathy. A. E. Bunner, J. Gonzalez, U. Agarwal, F. Valente and N. D. Barnard. Diabetes 2014: A578

The effects of treatment modalities on outcome in diabetic foot patients. E. Ozay, S. Bilgic, O. Rodop and O. Ersen. European Surgical Research 2014: 241

Helping patient with diabetes through physical activity. S. Zeqiri, N. Zeqiri and A. Ylli. Annals of Physical and Rehabilitation Medicine 2014: e323-e324

Complex neurorehabilitation programme improves quality of life of patients with diabetic polyneuropathy and diabetic foot. Y. Koleva. Annals of Physical and Rehabilitation Medicine 2013: e38-e39

Determination of the the effectiveness of home exercise program in patients with diabetic neuropathy. L. CerrahoÃŠâ€¡lu, U. KoÃ…Å¸an and E. TopcÃ‚Â¸u. Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi 2013: 359

Efficacy of weight reduction program on obese patients with diabetic peripheral neuropathy. G. M. Ahmed, M. M. Mostafa, M. F. Farouk and A. E. G. El Gohary. Diabetes Technology and Therapeutics 2013: A123

Initial vascular response to clear cleat cycling in patients at risk for dfu. R. T. Crews, S. R. Smith and S. B. Liu. Diabetes 2012: A165-A166

Impact of one-year smoking cessation upon type 2 diabetes diagnosis. C. Voulgari, N. Tentolouris, K. Makrilakis, N. Papanas, C. Manes and N. Katsilambros. Diabetes 2011: A227-A228

Relationship between foot range of movement and plantar pressure distribution in diabetic neuropathic patients. C. D. Sartor, A. P. Picon, M. I. Roveri, R. C. Dinato and I. C. N. Sacco. Clinical Biomechanics 2011: 674

Gait, balance and plantar temperature fluctuation in charcot and diabetes patients with and without active foot ulcer. B. Najafi, G. S. Grewal, R. A. Menzies, T. K. Talal, M. A. Zirie and D. G. Armstrong. Diabetes 2011: A18

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Patient-reported outcomes in subjects with painful diabetic peripheral neuropathy: Pain description and quality of life. K. S. Ko, B. Y. Cha, C. H. Kim, H. S. Kwon, J. H. Lee, T. S. Park, J. C. Won, S. K. Ko and H. J. Park. Value in Health 2011: A66

Exploring postural compensation in diabetes-related neuropathy patients (DPN): The role of visual and somatosensory adaptation. B. Najafi, R. T. Crews, S. C. Wu and J. S. Wrobel. Diabetes 2010:

The toe-to-forefoot plantar pressure ratio is increased in severe diabetic neuropathy. Y. Fujioka, S. I. Taniguchi, H. Kinoshita, K. Sumi, H. Shiochi, N. Yamamoto, K. Matsuzawa, S. Izawa, T. Ohkura, H. Ohkura and C. Shigemasa. Diabetes 2010:

Game-based system for evaluation of balance control in diabetic sensory neuropathy. B. Najafi, S. Wu, N. S. Rivera, R. Crews, D. G. Armstrong and J. Wrobel. Diabetes 2009:

Effects of a combined strengthening, stretching and functional training program versus usual-care on gait biomechanics and foot function for diabetic neuropathy: a randomized controlled trial. C. D. Sartor, R. Watari, A. C. PÃƒÂ¡ssaro, A. P. Picon, R. H. Hasue and I. C. Sacco. BMC Musculoskelet Disord 2012: 36

Determination of the the effectiveness of home exercise program in patients with diabetic neuropathy, Diyabetik Noropatili Hastalarda Ev Egzersiz Programinin Etkinlitinin Belirlenmesi. [Turkish, English]. L. Cerrahotlu, U. Kosan and E. Topcu. Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi 2013: 359

Effects of exenatide on measures of small fiber neuropathy in patients with type 2 diabetes. M. Jaiswal, C. L. Martin and R. Pop Busui. Diabetes 2014: A149

A pilot study of intranasal insulin for the treatment of diabetic peripheral neuropathy. L. Korngut, S. Mawani, G. Francis, E. Mehina, B. Hemmelgarn, N. Jette, D. W. Zochodne, S. Wiebe and C. Toth. Journal of the Peripheral Nervous System 2013: S59

Effect of ruboxistaurin on albuminuria and estimated GFR in people with diabetic peripheral neuropathy: Results from a randomized trial. K. R. Tuttle, J. B. McGill, E. J. Bastyr, K. K. Poi, N. Shahri and P. W. Anderson. American Journal of Kidney Diseases 2015: 634-6

A multidisciplinary approach is effective in decreasing major lower extremity amputations. V. Provenzano, L. Ferrara, D. Brancato, A. Scorsone, V. Aiello, A. Di Noto, M. Fleres, F. Provenzano, G. Saura and L. Spano. Italian Journal of Medicine 2015: 88

Empowering and improving foot care in type 2 diabetic patients referred to diabetes clinic of semirom city isfahan province Iran:2012-2013 application of basnef model. M. Taghdisi, M. Afshari, K. Azam and A. Z. A. R. Tol. Diabetes Technology and Therapeutics 2015: A133

Hospitalizations and patient outcomes between a pharmacistphysician diabetes co-management service and usual care. A. Airee, A. W. Dake, P. Mahbubani, J. D. Williams and R. E. Heidel. Pharmacotherapy 2014: e234

Randomized double blind clinical trial: Utilization of umbilical cord blood-derived platelet gel for treatment of diabetic foot ulcers. E. S. Hosseini, A. Goodarzi, B. Molavi and N. Aghdami. Cell Journal 2014: 46-47

Control of lower extremity edema in patients with diabetes: Double-blind RCT assessing the efficacy of mild compression diabetic socks. S. C. Wu, R. T. Crews, M. Skratsky, M. Branigan, J. Ortiz and C. Andersen. Diabetes 2015: A37

Effect of intensive weight reduction on neuropathy progression in patients with diabetes: A 1-year controlled clinical trial. A. Mottalib, A. Morsi, M. Shehabeldin, M. Sakr and O. Hamdy. Diabetes 2015: A51-a52

Supervised structured exercise training for people with diabetic peripheral neuropathy: A randomised

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Reduction of complications and associated costs for type 2 diabetic patients using continuous subcutaneous insulin infusion in the UK. S. Roze, E. Duteil, N. Hallas and S. De Portu. Value in Health 2015: A360

Implementation of foot thermometry plus mHealth to prevent diabetic foot ulcers: study protocol for a randomized controlled trial. M. Lazo-Porras, A. Bernabe-Ortiz, K. A. Sacksteder, R. H. Gilman, G. Malaga, D. G. Armstrong and J. J. Miranda. Trials 2016: 206

Effect of Patient-Education on Health-Related Quality of Life of Diabetic Foot Ulcer Patients In A Tertiarycare Hospital. S. S. Miraj, R. T. Roy, M. Unnikrishnan, V. K, G. S. Rodrigues and C. Mukhopadhyay. Value Health 2015: A621

A Randomized Controlled Trial Comparing Telemedical and Standard Outpatient Monitoring of Diabetic Foot Ulcers. Diabetes Care 2015;38:1723-1729. M. Muller, S. David-Tchouda, J. Margier, M. Oreglia and P. Y. Benhamou. Diabetes Care 2016: e9-e10

A Randomized Controlled Trial Comparing Telemedical and Standard Outpatient Monitoring of Diabetic Foot Ulcers. Diabetes Care 2015;38:1723-1729. K. B. Yderstraede, J. Froekjaer and B. S. B. Rasmussen. Diabetes Care 2016: e11

Evaluate the effectiveness of a dedicated diabetes specialist nurse in a joint podiatry setting over a 6 month period to compare pre and post biometric data. G. Taft and B. Huda. Diabetic Medicine 2016: 184

Not relevant to Key question

Topically Applied Vancomycin Powder Reduces the Rate of Surgical Site Infection in Diabetic Patients Undergoing Foot and Ankle Surgery. D. K. Wukich, J. W. Dikis, S. J. Monaco, K. Strannigan, N. C. Suder and B. L. Rosario. Foot Ankle Int 2015: 1017-24

Diabetic foot complications and their risk factors from a large retrospective cohort study. K. Al-Rubeaan, M. Al Derwish, S. Ouizi, A. M. Youssef, S. N. Subhani, H. M. Ibrahim and B. N. Alamri. PLoS One 2015: e0124446

A cohort study of diabetic patients and diabetic foot ulceration patients in China. Y. Jiang, X. Wang, L. Xia, X. Fu, Z. Xu, X. Ran, L. Yan, Q. Li, Z. Mo, Z. Yan, Q. Ji and Q. Li. Wound Repair Regen 2015: 222-30

Relationship between glycemic control, microalbuminuria and cognitive functions in elderly type 2 diabetic patients. C. B. Gul, O. Oz Gul, S. Cander, A. Eroglu, M. Hartavi, N. Keni, A. Bayindir, C. Ersoy, E. Erturk, E. Tuncel and S. Imamoglu. Ren Fail 2014: 1258-62

Effect of oral nutritional supplementation on wound healing in diabetic foot ulcers: a prospective randomized controlled trial. D. G. Armstrong, J. R. Hanft, V. R. Driver, A. P. Smith, J. L. Lazaro-Martinez, A. M. Reyzelman, G. J. Furst, D. J. Vayser, H. L. Cervantes, R. J. Snyder, M. F. Moore, P. E. May, J. L. Nelson, G. E. Baggs, A. C. Voss and G. Diabetic Foot Nutrition Study. Diabet Med 2014: 1069-77

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Determination of efficacy of reflexology in managing patients with diabetic neuropathy: a randomized controlled clinical trial. K. Dalal, V. B. Maran, R. M. Pandey and M. Tripathi. Evid Based Complement Alternat Med 2014: 843036

Current glycemic status and diabetes related complications among type 2 diabetes patients in India: data from the A1chieve study. V. Mohan, S. Shah and B. Saboo. J Assoc Physicians India 2013: 12-5

Effect of glycemic treatment and microvascular complications on menopause in women with type 1 diabetes in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) cohort. C. Kim, P. A. Cleary, C. C. Cowie, B. H. Braffett, R. L. Dunn, M. E. Larkin, P. M. Gatcomb, H. B. Wessells, D. M. Nathan, A. V. Sarma and D. E. R. Group. Diabetes Care 2014: 701-8

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Mortality and other important diabetes-related outcomes with insulin vs other antihyperglycemic therapies in type 2 diabetes. C. J. Currie, C. D. Poole, M. Evans, J. R. Peters and C. L. Morgan. J Clin Endocrinol Metab 2013: 668-77

Lower incidence of recorded cardiovascular outcomes in patients with type 2 diabetes using insulin aspart vs. those on human regular insulin: observational evidence from general practices. W. Rathmann and K. Kostev. Diabetes Obes Metab 2013: 358-63

Identifying the incidence of and risk factors for reamputation among patients who underwent foot amputation. Y. Kono and R. R. Muder. Ann Vasc Surg 2012: 1120-6

Effect of selected exercises on in-shoe plantar pressures in people with diabetes and peripheral neuropathy. K. M. Shah and M. J. Mueller. Foot (Edinb) 2012: 130-4

Selection of an above or below-ankle orthosis for individuals with neuropathic partial foot amputation: a pilot study. S. E. Spaulding, T. Chen and L. S. Chou. Prosthet Orthot Int 2012: 217-24

Functional balance in elderly with diabetic neuropathy. T. Ghanavati, M. J. Shaterzadeh Yazdi, S. Goharpey and A. A. Arastoo. Diabetes Res Clin Pract 2012: 24-8

A multidisciplinary diabetic foot ulcer treatment programme significantly improved the outcome in patients with infected diabetic foot ulcers. C. C. Chiu, C. L. Huang, S. F. Weng, L. M. Sun, Y. L. Chang and F. C. Tsai. J Plast Reconstr Aesthet Surg 2011: 867-72

Long-term effects of a randomised trial of a 6-year lifestyle intervention in impaired glucose tolerance on diabetes-related microvascular complications: the China Da Qing Diabetes Prevention Outcome Study. Q. Gong, E. W. Gregg, J. Wang, Y. An, P. Zhang, W. Yang, H. Li, H. Li, Y. Jiang, Y. Shuai, B. Zhang, J. Zhang, R. B. Gerzoff, G. Roglic, Y. Hu, G. Li and P. H. Bennett. Diabetologia 2011: 300-7

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Static magnetic field therapy for symptomatic diabetic neuropathy: a randomized, double-blind, placebo-controlled trial. M. I. Weintraub, G. I. Wolfe, R. A. Barohn, S. P. Cole, G. J. Parry, G. Hayat, J. A. Cohen, J. C. Page, M. B. Bromberg, S. L. Schwartz and G. Magnetic Research. Arch Phys Med Rehabil 2003: 736-46

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Appendix D. Evidence Tables

Evidence Table D-1. Study characteristics for pharmacological treatment (KQ1a)

Author, year	Study design Site(s) Location	Recruitment period (start year – end year)	Diabetes type	Key exclusions	Treatment duration or follow-up time If applicable washout period, run-In period	Description of intervention in each group	Funding support
Knatterud, 1978[1] UGDP	RCT Multi-site U.S.	1961-65	T2DM	A prior history of ketoacidosis	12 years	Group A. Insulin variable. Goal is normal glucose - fasting blood glucose level below 110 mg/100 Group B. Control. Insulin standard. No changes.	NIH
Reichard, 1993[2] Rathsman, 2014[3] SDIS trial	Original RCT observational follow-up Sweden	1982-84 intervention end: 1992 Observational follow-up ended: 2011	T1DM	History of or ongoing ischemic foot ulcer or foot and/or leg amputation; osteoarthropathy; alcohol/drugs abuse, mental illness.	7.5 years of treatment with 28 years of follow-up in sub-group	Group A: ICT, intensified conventional treatment, multiple insulin injections daily (pre-meal + basal) Group B: ST, standard treatment (2-3 insulin injections/day)	Novo-Nordisk, Boerhinger-Mannheim
Abraira, 1997[4] VACSDM	RCT Multi-site U.S.	Start - 1991	T2DM	Serious illness , T2DM >15, CV events in last 6 mos, h/o gangrene.	7.8 +/- 4 years	Group A. intensive. Stepped plan, starting with once daily insulin ± glipizide, to multiple daily injections) designed to reach goal of HbA1c < 7.5% Group B. standard (once daily insulin)	Veterans Affairs and Roerig/ Pfizer Pharmaceuticals

Author, year	Study design Site(s) Location	Recruitment period (start year – end year)	Diabetes type	Key exclusions	Treatment duration or follow-up time If applicable washout period, run-In period	Description of intervention in each group	Funding support
UKPDS, 1998[5]	RCT with observational followup Multisite Europe	1977-1991	T2DM	Ketonuria, serum creatinine greater than 175 µmol/L; myocardial infarction in the previous year; current angina or heart failure; more than one major vascular event.	Median follow-up 10.7 years (IQR 7.7-12.4)	Group A. Intensive. FPG < 6 mmol/L, in insulin treated patients, pre-meal glucose 4-7 mmol/L (72 -126 mg/dl) (mean A1c over 10 years 7.0%) Group B: Conventional. FPG < 15 mmol/L (<270mg/dl) and avoidance of hyperglycemia symptoms (mean A1c over 10 years 7.9%)	National Health service, Smith Kline, Glaxo Wellcome, Pfizer, Zeneca, pharmacia, Upjohn, Roche.
Gaede, 2003[6] and Gaede, 2008[7] Steno-2	RCT, open with observation follow-up Denmark	1993-2001	T2DM	Age > 65 or < 40; malignancy; or life-threatening disease with death probable within 4 years.	Mean treatment 7.8 years, followed for mean of 5.5 more years	Group A: conventional treatment, by GP, according to the 1988 recommendations of the Danish Medical Association Group B: intensive multifactorial intervention involving strict treatment goals to be achieved through behavior modification and a stepwise introduction of pharmacologic therapy overseen by a project team (doctor, nurse, and dietitian) at the Steno Diabetes Center	Danish Health Research Council.
Dormandy, 2005[8] PROactive	RCT Multi-site Europe	2001-2022	T2DM Also evidence of extensive macrova scular disease	Taking only insulin; had planned coronary or peripheral revascularisation; heart failure, ischaemic ulcers, gangrene, or rest pain in the leg; haemodialysis; or had greater than 2·5 times the upper limit of normal concentrations of alanine aminotransferase.	Mean follow-up 34.5 months	Group A: Pioglitazone + background meds (oral pioglitazone 15 mg for the first month, 30 mg for the second month, and 45 mg thereafter to achieve the maximum tolerated dose, according to the licensed dose range for pioglitazone.) Group B: placebo + background meds	Takeda Pharmaceutical Company and Eli Lilly and Company,

Author, year	Study design Site(s) Location	Recruitment period (start year – end year)	Diabetes type	Key exclusions	Treatment duration or follow-up time If applicable washout period, run-In period	Description of intervention in each group	Funding support
Martin, 2006[9 10] (parent trial) DCCT/EDIC	RCT with observational follow-up	Recruitment 1983-1989 EDIC began in 1994, 1 yr after trial completion	T1DM	Diabetes duration < 1 years or > 15 years, no CKD or severe retinopathy	Original trial follow-up was 4-9 years, mean 6.5 years Cohort analysis is at years 8	Group A: intensive therapy (administering insulin three or more times daily by injection or by an external insulin pump) Group B: conventional therapy (one to two injections of insulin daily)	NIH
Duckworth, 2009[11] VADT	RCT Multi-site U.S.	2000-2003	T2DM	Recent CVD event, A1c <=7.5%, CHF, severe angina	Median 5.6 years	Group A: Intensive glycemic control, < 6% Group B: standard treatment	Dept. of VA Affairs, Medications provided by Pharma comps.
Griffin, 2011[12] ADDITION	RCT, cluster randomized Multi-site Europe	2001-2006	T2DM	Age <40,age >69	5·3 (SD 1·6) years	Group A: Screening + intensive treatment to goal A1c <7.0% Group B: Usual care	National Health Service Denmark, Danish Council for Strategic Research, Danish Research Foundation, Danish National Board of Health, Danish Medical Research Council, Aarhus University Research Foundation, Wellcome Trust, UK Medical Research Council, UK NIHR Health Technology Assessment Programme, UK National Health Service R&D, UK National Institute for Health Research, Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, Novo Nordisk, Astra, Pfi zer, GlaxoSmithKline, Servier, HemoCue, Merck

Author, year	Study design Site(s) Location	Recruitment period (start year – end year)	Diabetes type	Key exclusions	Treatment duration or follow-up time If applicable washout period, run-In period	Description of intervention in each group	Funding support
Araki, 2012[13] J-EDIT	RCT Multi-site Japan	2001-2002	T2DM	Age<65 or >85, A1c <8% and CVD risk factors	3 years	Group A: Intensive. The treatment goal in the intensive treatment group was HbA1c 6.9% and other CVD management goals. Group B: conventional treatment group continued their baseline treatment for diabetes, hypertension or dyslipidemia without a specific treatment goal.	Japanese Ministry of Health and Labour, and Welfare, Japan Foundation for Aging and Health.
Kostev, 2012[14]	Retrospective cohort study Germany	July 2000 and September 2007	T2DM	Patients who did not meet the continuity of follow-up criteria, received another basal insulin or premixed insulin during the observation period.	24 months	Group A: Glargine basal insulin Group B: NPH basal insulin	NR
Jaiswal, 2015[15]	RCT, open label Single site, university setting U.S.	2008-2014	T2DM	Neuropathy independent of diabetes, or any condition other than diabetes associated with neuropathy (e.g. hepatitis C, end stage renal disease, lupus), any lower extremity amputation or severe deformity of lower extremity, HbA1c<=7%, HbA1c > 10.	18 months	Group A: Exenatide, 5 µg twice daily for 4 weeks and then increased to 10 µg daily Group B: Insulin Glargine, 10 units daily, titrated in 2-unit increments to achieve a fasting blood glucose target level of 100 mg/dL without recurrent or severe hypoglycemia.	Amylin Pharmaceuticals, LLC, Eli Lilly and Company, Bristol-Myers Squibb Company and Astra-Zeneca

ADDITION = Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen Detected Diabetes in Primary Care; CKD = Chronic Kidney Disease ; CVD = Cardiovascular disease; DCCT/EDIC = Diabetes Control and Complications Trial / Epidemiology of Diabetes Interventions and Complications; J-EDIT = Japanese Elderly Diabetes Trial; NIH = National Institute of Health; NR = Not Reported; PROactive = Prospective Pioglitazone Clinical Trial in Macrovascular Events; RCT = Randomized Control Trials; SDIS = Stockholm Diabetes Intervention Study; T1DM = Type 1 Diabetes Mellitus; T2DM = Type 2 Diabetes Mellitus; UGDP = University Group Diabetes Program; UKPDS = United Kingdom Prospective Diabetes Study; US = United States; VACSDM = Veterans Affairs Cooperative Study on glycemic control and complications in type 2 Diabetes Mellitus; VADT = Veterans Affairs Diabetes Trial;

Evidence Table D-2. Patient characteristics for pharmacological treatment (KQ1a)

Baseline population characteristics Author, year	Group, N	Age Mean Median SD	Diabetes duration (years)	Female N (%)	Race N (%)	HbA1c Mean Median SD	BMI Mean Median SD	Neuropathic symptoms and findings at baseline	N of withdrawals
Knatterud, 1978[1] UGDP	Total sample N=1027	52.7 (11.2)	NR	733 (71.4)	White (vs non-white): 53.9%	NR	NR	NR	NR
Reichard, 1993[2] SDIS	Group A: ICT, intensified conventional treatment, 48	Mean (SD): 30 (8)	18 (6)	22	NR	9.5 (1.3)	22.6 (2.1)	5 (12%)	6
Reichard, 1993[2] SDIS	Group B: ST standard treatment with insulin, 54	Mean (SD): 32 (7)	16 (4)	26	NR	9.4 (1.4)	22.8 (2.2)	8 (17%)	7
Abraira, 1997[4] VACSDM	Group A: intensive, 75	60.4 ± 6.4	8.0 + 3.6	0 (0%)	W: 47 (62.7) B: 26 (34.7) O: 2 (2.7)	9.3 ± 1.3	30.7 ± 4.4	NR	N = 4
Abraira, 1997[4] VACSDM	Group B: standard, 78	59.9 ± 6.7	7.7 ± 4.3	0 (0%)	W: 52 (66.7) B: 22 (28.2) O: 4(5.1)	9.5 ± 1.5	31.3 ± 5.5	NR	NR
Gaede, 2003[6] and Gaede, 2008[7] Steno-2	Group A: conventional treatment for multiple risk factor, 80	55.2 (7.2)	Median 6 years Range 4-10	24 females (24/80)	NR	8.8 (1.7)	Men: 30.3 (5.3) Women: 28.9 (3.8)	29/80	2
Gaede, 2003[6] and Gaede, 2008[7] Steno-2	Group B: intensive, 80	54.9 (7.2)	Median 5.5 Range 20-8.8	17 females (17/80)	NR	8.4 (1.6)	Men: 29.3 (3.6) Women: 31.1 (4.5)	26/80	1

Baseline population characteristics **Author, year**	**Group, N**	**Age** **Mean** **Median** **SD**	**Diabetes duration (years)**	**Female N (%)**	**Race N (%)**	**HbA1c** **Mean** **Median** **SD**	**BMI** **Mean** **Median** **SD**	**Neuropathic symptoms and findings at baseline**	**N of withdrawals**
Dormandy, 2005[8] PROactive	Group A: Pioglitazone, 2605	Median (IQR) 61·9 (7·6)	Median (IQR) 8 (4–13	Male: 1735 (67%)	White 2564 (98%)	Median (IQR) 7·8 (7·0–8·9)	30·7 (4·7) 31·0 (4·8)	NR	1 lost to follow-up; 427 discontinued med; 149 withdrew consent; 43 other
Dormandy, 2005[8] PROactive	Group B: placebo, 2633	Median (IQR) 61·6 (7·8)	Median (IQR) 8 (4–14)	Male: 1728 (66%)	White 2600 (99%)	Median (IQR) 7·9 (7·1–8·9)	31·0 (4·8)	NR	1 lost to follow-up; 438 discontinued medication; 167 withdrew consent; 69 other
Martin, 2006[9] DCCT/EDIC	Group A: (intensive), 711 at baseline Note: subgroup, 624 participated in the Neuropathy subgroup who had Neuropathy assessed at baseline, RefID 2079)	27 (7)	6 (4)	345 (49)	NR	9.1 (1.6)	23.3 (2.7)	15% (at completion of DCCT)	NR
Martin, 2006[9] DCCT/EDIC	Group B: (less), 730 at baseline Subgroup, 633	27 (7)	5 (4)	335 (46)	NR	9.1 (1.6)	23.4 (2.9)	20%	NR
Duckworth, 2009[11] VADT	Group A: intensive , 892	60.5 (9.0	11.5 (8.0)	N = 26 (3%)	NHW: 539 Hisp: 155 (17%) Bl: 152 (17%) Other: 46	9.4 (2.0)	31.3 (3.0)	NR	120 (13.5%)

Baseline population characteristics **Author, year**	**Group, N**	**Age** **Mean** **Median** **SD**	**Diabetes duration (years)**	**Female N (%)**	**Race N (%)**	**HbA1c** **Mean** **Median** **SD**	**BMI** **Mean** **Median** **SD**	**Neuropathic symptoms and findings at baseline**	**N of withdrawals**
Duckworth, 2009[11] VADT	Group B. standard treatment, 760	60.3 (9.0)	11.5 (7.0)	N = 26 (3%)	NHW: 572 Hisp: 136 (18%) Bl: 147 (19%) Other: 44	9.4 (2.0)	31.2 (4.0)	NR	139 (15.5%)
Griffin, 2011[12] ADDITION	Intensive, 1678	60.3 (6.9)	0	41.5	W: 1539 (95.8%)	Mean 7・0 (1・6)	31・6 (5・6)	NR	1678-1574 = 104
Griffin, 2011[12] ADDITION	Routine, 1379	60.2 (6.8)	0	42.7	W: 1246 (93.4%)	Mean 7・0 (1・5)	31・6 (5・6)	NR	1379-1285 = 94
Araki, 2012[13] J-EDIT	Group A: intensive, 585	71.9 1 4.6	16.7 1 8.5	53.7	Asian: 100%	8.4 ± 0.8*	24.0 ± 3.9	Paresthesia: 22.3%	Total - 8.9% (104 cases)
Araki, 2012[13] J-EDIT	Group B: Standard, 588	71.7 1 4.7	18.0 1 9.9	53.7	Asian: 100%	8.5 ± 0.9	24.3 ± 7.3	Paresthesia: 18.5%	NA
Kostev, 2012[14]	Group A: Glargine, 9638	61.3 ± 15.2	6.1 ± 8.7	Male: 5326 (55%)	West Germany: 6813 (71%)	8.0 ± 1.7	29.5 ± 5.7	943 (9.8%)	NA
Kostev, 2012[14]	Group B: (NPH), 13 757	60.2 ± 14.1	5.3 ± 7.9	Male: 7427 (54%)	West Germany: 10,467 (76%)	8.0 ± 1.7	30.7 ± 5.5	1486 (11%)	NA
Jaiswal, 2015[15]	Group A: Exenatide, 22	Mean (SD) 51 (13)	8 (5)	9 (41%)	White: 19 (86%)	8.2 ± 1.1	35 ± 3	DPN Symptoms: 21 (96%) DPN confirmed by clinical testing: 14 (67%)	3
Jaiswal, 2015[15]	Group B: Insulin Glargine, 24	Mean (SD) 54 (9)	7(4)	11 (46%)	White: 21 (87%)	8.4 ± 1.4	37 ± 6	DPN symptoms: 22 (92%) DPN confirmed by clinical testing: 18 (75%)	0
Reichard, 1993[2] and Rathsman, 2014[3] SDIS	Sub-analysis 5.5 years after trial end, following iontophoresis, 35 in ICT	Mean (range) 42 (28–63)	28 (19–45)	21	NR	7.4 (5.8–9.4)	NR	N = 2	NR

Baseline population characteristics Author, year	Group, N	Age Mean Median SD	Diabetes duration (years)	Female N (%)	Race N (%)	HbA1c Mean Median SD	BMI Mean Median SD	Neuropathic symptoms and findings at baseline	N of withdrawals
Reichard, 1993[2] and Rathsman, 2014[3] SDIS	ST, 37	Mean (range) 42 (31–63)	27 (19–39)	22	NR	8.4 (5.9–10.9)	NR	N = 8	NR
UKPDS[16]	Group A: intensive, 2729	53.2 (8.6)	Newly diagnosed	Female: 444/2729	White: 81% Indian: 10% Afro-Carib: 8% Other: 1%	Mean % (SD) 7.09 (1.54)	27.5 (5.1)	NR	N=122 122/2729= %
UKPDS[16]	Group B: conventional, 1138	Mean (SD) 53.4 (8.6)	Newly diagnosed	Female: 433/1138	White: 81% Indian: 11% Afro-Carib: 7% Other: 1%	Mean % (SD) 7.05 (1.42)	27.8 (5.5)	NR	N = 45 45/1138 = %

ADDITION = Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care; Bl = Black; DCCT/EDIC = Diabetes Control and Complications Trial / Epidemiology of Diabetes Interventions and Complications; DPN = diabetic peripheral neuropathy; Hisp = Hispanic; ICT =Intensified Conventional Treatment ; J-EDIT = Japanese Elderly Diabetes Trial; NA = Not Applicable; NHW = Non-Hispanic white; NR = Not Reported; PROactive = Prospective Pioglitazone Clinical Trial in Macrovascular Events; SDIS = Stockholm Diabetes Intervention Study; ST = Standard Treatment; Steno-2 = Randomized open parallel trial for patients with type 2 diabetes Mellitus at the Steno Diabetes Center in Denmark ; UGDP = University Group Diabetes Program; UKPDS = United Kingdom Prospective Diabetes Study; VACSDM = Veterans Affairs Cooperative Study on glycemic control and complications in type 2 Diabetes Mellitus; VADT = Veterans Affairs Diabetes Trial;

Evidence Table D-3. Outcomes for pharmacological treatment (KQ1a)

Author, year	Group, N	Outcome Units	Instrument or measure	Baseline N	Baseline outcome	Time point(s)	N at time point(s)	Outcome at time point(s)	Within arm comparison	Between arm comparison
Quality of Life										
Jaiswal, 2015[15]	Group A: Exenatide, 22	Quality of life	Neuropathy specific quality of life (NeuroQOL), Global score	22	2.4 ± 1.1	18 m	19	2.3 ± 1.5	Change from baseline: 0.16 ± 1.0	NR
Jaiswal, 2015[15]	Group B: Insulin Glargine, 24	Quality of life	Neuropathy specific quality of life (NeuroQOL), Global score	24	2.9 ± 1.0	18 m	24	2.5 ± 0.9	Change from baseline: 0.40 ± 0.9	NR
Diabetic foot Ulcer										
Reichard, 1993[2] SDIS	Group A: ICT, intensified conventional treatment, 48	Diabetic foot ulcer	NR	48	NA	Median 7.5	48	0 events after 7.5 years	NA	NR
Reichard, 1993[2] SDIS	Group B: ST standard treatment with insulin, 54	Diabetic foot ulcer	NR	54	NA	Median 7.5	54	3 events after 7.5 years	NA	NR
Abraira, 1997[4] VACSDM	Group A: intensive	Ischemic foot ulcer	NR	75	NA	7.8 ± 4 years	75	N = 0	NA	NR
Abraira, 1997[4] VACSDM	Group B: standard	Ischemic foot ulcer	NR	78	NA	7.8 ± 4 years	78	N = 1	NA	NR
Martin, 2006[9] DCCT/EDIC	Group A	Diabetic foot ulcers	NR	624	NA	8 years	624	Group A: 4	NA	P = 0.01
Martin, 2006[9] DCCT/EDIC	Group B	Diabetic foot ulcers	NR	633	NA	8 years	633	Group B: 11	NA	NR
Araki, 2012[13] J-EDIT	Group A: intensive	Ulcer or gangrene	NR	585	NA	NA	NA	N = 12 events total in 2 groups	NA	P = 0.564 for between Group diff
Araki, 2012[13] J-EDIT	Group B: standard	Ulcer or gangrene	NR	588	NA	NA	NA	NA	NA	NR

Author, year	Group, N	Outcome Units	Instrument or measure	Baseline N	Baseline outcome	Time point(s)	N at time point(s)	Outcome at time point(s)	Within arm comparison	Between arm comparison
Kostev, 2012[14]	Group A: Glargine, 9638	Diabetic foot ulcer	There is no specific ICD-10 code for DFU, hence diagnosis was identified on the basis of the original handwritten diagnosis of the treating physician.	9638	NR	2 years to 6 years (mean NR)	NR	NR	NR	HR: 0.61; 95%CI: 0.38–0.98; P = 0.041 for Glargine vs. NPH
Kostev, 2012[14]	Group B: NPH, 13 757	Diabetic foot ulcer	There is no specific ICD-10 code for DFU, hence diagnosis was identified on the basis of the original handwritten diagnosis of the treating physician.	757	NR	2 years to 6 years (mean NR)	NR	NR	NR	NR
Rathsman, 2014[3] SDIS – subrgp	Group A: ICT, 35	Diabetic foot ulcer hospitalization	ICD9 codes – discharge diagnosis	35	NA	28 years	35	3	NA	Logrank test p = 0.035 comparing Groups A and B
Rathsman, 2014[3] SDIS – subrgp	Group B: ST, 37	Diabetic foot ulcer hospitalization	ICD9 codes – discharge diagnosis	37	NA	28 years	37	10	NA	NR
Amputations										
Knatterud, 1978[1] UGDP	Group A: insulin variable	Amputation of all or part of either lower limb	NR	NR	NR	NR	190	3 (1.6%)	NR	NR
1978[1] UGDP	Group B: insulin standard	Amputation of all or part of either lower limb	NR	NR	NR	NR	198	1 (0.5%)	NR	NR

Author, year	Group, N	Outcome Units	Instrument or measure	Baseline N	Baseline outcome	Time point(s)	N at time point(s)	Outcome at time point(s)	Within arm comparison	Between arm comparison
1978[1] UGDP	Group C: placebo	Amputation of all or part of either lower limb	NR	NR	NR	NR	194	3 (1.5%)	NR	NR
Abraira, 1997[4] VACSDM	Group A: intensive	Amputation	NR	75	NA	7.8 ± 4 years	75	N = 1	NR	NR
Abraira, 1997[4] VACSDM	Group B: standard	Amputation	NR	78	NA		78	N = 0	NR	NR
UKPDS, 1998[5]	Group A: intensive, 2729	Amputation of at least 1 digit	NR	2729	NA	Group B: intensive N = 80	2729	N = 27	Absolute risk per 1000 patients: 1.0	Log rank p-value for comp of ARR: 0.059 RR for intensive vs. conventional 0.81 (0.28-1.33)
UKPDS, 1998[5]	Group B: conventional, 1138	Amputation of at least 1 digit	NR	1138	NA	10 years	1138	N = 18	Absolute risk per 1000 patients: 1.6	NR
Gaede, 2003[6] and Gaede, 2008[7] Steno-2	Group A: conventional treatment, 80	Amputations	NR	80	NA	6 years	80	N = 14	NR	NR
Gaede, 2003[6] and Gaede, 2008[7] Steno-2	Group B: intensive, 80	Amputations	NR	80	NA	6 years	80	N = 7	NR	NR
Dormandy, 2005[8] PROactive	Group A: Pioglitazone, 2605	Leg amputation above the ankle, first events	NR	2605	NA	34.5 months	2605	Group A: 26 first events Group A: 28 total events	NR	For first events - HR 1·01 (0·58–1·73)
Dormandy, 2005[8] PROactive	Group B: placebo, 2633	Leg amputation above the ankle, first events	NR	2633	NA	34.5 months	2633	Group B: 26 Group B: 28 total events	NR	NR

Author, year	Group, N	Outcome Units	Instrument or measure	Baseline N	Baseline outcome	Time point(s)	N at time point(s)	Outcome at time point(s)	Within arm comparison	Between arm comparison
Martin, 2006[9] DCCT/EDIC	Group A	Lower extremity amputation	NR	624	NA	8 years	624	Group A: 2	NA	P = 0.45
Martin, 2006[9] DCCT/EDIC	Group B	Lower extremity amputation	NR	633	NA		633	Group B: 5	NA	NR
Gaede, 2008[7] observational follow-up	Group A: conventional treatment for multiple risk factors, 80	Amputations	NR	80	Na	13.3 years	55	N = 14 patients (with 33 events)	NR	NR
Gaede, 2008[7] observational follow-up	Group B: Intensive, 80	Amputations	NR	80	NA	13.3 years	38	N = 6 patients (with 10 events)	NR	NR
Duckworth, 2009[11] VADT	Group A: intensive, 892	Amputation	NR	892	NA	6 years	892	11	Event free rate = 0.98	HR 0.65 (95% CI 0.31-1.39)
Duckworth, 2009[11] VADT	Group B: standard treatment, 760	Amputation	NR	760	NA	6 years	760	17	Event free rate = 0.98 p-value = 0.26	NR
Griffin, 2011[12] and Simmons RK, 2012[17] ADDITION	Intensive, 1678	Amputation	In Denmark, the national patient register was searched for deaths and for International Classification of Diseases (ICD)-10 codes for cardiovascular events and surgical procedures concerning amputations. In Cambridge and Leicester, participants were registered with the England and Wales Office of National Statistics, which provided copies of death certificates. Sensitive electronic searches of general practice records were conducted	NR	NR	Mean 5.3 years	1377	First event: N = 0, 2nd event: N = 0, 3 or more events: N = 1, Total events: N = 1	NR	NR

Author, year	Group, N	Outcome Units	Instrument or measure	Baseline N	Baseline outcome	Time point(s)	N at time point(s)	Outcome at time point(s)	Within arm comparison	Between arm comparison
Griffin, 2011[12] and Simmons RK, 2012[17] ADDITION	Routine, 1379	Amputation	NR	NR	NR	Mean 5.3 years	1678	First event: N = 0, 2nd event: N = 1, 3 or more events: N = 0, Total events: N = 1	NR	NR

ADDITION = Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care; DCCT/EDIC = Diabetes Control and Complications Trial / Epidemiology of Diabetes Interventions and Complications; HR = Hazard Ratio; ICD-10 = 10th revision of the International Statistical Classification of Diseases and Related Health Problems ; J-EDIT = Japanese Elderly Diabetes Trial; NA = Not Applicable; NR = Not Reported; PROactive = Prospective Pioglitazone Clinical Trial in Macrovascular Events; SDIS = Stockholm Diabetes Intervention Study; Steno-2 = Randomized open parallel trial for patients with type 2 diabetes Mellitus at the Steno Diabetes Center in Denmark ; UGDP = University Group Diabetes Program; UKPDS = United Kingdom Prospective Diabetes Study; VACSDM = Veterans Affairs Cooperative Study on glycemic control and complications in type 2 Diabetes Mellitus; VADT = Veterans Affairs Diabetes Trial;

Evidence Table D- 4. Harms for pharmacological treatment (KQ1a)

Author, year	Arm	Harm	N for analysis	Time point (s)	N of patients with outcomes	% of patients with outcomes
Abraira, 1997[4] VACSDM	Group A: intensive	Hypoglycemia	75	7.8 years	5	6%
Abraira, 1997[4] VACSDM	Group B: standard	Hypoglycemia	78	7.8 years	2	2.5%
UKPDS[5]	Arm 1: intensive glycemic control	Severe hypoglycemia	2729	10.7 years	NR	1.2% - Chlorpropamide arm; 1.0%- Glibenclamine arm; 2.0% insulin arm
UKPDS[5]	Arm 2: conventional treatment	Severe hypoglycemia	1138	10.7 years	NR	0.7% conventional 0.6% metformin arms
Gaede, 2003[6] Steno-2	Arm 1: intensive glycemic control	Severe hypoglycemia	80	7.8 years	12	15%
Gaede, 2003[6] Steno-2	Arm 2: conventional treatment	Severe hypoglycemia	80	7.8 years	5	6%
Dormandy, 2005[8] PROactive	Arm 1: Pioglitazone	Hypoglycemia	2605	34.5 months	728	28%
Dormandy, 2005[8] PROactive	Arm 2: placebo	Hypoglycemia	2633	34.5 months	528	20%
Duckworth, 2009[11] VADT	Arm 1: intensive glycemic control	Hypoglycemia	892	6 years	76	9%
Duckworth, 2009[11] VADT	Arm 2: standard	Hypoglycemia	760	6 years	28	5%
Jaiswal, 2015[15]	Arm 1: Exenatide	Severe hypoglycemia	22	18 months	0	1%
Jaiswal, 2015[15]	Arm 2: insulin Glargine	Severe hypoglycemia	24	18 months	1	4%
Jaiswal, 2015[15]	Arm 1: Exenatide	GI problems	22	18 months	6	27%
Jaiswal, 2015[15]	Arm 2: insulin Glargine,	GI problems	24	18 months	4	17%

GI = Gastrointestinal; PROactive = Prospective Pioglitazone Clinical Trial in Macrovascular Events; Steno-2 = Randomized open parallel trial for patients with type 2 diabetes Mellitus at the Steno Diabetes Center in Denmark ; UKPDS = United Kingdom Prospective Diabetes Study; VACSDM = Veterans Affairs Cooperative Study on glycemic control and complications in type 2 Diabetes Mellitus; VADT = Veterans Affairs Diabetes Trial;

Evidence Table D-5. Study and participant characteristics for balance intervention (KQ1b)

Author, year Country	Study design, duration of follow-up	Intervention groups, N	Total # participants	Mean age (SD)	Female, % Race, %	HbA1c mean % (SD)	BMI mean (SD)	Outcomes reported
Richardson, 2001[18] North America	RCT, 3 weeks	Control, N = 10	20	64.8 (9.4)	53.0 NR	NR	37.3 (8.0)	Physical activity, perceived fall risk, drop outs
Richardson, 2001[18] North America	RCT, 3 weeks	Balance training, N = 10		66.3 (10.6)	49.0 NR	NR	36.0 (8.2)	
Kruse, 2010[19] and LeMaster, 2008[20] North America	RCT,12 months	Control, N = 38	79	64.8 (9.4)	53 Non-white 8	NR	37.2 (8.0)	Falls, Perceived fall risk, incident/recurrent ulcer, physical activity
Kruse, 2010[19] and LeMaster, 2008[20] North America	RCT,12 months	Physical therapy, N = 41		66.6 (10.4)	47.0 Non-white 7	NR	35.9 (8.2)	
Song, 2011[21] Asia	RCT, 8 weeks	Control, N = 19	38	73.2	57.9 (5.4)	NR	NR	Physical activity
Song, 2011[21] Asia	RCT, 8 weeks	Balance training, N = 19		72.9	63.2 (5.6)	NR	NR	
Lee, 2013[22] Asia	RCT, 6 weeks	Control, N = 20	60	75.8 (5.7)	50.0 NR	6.9 (1.1)	NR	Physical activity
Lee, 2013[22] Asia	RCT, 6 weeks	Whole body vibration and balance training, N = 20		76.3 (4.8)	50.0 NR	7.1 (1.2)	NR	
Lee, 2013[22] Asia	RCT, 6 weeks	Balance training, N = 20		74.05 (5.4)	55.0 NR	7.0 (1.1)	NR	
Eftekhar-Sadat, 2015[23] Asia	RCT, unclear	Control, N = 22	44	59.1 (NR)	70.6 NR	NR	26.7 (NR)	Perceived fall risk, physical activity
Eftekhar-Sadat, 2015[23] Asia	RCT, unclear	Balance training, N = 22		58.8 (NR)	58.8 NR	NR	27.8 (NR)	

Author, year Country	Study design, duration of follow-up	Intervention groups, N	Total # participants	Mean age (SD)	Female, % Race, %	HbA1c mean % (SD)	BMI mean (SD)	Outcomes reported
Grewal, 2015, North America[24] Asia	RCT, 6 weeks	Control, N = 20	39	64.9 (8.5)	50.0 NR	65.4 (29.7)	29.6 (4.2)	Perceived fall risk, quality of life, physical activity and dropouts
Grewal, 2015, North America[24] Asia	RCT, 6 weeks	Balance training, N = 19		62.6 (7.9)	57.9 NR	65.2 (19.7)	31.8 (7.5)	
Kordi, 2015[25] Asia	RCT, 6 weeks	Control, N = 20	40	57.0 (1.5)	40.0 NR	NR	28.9 (1.0)	Physical activity
Kordi, 2015[25] Asia	RCT, 6 weeks	Whole body vibration, N = 20		57.0 (1.8)	40.0 NR	NR	28.5 (1.0)	

N = Number; NR = Not Reported; RCT = Randomized Control Trials; SD = Standard Deviation;

Evidence Table D-6. Balance intervention characteristics (KQ1b)

Author, year	Intervention	Description of intervention	Frequency, n per week	Time per session	Total duration of study, weeks	Total sessions, n
Richardson, 2001[18]	Control	Exercises performed in seated position- neck flexion, rotation, stretching then resistance band exercises	5 or more	NR	3 weeks	NR
Richardson, 2001[18]	Balance training	Exercises consisted of warm up, bipedal toe raise, heel raise inversion, eversion, unipedal toe raise, heel raise, inversion, eversion, wall slides and unipedal balance	7	NR	3 weeks	NR
Kruse, 2010[19] and LeMaster, 2008[20]	Control	Participants received diabetes self-care. Participants also received telephone calls to record recent activities	NA	NA	NA	NA
Kruse, 2010[19] and LeMaster, 2008[20]	Physical therapy	First three months, intervention comprised of 8 individual sessions with PT that focused on exercises to progressively strengthen legs and promote balance with 3 additional weekly 1 hr sessions at home. Next eight months, motivational techniques to enhance exercise via regular telephone calls were implemented	NR	NR	48	8 during first 3 months
Song, 2011[21]	Control	Health education sessions	1	50 min	8 weeks	NR
Song, 2011[21]	Balance training	Exercises consisted of 10 min warm up, 40 min balance exercise and 10 min cool down. Exercise consisted of 3 parts: standing on stable surface, foam and progressive balance exercises. Participants also received health education as control group	2	60 min	8 weeks	NR
Lee, 2013[22]	Control	NR	NA	NA	NA	NA
Lee, 2013[22]	Whole body vibration and balance training	It was conducted on an individual basis, Subjects stood upright on the platform, and were vibrated in a 110° squatting position, at frequency of 15-30 Hz and amplitude of 1-3 mm. They also underwent balance exercise described below.	WBV 3, Balance exercise 2	60 min	6 weeks	NR
Lee, 2013[22]	Balance training	Exercises were similar to Richardson 2001 and Song 2011. 10 min of warm-up activities, 40 min of balance training, and 10 min of cool-down activities. it consisted of 3 parts- static, dynamic and progressive balance exercises	2	60 min	6 weeks	NR
Eftekhar-Sadat, 2015[23]	Control	Physiotherapy with infrared and transcutaneous electrical nerve stimulation (TENS)	3	30 min	NR	NR
Eftekhar-Sadat, 2015[23]	Balance training	Biodex balance system simulates specific movement patterns or strategies by placing markers on specific locations on the screen grid; performed by a trainer. Participants also received physiotherapy similar to control group	NR	NR	NR	10
Grewal, 2015[24]	Control	standard of care	NA	NA	NA	NA
Grewal, 2015[24]	Balance training	Included a point-to-point ankle reaching task and a virtual obstacle-crossing task with appropriate audio-visual feedback. LegSys kinematic data were processed in real-time	2	45 min	4 weeks	NR
Kordi, 2015 [25]	Control	NR	NA	NA	NA	NA
Kordi, 2015 [25]	Whole body vibration	Received applied frequency of 30 Hz, peak-peak amplitude of 2 mm	2	Increased every 2 weeks from 30 s to 45 s to 1 min	6	12

NA = Not Applicable; NR = Not Reported;

Evidence Table D-7. Incident or recurrent foot ulcer outcomes for balance intervention (KQ1b)

Author, year	Arm	Outcome	Baseline N, mean, SD	Time point(s)	At time point(s), N Incidence rate (per person year at risk)	Within arm comparison	Between arm comparison
LeMaster, 2008[20]	Arm 1 - control	No. of lesions	N: 32, Mean: NR, SD: NR	12 months	N: 32, Rate: 0.51	NR	Rate Ratio: 1.24 (95% CI: 0.7-2.19) p = NR
LeMaster, 2008[20]	Arm 2 - intervention	No. of lesions	N: 37, Mean: NR, SD: NR	12 months	N: 37, Rate: 0.63	NR	Rate Ratio: 0.96 (95% CI: 0.38-2.42) p = NR

N = Number; NR = Not Reported; SD = Standard Deviation;

Evidence Table D-8. Falls outcomes for balance intervention (KQ1b)

Author, year	Arm	N for analysis	Outcome	Time point	Mean outcome at time point	n (%) of PATIENTS with outcomes	Between arm comparison
Kruse, 2010[19]	Arm 1 - control	38	Falls/1000 person-days of follow up	12 months	2.02	NR	NR
Kruse, 2010[19]	Arm 2 - intervention	41	Falls/1000 person-days of follow up	12 months	2.06	NR	Comparator arm: control, p: 0.95
Kruse, 2010[19]	Arm 1 - control	38	N participants with no falls in 12 month period	12 months	NR	22 (58)	NR
Kruse, 2010[19]	Arm 2 - intervention	41	N participants with no falls in 12 month period	12 months	NR	25 (61)	Difference in number of falls: comparator arm: control, p: 0.4

NR = Not Reported;

Evidence Table D-9. Perceived fall risk for balance intervention (KQ1b)

Author, year	Arm	Outcome	Baseline N, mean, SD	Time point(s)	At time point(s), N, Mean, SD	Within arm comparison	Between arm comparison
Richardson, 2000[18]	Arm 1 - control	ABC (activities-specific balance and confidence) scale	N: 7, Mean: 80, SD: 21	3 weeks	N: 7, Mean: 80, SD: 20	% change from baseline:, p: 0.64	NR
Richardson, 2000[18]	Arm 2 - intervention	ABC (activities-specific balance and confidence) scale	N: 9, Mean: 80, SD: 21	3 weeks	N: 9, Mean: 88, SD: 11	% change from baseline, p: 0.14	NR
Kruse, 2010[19]	Arm 1 - control	Falls Efficacy Scale (FES) score	N: 38, Mean: 8.3, SD: 12	12 months	N: 38, Mean: 10.9, SD: NR	NR	NR
Kruse, 2010[19]	Arm 2 - intervention	Falls Efficacy Scale (FES) score	N: 41, Mean: 10.4, SD: 13.9	12 months	N: 41, Mean: 13, SD:	NR	Mean difference from baseline, Comparator arm: control, p: 0.73
Sartor, 2014[26]	Arm 1 - control	ABC (activities-specific balance and confidence) scale	N: 29, Mean: 78, SD: 18	12 weeks	N: 29, Mean: 78, SD: 19	NR	NR
Sartor, 2014[26]	Arm 2 - intervention	ABC (activities-specific balance and confidence) scale	N: 26, Mean: 84, SD: 16	12 weeks	N: 26, Mean: 86, SD: 8	NR	Median difference from baseline, 0.5, Comparator arm: control, p: NS
Eftekhar, 2015[23]	Arm 1 - control	Fall risk index	N:17, Mean: 2.11, SD: NR	NR	N:17, Mean: 1.87, SD:	% change from baseline: -12.58, p: NR	
Eftekhar, 2015[23]	Arm 2 - intervention	Fall risk index	N:17, Mean: 2.77, SD: NR	NR	N: 17, Mean: 0.86, SD:	% change from baseline: -56.96, p: NR	% change from baseline, Comparator arm: control, p: <0.001
Grewal, 2015[24]	Arm 1 - control	FES-I score	N:16, Mean: 35.4, SD: 11.47	4 weeks	N:16, Mean: 32.03, SD: 12.22	Mean difference from baseline: 6.99, p: NR	
Grewal, 2015[24]	Arm 2 - intervention	FES-I score	N:19, Mean: 32.32, SD: 12.34	4 weeks	N:19, Mean: 27.5, SD: 9.17	Mean difference from baseline: 14.91, p: NR	Mean difference from baseline, Comparator arm: control, p: 0.305

N = Number; NR = Not Reported; SD = Standard Deviation;

Evidence Table D-10. Quality of life for balance intervention (KQ1b)

Author, year	Arm	Instrument	Baseline N, mean, SD	Time point(s)	At time point(s), N, mean, SD	Within arm comparison	Between arm comparison
Grewal, 2015[24]	Arm 1 - control	SF-12 physical component	N: 16, Mean: 37.5, SD: 9.81	4 weeks	N: 16, Mean: 40.12, SD: 8.4	% difference from baseline: 6.99, p: NR	NR
Grewal, 2015[24]	Arm 2 - intervention	SF-12 physical component	N: 19, Mean: 37.62, SD: 10.36	4 weeks	N: 19, Mean: 40.36, SD: 10.37	% difference from baseline: 7.28, p: NR	Mean difference from baseline, Comparator arm: control, p: 0.643

N = Number; NR = Not Reported; SD = Standard Deviation;

Evidence Table D-11. Physical activity level for balance intervention (KQ1b)

Author, year	Arm	Outcome	Baseline N, mean, SD	Time point(s)	At time point(s), N, mean, SD	Within arm comparison	Between arm comparison
Richardson, 2001[18]	Arm 1 - control	Functional reach	N: 7, Mean: 11.3, SD: 3.6	3 weeks	N: 7, Mean: 11.9, SD: 2.8	NR	NR
Richardson, 2001[18]	Arm 2 - intervention	Functional reach	N: 9, Mean: 10.5, SD: 2.1	3 weeks	N: 9, Mean: 11.5, SD: 2.2	NR	NR
LeMaster, 2008[20]	Arm 1 - control	Total daily steps	N: 32, Mean: 3350, SD: 247 (sem)	12 months	N: 35, Mean: 2921, SD: 243 (sem)	Mean difference from baseline: , SD: , p: <0.05	Mean difference from baseline: 0.16, SD: NR , p: NR
LeMaster, 2008[20]	Arm 2 - intervention	Total daily steps	N: 37, Mean: 3335, SD: 246 (sem)	12 months	N: 35, Mean: 3183, SD: 240 (sem)	Mean difference from baseline: , SD: , p: NS	
LeMaster, 2008[20]	Arm 1 - control	6 min walk	N: 32, Mean: 1103, SD: 57 (sem)	12 months	N: 35, Mean: 1012, SD: 82 (sem)	Mean difference from baseline: , SD: , p: NS	Mean difference from baseline: -0.04, SD: NR, p: NR
LeMaster, 2008[20]	Arm 2 - intervention	6 min walk	N: 37, Mean: 1096, SD: 57 (sem)	12 months	N: 35, Mean: 996, SD: 82 (sem)	Mean difference from baseline: , SD: , p: NS	NR
Kruse, 2010[19]	Arm 1 - control	Berg Balance Scale	N: 38, Mean: 49.1, SD: NR	12 months	N: 38, Mean: 47.9, SD: NR	NR	NR
Kruse, 2010[19]	Arm 2 - intervention	Berg Balance Scale	N: 41, Mean: 48.1, SD: NR	12 months	N: 41, Mean: 47.1, SD: NR	NR	NR
Kruse, 2010[19]	Arm 1 - control	TUG	N: 38, Mean: 12.3, SD: NR	12 months	N: 38, Mean: 13.2, SD: NR	NR	NR
Kruse, 2010[19]	Arm 2 - intervention	TUG	N: 41, Mean: 12.8, SD: NR	12 months	N: 41, Mean: 13.8, SD: NR	NR	NR
Song, 2011[21]	Arm 1 - control	AP sway, EO (Eyes open)	N: 19, Mean: 43.5, SD: 14.7	8 weeks	N: 19, Mean: 45.4, SD: 13.7	NR	NR

Author, year	Arm	Outcome	Baseline N, mean, SD	Time point(s)	At time point(s), N, mean, SD	Within arm comparison	Between arm comparison
Song, 2011[21]	Arm 2 - exercise	AP sway, EO (Eyes open)	N: 19, Mean: 45.9, SD: 12.3	8 weeks	N: 19, Mean: 33.3, SD: 7.9	NR	NR
Song, 2011[21]	Arm 1 - control	AP sway, EC (Eyes closed)	N: 19, Mean: 59.5, SD: 20.2	8 weeks	N: 19, Mean: 59, SD: 13.5	NR	NR
Song, 2011[21]	Arm 2 - exercise	AP sway, EC (Eyes closed)	N: 19, Mean: 62, SD: 19.9	8 weeks	N: 19, Mean: 49.3, SD: 13.6	NR	NR
Song, 2011[21]	Arm 1 - control	ML sway, EO	N: 19, Mean: 42.4, SD: 14.3	8 weeks	N: 19, Mean: 42.3, SD: 13.5	NR	NR
Song, 2011[21]	Arm 2 - exercise	ML sway, EO	N: 19, Mean: 50.4, SD: 29.3	8 weeks	N: 19, Mean: 33.2, SD: 6.9	NR	NR
Song, 2011[21]	Arm 1 - control	ML sway, EC	N: 19, Mean: 59.6, SD: 26.1	8 weeks	N: 19, Mean: 61.1, SD: 22.8	NR	NR
Song, 2011[21]	Arm 2 - exercise	ML sway, EC	N: 19, Mean: 58.8, SD: 27.1	8 weeks	N: 19, Mean: 49.9, SD: 16.8	NR	NR
Song, 2011[21]	Arm 1 - control	Total body sway, EO	N: 19, Mean: 68.7, SD: 21.2	8 weeks	N: 19, Mean: 66.8, SD: 19.5	NR	NR
Song, 2011[21]	Arm 2 - exercise	Total body sway, EO	N: 19, Mean: 76.1, SD: 32.4	8 weeks	N: 19, Mean: 52.3, SD: 11.5	NR	NR
Song, 2011[21]	Arm 1 - control	Total body sway, EC	N: 19, Mean: 94, SD: 32.7	8 weeks	N: 19, Mean: 94.2, SD: 19.3	NR	NR
Song, 2011[21]	Arm 2 - exercise	Total body sway, EC	N: 19, Mean: 94.9, SD: 36.8	8 weeks	N: 19, Mean: 79.3, SD: 25.6	NR	NR
Song, 2011[21]	Arm 1 - control	Berg Balance Scale	N: 19, Mean: 53.2, SD: 1.9	8 weeks	N: 19, Mean: 53.3, SD: 2.3	NR	NR

Author, year	Arm	Outcome	Baseline N, mean, SD	Time point(s)	At time point(s), N, mean, SD	Within arm comparison	Between arm comparison
Song, 2011[21]	Arm 2 - exercise	Berg Balance Scale	N: 19, Mean: 53, SD: 2.3	8 weeks	N: 19, Mean: 55.1, SD: 1.1	NR	NR
Song, 2011[21]	Arm 1 - control	FRT	N: 19, Mean: 27.3, SD: 3.2	8 weeks	N: 19, Mean: 27.4, SD: 4.4	NR	NR
Song, 2011[21]	Arm 2 - exercise	FRT	N: 19, Mean: 27.1, SD: 7.4	8 weeks	N: 19, Mean: 30.9, SD: 6.1	NR	NR
Song, 2011[21]	Arm 1 - control	TUG	N: 19, Mean: 11.9, SD: 2.2	8 weeks	N: 19, Mean: 11.8, SD: 2.2	NR	NR
Song, 2011[21]	Arm 2 - exercise	TUG	N: 19, Mean: 11.8, SD: 2.3	8 weeks	N: 19, Mean: 10.1, SD: 2.1	NR	NR
Song, 2011[21]	Arm 1 - control	10-min walk	N: 19, Mean: 9.7, SD: 1.5	8 weeks	N: 19, Mean: 9.5, SD: 1.3	NR	NR
Song, 2011[21]	Arm 2 - exercise	10-min walk	N: 19, Mean: 9.6, SD: 1.4	8 weeks	N: 19, Mean: 8.7, SD: 1.2	NR	NR
Lee, 2013[22]	Arm 2 – WBV + BE	AP sway velocity, eyes closed	N: 19, Mean: 14.09, SD: 5.27	6 weeks	N: 19, Mean: 8.35, SD: 4.48	Mean difference from baseline: -5.74, SD: 2.53, p: 0.026	NR
Lee, 2013[22]	Arm 3 - BE	AP sway velocity, eyes closed	N: 18, Mean: 14.34, SD: 4.86	6 weeks	N: 18, Mean: 11.54, SD: 6.59	Mean difference from baseline: -2.8, SD: 4.86, p: 0.002	NR
Lee, 2013[22]	Arm 1 - control	ML sway velocity, eyes closed	N: 18, Mean: 9.31, SD: 3.42	6 weeks	N: 18, Mean: 8.96, SD: 2.96	Mean difference from baseline: -0.34, SD: 3.34, p: 0.46	p: 0.000
Lee, 2013[22]	Arm 2 – WBV + BE	ML sway velocity, eyes closed	N: 19, Mean: 9.83, SD: 3.39	6 weeks	N: 19, Mean: 6.11, SD: 2.66	Mean difference from baseline: -3.72, SD: 3.02, p: 0.026	NR
Lee, 2013[22]	Arm 3 - BE	ML sway velocity, eyes closed	N: 18, Mean: 9.49, SD: 4.12	6 weeks	N: 18, Mean: 7.86, SD: 3.67	Mean difference from baseline: -1.62, SD: 2.92, p: 0.001	NR

Author, year	Arm	Outcome	Baseline N, mean, SD	Time point(s)	At time point(s), N, mean, SD	Within arm comparison	Between arm comparison
Lee, 2013[22]	Arm 1 - control	Berg Balance Scale	N: 18, Mean: 50.28, SD: 2.47	6 weeks	N: 18, Mean: 50.17, SD: 2.5	Mean difference from baseline: -0.11, SD: 0.47, p: 0.331	p: 0.000
Lee, 2013[22]	Arm 2 – WBV + BE	Berg Balance Scale	N: 19, Mean: 49.47, SD: 2.57	6 weeks	N: 19, Mean: 51.37, SD: 1.8	Mean difference from baseline: 1.89, SD: 1.52, p: 0.001	NR
Lee, 2013[22]	Arm 3 - BE	Berg Balance Scale	N: 18, Mean: 48.67, SD: 2.7	6 weeks	N: 18, Mean: 49.28, SD: 3.23	Mean difference from baseline: 0.61, SD: 1.2, p: 0.045	NR
Lee, 2013[22]	Arm 1 - control	Functional reach test (FRT)	N: 18, Mean: 27.66, SD: 4.23	6 weeks	N: 18, Mean: 26.98, SD: 2.6	Mean difference from baseline: -6.84, SD: 2.29, p: 0.336	p: 0.000
Lee, 2013[22]	Arm 2 – WBV + BE	Functional reach test (FRT)	N: 19, Mean: 27.89, SD: 7.52	6 weeks	N: 19, Mean: 32.35, SD: 6.54	Mean difference from baseline: 4.45, SD: 3.52, p: 0.001	NR
Lee, 2013[22]	Arm 3 - BE	Functional reach test (FRT)	N: 18, Mean: 27.77, SD: 4.02	6 weeks	N: 18, Mean: 29.91, SD: 4.07	Mean difference from baseline: 2.13, SD: 3.11, p: 0.01	NR
Lee, 2013[22]	Arm 1 - Control	TUG (Timed up and go)	N: 18, Mean: 13.43, SD: 1.85	6 weeks	N: 18, Mean: 13.45, SD: 1.51	Mean difference from baseline: 0.02, SD: 0.7, p: 0.921	p: 0.000
Lee, 2013[22]	Arm 2 – WBV + BE	TUG (Timed up and go)	N: 19, Mean: 13.31, SD: 2.25	6 weeks	N: 19, Mean: 11.53, SD: 1.7	Mean difference from baseline: -1.79, SD: 1.09, p: 0.001	NR
Lee, 2013[22]	Arm 3 - BE	TUG (Timed up and go)	N: 18, Mean: 13.66, SD: 2.07	6 weeks	N: 18, Mean: 12.84, SD: 1.84	Mean difference from baseline: -0.82, SD: 1.5, p: 0.034	NR
Lee, 2013[22]	Arm 1 - control	FTSTS- Five time sit to stand test	N: 18, Mean: 16.42, SD: 5.01	6 weeks	N: 18, Mean: 16.91, SD: 4.92	Mean difference from baseline: 0.5, SD: 2.75, p: 0.455	p: 0.000
Lee, 2013[22]	Arm 2 – WBV + BE	FTSTS- Five time sit to stand test	N: 19, Mean: 17.03, SD: 5.44	6 weeks	N: 19, Mean: 13.35, SD: 4.39	Mean difference from baseline: -3.68, SD: 2.4, p: 0.001	NR

Author, year	Arm	Outcome	Baseline N, mean, SD	Time point(s)	At time point(s), N, mean, SD	Within arm comparison	Between arm comparison
Lee, 2013[22]	Arm 3 - BE	FTSTS- Five time sit to stand test	N: 18, Mean: 18.03, SD: 4.61	6 weeks	N: 18, Mean: 15.92, SD: 4.66	Mean difference from baseline: -1.52, SD: 2.81, p: 0.035	NR
Kordi Yoosefinejad, 2015[25]	Arm 1 - control	TUG (sec)	N: 10, Mean: 9.15, SD: 0.4	6 weeks	N: 10, Mean: 9.8, SD: 0.3	NR	p: 0.002
Kordi Yoosefinejad, 2015[25]	Arm 2 - WBV	TUG (sec)	N: 10, Mean: 9.3, SD: 0.8	6 weeks	N: 10, Mean: 8.5, SD: 0.7	NR	NR
Eftekhar, 2015[23]	Arm 1 - control	TUG	N: 17, Mean: 10.8, SD: NR	Unclear	N: 17, Mean: 10.8, SD: NR	% difference from baseline: 0, SD: NR, p: NR	p: <0.001
Eftekhar, 2015[23]	Arm 2 - intervention	TUG	N: 17, Mean: 11.18, SD: NR	Unclear	N: 17, Mean: 10.97, SD: NR	% difference from baseline: -2.12, SD: NR, p: NR	NR
Eftekhar, 2015[23]	Arm 1 - control	Berg Balance Scale	N: 17, Mean: 53, SD: NR	Unclear	N: 17, Mean: 53.05, SD: NR	% difference from baseline: 0.13, SD: NR, p: NR	p: 0.33
Eftekhar, 2015[23]	Arm 2 - intervention	Berg Balance Scale	N: 17, Mean: 52.58, SD: NR	Unclear	N: 17, Mean: 53, SD: NR	% difference from baseline: 0.78, SD: NR, p: NR	NR
Eftekhar, 2015[23]	Arm 1 - control	API (Anterior-posterior index) sway	N: 17, Mean: 0.59, SD: NR	Unclear	N: 17, Mean: 0.54, SD: NR	% difference from baseline: -17.28, SD: NR, p: NR	p: 0.49
Eftekhar, 2015[23]	Arm 2 - intervention	API (Anterior-posterior index) sway	N: 17, Mean: 0.51, SD: NR	Unclear	N: 17, Mean: 0.24, SD: NR	% difference from baseline: -25.89, SD: NR, p: NR	NR
Eftekhar, 2015[23]	Arm 1 - control	MLI (Medial lateral index) sway	N: 17, Mean: 0.33, SD: NR	Unclear	N: 17, Mean: 0.44, SD: NR	% difference from baseline: 20.34, SD: NR, p: NR	p: 0.16
Eftekhar, 2015[23]	Arm 2 - intervention	MLI (Medial lateral index) sway	N: 17, Mean: 0.28, SD: NR	Unclear	N: 17, Mean: 0.14, SD: NR	% difference from baseline: -26.04, SD: NR, p: NR	NR
Eftekhar, 2015[23]	Arm 1 - control	OSI (Overall stability index) sway	N: 17, Mean: 0.75, SD: NR	Unclear	N: 17, Mean: 0.82, SD: NR	% difference from baseline: -2.12, SD: NR, p: NR	p: 0.2
Eftekhar, 2015[23]	Arm 2 - intervention	OSI (Overall stability index) sway	N: 17, Mean: 0.65, SD: NR	Unclear	N: 17, Mean: 0.32, SD: NR	% difference from baseline: -26.93, SD: NR, p: NR	NR

Author, year	Arm	Outcome	Baseline N, mean, SD	Time point(s)	At time point(s), N, mean, SD	Within arm comparison	Between arm comparison
Grewal, 2015[24]	Arm 1 - control	Center of mass (CoM) sway with eyes open	N: 16, Mean: 2.18, SD: 1.49	4 weeks	N: 16, Mean: 2.01, SD: 1.44	% difference from baseline: 7.8, SD: NR, p: NR	p: 0.009
Grewal, 2015[24]	Arm 2 - intervention	Center of mass (CoM) sway with eyes open	N: 19, Mean: 3.67, SD: 2.99	4 weeks	N: 19, Mean: 1.53, SD: 1.44	% difference from baseline: 58.31, SD: NR, p: NR	NR
Grewal, 2015[24]	Arm 1 - control	CoM sway with eyes closed	N: 16, Mean: 4.91, SD: 3.97	4 weeks	N: 16, Mean: 4.26, SD: 4.12	% difference from baseline: 13.24, SD: NR, p: NR	p: 0.056
Grewal, 2015[24]	Arm 2 - intervention	CoM sway with eyes closed	N: 19, Mean: 8.12, SD: 11.23	4 weeks	N: 19, Mean: 3.03, SD: 3.09	% difference from baseline: 62.68, SD: NR, p: NR	NR
Grewal, 2015[24]	Arm 1 - control	CoM AP sway with eyes open	N: 16, Mean: 1.3, SD: 0.58	4 weeks	N: 16, Mean: 1.23, SD: 0.42	% difference from baseline: 5.38, SD: NR, p: NR	p: 0.382
Grewal, 2015[24]	Arm 2 - intervention	CoM AP sway with eyes open	N: 19, Mean: 1.61, SD: 0.98	4 weeks	N: 19, Mean: 1.19, SD: 0.78	% difference from baseline: 26.09, SD: NR, p: NR	NR
Grewal, 2015[24]	Arm 1 - control	CoM AP sway with eyes closed	N: 16, Mean: 1.91, SD: 0.93	4 weeks	N: 16, Mean: 1.89, SD: 1.06	% difference from baseline: 1.05, SD: NR, p: NR	p: 0.031
Grewal, 2015[24]	Arm 2 - intervention	CoM AP sway with eyes closed	N: 19, Mean: 2.45, SD: 1.83	4 weeks	N: 19, Mean: 1.66, SD: 1.03	% difference from baseline: 32.24, SD: NR, p: NR	NR
Grewal, 2015[24]	Arm 1 - control	CoM ML sway with eyes open	N: 16, Mean: 1.54, SD: 0.49	4 weeks	N: 16, Mean: 1.51, SD: 0.6	% difference from baseline: 1.95, SD: NR, p: NR	p: 0.008
Grewal, 2015[24]	Arm 2 - intervention	CoM ML sway with eyes open	N: 19, Mean: 1.91, SD: 0.88	4 weeks	N: 19, Mean: 1.15, SD: 0.52	% difference from baseline: 39.79, SD: NR, p: NR	NR
Grewal, 2015[24]	Arm 1 - control	CoM ML sway with eyes open	N: 16, Mean: 2.33, SD: 1.21	4 weeks	N: 16, Mean: 1.92, SD: 0.84	% difference from baseline: 17.6, SD: NR, p: NR	p: 0.103

Author, year	Arm	Outcome	Baseline N, mean, SD	Time point(s)	At time point(s), N, mean, SD	Within arm comparison	Between arm comparison
Grewal, 2015[24]	Arm 2 - intervention	CoM ML sway with eyes open	N: 19, Mean: 2.54, SD: 1.31	4 weeks	N: 19, Mean: 1.54, SD: 0.92	% difference from baseline: 39.37, SD: NR, p: NR	NR
Grewal, 2015[24]	Arm 1 - control	Daily physical activity during 48 h, % time spent sitting	N: 16, Mean: 45.91, SD: 20.22	4weeks	N: 16, Mean: 48.93, SD: 17.88	% difference from baseline: -0.04, SD: NR, p: NR	p: 0.621
Grewal, 2015[24]	Arm 2 - intervention	Daily physical activity during 48 h, % time spent sitting	N: 19, Mean: 49.87, SD: 15.35	4 weeks	N: 19, Mean: 49.85, SD: 16.31	% difference from baseline: 6.58, SD: NR, p: NR	NR
Grewal, 2015[24]	Arm 1 - control	Daily physical activity during 48 h, % time spent standing	N: 16, Mean: 14.73, SD: 6.57	4weeks	N: 16, Mean: 14.66, SD: 7.05	% difference from baseline: -0.48, SD: NR, p: NR	p: 0.359
Grewal, 2015[24]	Arm 2 - intervention	Daily physical activity during 48 h, % time spent standing	N: 19, Mean: 13.74, SD: 4.98	4weeks	N: 19, Mean: 15.96, SD: 5.1	% difference from baseline: 16.16, SD: NR, p: NR	NR
Grewal, 2015[24]	Arm 1 - control	Daily physical activity during 48 h, % time spent walking	N: 16, Mean: 7.53, SD: 5.62	4weeks	N: 16, Mean: 7.25, SD: 5.4	% difference from baseline: -3.72, SD: NR, p: NR	p: 0.076
Grewal, 2015[24]	Arm 2 - intervention	Daily physical activity during 48 h, % time spent walking	N: 19, Mean: 6.75, SD: 3.4	4weeks	N: 19, Mean: 8.59, SD: 3.98	% difference from baseline: 27.26, SD: NR, p: NR	NR
Grewal, 2015[24]	Arm 1 - control	Total steps taken	N: 16, Mean: 9785, SD: 8081	4weeks	N: 16, Mean: 9264, SD: 7670	% difference from baseline: -5.32, SD: NR, p: NR	p: 0.064
Grewal, 2015[24]	Arm 2 - intervention	Total steps taken	N: 19, Mean: 8656, SD: 4589	4weeks	N: 19, Mean: 11052, SD: 5365	% difference from baseline: 27.68, SD: NR, p: NR	NR

AP = Anterioposterior; BE = Balance Exercise; CoM = Center of Mass; FRT = Functional Reach Test; ML = Mediolateral; N = Number; NR = Not Reported; NS = Not Significant; SD = Standard Deviation; TUG = Timed-Up and Go test; WBV = Whole Body Vibration

Evidence Table D-12. Drop outs for balance intervention (KQ1b)

Author, year	Select arm	Dropouts due to adverse effects, N	Dropouts due to adverse effects, %
Richardson, 2001[18]	Arm 1 - control	0	0
Richardson, 2001[18]	Arm 2 - intervention	1	NR
Grewal, 2015[24]	Arm 1 - control	0	0
Grewal, 2015[24]	Arm 2 - intervention	0	0

NR = Not Reported

Evidence Table D-13. Study characteristics for exercise intervention (KQ1b)

Author, year	Study design Study site	Funding source	Recruitment Start YEAR - End YEAR	Was run-in period reported?	Comments
LeMaster 2003[27]	Prospective cohort Single center: North America	Government	NR	No	
Dixit, 2013[28]	Parallel randomized controlled trial Single center: Asia	NR	2009-2012	No	
Taveggia, 2013[29]	Parallel randomized controlled trial Single center: Europe	No funding	2009-2009	No	
Sartor, 2014[26]	Parallel randomized controlled trial Single center: South America	NR	2010-2012	No	Initially started out as randomized cross over but due to adherence issues, was only assessed as a parallel RCT

NR = Not Reported

Evidence Table D-14. Exercise interventions characteristics (KQ1b)

Author, year	Arm	Time per session Total number of sessions	Comments
LeMaster 2003[27]	Arm 1 - CONTROL-least active	Fewer than 4.5 active hours per day	
LeMaster 2003[27]	Arm 2 - moderately active	4.6- 7.4 active hours per day	
LeMaster 2003[27]	Arm 3-most active	More than 7.5 active hours per day	
Dixit, 2013[28]	Arm 1 - CONTROL-control	Standard medical care, education for foot care and diet	
Dixit, 2013[28]	Arm 2 - intervention	5-6/week 150-360 minutes/ week	Moderate intensity supervised exercise training (target heart rate 40-60% of heart rate reserve) using treadmill
Taveggia, 2013[29]	Arm 1-CONTROL-standard care	5 per week 60 minutes/ session	Activities targeted to improve the endurance, manual exercises of lower limb muscle strengthening, and stretching exercises, in substitution of the robotic treadmill and dynamometer (ie, sitting to standing, walking up and down a slope, and stair climbing). Feedback focused, isokinetic dynamometric muscle strengthening, and balance retraining on dynamic balance platform or a standard care intervention for activities targeted to improve endurance, manual exercises of muscle strengthening, stretching exercises, gait, and balance exercises.
Taveggia, 2013[29]	Arm 2 - experimental	Multimodal, 20 mins of analyzing treadmill with feedback focused on symmetry and length of stride, 20 mins of isokinetic dynamometric muscle strengthening of flexor and extensor muscles of tibio tarsal and 20 mins of balance retraining on dynamic balance platform	

Evidence Table D-15. Exercise intervention- participant characteristics (KQ1b)

Author, year	Arm, N at enrollment	Actual length of follow-up-MEAN Unit for follow-up	Women, n (%)	Age, years:	HbA1c	BMI	Duration of pain	Duration of neuropathic symptoms	Number of withdrawals and/or losses to follow-up: N
LeMaster 2003[27]	Arm 1 – CONTROL - least active	2 years	(13)	mean: 64, SD: 10	NR	NR	NR	NR	NR
LeMaster 2003[27]	Arm 2 - moderately active	2 years	(24)	mean: 63, SD: 10	NR	NR	NR	NR	NR
LeMaster 2003[27]	Arm 3 - most active	2 years	(31)	mean: 60, SD: 9	NR	NR	NR	NR	NR
Dixit, 2013[28]	Arm 1 – CONTROL - control	8 weeks	17(35.4)	mean: 59.45, SD: 1.16	NR	mean: 25.95, SD: 5.68	NR	NR	10
Dixit, 2013[28]	Arm 2 - intervention	8 weeks	17(43.6)	mean: 54.4, SD: 1.24	NR	mean: 26.38, SD: 3.77	NR	NR	11
Taveggia, 2013[29]	Arm 1-CONTROL-standard care	4 weeks	9(64.3)	mean: 71, SD: 7	mean: 8.5, SD: 1.5	mean: 35.3, SD: 6.7	NR	NR	NR
Taveggia, 2013[29]	Arm 2-experimental	4 weeks	8(61.5)	mean: 73, SD: 10	mean: 8.8, SD: 1.9	mean: 29.6, SD: 5.9	NR	NR	NR

NR = Not Reported; SD = Standard Deviation

Evidence Table D-16. Exercise intervention - physical activity level (KQ1b)

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean SD:	Within arm comparison	Between arm comparison
Taveggia, 2013[29]	Arm 1 - standard care	6 minute walk	N:13, Mean: 313.8, SD:102.9	4 weeks	N:13, Mean: 5.4, SD:1.7	Mean difference from baseline: 59.8, p: 0.049	Mean difference from baseline: -44.1, p: NR
Taveggia, 2013[29]	Arm 2 - experimental	6 minute walk	N:14, Mean: 330.1, SD:151.1	4 weeks	N:14, Mean: 6.2, SD:1.9	Median difference from baseline: 35.2, p: 0.009	NR

N = Number; NR = Not Reported; SD = Standard Deviation

Evidence Table D-17. Exercise intervention - incidence or reoccurrence of ulcers outcome (KQ1b)

Author, year	Arm	Outcome	Time point	N for analysis	Incidence rate, per person year at risk	Between arm comparison
LeMaster, 2003[27]	Arm 1 - least active	Re-ulceration in feet	2 years	133	16.5 (95% CI: 10.4-25%)	p: NS
LeMaster, 2003[27]	Arm 2 - moderately active	Re-ulceration in feet	2 years	134	13.4 (95% CI: 7.9-21.2)	p: NS
LeMaster, 2003[27]	Arm 3 - most active	Re-ulceration in feet	2 years	123	13 (95% CI: 7.4-21.1)	p: NS

N = Number; NS = Not Significant

Evidence Table D-18. Exercise intervention - quality of life outcome (KQ1b)

Author, year	Arm	Instrument	Baseline N, mean SD	Time point(s)	At time point(s), N mean SD	Within arm comparison
Dixit, 2013[28]	Arm 1 - control	Neuro - Quality of life score	N:47, Mean: 33.55, SD:1.37	8 weeks	N:37, Mean: 34.16, SD:1.37	% difference from baseline: -4.12, p: <0.001
Dixit, 2013[28]	Arm 2 - intervention	Neuro - Quality of life score	N:40, Mean: 32.85, SD:1.32	8 weeks	N:29, Mean: 24.41, SD:1.12	% difference from baseline: 24.28, p: NR

N = Number; NR = Not Reported;SD = Standard Deviation;

Evidence Table D-19. Exercise intervention - harms (KQ1b)

Author, year	Select arm	Adverse events	N for analysis	Patients with adverse events, N (%)
Dixit, 2013[28]	Arm 1 - control	Hypoglycemia (severe and total)	47	11 (23.4)
Dixit, 2013[28]	Arm 2 - intervention	Hypoglycemia (severe and total)	40	2 (5.0)

N = Number

Evidence Table D-20. Study characteristics for physical therapy interventions (KQ1b)

Author, year	Study design Study site	Funding source	Recruitment Start YEAR - End YEAR	Was run-in period reported?
Mueller, 2013[30]	Parallel randomized controlled trial Single center: North America	Government	2009-2011	No
Chatchawan, 2015[31]	Parallel randomized controlled trial Single center: Asia	University	NR	No

NR = Not Reported

Evidence Table D-21. Physical therapy interventions characteristics (KQ1b)

Author, year	Arm	Time per session Total number of sessions	Session with physical therapist	Comments
Mueller, 2013[30]	Arm 1 - CONTROL-non weight bearing	12 weeks 14 min/36 sessions	Yes	All exercises were conducted in sitting or lying position. elastic resistance bands with increasing stiffness for load resistance used, stationary upright or recumbent cycle ergometer for aerobic exercise
Mueller, 2013[30]	Arm 2 - weight bearing	12 weeks 15 min/36 sessions	Yes	Participants were instructed to increase center-based step count every 2 weeks by 24%. they conducted most of exercises in standing position, used body weight for resistance exercises and treadmill or walking around circular hallways for aerobic exercise
Chatchawan, 2015[31]	Arm 1 – CONTROL - control	2 weeks 30 min/6 sessions	No	Health education on foot self-care and active foot exercises at home
Chatchawan, 2015[31]	Arm 2 - Thai foot massage	2 weeks 30 min/6 sessions	No	Modified foot massage performed by traditional Thai massage therapist

Evidence Table D-22. Physical therapy intervention - participant characteristics (KQ1b)

Author, year	Arm, N at enrollment	Actual length of follow-up-MEAN unit for follow-up	Women, n (%)	Age, years:	HbA1c	BMI	Duration of pain	Duration of neuropathic symptoms	Number of withdrawals and/or losses to follow-up: N
Mueller, 2013[30]	Arm 1 – CONTROL - non weight bearing	12 weeks	7(50)	mean: 63.9, SD: 12.5	NR	mean: 33.1, SD: 7.3	NR	NR	NR
Mueller, 2013[30]	Arm 2 - weight bearing	12 weeks	5(33.3)	mean: 65.2, SD: 12.8	NR	mean: 36.8, SD: 6.3	NR	NR	NR
Chatchawan, 2015[31]	Arm 1 – CONTROL - control	2 weeks	20(66.7)	mean: 57.6, SD: 6.5	NR	mean: 25.9, SD: 3.7	NR	NR	0
Chatchawan, 2015[31]	Arm 2 - Thai foot massage	2 weeks	20(66.7)	mean: 57.8, SD: 6.5	NR	mean: 25.3, SD: 2.7	NR	NR	0

n = Number; NR = Not Reported; SD = Standard Deviation

Evidence Table D-23. Physical therapy intervention - physical activity level (KQ1b)

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean SD:	Within arm comparison	Between arm comparison
Mueller, 2013[30]	Arm 1 - NWB	Average daily steps	N: 14, Mean: 6571, SD: 2186	12 weeks	N: 14, Mean: 6078, SD: 2023	Mean difference from baseline:-493 (95% CI:-1232 to 246), p: NR	Mean difference from baseline:1178 (95% CI:150 to 2205), p: 0.026
Mueller, 2013[30]	Arm 2 - WB	Average daily steps	N: 15, Mean: 4909, SD: 1398	12 weeks	N: 15, Mean: 5593, SD: 1449	Mean difference from baseline:685 (95% CI:-29 to 1399), p: NR	
Mueller, 2013[30]	Arm 1 - NWB	6 min walk	N: 14, Mean: 418, SD: 106	12 weeks	N: 14, Mean: 417, SD: 112	Mean difference from baseline:-2 (95% CI:-18 to 14), p: NR	Mean difference from baseline:29 (95% CI:6 to 51), p: 0.014
Mueller, 2013[30]	Arm 2 - WB	6 min walk	N: 15, Mean: 378, SD: 72	12 weeks	N: 15, Mean: 404, SD: 78	Mean difference from baseline:27 (95% CI:11 to 42), p: NR	
Chatchawan, 2015[31]	Arm 1 - control	TUG	N: 30, Mean: 8.8, SD: 1.91	2 weeks	N: 30, Mean: 8.56, SD: 1.67	P: <0.05	p: <0.05
Chatchawan, 2015[31]	Arm 2 - Thai foot massage	TUG	N: 30, Mean: 8.31, SD: 1.42	2 weeks	N: 30, Mean: 7.06, SD: 1.14	P: <0.05	

N = Number; NR = Not Reported; NWB = Non Weight Bearing; SD = Standard Deviation; TUG = Timed-Up and Go test; WB = Weight Bearing;

Evidence Table D-24. Physical therapy intervention incidence or reoccurrence of ulcers outcome (KQ1b)

Author, year	Arm	Outcome	Time point	N for analysis	Incidence, N	Between arm comparison
Mueller, 2013[30]	Arm 1 - NWB	Number of lesions- superficial injury	12 weeks	14	6	P: NR
Mueller, 2013[30]	Arm 2 - WB	Number of lesions- superficial injury	12 weeks	15	7	P: NR
Mueller, 2013[30]	Arm 1 - NWB	Number of ulcers- full thickness skin wound	12 weeks	14	3	P: NR
Mueller, 2013[30]	Arm 2 - WB	Number of ulcers- full thickness skin wound	12 weeks	15	1	P: NR

N = Number; NR = Not Reported; NWB = Non Weight Bearing; WB = Weight Bearing;

Evidence Table D-25. Study characteristics for lifestyle intervention (KQ1b)

Author, year	Study design Site(s) Location	Recruitment period (Start year –End year)	Diabetes type	Key inclusions and exclusions	Treatment duration Washout period Run-in period If applicable	Groups (dose)	Funding support	Comments
Bunner, 2015[32]	RCT Single site U.S. (Washington DC)	November 2012 to January 2013 and October 2013 to January 2014.	Type 2	+ Symptoms of painful diabetic neuropathy for 6 months Exclude B12 deficiency, current vegan diet	20-weeks	Group A: intervention group – received vitamin B12 supplement (1000 mcg daily) instructed to follow the low-fat vegetarian diet and attend weekly nutrition classes offering education and social support for 20 weeks. Group B: Control group: Vitamin B12 supplement (1000 mcg daily)	Physicians Committee for Responsible Medicine	Note on dietary adherence Two-day diet records conducted at midpoint and 20 weeks showed that 13 of 17 intervention-group participants avoided all animal products at the midpoint and endpoint assessments. Of those 13, 8 reported consuming a low-fat (25% kcal or less from fat) diet at both time points. An additional three of those thirteen reported consuming a low-fat diet at one of the two time points. An additional 2 of the 17 intervention-group participants were fully compliant with the low-fat guidelines at both assessments, but reported consuming at least modest amounts of animal products in one diet record, and two participants were noncompliant with the low-fat guidelines and the plant-based guidelines. No data on vitamin B12 supplement adherence were collected.

RCT = Randomized Control Trials; US = United States

Evidence Table D-26. Lifestyle intervention - participant characteristics (KQ1b)

Author, year	Group, N (dose)	Age mean, median, SD	Female N (%)	Race N (%)	HbA1c mean, median SD	BMI mean, median SD	Pain on visual analog scale (cm)	N of withdrawals
Bunner, 2015[32]	Group A, N = 17	Mean 57 (SD 6)	11 (65%)	Black: 11 (65%) Hispanic: 4 (25%):	8.0 (1.7)	36 (6)	5.3 (2.7)	0
	Group B, N = 17 (n = 18 randomized)	Mean 58 (SD 6)	8 (47%)	Black: 5 (29%) Hispanic: 1 (6%)	7.8 (1.6)	36 (7)	5.8 (2.4)	2 (n = 1 not included in Table 1 b/c withdrew)

BMI = Body Mass Index; HbA1c = Glycated Hemoglobin; N = Number; SD = Standard Deviation

Evidence Table D-27. Lifestyle intervention outcomes (KQ1b)

Author, year	Group, N (dose)	Outcome Units	Baseline N	Baseline Outcome	Time point(s)	N at time point(s)	Outcome at time point(s)	Within arm comparisons	Between arm comparisons
Bunner, 2015[32]	Group A, N=17	Quality of life (total score)- Norfolk Quality of Life Questionnaire	17	27.9 (14.3)	20 weeks	17	19.6 (17.9)	− 8.4 (13.6)‡	− 4.0 (−15.1 to 7.1) 0.43
	Group B, N=17 (n=18 randomized)		17	29.6 (15.7) −	20 weeks	17	24.6 (17.5)	-5.1 (10.5)a	

N = Number

Foot care intervention:

The evidence tables from the Netten et al review are available at: http://www.iwgdf.org/files/2015/PreventionSR.pdf
The data from the newly identified tables are described in the following tables:

Evidence Table D-28. Study characteristics for foot care intervention (KQ1b)

Author, year	Study design	Study site Study location	Funding	Recruitment Start YEAR - End YEAR	Incident or recurrent foot ulcer	Amputation	Adverse effect
Skafjeld, 2015[33]	Parallel randomized controlled trial	Single center: Europe; Norway	Non-profit.	NR	x		x
Shah, 2015[34]	Retrospective cohort study	Multi-center: North America; Canada; Ontario	Non-profit and government.	2006-2012	x	x	x
Monami, 2015[35]	Parallel randomized controlled trial	Single center: Europe; Italy	Not Reported	NR	x	x	
Gibson, 2014[36]	Retrospective cohort study	Multiple center: MarketScan database	Non-profit	2005-2009		x	
Chin, 2014[37]	Retrospective cohort study	Multiple center: Asia; Two hospitals in Taiwan	Non-profit	2010-2011	x		

NR = Not Reported

Evidence Table D-29. Foot care intervention - participant characteristics (KQ1b)

Author, year	Arm ,N at enrollment (i.e., at randomization or at beginning of exposure period)	Length of follow-up	Female, n, % Age (years), mean, SD Race, n, %	HbA1c BMI	Patients with type 1/2/1&2 diabetes, n %	Number of withdrawals and/or losses to provide follow-up: N	Comments
Skafjeld, 2015[33]	Control, 20	mean: 1 year	Female: n: NR, %: 25 Age: mean: 59.4, SD:13 Race: 100% Caucasian	HbA1c Mean: 7.9% BMI Mean: 31.1	Type 1:%: 30, Type 2:%: 70,	0	% with Urinary albumin/creatinine ratio > 3: 20% in control, 65% in intervention (p<0.01)
Skafjeld, 2015[33]	Intervention, 21	mean: 1 year	Female: n: NR, %: 14 Age: mean: 57.1, SD:10.2 Race: 100% Caucasian	HbA1c Mean: 8.3% BMI Mean: 31.4	Type 1: %:29 Type 2:%: 71,	3	
Shah, 2015[34]	Non-attendee ,8260	median: 5.3year	Female: n: 4334, %: 52.5 Age: mean: 73.1, SD: 5.4	NR	Type 2:%: 100,	0	Two groups differed in all aspects of baseline characteristics after propensity score matching
Shah, 2015[34]	Attendee ,8260	median: 5.3year	Female: n: 4334, %: 52.5 Age: mean: 73.1, SD: 5.4	NR	Type 2:%: 100,	0	
Monami, 2015[35]	Standard Care ,61	mean: 6 month	Female: n: 28, %: 46.7 Age: mean: 69.4 ± 11.3, SD: 11.3	HbA1c 7.3 ± 1.4 BMI 30.0 ± 5.6	Type 2:%: 100	0	Total N = 121; Only reported N = 120 (completers)
Monami, 2015[35]	Educational Program ,60	mean: 6 month	Female: n: 20, %: 33.3 Age: mean: 72.0 ± 8.9, SD: 8.9	HbA1c 7.4 ± 1.3 BMI 29.4 ± 4.7	Type 2:%: 100,	1	
Gibson, 2014[36]	Arm 1 - CONTROL: Commercial, Podiatrist visit, n = 7597	23.22 (SD 15.04)	Female: %: 44·7 Age: mean: 55·0, SD: 6.8	NR	NR	0	
Gibson, 2014[36]	Arm 2: Commercial, No Podiatrist visit, n = 12611	21.85 (SD: 14.93)	Female: n:, %: 38·1 Age: mean: 53·7, SD: 7.6	NR	NR	0	

Author, year	Arm ,N at enrollment (i.e., at randomization or at beginning of exposure period)	Length of follow-up	Female, n, % Age (years), mean, SD Race, n, %	HbA1c BMI	Patients with type 1/2/1&2 diabetes, n %	Number of withdrawals and/or losses to provide follow-up: N	Comments
Gibson, 2014[36]	Arm 3: Medicare, Podiatrist visit, n = 13692	23.26 (SD: 15.50) months	Female: %: 48·5 Age: mean: 77·6, SD: 6.9	NR	NR	0	
Gibson, 2014[36]	Arm 4:Medicare, no podiatrist visit, n = 13853	21.24 (SD: 15.24)	Female: %: 44·4 Age: mean: 76·7, SD: 6.9	NR	NR	0	
Chin, 2014[37]	Overall :295; only report baseline characteristics & results for n = 290 not lost to follow-up	mean: 1 year	Female: n: 141, %: 50.7 Age: mean: 66.97, SD:11.01 Race Asian, n: 295, %: 100	HbA1c Mean: 8.53 SD: 1.77	Type 2: n: 295, %: 100,	5- unclear which arm	

BMI = Body Mass Index; HbA1c = Glycated Hemoglobin; N = Number; NR = Not Reported; SD = Standard Deviation;

Evidence Table D-30. Foot care interventions characteristics (KQ1b)

Author, year	Arm	Foot care intervention	Duration (weeks)	Time/session	Total number of sessions	Adherence to the intervention
Skafjeld, 2015[33]	Arm 1 - control	Advised to always wear their customized footwear.	52 weeks	The percentage of days with a check indicating foot inspection was recorded in the daily log in the course of the study.	NR	70 % (14/20) recorded foot observations ≥80 % of the time.
Skafjeld, 2015[33]	Arm 2 - intervention	Trained to use a digital infrared thermometer to monitor foot temperature. Instructed to record daily physical activity using a step-counter during the first week of the study.	52 weeks	Adherence to skin temperature monitoring was recorded as the percentage of days with foot temperature measurements recorded in the daily log in the course of the study.	NR	67 % (14/21) recorded foot observations and skin temperatures ≥80 % of the time.
Shah, 2015[34]	Arm 1 - non-Attendee-di not attend self-management program	NA	5 years	NA	NA	NA
Shah, 2015[34]	Arm 2 - Attendee - attended group or in-person self-management program	By linking with the registry of self-management education program visits, those individuals who attended a program in 2006 were identified.	5 years	Attended self-management program	One or more	NA
Monami, 2015[35]	Arm 1 - standard care	Provided brief leaflet with some recommendations for ulcer prevention	Once	NR	One	NR

Author, year	Arm	Foot care intervention : DESCRIPTION	Duration (weeks)	Time/session	Total number of sessions	Adherence to the intervention
Monami, 2015[35]	Arm 2 - educational program	Two-hour program provided to groups of 5–7 patients (mean: n = 6), including a 30-minute face-to-face lesson on risk factors for foot ulcers, and a 90- minute interactive session with practical exercises on behaviors for reducing risk. The intervention involved a physician (for 15 minutes) and a nurse (for the remaining 105 minutes).	Once	2 hours	1	NR
Gibson, 2014[36]	Podiatry care	if the patient received care from a podiatrist during the year prior to the index diabetic foot ulcer diagnosis	NA	The primary analyses compared patients without any visits to a podiatrist during the year prior to the index date (comparison) with those having one or more visits (case).	The primary analyses compared patients without any visits to a podiatrist during the year prior to the index date (comparison) with those having one or more visits (case).	NR
Gibson, 2014[36]	No podiatry care)	N/A	NA	NA	NA	NR
Chin, 2014[37]	Arm 1 – CONTROL	Less self-reported care	NA	NA	NA	NR
Chin, 2014[37]	Arm 2 - self-reported Diabetes Foot Self-Care	Self-reported Diabetes Foot Self-Care Behavior Scale (inspecting the bottom of the foot and between toes, washing and drying between toes, applying moisturizing lotion, inspecting inside of the shoes, and breaking in the shoes)	NA	NA	NA	NR

NA = Not Applicable; NR = Not Reported

Evidence Table D-31. Footcare intervention – ulcer incidence or recurrent outcome (KQ1b)

Author, year	Arm	Outcome	Baseline N, mean: SD	Time point(s)	At time point(s), N, mean:	Between arm comparison
Skafjeld, 2015[33]	Arm 1 - control	Incident diabetic foot ulcer assessed with clinical examination by nurse-	N: 20	1 year	N = 10/20(50%)	Comparator arm: control, p:0.532
Skafjeld, 2015[33]	Arm 2 - intervention		N: 21	1 year	N = 7/21 (39%)	
Shah, 2015[34]	Arm 1 - non attendee	Hospital discharge diagnosis -rate per 1000 person-year	N: 8260	5 years	Incidence rate mean: 8.92per 1000 person year	Comparator arm: not attendee, relative hazard:1.16, 95% CI: 0.95-1.41, p:0.055
Shah, 2015[34]	Arm 2 - attendee		N: 8260	5 years	Incidence rate mean: 10.04 per 1000 person year	
Monami, 2015[35]	Arm 1 - standard care	Clinical diagnosis-n, % foot ulcer	N: 60	6 month	N = 6 (10%)	Comparator arm: standard care, p:0.012
Monami, 2015[35]	Arm 2 - educational program		N: 61	6 month	N = 0 (0%)	
Chin, 2014[37]	Arm 1 - no self-care	Diabetic foot ulcer	N = 290	1 year	NR	Reference group
Chin, 2014[37]	Arm 2 – self-care, examine bottom of feet			1 year	NR	Comparator arm: no self-care, relative hazard:1.1, 95% CI:0.97-1.25, p:0.132
Chin, 2014[37]	Arm 3 - examine between toes			1 year	NR	Comparator arm: no self-care, relative hazard:1.05, 95% CI:0.93-1.19, p:0.446
Chin, 2014[37]	Arm 4 - lotion application			1 year	NR	Comparator arm: no self-care, relative hazard:1.19, 95% CI:1.04-1.36, p:0.012

N = Number; NR = Not Reported; SD = Standard Deviation;

Evidence Table D-32. Footcare intervention - lower extremity amputation outcome (KQ1b)

Author, year	Arm, N for analysis	Outcome	Time point	n of PATIENTS with outcomes	Between arm comparison
Shah, 2015[34]	Arm 1 - not attendee, 8260	Hospital discharge diagnosis of lower extremity amputation -rate per 1000 person-year	5 years	0.76 per 1000 person year	Comparator arm: non-attendee, Relative hazard: 1.41, 95%CI: 99% CI: 0.40-5.04, p: 0.484
Shah, 2015[34]	Arm 2 - attendee, 8260	Hospital discharge diagnosis -rate per 1000 person-year	5 years	0.60 per 1000 person year	
Monami, 2015[35]	Arm 1 - control, 60	NR	6 month	N = 0	NA
Monami, 2015[35]	Arm 2 - education, 59	NR	6 month	N = 0	
Gibson, 2014[36]	Arm 1 - Commercial, No pre-period podiatrist visit, 7597	Lower extremity amputation using procedure codes on the claims-incidence amputation	5 years study; 40% of enrollees could be followed over 24months	1682	Comparator arm: Arm 1, Relative hazard: 0·748, 95%CI: 0·686–0·816, p: <0.001
Gibson, 2014[36]	Arm 2 - Commercial, 1+ pre-period podiatrist visit, 12 611	Lower extremity amputation using procedure codes on the claims-incidence amputation		811	
Gibson, 2014[36]	Arm 3 - Medicare, No pre-period podiatrist visit, 13 692	Lower extremity amputation using procedure codes on the claims-incidence amputation		1240	Comparator arm: Arm 3, Relative hazard: 0·796, 95%CI: 0·730–0·867, p: <0.001
Gibson, 2014[36]	Arm 4 - Medicare, 1+ pre-period podiatrist visit, 13 853	Lower extremity amputation using procedure codes on the claims-incidence amputation		1042	

Author, year	Arm, N for analysis	Outcome	Time point	n of PATIENTS with outcomes	Between arm comparison
Gibson, 2014[36]	Arm 1 - Commercial, No pre-period podiatrist visit, 7597	Major amputation- knee or higher.		380	Comparator arm: Arm1, Relative hazard: 0·691, 95%CI: 0·578–0·825, p: <0.001
Gibson, 2014[36]	Arm 2 - Commercial, 1+ pre-period podiatrist visit, 12 611	Major amputation- knee or higher.		179	
Gibson, 2014[36]	Arm 3 - Medicare, No pre-period podiatrist visit, 13 692	Major amputation- knee or higher.		407	Comparator arm:Arm3, Relative hazard: 0·652, 95%CI: 0·555–0·766, p: <0.001
Gibson, 2014[36]	Arm 4 - Medicare, 1+ pre-period podiatrist visit, 13 853	Major amputation- knee or higher.		280	

N = Number; NA = Not Applicable; NR = Not Reported;

Evidence Table D-33. Footcare intervention - harms (KQ1b)

Author, year	Arm, N for analysis	Adverse effects	EVENTS with outcomes, n, %	Between arm comparison
Skafjeld, 2015[33]	Arm 1 - control, 20	Dropouts	0	NR
	Arm 2 - intervention, 21		3 withdraws: 1 dropout; 2 illness	NR
Shah, 2015[34]	Arm 1 - non attendee, 8260	Glycaemia-related ED visit)	n: 44, %: 0.60%	Comparator arm: Non attendee, Relative hazard:1.02, 99% CI: 0.58-1.77, p: 0.938
	Arm 2 - attendee, 8260		n: 43, %: 0.50	
Shah, 2015[34]	Arm 1 - non attendee, 8260	Coronary artery disease	15.14 per 1000 person year	Comparator arm: non attendee, Relative hazard:1.13, 99% CI: 0.97 - 1.31, p: 0.036
	Arm 2 - attendee, 8260		16.66 per 1000 person year	

N = Number; NR = Not Reported

Evidence Table D-34. Surgery intervention - patient characteristics (KQ1b)

Author, year	Arm ,N at enrollment (i.e., at randomization or at beginning of exposure period)	Length of follow-up	Female, n, % Age (years), mean, SD Race, n, %	HbA1c BMI	Patients with type 1/2/1&2 diabetes, n %	Number of withdrawals and/or losses to follow-up: N	Comments
Mueller, 2004[38]	Control, TCC Only, n = 14	mean: 8 months	Female: n: 4, %: NR Age: mean: 54.8, SD: 9.5 Race: NR	HbA1c Mean: 8.9% BMI Mean: 31.8	Type 1:n: 5, Type 2:n: 9,	0	Original trial included Subjects with ATL followed by TCC (ATL group; n 31) or TCC alone (TCC group; n 3).the analyses described in this study include only those subjects who completed testing on all three test occasions
Mueller, 2004[38]	Intervention, TCC plus ATL, n = 14	mean: 8 months	Female: n: 3, %:NR Age: mean: 54.3, SD: 9.9 Race: NR	HbA1c Mean: 8.7% BMI Mean: 33.6	Type 1: n: 3 Type 2:n: 11	0	

ATL = Achilles tendon-lengthening; BMI = Body Mass Index; HbA1c = Glycated Hemoglobin; N = Number; NR = Not Reported; SD = Standard Deviation; TCC = Total Contact Casting;

Evidence Table D-35. Surgery interventions characteristics (KQ1b)

Author, year	Arm	Foot care intervention : DESCRIPTION	Duration (weeks)	Time/session	Total number of sessions	Adherence to the intervention
Mueller, 2004[38]	Arm 1 - TCC	Total contact casting (TCC)	NA	NA	Once	NA
Mueller, 2004[38]	Arm 2 - ATL	TCC plus ATL: Achilles tendon–lengthening: After wound debridement, subjects assigned to the ATL group underwent a percutaneous ATL procedure before application of a TCC using a modified Hoke triple hemisection technique.	NA	NA	Once	NA

ATL = Achilles tendon-lengthening; NA = Not Applicable; TCC = Total Contact Casting;

Evidence Table D-36. Surgery intervention - ulcer incidence or recurrent outcome (KQ1b)

Author, year	Arm	Outcome	Baseline N, mean: SD	Time point(s)	At time point(s), N, %	Between arm comparison
Mueller, 2004[38]	Arm 1 –TCC	Foot ulcer recurrence assessed with clinical examination	N: 14	8 months	38%	NA
Mueller, 2004[38]	Arm 2 - ATL		N: 14	8 months	21%	NA

ATL = Achilles tendon-lengthening; N = Number; NA = Not Applicable; TCC = Total Contact Casting;

Evidence Table D-37. Surgery intervention - quality of life outcome (KQ1b)

Author, year	Arm, N for analysis	Outcome	Baseline score mean; SD	Time point	Follow-up score Mean; SD	Between arm comparison
Mueller, 2004[38]	Arm 1 - TCC, n = 14	SF-36 Physical Summary	33.9; 7.5	8 months	39.4; 10.9	Comparator arm: TCC, P = 0.035
Mueller, 2004[38]	Arm 2 - ATL, n = 14	SF-36 Physical Summary	35.5; 6.9	8 months	31.0; 6.2	
Mueller, 2004[38]	Arm 1 - TCC, n = 14	SF-36 mental summary	49.9; 11.3	8 months	51.8; 11.5	Comparator arm: TCC, P = 0.56
Mueller, 2004[38]	Arm 2 - ATL, n = 14	SF-36 mental summary	51.2; 12.3	8 months	51.6; 13	

ATL = Achilles tendon-lengthening; N = Number; SD = Standard Deviation; TCC = Total Contact Casting;

Evidence Table D-38. Surgery intervention - physical activity level (KQ1b)

Author, year	Arm, N for analysis	Outcome	Baseline score mean; SD	Time point	Follow-up score mean; SD	Between arm comparison
Mueller, 2004[38]	Arm 1 - TCC, n = 14	Simulated dressing	2.9; 0.7	8 months	2.7; 1.1	Comparator arm: TCC, P = 1.0
Mueller, 2004[38]	Arm 2 - ATL, n = 14	Simulated dressing	2.6 ; 0.9	8 months	2.4; 1.1	
Mueller, 2004[38]	Arm 1 - TCC, n = 14	50-foot walking test	15.9; 4.8	8 months	15.1; 4	Comparator arm: TCC, P = 0.1
Mueller, 2004[38]	Arm 2 - ATL, n = 14	50-foot walking test	15.2; 2.8	8 months	15.5; 3.4	
Mueller, 2004[38]	Arm 1 - TCC, n = 14	Climb one flight	2.3 ; 1	8 months	2.4; 1.2	Comparator arm: TCC, P = 0.54
Mueller, 2004[38]	Arm 2 - ATL, n = 14	Climb one flight	2.3; 0.9	8 months	2.1; 1.1	
Mueller, 2004[38]	Arm 1 - TCC, n = 14	Walking velocity	63.2; 21.2	8 months	64.8; 17.9	Comparator arm: TCC, P = 0.97
Mueller, 2004[38]	Arm 2 - ATL, n = 14	Walking velocity	61.8; 10.4	8 months	61.9; 15.9	

ATL = Achilles tendon-lengthening; N = Number; SD = Standard Deviation; TCC = Total Contact Casting;

Evidence Table D-39. Risk of bias for RCTs (KQ1a)

Author, year	Random sequence generation	Allocation concealment	Blinding of personnel	Blinding of outcome assessors	Incomplete outcome data	Selective reporting of outcomes	Other sources of bias	Overall quality
Jaiswal, 2015[15]	Unclear	Unclear	High	Unclear	Low	Low	Low	Unclear
Reichard P, 1993[2] and Rathsman, 2014[3]	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Dormandy, 2005[8]	Low	Low	Low	Low	Low	Low	Low	Low
Gaede, 2008[7] and Gaede, 2003[6]	Low	Low	Low	Low	Low	Low	Low	Low
UKPDS, 1998[16]	Low	Low	Low	Low	Low	Low	Low	Low
Martin, 2006[9] and 1998[10]	Low	Low	Low	Low	Low	Low	Low	Low
Duckworth, 2009[11]	Low	Low	Low	Low	Low	Low	Low	Low
Griffin, 2011[12]	Unclear	Unclear	Low	Low	Low	Low	Low	Unclear
Abraira, 1997[4]	Unclear	Low	Low	Low	Low	Low	Low	Unclear
Knatterud, 1978[1]	Low	Low	Low	Low	Low	Low	Low	Low
Araki, 2012[13]	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low

Evidence Table D-40. Risk of bias for cohort studies (KQ1a)

Author, year	Bias due to confounding	Bias in selection of participants into the study	Bias in measurement of interventions	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall bias
Kostev, 2012[14]	High	High	Low	High	High	High	Low	High

Evidence Table D-41. Risk of bias for RCTs (KQ1b)

Author,year	Random sequence generation	Allocation concealment	Blinding of personnel	Blinding of outcome assessors	Assessing blinding outcome: outcome assessor blinded by critical outcomes	Incomplete outcome data	Selective reporting of outcomes	Other sources of bias	Overall quality
Balance									
Song, 2011[21]	Unclear	Unclear	NA	Unclear		Low	Low	Low	Unclear
Kordi Yoosefinejad, 2015[25]	Low	Unclear	NA	Unclear		Unclear	Low	Unclear	Unclear
Lemaster, 2008[20] and Kruse, 2010[19]	Low	Low	NA	Low		Low	Low	Low	Low
Grewal, 2015[24]	Low	Unclear	NA	Low		Low	Low	Low	Low
Lee, 2013[22]	Low	Low	NA	Unclear		Low	Low	Low	Low
Eftekhar-Sadat, 2015[23]	Low	Unclear	NA	Low		Low	Low	Low	Low
Richardson, 2001[18]	High	High	NA	Unclear		High	Low	Low	High
Physical Therapy									
Chatchawan, 2015[31]	Low	Low	NA	Unclear		Low	Low	Low	Low
Mueller, 2013[30]	Low	Low	NA	Low		Low	Low	Low	Low
Exercise									
Dixit, 2014[28]	Low	Low	NA	Low		Unclear	Low	Low	Low
Taveggia, 2014[29]	Low	Low	NA	Low		Low	Low	Low	Low
Lemaster, 2008[20] and Kruse, 2010[19]	Low	Low	NA	Low		Low	Low	Low	Low
Sartor, 2014[26]	Low	Unclear	NA	Low		Low	Low	Unclear	Low
Lifestyle									
Bunner, 2015[32]	Low	Low	Low	Low		High	Low	Low	High
Footcare									
Skafjeld, 2015[33]	Low	Low	High	High	Unclear	Low	Low	Low	Unclear
Monami, 2015[35]	Low	Low	High	High	High	Low	Unclear	Low	High

NA = Not Applicable

Evidence Table D-42. Risk of bias for cohort studies (KQ1b)

Author, year	Bias due to confounding	Bias in selection of participants into the study	Bias in measurement of interventions	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall bias
Exercise								
Lemaster, 2003[27]	Moderate	Moderate	Low	Moderate	Moderate	Low	Unclear	Moderate
Footcare								
Shah, 2015[34]	low	low	low	low	low	low	low	Low
Gibson, 2014[36]	low	low	low	low	low	low	low	Low
Chin, 2014[37]	moderate	low	low	moderate	low	low	moderate	Moderate

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Evidence Tables for KQ2a and b

The evidence tables from the Griebeler et al review are available at: http://www.ncbi.nlm.nih.gov/pubmed/23198755
The data from the newly identified tables are described in the following tables:

Evidence Table D-43. Study characteristics for pharmacological treatments (KQ2a)

Author, year	Study design Study site	Funding source	Recruitment Start YEAR - End YEAR	Was run-in period reported?	Comments
Allen, 2014[1]	Parallel randomized controlled trial Multiple center: North America	Industry	2006-2009	No	
Arezzo, 2008[2]	Parallel randomized controlled trial Multiple center: North America	Industry	NR	Yes	
Atli, 2005[3]	Parallel randomized controlled trial Single center: NR	Academic Industry	NR	Yes	
Campbell, 2012[4]	Parallel randomized controlled trial Multiple center: North America	Industry	NR	No	
Chad, 1990[5]	Parallel randomized controlled trial Multiple center: North America	NR	NR	No	
Freeman, 2007[6]	Parallel randomized controlled trial Multiple center: North America	Industry	NR	No	
Gao, 2015[7]	Parallel randomized controlled trial Multiple center: Asia	Industry	NR	No	
Ghasemi, 2014[8]	Parallel randomized controlled trial Multiple center: Asia	Academic	2011-2012	No	
Hanna, 2008[9]	Parallel randomized controlled trial Multiple center: Europe, Australia	Industry	2003-2005	Yes	

Author, year	Study design Study site	Funding source	Recruitment Start YEAR - End YEAR	Was run-in period reported?	Comments
Harati, 1998[10]	Parallel randomized controlled trial Multiple center: NR	Industry	NR	Yes	Assume North America; run-in period 7-21 days (some drugs stopped for 7 and some 21 days)
Jiang, 2011[11]	Parallel randomized controlled trial Single center:NR	Industry	2006-2008	No	
Karmakar, 2014[12]	Crossover randomized controlled trial Single center: North America	Industry	2011-2013	Yes	
Kulkantrakorn, 2013[13]	Crossover randomized controlled trial Single center: Asia	Academic	2009-2011	No	
Niesters, 2014[14]	Parallel randomized controlled trial Single center: Europe	Academic	2012-2012	No	Study intervention listed as analgesic agent
Raskin, 2014[15]	Parallel randomized controlled trial Multiple center: North America, Africa	Industry	2010-2012	Yes	
Rauck, 2013[16]	Parallel randomized controlled trial Multiple center: North America	Industry	2008-2009	No	
Rowbotham, 2012[17]	Parallel randomized controlled trial Multiple center: NR	Industry	2007-2008	Yes	
Sandercock, 2012[18]	Parallel randomized controlled trial Multiple center: North America	Industry	2006	Yes	

Author, year	Study design Study site	Funding source	Recruitment Start YEAR - End YEAR	Was run-in period reported?	Comments
Schwartz, 2015[19]	Parallel randomized controlled trial Multiple center: NR	Industry	NR	Yes	Note that this is a 2ry analysis of other studies that are included - therefore characteristics should not be reported separately. Open label run in period - all patients received tapentadol 50mg bid x 3 days, then 100mg bid then in 50mg increments up to 250mg bid as tolerated
Shaibani, 2012[20]	Parallel randomized controlled trial Multiple center: NR	Industry	NR	Yes	
Tesfaye, 2013[21]	Parallel randomized controlled trial Multiple center: Europe, Asia, North America, Australia	Industry	2010-2011	No	Head to head and dose; combination comparison; several authors are Lilly employees
Toth, 2012[22]	Parallel randomized controlled trial Single center: North America	Industry	2006-2011	Yes	
Vinik, 2014[23]	Parallel randomized controlled trial Multiple center: North America	Industry	2009-2011	Yes	Analgesic intervention. All participants started out in a titration period. After randomization, placebo group was down-titrated before start of placebo to avoid withdrawal symptoms.
Yuan, 2009[24]	Crossover randomized controlled trial Single center: Asia	Industry	NR	No	
Ziegler, 2015[25]	Parallel randomized controlled trial Multiple center: NR	Industry	2011-2011	Yes	

NR = Not Reported

Evidence Table D-44. Participant characteristics for pharmacological treatments (KQ2a)

Author, year	Arm, N at enrollment	Actual length of follow-up-MEAN unit for follow-up	Women, n (%)	Age, years:	HbA1c	BMI	Duration of pain	Duration of neuropathic symptoms	Number of withdrawals and/or losses to follow-up: N
Allen, 2014[1]	Arm 1 - placebo	13 weeks	25 (28)	mean: 59, SD: 8.5	NR	NR	42.1 years	NR	25
Allen, 2014[1]	Arm 2 - Desvenlafaxine 50mg	13 weeks	16 (25)	mean: 61.6, SD: 8.6	NR	NR	41.8 years	NR	12
Allen, 2014[1]	Arm 3 - Desvenlafaxine 100mg	13 weeks	20 (23)	mean: 60.7, SD: 9.2	NR	NR	45.3 years	NR	18
Allen, 2014[1]	Arm 4 - Desvenlafaxine 200mg	13 weeks	30 (30)	mean: 59.8, SD: 9.4	NR	NR	40.6 years	NR	31
Allen, 2014[1]	Arm 5 - Desvenlafaxine 400mg	13 weeks	17 (25)	mean: 61.1, SD: 10	NR	NR	40.4 years	NR	27
Arezzo, 2008[2]	Arm 1 - placebo	13 weeks	40 (47.1)	mean: 58.3, SD: 10.9	NR	mean: 35.8, SD: 8.4	NR	4.4 years	24
Arezzo, 2008[2]	Arm 2 - Pregabalin	13 weeks	24 (29.3)	mean: 58.2, SD: 9.6	NR	mean: 36.6, SD: 8.3	NR	4.9 years	28
Atli, 2005[3]	Arm 1 - placebo	14 weeks	NR	mean: 61.5, SD: 10.2	NR	mean: 31.7, SD: NR	NR	NR	1
Atli, 2005[3]	Arm 2 - Zonisamide	14 weeks	NR	mean: 55.9, SD: 9.5	NR	mean: 36.8, SD: NR	NR	NR	8
Campbell, 2012[4]	Arm 1 - placebo	16 weeks	48 (53)	mean: 57.6, SD: 9.5	NR	NR	2.9 years	NR	NR
Campbell, 2012[4]	Arm 2 - Clonindine	16 weeks	45 (51)	mean: 59.4, SD: 9.9	NR	NR	3 years	NR	NR
Chad, 1990[5]	Arm 1 – Control - Vehicle	4 weeks	NR	NR	NR	NR	NR	NR	NR
Chad, 1990[5]	Arm 2 - Capsaicin	4 weeks	NR	NR	NR	NR	NR	NR	NR
Freeman, 2007[6]	Arm 1 - placebo	18 weeks	10 (31)	mean: 57.8, SD: 11.53	NR	mean: 31.2, SD: 4.7	NR	NR	4
Freeman, 2007[6]	Arm 2 - Topiramate	18 weeks	13 (39)	mean: 58.5, SD: 8.51	NR	mean: 33.9, SD: 5.3	NR	NR	9

Author, year	Arm, N at enrollment	Actual length of follow-up- MEAN unit for follow-up	Women, n (%)	Age, years:	HbA1c	BMI	Duration of pain	Duration of neuropathic symptoms	Number of withdrawals and/or losses to follow-up: N
Gao, 2015[7]	Arm 1 - placebo	12 weeks	111 (55)	mean: 61.2, SD: 9.4	NR	mean: 24.5, SD: 3.2	NR	3.1 years	26
Gao, 2015[7]	Arm 2 - Duloxetine	12 weeks	112 (55.2)	mean: 61.6, SD: 9.7	NR	mean: 24.6, SD: 3.6	NR	3.5 years	30
Gao, 2015[7]	Overall - total	12 weeks	223 (55.1)	mean: 61.4, SD: 9.5	NR	mean: 24.6, SD: 3.4	NR	3.3 years	56
Ghasemi, 2014[8]	Arm 1 - placebo	3 weeks	11 (NR)	mean: 59.3, SD: 9.6	NR	NR	NR	NR	0
Ghasemi, 2014[8]	Arm 2 - Boutlinum	3 weeks	7 (NR)	mean: 62.7, SD: 9.9	NR	NR	NR	NR	0
Hanna, 2008[9]	Overall - total	12 weeks	118 (36)	mean: 60.1, SD: 10.24	NR	NR	NR	NR	89
Hanna, 2008[9]	Arm 1 – Control – Placebo + Gabapentin	12 weeks	55 (33)	mean: 60.7, SD: 9.93	NR	NR	NR	NR	41
Hanna, 2008[9]	Arm 2 – Oxycodon + Gabapentin	12 weeks	63 (39)	mean: 59.6, SD: 10.54	NR	NR	NR	NR	48
Harati, 1998[10]	Arm 1 – control – placebo	42 days	27 (41)	mean: 59, SD: NR	mean: 10.6, SD: NR	NR	NR	NR	22
Harati, 1998[10]	Arm 2 - Tramadol	42 days	26 (40)	mean: 59, SD: NR	mean: 10.8, SD: NR	NR	NR	NR	22
Kulkantrakorn, 2013[13]	Overall - total	8 weeks	17 (51.5)	mean: 58.0, SD: NR	NR	NR	4.7	NR	25
Jiang, 2011[11]	Arm 1 - Control-Placebo	4 weeks	6 (30)	mean: 59.7, SD: 12.5	7.96, SD: 1.98	mean: 32.3, SD: 8.7	4.66 years	NR	6
Jiang, 2011[11]	Arm 2 - Pregabalin	4 weeks	9 (45)	mean: 55.1, SD: 14.4	8.33, SD: 2.9	mean: 31, SD: 8.1	10.1 years	NR	5
Karmakar, 2014[12]	Overall - all study subjects	15 weeks	11 (39)	mean: 64.6, SD: 10.4	NR	NR	NR	5.7 years	4
Niesters, 2014[14]	Arm 1 - placebo	4 weeks	5 (NR)	median: 64, SD: NR	NR	NR	NR	6.5 years	0
Niesters, 2014[14]	Arm 2 - Tapentadol	4 weeks	5 (NR)	median: 63, SD: NR	NR	NR	NR	6	0

Author, year	Arm, N at enrollment	Actual length of follow-up-MEAN unit for follow-up	Women, n (%)	Age, years:	HbA1c	BMI	Duration of pain	Duration of neuropathic symptoms	Number of withdrawals and/or losses to follow-up: N
Raskin, 2014[15]	Overall – single blind phase	6 weeks	302 (45.4)	mean: 58.4, SD: 10.1	NR	NR	5.5	4.9	371
Raskin, 2014[15]	Arm 1 - Control-Placebo	13 weeks	67 (45.6)	mean: 58.3, SD: 10.5	NR	NR	5.8	5.2	34
Raskin, 2014[15]	Arm 2 – Pregabalin	13 weeks	72 (49.0)	mean: 58.8, SD: 9.2	NR	NR	5.4	5.0	22
Rauck, 2013[16]	Overall	16 weeks	171 (41)	mean: 58.7, SD: 10.2	NR	NR	NR	NR	NR
Rauck, 2013[16]	Arm 1 – placebo	16 weeks	47 (39)	mean: 60.1, SD: 10.63	NR	NR	NR	NR	NR
Rauck, 2013[16]	Arm 2 - Gabapentin enacarbil, 1200mg	16 weeks	28 (45)	mean: 57.5, SD: 10.32	NR	NR	NR	NR	NR
Rauck, 2013[16]	Arm 3 - Gabapentin enacarbil, 2400mg	16 weeks	19 (34)	mean: 60.8, SD: 8.97	NR	NR	NR	NR	NR
Rauck, 2013[16]	Arm 4 - Gabapentin enacarbil, 3600mg	16 weeks	45 (39)	mean: 57.5, SD: 9.87	NR	NR	NR	NR	NR
Rauck, 2013[16]	Arm 5 - Pregabalin, 300mg	16 weeks	32 (48)	mean: 57.7, SD: 10.59	NR	NR	NR	NR	NR
Rowbotham, 2012[17]	Arm 1 - Control-Placebo	8 weeks	23 (45.1)	mean: 59.6, SD: 7.0	NR	NR	4.4	NR	7
Rowbotham, 2012[17]	Arm 2 – Duloxetine	8 weeks	25 (43.9)	mean: 60.1, SD: 7.8	NR	NR	4.8	NR	13
Sandercock, 2012[18]	Arm 1 - Control-Placebo	5 weeks	19 (33)	mean: 58, SD: 9.1	mean: 7.1, SD: 1.4	mean: 33.4, SD: 8.2	NR	NR	5
Sandercock, 2012[18]	Arm 2 - Gabapentin single dose, 3000mg	5 weeks	29 (63)	mean: 58, SD: 8.0	mean: 7.6, SD: 1.4	mean: 34.2, SD: 6.7	NR	NR	4
Sandercock, 2012[18]	Arm 3 – Gabapentin asymmetric dose, 3000mg	5 weeks	18 (36)	mean: 60, SD: 7.5	mean: 7.0, SD: 1.5	mean: 34.3, SD: 7.2	NR	NR	7
Shaibani, 2012[20]	Arm 1 - placebo	13 weeks	55 (44.7)	mean: 62.0, SD: 9.8	mean: 7.4, SD: 1.7	NR	3.2	3.8	34

Author, year	Arm, N at enrollment	Actual length of follow-up-MEAN unit for follow-up	Women, n (%)	Age, years:	HbA1c	BMI	Duration of pain	Duration of neuropathic symptoms	Number of withdrawals and/or losses to follow-up: N
Shaibani, 2012[20]	Arm 2 – Dextromethorphan/Quinidine (45/30)	13 weeks	50 (38.2)	mean: 61.0, SD: 10.4	mean: 7.3, SD: 1.4	NR	3.8	4.0	52
Shaibani, 2012[20]	Arm 3 - Dextromethorphan/Quinidine (30/30)	13 weeks	40 (32.0)	mean: 59.8, SD: 10.1	mean: 7.2, SD: 1.3	NR	3.0	3.6	51
Tesfaye, 2013[21]	Arm 1 – control - Duloxetine 60mg, then Duloxetine 120mg	18 weeks	NR	mean: 61.5, SD: 10.62	mean: 8, SD: 1.7	mean: 30.7, SD: 6.18	2 years	2 years	124
Tesfaye, 2013[21]	Arm 2 - Duloxetine 60mg, then combination therapy	18 weeks	NR	mean: 61.5, SD: 10.62	mean: 8, SD: 1.7	mean: 30.7, SD: 6.18	2 years	2 years	129
Tesfaye, 2013[21]	Arm 3 - Pregablin 300mg, then combination therapy	18 weeks	NR	mean: 61.9, SD: 10.95	mean: 7.9, SD: 1.57	mean: 30.9, SD: 5.94	2 years	2 years	107
Tesfaye, 2013[21]	Arm 4 - Pregablin 300mg, then Pregablin 600mg	18 weeks	NR	mean: 61.9, SD: 10.95	mean: 7.9, SD: 1.57	mean: 30.9, SD: 5.94	2 years	2 years	105
Toth, 2012[22]	Arm 1 - placebo	5 weeks	4 (31)	mean: 61.6, SD: 14.6	mean: 7.2, SD: 1.6	NR	NR	7.1 years	0
Toth, 2012[22]	Arm 2 - Nabilone	5 weeks	8 (62)	mean: 60.8, SD: 15.3	mean: 7.1, SD: 1.8	NR	NR	7.2 years	1
Vinik, 2014[23]	Arm 1 – placebo	12 weeks	64 (42.1)	mean: 59, SD: 9	NR	mean: 34.5, SD: 7.84	NR	NR	45
Vinik, 2014[23]	Arm 2 - Tapentadol ER	12 weeks	67 (40.4)	mean: 58.5, SD: 10.63	NR	mean: 35.1, SD: 11.47	NR	NR	46
Yuan, 2009[24]	Overall	12 weeks	12	mean: 65.6, SD: 9.2	NR	NR	NR	NR	2
Ziegler, 2015[25]	Arm 1 - placebo	7 weeks	26 (42)	mean: 58.9, SD: 8.6	mean: 7.4, SD: 1.25	mean: 31.3, SD: 5.36	NR	6.1 years	2
Ziegler, 2015[25]	Arm 2 - Pregabalin	7 weeks	34 (49)	mean: 59.6, SD: 8.75	mean: 7.2, SD: 1.11	mean: 33.3, SD: 8.36	NR	5.3 years	5

BMI = Body Mass Index; HbA1c = Glycated Hemoglobin; N = Number; NR = Not Reported; SD = Standard Deviation;

Evidence Table D-45. Intervention characteristics for pharmacological treatments (KQ2a)

Author, year	Arm	Administration route Dosage	Comments
Allen, 2014[1]	Arm 1 - placebo	Oral	
Allen, 2014[1]	Arm 2 - Desvenlafaxine 50mg	Oral 50 mg/day	
Allen, 2014[1]	Arm 3 - Desvenlafaxine 100mg	Oral 100 mg/day	
Allen, 2014[1]	Arm 4 - Desvenlafaxine 200mg	Oral 200 mg/day	
Allen, 2014[1]	Arm 5 - Desvenlafaxine 400mg	Oral 400 mg/day	
Allen, 2014[1]	Arm 6 - Open label extension phase	Oral 100mg/day up to 400mg/day per patient	
Arezzo, 2008[2]	Arm 1 - placebo	Oral Placebo given same time as intervention	
Arezzo, 2008[2]	Arm 2 - Pregabalin	Oral Daily dosage escalated for 1 week from 150mg to 300mg BID, which was continued for 12 weeks.	
Atli, 2005[3]	Arm 1 - placebo	Oral Placebo given same time as intervention, contains small amount of lactulose	
Atli, 2005[3]	Arm 2 - Zonisamide	Oral Administered 100-600mg per day, with minimum target dosage of 300mg per day	
Campbell, 2012[4]	Arm 1 - placebo	Topical Placebo	
Campbell, 2012[4]	Arm 2 - Clonindine	Topical 3.9mg per day (both feet) 0.65mg clonidine per dose, 3x per day per feet (topical application)	

Author, year	Arm	Administration route Dosage	Comments
Chad, 1990[5]	Arm 1 – Control - Vehicle	Topical Vehicle	
Chad, 1990[5]	Arm 2 - Capsaicin	Topical 0.075% capsaicin, 4 times a day for 4 weeks	
Freeman, 2007[6]	Arm 1 - placebo	Oral Placebo given same time as intervention	
Freeman, 2007[6]	Arm 2 - Topiramate	Oral 200	Median average daily dose was 156.2 mg/day
Gao, 2015[7]	Arm 1 - placebo	Oral 60	
Gao, 2015[7]	Arm 2 - Duloxetine	Oral 60	
Ghasemi, 2014[8]	Arm 1 - placebo	Intradermal 100 units	
Ghasemi, 2014[8]	Arm 2 - Boutlinum	Intradermal 100 units	
Hanna, 2008[9]	Arm 1 – Control – Placebo + Gabapentin	Oral Placebo pill taken 12 hourly. Gabapentin dose determined by investigator	
Hanna, 2008[9]	Arm 2 – Oxycodon + Gabapentin	Oral Oxycodon pill taken 12 hourly. Gabapentin dose determined by investigator	
Harati, 1998, 306	Arm 1 - placebo	Oral Titrated from 50mg/day up to max of 400mg/day per patient. Must be minimum of 100mg/day by day 14. Average tramadol dose 210 +/- 113 mg/day	
Harati, 1998, 306	Arm 2 - Tramadol	Oral Titrated from 50mg/day up to max of 400mg/day per patient. Must be minimum of 100mg/day by day 14. Average tramadol dose 210 +/- 113 mg/day	

Author, year	Arm	Administration route Dosage	Comments
Jiang, 2011[11]	Arm 1 - Control-Placebo	Oral Placebo	Mean dose 535.7mg (SD: 140.6, Range 150-600)
Jiang, 2011[11]	Arm 2 - Pregabalin	Oral 75mg BID, titrated up to 150mg BID in 7 days, then 300mg BID for 2 weeks	Mean dose 460mg (SD:165, Range 150-600)
Karmakar, 2014[12]	Overall - all study subjects	Oral 150mg x 7 days, 300mg x 7 days then 600mg	Pregabalin first mean dose 205.8mg, Placebo first mean dose 188.1mg
Kulkantrakorn, 2013[13]	Arm 1 - Control-Placebo	Topical Placebo	
Kulkantrakorn, 2013[13]	Arm 2 - Capsaicin	Topical 0.025%, 2 inches of gel around feet three to four times daily	
Niesters, 2014[14]	Arm 1 - Control-Placebo	Oral Placebo	
Niesters, 2014[14]	Arm 2 - Tapentadol	Oral 100mg BID in week1, 200 mg BID in week2, 250mg BID in week3 and week4	
Raskin, 2014[15]	Arm 1 - Placebo	Oral Single-blind stage: 150-300mg/day pregabalin Double-blind stage: Placebo	Withdrawal trial. Data was reported from baseline of single-blind stage, not from start of randomization in double-blind stage.

Author, year	Arm	Administration route Dosage	Comments
Raskin, 2014[15]	Arm 2 – Pregabalin	Oral Single-blind stage: 150-300mg/day Double-blind stage: 150-300mg/day	
Rauck, 2013[16]	Arm 1 - Control-Placebo	Oral Placebo tablets presented same frequency as intervention arms	
Rauck, 2013[16]	Arm 2 - Gabapentin enacarbil, 1200mg	Oral 1200mg per day, in 600mg tablets	
Rauck, 2013[16]	Arm 3 - Gabapentin enacarbil, 2400mg	Oral 2400mg per day, in 600mg tablets	
Rauck, 2013[16]	Arm 4 - Gabapentin enacarbil, 3600mg	Oral 3600mg per day, in 600mg tablets	
Rauck, 2013[16]	Arm 5 - Pregabalin, 300mg	Oral 300mg per day, in 50 and 100mg tablets	
Rowbotham, 2012[17]	Arm 1 - Control-Placebo	Oral Placebo	
Rowbotham, 2012[17]	Arm 2 – Duloxetine	Oral 60mg per day	
Sandercock, 2012[18]	Arm 1 - Control-Placebo	Oral Placebo tablets	
Sandercock, 2012[18]	Arm 2 - Gabapentin single dose, 3000mg	Oral 3000mg per day, given in one dose tablets	
Sandercock, 2012[18]	Arm 3 – Gabapentin asymmetric dose, 3000mg	Oral 3000mg per day, given 1800mg in the evening and 1200mg in morning tablets	

Author, year	Arm	Administration route Dosage	Comments
Shaibani, 2012[20]	Arm 1 - placebo	Oral Placebo	
Shaibani, 2012[20]	Arm 2 – Dextromethorphan/Quinidine (45/30)	Oral 45mg of Dextromethorphan and 30mg Quinidine per tablet. 1 tablet per day in run-in, 2 tablets per day in rest of trial	Note that quinidine is administered to maintain bioavailability of dextromethorphan and is a very sub therapeutic dose
Shaibani, 2012[20]	Arm 3 - Dextromethorphan/Quinidine (30/30)	Oral 30mg of Dextromethorphan and 30mg Quinidine per tablet. 1 tablet per day in run-in, 2 tablets per day in rest of trial	
Tesfaye, 2013[21]	Arm 1 – control - Duloxetine 60mg, then Duloxetine 120mg	Oral 60mg per day duloxetine for 7 weeks, increased to 120mg per day duloxetine for 7 weeks.	
Tesfaye, 2013[21]	Arm 2 - Duloxetine 60mg, then combination therapy	Oral 60mg per day duloxetine for 7 weeks, then was switched to 300mg per day pregablin + 60mg per day duloxetine for 7 weeks	
Tesfaye, 2013[21]	Arm 3 - Pregablin 300mg, then combination therapy	Oral 300mg per day pregablin for 7 weeks, then was switched to 300mg per day pregablin + 60mg per day duloxetine for 7 weeks	
Tesfaye, 2013[21]	Arm 4 - Pregablin 300mg, then Pregablin 600mg	Oral 300mg per day pregablin for 7 weeks, increased to 600mg per day pregablin for 7 weeks.	
Toth, 2012[22]	Arm 1 - placebo	Oral Placebo	
Toth, 2012[22]	Arm 2 - Nabilone	Oral Starting dose of 1.0mg per day and titrated as high as 4.0mg per day as tolerated over 3 weeks. This was continued in the double blind phase	
Vinik, 2014[23]	Arm 1 - placebo	Oral Placebo given same time as intervention"	After randomization, placebo group was down-titrated for 3 days before start of placebo to avoid withdrawal symptoms.

Author, year	Arm	Administration route Dosage	Comments
Vinik, 2014[23]	Arm 2 - Tapentadol ER	Oral 200 - 500	Variable dose based on response in open-label initial phase. 100 - 250 mg BID
Yuan, 2009[24]	Arm 1 - placebo	Intradermal Injection 0.9% Saline	
Yuan, 2009[24]	Arm 2 – Botulinum toxin	Intradermal Injection 50 units BoNT/A in 1.2 0.9% saline	
Ziegler, 2015[25]	Arm 1 - placebo	Oral 2 placebo capsules twice daily	
Ziegler, 2015[25]	Arm 2 - Pregabalin	Oral 150mg x 7 days then 300mg	

BID = Twice a day; Mg = Milligram; SD = Standard Deviation;

Evidence Table D-46. Pain continuous outcomes for pharmacological treatments (KQ2a)

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Allen, 2014[1]	Arm 1 - placebo	NRS: 0-10 scale	N: 90, Mean: 6.61, SD: 1.6	13 weeks	N: 89, Mean: NR, SD: NR	Mean change from baseline: -1.83, SD: NR, p: NR	Mean change from baseline: NA (95% CI:NR), SD: NR, Comparator arm: NA, p: NA
Allen, 2014[1]	Arm 2 - Desvenlafaxine 50mg	NRS: 0-10 scale	N: 63, Mean: 6.44, SD: 1.66	13 weeks	N: 63, Mean: NR, SD: NR	Mean change from baseline: -2.41, SD: NR, p: NR	Mean change from baseline NR Comparator arm: vs Placebo, p: 0.084
Allen, 2014[1]	Arm 3 - Desvenlafaxine 100mg	NRS: 0-10 scale	N: 87, Mean: 6.14, SD: 1.62	13 weeks	N: 86, Mean: NR, SD: NR	Mean change from baseline: -2.42, SD: NR, p: NR	Mean change from baseline NR Comparator arm: vs Placebo, p: 0.084
Allen, 2014[1]	Arm 4 - Desvenlafaxine 200mg	NRS: 0-10 scale	N: 99, Mean: 6.55, SD: 1.52	13 weeks	N: 99, Mean: NR, SD: NR	Mean change from baseline: -2.93, SD: NR, p: NR	Mean change from baseline: 1.1 (95% CI:NR), SD: NR, Comparator arm: vs Placebo, p: 0.001
Allen, 2014[1]	Arm 5 - Desvenlafaxine 400mg	NRS: 0-10 scale	N: 69, Mean: 6.48, SD: 1.42	13 weeks	N: 68, Mean: NR, SD: NR	Mean change from baseline: -2.74, SD: NR, p: NR	Mean change from baseline: 0.91 (95% CI:NR), SD: NR, Comparator arm: vs Placebo, p: 0.027
Allen, 2014[1]	Arm 6 - Desvenlafaxine Open Label	NRS: 0-10 scale	N: 240, Mean: 3.86, SD: NR	9 months	N: 223, Mean: 3.35, SD: NR	Mean change from baseline: -0.53, SD: NR, p: NR	Mean change from baseline NR Comparator arm: NR, p: NR
Arezzo, 2008[2]	Arm 1 - placebo	NRS: 0-10 scale	N: 85, Mean: 6.58, SD: 1.58	13 weeks	N: 85, Mean: 4.82, SD: NR	NR	NR

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Arezzo, 2008[2]	Arm 2 - Pregabalin	NRS: 0-10 scale	N: 82, Mean: 6.28, SD: 1.47	13 weeks	N: 82, Mean: 3.54, SD: NR	NR	Mean change from baseline: -1.28 (95% CI:-1.96, -0.60), SD: NR, p: 0.0003
Arezzo, 2008[2]	Arm 1 - placebo	SF-MPQ, Present Pain Intensity: 0-5 scale	N: 85, Mean: NR, SD: NR	12 weeks	N: 85, Mean: NR, SD: NR	NR	NR
Arezzo, 2008[2]	Arm 2 - Pregabalin	SF-MPQ, Present Pain Intensity: 0-5 scale	N: 82, Mean: NR, SD: NR	12 weeks	N: 82, Mean: NR, SD: NR	NR	Mean change from baseline: -0.34 (95% CI:-0.65, -0.03), SD: NR, p: 0.0311
Arezzo, 2008[2]	Arm 1 - placebo	SF-MPQ, VAS: 0-100 scale	N: 85, Mean: NR, SD: NR	NR	N: 85, Mean: NR, SD: NR	NR	NR
Arezzo, 2008[2]	Arm 2 - Pregabalin	SF-MPQ, VAS: 0-100 scale	N: 82, Mean: NR, SD: NR	NR	N: 82, Mean: NR, SD: NR	NR	Mean difference from baseline: 11.06 (95% CI:-18.89, -3.22), SD: NR, p: 0.006
Atli, 2005[3]	Arm 1 - placebo	Likert scale, LOCF imputation: 0-10 scale	N: 12, Mean: 6.63, SD: 1.7	14 weeks	N: 12, Mean: 6.03, SD: 1.7	Mean change from baseline: 0.6, SD: 1.4, p: NR	NR
Atli, 2005[3]	Arm 2 - Zonisamide	Likert scale, LOCF imputation: 0-10 scale	N: 13, Mean: 6.45, SD: 1.1	14 weeks	N: 11, Mean: 4.89, SD: 2.1	Mean change from baseline: 1.56, SD: 1.9, p: NR	p: 0.18

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Atli, 2005[3]	Arm 1 - placebo	VAS, LOCF imputation: 0-100 scale	N: 12, Mean: 63.9, SD: 18.1	14 weeks	N: 12, Mean: 57, SD: 19.9	Mean change from baseline: 6.9, SD: 15.4, p: NR	NR
Atli, 2005[3]	Arm 2 - Zonisamide	VAS, LOCF imputation: 0-100 scale	N: 13, Mean: 58.9, SD: 9.4	14 weeks	N: 11, Mean: 41.2, SD: 21.2	Mean change from baseline: 17.7, SD: 19, p: NR	p: 0.15
Campbell, 2012[4]	Arm 1 – control placebo	BPI, average pain: 0-10 scale	N: 30, Mean: 6.3, SD: 1.5	12 weeks	N: 30, Mean: NR, SD: NR	Mean change from baseline: -1.3, SD: 1.7, p: NR	NR Comparator arm: Placebo, p: 0.06
Campbell, 2012[4]	Arm 2 - Clonindine	BPI, average pain: 0-10 scale	N: 33, Mean: 6.5, SD: 1.6	12 weeks	N: 33, Mean: NR, SD: NR	Mean change from baseline: -2.2, SD: 1.9, p: NR	NR Comparator arm: Placebo, p: 0.06
Campbell, 2012[4]	Arm 1 - placebo	BPI, functional interference scale-0-70 scale	N: 30, Mean: 37.2, SD: 17.1	12 weeks	N: 30, Mean: NR, SD: NR	Mean change from baseline: -8.7, SD: 13.2, p: NR	NR Comparator arm: Placebo, p: 0.43
Campbell, 2012[4]	Arm 2 - Clonindine	BPI, functional interference scale-0-70 scale	N: 33, Mean: 37.1, SD: 17.5	12 weeks	N: 33, Mean: NR, SD: NR	Mean change from baseline: -13, SD: 15.2, p: NR	NR Comparator arm: Placebo, p: 0.43

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Campbell, 2012[4]	Arm 1 - placebo	BPI, severity scale-0-40 scale	N: 30, Mean: 25.4, SD: 5.8	12 weeks	N: 30, Mean: NR, SD: NR	Mean change from baseline: -5.3, SD: 7.8, p: NR	NR Comparator arm: Placebo, p: 0.18
Campbell, 2012[4]	Arm 2 - Clonindine	BPI, severity scale-0-40 scale	N: 33, Mean: 25.1, SD: 7.3	12 weeks	N: 33, Mean: NR, SD: NR	Mean change from baseline: -7.8, SD: 7.2, p: NR	NR Comparator arm: Placebo, p: 0.18
Campbell, 2012[4]	Arm 1 - placebo	NPRS, average pain severity from diary-NR scale	N: 30, Mean: 6.3, SD: 1.4	12 weeks	N: 30, Mean: NR, SD: NR	Mean change from baseline: -1.4, SD: 1.8, p: NR	NR Comparator arm: Placebo, p: 0.01
Campbell, 2012[4]	Arm 2 - Clonindine	NPRS, average pain severity from diary-NR scale	N: 33, Mean: 6.3, SD: 1.5	12 weeks	N: 33, Mean: NR, SD: NR	Mean change from baseline: -2.6, SD: 2, p: NR	NR Comparator arm: Placebo, p: 0.01
Freeman, 2007[6]	Arm 1 - placebo	VAS: 0-100 scale	N: 32, Mean: NR, SD: NR	18 weeks	N: 32, Mean: NR, SD: NR	Mean change from baseline: -11.5, SD: 38.9, p: NR	NR
Freeman, 2007[6]	Arm 2 - Topiramate	VAS: 0-100 scale	N: 35, Mean: NR, SD: NR	18 weeks	N: 35, Mean: NR, SD: NR	Mean change from baseline: -16.2, SD: 27.3, p: NR	p: 0.35
Gao, 2015[7]	Arm 1 - placebo	Weekly mean 24h average pain: 0-10 scale	N: 202, Mean: 5.6, SD: 1.7	12 weeks	N: 173, Mean: NR, SD: NR	Mean change from baseline: -1.97, SD: NR, p: NR	Mean change from baseline: NA (95% CI:NA), SD: NR, Comparator arm: p: NA

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Gao, 2015[7]	Arm 2 - Duloxetine	Weekly mean 24h average pain: 0-10 scale	N:203, Mean:5.7, SD:1.7	12 weeks	N: 172, Mean: NR, SD: NR	Mean change from baseline: -2.4, SD: NR, p: NR	Mean change from baseline: -0.43 (95% CI:(-0.82, -0.04)), SD: NR, Comparator arm: vs Placebo, p: 0.03
Ghasemi, 2014[8]	Arm 1 - placebo	Neuropathy Pain Scale (NPS), Pain Intensity: 0-10 scale	N: 20, Mean: 7.1, SD: 2.2	3 weeks	N: 20, Mean: 7, SD: 2	Mean change from baseline: NR, SD: NR, p: 0.8	Mean change from baseline NR Comparator arm: NA, p: NA
Ghasemi, 2014[8]	Arm 2 - Boutlinum	Neuropathy Pain Scale (NPS), Pain Intensity: 0-10 scale	N: 20, Mean: 6.9, SD: 2.1	3 weeks	N: 20, Mean: 5.1, SD: 2.3	Mean change from baseline: NR, SD: NR, p: <0.001	Mean change from baseline NR Comparator arm: vs Placebo, p: 0.009
Ghasemi, 2014[8]	Arm 1 – control placebo	Neuropathy Pain Scale (NPS), Sharp sensation: 0-10 scale	N: 20, Mean: 5.4, SD: 2.6	3 weeks	N: 20, Mean: 4.9, SD: 2.6	Mean change from baseline: NR, SD: NR, p: 0.1	Mean change from baseline NR Comparator arm: NA, p: NA
Ghasemi, 2014[8]	Arm 2 - Boutlinum	Neuropathy Pain Scale (NPS, sharp sensation: 0-10 scale	N: 20, Mean: 5.4, SD: 2.4	3 weeks	N: 20, Mean: 4.2, SD: 2.7	Mean change from baseline: NR, SD: NR, p: <0.001	Mean change from baseline NR Comparator arm: vs Placebo, p: 0.41
Hanna, 2008[9]	Arm 1 – Control – Placebo + Gabapentin	Box Scale -11 (BS-11)	N: 145, Mean: 6.5, SD: 1.7	12 weeks	N: 145, Mean: NR, SD: NR	Mean change from baseline:-1.5, SD: 2.4, p: NR	Mean change from baseline NR Comparator arm: NA, p: NA
Hanna, 2008[9]	Arm 2 – Oxycodon + Gabapentin	Box Scale -11 (BS-11)	N: 138, Mean: 6.4, SD: 1.8	12 weeks	N: 138, Mean: NR, SD: NR	Mean change from baseline: -2.1, SD: 2.6, p: NR	Mean change from baseline: 0.55 (95% CI: 0.15, 0.95), p=0.007

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Hanna, 2008[9]	Arm 1 – Control – Placebo + Gabapentin	BPI	N:145, Mean: NR, SD: NR	12 weeks	N:145, Mean: NR, SD: NR	NR	Mean change from baseline NR Comparator arm: NA, p: NA
Hanna, 2008[9]	Arm 2 – Oxycodon + Gabapentin	BPI	N: 138, Mean: NR, SD: NR	12 weeks	N: 138, Mean: NR, SD: NR	NR	Mean change from baseline: NR p<0.001
Harati, 1998[10]	Arm 1 - placebo	Pain Intensity Scale (Likert): 0-4 scale	N: 66, Mean: 2.6, SD: 0.1	42 days	N: 64, Mean: 2.2, SD: 0.1	NR	Mean difference from baseline: p: NA
Harati, 1998[10]	Arm 2 - Tramadol	Pain Intensity Scale (Likert): 0-4 scale	N: 65, Mean: 2.5, SD: 0.1	42 days	N: 63, Mean: 1.4, SD: 0.1	NR	Mean change from baseline NR Comparator arm: vs Placebo, p: <0.001
Harati, 1998[10]	Arm 1 - placebo	Pain Relief Rating Scale (Likert): -1-4 scale	N: 66, Mean: NR, SD: NR	42 days	N: 64, Mean: 0.9, SD: 0.2	NR	Mean change from baseline NR Comparator arm: p: NA
Harati, 1998[10]	Arm 2 - Tramadol	Pain Relief Rating Scale (Likert): -1-4 scale	N: 65, Mean: NR, SD: NR	42 days	N: 63, Mean: 2.1, SD: 0.2	NR	Mean change from baseline NR Comparator arm: vs Placebo, p: <0.001

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Jiang, 2011[11]	Arm 1 - Control-Placebo	VAS: 0-100 scale	N: 20, Mean: 75.4, SD: 12.9	4 weeks	N: 14, Mean: NR, SD: NR	Mean change from baseline: -21.29, SD: 35.6, p: NR	P:0.092
Jiang, 2011[11]	Arm 2 - Pregabalin	VAS: 0-100 scale	N: 20, Mean: 70.78, SD: 18.8	4 weeks	N: 15, Mean: NR, SD: NR	Mean change from baseline: -43.27, SD: 32.0, p: NR	P:0.092
Jiang, 2011[11]	Arm 1 - Control-Placebo	BPI, total pain score	N: 20, Mean: 16.9, SD: 7.8	4 weeks	N: 14, Mean: NR, SD: NR	Mean change from baseline: -1.36, SD: 9.01, p: NR	P:0.03
Jiang, 2011[11]	Arm 2 - Pregabalin	BPI, total pain score	N: 20, Mean: 18.1, SD: 9.08	4 weeks	N: 15, Mean: NR, SD: NR	Mean change from baseline: -9.13, SD: 9.63, p: NR	P:0.03
Jiang, 2011[11]	Arm 1 - Control-Placebo	NPS, total pain score	N: 20, Mean: 50.9, SD: 12.35	4 weeks	N: 14, Mean: NR, SD: NR	Mean change from baseline: -10.31, SD: 11.15, p: NR	P:0.053
Jiang, 2011[11]	Arm 2 - Pregabalin	NPS, total pain score	N: 20, Mean: 53.05, SD: 19.64	4 weeks	N: 15, Mean: NR, SD: NR	Mean change from baseline: -27.33, SD: 22.95, p: NR	P:0.053

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Karmakar, 2014[12]	Arm 1 - Control-Placebo	VAS	N: 19, Mean: 6.17, SD: 3.47	8 weeks	N: 19, Mean: 5.02, SD: 4.04	NR	Reference group
Karmakar, 2014[12]	Arm 2 – Pregabalin	VAS	N: 19, Mean: 5.33, SD: 4.38	8 weeks	N: 19, Mean: 3.22, SD: 6.84	NR	p=NS
Kulkantrakorn, 2013[13]	Arm 1 - Control-Placebo	VAS: 0-100 scale	N: 17, Mean: 50.0, SD: 2.93	8 weeks	N: 17, Mean: 3.46, SD: 2.89	NR	P:0.531
Kulkantrakorn, 2013[13]	Arm 2 - Capsaicin	VAS: 0-100 scale	N: 16, Mean: 44.1, SD: 2.49	8 weeks	N: 16, Mean: 2.88, SD: 2.18	NR	P:0.531
Kulkantrakorn, 2013[13]	Arm 1 - Control-Placebo	NPS	N: 17, Mean: 42.43, SD: 21.41	8 weeks	N: 17, Mean: 31.29, SD: 21.29	NR	P:0.805
Kulkantrakorn, 2013[13]	Arm 2 - Capsaicin	NPS	N: 16, Mean: 38.46, SD: 20.76	8 weeks	N: 16, Mean: 29.38, SD: 16.07	NR	P:0.805
Kulkantrakorn, 2013[13]	Arm 1 - Control-Placebo	SF-MPQ	N: 17, Mean: 19.18, SD: 8.89	8 weeks	N: 17, Mean: 7.71, SD: 10.16	NR	P:0.953
Kulkantrakorn, 2013[13]	Arm 2 - Capsaicin	SF-MPQ	N: 16, Mean: 18.06, SD: 9.15	8 weeks	N: 16, Mean: 7.40, SD: 6.19	NR	P:0.953

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Niesters, 2014[14]	Arm 1 - placebo	Conditioned Pain Modulation (CPM): 0-100 scale	N: 12, Mean: 9.1, SD: 5.4	4 weeks	N: 12, Mean: 14.3, SD: 7.2	Mean change from baseline: NR, SD: NR, p: 0.04	NR
Niesters, 2014[14]	Arm 2 - Tapentadol	Conditioned Pain Modulation (CPM): 0-100 scale	N: 12, Mean: 9.1, SD: 5.4	4 weeks	N: 12, Mean: 24.2, SD: 7.7	Mean change from baseline: NR, SD: NR, p: <0.01	Mean difference from baseline:, p: <0.001
Niesters, 2014[14]	Arm 1 – control – placebo	VAS (NRS): 0-10 scale	N: 12, Mean: 6.5, SD: 0.6	4 weeks	N: 12, Mean: 4.8, SD: 0.7	NR	NR
Niesters, 2014[14]	Arm 2 - Tapentadol	VAS (NRS): 0-10 scale	N: 12, Mean: 6.5, SD: 0.6	4 weeks	N: 12, Mean: 3.9, SD: 0.6	NR	Mean difference from baseline:, p: 0.03

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Raskin, 2014[15]	Arm 1 - Control-Placebo	NRS	N:147, Mean: 6.7, SD: 1.3	19 weeks	N:147, Mean: 3.2, SD: 1.9	Mean change from baseline: -3.5, SD: 2.1, p: NR	NR
Raskin, 2014[15]	Arm 2 – Pregabalin	NRS	N:147, Mean: 6.8, SD: 1.2	19 weeks	N:147, Mean: 2.9, SD: 1.7	Mean change from baseline: -3.9, SD: 1.9, p: NR	Comparator arm: placebo; Least squares mean difference in change from baseline -0.32 (95% CI, -0.74 to 0.09, NS) (LOCF data, reported as primary outcome)
Rauck, 2013[16]	Arm 1 – control – placebo	BPI severity: scale NR	N: 120, Mean: NR, SD: NR	16 weeks	N: 120, Mean: NR, SD: NR	NR	Mean difference from baseline: Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 2 - Gabapentin enacarbil, 1200mg	BPI severity: scale NR	N: 62, Mean: NR, SD: NR	16 weeks	N: 62, Mean: NR, SD: NR	NR	Mean difference from baseline: -0.3 (95% CI:-0.96, 0.44), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 3 - Gabapentin enacarbil, 2400mg	BPI severity: scale NR	N: 56, Mean: NR, SD: NR	16 weeks	N: 56, Mean: NR, SD: NR	NR	Mean difference from baseline: -0.3 (95% CI:-1.06, 0.47), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 4 - Gabapentin enacarbil, 3600mg	BPI severity: scale NR	N: 116, Mean: NR, SD: NR	16 weeks	N: 116, Mean: NR, SD: NR	NR	Mean difference from baseline: -0.7 (95% CI:-1.29, 0.12), SD: NR, Comparator arm: Placebo, p: NR

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Rauck, 2013[16]	Arm 5 - Pregabalin, 300mg	BPI severity: scale NR	N: 66, Mean: NR, SD: NR	16 weeks	N: 66, Mean: NR, SD: NR	NR	Mean difference from baseline: 0.4 (95% CI:-0.28, 1.08), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 1 - placebo	NPS 10: 0-10 scale	N: 120, Mean: NR, SD: NR	16 weeks	N: 120, Mean: NR, SD: NR	NR	Mean difference from baseline: Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 2 - Gabapentin enacarbil, 1200mg	NPS 10: 0-10 scale	N: 62, Mean: NR, SD: NR	16 weeks	N: 62, Mean: NR, SD: NR	NR	Mean difference from baseline: 0.49 (95% CI:-5.96, 6.93), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 3 - Gabapentin enacarbil, 2400mg	NPS 10: 0-10 scale	N: 56, Mean: NR, SD: NR	16 weeks	N: 56, Mean: NR, SD: NR	NR	Mean difference from baseline: -3.33 (95% CI:-10.3, 3.69), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 4 - Gabapentin enacarbil, 3600mg	NPS 10: 0-10 scale	N: 116, Mean: NR, SD: NR	16 weeks	N: 116, Mean: NR, SD: NR	NR	Mean difference from baseline: -6.57 (95% CI:-12.0, -1.18), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 5 - Pregabalin, 300mg	NPS 10: 0-10 scale	N: 66, Mean: NR, SD: NR	16 weeks	N: 66, Mean: NR, SD: NR	NR	Mean difference from baseline: 2.76 (95% CI:-3.55, 9.07), SD: NR, Comparator arm: Placebo, p: NR

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Rauck, 2013[16]	Arm 1 - placebo	NPS 4: 0-10 scale	N: 120, Mean: NR, SD: NR	16 weeks	N: 120, Mean: NR, SD: NR	NR	Mean difference from baseline: Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 2 - Gabapentin enacarbil, 1200mg	NPS 4: 0-10 scale	N: 62, Mean: NR, SD: NR	16 weeks	N: 62, Mean: NR, SD: NR	NR	Mean difference from baseline: -0.36 (95% CI:-7.49, 6.78), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 3 - Gabapentin enacarbil, 2400mg	NPS 4: 0-10 scale	N: 56, Mean: NR, SD: NR	16 weeks	N: 56, Mean: NR, SD: NR	NR	Mean difference from baseline: -4.61 (95% CI:-12.4, 3.16), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 4 - Gabapentin enacarbil, 3600mg	NPS 4: 0-10 scale	N: 116, Mean: NR, SD: NR	16 weeks	N: 116, Mean: NR, SD: NR	NR	Mean difference from baseline: -7.3 (95% CI:-13.3, -1.32), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 5 - Pregabalin, 300mg	NPS 4: 0-10 scale	N: 66, Mean: NR, SD: NR	16 weeks	N: 66, Mean: NR, SD: NR	NR	Mean difference from baseline: 4.48 (95% CI:-2.51, 11.47), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 1 - placebo	NPS 8: 0-10 scale	N: 120, Mean: NR, SD: NR	16 weeks	N: 120, Mean: NR, SD: NR	NR	Mean difference from baseline: Comparator arm: Placebo, p: NR

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Rauck, 2013[16]	Arm 2 - Gabapentin enacarbil, 1200mg	NPS 8: 0-10 scale	N: 62, Mean: NR, SD: NR	16 weeks	N: 62, Mean: NR, SD: NR	NR	Mean difference from baseline: 0.9 (95% CI:-5.50, 7.29), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 3 - Gabapentin enacarbil, 2400mg	NPS 8: 0-10 scale	N: 56, Mean: NR, SD: NR	16 weeks	N: 56, Mean: NR, SD: NR	NR	Mean difference from baseline: -3.11 (95% CI:-10.1, 3.85), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 4 - Gabapentin enacarbil, 3600mg	NPS 8: 0-10 scale	N: 116, Mean: NR, SD: NR	16 weeks	N: 116, Mean: NR, SD: NR	NR	Mean difference from baseline: -6.41 (95% CI:-11.8, -1.05), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 5 - Pregabalin, 300mg	NPS 8: 0-10 scale	N: 66, Mean: NR, SD: NR	16 weeks	N: 66, Mean: NR, SD: NR	NR	Mean difference from baseline: 2.54 (95% CI:-3.72, 8.80), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 1 - placebo	NPS: 0-10 scale	N: 120, Mean: NR, SD: NR	16 weeks	N: 120, Mean: NR, SD: NR	NR	Mean difference from baseline: Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 2 - Gabapentin enacarbil, 1200mg	NPS: 0-10 scale	N: 62, Mean: NR, SD: NR	16 weeks	N: 62, Mean: NR, SD: NR	NR	Mean difference from baseline: 0.49 (95% CI:-6.24, 7.22), SD: NR, Comparator arm: Placebo, p: NR

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Rauck, 2013[16]	Arm 3 - Gabapentin enacarbil, 2400mg	NPS: 0-10 scale	N: 56, Mean: NR, SD: NR	16 weeks	N: 56, Mean: NR, SD: NR	NR	Mean difference from baseline: -3.49 (95% CI:-10.8, 3.84), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 4 - Gabapentin enacarbil, 3600mg	NPS: 0-10 scale	N: 116, Mean: NR, SD: NR	16 weeks	N: 116, Mean: NR, SD: NR	NR	Mean difference from baseline: -6.98 (95% CI:-12.6, -1.34), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 5 - Pregabalin, 300mg	NPS: 0-10 scale	N: 66, Mean: NR, SD: NR	16 weeks	N: 66, Mean: NR, SD: NR	NR	Mean difference from baseline: 3.74 (95% CI:-2.85, 10.33), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 1 - placebo	Pain Intensity Numerical Rating Scale (PI-NRS): 0-10 scale	N: 120, Mean: 6.49, SD: 1.26	16 weeks	N: 120, Mean: NR, SD: NR	Mean change from baseline: -2.09, SD: 2.07, p: NR	Mean difference from baseline: Comparator arm: Placebo, p: NA
Rauck, 2013[16]	Arm 2- Gabapentin enacarbil, 1200mg	Pain Intensity Numerical Rating Scale (PI-NRS): 0-10 scale	N: 62, Mean: 6.64, SD: 1.47	16 weeks	N: 62, Mean: NR, SD: NR	Mean change from baseline: -2.55, SD: 2.54, p: NR	Mean difference from baseline: -0.35 (95% CI:-1.02, 0.31), SD: NR, Comparator arm: Placebo, p: 0.295
Rauck, 2013[16]	Arm 3 - Gabapentin enacarbil, 2400mg	Pain Intensity Numerical Rating Scale (PI-NRS): 0-10 scale	N: 56, Mean: 6.26, SD: 1.22	16 weeks	N: 56, Mean: NR, SD: NR	Mean change from baseline: -1.9, SD: 2.05, p: NR	Mean difference from baseline: -0.02 (95% CI:-0.71, 0.66), SD: NR, Comparator arm: Placebo, p: 0.946

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Rauck, 2013[16]	Arm 4 - Gabapentin enacarbil, 3600mg	Pain Intensity Numerical Rating Scale (PI-NRS): 0-10 scale	N: 116, Mean: 6.48, SD: 1.43	16 weeks	N: 116, Mean: NR, SD: NR	Mean change from baseline: -2.54, SD: 2.42, p: NR	Mean difference from baseline: -0.55 (95% CI:-1.10, 0.01), SD: NR, Comparator arm: Placebo, p: 0.105
Rauck, 2013[16]	Arm 5 - Pregabalin, 300mg	Pain Intensity Numerical Rating Scale (PI-NRS): 0-10 scale	N: 66, Mean: 6.51, SD: 1.27	16 weeks	N: 66, Mean: NR, SD: NR	Mean change from baseline: -1.66, SD: 1.83, p: NR	Mean difference from baseline: 0.43 (95% CI:-0.22, 1.08), SD: NR, Comparator arm: Placebo, p: NA
Rauck, 2013[16]	Arm 1 - placebo	PI-NRS, Daytime average pain: 0-10 scale	N: 120, Mean: NR, SD: NR	16 weeks	N: 120, Mean: NR, SD: NR	NR	Mean difference from baseline: Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 2 - Gabapentin enacarbil, 1200mg	PI-NRS, Daytime average pain: 0-10 scale	N: 62, Mean: NR, SD: NR	16 weeks	N: 62, Mean: NR, SD: NR	NR	Mean difference from baseline: -0.28 (95% CI:-0.94, 0.38), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 3 - Gabapentin enacarbil, 2400mg	PI-NRS, Daytime average pain: 0-10 scale	N: 56, Mean: NR, SD: NR	16 weeks	N: 56, Mean: NR, SD: NR	NR	Mean difference from baseline: 0 (95% CI:-0.68, 0.68), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 4 - Gabapentin enacarbil, 3600mg	PI-NRS, Daytime average pain: 0-10 scale	N: 116, Mean: NR, SD: NR	16 weeks	N: 116, Mean: NR, SD: NR	NR	Mean difference from baseline: -0.47 (95% CI:-1.02, 0.08), SD: NR, Comparator arm: Placebo, p: NR

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Rauck, 2013[16]	Arm 5 - Pregabalin, 300mg	PI-NRS, Daytime average pain: 0-10 scale	N: 66, Mean: NR, SD: NR	16 weeks	N: 66, Mean: NR, SD: NR	NR	Mean difference from baseline: 0.57 (95% CI:-0.08, 1.21), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 1 - placebo	PI-NRS, Nightime average pain: 0-10 scale	N: 120, Mean: NR, SD: NR	16 weeks	N: 120, Mean: NR, SD: NR	NR	Mean difference from baseline: Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 2 - Gabapentin enacarbil, 1200mg	PI-NRS, Nightime average pain: 0-10 scale	N: 62, Mean: NR, SD: NR	16 weeks	N: 62, Mean: NR, SD: NR	NR	Mean difference from baseline: -0.16 (95% CI:-0.84, 0.52), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 3 - Gabapentin enacarbil, 2400mg	PI-NRS, Nightime average pain: 0-10 scale	N: 56, Mean: NR, SD: NR	16 weeks	N: 56, Mean: NR, SD: NR	NR	Mean difference from baseline: -0.05 (95% CI:-0.76, 0.66), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 4 - Gabapentin enacarbil, 3600mg	PI-NRS, Nightime average pain: 0-10 scale	N: 116, Mean: NR, SD: NR	16 weeks	N: 116, Mean: NR, SD: NR	NR	Mean difference from baseline: -0.72 (95% CI:-1.29, -0.15), SD: NR, Comparator arm: Placebo, p: NR

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Rauck, 2013[16]	Arm 5 - Pregabalin, 300mg	PI-NRS, Nightime average pain: 0-10 scale	N: 66, Mean: NR, SD: NR	16 weeks	N: 66, Mean: NR, SD: NR	NR	Mean difference from baseline: 0.16 (95% CI:-0.51, 0.83), SD: NR, Comparator arm: Placebo, p: NR
Rowbotham, 2012[17]	Arm 1 - Control-Placebo	24 hour average pain	N: 50, Mean: 6.6, SD: 1.2	8 weeks	N: 50, Mean: NR, SD: NR	Least squares mean change from baseline: -2.1, SE: 0.3, p: NS	Mean change from baseline NR Comparator arm: vs Placebo, p: NA
Rowbotham, 2012[17]	Arm 2 – Duloxetine	24 hour average pain	N: 54, Mean: 6.6, SD: 1.4	8 weeks	N: 54, Mean: NR, SD: NR	Least squares mean change from baseline: -2.8, SE: 0.3, p: 0.05	Mean change from baseline NR Comparator arm: vs Placebo, p: 0.032
Rowbotham, 2012[17]	Arm 1 - Control-Placebo	BPI average pain	N: 50, Mean: 6.5, SD: 1.5	8 weeks	N: 50, Mean: NR, SD: NR	Least squares mean change from baseline: -1.9, SE: 0.3, p: NS	NR
Rowbotham, 2012[17]	Arm 2 – Duloxetine	BPI average pain	N: 56, Mean: 6.4, SD: 1.3	8 weeks	N: 56, Mean: NR, SD: NR	Least squares mean change from baseline: -2.3, SE: 0.3, p: NS	NR
Sandercock, 2012[18]	Arm 1 - Control-Placebo	NRS: 0-10 scale	N: 51, Mean: 6.74, SD: 1.37	4 weeks	N: 49, Mean: NR, SD: NR	Mean change from baseline: -1.3 (95% CI:-1.8, -0..7), SD: NR, p: NR	Mean change from baseline NR Comparator arm: vs Placebo, p: NA

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Sandercock, 2012[18]	Arm 2 - Gabapentin single dose, 3000mg	NRS: 0-10 scale	N: 46, Mean: 6.71, SD: 1.34	4 weeks	N: 43, Mean: NR, SD: NR	Mean change from baseline: -2.5 (95% CI:-3.0, -1.9), SD: NR, p: NR	Mean change from baseline NR Comparator arm: vs Placebo, p: 0.002
Sandercock, 2012[18]	Arm 3 – Gabapentin asymmetric dose, 3000mg	NRS: 0-10 scale	N: 50, Mean: 6.44, SD: 1.51	4 weeks	N: 46, Mean: NR, SD: NR	Mean change from baseline: -1.8 (95% CI:-2.3, -1.2), SD: NR, p: NR	Mean change from baseline NR Comparator arm: vs Placebo, p: 0.190
Shaibani, 2012[20]	Arm 1 - placebo	Pain Rating Scale	N: 123, mean: 4.4, SD: 2.5	13 weeks	N: 89, mean: NR, SD: NR	Mean change from baseline: -2.0, SE: 0.05, p: NR	Mean change from baseline: NA , SD: NR, Comparator arm: NA, p: NA
Shaibani, 2012[20]	Arm 2 – Dextromethorphan/ Quinidine (45/30)	Pain Rating Scale	N: 131, mean: 4.9, SD: 2.4	13 weeks	N: 79, mean: NR, SD: NR	Mean change from baseline: -2.6, SE: 0.05, p: NR	Mean change from baseline: NR, SD:NR, Comparator arm: Placebo, p: <0.0001
Shaibani, 2012[20]	Arm 3 - Dextromethorphan/ Quinidine (30/30)	Pain Rating Scale	N: 125, mean: 4.7, SD: .24	13 weeks	N: 74, mean: NR, SD: NR	Mean change from baseline: -2.2, SE: 0.06, p: NR	Mean change from baseline: NR, SD:NR, Comparator arm: Placebo, p: 0.009
Toth, 2012[22]	Arm 1 - placebo	NRS: 0-10 scale	N: 13, Mean: 5.8, SD: 1.6	4 weeks	N: 13, Mean: 5.4, SD: 1.7	Mean change from baseline: 3, SD: 1.5, p: <0.01	NR Comparator arm: NR, p: NR

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Toth, 2012[22]	Arm 2 - Nabilone	NRS: 0-10 scale	N: 13, Mean: 5.8, SD: 1.8	4 weeks	N: 13, Mean: 3.5, SD: 1.3	Mean change from baseline: 1.1, SD: 1.2, p: <0.01	NR Comparator arm: NR, p: NR
Toth, 2012[22]	Arm 1 – control placebo	VAS, pain severity: 0-100 scale	N: 13, Mean: 65.9, SD: 20.3	4 weeks DAY 28	N: 13, Mean: 54.3, SD: 4.5	Mean change from baseline: NR, SD: NR, p: NS	Mean difference from baseline NR Comparator arm: Placebo, p: <0.05
Toth, 2012[22]	Arm 2 - Nabilone	VAS, pain severity: 0-100 scale	N: 13, Mean: 65.4, SD: 19.1	4 weeks	N: 13, Mean: 35.4, SD: 4	Mean change from baseline: NR, SD: NR, p: NS	Mean difference from baseline NR Comparator arm: Placebo, p: <0.05
Vinik, 2014[23]	Arm 1 - placebo	BPI, pain intensity: 0-10 scale	N: 152, Mean: 6.8, SD: 1.54	15 weeks	N: 137, Mean: NR, SD: NR	Mean change from baseline: -2.3, SD: 2.33, p: NR	NR
Vinik, 2014[23]	Arm 2 - Tapentadol ER	BPI, pain intensity: 0-10 scale	N: 166, Mean: 6.6, SD: 1.52	15 weeks	N: 147, Mean: NR, SD: NR	Mean change from baseline: -3, SD: 2.16, p: 0.003	NR
Vinik, 2014[23]	Arm 1 - placebo	NPSI paroxysmal pain: 0-10 scale	N: 152, Mean: 2.9, SD: 2.42	12 weeks	N: 124, Mean: NR, SD: NR	Mean change from baseline: 0.92, SD: 3.02, p: NR	NR

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Vinik, 2014[23]	Arm 2 - Tapentadol ER	NPSI paroxysmal pain: 0-10 scale	N: 166, Mean: 2.96, SD: 2.32	12 weeks	N: 137, Mean: NR, SD: NR	Mean change from baseline: 0.12, SD: 2.53, p: 0.009	NR
Vinik, 2014[23]	Arm 1 - placebo	NPSI, burning pain: 0-10 scale	N: 152, Mean: 3.11, SD: 2.35	12 weeks	N: 124, Mean: NR, SD: NR	Mean change from baseline: 1.27, SD: 3.07, p: NR	NR
Vinik, 2014[23]	Arm 2 - Tapentadol ER	NPSI, burning pain: 0-10 scale	N: 166, Mean: 3.09, SD: 2.55	12 weeks	N: 137, Mean: NR, SD: NR	Mean change from baseline: 0.26, SD: 2.86, p: 0.005	NR
Vinik, 2014[23]	Arm 1 - placebo	NPSI, Evoked pain: 0-10 scale	N: 152, Mean: 2.43, SD: 2.18	12 weeks	N: 124, Mean: NR, SD: NR	Mean change from baseline: 0.78, SD: 2.64, p: NR	NR
Vinik, 2014[23]	Arm 2 - Tapentadol ER	NPSI, Evoked pain: 0-10 scale	N: 166, Mean: 2.39, SD: 2.23	12 weeks	N: 137, Mean: NR, SD: NR	Mean change from baseline: 0.16, SD: 2.15, p: 0.015	NR
Vinik, 2014[23]	Arm 1 - placebo	NPSI, pressing pain: 0-10 scale	N: 152, Mean: 2.44, SD: 2.22	12 weeks	N: 124, Mean: NR, SD: NR	Mean change from baseline: 1.03, SD: 2.97, p: NR	NR

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Vinik, 2014[23]	Arm 2 - Tapentadol ER	NPSI, pressing pain: 0-10 scale	N: 166, Mean: 2.5, SD: 2.2	12 weeks	N: 137, Mean: NR, SD: NR	Mean change from baseline: 0.15, SD: 2.29, p: 0.01	NR
Vinik, 2014[23]	Arm 1 - placebo	NPSI, total score-NR scale	N: 152, Mean: 28.35, SD: 19.98	12 weeks	N: 124, Mean: NR, SD: NR	Mean change from baseline: 10.1, SD: 24.38, p: NR	NR
Vinik, 2014[23]	Arm 2 - Tapentadol ER	NPSI, total score-NR scale	N: 166, Mean: 28.82, SD: 18.94	12 weeks	N: 137, Mean: NR, SD: NR	Mean change from baseline: 1.26, SD: 19.8, p: <0.001	NR
Vinik, 2014[23]	Arm 1 - placebo	NRS: 0-10 scale	N: 152, Mean: 3.53, SD: 2.17	12 weeks	N: 152, Mean: NR, SD: NR	Mean change from baseline: 1.3, SD: 2.43, p: NR	
Vinik, 2014[23]	Arm 2 - Tapentadol ER	NRS: 0-10 scale	N: 166, Mean: 3.7, SD: 1.78	12 weeks	N: 166, Mean: NR, SD: NR	Mean change from baseline: -0.95 (95% CI:-1.42, -0.49), SD: NR, p: <0.001	

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Yuan, 2009[24]	Arm 1 - placebo	VAS	N: 20, Mean: 5.97, SD: 1.51	12 weeks	N: 18, Mean: NR, SD: NR	Mean change from baseline: -0.53, SD: 1.57, p: NR	P:0.024
Yuan, 2009[24]	Arm 2 – Botulinum toxin	VAS	N: 20, Mean: 6.42, SD: 1.11	12 weeks	N: 18, Mean: NR, SD: NR	Mean change from baseline: -2.53, SD: 2.48, p: NR	P:0.024
Ziegler, 2015[25]	Arm 1 - placebo	NRS, mean average pain in 24 hours: 0-10 scale	N: 62, Mean: 6.6, SD: 1.27	6 weeks	N: 57, Mean: 4.34, SD: 2.35	Mean change from baseline: -2.36, SD: NR, p: NR	Mean difference from baseline NR Comparator arm: Placebo, p: NA
Ziegler, 2015[25]	Arm 2 - Pregabalin	NRS, mean average pain in 24 hours: 0-10 scale	N: 70, Mean: 6.6, SD: 1.26	6 weeks	N: 65, Mean: 4.51, SD: 2.17	Mean change from baseline: -2.19, SD: NR, p: NR	Mean difference from baseline NR Comparator arm: Placebo, p: 0.68

BPI = Brief Pain Inventory; CI = Confidence Interval; LOCF = Last Observation Carried Forward; Mg = Milligram; N = Number; NA = Not Applicable; NPRS = Numeric Pain Rating Scale ; NPS = Neuropathy Pain Scale; NPSI = Neuropathic Pain Symptoms Inventory; NR = Not Reported; NRS = New Risk Score; NRS = Numeric Rating Scale; PI-NRS = Pain Intensity Numerical Rating Scale; SD = Standard Deviation; SF-MPQ = Short-Form McGill Pain Questionnaire; VAS = Visual Analog Scale ;

Evidence Table D-47. Pain categorical outcomes for pharmacological treatments (KQ2a)

Author, year	Arm	N for analysis	Instrument name	Time point	n (%) of PATIENTS with outcomes	Between arm comparison
Allen, 2014[1]	Arm 1 - placebo	89	>50% reduction-% of patients scale	13 week	(26)	NA
Allen, 2014[1]	Arm 2 - Desvenlafaxine 50mg	63	>50% reduction-% of patients scale	13 week	(35)	NR Comparator arm: Placebo, p: NS
Allen, 2014[1]	Arm 3 - Desvenlafaxine 100mg	86	>50% reduction-% of patients scale	13 week	(37)	NR Comparator arm: Placebo, p: NS
Allen, 2014[1]	Arm 4 - Desvenlafaxine 200mg	99	>50% reduction-% of patients scale	13 week	(36)	NR Comparator arm: Placebo, p: NS
Allen, 2014[1]	Arm 5 - Desvenlafaxine 400mg	68	>50% reduction-% of patients scale	13 week	(32)	NR Comparator arm: Placebo, p: NS
Arezzo, 2008[2]	Arm 1 - placebo	NR	>50% pain reduction-% scale	13 weeks	(49)	NA
Arezzo, 2008[2]	Arm 2 - Pregabalin	NR	>50% pain reduction-% scale	13 weeks	(23)	P <0.001

Author, year	Arm	N for analysis	Instrument name	Time point	n (%) of PATIENTS with outcomes	Between arm comparison
Atli, 2005[3]	Arm 1 - placebo	12	>50% pain reduction-% scale	12 weeks	0(0)	NR
Atli, 2005[3]	Arm 2 - Zonisamide	11	>50% pain reduction-% scale	12 weeks	3(27)	NR
Chad, 1990[5]	Arm 1 – Control - Vehicle	22	≥20% improvement for pain severity	4 weeks	(46)	P=NS
Chad, 1990[5]	Arm 2 - Capsaicin	24	≥20% improvement for pain severity	4 weeks	(71)	P=NS
Chad, 1990[5]	Arm 1 – Control - Vehicle	22	≥20% improvement for pain relief	4 weeks	(41)	NR
Chad, 1990[5]	Arm 2 - Capsaicin	24	≥20% improvement for pain relief	4 weeks	(71)	P<0.05

Author, year	Arm	N for analysis	Instrument name	Time point	n (%) of PATIENTS with outcomes	Between arm comparison
Freeman, 2007[6]	Arm 1 - placebo	32	Categorical Pain Score-0-4 scale	18 weeks	NR	NR
Freeman, 2007[6]	Arm 2 - Topiramate	35	Categorical Pain Score-0-4 scale	18 weeks	NR	NR
Gao, 2015[7]	Arm 1 - placebo	NR	>30% reduction in 24h average pain-% of patients scale	12 week	(49)	NR
Gao, 2015[7]	Arm 2 - Duloxetine	NR	>30% reduction in 24h average pain-% of patients scale	12 week	(61.5)	% difference from baseline: NR (95% CI:NR), SD: NR, Comparator arm: Placebo, p: 0.014
Ghasemi, 2014[8]	Arm 1 - placebo	20	No Pain after Intervention-% of patients scale	3 week	0(0)	NA
Ghasemi, 2014[8]	Arm 2 - Boutlinum	20	No Pain after Intervention-% of patients scale	3 week	6(30)	NR Comparator arm: Placebo, p: 0.01

Author, year	Arm	N for analysis	Instrument name	Time point	n (%) of PATIENTS with outcomes	Between arm comparison
Kulkantrakorn, 2013[13]	Arm 1 - Control-Placebo	17	>50% pain relief	8 weeks	9	NR
Kulkantrakorn, 2013[13]	Arm 2 - Capsaicin	16	>50% pain relief	8 weeks	6	NR
Kulkantrakorn, 2013[13]	Arm 1 - Control-Placebo	17	>30% pain relief	8 weeks	10	NR
Kulkantrakorn, 2013[13]	Arm 2 - Capsaicin	16	>30% pain relief	8 weeks	9	NR
Shaibani, 2012[20]	Arm 1 - placebo	89	>50% pain relief	13 weeks	(39)	NR
Shaibani, 2012[20]	Arm 2 – Dextromethorphan/Quinidine (45/30)	79	>50% pain relief	13 weeks	(66)	p=0.001 compared to placebo

Author, year	Arm	N for analysis	Instrument name	Time point	n (%) of PATIENTS with outcomes	Between arm comparison
Shaibani, 2012[20]	Arm 3 - Dextromethorphan/Quinidine (30/30)	74	>50% pain relief	13 weeks	(54)	p=0.06 compared to placebo
Shaibani, 2012[20]	Arm 1 - placebo	89	>30% pain relief	13 weeks	(61)	NR
Shaibani, 2012[20]	Arm 2 – Dextromethorphan/Quinidine (45/30)	79	>30% pain relief	13 weeks	(83)	p=0.002 compared to placebo
Shaibani, 2012[20]	Arm 3 - Dextromethorphan/Quinidine (30/30)	74	>30% pain relief	13 weeks	(75)	p=0.054 compared to placebo
Sandercock, 2012[18]	Arm 1 - Control-Placebo	49	>50% reduction-% of patients scale	4 week	(7.8)	NA
Sandercock, 2012[18]	Arm 2 - Gabapentin single dose, 3000mg	43	>50% reduction-% of patients scale	4 week	(34.8)	NR Comparator arm: Placebo, p: 0.001
Sandercock, 2012[18]	Arm 3 – Gabapentin asymmetric dose, 3000mg	46	>50% reduction-% of patients scale	4 week	(26.0)	NR Comparator arm: Placebo, p: 0.015

Author, year	Arm	N for analysis	Instrument name	Time point	n (%) of PATIENTS with outcomes	Between arm comparison
Tesfaye, 2013[21]	Arm 1 – control - Duloxetine 60mg, then Duloxetine 120mg	67	Brief Pain Inventory Modified Short Form (BPI-MSF), ≥2 point reduction in 24-hour average pain: 0-10 scale	18 weeks	39(58.2)	NR
Tesfaye, 2013[21]	Arm 2 - Duloxetine 60mg, then combination therapy	74	Brief Pain Inventory Modified Short Form (BPI-MSF), ≥2 point reduction in 24-hour average pain: 0-10 scale	18 weeks	48(64.9)	NR
Tesfaye, 2013[21]	Arm 3 - Pregablin 300mg, then combination therapy	91	Brief Pain Inventory Modified Short Form (BPI-MSF), ≥2 point reduction in 24-hour average pain: 0-10 scale	18 weeks	62(68.1)	NR
Tesfaye, 2013[21]	Arm 4 - Pregablin 300mg, then Pregablin 600mg	96	Brief Pain Inventory Modified Short Form (BPI-MSF), ≥2 point reduction in 24-hour average pain: 0-10 scale	18 weeks	66(68.8)	NR
Toth, 2012[22]	Arm 1 - placebo	13	NRS, ≥50% pain reduction: 0-10 scale	5 weeks	1(8)	NR p: NS
Toth, 2012[22]	Arm 2 - Nabilone	13	NRS, ≥50% pain reduction: 0-10 scale	5 weeks	4(31)	NR p: NS

Author, year	Arm	N for analysis	Instrument name	Time point	n (%) of PATIENTS with outcomes	Between arm comparison
Vinik, 2014[23]	Arm 1 - placebo	152	≥30% pain reduction-% scale	12 weeks	69(45.4)	NA
Vinik, 2014[23]	Arm 2 - Tapentadol ER	166	≥30% pain reduction-% scale	12 weeks	92(55.4)	P= 0.032
Yuan, 2009[24]	Arm 1 - placebo	18	≥3 VAS pain reduction	12 weeks	0 (0)	P<0.005
Yuan, 2009[24]	Arm 2 – Botulinum toxin	18	≥3 VAS pain reduction	12 weeks	8 (44.4)	P<0.005
Ziegler, 2015[25]	Arm 1 - placebo	57	NRS, >30% improvement-% scale	6 weeks	28(49)	NA
Ziegler, 2015[25]	Arm 2 - Pregabalin	65	NRS, >30% improvement-% scale	6 weeks	25(38)	Mean change from baseline: NR (95% CI:NR), SD: NR, Comparator arm: Placebo, p: 0.151

Mg = Milligram; N = Number; NA = Not Applicable; NR = Not Reported; NRS = New Risk Score; VAS = Visual Analog Scale;

Evidence Table D-48. Paresthesias outcomes for pharmacological treatments (KQ2a)

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean SD:	Within arm comparison	Between arm comparison
Vinik, 2014[23]	Arm 1 - placebo	NPSI, Paresthesia/dysesthesia: 0-10 scale	N: 152, Mean: 3.64, SD: 2.69	12 weeks	N: 124, Mean: NR, SD: NR	Mean change from baseline: 1.29, SD: 2.95, p: NR	NR
Vinik, 2014[23]	Arm 2 - Tapentadol ER	NPSI, Paresthesia/dysesthesia: 0-10 scale	N: 166, Mean: 3.81, SD: 2.53	12 weeks	N: 137, Mean: NR, SD: NR	Mean change from baseline: -0.01, SD: 2.79, p: <0.001	NR

N = Number; NPSI = Neuropathic Pain Symptoms Inventory; NR = Not Reported; SD = Standard Deviation;

Evidence Table D-49. Quality of life outcomes for pharmacological treatments (KQ2a)

Author, year	Arm	Instrument	Baseline N, mean SD	Time point(s)	At time point(s), N mean SD	Within arm comparison	Between arm comparison
Allen, 2014[1]	Arm 1 - placebo	EQ-5D	N: 90, Mean: NR, SD: NR	13 weeks	N: 89, Mean: NR, SD: NR	Mean change from baseline: 0.09, SE: 0.02, SD: NR, p: NR	Mean difference from baseline: NR (95% CI:NR), SD: NR, Comparator arm: NA , p: NA
Allen, 2014[1]	Arm 2 - Desvenlafaxine 50mg	EQ-5D	N: 63, Mean: NR, SD: NR	13 weeks	N: 63, Mean: NR, SD: NR	NR	Mean difference from baseline: NR (95% CI:NR), SD: NR, Comparator arm: vs placebo, p: NS
Allen, 2014[1]	Arm 3 - Desvenlafaxine 100mg	EQ-5D	N: 87, Mean: NR, SD: NR	13 weeks	N: 86, Mean: NR, SD: NR	NR	Mean difference from baseline: Comparator arm: Placebo, p: NS
Allen, 2014[1]	Arm 4 - Desvenlafaxine 200mg	EQ-5D	N: 99, Mean: NR, SD: NR	13 weeks	N: 99, Mean: NR, SD: NR	Mean change from baseline: 0.15, SE: 0.02, SD: NR, p: NR	Mean difference from baseline: NR (95% CI:NR), SD: NR, Comparator arm: vs placebo, p: 0.024
Allen, 2014[1]	Arm 5 - Desvenlafaxine 400mg	EQ-5D	N: 69, Mean: NR, SD: NR	13 weeks	N: 68, Mean: NR, SD: NR	NR	Mean difference from baseline: NR (95% CI:NR), SD: NR, Comparator arm: vs placebo, p: NS
Allen, 2014[1]	Arm 1 - placebo	SF-36 Physical component summary score	N: 90, Mean: NR, SD: NR	13 weeks	N: 89, Mean: NR, SD: NR	Mean change from baseline: 3.5, SE: 0.77, SD: NR, p: NR	NA
Allen, 2014[1]	Arm 2 - Desvenlafaxine 50mg	SF-36 Physical component summary score	N: 63, Mean: NR, SD: NR	13 weeks	N: 63, Mean: NR, SD: NR	Mean change from baseline: 6.22, SE: 0.9, SD: NR, p: NR	Mean difference from baseline: NR (95% CI:NR), SD: NR, Comparator arm: vs placebo, p: 0.022
Allen, 2014[1]	Arm 3 - Desvenlafaxine 100mg	SF-36 Physical component summary score	N: 87, Mean: NR, SD: NR	13 weeks	N: 86, Mean: NR, SD: NR	NR	Mean difference from baseline: Comparator arm: Placebo, p: NS
Allen, 2014[1]	Arm 4 - Desvenlafaxine 200mg	SF-36 Physical component summary score	N: 99, Mean: NR, SD: NR	13 weeks	N: 99, Mean: NR, SD: NR	NR	Mean difference from baseline: NR (95% CI:NR), SD: NR, Comparator arm: vs placebo, p: NS
Allen, 2014[1]	Arm 5 - Desvenlafaxine 400mg	SF-36 Physical component summary score	N: 69, Mean: NR, SD: NR	13 weeks	N: 68, Mean: NR, SD: NR	NR	Mean difference from baseline: NR (95% CI:NR), SD: NR, Comparator arm: vs placebo, p: NS
Harati, 1998[10]	Arm 1 - placebo	SF-36 Bodily pain	N: NR, Mean: NR, SD: NR	42 days	N: NR, Mean: 41.9, SD: 2.9	NR	NA
Harati, 1998[10]	Arm 2 - Tramadol	SF-36 Bodily pain	N: NR, Mean: NR, SD: NR	42 days	N: NR, Mean: 54.8, SD: 2.6	NR	NR: NR (95% CI:NR), SD: NR, Comparator arm: placebo, p: <0.001

Author, year	Arm	Instrument	Baseline N, mean SD	Time point(s)	At time point(s), N mean SD	Within arm comparison	Between arm comparison
Harati, 1998[10]	Arm 1 - placebo	SF-36 Physical functioning	N: NR, Mean: NR, SD: NR	42 days	N: NR, Mean: 55.1, SD: 4	NR	NA
Harati, 1998[10]	Arm 2 - Tramadol	SF-36 Physical functioning	N: NR, Mean: NR, SD: NR	42 days	N: NR, Mean: 64.3, SD: 3.8	NR	NR: NR (95% CI:NR), SD: NR, Comparator arm: placebo, p: 0.02
Harati, 1998[10]	Arm 1 - placebo	SF-36 Role-physical	N :NR, Mean: NR, SD: NR	42 days	N: NR, Mean: NR, SD: NR	NR	NA
Harati, 1998[10]	Arm 2 - Tramadol	SF-36 Role-physical	N: NR, Mean: NR, SD: NR	42 days	N: NR, Mean: NR, SD: NR	NR	NR: NR (95% CI:NR), SD: NR, Comparator arm: placebo, p: NS
Raskin, 2014[15]	Overall	Quality of life -DN- -4-136 scale	N: 665, Mean: 42.6, SD: 22.2	6 weeks	NA	NA	NR
Raskin, 2014[15]	Arm 1 - Control-Placebo	Quality of life -DN- -4-136 scale	NR	19 weeks	N: 147, Mean: NR, SD: NR	Mean change from baseline: -14.4, SD: 20.4	P<0.05
Raskin, 2014[15]	Arm 2 – Pregabalin	Quality of life -DN- -4-136 scale	NR	19 weeks	N: 147, Mean: NR, SD: NR	Mean change from baseline: -20.6, SD: 21.4	P<0.05
Rauck, 2013[16]	Arm 1 - placebo	SF-36 mental component	N: 120, Mean: NR, SD: NR	16 weeks	N: 120, Mean: NR, SD: NR	NR	NA
Rauck, 2013[16]	Arm 2 - Gabapentin enacarbil, 1200mg	SF-36 mental component	N: 62, Mean: NR, SD: NR	16 weeks	N: 62, Mean: NR, SD: NR	NR	Mean difference from baseline: -2.1 (95% CI:-5.09, 0.90), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 3 - Gabapentin enacarbil, 2400mg	SF-36 mental component	N: 56, Mean: NR, SD: NR	16 weeks	N: 56, Mean: NR, SD: NR	NR	Mean difference from baseline: -1 (95% CI:-4.24, 2.30), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 4 - Gabapentin enacarbil, 3600mg	SF-36 mental component	N: 116, Mean: NR, SD: NR	16 weeks	N: 116, Mean: NR, SD: NR	NR	Mean difference from baseline: -0.8 (95% CI:-3.34, 1.64), SD: NR, Comparator arm: Placebo, p: NR

Author, year	Arm	Instrument	Baseline N, mean SD	Time point(s)	At time point(s), N mean SD	Within arm comparison	Between arm comparison
Rauck, 2013[16]	Arm 5 - Pregabalin, 300mg	SF-36 mental component	N: 66, Mean: NR, SD: NR	16 weeks	N: 66, Mean: NR, SD: NR	NR	Mean difference from baseline: -1.8 (95% CI:-4.68, 1.17), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 1 - placebo	SF-36 physical component	N: 120, Mean: NR, SD: NR	16 weeks	N: 120, Mean: NR, SD: NR	NR	NA
Rauck, 2013[16]	Arm 2 - Gabapentin enacarbil, 1200mg	SF-36 physical component	N: 62, Mean: NR, SD: NR	16 weeks	N: 62, Mean: NR, SD: NR	NR	Mean difference from baseline: 0.3 (95% CI:-1.92, 2.62), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 3 - Gabapentin enacarbil, 2400mg	SF-36 physical component	N: 56, Mean: NR, SD: NR	16 weeks	N: 56, Mean: NR, SD: NR	NR	Mean difference from baseline: 0.6 (95% CI:-1.88, 3.06), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 4 - Gabapentin enacarbil, 3600mg	SF-36 physical component	N: 116, Mean: NR, SD: NR	16 weeks	N: 116, Mean: NR, SD: NR	NR	Mean difference from baseline: 1.4 (95% CI:-0.46, 3.31), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 5 - Pregabalin, 300mg	SF-36 physical component	N: 66, Mean: NR, SD: NR	16 weeks	N: 66, Mean: NR, SD: NR	NR	Mean difference from baseline: 0.6 (95% CI:-1.60, 2.83), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 1 - placebo	SF-MPQ affective	N: 120, Mean: NR, SD: NR	16 weeks	N: 120, Mean: NR, SD: NR	NR	NA
Rauck, 2013[16]	Arm 2 - Gabapentin enacarbil, 1200mg	SF-MPQ affective	N: 62, Mean: NR, SD: NR	16 weeks	N: 62, Mean: NR, SD: NR	NR	Mean difference from baseline: -0.02 (95% CI:-0.86, 0.82), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 3 - Gabapentin enacarbil, 2400mg	SF-MPQ affective	N: 56, Mean: NR, SD: NR	16 weeks	N: 56, Mean: NR, SD: NR	NR	Mean difference from baseline: 0.19 (95% CI:-0.73, 1.10), SD: NR, Comparator arm: Placebo, p: NR

Author, year	Arm	Instrument	Baseline N, mean SD	Time point(s)	At time point(s), N mean SD	Within arm comparison	Between arm comparison
Rauck, 2013[16]	Arm 4 - Gabapentin enacarbil, 3600mg	SF-MPQ affective	N: 116, Mean: NR, SD: NR	16 weeks	N: 116, Mean: NR, SD: NR	NR	Mean difference from baseline: -0.44 (95% CI:-1.14, 0.26), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 5 - Pregabalin, 300mg	SF-MPQ affective	N: 66, Mean: NR, SD: NR	16 weeks	N: 66, Mean: NR, SD: NR	NR	Mean difference from baseline: 0.37 (95% CI:-0.44, 1.18), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 1 - placebo	SF-MPQ sensory	N: 120, Mean: NR, SD: NR	16 weeks	N: 120, Mean: NR, SD: NR	NR	NA
Rauck, 2013[16]	Arm 2 - Gabapentin enacarbil, 1200mg	SF-MPQ sensory	N: 62, Mean: NR, SD: NR	16 weeks	N: 62, Mean: NR, SD: NR	NR	Mean difference from baseline: -0.58 (95% CI:-2.88, 1.71), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 3 - Gabapentin enacarbil, 2400mg	SF-MPQ sensory	N: 56, Mean: NR, SD: NR	16 weeks	N: 56, Mean: NR, SD: NR	NR	Mean difference from baseline: -1.06 (95% CI:-3.56, 1.43), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 4 - Gabapentin enacarbil, 3600mg	SF-MPQ sensory	N: 116, Mean: NR, SD: NR	16 weeks	N: 116, Mean: NR, SD: NR	NR	Mean difference from baseline: -1.25 (95% CI:-3.15, 0.65), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 5 - Pregabalin, 300mg	SF-MPQ sensory	N: 66, Mean: NR, SD: NR	16 weeks	N: 66, Mean: NR, SD: NR	NR	Mean difference from baseline: 1.52 (95% CI:-0.70, 3.74), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 1 - placebo	SF-MPQ Total	N: 120, Mean: NR, SD: NR	16 weeks	N: 120, Mean: NR, SD: NR	NR	NA
Rauck, 2013[16]	Arm 2 - Gabapentin enacarbil, 1200mg	SF-MPQ Total	N: 62, Mean: NR, SD: NR	16 weeks	N: 62, Mean: NR, SD: NR	NR	Mean difference from baseline: -0.7 (95% CI:-3.64, 2.24), SD: NR, Comparator arm: Placebo, p: NR

Author, year	Arm	Instrument	Baseline N, mean SD	Time point(s)	At time point(s), N mean SD	Within arm comparison	Between arm comparison
Rauck, 2013[16]	Arm 3 - Gabapentin enacarbil, 2400mg	SF-MPQ Total	N: 56, Mean: NR, SD: NR	16 weeks	N: 56, Mean: NR, SD: NR	NR	Mean difference from baseline: -0.9 (95% CI:-4.10, 2.29), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 4 - Gabapentin enacarbil, 3600mg	SF-MPQ Total	N: 116, Mean: NR, SD: NR	16 weeks	N: 116, Mean: NR, SD: NR	NR	Mean difference from baseline: -1.71 (95% CI:-4.14, 0.73), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[16]	Arm 5 - Pregabalin, 300mg	SF-MPQ Total	N: 66, Mean: NR, SD: NR	16 weeks	N: 66, Mean: NR, SD: NR	NR	Mean difference from baseline: 1.84 (95% CI:-1.00, 4.69), SD: NR, Comparator arm: Placebo, p: NR
Rowbotham, 2012[17]	Arm 1 - Control-Placebo	SF-36 Physical component	N: 49, Mean: 33.2, SD: 6.9	8 weeks	N: 49, Mean: NR, SD: NR	Least squares mean difference from baseline: 3.8 SE: 0.9, p: NR	NR
Rowbotham, 2012[17]	Arm 2 – Duloxetine	SF-36 Physical component	N: 55, Mean: 35.2, SD: 7.4	8 weeks	N: 55, Mean: NR, SD: NR	Least squares mean difference from baseline: 6.8, SE: 0.8, p: 0.05	NR
Rowbotham, 2012[17]	Arm 1 - Control-Placebo	SF-36 Mental component	N: 49, Mean: NR, SD: NR	8 weeks	N: 49, Mean: NR, SD: NR	Mean difference from baseline: 2.8, SD: 1.2, p: NR	NR
Rowbotham, 2012[17]	Arm 2 – Duloxetine	SF-36 Mental component	N: 55, Mean: NR, SD: NR	8 weeks	N: 55, Mean: NR, SD: NR	Mean difference from baseline: 2.3, SD: 1.2, p: NS	NR
Rowbotham, 2012[17]	Arm 1 - Control-Placebo	EQ-5D	N: 49, Mean: 0.66, SD: 0.16	8 weeks	N: 49, Mean: NR, SD: NR	Least squares mean difference from baseline: 0.07, SE: 0.02, p: NR	NR
Rowbotham, 2012[17]	Arm 2 – Duloxetine	EQ-5D	N: 55, Mean: 0.67, SD: 0.16	8 weeks	N: 55, Mean: NR, SD: NR	Least squares mean difference from baseline: 0.07, SE: 0.02, p: NS	NR
Toth, 2012[22]	Arm 1 - placebo	EQ-5D index score	N: 13, Mean: 0.58, SD: 0.2	4 weeks	N: 13, Mean: 0.6, SD: 0.08	Mean change from baseline: NR, SE: NR, SD: NR, p: NS	Mean difference from baseline: Comparator (95% CI:NR), SD: NR, Comparator arm: Placebo, p: <0.05
Toth, 2012[22]	Arm 2 - Nabilone	EQ-5D index score	N: 13, Mean: 0.58, SD: 0.2	4 weeks	N: 13, Mean: 0.74, SD: 0.03	Mean change from baseline: NR, SE: NR, SD: NR, p: NS	Mean difference from baseline: NR (95% CI:NR), SD: NR, Comparator arm: Placebo, p: <0.05

Author, year	Arm	Instrument	Baseline N, mean SD	Time point(s)	At time point(s), N mean SD	Within arm comparison	Between arm comparison
Toth, 2012[22]	Arm 1 - placebo	EQ-5D utility score	N: 13, Mean: 58.4, SD: 16.7	4 weeks	N: 13, Mean: 61.4, SD: 6.7	Mean change from baseline: NR, SE: NR, SD: NR, p: NS	Mean difference from baseline:, Comparator arm: Placebo, p: NS
Toth, 2012[22]	Arm 2 - Nabilone	EQ-5D utility score	N: 13, Mean: 55.8, SD: 17.2	4 weeks	N: 13, Mean: 72.6, SD: 4.7	Mean change from baseline: NR, SE: NR, SD: NR, p: NS	Mean difference from baseline: Comparator arm: Placebo, p: NS
Vinik, 2014[23]	Arm 1 - placebo	EQ-5D health status index	N: 152, Mean: 0.71, SD: 0.16	12 weeks	N: 152, Mean: NR, SD: NR	Mean change from baseline: -0.1, SD: 0.26, p: NR	Mean difference from baseline: Comparator (95% CI:NA), p: NA
Vinik, 2014[23]	Arm 2 - Tapentadol ER	EQ-5D health status index	N: 166, Mean: 0.7, SD: 0.14	12 weeks	N: 166, Mean: NR, SD: NR	Mean change from baseline: 0, SD: 0.2, p: NR	Mean difference from baseline: 0.1 (95% CI:0.05, 0.16), p: <0.001
Vinik, 2014[23]	Arm 1 - placebo	SF-36, Bodily pain	N: 152, Mean: 44.2, SD: 7.34	12 weeks	N: 131, Mean: NR, SD: NR	Mean change from baseline: -3.9, SD: 8.8, p: NR	Mean difference from baseline: Comparator (95% CI:NA), p: NA
Vinik, 2014[23]	Arm 2 - Tapentadol ER	SF-36, Bodily pain	N: 166, Mean: 42.4, SD: 7.03	12 weeks	N: 146, Mean: NR, SD: NR	Mean change from baseline: 0, SD: 7.55, p: NR	Mean difference from baseline: 3 (95% CI:1.24, 4.69), p: <0.001
Vinik, 2014[23]	Arm 1 - placebo	SF-36, physical component	N: 152, Mean: 40.1, SD: 8.87	12 weeks	N: 131, Mean: NR, SD: NR	Mean change from baseline: -2.3, SD: 6.4, p: NR	Mean difference from baseline: Comparator (95% CI:NA), p: NA
Vinik, 2014[23]	Arm 2 - Tapentadol ER	SF-36, physical component	N: 166, Mean: 39.1, SD: 8.52	12 weeks	N: 146, Mean: NR, SD: NR	Mean change from baseline: 0.1, SD: 6.52, p: NR	Mean difference from baseline: 2.1 (95% CI:0.67, 3.57), p: 0.004
Vinik, 2014[23]	Arm 1 - placebo	SF-36, physical functioning	N: 152, Mean: 38.2, SD: 11.35	12 weeks	N: 131, Mean: NR, SD: NR	Mean change from baseline: -1.7, SD: 7.44, p: NR	Mean difference from baseline: Comparator (95% CI:NA), p: NA
Vinik, 2014[23]	Arm 2 - Tapentadol ER	SF-36, physical functioning	N: 166, Mean: 37.3, SD: 10.49	12 weeks	N: 146, Mean: NR, SD: NR	Mean change from baseline: 0.1, SD: 7.5, p: NR	Mean difference from baseline: 1.5 (95% CI:-0.21, 3.23), p: 0.085
Vinik, 2014[23]	Arm 1 - placebo	SF-36, role-physical	N: 152, Mean: 41.9, SD: 10.33	12 weeks	N: 131, Mean: NR, SD: NR	Mean change from baseline: -2.1, SD: 7.14, p: NR	Mean difference from baseline: Comparator (95% CI:NA), p: NA
Vinik, 2014[23]	Arm 2 - Tapentadol ER	SF-36, role-physical	N: 166, Mean: 41.7, SD: 9.89	12 weeks	N: 146, Mean: NR, SD: NR	Mean change from baseline: 0.8, SD: 8.12, p: NR	Mean difference from baseline: 2.6 (95% CI:0.85, 4.29), p: 0.004

Author, year	Arm	Instrument	Baseline N, mean SD	Time point(s)	At time point(s), N mean SD	Within arm comparison	Between arm comparison
Yuan, 2009[24]	Arm 1 - placebo	SF-36, physical component score	N:20, Mean: 33.8, SD: 4.17	12 weeks	N:18, Mean: 39.8, SD: 18.3	Mean change from baseline: -1.06, SD: 7.83, p: NR	P:0.072
Yuan, 2009[24]	Arm 2 – Botulinum toxin	SF-36, physical component score	N:20, Mean: 39.05, SD: 18.1	12 weeks	N:18, Mean: 42.2, SD: 16.1	Mean change from baseline: -0.35, SD: 4.2, p: NR	P:0.072
Yuan, 2009[24]	Arm 1 - placebo	SF-36, mental component score	N:20, Mean: 64.4, SD: 17.4	12 weeks	N:18, Mean: 60.6, SD: 19.5	Mean change from baseline:-0.93, SD: 1.91, p: NR	P:0.072
Yuan, 2009[24]	Arm 2 – Botulinum toxin	SF-36, mental component score	N:20, Mean: 60.9, SD: 20.4	12 weeks	N:18, Mean: 64.1, SD: 23.5	Mean change from baseline: 0.37, SD: 6.19, p: NR	P:0.072
Ziegler, 2015[25]	Arm 1 - placebo	EQ-5D-5L, weighted index score	N: 57, Mean: 0.7, SD: 0.14	6 weeks	N: 57, Mean: NR, SD: NR	Mean change from baseline: 0.07, SE: 0.02, SD: NR, p: NR	NA
Ziegler, 2015[25]	Arm 2 - Pregabalin	EQ-5D-5L, weighted index score	N: 65, Mean: 0.6, SD: 0.15	6 weeks	N: 65, Mean: NR, SD: NR	Mean change from baseline: 0.07, SE: 0.02, SD: NR, p: NR	Mean difference from baseline: Comparator arm: Placebo, p: NS
Ziegler, 2015[25]	Arm 1 - placebo	Neuropathic Pain Impact on Quality of-Life Questionnaire (NePIQoL)	N: 57, Mean: 127.3, SD: 28.74	6 weeks	N: 57, Mean: NR, SD: NR	Mean change from baseline: -2.97, SE: 0.69, SD: NR, p: NR	NA
Ziegler, 2015[25]	Arm 2 - Pregabalin	Neuropathic Pain Impact on Quality of-Life Questionnaire (NePIQoL)	N: 65, Mean: 128.8, SD: 23.7	6 weeks	N: 65, Mean: NR, SD: NR	Mean change from baseline: -2.84, SE: 0.65, SD: NR, p: NR	Mean difference from baseline: Comparator arm: Placebo, p: NS

CI = Confidence Interval; EQ-5D = the EuroQol EQ-5D instrument ; Mg = Milligram; N = Number; NA = Not Applicable; NePIQoL = Neuropathic Pain Impact on Quality of-Life Questionnaire; NR = Not Reported; NS = Not Significant; QOL-DN = the Quality of Life for Diabetic Neuropathy; SD = Standard Deviation; SF-36 = the 36-Item Short Form Health Survey; SF-MPQ = Short-Form McGill Pain Questionnaire;

Evidence Table D-50. Harms for pharmacological treatments (KQ2a)

Author, year	Select arm	Adverse effect	Patients with outcomes, n	Patients with outcomes, %	Comments
Allen, 2014[1]	Arm 1 - placebo	Dizziness	7	7.8	
Allen, 2014[1]	Arm 2 - Desvenlafaxine 50mg	Dizziness	1	1.6	
Allen, 2014[1]	Arm 3 - Desvenlafaxine 100mg	Dizziness	7	8	
Allen, 2014[1]	Arm 4 - Desvenlafaxine 200mg	Dizziness	18	18.2	
Allen, 2014[1]	Arm 5 - Desvenlafaxine 400mg	Dizziness	18	26.1	
Allen, 2014[1]	Arm 6 - Desvenlafaxine Open Label	Dizziness	NR	12.2	
Allen, 2014[1]	Arm 1 - placebo	Dry mouth	2	2.2	
Allen, 2014[1]	Arm 2 - Desvenlafaxine 50mg	Dry mouth	2	3.2	
Allen, 2014[1]	Arm 3 - Desvenlafaxine 100mg	Dry mouth	4	4.6	
Allen, 2014[1]	Arm 4 - Desvenlafaxine 200mg	Dry mouth	6	6.1	
Allen, 2014[1]	Arm 5 - Desvenlafaxine 400mg	Dry mouth	9	13	
Allen, 2014[1]	Arm 1 - placebo	Fatigue	4	4.4	
Allen, 2014[1]	Arm 2 - Desvenlafaxine 50mg	Fatigue	4	6.3	
Allen, 2014[1]	Arm 3 - Desvenlafaxine 100mg	Fatigue	6	6.9	
Allen, 2014[1]	Arm 4 - Desvenlafaxine 200mg	Fatigue	8	8.1	

Author, year	Select arm	Adverse effect	Patients with outcomes, n	Patients with outcomes, %	Comments
Allen, 2014[1]	Arm 5 - Desvenlafaxine 400mg	Fatigue	8	11.6	
Allen, 2014[1]	Arm 1 - placebo	Nausea	2	2.2	
Allen, 2014[1]	Arm 2 - Desvenlafaxine 50mg	Nausea	9	14.3	
Allen, 2014[1]	Arm 3 - Desvenlafaxine 100mg	Nausea	11	12.6	
Allen, 2014[1]	Arm 4 - Desvenlafaxine 200mg	Nausea	27	27.3	
Allen, 2014[1]	Arm 5 - Desvenlafaxine 400mg	Nausea	12	17.4	
Allen, 2014[1]	Arm 1 - placebo	Overall	68	75.6	
Allen, 2014[1]	Arm 2 - Desvenlafaxine 50mg	Overall	47	74.6	
Allen, 2014[1]	Arm 3 - Desvenlafaxine 100mg	Overall	65	74.7	
Allen, 2014[1]	Arm 4 - Desvenlafaxine 200mg	Overall	82	82.8	
Allen, 2014[1]	Arm 5 - Desvenlafaxine 400mg	Overall	63	91.3	
Allen, 2014[1]	Arm 6 - Desvenlafaxine Open Label	Overall	NR	80.2	
Allen, 2014[1]	Arm 1 - placebo	Vomiting	2	2.2	
Allen, 2014[1]	Arm 2 - Desvenlafaxine 50mg	Vomiting	3	4.8	
Allen, 2014[1]	Arm 3 - Desvenlafaxine 100mg	Vomiting	3	3.4	

Author, year	Select arm	Adverse effect	Patients with outcomes, n	Patients with outcomes, %	Comments
Allen, 2014[1]	Arm 4 - Desvenlafaxine 200mg	Vomiting	10	10.1	
Allen, 2014[1]	Arm 5 - Desvenlafaxine 400mg	Vomiting	2	2.9	
Arezzo, 2008, 2014	Arm 1 - placebo	Any AE	NR	78	
Arezzo, 2008, 2014	Arm 2 - Pregabalin	Any AE	NR	84	
Arezzo, 2008, 2014	Arm 1 - placebo	Dizziness	5	5.9	
Arezzo, 2008, 2014	Arm 2 - Pregabalin	Dizziness	27	32.9	
Arezzo, 2008, 2014	Arm 1 - placebo	Peripheral edema	27	31.8	
Arezzo, 2008, 2014	Arm 2 - Pregabalin	Peripheral edema	30	36.6	
Arezzo, 2008, 2014	Arm 1 - placebo	Somnolence	5	5.9	
Arezzo, 2008, 2014	Arm 2 - Pregabalin	Somnolence	11	13.4	
Arezzo, 2008, 2014	Arm 1 - placebo	Weight gain	1	1.2	
Arezzo, 2008, 2014	Arm 2 - Pregabalin	Weight gain	12	14.6	
Atli, 2005[3]	Arm 1 - placebo	Any AE	10	83.3	
Atli, 2005[3]	Arm 2 - Zonisamide	Any AE	11	91.7	
Atli, 2005[3]	Arm 1 - placebo	Cardiovascular	1	8.3	

Author, year	Select arm	Adverse effect	Patients with outcomes, n	Patients with outcomes, %	Comments
Atli, 2005[3]	Arm 2 - Zonisamide	Cardiovascular	3	25	
Atli, 2005[3]	Arm 1 - placebo	Dermatological	3	25	
Atli, 2005[3]	Arm 2 - Zonisamide	Dermatological	4	33.3	
Atli, 2005[3]	Arm 1 - placebo	Dizziness	0	0	
Atli, 2005[3]	Arm 2 - Zonisamide	Dizziness	3	25	
Atli, 2005[3]	Arm 1 - placebo	Drowsiness	2	16.7	
Atli, 2005[3]	Arm 2 - Zonisamide	Drowsiness	2	16.7	
Atli, 2005[3]	Arm 1 - placebo	Gastrointestinal	NR	NR	
Atli, 2005[3]	Arm 2 - Zonisamide	Gastrointestinal	NR	NR	P: 0.04
Atli, 2005[3]	Arm 1 - placebo	Headache	3	25	
Atli, 2005[3]	Arm 2 - Zonisamide	Headache	2	16.7	
Atli, 2005[3]	Arm 1 - placebo	Musculoskeletal	3	25	
Atli, 2005[3]	Arm 2 - Zonisamide	Musculoskeletal	3	25	
Atli, 2005[3]	Arm 1 - placebo	Neurological	6	50	
Atli, 2005[3]	Arm 2 - Zonisamide	Neurological	8	66.7	

Author, year	Select arm	Adverse effect	Patients with outcomes, n	Patients with outcomes, %	Comments
Atli, 2005[3]	Arm 1 – CONTROL – placebo	Respiratory	3	25	
Atli, 2005[3]	Arm 2 - Zonisamide	Respiratory	4	33.3	
Atli, 2005[3]	Arm 1 - placebo	Restlessness/Insomnia	0	0	
Atli, 2005[3]	Arm 2 - Zonisamide	Restlessness/Insomnia	3	25	
Atli, 2005[3]	Arm 1 - placebo	Special senses	0	0	
Atli, 2005[3]	Arm 2 - Zonisamide	Special senses	2	16.7	
Atli, 2005[3]	Arm 1 - placebo	Urinary	0	0	
Atli, 2005[3]	Arm 2 - Zonisamide	Urinary	3	25	
Atli, 2005[3]	Arm 1 - placebo	Weight change	1	8.3	
Atli, 2005[3]	Arm 2 - Zonisamide	Weight change	3	25	
Campbell, 2012[4]	Arm 1 - placebo	Administration site	2	2.2	
Campbell, 2012[4]	Arm 2 - Clonidine	Administration site	1	1.1	
Campbell, 2012[4]	Arm 1 - placebo	Musculoskeletal	2	2.2	
Campbell, 2012[4]	Arm 2 - Clonidine	Musculoskeletal	0	0	
Campbell, 2012[4]	Arm 1 - placebo	Nervous system	2	2.2	

Author, year	Select arm	Adverse effect	Patients with outcomes, n	Patients with outcomes, %	Comments
Campbell, 2012[4]	Arm 2 - Clonidine	Nervous system	2	2.2	
Campbell, 2012[4]	Arm 1 - placebo	Psychiatric disorders	1	1.1	
Campbell, 2012[4]	Arm 2 - Clonidine	Psychiatric disorders	0	0	
Campbell, 2012[4]	Arm 1 - placebo	Respiratory disorders	0	0	
Campbell, 2012[4]	Arm 2 - Clonidine	Respiratory disorders	1	1.1	
Campbell, 2012[4]	Arm 1 - placebo	Skin disorders	5	5.6	
Campbell, 2012[4]	Arm 2 - Clonidine	Skin disorders	0	0	
Freeman, 2007[6]	Arm 1 - placebo	Abnormal vision	0	0	
Freeman, 2007[6]	Arm 2 - Topiramate	Abnormal vision	4	11	
Freeman, 2007[6]	Arm 1 - placebo	Anorexia	0	0	
Freeman, 2007[6]	Arm 2 - Topiramate	Anorexia	7	20	
Freeman, 2007[6]	Arm 1 - placebo	Back pain	2	6	
Freeman, 2007[6]	Arm 2 - Topiramate	Back pain	4	11	

Author, year	Select arm	Adverse effect	Patients with outcomes, n	Patients with outcomes, %	Comments
Freeman, 2007[6]	Arm 1 - placebo	Diarrhea	2	6	
Freeman, 2007[6]	Arm 2 - Topiramate	Diarrhea	4	11	
Freeman, 2007[6]	Arm 1 - placebo	Fatigue	2	6	
Freeman, 2007[6]	Arm 2 - Topiramate	Fatigue	4	11	
Freeman, 2007[6]	Arm 1 - placebo	Headache	7	22	
Freeman, 2007[6]	Arm 2 - Topiramate	Headache	5	14	
Freeman, 2007[6]	Arm 1 - placebo	Nausea	5	16	
Freeman, 2007[6]	Arm 2 - Topiramate	Nausea	4	11	
Freeman, 2007[6]	Arm 1 - placebo	Paresthesia	3	9	
Freeman, 2007[6]	Arm 2 - Topiramate	Paresthesia	7	20	
Freeman, 2007[6]	Arm 1 - placebo	Somnolence	0	0	
Freeman, 2007[6]	Arm 2 - Topiramate	Somnolence	4	11	
Freeman, 2007[6]	Arm 1 - placebo	Taste perversion	0	0	
Freeman, 2007[6]	Arm 2 - Topiramate	Taste perversion	5	14	

Author, year	Select arm	Adverse effect	Patients with outcomes, n	Patients with outcomes, %	Comments
Freeman, 2007[6]	Arm 1 - placebo	Upper respiratory tract infection	4	13	
Freeman, 2007[6]	Arm 2 - Topiramate	Upper respiratory tract infection	3	9	
Freeman, 2007[6]	Arm 1 - placebo	Vomiting	2	6	
Freeman, 2007[6]	Arm 2 - Topiramate	Vomiting	4	11	
Freeman, 2007[6]	Arm 1 - placebo	Weight decrease	2	6	
Freeman, 2007[6]	Arm 2 - Topiramate	Weight decrease	5	14	
Gao, 2015[7]	Arm 1 - placebo	Nausea	7	3.5	P: 0.01
Gao, 2015[7]	Arm 2 - Duloxetine	Nausea	21	10.4	
Gao, 2015[7]	Arm 1 - placebo	Pts with > 1 TEAE	72	35.6	
Gao, 2015[7]	Arm 2 - Duloxetine	Pts with > 1 TEAE	94	46.5	P: 0.034
Hanna, 2008[9]	Arm 1 – Control – Placebo + Gabapentin	Any AE	119	71	
Hanna, 2008[9]	Arm 2 – Oxycodon + Gabapentin	Any AE	147	88	
Hanna, 2008[9]	Arm 1 – Control – Placebo + Gabapentin	Gastrointestinal disorders	45	27	
Hanna, 2008[9]	Arm 2 – Oxycodon + Gabapentin	Gastrointestinal disorders	91	54	

Author, year	Select arm	Adverse effect	Patients with outcomes, n	Patients with outcomes, %	Comments
Hanna, 2008[9]	Arm 1 – Control – Placebo + Gabapentin	Fatigue	14	8	
Hanna, 2008[9]	Arm 2 – Oxycodon + Gabapentin	Fatigue	31	18	
Hanna, 2008[9]	Arm 1 – Control – Placebo + Gabapentin	Infections and infestations	30	18	
Hanna, 2008[9]	Arm 2 – Oxycodon + Gabapentin	Infections and infestations	60	30	
Hanna, 2008[9]	Arm 1 – Control – Placebo + Gabapentin	Injury, poisoning and procedural complications	16	10	
Hanna, 2008[9]	Arm 2 – Oxycodon + Gabapentin	Injury, poisoning and procedural complications	12	7	
Hanna, 2008[9]	Arm 1 – Control – Placebo + Gabapentin	Investigations	16	10	
Hanna, 2008[9]	Arm 2 – Oxycodon + Gabapentin	Investigations	17	10	
Hanna, 2008[9]	Arm 1 – Control – Placebo + Gabapentin	Musculoskeletal and connective tissue disorders	26	16	
Hanna, 2008[9]	Arm 2 – Oxycodon + Gabapentin	Musculoskeletal and connective tissue disorders	31	18	
Hanna, 2008[9]	Arm 1 – Control – Placebo + Gabapentin	Nervous system disorders	39	23	
Hanna, 2008[9]	Arm 2 – Oxycodon + Gabapentin	Nervous system disorders	81	48	
Hanna, 2008[9]	Arm 1 – Control – Placebo + Gabapentin	Psychiatric disorders	16	10	
Hanna, 2008[9]	Arm 2 – Oxycodon + Gabapentin	Psychiatric disorders	29	17	

Author, year	Select arm	Adverse effect	Patients with outcomes, n	Patients with outcomes, %	Comments
Hanna, 2008[9]	Arm 1 – Control – Placebo + Gabapentin	Skin and subcutaneous tissue disorders	19	11	
Hanna, 2008[9]	Arm 2 – Oxycodon + Gabapentin	Skin and subcutaneous tissue disorders	34	20	
Harati, 1998[10]	Arm 1 - placebo	Constipation	2	3	
Harati, 1998[10]	Arm 2 - Tramadol	Constipation	14	22	
Harati, 1998[10]	Arm 1 - placebo	Headache	3	5	
Harati, 1998[10]	Arm 2 - Tramadol	Headache	11	17	
Harati, 1998[10]	Arm 1 - placebo	Nausea	2	3	
Harati, 1998[10]	Arm 2 - Tramadol	Nausea	15	23	
Harati, 1998[10]	Arm 1 - placebo	Rhinitis	8	12	
Harati, 1998[10]	Arm 2 - Tramadol	Rhinitis	3	5	
Harati, 1998[10]	Arm 1 - placebo	Somnolence	4	6	
Harati, 1998[10]	Arm 2 - Tramadol	Somnolence	8	12	
Jiang, 2011[11]	Arm 1 - Control-Placebo	Dizziness	0	0	
Jiang, 2011[11]	Arm 2 - Pregabalin	Dizziness	2	10	

Author, year	Select arm	Adverse effect	Patients with outcomes, n	Patients with outcomes, %	Comments
Karmakar, 2014[12]	Overall	Complications present	3	16	Unspecified adverse events
Kulkantrakorn, 2013[13]	Arm 1 - Control-Placebo	Any skin reaction	0	0	
Kulkantrakorn, 2013[13]	Arm 2 - Capsaicin	Any skin reaction	5	14.7	
Kulkantrakorn, 2013[13]	Arm 1 - Control-Placebo	Hypertension	12	36.4	
Kulkantrakorn, 2013[13]	Arm 2 - Capsaicin	Hypertension	11	33.3	
Rauck, 2013[16]	Arm 1 - placebo	Any AE	79	66	
Rauck, 2013[16]	Arm 2 - Gabapentin enacarbil, 1200mg	Any AE	45	73	
Rauck, 2013[16]	Arm 3 - Gabapentin enacarbil, 2400mg	Any AE	38	68	

Author, year	Select arm	Adverse effect	Patients with outcomes, n	Patients with outcomes, %	Comments
Rauck, 2013[16]	Arm 4 - Gabapentin enacarbil, 3600mg	Any AE	86	74	
Rauck, 2013[16]	Arm 5 - Pregabalin, 300mg	Any AE	47	71	
Rauck, 2013[16]	Arm 1 - placebo	Dizziness	7	6	
Rauck, 2013[16]	Arm 2 - Gabapentin enacarbil, 1200mg	Dizziness	9	15	
Rauck, 2013[16]	Arm 3 - Gabapentin enacarbil, 2400mg	Dizziness	8	14	
Rauck, 2013[16]	Arm 4 - Gabapentin enacarbil, 3600mg	Dizziness	16	14	
Rauck, 2013[16]	Arm 5 - Pregabalin, 300mg	Dizziness	9	14	
Rauck, 2013[16]	Arm 1 - placebo	Nausea	9	8	
Rauck, 2013[16]	Arm 2 – Gabapentin enacarbil, 1200mg	Nausea	7	11	
Rauck, 2013[16]	Arm 3 - Gabapentin enacarbil, 2400mg	Nausea	4	7	
Rauck, 2013[16]	Arm 4 - Gabapentin enacarbil, 3600mg	Nausea	7	6	
Rauck, 2013[16]	Arm 5 - Pregabalin, 300mg	Nausea	3	5	
Rauck, 2013[16]	Arm 1 - placebo	Peripheral edema	5	4	
Rauck, 2013[16]	Arm 2 - Gabapentin enacarbil, 1200mg	Peripheral edema	2	3	

Author, year	Select arm	Adverse effect	Patients with outcomes, n	Patients with outcomes, %	Comments
Rauck, 2013[16]	Arm 3 - Gabapentin enacarbil, 2400mg	Peripheral edema	0	0	
Rauck, 2013[16]	Arm 4 - Gabapentin enacarbil, 3600mg	Peripheral edema	11	9	
Rauck, 2013[16]	Arm 5 - Pregabalin, 300mg	Peripheral edema	11	17	
Rauck, 2013[16]	Arm 1 - placebo	Somnolence	5	4	
Rauck, 2013[16]	Arm 2 - Gabapentin enacarbil, 1200mg	Somnolence	2	3	
Rauck, 2013[16]	Arm 3 - Gabapentin enacarbil, 2400mg	Somnolence	7	13	
Rauck, 2013[16]	Arm 4 - Gabapentin enacarbil, 3600mg	Somnolence	14	12	
Rauck, 2013[16]	Arm 5 - Pregabalin, 300mg	Somnolence	9	14	
Rowbotham, 2012[17]	Arm 1 - Control-Placebo	Any AE	32	62.7	
Rowbotham, 2012[17]	Arm 2 – Duloxetine	Any AE	42	73.7	
Rowbotham, 2012[17]	Arm 1 - Control-Placebo	Nausea	2	3.9	
Rowbotham, 2012[17]	Arm 2 – Duloxetine	Nausea	9	15.8	
Rowbotham, 2012[17]	Arm 1 - Control-Placebo	Fatigue	2	3.9	
Rowbotham, 2012[17]	Arm 2 – Duloxetine	Fatigue	7	12.3	

Author, year	Select arm	Adverse effect	Patients with outcomes, n	Patients with outcomes, %	Comments
Sandercock, 2012[18]	Arm 1 - Control-Placebo	Any AE	20	39.2	
Sandercock, 2012[18]	Arm 2 - Gabapentin single dose, 3000mg	Any AE	27	57.4	
Sandercock, 2012[18]	Arm 3 – Gabapentin asymmetric dose, 3000mg	Any AE	23	46.9	
Sandercock, 2012[18]	Arm 1 - Control-Placebo	Dizziness	0	0	
Sandercock, 2012[18]	Arm 2 - Gabapentin single dose, 3000mg	Dizziness	8	17.0	
Sandercock, 2012[18]	Arm 3 – Gabapentin asymmetric dose, 3000mg	Dizziness	6	12.2	
Sandercock, 2012[18]	Arm 1 - Control-Placebo	Somnolence	0	0	
Sandercock, 2012[18]	Arm 2 - Gabapentin single dose, 3000mg	Somnolence	6	12.8	
Sandercock, 2012[18]	Arm 3 – Gabapentin asymmetric dose, 3000mg	Somnolence	2	4.1	
Shaibani, 2012[20]	Arm 1 - placebo	Any AE	98	79.7	
Shaibani, 2012[20]	Arm 2 – Dextromethorphan/Quinidine (45/30)	Any AE	119	90.8	
Shaibani, 2012[20]	Arm 3 - Dextromethorphan/Quinidine (30/30)	Any AE	97	78.2	

Author, year	Select arm	Adverse effect	Patients with outcomes, n	Patients with outcomes, %	Comments
Toth, 2012[22]	Arm 1 - placebo	Any AE	6	46	
Toth, 2012[22]	Arm 2 - Nabilone	Any AE	7	13	
Vinik, 2014[23]	Arm 1 - placebo	Any AE	93	61.2	
Vinik, 2014[23]	Arm 2 - Tapentadol ER	Any AE	132	79.5	
Vinik, 2014[23]	Arm 1 - placebo	Dizziness	3	2	
Vinik, 2014[23]	Arm 2 - Tapentadol ER	Dizziness	12	7.2	
Vinik, 2014[23]	Arm 1 - placebo	Headache	8	5.3	
Vinik, 2014[23]	Arm 2 - Tapentadol ER	Headache	4	2.4	
Vinik, 2014[23]	Arm 1 - placebo	Nausea	15	9.9	
Vinik, 2014[23]	Arm 2 - Tapentadol ER	Nausea	35	21.1	
Vinik, 2014[23]	Arm 1 - placebo	Somnolence	1	0.7	
Vinik, 2014[23]	Arm 2 - Tapentadol ER	Somnolence	10	6	
Vinik, 2014[23]	Arm 1 - placebo	Vomiting	7	4.6	
Vinik, 2014[23]	Arm 2 - Tapentadol ER	Vomiting	21	12.7	

Author, year	Select arm	Adverse effect	Patients with outcomes, n	Patients with outcomes, %	Comments
Ziegler, 2015[25]	Arm 1 - placebo	Any AE	NR	55	
Ziegler, 2015[25]	Arm 2 - Pregabalin	Any AE	NR	54	
Ziegler, 2015[25]	Arm 1 - placebo	Peripheral Edema	0	0	
Ziegler, 2015[25]	Arm 2 - Pregabalin	Peripheral Edema	7	10	P: <0.05

AE = Adverse Effects; Mg = Milligram; n = Number; NR = Not Reported; TEAE = Treatment-Emergent A**dverse** Events

Evidence Table D-51. Drop outs for pharmacological treatments (KQ2a)

Author, year	Select arm	Dropouts due to adverse effects, N	Dropouts due to adverse effects, %	Comments
Allen, 2014[1]	Arm 1 - placebo	5	5.6	
Allen, 2014[1]	Arm 2 - Desvenlafaxine 50mg	8	12.7	
Allen, 2014[1]	Arm 3 - Desvenlafaxine 100mg	7	8	
Allen, 2014[1]	Arm 4 - Desvenlafaxine 200mg	21	21.2	
Allen, 2014[1]	Arm 5 - Desvenlafaxine 400mg	21	30.4	
Allen, 2014[1]	Arm 6 - Desvenlafaxine Open Label	37	15.6	
Arezzo, 2008[2]	Arm 1 - placebo	15	17.6	
Arezzo, 2008[2]	Arm 2 - Pregabalin	21	25.6	
Atli, 2005[3]	Arm 1 - placebo	0	0	
Atli, 2005[3]	Arm 2 - Zonisamide	5	38.5	
Campbell, 2012[4]	Arm 1 - placebo	3	NR	
Campbell, 2012[4]	Arm 2 - Clonidine	1	NR	
Freeman, 2007[6]	Arm 1 - placebo	3	9	
Freeman, 2007[6]	Arm 2 - Topiramate	4	12	

Author, year	Select arm	Dropouts due to adverse effects, N	Dropouts due to adverse effects, %	Comments
Gao, 2015[7]	Arm 1 - placebo	8	4	
Gao, 2015[7]	Arm 2 - Duloxetine	17	8.4	P = 0.097
Ghasemi, 2014[8]	Arm 1 - placebo	0	0	
Ghasemi, 2014[8]	Arm 2 - Boutlinum	0	0	
Harati, 1998[10]	Arm 1 - placebo	1	NR	
Harati, 1998[10]	Arm 2 - Tramadol	9	NR	
Jiang, 2011[11]	Arm 1 - Control-Placebo	0	0	
Jiang, 2011[11]	Arm 2 - Pregabalin	3	15	
Raskin, 2014[15]	Arm 1 - Control-Placebo	11	NR	
Raskin, 2014[15]	Arm 2 – Pregabalin	8	NR	
Rowbotham, 2012[17]	Arm 1 - Control-Placebo	3	5.9	
Rowbotham, 2012[17]	Arm 2 – Duloxetine	11	19.3	

Author, year	Select arm	Dropouts due to adverse effects, N	Dropouts due to adverse effects, %	Comments
Shaibani, 2012[20]	Arm 1 - placebo	13	10.6	
Shaibani, 2012[20]	Arm 2 – Dextromethorphan/Quinidine (45/30)	33	25.2	
Shaibani, 2012[20]	Arm 3 - Dextromethorphan/Quinidine (30/30)	25	20.2	
Vinik, 2014[23]	Arm 1 - placebo	13	8.6	
Vinik, 2014[23]	Arm 2 - Tapentadol ER	23	13.8	
Ziegler, 2015[25]	Arm 1 - placebo	2	3	
Ziegler, 2015[25]	Arm 2 - Pregabalin	4	6	

Mg = Milligram; N = Number; NR = Not Reported;

Evidence Table D-52. Summary of findings from Griebler et al. (2014) review (KQ2a)

	Intervention	Number of Studies
Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)	Venlafaxine	2
	Duloxetine	5
Topical Agents	Capsaicin	2
Tricyclic antidepressants (TCAs)	Imipramine	2
	Amitriptyline	1
	Desipramine	2
Anticonvulsants	Carbamazepine	1
	Gabapentin	3
	Lamotrigine	2
	Valproic acid	2
	Topiramate	2
	Pregabalin	6
	Oxcarbazepine	3
	Lamotrigine	1
N-methyl-D-aspartate receptor antagonists	Dextromethorphan	2
Lacosamide	Lacosamide	4

	Intervention	Number of Studies
Opiates	Oxycodone	3
	Tramadol/ Acetaminophen	1
	Tapentadol ER	1
Class IB antiarrhythmics	Mexiletine	5
Trials Comparing Medications of Different Classes	Imipramine vs. Paroxetine	1
	Amitriptyline vs. Topical Capsaicin 0.075%	1
	Amitriptyline vs. Maprotiline vs. Placebo	1
	Gabapentin vs. Amitriptyline	1

	Intervention	Number of Studies
	Venlafaxine vs. Carbamazepine	1
	Amitriptyline vs. Lamotrigine	1
	Pregabalin vs. Amitriptyline	1
	Amitriptyline vs. Duloxetine vs. Pregabalin	1

Evidence Table D-53. Summary of network meta-analysis findings from Griebler et al. (2014) review (KQ2a)

Network Meta-Analysis Findings
All results are from network meta-analysis: Placebo-Controlled Comparisons by Drug Class within 3 months of treatment: • SNRIs were superior to placebo (SMD, -1.36 [CrI, -1.77 to -0.95]), • TCAs were superior to placebo (SMD, -0.78 [CrI, -1.24 to -0.33]) • Anticonvulsants were superior to placebo (SMD, -0.67 [CrI, -0.97 to -0.37]) • Topical capsaicin 0.075% was superior to placebo (SMD, -0.91 [CrI, -1.18 to -0.08]) • There was no difference with opioids, dextromethorphan, mexiletine, or lacosamide (a newer anticonvulsant) Placebo-Controlled Comparisons for key individual drugs within 3 months of treatment: Anticonvulsants: • Pregabalin was superior to placebo (SMD, -0.55 [CrI, -0.94 to -0.15]) • Gabapentin did not differ from placebo (SMD, -0.58 [CrI, -1.54 to 0.09]) • Topiramate did not differ from placebo (SMD, -0.45 [CrI, -1.98 to 1.08]) • Carbamazepine was superior to placebo (SMD, -1.57 [CrI, -2.83 to -0.31]) (only one study) SNRIs: • Venlafaxine was superior to placebo (SMD, -1.53 [CrI, -2.41 to -0.65]) • Duloxetine was superior to placebo (SMD, -1.33 [CrI, -1.82 to -0.86]) Tricyclic antidepressants: • Amitriptyline was superior to placebo (SMD, -0.72 [CrI, -1.35 to -0.08]) (only one study) Drug-Drug Comparisons: • SNRIs reduced pain more than did anticonvulsants (SMD, -0.69 [CrI, -1.17 to -0.21]) • Anticonvulsants did not differ from TCAs (SMD, 0.00 [CrI, -0.17 to 0.17])

SMD = Standardized Mean Difference; SNRI = Serotonin-Norepinephrine Reuptake Inhibitors; TCAs = Tricyclic Antidepressants;

Evidence Table D-54. List of additional outcomes from Griebler et al. (2014) (KQ2a)

Author, year	Pain	Paresthesia	Numbness	Quality of life	Adverse effects	Dropouts due to adverse effects
Backonja, 1998[26]				X		x
Bansal, 2009[27]						x
Beydoun, 2006[28]				X		x
Boyle, 2012[29]				X		x
Capsaicin study group, 1991[30]						x
Dejgard, 1988[31]		x				
Dogra, 2005[32]				X		x
Eisenberg, 2001[33]						x
Freeman, 2007[34]				X		x
Freynhagen, 2005[35]						x
Gao, 2010[36]				X		x
Gimbel, 2003[37]				X		x
Goldstein, 2005[38]				X		x
Grosskopf, 2006[39]				x		x
Jia, 2006[40]						x
Jose, 2007[41]						x
Kochar, 2002[42]						x
Kochar, 2004[43]						x
Kvinesdal, 1984[44]		x				
Lesser, 2004[45]				x		x
Max, 1991[46]						x
Max, 1992[47]						x
McCleane, 1999[48]			x	x		x
Raskin, 2004[49]				x		x

Author, year	Pain	Paresthesias	Numbness	Quality of life	Adverse effects	Dropouts due to adverse effects
Raskin, 2005[50]						x
Rauck, 2007[51]				x		x
Richter, 2005[52]				x		x
Rosenstock, 2004[53]				x		x
Rowbotham, 2004[54]						x
Sang, 2002[55]				x		
Satoh, 2011[56]		x	x	x		x
Scheffler, 1991[57]						x
Schwartz, 2011[58]						x
Shaibani, 2009[59]						x
Simpson, 2001[60]				x		
Sindrup, 1989[61]		x				
Sindrup, 1990[62]		x	x			
Tandan, 1992[63]						x
Thienel, 2004[64]						x
Tolle, 2008[65]				x		x
Vinik, 2007[66]						x
Vrethem, 1997[67]						x
Watson, 2003[68]						x
Wernicke, 2006[69]				x		x
Wilton, 1974[70]			x			
Wright, 1997[71]		x				x
Wymer, 2009[72]						x
Ziegler, 2010[73]						x

Evidence Table D-55. List of additional numbness outcomes from Griebler et al. (2014) (KQ2a)

Author, year	Arm	Instrument	Baseline N, Mean SD	Time point(s)	At time point(s), N Mean SD	Within arm comparison	Between arm comparison
McCleane, 1999[48]	Overall-	Numbness	N:100, Mean:3.98, SD: NR	56 days	N:NR, Mean: NR, SD:NR	NR	NR
McCleane, 1999[48]	Arm 1- Placebo	Numbness	N:50, Mean: NR, SD:NR	56 days	N:38, Mean: NR, SD:NR	Mean change from baseline:-0.14 (95% CI:), p:NS	NR
McCleane, 1999[48]	Arm 2- Lamotrigine	Numbness	N:50, Mean: NR, SD:NR	56 days	N:36, Mean: NR, SD:NR	Mean change from baseline:-0.02 (95% CI:), p:NS	NR
Satoh, 2011[56]	Arm 1- Placebo	Numbness	N:135, Mean: NR, SD:NR	14 weeks	N:135, Mean: NR, SD:NR	Mean change from baseline: (95% CI:), p:NS	p:NS
Satoh, 2011[56]	Arm 2- Pregabalin, 300 mg/day	Numbness	N:134, Mean: NR, SD:NR	14 weeks	N:134, Mean: NR, SD:NR	Mean change from baseline: (95% CI:), p:0.0072	p:NS
Satoh, 2011[56]	Arm 3- Pregabalin, 600 mg/day	Numbness	N:45, Mean: NR, SD:NR	14 weeks	N:45, Mean: NR, SD:NR	Mean change from baseline: (95% CI:), p:NS	p:NS
Sindrup, 1990[62]	Arm 1- Placebo	Paraesthesia	N:20, Mean: NR, SD:NR	6 weeks	N:20, Mean:0.04, SD: NR	NR	NR
Sindrup, 1990[62]	Arm 2- Paroxetine	Paraesthesia	N:20, Mean:NR, SD:NR	6 weeks	N:20, Mean:0.03, SD: NR	NR	NR
Sindrup, 1990[62]	Arm 3- Imipramine	Paraesthesia	N:20, Mean:NR, SD:NR	6 weeks	N:20, Mean:0.02, SD: NR	NR	NR
Wilton, 1974[70]	Arm 1- Placebo	Numbness	N:40, Mean:4.62, SD:0.88	1 week	N:40, Mean:2.18, SD:0.78	NR	NR
Wilton, 1974[70]	Arm 2- Tegretol	Numbness	N:40, Mean:5.92, SD:0.76	1 week	N:40, Mean:2.01, SD:0.63	NR	NR

Mg = Milligram; N = Number; NR = Not Reported; NS = Not Significant; SD = Standard Deviation;

Evidence Table D-56. List of additional parasthesias outcomes from Griebler et al. (2014) (KQ2a)

Author, year	Arm	Instrument	Baseline N, Mean SD	Time point(s)	At time point(s), N Mean SD	Within arm comparison	Between arm comparison
Dejgard, 1988[31]	Overall-	Paraesthesia	N:19, Mean:1.9, SD:0.8		N:16, Mean:, SD: NR	NR	NR
Dejgard, 1988[31]	Arm 1-Placebo	Paraesthesia	N:19, Mean: NR, SD:NR	26 weeks	N:16, Mean:1.8, SD:0.8	NR	p:<0.03
Dejgard, 1988[31]	Arm 2-Mexiltetine	Paraesthesia	N:19, Mean: NR, SD:NR	26 weeks	N:16, Mean:0.9, SD:0.7	NR	p:<0.03
Kvinesdal, 1984[44]	Arm 1-Placebo	Six item scale, includes paraethesia	N:12, Mean: NR, SD:NR	5 weeks	N:12, Mean: NR, SD:NR	NR	p:<0.10
Kvinesdal, 1984[44]	Arm 2-Imipramine	Six item scale, includes paraethesia	N:12, Mean: NR, SD:NR	5 weeks	N:12, Mean: NR, SD:NR	NR	p:<0.10
Satoh, 2011[56]	Arm 1-Placebo	NR	N:135, Mean: NR, SD:NR	14 weeks	N:135, Mean: NR, SD:NR	Mean change from baseline: p:NS	NR
Satoh, 2011[56]	Arm 2-Pregabalin, 300 mg/day	NR	N:134, Mean: NR, SD:NR	14 weeks	N:134, Mean: NR, SD:NR	Mean change from baseline: p:nS	NR
Satoh, 2011[56]	Arm 3-Pregabalin, 600 mg/day	NR	N:45, Mean: NR, SD:NR	14 weeks	N:45, Mean: NR, SD:NR	Mean change from baseline: p:0.0093	NR
Sindrup, 1989[61]	Arm 1-Placebo	Six item scale, includes paraethesia	N:9, Mean:, SD:	NR	NR	NR	p:<0.01
Sindrup, 1989[61]	Arm 2-Imipramine	Six item scale, includes paraethesia	N:9, Mean:, SD:	NR	NR	NR	p:<0.01
Sindrup, 1990[62]	Arm 1-Placebo	Paraesthesia	N:20, Mean: NR, SD:NR	6 weeks	N:20, Mean:1.48, SD: NR	NR	NR

Author, year	Arm	Instrument	Baseline N, Mean SD	Time point(s)	At time point(s), N Mean SD	Within arm comparison	Between arm comparison
Sindrup, 1990[62]	Arm 2-Paroxetine	Paraesthesia	N:20, Mean: NR, SD:NR	6 weeks	N:20, Mean:0.52, SD: NR	NR	p:<0.05
Sindrup, 1990[62]	Arm 3-Imipramine	Paraesthesia	N:20, Mean: NR, SD:NR	6 weeks	N:20, Mean:0.49, SD: NR	(95% CI:1, 4.5), p:NR	p:<0.05
Wright, 1997[71]	Arm 1-Placebo	FIS	N:16, Mean:11, SD:	3 weeks	N:15, Mean:6, SD: NR	Median change from baseline:2 (95% CI:2, 6), p:NR	
Wright, 1997[71]	Arm 2-Mexiltetine	FIS, includes paresthesia	N:15, Mean:9.5, SD:	3 weeks	N:14, Mean:4.5, SD: NR	Median change from baseline:5.5 (95% CI:), p:NR	NR

FIS = Fuzzy Interference Study; Mg = Milligram; N = Number; NR = Not Reported; SD = Standard Deviation;

Evidence Table D-57. Quality of life outcome from Griebler review (KQ2a)

Author, year	Arm	Instrument	Baseline N, Mean SD	Time point(s)	At time point(s), N Mean SD	Within arm comparison	Between arm comparison
Backonja, 1998[26]	Arm 1-Placebo	SF-36	N:81, Mean: NR, SD:NR	NR	NR	NR	Mean difference from baseline: (95% CI:) Comparator: , p:NS
Backonja, 1998[26]	Arm 2-Gabapentin	SF-36	N:84, Mean: NR, SD:NR	NR	NR	Mean difference from baseline: NR, SE:, p:0.01	Mean difference from baseline: (95% CI:) Comparator: , p:NS
Beydoun, 2006[28]	Arm 1-Placebo	SF-36	N:89, Mean: NR, SD:NR	12 weeks	NR	NR	p:NS
Beydoun, 2006[28]	Arm 2-Oxcarbazepine, 600mg	SF-36	N:83, Mean: NR, SD:NR	12 weeks	NR	NR	p:NS
Beydoun, 2006[28]	Arm 3-Oxcarbazepine, 1200mg	SF-36	N:87, Mean: NR, SD:NR	12 weeks	NR	NR	p:NS
Beydoun, 2006[28]	Arm 4-Oxcarbazepine, 1800mg	SF-36	N:88, Mean: NR, SD:NR	12 weeks	NR	NR	p:NS
Boyle, 2012[29]	Arm 1-Pregabalin	SF-36	N:27, Mean: NR, SD:NR	36 days	N:27, Mean:31.1, SD:10.9	NR	p:NS
Boyle, 2012[29]	Arm 2-Duloxetine	SF-36	N:28, Mean: NR, SD:NR	36 days	N:28, Mean:36.6, SD:9.4	NR	p:NS
Boyle, 2012[29]	Arm 3-Amitriptyline	SF-36	N:28, Mean: NR, SD:NR	36 days	N:28, Mean:38.5, SD:8.8	NR	p:NS
Dogra, 2005[32]	Arm 1-Placebo	SF-36	N:77, Mean: NR, SD:NR	14 weeks	N:70, Mean:50.2, SD:NR	NR	p:0.03
Dogra, 2005[32]	Arm 2-Oxcarbazepine	SF-36	N:69, Mean: NR, SD:NR	14 weeks	N:55, Mean:47.2, SD:NR	NR	p:0.03
Freeman, 2007[34]	Arm 1-Placebo	SF-36, physical functioning	N:134, Mean:46, SD:25.37	66 days	N:134, Mean:52.1, SD:26.09	Mean difference from baseline:6.1, SE:, p:0.082	NR
Freeman, 2007[34]	Arm 2-Tramadol/APAP	SF-36, physical functioning	N:143, Mean:47.9, SD:26.24	66 days	N:143, Mean:57.4, SD:29.44	Mean difference from baseline:9.5, SE:, p:0.082	NR
Freeman, 2007[34]	Arm 1-Placebo	SF-36, Role-physical	N:134, Mean:33.7, SD:38.07	66 days	N:134, Mean:54.7, SD:40.96	Mean difference from baseline:21.1, SE:, p:0.916	NR

Author, year	Arm	Instrument	Baseline N, Mean SD	Time point(s)	At time point(s), N Mean SD	Within arm comparison	Between arm comparison
Freeman, 2007[34]	Arm 2-Tramadol/APAP	SF-36, Role-physical	N:143, Mean:35.5, SD:38.67	66 days	N:143, Mean:55.1, SD:41.6	Mean difference from baseline:19.6, SE:, p:0.916	NR
Freeman, 2007[34]	Arm 1-Placebo	SF-36, physical component summary	N:134, Mean:32, SD:9.15	66 days	N:134, Mean:36.3, SD:9.91	Mean difference from baseline:4.3, SE:, p:0.063	NR
Freeman, 2007[34]	Arm 2-Tramadol/APAP	SF-36, physical component summary	N:143, Mean:31.3, SD:9.85	66 days	N:143, Mean:37.4, SD:10.77	Mean difference from baseline:6.1, SE:, p:0.063	NR
Gao, 2010[36]	Arm 1-Placebo	EQ-5D (US)	N:109, Mean: NR, SD:NR	14 weeks	N:109, Mean: NR, SD:NR	Mean difference from baseline:0.1, SE:, p:0.207	NR
Gao, 2010[36]	Arm 2-Duloxetine	EQ-5D (US)	N:106, Mean: NR, SD:NR	14 weeks	N:106, Mean: NR, SD:NR	Mean difference from baseline:0.12, SE:, p:0.207	NR
Gimbel, 2003[37]	Arm 1-Placebo	SF-36	N:77, Mean: NR, SD:NR	42 days	N:77, Mean: NR, SD:NR	NR	p:NS
Gimbel, 2003[37]	Arm 2-CR Oxycodone	SF-36	N:82, Mean: NR, SD:NR	42 days	N:82, Mean: NR, SD:NR	NR	p:NS
Gimbel, 2003[37]	Arm 1-Placebo	Rand Mental Health Survey	N:77, Mean: NR, SD:NR	42 days	N:77, Mean: NR, SD:NR	NR	p:NS
Gimbel, 2003[37]	Arm 2-CR Oxycodone	Rand Mental Health Survey	N:82, Mean: NR, SD:NR	42 days	N:82, Mean: NR, SD:NR	NR	p:NS
Goldstein, 2005[38]	Arm 1-Placebo	SF-36, physical functioning	N:115, Mean: NR, SD:NR	12 weeks	N:115, Mean: NR, SD:NR	Mean difference from baseline:3.94, SE:, p:NS	NR
Goldstein, 2005[38]	Arm 2-Duloxetine, 20 mg/d	SF-36, physical functioning	N:115, Mean: NR, SD:NR	12 weeks	N:115, Mean: NR, SD:NR	Mean difference from baseline:3.67, SE:, p:NS	NR
Goldstein, 2005[38]	Arm 3-Duloxetine, 60 mg/d	SF-36, physical functioning	N:114, Mean: NR, SD:NR	12 weeks	N:114, Mean: NR, SD:NR	Mean difference from baseline:5.86, SE:, p:NS	NR
Goldstein, 2005[38]	Arm 4-Duloxetine, 120 mg/d	SF-36, physical functioning	N:113, Mean: NR, SD:NR	12 weeks	N:113, Mean: NR, SD:NR	Mean difference from baseline:5.85, SE:, p:NS	NR

Author, year	Arm	Instrument	Baseline N, Mean SD	Time point(s)	At time point(s), N Mean SD	Within arm comparison	Between arm comparison
Goldstein, 2005[38]	Arm 1-Placebo	SF-36, bodily pain	N:115, Mean: NR, SD:NR	12 weeks	N:115, Mean: NR, SD:NR	Mean difference from baseline:10.32, SE:, p:<0.01	NR
Goldstein, 2005[38]	Arm 2-Duloxetine, 20 mg/d	SF-36, bodily pain	N:115, Mean: NR, SD:NR	12 weeks	N:115, Mean: NR, SD:NR	Mean difference from baseline:13.22, SE:, p:<0.01	NR
Goldstein, 2005[38]	Arm 3-Duloxetine, 60 mg/d	SF-36, bodily pain	N:114, Mean: NR, SD:NR	12 weeks	N:114, Mean: NR, SD:NR	Mean difference from baseline:18, SE:, p:<0.01	NR
Goldstein, 2005[38]	Arm 4-Duloxetine, 120 mg/d	SF-36, bodily pain	N:113, Mean: NR, SD:NR	12 weeks	N:113, Mean: NR, SD:NR	Mean difference from baseline:18.32, SE:, p:<0.01	NR
Goldstein, 2005[38]	Arm 1-Placebo	EQ-5D	N:115, Mean: NR, SD:NR	12 weeks	N:115, Mean: NR, SD:NR	Mean difference from baseline:0.08, SE:, p:<0.05	NR
Goldstein, 2005[38]	Arm 2-Duloxetine, 20 mg/d	EQ-5D	N:115, Mean: NR, SD:NR	12 weeks	N:115, Mean: NR, SD:NR	Mean difference from baseline:0.1, SE:, p:<0.05	NR
Goldstein, 2005[38]	Arm 3-Duloxetine, 60 mg/d	EQ-5D	N:114, Mean: NR, SD:NR	12 weeks	N:114, Mean: NR, SD:NR	Mean difference from baseline:0.13, SE:, p:<0.05	NR
Goldstein, 2005[38]	Arm 4-Duloxetine, 120 mg/d	EQ-5D	N:113, Mean: NR, SD:NR	12 weeks	N:113, Mean: NR, SD:NR	Mean difference from baseline:0.13, SE:, p:<0.05	NR
Grosskopf, 2006[39]	Arm 1-Placebo	SF-36	N:70, Mean: NR, SD:NR	16 weeks	N:70, Mean: NR, SD:NR	NR	p:NS
Grosskopf, 2006[39]	Arm 2-Oxcarbazepine	SF-36	N:71, Mean: NR, SD:NR	16 weeks	N:71, Mean: NR, SD:NR	NR	p:NS
Lesser, 2004[45]	Arm 1-Placebo	SF-36, social domain	N:97, Mean: NR, SD:NR	5 weeks	N:88, Mean: NR, SD:NR	NR	p:NS
Lesser, 2004[45]	Arm 2-Pregabalin, 75 mg/day	SF-36, social domain	N:77, Mean: NR, SD:NR	5 weeks	N:67, Mean: NR, SD:NR	NR	p:NS
Lesser, 2004[45]	Arm 3-Pregabalin, 300 mg/day	SF-36, social domain	N:81, Mean: NR, SD:NR	5 weeks	N:70, Mean: NR, SD:NR	NR	Mean difference from baseline: (95% CI:) Comparator: , p:<0.05

Author, year	Arm	Instrument	Baseline N, Mean SD	Time point(s)	At time point(s), N Mean SD	Within arm comparison	Between arm comparison
Lesser, 2004[45]	Arm 4-Pregabalin, 600 mg/day	SF-36, social domain	N:82, Mean: NR, SD:NR	5 weeks	N:70, Mean: NR, SD:NR	NR	Mean difference from baseline: (95% CI:) Comparator: , p:<0.01
Lesser, 2004[45]	Arm 1-Placebo	SF-36, bodily pain	N:97, Mean: NR, SD:NR	5 weeks	N:88, Mean: NR, SD:NR	NR	Mean difference from baseline: (95% CI:) Comparator: , p:NS
Lesser, 2004[45]	Arm 2-Pregabalin, 75 mg/day	SF-36, bodily pain	N:77, Mean: NR, SD:NR	5 weeks	N:67, Mean: NR, SD:NR	NR	Mean difference from baseline: (95% CI:) Comparator: , p:NS
Lesser, 2004[45]	Arm 3-Pregabalin, 300 mg/day	SF-36, bodily pain	N:81, Mean: NR, SD:NR	5 weeks	N:70, Mean: NR, SD:NR	NR	Mean difference from baseline: (95% CI:) Comparator: , p:<0.005
Lesser, 2004[45]	Arm 4-Pregabalin, 600 mg/day	SF-36, bodily pain	N:82, Mean: NR, SD:NR	5 weeks	N:70, Mean: NR, SD:NR	NR	Mean difference from baseline: (95% CI:) Comparator: , p:<0.0005
Lesser, 2004[45]	Arm 1-Placebo	SF-36, vitality	N:97, Mean: NR, SD:NR	5 weeks	N:88, Mean: NR, SD:NR	NR	Mean difference from baseline: (95% CI:) Comparator: , p:NS
Lesser, 2004[45]	Arm 2-Pregabalin, 75 mg/day	SF-36, vitality	N:77, Mean: NR, SD:NR	5 weeks	N:67, Mean: NR, SD:NR	NR	Mean difference from baseline: (95% CI:) Comparator: , p:<0.05
Lesser, 2004[45]	Arm 3-Pregabalin, 300 mg/day	SF-36, vitality	N:81, Mean: NR, SD:NR	5 weeks	N:70, Mean: NR, SD:NR	NR	Mean difference from baseline: (95% CI:) Comparator: , p:<0.01
Lesser, 2004[45]	Arm 4-Pregabalin, 600 mg/day	SF-36, vitality	N:82, Mean: NR, SD:NR	5 weeks	N:70, Mean: NR, SD:NR	NR	Mean difference from baseline: (95% CI:) Comparator: , p:NS
McCleane, 1999[48]	Overall-	VAS score, Quality of life	N:100, Mean:4.68, SD:NR	56 days	N:, Mean: NR, SD:NR	NR	NR
McCleane, 1999[48]	Arm 1-Placebo	VAS score, Quality of life	N:50, Mean: NR, SD:NR	56 days	N:38, Mean: NR, SD:NR	Mean difference from baseline:-0.15, SE:, p:NS	NR
McCleane, 1999[48]	Arm 2-Lamotrigine	VAS score, Quality of life	N:50, Mean: NR, SD:NR	56 days	N:36, Mean: NR, SD:NR	Mean difference from baseline:-0.38, SE:, p:NS	NR
Raskin, 2004[49]	Arm 1-Placebo	SF-36, physical functioning	N:109, Mean:32.4, SD:8.7	12 weeks	N:109, Mean:34.9, SD:9.4	NR	Mean difference from baseline: (95% CI:) Comparator: , p:0.066

Author, year	Arm	Instrument	Baseline N, Mean SD	Time point(s)	At time point(s), N Mean SD	Within arm comparison	Between arm comparison
Raskin, 2004[49]	Arm 2- Topiramate	SF-36, physical functioning	N:208, Mean:33.2, SD:9.8	12 weeks	N:208, Mean:32.4, SD:8.7	NR	Mean difference from baseline: (95% CI :) Comparator: , p:0.066
Rauck, 2007[51]	Arm 1- Placebo	SF-36, bodily pain	N:59, Mean: NR, SD:NR	10 weeks	N:48, Mean: NR, SD:NR	NR	Mean difference from baseline: (95% CI :) Comparator: , p:0.022
Rauck, 2007[51]	Arm 2- Lacosamide	SF-36, bodily pain	N:60, Mean: NR, SD:NR	10 weeks	N:46, Mean: NR, SD:NR	NR	Mean difference from baseline: (95% CI :) Comparator: , p:0.022
Rauck, 2007[51]	Arm 1- Placebo	SF-36, vitality	N:59, Mean: NR, SD:NR	10 weeks	N:48, Mean: NR, SD:NR	NR	Mean difference from baseline: (95% CI :) Comparator: , p:0.024
Rauck, 2007[51]	Arm 2- Lacosamide	SF-36, vitality	N:60, Mean: NR, SD:NR	10 weeks	N:46, Mean: NR, SD:NR	NR	Mean difference from baseline: (95% CI :) Comparator: , p:0.024
Richter, 2005[52]	Arm 1- Placebo	SF-36, bodily pain	N:85, Mean: NR, SD:NR	6 weeks	N:85, Mean: NR, SD:NR	NR	Mean difference from baseline: (95% CI :) Comparator: , p:<0.0106
Richter, 2005[52]	Arm 2- Pregabalin, 150 mg/day	SF-36, bodily pain	N:79, Mean: NR, SD:NR	6 weeks	N:79, Mean: NR, SD:NR	NR	Mean difference from baseline: (95% CI :) Comparator: , p:<0.0106
Richter, 2005[52]	Arm 3- Pregabalin, 600 mg/day	SF-36, bodily pain	N:82, Mean: NR, SD:NR	6 weeks	N:82, Mean: NR, SD:NR	NR	Mean difference from baseline: (95% CI :) Comparator: , p:<0.0106
Rosenstock, 2004[53]	Arm 1- Placebo	SF-36, bodily pain	N:70, Mean: NR, SD:NR	8 weeks	N:61, Mean:46.96, SD:2.37	NR	Mean difference from baseline:6.87 (95% CI:0.70, 13.04) Comparator: Placebo, p:0.0294
Rosenstock, 2004[53]	Arm 2- Pregabalin	SF-36, bodily pain	N:76, Mean: NR, SD:NR	8 weeks	N:62, Mean:53.83, SD:2.24	NR	NR
Rosenstock, 2004[53]	Arm 1- Placebo	SF-36, mental health	N:70, Mean: NR, SD:NR	8 weeks	N:61, Mean:72.36, SD:1.97	NR	Mean difference from baseline:3.47 (95% CI:-1.73, 8.66) Comparator: Placebo, p:0.1893
Rosenstock, 2004[53]	Arm 2- Pregabalin	SF-36, mental health	N:76, Mean: NR, SD:NR	8 weeks	N:62, Mean:75.82, SD:1.9	NR	NR
Rosenstock, 2004[53]	Arm 1- Placebo	SF-36, vitality	N:70, Mean: NR, SD:NR	8 weeks	N:61, Mean:43.57, SD:2.05	NR	Mean difference from baseline:3.24 (95% CI:-2.13, 8.61) Comparator: Placebo, p:0.2343
Rosenstock, 2004[53]	Arm 2- Pregabalin	SF-36, vitality	N:76, Mean: NR, SD:NR	8 weeks	N:62, Mean:46.82, SD:1.96	NR	NR
Sang, 2002[55]	Arm 1- Placebo	SF-36	N:19, Mean: NR, SD:NR	9 weeks	N:19, Mean: NR, SD:NR	NR	p:NS

Author, year	Arm	Instrument	Baseline N, Mean SD	Time point(s)	*At time point(s), N* *Mean* *SD*	Within arm comparison	Between arm comparison
Sang, 2002[55]	Arm 2-Dextromethorpan	SF-36	N:19, Mean: NR, SD:NR	9 weeks	N:19, Mean: NR, SD:NR	*NR*	Mean difference from baseline: NR (95% CI :) Comparator: Placebo, p:<0.05
Sang, 2002[55]	Arm 3-Memantine	SF-36	N:19, Mean: NR, SD:NR	9 weeks	N:19, Mean: NR, SD:NR	NR	p:NS
Satoh, 2011[56]	Arm 1-Placebo	SF-36	N:135, Mean: NR, SD:NR	14 weeks	N:135, Mean: NR, SD:NR	NR	p:NS
Satoh, 2011[56]	Arm 2-Pregabalin, 300 mg/day	SF-36	N:134, Mean: NR, SD:NR	14 weeks	N:134, Mean: NR, SD:NR	NR	p:NS
Satoh, 2011[56]	Arm 3-Pregabalin, 600 mg/day	SF-36	N:45, Mean: NR, SD:NR	14 weeks	N:45, Mean: NR, SD:NR	NR	Mean difference from baseline: NR (95% CI :) Comparator: Placebo, p:<0.05
Simpson, 2001[60]	Arm 1-Placebo	SF-36, bodily pain	N:30, Mean: NR, SD:NR	8 weeks	N:30, Mean: NR, SD:NR	NR	NR
Simpson, 2001[60]	Arm 2-Gabapentin+venlafaxine	SF-36, bodily pain	N:30, Mean: NR, SD:NR	8 weeks	N:30, Mean:90, SD:NR	NR	NR
Simpson, 2001[60]	Arm 1-Placebo	SF-36, mental health	N:30, Mean: NR, SD:NR	8 weeks	N:30, Mean: NR, SD:NR	NR	NR
Simpson, 2001[60]	Arm 2-Gabapentin+venlafaxine	SF-36, mental health	N:30, Mean: NR, SD:NR	8 weeks	N:30, Mean:75, SD:NR	NR	NR
Simpson, 2001[60]	Arm 1-Placebo	SF-36, vitality	N:30, Mean: NR, SD:NR	8 weeks	N:30, Mean: NR, SD:NR	NR	NR
Simpson, 2001[60]	Arm 2-Gabapentin+venlafaxine	SF-36, vitality	N:30, Mean: NR, SD:NR	8 weeks	N:30, Mean:65, SD:NR	NR	NR
Tolle, 2008[65]	Arm 1-Placebo	EQ-5D	N:96, Mean: NR, SD:NR	12 weeks	N:90, Mean: NR, SD:NR	NR	NR
Tolle, 2008[65]	Arm 2-Pregabalin, 150 mg/day	EQ-5D	N:99, Mean: NR, SD:NR	12 weeks	N:92, Mean: NR, SD:NR	NR	Mean difference from baseline:0.1 (95% CI:0.03, 0.16) Comparator: , p:0.0092
Tolle, 2008[65]	Arm 3-Pregabalin, 300 mg/day	EQ-5D	N:99, Mean: NR, SD:NR	12 weeks	N:92, Mean: NR, SD:NR	NR	Mean difference from baseline:0.08 (95% CI:0.01, 0.14) Comparator: , p:0.0263

Author, year	Arm	Instrument	Baseline N, Mean SD	Time point(s)	At time point(s), N Mean SD	Within arm comparison	Between arm comparison
Tolle, 2008[65]	Arm 4-Pregabalin, 600 mg/day	EQ-5D	N:101, Mean: NR, SD:NR	12 weeks	N:90, Mean: NR, SD:NR	NR	Mean difference from baseline:0.14 (95% CI:0.07, 0.20) Comparator: , p:0.003
Wernicke, 2006[69]	Arm 1-Placebo	SF-36, Physical functioning	N:108, Mean: NR, SD:NR	12 weeks	N:101, Mean: NR, SD:NR	Mean difference from baseline:3.64, SE:1.9, p:NS	NR
Wernicke, 2006[69]	Arm 2-Dutoxetine, 60mg	SF-36, Physical functioning	N:114, Mean: NR, SD:NR	12 weeks	N:109, Mean: NR, SD:NR	Mean difference from baseline:11.96, SE:1.81, p:<0.01	NR
Wernicke, 2006[69]	Arm 3-Dutoxetine, 120mg	SF-36, Physical functioning	N:112, Mean: NR, SD:NR	12 weeks	N:108, Mean: NR, SD:NR	Mean difference from baseline:11.2, SE:11.2, p:<0.01	NR
Wernicke, 2006[69]	Arm 1-Placebo	SF-36, role physical	N:108, Mean: NR, SD:NR	12 weeks	N:101, Mean: NR, SD:NR	Mean difference from baseline:12.14, SE:3.77, p:NS	NR
Wernicke, 2006[69]	Arm 2-Dutoxetine, 60mg	SF-36, role physical	N:114, Mean: NR, SD:NR	12 weeks	N:109, Mean: NR, SD:NR	Mean difference from baseline:22.85, SE:3.63, p:<0.05	NR
Wernicke, 2006[69]	Arm 3-Dutoxetine, 120mg	SF-36, role physical	N:112, Mean: NR, SD:NR	12 weeks	N:108, Mean: NR, SD:NR	Mean difference from baseline:25.01, SE:3.67, p:<0.05	NR
Wernicke, 2006[69]	Arm 1-Placebo	SF-36, role emotional	N:108, Mean: NR, SD:NR	12 weeks	N:101, Mean: NR, SD:NR	Mean difference from baseline:2.13, SE:3.44, p:NS	NR
Wernicke, 2006[69]	Arm 2-Dutoxetine, 60mg	SF-36, role emotional	N:114, Mean: NR, SD:NR	12 weeks	N:109, Mean: NR, SD:NR	Mean difference from baseline:10.66, SE:3.32, p:NS	NR
Wernicke, 2006[69]	Arm 3-Dutoxetine, 120mg	SF-36, role emotional	N:112, Mean: NR, SD:NR	12 weeks	N:108, Mean: NR, SD:NR	Mean difference from baseline:9, SE:3.35, p:NS	NR

Author, year	Arm	Instrument	Baseline N, Mean SD	Time point(s)	At time point(s), N Mean SD	Within arm comparison	Between arm comparison
Wernicke, 2006[69]	Arm 1-Placebo	SF-36, bodily pain	N:108, Mean: NR, SD:NR	12 weeks	N:101, Mean: NR, SD:NR	Mean difference from baseline:12.17, SE:2.1, p:NS	NR
Wernicke, 2006[69]	Arm 2-Dutoxetine, 60mg	SF-36, bodily pain	N:114, Mean: NR, SD:NR	12 weeks	N:109, Mean: NR, SD:NR	Mean difference from baseline:15.3, SE:1.98, p:NS	NR
Wernicke, 2006[69]	Arm 3-Dutoxetine, 120mg	SF-36, bodily pain	N:112, Mean: NR, SD:NR	12 weeks	N:108, Mean: NR, SD:NR	Mean difference from baseline:20.59, SE:2.04, p:<0.01	NR
Wernicke, 2006[69]	Arm 1-Placebo	SF-36, vitality	N:108, Mean: NR, SD:NR	12 weeks	N:101, Mean: NR, SD:NR	Mean difference from baseline:2.79, SE:1.78, p:NS	NR
Wernicke, 2006[69]	Arm 2-Dutoxetine, 60mg	SF-36, vitality	N:114, Mean: NR, SD:NR	12 weeks	N:109, Mean: NR, SD:NR	Mean difference from baseline:8.47, SE:1.73, p:<0.05	NR
Wernicke, 2006[69]	Arm 3-Dutoxetine, 120mg	SF-36, vitality	N:112, Mean: NR, SD:NR	12 weeks	N:108, Mean: NR, SD:NR	Mean difference from baseline:6.36, SE:1.74, p:NS	NR
Wernicke, 2006[69]	Arm 1-Placebo	SF-36, mental health	N:108, Mean: NR, SD:NR	12 weeks	N:101, Mean: NR, SD:NR	Mean difference from baseline:-0.31, SE:1.52, p:NS	NR
Wernicke, 2006[69]	Arm 2-Dutoxetine, 60mg	SF-36, mental health	N:114, Mean: NR, SD:NR	12 weeks	N:109, Mean: NR, SD:NR	Mean difference from baseline:1.63, SE:1.48, p:NS	NR
Wernicke, 2006[69]	Arm 3-Dutoxetine, 120mg	SF-36, mental health	N:112, Mean: NR, SD:NR	12 weeks	N:108, Mean: NR, SD:NR	Mean difference from baseline:3.82, SE:1.49, p:<0.05	NR
Wernicke, 2006[69]	Arm 1-Placebo	SF-36, Physical component	N:108, Mean: NR, SD:NR	12 weeks	N:101, Mean: NR, SD:NR	Mean difference from baseline:3.67, SE:0.78, p:NS	NR
Wernicke, 2006[69]	Arm 2-Dutoxetine, 60mg	SF-36, Physical component	N:114, Mean: NR, SD:NR	12 weeks	N:109, Mean: NR, SD:NR	Mean difference from baseline:6.85, SE:0.76, p:<0.01	NR
Wernicke, 2006[69]	Arm 3-Dutoxetine, 120mg	SF-36, Physical component	N:112, Mean: NR, SD:NR	12 weeks	N:108, Mean: NR, SD:NR	Mean difference from baseline:7.46, SE:0.77, p:<0.001	NR
Wernicke, 2006[69]	Arm 1-Placebo	SF-36, Mental component	N:108, Mean: NR, SD:NR	12 weeks	N:101, Mean: NR, SD:NR	Mean difference from baseline:-0.29, SE:0.83, p:NS	NR

Author, year	Arm	Instrument	Baseline N, Mean SD	Time point(s)	At time point(s), N Mean SD	Within arm comparison	Between arm comparison
Wernicke, 2006[69]	Arm 2-Dutoxetine, 60mg	SF-36, Mental component	N:114, Mean: NR, SD:NR	12 weeks	N:109, Mean: NR, SD:NR	Mean difference from baseline:0.77, SE:0.81, p:NS	NR
Wernicke, 2006[69]	Arm 3-Dutoxetine, 120mg	SF-36, Mental component	N:112, Mean: NR, SD:NR	12 weeks	N:108, Mean: NR, SD:NR	Mean difference from baseline:1.09, SE:0.82, p:NS	NR
Wernicke, 2006[69]	Arm 1-Placebo	EQ-5D	N:108, Mean: NR, SD:NR	12 weeks	N:101, Mean: NR, SD:NR	Mean difference from baseline:0.08, SE:0.02, p:NS	NR
Wernicke, 2006[69]	Arm 2-Dutoxetine, 60mg	EQ-5D	N:114, Mean: NR, SD:NR	12 weeks	N:109, Mean: NR, SD:NR	Mean difference from baseline:0.15, SE:0.02, p:<0.05	NR
Wernicke, 2006[69]	Arm 3-Dutoxetine, 120mg	EQ-5D	N:112, Mean: NR, SD:NR	12 weeks	N:108, Mean: NR, SD:NR	Mean difference from baseline:0.15, SE:0.02, p:<0.05	NR

CI = Confidence Interval; EQ-5D = EuroQol-5D (Health related Quality of Life Instrument); Mg = Milligram; N = Number; NR = Not Reported; NS= Not Significant; SD = Standard Deviation; SE = Standard Error; SF-36 = 36-Item. Short-Form Health Survey;

Evidence Table D-58. Dropouts reported in Griebler review (KQ2a)

Author, year	Select arm	Dropouts due to adverse effects, N	Dropouts due to adverse effects, %	Comments
Backonja, 1998[26]	Arm 1-Placebo	5	6.17	
Backonja, 1998[26]	Arm 2-Gabapentin	7	8.33	
Bansal, 2009[27]	Arm 1-Pregabalin	9	40.91	
Bansal, 2009[27]	Arm 2-Amitriptyline	21	95.45	
Beydoun, 2006[28]	Arm 1-Placebo	6	6.74	
Beydoun, 2006[28]	Arm 2-Oxcarbazepine, 600mg	9	10.84	
Beydoun, 2006[28]	Arm 3-Oxcarbazepine, 1200mg	20	22.99	
Beydoun, 2006[28]	Arm 4-Oxcarbazepine, 1800mg	36	40.91	
Boyle, 2012[29]	Arm 1-Pregabalin	6	22.22	
Boyle, 2012[29]	Arm 2-Duloxetine	3	10.71	
Boyle, 2012[29]	Arm 3-Amitriptyline	1	3.57	
Capsaicin study group, 1991[30]	Arm 1-Vehicle	8	5.80	
Capsaicin study group, 1991[30]	Arm 2-Capsaicin	17	12.23	

Author, year	Select arm	Dropouts due to adverse effects, N	Dropouts due to adverse effects, %	Comments
Dogra, 2005[32]	Arm 1-Placebo	6	7.79	
Dogra, 2005[32]	Arm 2-Oxcarbazepine	19	27.54	
Eisenberg, 2001[33]	Arm 1-Placebo	2	7.69	
Eisenberg, 2001[33]	Arm 2-Lamotrigine	2	7.41	
Freeman, 2007[34]	Arm 1-Placebo	10	6.54	
Freeman, 2007[34]	Arm 2-Tramadol/APAP	13	8.13	
Freynhagen, 2005[35]	Arm 1-Placebo	5	7.69	
Freynhagen, 2005[35]	Arm 2-PGB fixed dose	33	25	
Freynhagen, 2005[35]	Arm 3-PGB flexible dose	24	17.02	
Gao, 2010[36]	Arm 1-Placebo	4	3.67	
Gao, 2010[36]	Arm 2-Duloxetine	15	13.76	
Gimbel, 2003[37]	Arm 1-Placebo	4	5.19	
Gimbel, 2003[37]	Arm 2-CR Oxycodone	7	8.54	
Grosskopf, 2006[39]	Arm 1-Placebo	4	5.71	

Author, year	Select arm	Dropouts due to adverse effects, N	Dropouts due to adverse effects, %	Comments
Grosskopf, 2006[39]	Arm 2-Oxcarbazepine	18	25.35	
Jia, 2006[40]	Arm 1-Venlafaxine	4	6.06	
Jia, 2006[40]	Arm 2-Carbamazepine	2	3.03	
Jose, 2007[41]	Arm 1-Amitriptyline	19	63.33	
Jose, 2007[41]	Arm 2-Lamotrigine	8	34.78	
Kochar, 2002[42]	Arm 1-Placebo	0	0	
Kochar, 2002[42]	Arm 2-Sodium Valproate	1	3.45	
Kochar, 2004[43]	Arm 1-Placebo	0	0.00	
Kochar, 2004[43]	Arm 2-Sodium Valproate	1	4.76	
Lesser, 2004[45]	Arm 1-Placebo	1	1.03	
Lesser, 2004[45]	Arm 2-Pregabalin, 75 mg/day	0	0.00	
Lesser, 2004[45]	Arm 3-Pregabalin, 300 mg/day	0	0.00	
Lesser, 2004[45]	Arm 4-Pregabalin, 600 mg/day	0	0.00	
Max, 1991[46]	Arm 1-Placebo	2	10.00	

Author, year	Select arm	Dropouts due to adverse effects, N	Dropouts due to adverse effects, %	Comments
Max, 1991[46]	Arm 2-Desipramine	2	10.00	
Max, 1992[47]	Arm 1-Placebo-Fluoxetine	5	9.26	
Max, 1992[47]	Arm 2-Desipramine-Amitriptyline	14	25.93	
McCleane, 1999[48]	Arm 1-Placebo	8	16.00	
McCleane, 1999[48]	Arm 2-Lamotrigine	10	20.00	
Raskin, 2004[49]	Arm 1-Placebo	9	8.26	
Raskin, 2004[49]	Arm 2-Topiramate	52	25.00	
Raskin, 2005[50]	Arm 1-Placebo	3	2.59	
Raskin, 2005[50]	Arm 2-Duloxetine, 60mg/day	5	4.31	
Raskin, 2005[50]	Arm 3-Duloxetine, 120mg/day	14	12.07	
Rauck, 2007[51]	Arm 1-Placebo	3	5.08	
Rauck, 2007[51]	Arm 2-Lacosamide	5	8.33	
Richter, 2005[52]	Arm 1-Placebo	4	4.71	
Richter, 2005[52]	Arm 2-Pregabalin, 150 mg/day	2	2.53	

Author, year	Select arm	Dropouts due to adverse effects, N	Dropouts due to adverse effects, %	Comments
Richter, 2005[52]	Arm 3-Pregabalin, 600 mg/day	7	8.54	
Rosenstock, 2004[53]	Arm 1-Placebo	8	11.43	
Rosenstock, 2004[53]	Arm 2-Pregabalin	21	27.63	
Rowbotham, 2004[54]	Arm 1-Placebo	3	3.75	
Rowbotham, 2004[54]	Arm 2-Venlafaxine 75mg	6	7.50	
Rowbotham, 2004[54]	Arm 3-Venlafaxine 150/225mg	8	9.76	
Satoh, 2011[56]	Arm 1-Placebo	2	1.48	
Satoh, 2011[56]	Arm 2-Pregabalin, 300 mg/day	4	2.99	
Satoh, 2011[56]	Arm 3-Pregabalin, 600 mg/day	8	17.78	
Scheffler, 1991[57]	Arm 1-Vehicle	2	7.69	
Scheffler, 1991[57]	Arm 2-Capsaicin	9	32.14	
Schwartz, 2011[58]	Arm 1-Placebo	15	7.65	
Schwartz, 2011[58]	Arm 2-Tapentadol ER	29	14.57	
Shaibani, 2009[59]	Arm 1-Placebo	9	13.85	

Author, year	Select arm	Dropouts due to adverse effects, N	Dropouts due to adverse effects, %	Comments
Shaibani, 2009[59]	Arm 2-Lacosamide, 200mg/day	17	12.06	
Shaibani, 2009[59]	Arm 3-Lacosamide, 400mg/day	30	24.00	
Shaibani, 2009[59]	Arm 4-Lacosamide, 600mg/day	58	42.34	
Tandan, 1992[63]	Arm 1-Vehicle	1	4.55	
Tandan, 1992[63]	Arm 2-Capsaicin	1	4.55	
Thienel, 2004[64]	Arm 1-Placebo	32	8.33	
Thienel, 2004[64]	Arm 2-Topiramate, 100mg/day	41	16.21	
Thienel, 2004[64]	Arm 3-Topiramate, 200mg/day	93	25.00	
Thienel, 2004[64]	Arm 4-Topiramate, 400mg/day	79	30.38	
Tolle, 2008[65]	Arm 1-Placebo	3	3.13	The NNH for one discontinuation due to AEs was 10.3 (95% confidence interval 5.8, 42)
Tolle, 2008[65]	Arm 2-Pregabalin, 150 mg/day	5	5.05	The NNH for one discontinuation due to AEs was 10.3 (95% confidence interval 5.8, 42)
Tolle, 2008[65]	Arm 3-Pregabalin, 300 mg/day	11	11.11	The NNH for one discontinuation due to AEs was 10.3 (95% confidence interval 5.8, 42)

Author, year	Select arm	Dropouts due to adverse effects, N	Dropouts due to adverse effects, %	Comments
Tolle, 2008[65]	Arm 4-Pregabalin, 600 mg/day	13	12.87	The NNH for one discontinuation due to AEs was 10.3 (95% confidence interval 5.8, 42)
Vinik, 2007[66]	Arm 1-Placebo	4	4.44	
Vinik, 2007[66]	Arm 2-Lamotrigine, 200 mg/day	5	5.56	
Vinik, 2007[66]	Arm 3-Lamotrigine, 300 mg/day	8	8.89	
Vinik, 2007[66]	Arm 4-Lamotrigine, 400 mg/day	10	11.11	
Vrethem, 1997[67]	Arm 1-Placebo	NR	NR	
Vrethem, 1997[67]	Arm 2-Amitriptyline	3	15.79	
Vrethem, 1997[67]	Arm 3-Maprotiline	2	10.53	
Watson, 2003[68]	Arm 1-Placebo	1	9.09	
Watson, 2003[68]	Arm 2-CR Oxycodone	7	70.00	
Wernicke, 2006[69]	Arm 1-Placebo	8	7.41	
Wernicke, 2006[69]	Arm 2-Dutoxetine, 60mg	17	14.91	
Wernicke, 2006[69]	Arm 3-Dutoxetine, 120mg	20	17.86	

Author, year	Select arm	Dropouts due to adverse effects, N	Dropouts due to adverse effects, %	Comments
Wright, 1997[71]	Arm 1-Placebo	2	12.50	
Wright, 1997[71]	Arm 2-Mexiltetine	2	13.33	
Wymer, 2009[72]	Arm 1-Placebo	8	8.60	
Wymer, 2009[72]	Arm 2-Lacosamide, 200mg/day	8	8.60	
Wymer, 2009[72]	Arm 3-Lacosamide, 400mg/day	21	23.08	
Wymer, 2009[72]	Arm 4-Lacosamide, 600mg/day	37	39.78	
Ziegler, 2010[73]	Arm 1-Placebo	NR	NR	
Ziegler, 2010[73]	Arm 2-Lacosamide, 400mg/day slow titration	NR	13	
Ziegler, 2010[73]	Arm 3-Lacosamide, 400mg/day standard titraion	NR	8.20	
Ziegler, 2010[73]	Arm 4-Lacosamide, 600mg/day	NR	NR	

% = percent; AE = adverse events; APAP = acetaminophen; CR = controlled release; Mg = milligram; Mg/day=milligram per day; N = sample size; NNH = number needed to harm; NR = not reported; PGB = pregabalin

Evidence Table D-59. Study and intervention characteristics of supplement intervention (KQ2b)

Author, year Trial name	Study design Site(s)	Funding source	Start year of recruitment End year of recruitment	Run- in period	Study intervention Drug dosage (mg daily) Drug administration route
Ziegler, 2011[74] The Nathan 1 Trial	Parallel randomized controlled trial Multiple center: US, Canada and Europe	Industry MEDA GmbH & Co. KG, Bad Homburg, Germany	Not reported	Yes	Alpha-lipoic acid 600 Oral
Ziegler, 2006[75] SYDNEY 2 Trial	Parallel randomized controlled trial Multiple center: Israel and Russia	Industry, MEDA Pharma, Bad Homburg, Germany	Not reported	Yes	Alpha-lipoic acid 600 Oral
Ziegler, 1999[76] ALADIN III	Parallel randomized controlled trial Multiple center: Europe, 71 centers in Germany	Industry	Not reported	No	Alpha-lipoic acid 600mg x 3 weeks then 1800mg (IV x 3 weeks then PO) Intravenous
Ziegler, 1996[77] ALADIN	Parallel randomized controlled trial, Multiple center: Europe, 38 centers in Germany	Industry	Not reported	No	Alpha-lipoic acid 1200,600,100 (Received on weekdays only) Intravenous
Ametov, 2003[78] SYDNEY Trial	Parallel randomized controlled trial, Single center: Europe	Industry ASTA Medica	Not reported	Yes	Alpha-lipoic acid 600 Intravenous

Author, year Trial name	Study design Site(s)	Funding source	Start year of recruitment End year of recruitment	Run- in period	Study intervention Drug dosage (mg daily) Drug administration route
Ruhnau, 1999[79] ORPIL	Parallel randomized controlled trial Single center: Europe	Industry, ASTA Medica	Not reported	No	Alpha-lipoic acid 1800 (Given 14 days total, 5 days/ week) Oral
De Grandis, 2002*[80]	Parallel randomized controlled trial Multiple center: Europe	Industry, Sigma Tau	Not reported	Yes	Acetyl-L-carnitine 2000 Oral

ALADIN = Alpha-Lipoic Acid in Diabetic Neuropathy trial; ALADIN III = Alpha-Lipoic Acid in Diabetic Neuropathy trial phase 3; ASTA Medical; BID = twice daily; IV = intravenous; MEDA GmbH KG; ORPIL= Oral Pilot Trial; PO = per os; SYDNEY 2 = Symptomatic Diabetic Neuropathy trial; US = United States

* Received 1000mg IM BID X 10 days

Evidence Table D-60. Patient characteristics of supplement intervention (KQ2b)

Author, year	Arm name, N at enrollment	Actual length of mean follow-up	Female, n (%) Age	HbA1c, BMI	Duration of neuropathic symptoms	Number of withdrawals and/or losses to follow-up: N (%)
Ziegler, 2011[74]	Arm 1: ALA, N: 233	4 years	Female: (33.9) Age: mean: 53.3, SD: 8.3	HbA1c: mean: 8.9, SD:1.8 BMI: mean: 29.7, SD: 6.1	3 Years	(3)
Ziegler, 2011[74]	Arm 2: placebo, N: 227	4 years	Female: (33) Age: mean: 53.9, SD: 7.6	HbA1c: mean: 8.8, SD: 1.9 BMI: mean: 29.8, SD: 6.1	3.2 Years	(3)
Ziegler, 2006[75]	Arm 1: placebo, N: 43	5 weeks	Female: (65) Age: mean: 57, SD: 11	HbA1c: mean: 7.53, SD: 1.18 BMI: mean: 29.1, SD: 4.4	4.9 Years	(0)
Ziegler, 2006[75]	Arm 2: ALA600, N: 45	5 weeks	Female: (56) Age: mean: 56, SD: 12	HbA1c: mean: 7.58, SD: 1.09 BMI: mean: 28.7, SD: 3.9	4.8 Years	(0)
Ziegler, 2006[75]	Arm 3: ALA1200, N: 47	5 weeks	Female: (60) Age: mean: 59, SD: 12	HbA1c: mean: 7.85, SD: 1.31 BMI: mean: 30.9, SD: 4.5	5 Years	(0)

Author, year	Arm name, N at enrollment	Actual length of mean follow-up	Female, n (%) Age	HbA1c, BMI	Duration of neuropathic symptoms	Number of withdrawals and/or losses to follow-up: N (%)
Ziegler, 2006[75]	Arm 4: ALA1800, N: 46	5 weeks	Female: (59) Age: mean: 59, SD: 9	HbA1c: mean: 7.81, SD: 1.14 BMI: mean: 28.4, SD: 4.8	4.9 Years	(0)
Ziegler, 1999[76]	Arm 1: A-A, N: 165	7 months	Female: (54.5) Age: mean: 56.5, SD: 7.1	HbA1c: mean: 8.5, SD: 1.9 BMI: mean: 29, SD: 4.8	37.7 Months	(43)
Ziegler, 1999[76]	Arm 2: A-P, N: 173	7 months	Female: (45.7) Age: mean: 57, SD: 6.2	HbA1c: mean: 8.7, SD: 1.8 BMI: mean: 28.8, SD: 4.2	35.1 Months	(45)
Ziegler, 1999[76]	Arm 3: P-P, N: 165	7 months	Female: (49.7) Age: mean: 57.3, SD: 5.5	HbA1c: mean: 8.7, SD: 1.8 BMI: mean: 29.5, SD: 4.8	38 Months	(38)
Ziegler, 1996[77]	Arm 1: ALA 1200, N: 86	19 days	Female: (60) Age: mean: 59.2, SD: 7.7	HbA1c: mean: 8.8, SD: 1.9 BMI: mean: 29.2, SD: 4.8	3.3 Years	(21)

Author, year	Arm name, N at enrollment	Actual length of mean follow-up	Female, n (%) Age	HbA1c, BMI	Duration of neuropathic symptoms	Number of withdrawals and/or losses to follow-up: N (%)
Ziegler, 1996[77]	Arm 2: ALA 600, N: 77	19 days	Female : (63) Age: mean: 57.5, SD: 8.7	HbA1c: mean: 9.2, SD: 2.5 BMI: mean: 27.7, SD: 4.9	2.8 Years	(14)
Ziegler, 1996[77]	Arm 3: ALA 100, N: 81	19 days	Female: (49) Age: mean: 58.7, SD: 7.9	HbA1c: mean: 9, SD: 2.1 BMI: mean: 27.8, SD: 4.4	2.8 Years	(15)
Ziegler, 1996[77]	Arm 4: placebo, N: 82	19 days	Female: (65) Age: mean: 60.2, SD: 7.7	HbA1c: mean: 9.4, SD: 2.6 BMI: mean: 29.7, SD: 4.9	3.4 Years	(16)
Ametov, 2003**[78]	Arm 1: placebo, N: 60	3 weeks	Female: 36 (72) Age: mean: 55.4, SD: 8.66	HbA1c: NR BMI: mean: 29.3, SD: 5.23	3.4 Years	3.3(2)
Ametov, 2003[78]	Arm 2: ALA, N: 60	3 weeks	Female: 46 (77) Age: mean: 56.8, SD: 9.65	HbA1c: NR BMI: mean: 29.4, SD: 4.93	3.7 Years	0(0)

Author, year	Arm name, N at enrollment	Actual length of mean follow-up	Female, n (%) Age	HbA1c, BMI	Duration of neuropathic symptoms	Number of withdrawals and/or losses to follow-up: N (%)
Ruhnau, 1999[79]	Arm 1: TA, N: 12	3 weeks	Female: 6 (50) Age: mean: 60.5, SD: 6.9	HbA1c: mean: 7.7, SD: 1.3 BMI: mean: 29.6, SD: 4	4.1 Years	8.3(1)
Ruhnau, 1999[79]	Arm 2: placebo, N: 12	3 weeks	Female: 6 (50) Age: mean: 62.1, SD: 4.5	HbA1c: mean: 7.1, SD: 1.8 BMI: mean: 28.5, SD: 3.9	3.8 Years	8.3(1)
De Grandis, 2002[80]	Arm 1: LAC, N: 167	1 year	Female: 62 Age: NR	NR	NR	12(20)
De Grandis, 2002[80]	Arm 2: placebo, N: 166	1 year	Female: 66 Age: NR	NR	NR	11.4(19)

% = percentage; A-A = alpha-lipoic acid followed by alpha-lipoic acid treatment; ALA=alpha-lipoic acid; A-P = alpha-lipoic acid followed by placebo treatment; BMI = Body Mass Index; HbA1c = Glycated Haemoglobin; N = sample size; P-P = placebo followed by placebo treatment; SD = standard deviation

*Race is not reported

** Higher ration of men to women in placebo group, Figure 2 with the results is not in the article; ITT analysis

RefID 4763: "No significant differences were noted for any of the parameters listed, except for treatment with oral antidiabetic agens (p=0.018) and BMI (p=0.036), Not clear difference between WHICH groups

Evidence Table D-61. Supplement intervention - pain continuous outcomes (KQ2b)

Author, year	Arm	Instrument name	Baseline outcome	Time point(s)	Outcome at timepoint(s)	Within arm comparison	NOTES
*Ziegler, 2006[75]	Arm 1: placebo	TSS Stabbing Pain	N: 43, mean: 2.21, SD: 0.77	5 weeks	NR	Mean change from baseline: -0.83, SD:1.14 ALA600 vs placebo, p: <0.05	
Ziegler, 2006[75]	Arm 2: ALA600	TSS Stabbing Pain	N: 45, mean: 2.32, SD: 0.94	5 weeks	NR	Mean change from baseline: -1.4, SD: 1.15 ALA1200 vs placebo, p: <0.05	
Ziegler, 2006[75]	Arm 3: ALA1200	TSS Stabbing Pain	N: 47, mean: 2.38, SD: 0.89	5 weeks	NR	Mean change from baseline: -1.56, SD: 1.07 ALA1800 vs placebo, p: <0.05	
Ziegler, 2006[75]	Arm 4: ALA1800	TSS Stabbing Pain	N: 46, mean: 2.03, SD: 0.88	5 weeks	NR	Mean change from baseline: -1.46, SD: 1.2	
Ametov, 2003[78]	Arm 1: placebo	NSC(LL) Pain- severity	N: 58, mean: 10.6, SD: NR	3 weeks	N: 58, mean: NR, SD: NR	Mean change from baseline: -4.6, SD: NR	
Ametov, 2003[78]	Arm 2: ALA	NSC(LL) Pain- severity	N: 60, mean: 10, SD: NR	3 weeks	N: 60, mean: NR, SD: NR	Mean change from baseline: -7.3, SD: NR	
Ruhnau, 1999[79]	Arm 2: placebo	TSS pain -points	N: 11, mean: 1.47, SD: 0.54	Day 19	N: 11, mean: NR, SD: NR	Mean change from baseline: 0.79, SD: 0.81	
Ruhnau, 1999[79]	Arm 1: TA	TSS pain-points	N: 11, mean: 1.69, SD: 0.58	Day 19	N: 11, mean: NR, SD: NR	Mean change from baseline: -1.39, SD: 0.84 Mean change from baseline placebo p: 0.099	
De Grandis, 2002[80]	Arm 2: placebo	VAS-mm	N: 166, mean: 44.68, SD: 3.4	Month 12	N: 95, mean: 40.87, SD: 4	Mean change from baseline: -3.5, SD: 11	

Author, year	Arm	Instrument name	Baseline outcome	Time point(s)	Outcome at timepoint(s)	Within arm comparison	NOTES
De Grandis, 2002[80]	Arm 1: LAC	VAS-mm	N: 167, mean: 45.37, SD: 2.9	Month 12	N: 104, mean: 25.16, SD: 4.6	Mean change from baseline: -19.3, SD: 20.9 Mean change from baseline placebo p:<0.01	Data from figure 1

ALA = alpha-lipoic acid; LAC = levacecarnine; N = sample size; NR = not reported; NSC(LL) = Neuropathy Symptom Change Score – Lower Legs; p = p-value; SD = standard deviation; TSS = Total Symptom Score; VAS = Visual Analogue Scale

* Burning also reported but not abstracted

Evidence Table D-62. Supplement intervention - composite outcomes categorical total symptom score (KQ2b)

Author, year	Arm	Instrument name	Baseline outcome	Time point(s)	Outcome at time point(s)	Within arm comparison	Comments
Ziegler, 2011[74]	Arm 2: placebo	TSS Total (COMPOSITE, NOT PAIN)	N: 224, mean: 2.6, SD: 1.8	4 years	N:207,mean:NR,SD:NR	Mean change from baseline:-0.21,SD:2.45	
Ziegler, 2011[74]	Arm 1:ALA	TSS Total (COMPOSITE, NOT PAIN)	N: 230, mean: 2.4, SD: 1.9	4 years	N: 215, mean: NR, SD: NR	Mean change from baseline: -0.22, SD: 2.42 Mean change from baseline1 vs 2 p: NS	
Ziegler, 2006[75]	Arm 1: placebo	TSS Total (COMPOSITE, NOT PAIN)	N: 43, mean: 9.27, SD: 1.56	5 weeks	N: NR, mean: NR, SD: NR	Mean change from baseline: -2.92, SD: 3.18 ALA600 vs placebo, p: <0.05	
Ziegler, 2006[75]	Arm 2: ALA600	TSS Total (COMPOSITE, NOT PAIN)	N: 45, mean: 9.44, SD: 1.86	5 weeks	N: NR, mean: NR, SD: NR	Mean change from baseline: -4.85, SD: 3.03 ALA1200 vs placebo, p: <0.05	
Ziegler, 2006[75]	Arm 3: ALA1200	TSS Total (COMPOSITE, NOT PAIN)	N: 47, mean: 9.4, SD: 1.64	5 weeks	N: NR, mean: NR, SD: NR	Mean change from baseline: -4.5, SD: 3.28 ALA1800 vs placebo, p: <0.05	
Ziegler, 2006[75]	Arm 4: ALA1800	TSS Total (COMPOSITE, NOT PAIN)	N: 46, mean: 9.02, SD: 1.61	5 weeks	N: NR, mean: NR, SD: NR	Mean change from baseline: -4.7, SD: 3.54	
Ziegler, 1999[76]	Arm 2: placebo	TSS Total	N: 165, mean: 8.4, SD: 3.2	19 days	N: 165, mean: NR, SD: NR	Median change from baseline: -3, SD: NR ALA vs placebo, p:0.447 Median change from baseline - range reported: -12.3, 8. Post-hoc analysis with AUC - p=0.033	

Author, year	Arm	Instrument name	Baseline outcome	Time point(s)	Outcome at time point(s)	Within arm comparison	Comments
Ziegler, 1999[76]	Arm 1: ALA	TSS Total	N: 338, mean: NR, SD: NR	19 days	N: 338, mean: NR, SD: NR	Median change from baseline: -3.7, SD: NR Median change from baseline - range reported: -12.6, 5.	Note that in this study, Arm 1 and Arm 2 are used for the initial period, and then this is split into 3 arms for the longer-term study. Here we are reporting the initial period separately
Ziegler, 1999[76]	Arm 1: A-A	TSS Total	N: 165, mean: 8.1, SD: 3	7 months	N: 165, mean: NR, SD: NR	Median change from baseline: -3.98,SD: NR Median change from baseline - range reported: -12.64, 5.66	
Ziegler, 1999[76]	Arm 2 :A-P	TSS Total	N: 173, mean: 8.3, SD: 2.9	7 months	N: 173, mean: NR, SD: NR	Median change from baseline: -3.99, SD: NR Median change from baseline - range reported: -12.31, 5.33	
Ziegler, 1999[76]	Arm 3: P-P	TSS Total	N: 165, mean: 8.4, SD: 3.2	7 months	N: 165, mean: NR, SD: NR	Median change from baseline: -3.98, SD: NR Median change from baseline - range reported: -12.32, 8.32	
Ziegler, 1996[77]	Arm 4: placebo	TSS Total	N: 66, mean: NR, SD: NR	19 days	N: 66, mean: NR, SD: NR	Mean change from baseline: -2.5, SD: 3.2	Data taken from figure 1
Ziegler, 1996[77]	Arm 3: ALA100	TSS Total	N: 66, mean: NR, SD: NR	19 days	N: 66, mean: NR, SD: NR	Mean change from baseline: -3.3, SD: 2.8 P: NS	Data taken from figure 1

Author, year	Arm	Instrument name	Baseline outcome	Time point(s)	Outcome at time point(s)	Within arm comparison	Comments
Ziegler, 1996[77]	Arm 2: ALA600	TSS Total	N: 63, mean: NR, SD: NR	19 days	N: 63, mean: NR, SD: NR	Mean change from baseline -4.9, SD: 4.1 p: <0.05	Data taken from figure 1
Ziegler, 1996[77]	Arm 1: ALA1200	TSS Total	N: 65, mean: NR, SD: NR	19 days	N: NR, mean: NR, SD: NR	Mean change from baseline: -4.4, SD: 3.7 p:<0.05	Data taken from figure 1
Ruhnau, 1999[79]	Arm 2: placebo	TSS Total-points	N: 11, mean: 8.18, SD: 0.89	Day 19	N: 11, mean: NR, SD: NR	Mean change from baseline: -1.94, SD: 1.5	
Ruhnau, 1999[79]	Arm 1: TA	TSS Total-points (COMPOSITE)	N: 11, mean: 7.99, SD: 0.97	Day 19	N: 11, mean: NR, SD: NR	Mean change from baseline: -3.75, SD: 1.88 Mean change from baseline placebo p: 0.021	
Ametov, 2003[78] Sydney trial	Arm 1: placebo	TSS -points	N: 60, mean: 8.2, SD: 1.06	3 weeks	N: 58, mean: 6.4, SD: 1.97	Mean change from baseline: -1.83, SD: 1.97	Data taken from figure 2
Ametov, 2003[78]	Arm 2: ALA	TSS-points (COMPOSITE)	N: 60, mean: 8.8, SD: 1.02	3 weeks	N: 60, mean: 3, SD: 1.38	Mean change from baseline: -5.72, SD: 1.53 p: <0.001	

ALA = alpha-lipoic acid; N = sample size; NR = note reported; p = p-value; SD = standard deviation; TSS = Total Symptom Score

Evidence Table D-63. Supplement intervention - neuropathy symptom change severity (KQ2b)

Author, year	Arm	Instrument name	Baseline outcome	Time point(s)	Outcome at time point(s)	Within arm comparison
**Ziegler, 2006[75]	Arm 1: placebo	NSC(COMPOSITE NOT PAIN) Severity	N: 43, mean: 14.1, SD: 4.3	5 weeks	NR	Mean change from baseline: -4.9, SD: 4.3
Ziegler, 2006	Arm 2: ALA600	NSC Severity	N: 45, mean: 14.4, SD: 4.4	5 weeks	NR	Mean change from baseline: -7.4, SD: 4.6 ALA600 vs placebo, p: <0.05
Ziegler, 2006[75]	Arm 3: ALA1200	NSC Severity	N: 47, mean: 14.7, SD: 4.5	5 weeks	NR	Mean change from baseline: -7.2, SD: 5 ALA1200 vs placebo, p: <0.05
Ziegler, 2006[75]	Arm 4: ALA1800	NSC Severity	N: 46, mean: 13.5, SD: 3.5	5 weeks	NR	Mean change from baseline: -7.6, SD: 4.2 ALA1800 vs placebo, p: <0.05

ALA = alpha-lipoic acid; N = sample size; NR = note reported; NSC = Neuropathy Symptom Change; p = p-value; SD = standard deviation

** Study also reported NSC number of symptoms and change score

Evidence Table D-64. Supplement intervention - pain categorical outcomes (KQ2b)

Author, year	Arm	Instrument Name	N for analysis	Time point	Patients with outcomes, n, %	Between arm comparison
Ziegler, 2006[75]	Arm 1: placebo	TSS: >50% reduction	NR	5 weeks	n: NR, %: 26	% difference from baseline: 26
Ziegler, 2006[75]	Arm 2: ALA600	TSS: >50% reduction	NR	5 weeks	n: NR, %: 62	% difference from baseline: 62, ALA600 vs placebo, p: <0.05
Ziegler, 2006[75]	Arm 3: ALA1200	TSS: >50% reduction	NR	5 weeks	n: NR, %: 50	% difference from baseline: 50, ALA1200 vs placebo, p: <0.05
Ziegler, 2006[75]	Arm 4: ALA1800	TSS: >50% reduction	NR	5 weeks	n: NR, %: 56	% difference from baseline:56, ALA1800 vs placebo, p:<0.05
Ziegler, 1996[77]	Arm 4:placebo	TSS: >30% reduction	66	19 days	n: 38, %: 57.6	NR
Ziegler, 1996[77]	Arm 3: ALA100	TSS: >30% reduction	66	19 days	n: 43, %: 65.2	NR
Ziegler, 1996[77]	Arm 2: ALA600	TSS: >30% reduction	63	19 days	n: 52, %: 82.5	ALA600 vs placebo, p: 0.002
Ziegler, 1996[77]	Arm 1: ALA1200	TSS: >30% reduction	65	19 days	n: 46, %: 70.8	NS (Not reported as NS but assume these were)

% = percent ALA = alpha-lipoic acid; N = sample size; NR = note reported; NS = not significant; p = p-value; TSS = Total Symptom Score

Evidence Table D-65. Supplement intervention - paresthesia continuous outcomes (KQ2b)

Author, year	Arm	Instrument Name	Baseline N Mean SD	Time point(s)	N at time point(s)	Within arm comparison	Between arm comparison	Comments
Ziegler, 2006[75]	Arm 1: placebo	TSS Paresthesia	N: 43, mean: 2.21, SD: 0.63	5 weeks	N: NR	Mean change from baseline: -.8, SD: 1.17	NR	Instrument name is TSS, subscale parethesia
Ziegler, 2006[75]	Arm 2: ALA600	TSS Paresthesia	N: 45, mean: 2.32, SD: 0.8	5 weeks	N: NR	Mean change from baseline: -1.16, SD: 1.26	Mean change from baseline: ALA600 vs placebo, p: NS	NR
Ziegler, 2006[75]	Arm 3: ALA1200	TSS Paresthesia	N: 47, mean: 2.12, SD: 0.8	5 weeks	N: NR	Mean change from baseline: -0.85, SD: 1.21	Mean change from baseline: ALA1200 vs placebo, p: NS	NR
Ziegler, 2006[75]	Arm 4: ALA1800	TSS Paresthesia	N: 46, mean: 2.17, SD: 0.69	5 weeks	N: NR	Mean change from baseline: -1.12, SD: 1.2	Mean change from baseline: ALA1800 vs placebo, p: NS	NR
Ziegler, 1996[77]	Arm 4: placebo	TSS Paresthesia	N: 66, mean: 1.98, SD: 1.12	19 days	N: NR	Mean change from baseline: 0.8	Mean change from baseline: NA	Data taken from figure 2
Ziegler, 1996[77]	Arm 3: ALA100	TSS Paresthesia	N: 66, mean: 2.04, SD: 1.3	19 days	N: NR	Mean change from baseline: 1	Mean change from baseline: placebo, p: NS	Data taken from figure 2
Ziegler, 1996[77]	Arm 2: ALA600	TSS Paresthesia	N: 63, mean: 1.93, SD: 1.23	19 days	N: NR	Mean change from baseline: 1.4	Mean change from baseline: ALA600 vs placebo, p: <0.05	Data taken from figure 2
Ziegler, 1996[77]	Arm 1: ALA1200	TSS Paresthesia	N: 65, mean: 2.06, SD: 1.08	19 days	N: NR	Mean change from baseline: 1.2	Mean change from baseline: ALA1200 vs placebo, p: <0.05	Data taken from figure 2
Ametov, 2003[78]	Arm 1: placebo	NSC(LL) Positive Sensation—severity NR	N: 58, mean: 12.9, SD: NR	3 weeks	N: 58	mean change from baseline: -5, SD: NR	Mean change from baseline: NA	NR
Ametov, 2003[78]	Arm 2: ALA	NSC(LL) Positive Sensation—severity NR	N: 60, mean: 12.2, SD: NR	3 weeks	N: 60	mean change from baseline: -8.3, SD: NR	Mean change from baseline: placebo, p: <0.001	Not totally sure what this is but appears to be paresthesia
Ruhnau, 1999[79]	Arm 2: placebo	TSS paresthesia, points	N: 11, mean: 2, SD: 0.74	Day 19	N: 11	Mean change from baseline: -0.51,SD: 0.98	NR	NR
Ruhnau, 1999[79]	Arm 1: TA	TSS paresthesia, points	N: 11, mean: 1.91, SD: 0.57	Day 19	N: 11	Mean change from baseline: -0.82, SD: 0.6	Mean change from baseline: placebo, p: 0.517	NR

Evidence Table D-66. Supplement intervention - numbness continuous outcome (KQ2b)

Author, year	Arm	Instrument Name	Baseline N Mean SD	Time point(s)	N at time point(s)	Within arm comparison
Ziegler, 2006[75]	Arm 1: placebo	TSS Numbness	N: 43, mean: 2.74, SD: 0.67	5 weeks	NR	Mean change from baseline: -0.79, SD: 1.09 Mean change from baseline: ALA600 vs placebo, p: NS
Ziegler, 2006[75]	Arm 2: ALA600	TSS Numbness	N: 45, mean: 2.58, SD: 0.67	5 weeks	NR	Mean change from baseline: -0.97, SD: 1.06
Ziegler, 2006[75]	Arm 3: ALA1200	TSS Numbness	N: 47, mean: 2.73, SD: 0.66	5 weeks	NR	Mean change from baseline: -0.99, SD: 1.13 Mean change from baseline: ALA1200 vs placebo, p: NS
Ziegler, 2006[75]	Arm 4: ALA1800	TSS Numbness	N: 46, mean: 2.67, SD: 0.72	5 weeks	NR	Mean change from baseline: -0.98, SD: 1.16 Mean change from baseline: ALA1800 vs placebo, p: NS
Ziegler, 1996[77]	Arm 1: ALA1200	TSS Numbness	N: 65, mean: 2.04, SD: 1.24	19 days	NR	Mean change from baseline: 1.1, SD: NR Mean change from baseline: ALA1200 vs placebo, p: <0.05
Ziegler, 1996[77]	Arm 2: ALA600	TSS Numbness	N: 63, mean: 2.17, SD: 1.28	19 days	NR	Mean change from baseline: 1.1, SD: NR ALA600 vs placebo, p: <0.05
Ziegler, 1996[77]	Arm 3: ALA100	TSS Numbness	N: 63, mean: 1.95, SD: 1.34	19 days	NR	Mean change from baseline: 0.7, p: NS
Ziegler, 1996[77]	Arm 4: placebo	TSS Numbness	N: 63, mean: 1.89, SD: 1.32	19 days	NR	Mean change from baseline: 0.7, (Data taken from figure 2)
Ametov, 2003[78]	Arm 1: placebo	NSC(LL) Negative Sensation—severity	N: 58, mean: 3.5, SD: NR	3 weeks	58	mean change from baseline: -0.7, SD: NR

Author, year	Arm	Instrument Name	Baseline N Mean SD	Time point(s)	N at time point(s)	Within arm comparison
Ametov, 2003[78]	Arm 2: ALA	NSC(LL) Negative Sensation—severity	N: 60, mean: 2.7, SD: NR	3 weeks	60	mean change from baseline: -1.2, SD: NR Mean change from baseline: placebo, p: 0.043 Not totally sure what this is but appears to be numbness
Ruhnau, 1999[79]	Arm 1: TA	TSS numbness - points	N: 11, mean: 2.36, SD: 0.5	Day 19	11	Mean change from baseline: -0.12, SD: 0.92 Mean change from baseline: placebo, p: 0.67
Ruhnau, 1999[79]	Arm 2: placebo	TSS numbness-points	N: 11, mean: 2.61, SD: 0.13	Day 19	11	Mean change from baseline: 0, SD: 0

ALA = alpha-lipoic acid; N = sample size; NR = note reported; NS = not significant; NSC(LL) = Neuropathy Symptom Change Score – Lower Legs; p = p-value; SD = standard deviation; TSS = Total Symptom Score

Evidence Table D-67. Supplement intervention - harms (KQ2b)

Author, year	Arm	Adverse effect	N for analysis	Time point (s)	Patients with outcomes, n, %	Results
Ametov, 2003[78]	Arm 1: placebo	NR	NR	NR	n: NR, %: NR	NR
Ametov, 2003[78]	Arm 2: ALA	NR	NR	NR	n: NR, %: NR	NR
Ruhnau, 1999[79]	Arm 1: TA	NR	NR	NR	n: NR, %: NR	NR
Ruhnau, 1999[79]	Arm 2: placebo	NR	NR	NR	n: NR, %: NR	Not reported - only adverse events (1 pt had MI)
Ziegler, 1996[77]	Arm 1: ALA1200	Total	86	NR	n: 28, %: 32.6	NR
Ziegler, 1996[77]	Arm 2: ALA600	Total	77	NR	n: 14, %: 18.2	NR
Ziegler, 1996[77]	Arm 3: ALA100	Total	81	NR	n: 11, %: 13.6	NR
Ziegler, 1996[77]	Arm 4: placebo	Total	82	NR	n: 17, %: 20.7	NR
Ziegler, 1996[77]	Arm 1: ALA1200	Headache	86	NR	n: 5, %: NR	NR
Ziegler, 1996[77]	Arm 2: ALA600	Headache	77	NR	n: 6, %: NR	NR
Ziegler, 1996[77]	Arm 3: ALA100	Headache	81	NR	n: 6, %: NR	NR
Ziegler, 1996[77]	Arm 4: placebo	Headache	82	NR	n: 8, %: NR	NR
Ziegler, 1996[77]	Arm 1: ALA1200	Nausea	86	NR	n: 13, %: NR	NR
Ziegler, 1996[77]	Arm 2: ALA600	Nausea	77	NR	n: 2, %: NR	NR
Ziegler, 1996[77]	Arm 3: ALA100	Nausea	81	NR	n: 1, %: NR	NR
Ziegler, 1996[77]	Arm 4: placebo	Nausea	82	NR	n: 1, %: NR	NR
Ziegler, 1996[77]	Arm 1: ALA1200	Vomiting	86	NR	n: 8, %: NR	ALA1200 vs other groups, p: <0.05
Ziegler, 1996[77]	Arm 2: ALA600	Vomiting	77	NR	n: 0, %: NR	NR
Ziegler, 1996[77]	Arm 3: ALA100	Vomiting	81	NR	n: 0, %: NR	NR
Ziegler, 1996[77]	Arm 4: placebo	Vomiting	82	NR	n: 0, %: NR	NR
Ziegler, 1999[76]	Arm 1: ALA	Total	341	19 days	n: 72, %: 21.1	significant difference between groups

Author, year	Arm	Adverse effect	N for analysis	Time point (s)	Patients with outcomes, n, %	Results
Ziegler, 1999[76]	Arm 2: placebo	Total	168	19 days	n: 41, %: 24.4	significant difference between groups
Ziegler, 1999[76]	Arm 1: A-A	Total	167	7 months	n: 77, %: 46.1	significant difference between groups
Ziegler, 1999[76]	Arm 2: A-P	Total	174	7months	n: 66, %: 37.9	significant difference between groups
Ziegler, 1999[76]	Arm 3: P-P	Total	168	7months	n: 75, %: 44.6	significant difference between groups
Ziegler, 2006[75]	Arm 1: placebo	Nausea	43	NR	n: 0, %: 0	NR
Ziegler, 2006[75]	Arm 2: ALA600	Nausea	45	NR	n: 6, %: 13	ALA600 vs placebo, p: <0.05
Ziegler, 2006[75]	Arm 3: ALA1200	Nausea	47	NR	n: 10, %: 21	ALA1200 vs placebo, p: <0.05
Ziegler, 2006[75]	Arm 4: ALA1800	Nausea	46	NR	n: 22, %: 48	ALA1800 vs placebo, p: <0.05
Ziegler, 2006[75]	Arm 1: placebo	Overall	43	NR	n: 9, %: 21	NR
Ziegler, 2006[75]	Arm 2: ALA600	Overall	45	NR	n: 12, %: 27	ALA600 vs placebo, p: 0.53
Ziegler, 2006[75]	Arm 3: ALA1200	Overall	47	NR	n: 20, %: 43	ALA1200 vs placebo, p: 0.03
Ziegler, 2006[75]	Arm 4: ALA1800	Overall	46	NR	n: 25, %: 54	ALA1800 vs placebo, p: 0.001
Ziegler, 2006[75]	Arm 1: placebo	Vertigo	43	NR	n: 0, %: 0	NR
Ziegler, 2006[75]	Arm 2: ALA600	Vertigo	45	NR	n: 2, %: 4	ALA600 vs placebo, p: NS
Ziegler, 2006[75]	Arm 3: ALA1200	Vertigo	47	NR	n: 2, %: 4	ALA1200 vs placebo, p: NS
Ziegler, 2006[75]	Arm 4: ALA1800	Vertigo	46	NR	n: 5, %: 11	ALA1800 vs placebo, p: 0.056
Ziegler, 2006[75]	Arm 1: placebo	Vomiting	43	NR	n: 0, %: 0	NR
Ziegler, 2006[75]	Arm 2: ALA600	Vomiting	45	NR	n: 1, %: 2	ALA600 vs placebo, p: NS
Ziegler, 2006[75]	Arm 3: ALA1200	Vomiting	47	NR	n: 2, %: 4	ALA1200 vs placebo, p: NS
Ziegler, 2006[75]	Arm 4: ALA1800	Vomiting	46	NR	n: 12, %: 26	ALA1800 vs placebo, p: <0.05

ALA = alpha-lipoic acid; N = sample size; NR = not reported; p = p-value

Evidence Table D-68. Supplement intervention - dropouts (KQ2b)

Author, year	Arm	Dropouts due to adverse effects, n , %	Comments
Ziegler, 2011[74]	Arm 2: placebo	n: 1, %: 0.7	
Ziegler, 2011[74]	Arm 1: ALA	n: 2, %: 0.9	Adverse effects not reported - only events by system (eg, cardiovascular) that occurred over course of the study
Ziegler, 2006[75]	Overall	n: 12, %: 6.6	
Ziegler, 2006[75]	Arm 1: placebo	n: 1, %: 2.3	
Ziegler, 2006[75]	Arm 2: ALA600	n: 0, %: 0	
Ziegler, 2006[75]	Arm 3: ALA1200	n: 5, %: 10.6	
Ziegler, 2006[75]	Arm 4: ALA1800	n: 6, %: 13	
Ziegler, 1999[76]	Arm 1: A-A	n: 4, %: 2.7	
Ziegler, 1999[76]	Arm 2: A-P	n: 1, %: 0.6	
Ziegler, 1999[76]	Arm 3: P-P	n: 6, %: 3.6	

Author, year	Arm	Dropouts due to adverse effects, n , %	Comments
Ziegler, 1996[77]	Arm 4: placebo	n: 1, %: 1.5	
Ziegler, 1996[77]	Arm 3: ALA100	n: 1, %: 1.5	
Ziegler, 1996[77]	Arm 2: ALA600	n: 1, %: 1.6	
Ziegler, 1996[77]	Arm 1: ALA1200	n: 5, %: 7.7	
Ametov, 2003[78]	Arm 1: placebo	n: 2, %: 1.6	Very difficult to interpret drop outs and AEs
Ametov, 2003[78]	Arm 2: ALA	n: 0, %: 0	
Ruhnau, 1999[79]	Arm 2: placebo	n: 1, %: 9.1	MI
Ruhnau, 1999[79]	Arm 1: TA	n: 1, %: 9.1	Lack of efficacy
De Grandis, 2002[80]	Arm 2: placebo	n: 2, %: 1.9	Multiple reasons

Author, year	Arm	Dropouts due to adverse effects, n , %	Comments
De Grandis, 2002[80]	Arm 1: LAC	n: 6, %: 6.3	LAC 15, placebo 10 dropouts not due to AEs

% = percent; AE = adverse events; ALA = alpha-lipoic acid; LAC = levacecarnine; N = sample size; NR = not reported; TA = thioctic acid

Evidence Table D-69. Acupuncture intervention - study characteristics (KQ2b)

Author, year	Study Design Study site	Funding source	Recruitment Start YEAR - End YEAR	Was run-in period reported?
Garrow, 2014[81]	Parallel randomized controlled trial Single center: Europe	Government	2008-2010	No

Evidence Table D-70. Acupuncture interventions characteristics (KQ2b)

Author, year	Arm	Time per session Total number of sessions
Garrow, 2014[81]	Arm 1 - Sham	10 weeks 45 min per session, 1 session per week
Garrow, 2014[81]	Arm 2 - Acupuncture	10 weeks 45 min per session, 1 session per week

min = minutes

Evidence Table D-71. Acupuncture intervention - participant characteristics

Author, year	Arm, N at enrollment	Actual length of follow-up-MEAN unit for follow-up	Women, n (%)	Age, years:	HbA1c	BMI	Duration of pain	Duration of neuropathic symptoms	Number of withdrawals and/or losses to follow-up: N
Garrow, 2014[81]	Arm 1 - Sham	10 weeks	(29)	mean: 63, SD: 10.8	NR	NR	NR	NR	10
Garrow, 2014[81]	Arm 2 - Acupuncture	10 weeks	(33)	mean: 68, SD: 11.1	NR	NR	NR	NR	4

BMI = Body Mass Index; HbA1c = glycated haemoglobin; N = sample size; NR = not reported; SD = standard deviation

Evidence Table D-72. Acupuncture intervention - pain continuous outcomes (KQ 2b)

Author, year	Arm	Instrument Name	Baseline N, Mean, SD	Time point(s)	at time point(s), N Mean SD:	Within arm comparison	Between arm comparison
Garrow, 2014[81]	Arm 1 - Sham	VAS	N: 21, Mean: 67, SD: 19	10 weeks	N: 21, Mean: 62, SD: 23	Mean change from baseline: -5 (95% CI:-11,1.1)	NR
Garrow, 2014[81]	Arm 2 - Acupuncture	VAS	N: 24, Mean: 73, SD: 24	10 weeks	N:24, Mean:58, SD:26	Mean change from baseline: -15 (95% CI:-26,-3.5)	Change score: 7 (95% CI:-4, 19), p: NS

CI = confidence interval; N = sample size; NR = not reported; NS = not significant; SD = standard deviation; VAS = Visual Analogue Scale

Evidence Table D-73. Acupuncture intervention - quality of life (KQ2b)

Author, year	Arm	Instrument	Baseline N, Mean SD	Time point(s)	at time point(s), N Mean SD	Within arm comparison	Between arm comparison
Garrow, 2014[81]	Arm 1 - Sham	SF-36 physical component score	N: 21, Mean: 32.1, SD: 9.8	10 weeks	N: 21, Mean: 31.5, SD: 10.3	Mean difference from baseline: -0.6 (95% CI:-2.7, 1.5)	Mean difference from baseline: -2.2 (95% CI:-5.2,0.77), Comparator: Sham, p: NS
Garrow, 2014[81]	Arm 2 - Acupuncture	SF-36 physical component score	N: 24, Mean: 31.9, SD: 9.2	10 weeks	N: 24, Mean: 33.6, SD: 8.7	Mean difference from baseline: 1.6 (95% CI:-0.7, 3.9)	Mean difference from baseline: -2.2 (95% CI:-5.2,0.77), Comparator: Sham, p: NS
Garrow, 2014[81]	Arm 1 - Sham	SF-36 bodily pain score	N: 21, Mean: 27.7, SD: 16.9	10 weeks	N: 21, Mean: 33.9, SD: 20.9	Mean change from baseline: 6.3 (95% CI:-4.8, 17.5)	Mean change from baseline: -1.2 (95% CI:-10.8, 8.4), Comparator: Sham, p: NS
Garrow, 2014[81]	Arm 2 - Acupuncture	SF-36 bodily pain score	N: 24, Mean: 37.7, SD: 27.4	10 weeks	N: 24, Mean: 40.2, SD: 20.2	Mean change from baseline: 2.5 (95% CI:-5.8, 10.7)	Mean change from baseline: -1.2 (95% CI:-10.8, 8.4), Comparator: Sham, p: NS

CI = confidence interval; N = sample size; NR = not reported; NS = not significant; p = p-value; SD = standard deviation; SF-36 = 36 item Short Form Survey; VAS = Visual Analogue Scale

Evidence Table D-74. Acupuncture intervention - harms (KQ2b)

Author, year	Select Arm	Adverse events	N for analysis	Patients with adverse events, N (%)
Garrow, 2014[81]	Arm 1 - Sham	NR	21	1(4.76)
Garrow, 2014[81]	Arm 2 - Acupuncture	NR	24	2(8.33)

% = percent; N = sample size; NR = not reported

Evidence Table D-75. Study characteristics of cognitive therapy intervention (KQ2b)

Author, year	Study Design Study site	Funding source	Recruitment Start YEAR - End YEAR	Was run-in period reported?
Otis, 2013[82]	Parallel randomized controlled trial Single center: North America	Government	NR	No

NR = not reported

Evidence Table D-76. Cognitive therapy intervention - participant characteristics (KQ2b)

Author, year	Arm, N at enrollment	Actual length of follow-up-MEAN unit for follow-up	Women, n (%)	Age, years:	HbA1c	BMI	Duration of pain	Duration of neuropathic symptoms	Number of withdrawals and/or losses to follow-up: N
Otis, 2013[82]	Arm 1 - Control (treatment as usual), 8	4 months	0(0)	63.38	NR	NR	NR	NR	0
Otis, 2013[82]	Arm 2 - Cognitive behavioral therapy (CBT), 11	4 months	0(0)	62.50	NR	NR	NR	NR	3

BMI = Body Mass Index; CBT = cognitibe behavioral therapy; HbA1c = glycated haemoglobin; N = sample size; NR = not reported

Evidence Table D-77. Cognitive therapy interventions characteristics (KQ2b)

Author, year	Arm	Voltage Pulse Current Session: duration of session frequency:
Otis, 2013[82]	Arm 1 - Control (treatment as usual)	Usual treatment therapy determined by participant's primary care provider.
Otis, 2013[82]	Arm 2 - Cognitive behavioral therapy (CBT)	Cognitive behavioral pain management therapy given weekly for 11 sessions

CBT = cognitibe behavioral therapy

Evidence Table D-78. Cognitive therapy intervention - pain continuous outcomes (KQ2b)

Author, year	Arm	Instrument Name	Baseline N, Mean, SD	Time point(s)	At time point(s), N Mean SD:	Within arm comparison	Between arm comparison
Otis, 2013[82]	Arm 1 - Control (treatment as usual)	WHYMPI	N: 8, Mean: 3.8, SD: 0.9	4 months	N: 8, Mean: 3.7, SD: 0.9	NR	NR
Otis, 2013[82]	Arm 2 - Cognitive behavioral therapy (CBT)	WHYMPI	N: 11, Mean: 3.9, SD: 1.4	4 months	N: 8, Mean: 2.8, SD: 1.3	NR	Mean change from baseline: -0.54, Comparator arm: control, p: <0.05

CBT = cognitive behavioral therapy; N = sample size; NR = not reported; p = p-value; SD = standard deviation; WHYMPI = West Haven Yale Multidimensional Pain Inventory

Evidence Table D-79. Study characteristics of electrical stimulation intervention (KQ2b)

Author, year	Study Design Study site	Funding source	Recruitment Start YEAR - End YEAR	Was run-in period reported?	Comments
Lacigova, 2013[83]	Crossover randomized controlled trial Single center: Europe	Academics	NR	No	
Gossrau, 2011[84]	Parallel randomized controlled trial Single center: Europe	NR	NR	No	
Forst, 2004[85]	Parallel randomized controlled trial NR: Europe	NR	NR	No	
Hamza, 2000[86]	Crossover randomized controlled trial NR: North America	Non-profit	NR	1 week	
Oyibo, 2004[87]	Crossover randomized controlled trial NR: Europe	Industry	NR	4 weeks	
Kumar, 1998[88]	Parallel randomized controlled trial NR: North America	Industry	NR	Yes	Amitryptiline run in
Kumar, 1997[89]	Parallel randomized controlled trial NR: North America	Industry	NR	NR	

NR = not reported

Evidence Table D-80. Electrical stimulation intervention - participant characteristics (KQ2b)

Author, year	Arm, N at enrollment	Actual length of follow-up-MEAN unit for follow-up	Women, n (%)	Age, years:	HbA1c	BMI	Duration of pain	Duration of neuropathic symptoms	Number of withdrawals and/or losses to follow-up: N	Comments
Lacigova, 2013[83]	Arm 1 – Control - Sham, 32	80 days	11 (NR)	mean: 62, SD: 7.2	NR	NR	NR	5.3 Years	2	
Lacigova, 2013[83]	Arm 2 - Mesodiencephalic moedulation (MDM), 32	80 days	11 (NR)	mean: 62, SD: 7.2	NR	NR	NR	5.3 Years	2	
Gossrau, 2011[84]	Arm 1 - Placebo, 19	8 weeks	NR (NR)	mean: 65.95, SD: 7.05	%mean: 7.02, SD: 0.84	mean: 29.86, SD: 4.09	58.12	NR	0	
Gossrau, 2011[84]	Arm 2 - micro-TENS (Microcurrent Transcutaneous Electric Nerve Stimulation), 21	8 weeks	NR (NR)	mean: 67.91, SD: 12.13	%mean: 7.04, SD: 0.71	mean: 29.05, SD: 3.64	46.31	NR	1	
Forst, 2004[85]	Arm 1 – Control - Sham, 11	12 weeks	3 (NR)	mean: 59.4, SD: 8.6	%mean: 6.5, SD: 0.7	mean: NR, SD: NR	NR	NR	4	
Forst, 2004[85]	Arm 2 - Transcutaneous electrical nerve stimulation (TENS), 13	12 weeks	6 (0.5)	mean: 57.6, SD: 11.5	%mean: 6.6, SD: 0.9	NR	NR	NR	1	
Hamza, 2000[86]	Overall - , 50	3 weeks	28 (NR)	mean: 55, SD: 9	NR	NR	NR	NR	NR	
Oyibo, 2004[87]	Overall - , 30	6 weeks	7 (NR)	mean: 57.7, SD: 10.7	%mean: 8.3, SD: 1.4	NR	NR	4 Years	16	
Kumar, 1998[88]	Arm 1 – Control - Sham, 9	12 weeks	3 (NR)	mean: 58, SD: 4	NR	mean: 32.4, SD: 2.9	NR	21 Months	NR	Only counted from electrotherapy portion of the study. Participants for electrotherapy session selected from patients with no improvement in the amitriptyline therapy session.

Author, year	Arm, N at enrollment	Actual length of follow-up- MEAN unit for follow-up	Women, n (%)	Age, years:	HbA1c	BMI	Duration of pain	Duration of neuropathic symptoms	Number of withdrawals and/or losses to follow-up: N	Comments
Kumar, 1998[88]	Arm 2 - Electrotherapy, 14	12 weeks	10 (NR)	mean: 59, SD: 2	NR	mean: 32.4, SD: 1.8	NR	22 Months	NR	Only counted from electrotherapy portion of the study. Participants for electrotherapy session selected from patients with no improvement in the amitriptyline therapy session.
Kumar, 1997[89]	Arm 1 - Sham, 13	4 weeks	8 (NR)	mean: 59, SD: 3	NR	mean: 30.5, SD: 1.8	NR	22 Months	NR	
Kumar, 1997[89]	Arm 2 - Transcutaneous electrostimulation, 18	4 weeks	11 (NR)	mean: 53, SD: 4	NR	mean: 29.2, SD: 2.9	NR	16 Months	NR	

% = percent; BMI = Body Mass Index; CBT = cognitibe behavioral therapy; HbA1c = glycated haemoglobin; MDM = Mesodiencephalic moedulation; Micro-TENS = Microcurrent Transcutaneous Electric Nerve Stimulation; N = sample size; NR = not reported; SD = standard deviation; TENS = Transcutaneous Electric Nerve Stimulation

Evidence Table D-81. Electrical stimulation interventions characteristics (KQ2b)

Author, year	Arm	Voltage Pulse Current Session: duration of session frequency:
Lacigova, 2013[83]	Arm 1 – Control - Sham	NR
Lacigova, 2013[83]	Arm 2 - Mesodiencephalic moedulation (MDM)	Voltage: Rectangular pulse: 230V, Pulse: NR, Current: 4mA-8mA, 10mA max, session: Twice daily treatment first 3 days, then daily for the remaining 10 days. Total 13 days, frequency: 50 Hz
Gossrau, 2011[84]	Arm 1 - Placebo	NA
Gossrau, 2011[84]	Arm 2 - micro-TENS (Microcurrent Transcutaneous Electric Nerve Stimulation)	Voltage: NR, Pulse: NR, Current: 30-40uA, session: 30 min/ 13 sessions, frequency: 2 Hz
Forst, 2004[85]	Arm 1 - Sham	NA
Forst, 2004[85]	Arm 2 - Transcutaneous electrical nerve stimulation (TENS)	Voltage: NR, Pulse: NR, Current: 5-70mA, session: 30 min, frequency: 4Hz
Hamza, 2000[86]	Arm 1 - Sham	NA
Hamza, 2000[86]	Arm 2 - Percutaneous Electrical Nerve Stimulation (PENS)	Voltage: Biphasic pulse, Pulse: 0.5ms, Current: 25mA, session: 30 min ,frequency: 15-30 Hz per 3s
Oyibo, 2004[87]	Arm 1 - Sham: wear stocking with electrodes but given insignificant current	Voltage: 5V, Pulse: NR, Current: NR, session: NR, frequency: NR

Author, year	Arm	Voltage Pulse Current Session: duration of session frequency:
Oyibo, 2004[87]	Arm 2 - Wear silver plated nylon-dacron stocking with electrodes	Voltage: 50V, Pulse: 80-80 pulses, Current: 50uA, session: NR, frequency: NR
Oyibo, 2004[87]	Arm 1 - Sham	NR
Oyibo, 200[87]	Arm 2 - Stocking electrodes	NR
Kumar, 1998[88]	Arm 1 - Sham: machine had inactive output terminals	NR
Kumar, 1998[88]	Arm 2 - Given working electrotherapy H-wave machines	Voltage: ≤35V, Pulse: Biphasic pulse: 4ms, Current: <35mA, session: NR, frequency: 2-70Hz
Kumar, 1997[89]	Arm 1 - Sham: machine had inactive output terminals	
Kumar, 1997[89]	Arm 2 - Transcutaneous electrostimulation: Given working electrotherapy H-wave machines	Voltage: ≤35V, Pulse: Biphasic pulse: 4ms, Current: <35mA, session: 30 min per day, frequency: 2-70Hz

Hz = Hertz; mA = milliamps; MDM = Mesodiencephalic moedulation; Micro-TENS = Microcurrent Transcutaneous Electric Nerve Stimulation; NA = not available; NR = not reported; PENS = Percutaneous Electrical Nerve Stimulation; TENS = Transcutaneous Electric Nerve Stimulation; uA = microamps; V = voltage

Evidence Table D-82. Electrical stimulation intervention - pain continuous outcomes (KQ2b)

Author, year	Arm	Instrument Name	Baseline N, Mean, SD	Time point(s)	At time point(s), N Mean SD:	Within arm comparison	Between arm comparison
Forst, 2004[85]	Arm 1 – Control - Sham	VAS: 0-10 scale	N: 7, Mean: 15.3, SD: 8.5	12 weeks	N: 7, Mean: 15, SD: 11.8	NR	NR
Forst, 2004[85]	Arm 2 - Transcutaneous electrical nerve stimulation (TENS)	VAS: 0-10 scale	N: 12, Mean: 19.8, SD: 5	12 weeks	N: 12, Mean: 17.8, SD: 8.8	NR	NR
Kumar, 1998[88]	Arm 1 – Control - Sham: machine had inactive output terminals	Pain scale (tool NR): 0-5 scale	N: 9, Mean: 2.8, SD: 0.3	12 weeks	N: 9, Mean: 1.9, SD: 0.5	Mean change from baseline: -0.9, SD: 0.3, p: <0.03	NR
Kumar, 1998[88]	Arm 2 - Given working electrotherapy H-wave machines	Pain scale (tool NR): 0-5 scale	N: 14, Mean: 3.2, SD: 0.2	12 weeks	N: 14, Mean: 1.4, SD: 0.4	Mean change from baseline: -1.8, SD: 0.3, p: <0.01	Mean change from baseline: , Comparator arm: Sham p:<0.03
Kumar, 1997[89]	Arm 1 – Control - Sham	Pain scale (tool NR): 0-5 scale	N: 13, Mean: 2.92, SD: 0.13	4 weeks	N: 13, Mean: 2.38, SD: 0.26	Mean change from baseline: -0.54, SD: 0.21, p: <0.04	% change from baseline: -27, Comparator arm: Sham, SD: 10, p: <0.05
Kumar, 1997[89]	Arm 2 - Transcutaneous electrostimulation	Pain scale (tool NR): 0-5 scale	N: 18, Mean: 3.17, SD: 0.12	4 weeks	N: 18, Mean: 1.44, SD: 0.25	Mean change from baseline: p: <0.01	% change from baseline:- 52, Comparator arm:, SD: 7, p: NR
Hamza, 2000[86]	Arm 1 – Control - Sham	VAS-10 cm	N: 50, Mean: 5.2, SD: 1.6	3 weeks	N: 50, Mean: 4.8, SD: 1.2	NR	Mean change from baseline: , Comparator arm: , p: <0.05
Hamza, 2000[86]	Arm 2 - Percutaneous Electrical Nerve Stimulation (PENS)	VAS-10 cm	N: 50, Mean: 6.2, SD: 1.3	3 weeks	N: 50, Mean: 2.6, SD: 0.9	Mean change from baseline:, p: <0.05	Mean change from baseline: , Comparator arm: Sham, p: <0.05
Lacigova, 2013[83]	Arm 1 – Control - Sham	VAS: 0-10 scale	N: 32, Mean: 4.3, SD: 1.9	30 days	N: 32, Mean: 4.1, SD: 1.8	Mean change from baseline: 0	NR
Lacigova, 2013[83]	Arm 2 - Mesodiencephalic moedulation (MDM)	VAS: 0-10 scale	N: 32, Mean: 4.4, SD: 1.4	30 days	N: 32, Mean: 4, SD: 2.1	Mean change from baseline: -0.4	Mean change from baseline: , Comparator arm: Sham, p: 0.46

Author, year	Arm	Instrument Name	Baseline N, Mean, SD	Time point(s)	At time point(s), N Mean SD:	Within arm comparison	Between arm comparison
Author, year	**Arm**	**Instrument Name**	**Baseline N, Mean, SD**	**Time point(s)**	**At time point(s), N Mean SD:**	**Within arm comparison**	**Between arm comparison**
Oyibo, 2004[87]	Arm 1 – Control - Sham	VAS-10 cm	N: 14, Mean: 7.1 (95% CI: 5.6-8.7), SD: NR	6 weeks	N: 14, Mean: 3.6 (95% CI: 1.8-6.0), SD: NR	Mean change from baseline: , p: 0.02	Median change from baseline: 49.2
Oyibo, 2004[87]	Arm 2 - Stocking electrodes	VAS-10 cm	N: 14, Mean: 6.2 (95% CI: 3.9-8.4), SD: NR	6 weeks	N: 14, Mean: 3.1 (95% CI: 1.0-5.1), SD: NR	Mean change from baseline: , p: 0.003	Median change from baseline: 40.1, Comparator arm: control, SD: NR, p: 0.7
Gossrau, 2011[84]	Arm 1 - placebo	Neuropathic pain score (NPS)	N: 19, Mean: 43.42, SD: 13.3	4 weeks	N: 19, Mean: 32.74, SD: 17.2	NR	Mean change from baseline:, Comparator arm: , p: >0.18
Gossrau, 2011[84]	Arm 2 - micro-TENS (Microcurrent Transcutaneous Electric Nerve Stimulation)	Neuropathic pain score (NPS)	N: 21, Mean: 43.18, SD: 12.9	4 weeks	N: 21, Mean: 36.23, SD: 15	NR	Mean change from baseline: , Comparator arm: placebo, p:> 0.18

% = percent; MDM = Mesodiencephalic moedulation; Micro-TENS = Microcurrent Transcutaneous Electric Nerve Stimulation; N = sample size; NPS = Neuropathic Pain Scale; NR = not reported; p = p-value; PENS = Percutaneous Electrical Nerve Stimulation; SD = standard deviation; TENS = Transcutaneous Electric Nerve Stimulation; VAS = Visual Analogue Scale

Evidence Table D-83. Electrical stimulation intervention - pain categorical outcomes (KQ2b)

Author, year	Arm	N for analysis	Instrument Name	Time point	n (%) of PATIENTS with outcomes	Between arm comparison
Gossrau, 2011[84]	Arm 1 - Placebo	19	Neuropathic pain score, >=30% reduction	4 weeks	10	NR
Gossrau, 2011[84]	Arm 2 - micro-TENS (Microcurrent Transcutaneous Electric Nerve Stimulation)	21	Neuropathic pain score, >=30% reduction	4 weeks	6	% change from baseline, comparator arm: Placebo, p: >.09

% = percent; Micro-TENS = Microcurrent Transcutaneous Electric Nerve Stimulation; NR = not reported; p = p-value

Evidence Table D-84. Electrical stimulation intervention - composite pain outcomes (KQ2b)

Author, year	Arm	Instrument Name	Baseline N, Mean, SD	Time point(s)	At time point(s), N Mean SD:	Within arm comparison	Between arm comparison
Lacigova, 2013[83]	Arm 1 – Control - Sham	Total symptom score	N: 32, Mean: 6.6, SD: 2.8	30 days	N: 32, Mean: 5.7, SD: 2.9	Mean change from baseline: -0.34	NR
Lacigova, 2013[83]	Arm 2 - Mesodiencephalic moedulation (MDM)	Total symptom score	N: 32, Mean: 6.9, SD: 2.8	30 days	N: 32, Mean: 5.2, SD: 3	Mean change from baseline: -1.5	Mean change from baseline: , Comparator arm: sham, p: 0.9

MDM = Mesodiencephalic Moedulation; N = sample size; NR = not reported; p = p-value; SD = standard deviation

Evidence Table D-85. Electrical stimulation intervention - paresthesia outcome (KQ2b)

Author, year	Arm	Instrument Name	Baseline N, Mean, SD	Time point(s)	At time point(s), N Mean SD:	Within arm comparison
Forst, 2004[85]	Arm 1 - Control	NTSS-6, prickling sensation	N: 7, Mean: 2.14, SD: 0.73	12 weeks	N: 7, Mean: 1.81, SD: 1.11	Mean change from baseline p: NS
Forst, 2004[85]	Arm 2 - Transcutaneous electrical nerve stimulation (TENS)	NTSS-6, prickling sensation	N: 12, Mean: 2.14, SD: 0.91	12 weeks	N: 12, Mean: 1.61, SD: 0.97	Mean change from baseline p: NS

N = sample size; NS = not significant; NTSS-6 = Neuropathy Total Symptom Score-6; p = p-value; SD = standard deviation; TENS = Transcutaneous Electric Nerve Stimulation

Evidence Table D-86. Electrical stimulation intervention - numbness outcome (KQ2b)

Author, year	Arm	Instrument Name	Baseline N, Mean, SD	Time point(s)	At time point(s), N Mean SD:	Within arm comparison
Forst, 2004[85]	Arm 1 – Control	NTSS-6, prickling sensation	N: 7, Mean: 1.86, SD: 1.47	12 weeks	N: 7, Mean: 1.47, SD: 1.44	Mean change from baseline p: NS
Forst, 2004[85]	Arm 2 - Transcutaneous electrical nerve stimulation (TENS)	NTSS-6, prickling sensation	N: 12, Mean: 2.19, SD: 1.05	12 weeks	N: 12, Mean: 1.86, SD: 1	Mean change from baseline p: NS

N = sample size; NS = not significant; NTSS-6 = Neuropathy Total Symptom Score-6; p = p-value; SD = standard deviation; TENS = Transcutaneous Electric Nerve Stimulation

Evidence Table D-87. Electrical stimulation intervention - quality of life outcome (KQ2b)

Author, year	Arm	Instrument	Baseline N, Mean SD	Time point(s)	At time point(s), N Mean SD	Within arm comparison	Between arm comparison
Hamza, 2000[86]	Arm 1 – Control - Sham	SF-36, physical component	N: 50, Mean: 31.2, SD: 7.3	3 weeks	N: 50, Mean: 32.4, SD: 7.5	Mean difference from baseline: , p: <0.05	Mean difference from baseline, Comparator arm: , p: <0.05
Hamza, 2000[86]	Arm 2 - Percutaneous Electrical Nerve Stimulation (PENS)	SF-36, physical component	N: 50, Mean: 31.2, SD: 7.3	3 weeks	N: 50, Mean: 36.8, SD: 6.7	Mean difference from baseline: , p: <0.01	Mean difference from baseline, Comparator arm: Sham, p: <0.05
Lacigova, 2013[83]	Arm 1 – Control - Sham	SF-36, physical component	N: 32, Mean: NR, SD: NR	30 days	N: 32, Mean: NR, SD: NR	Mean difference from baseline: -2,	NR
Lacigova, 2013[83]	Arm 2 - Mesodiencephalic moedulation (MDM)	SF-36, physical component	N: 32, Mean: NR, SD: NR	30 days	N: 32, Mean: NR, SD: NR	Mean difference from baseline: 2.5	Mean difference from baseline, Comparator arm: Sham, p: <0.01

MDM = Mesodiencephalic moedulation; N = sample size; NR = not reported; NS = not significant; p = p-value; PENS = Percutaneous Electrical Nerve Stimulation; SD = standard deviation; SF-36 = 36 item Short Form Survey

Evidence Table D-88. Electrical stimulation intervention - dropouts (KQ2b)

Author, year	Select Arm	Dropouts due to adverse effects, N	Dropouts due to adverse effects, %	Comments
Oyibo, 2004[87]	Overall	4	NR	Combined with "inconvenient"

% = percent; NR = not reported

Evidence Table D-89. Study characteristics of frequency-modulated electromagnetic neural stimulation intervention (KQ2b)

Author, year	Study Design Study site	Funding source	Recruitment Start YEAR - End YEAR	Was run-in period reported?
Bosi, 2013[90]	Parallel randomized controlled trial Multiple center - Europe	Industry	NR	NR
Bosi, 2005[91]	Crossover randomized controlled trial Multiple center - Europe	Industry	2001-2003	NR
Onesti, 2013[92]	Crossover randomized controlled trial Single center - Europe	No funding	NR	NR
Weintraub, 2009[93]	Parallel randomized controlled trial Multiple center – North America	NR	2005 -2007	NR

NR = not reported

Evidence Table D-90. Frequency-modulated electromagnetic neural stimulation intervention - participant characteristics (KQ2b)

Author, year	Arm, N at enrollment	Actual length of follow-up-MEAN unit for follow-up	Women, n (%)	Age, years:	HbA1c , %	BMI	Comments
Bosi, 2013[90]	Arm 1: Placebo, 51	51 weeks	(39)	mean: 61.3, SD: 8.3	mean: 7.6, SD: 1.2	Mean: 28.5, SD: 4.8	
Bosi, 2013[90]	Arm 2: Frequency-modulated electromagnetic neural stimulation (FREMS), 50	51 weeks	(28)	mean: 59 SD: 10.6	mean: 7.9, SD: 1.2	Mean: 28.8, SD: 4.8	
Bosi, 2005[91]	Arm 1: Sequence 1 - placebo 1st, 15	4 months	NR	mean: 63.1, SD: 3.1	mean: 8.3, SD: 0.4	NR	Participant characteristics reported as sequence 1 and sequence 2 (based on intervention randomization in crossover study). Was not reported by overall or individual arms.
Bosi, 2005[91]	Arm 2: Sequence 2 - FREMS 1st, 16	4 months	NR	mean: 59.2, SD: 3.1	mean: 8.2, SD: 0.3	NR	Participant characteristics reported as sequence 1 and sequence 2 (based on intervention randomization in crossover study). Was not reported by overall or individual arms.
Onesti, 2013[92]	Arm 1: Real-sham (Arm1 given real rTMS, then sham rTMS), 11	9 weeks	4	mean: 70.7, Range: NR, SD: 9.5	NR	NR	
Onesti, 2013[92]	Arm 2: Sham-real (Arm2 given sham rTMS, then real rTMS, 12	9 weeks	5	mean: 70.6, SD: 7.9	NR	NR	
Weintraub, 2009[93]	Arm 1: Sham, 118	3 months	(55.8)	mean: 60.6, Range:	mean: 7.4, SD: 1.8	NR	Participant characteristics based on those who completed study

Author, year	Arm, N at enrollment	Actual length of follow-up- MEAN unit for follow-up	Women , n (%)	Age, years:	HbA1c , %	BMI	Comments
				21-83, SD: 12.4			
Weintraub, 2009[93]	Arm 2: Pulsed electromagnetic fields (PEMF), 107	3 months	(56.7)	mean: 61.1, Range: 33-87, SD: 10.4	mean: 7.5, SD: 1.8	NR	Participant characteristics based on those who completed study

% = percent; FREMS = Frequency-modulated electromagnetic neural stimulation; HbA1c = glycated haemoglobin; N = sample size; NR = not reported; PEMF = Pulsed electromagnetic fields; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation

Evidence Table D-91. Frequency-modulated electromagnetic neural stimulation intervention characteristics (KQ2b)

Author, year	Arm	Voltage Pulse Current Session: duration of session frequency:	Comments
Bosi, 2013[90]	Arm 1 - Placebo	Voltage: NA, Pulse: NR, Current: NA, Session: 30 min, Frequency: NA	
Bosi, 2013[90]	Arm 2 – Frequency - modulated electromagnetic neural stimulation	Voltage: Max -300V, followed by smaller voltage 0.9-999 ms, Pulse: biphsic asymmetrical pulses, 10-100us, Current: NR, Session: 30 min, Frequency:1-1000 Hz	
Bosi, 2005[91]	Arm 1 - Placebo	Voltage: NA, Pulse: NR, Current: NA, Session: 30 min, Frequency: NA	
Bosi, 2005[91]	Arm 2 – Frequency - modulated electromagnetic neural stimulation	Voltage:0-255 V, Pulse: monophasic negative asymmetrical, 10-40 us , Current: NR, Session: 30 min, Frequency:1-50 Hz	
Onesti, 2013[92]	Arm 1 – Real - sham (Arm1 given real rTMS, then sham rTMS) (rTMS = repetitive transcranial magnetic stimulation)	Voltage: NR, Pulse: NR, Current: NR, Session: 30 consective trains of 50 stimuli at 100% resting motor, separated by intertrain intervals lasting 30 seconds, Frequency: 20 HZ	Sham treatment used a sham coil with negligible electric field.
Onesti, 2013[92]	Arm 2 – Sham - real (Arm2 given sham rTMS, then real rTMS) (rTMS = repetitive transcranial magnetic stimulation)	Voltage: NR, Pulse: NR, Current: NR, Session: 30 consective trains of 50 stimuli at 100% resting motor, separated by intertrain intervals lasting 30 seconds, Frequency: 20 HZ	Sham treatment used a sham coil with negligible electric field.
Weintraub, 2009[93]	Arm 1 - Sham	Voltage: NR, Pulse: NR, Current: NR, Session: Participant self administered 2 hours per day (in 10-30 minute sessions) for 3 months Frequency: NR	voltage = 6 volt DC motor (1800 G magnetic sphere unit)

Author, year	Arm	Voltage Pulse Current Session: duration of session frequency:	Comments
Weintraub, 2009[93]	Arm 2 - Pulsed electromagnetic fields (PEMF)	Voltage: NR, Pulse: NR, Current: NR, Session: Participant self administered 2 hours per day (in 10-30 minute sessions) for 3 months Frequency: NR	voltage = 6 volt DC motor (1800 G magnetic sphere unit)

Hz = Hertz; min = minutes; ms = millisecond; NA = not available; NR = not reported; PEMF = pulsed electromagnetic fields; rTMS = repetitive transcranial magnetic stimulation; us = microsecond; V = voltage

Evidence Table D-92. Frequency-modulated electromagnetic neural stimulation intervention - pain continuous outcomes (KQ2b)

Author, year	Arm	Instrument Name, Outcome unit- IF APPLICABLE	Baseline N Mean SD	Time point (s)	Nat time point(s), N Mean SD	Within arm comparison	Between arm comparison
Bosi, 2013[90]	Arm 1 - placebo	VAS, daytime pain score,0-100 scale	N 51, Mean: 40.9, SD: 24	3 weeks	N 45, Mean: 31.5, SD: 3.5	NR	NR
Bosi, 2013[90]	Arm 2 - FREMS	VAS, daytime pain score,0-100 scale	N 50, Mean: 31.6, SD: 26.3	3 weeks	N 47, Mean: 19.1, SD: 3.2	NR	Comparator arm-placebo, pvalue: <0.001
Bosi, 2013[90]	Arm 1 - placebo	VAS, daytime pain score,0-100 scale	N 51, Mean: 40.9, SD: 24	51 weeks	N 36, Mean: 22.5, SD: 6.9	NR	NA
Bosi, 2013[90]	Arm 2 - FREMS	VAS, daytime pain score,0-100 scale	N 50, Mean: 31.6, SD: 26.3	51 weeks	N 39, Mean: 25.7, SD: 4.1	NR	Comparator arm-placebo, p value: "not detectable" Pain significantly decreased at end of each treatment cycle but then back to baseline by beginning of next; endpoint was 14 weeks after completion of last cycle; note that placebo VAS scores gradually decreased over study period
Bosi, 2004[91]	Arm 1 - placebo	VAS, daytime pain score,	N 31, Mean: 31.2, SD: 3.9	30 weeks	N 31, Mean: 31.9, SD: 4.2	NR	NR
Bosi, 2004[91]	Arm 2 - FREMS	VAS, daytime pain score,	N 31, Mean: 37.1, SD: 5.3	30 weeks	N 31, Mean: 26.2, SD: 3.9	p value: 0.0025	NR Statistics between groups not reported
Onesti, 2013[92]	Arm 1 – Real - sham (Arm1 given real rTMS, then sham rTMS)	VAS,NR, presume 0-100	N 11, Mean: 68.64, SD: 5.5	3 weeks (T2)	N 11, Mean: 47.81, SD: NR	% change from baseline--0.43	Time x group effect -5.46, Comparator arm-NR, pvalue:0.005 Note this is the timex group effect seen at end of the 1st crossover period; also report that values decreased in real perio d significant at <0.01 and in sham did not decrease

Author, year	Arm	Instrument Name, Outcome unit- IF APPLICABLE	Baseline N Mean SD	Time point (s)	Nat time point(s), N Mean SD	Within arm comparison	Between arm comparison
Onesti, 2013[92]	Arm 2 – Sham - real (Arm2 given sham rTMS, then real rTMS	VAS,NR, presume 0-100	N 12, Mean: 63.75, SD: 7.6	3 weeks (T2)	N 12, Mean: 59.33, SD: NR	% change from baseline--0.07	Time x group effect (F) -, Comparator arm-NR, pvalue:
Weintraub, 2009[93]	Arm 1 - Sham	VAS,0-10 scale	N 104, Mean: 5.45, SD: 2.09	3 months	N 104, Mean: 4.13, SD: 2.47	NS	NR
Weintraub, 2009[93]	Arm 2 - Pulsed electromagnetic fields (PEMF)	VAS,0-10 scale	N 90, Mean: 5.59, SD: 2.26	3 months	N 90, Mean: 4.05, SD: 2.71	NS	Between group difference likely also not significant
Weintraub, 2009[93]	Arm 1 - Sham	NPS 10,0-100 scale	N 104, Mean: 56.53, SD: 18.25	3 months	N 104, Mean: 44.21, SD: 20.85	NS	NR
Weintraub, 2009[93]	Arm 2 - Pulsed electromagnetic fields (PEMF)	NPS 10,0-100 scale	N 90, Mean: 60.35, SD: 17.83	3 months	N 90, Mean: 45.2, SD: 21.18	NS	Between group difference likely also not significant

FREMS = Frequency-modulated electromagnetic neural stimulation; N = sample size; NPS = Neuropathic Pain Scale; NR = not reported; NS = not significant; p = p-value; PEMF = Pulsed electromagnetic fields; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation; VAS = Visual Analogue Scale

Evidence Table D-93. Frequency-modulated electromagnetic neural stimulation intervention - quality of life (KQ2b)

Author, year	Arm	Instrument Name	Baseline N, Mean, SD	Time point(s)	At time point(s), N Mean SD:	Within arm comparison	Between arm comparison
Bosi, 2004[91]	Arm 1 - placebo	SF-36 total	N: 31, Mean: 104.4, SD: 1.5	30 weeks	N: 31, Mean: 105.9, SD: 1.5	NS	NR
Bosi, 2004[91]	Arm 2 - Frequency-modulated electromagnetic neural stimulation (FREMS)	SF-36 total	N: 31, Mean: 103.7, SD: 1.5	30 weeks	N: 31, Mean: 105.6, SD: 1.3	NS	NR

FREMS = Frequency-modulated electromagnetic neural stimulation; N = sample size; NR = not reported; NS = not significant; SD = standard deviation; SF-36 = 36 item Short Form Survey

Evidence Table D-94. Frequency-modulated electromagnetic neural stimulation intervention - dropouts (KQ2b)

Author, year	Arm	Dropouts due to adverse effects, N	Dropouts due to adverse effects, %
Bosi, 2013[90]	Arm 1 - placebo	0	NR
Bosi, 2013[90]	Arm 2 - FREMS	0	NR
Bosi, 2004[91]	Arm 1 - placebo	0	NR
Bosi, 2004[91]	Arm 2 - FREMS	0	NR
Weintraub, 2009[93]	Arm 1 - Sham	2	NR
Weintraub, 2009[93]	Arm 2 - Pulsed electromagnetic fields (PEMF)	2	NR

% = percent; FREMS = Frequency-modulated electromagnetic neural stimulation; NR = not reported; PEMF = Pulsed electromagnetic fields

Evidence Table D-95. Study characteristics of surgical decompression (KQ2b)

Author, year	Study Design Study site	Funding source	Recruitment Start YEAR - End YEAR
van Maurik, 2015[94] and van Maurik, 2014[95] Lower Extremity Nerve Entrapment Study	Parallel randomized controlled trial Single center: Europe	Non-profit	2010-2013

Evidence Table D-96. Surgical decompression intervention - participants characteristics (KQ2b)

Author, year	Arm, N at enrollment	Actual length of follow-up- MEAN unit for follow-up	Women , n (%)	Age, years:	HbA1c	BMI	Number of withdrawals and/or losses to follow-up: N
van Maurik, 2015[94] and van Maurik, 2014[95]	Overall, 42	1 year	14 (35)	mean: 61.7, SD: 10.2	NR	Mean: 29 SD: 4.2	4

% = percentage; BMI = Body Mass Index; HbA1c = Glycated Haemoglobin; N = sample size; SD = standard deviation

Evidence Table D-97. Surgical decompression interventions characteristics (KQ2b)

Author, year	Arm	Comments
van Maurik, 2015[94] and van Maurik, 2014[95]	Arm 1 - Control (usual care)	Randomization of limbs. Control limb did not undergo surgical decompression
van Maurik, 2015[94] and van Maurik, 2014[95]	Arm 2 - Surgical decompression	Randomization of limbs. Decompression of the lower extremity nerves in one limb, i.e. of the tibial nerve at the ankle site, the common peroneal, deep peroneal and superficial peroneal nerve.

Evidence Table D-98. Surgical decompression pain continuous outcome (KQ2b)

Author, year	Arm	Instrument	Baseline N, Mean SD	Time point(s)	At time point(s), N Mean SD	Within arm comparison	Comments
van Maurik, 2015[94] and van Maurik, 2014[95]	Arm 1 - Control	Pain, Visual Analogue Scale	N: 38, Mean: 6.1,	12 months	N: 38, Mean: 5.3	p: NS	42.5% had clinically important difference change of >2.9 on VAS
van Maurik, 2015[94] and van Maurik, 2014[95]	Arm 2 - Intervention	Pain, Visual Analogue Scale	N: 38, Mean: 6.1,	12 months	N: 38, Mean: 3.5	p: <0.001	

% = percent; N = sample size; NS = not significant; SD = standard deviation; VAS = Visual Analogue Scale

Evidence Table D-99. Surgical decompression quality of life (KQ2b)

Author, year	Arm	Instrument	Baseline N Mean	Time point(s)	At time point(s) N Mean	Comment
van Maurik, 2015[94]	Arm 1 - Control	SF-36-Physical Functioning	N: 38, Mean: 56.4	12 months	N: 8, Mean: 55	Quality of life scores are same for both arms as these are the same people
van Maurik, 2015[94]	Arm 2 - Intervention	SF-36-Physical Functioning	N: 38, Mean: 56.4	12 months	N: 8, Mean: 55	
van Maurik, 2015[94]	Arm 1 - Control	SF-36-Role-physical	N: 38, Mean: 40.6	12 months	N: 8, Mean: 35.1	
van Maurik, 2015[94]	Arm 2 - Intervention	SF-36-Role-physical	N: 38, Mean: 40.6	12 months	N: 38, Mean: 35.1	
van Maurik, 2015[94]	Arm 1 - Control	SF-36-Bodily pain	N: 38, Mean: 46.4	12 months	N: 38, Mean:5 0.5	
van Maurik, 2015[94]	Arm 2 - Intervention	SF-36-Bodily pain	N: 38, Mean: 46.4	12 months	N: 38, Mean: 50.5	
van Maurik, 2015[94]	Arm 1 - Control	SF-36-Physical composite score	N: 38, Mean: 36.5	12 months	N: 38, Mean: 36.1	
van Maurik, 2015[94]	Arm 2 - Intervention	SF-36-Physical composite score	N: 38, Mean: 36.5	12 months	N: 38, , Mean: 36.1	
van Maurik, 2015[94]	Arm 1 - Control	EQ-5D index score	N: 38, Mean: 0.6	12 months	N: 38, Mean: 0.62	
van Maurik, 2015[94]	Arm 2 - Intervention	EQ-5D index score	N: 38, Mean: 0.6	12 months	N: 38, Mean: 0.62	

% = percent; EQ-5D = EuroQol; N = sample size; NS = not significant;SD = standard deviation; SF-36 = 36 item Short Form Survey; VAS = Visual Analogue Scale

Evidence Table D-100. Study characteristics of spinal cord stimulation intervention (KQ2b)

Author, year	Study Design Study site	Funding source	Recruitment Start YEAR - End YEAR	Was run-in period reported?	Comments
de Vos, 2014[96]	Parallel randomized controlled trial Multiple center: Europe	Industry	2008-2012	Yes	A trial stimulation period of 7 days maximum was allowed to test whether a patient responded positively to SCS
Slangen, 2014[97]	Parallel randomized controlled trial Multiple center: Europe	Industry	2010-2013	Yes	After a 2-week trial stimulation, the spinal cord stimulator (Synergy Versitrel or PrimeAdvanced; Medtronic) was im- planted if the NRS for the intensity of pain during daytime or nighttime for the last 4 days of the trial period was at least 50% lower than the baseline score, or if there was a score of 6 or higher (“much improved” or “very much improved”) on the PGIC scale for pain and sleep

NRS = Numeric Rating Scale; PGIC = Patient Global Impression of Change; SCS = spinal cord stimulation

Evidence Table D-101. Spinal cord stimulation intervention - participant characteristics (KQ2b)

Author, year	Arm, N at enrollment	Actual length of follow-up-MEAN unit for follow-up	Women, n (%)	Age, years:	HbA1c	BMI	Duration of pain	Duration of neuropathic symptoms	Number of withdrawals and/or losses to follow-up: N
de Vos, 2014[96]	Arm 1 - Control, 20	6 months	7 (NR)	mean: 61, SD: 12	NR	NR	7 Years	NR	2
de Vos, 2014[96]	Arm 2 - Spinal cord stimulation (SCS), 40	6 months	15 (NR)	mean: 58, SD: 11	NR	NR	7 Years	NR	4
Slangen, 2014[97]	Arm 1 – Control - Best medical treatment (BMT)(Control),14	6 months	5 (36)	mean: 56.5, SD: 8	%mean: 8.4, SD: 2.7	mean: 30.3, SD: 5.4	4.9 Years	NR	0
Slangen, 2014[97]	Arm 2 - Best medical treatment + Spinal Cord Stimulation (SCS),22	6 months	7 (32)	mean: 57.1, SD: 12.4	%mean: 8.3, SD: 2	mean: 29, SD: 4.3	6 Years	NR	3

% = percent; BMI = Body Mass Index; BMT = best medical treatment; HbA1c = glycated haemoglobin; N = sample size; NR = not reported; SCS = spinal cord stimulation; SD = standard deviation

Evidence Table D-102. Spinal cord stimulation interventions characteristics (KQ2b)

Author, Year	Arm	Voltage Pulse Current Session: duration of session frequency:	Comments
de Vos, 2014[96]	Arm 1 - Control (No SCS)	NR	Details on SCS intervention not reported. Only on placement of electrodes, but nothing on frequency, voltage, duration etc.
de Vos, 2014[96]	Arm 2 - Spinal cord stimulation (SCS)	NR	Details on SCS intervention not reported. Only on placement of electrodes, but nothing on frequency, voltage, duration etc.
Slangen, 2014[97]	Arm 1 - Control-Best medical treatment (BMT)(Control)	NR	Details on SCS intervention not reported. Only on placement of electrodes, but nothing on frequency, voltage, duration etc.
Slangen, 2014[97]	Arm 2 - Best medical treatment + Spinal Cord Stimulation (SCS)	NR	Details on SCS intervention not reported. Only on placement of electrodes, but nothing on frequency, voltage, duration etc.

BMT = best medical treatment; NR = not reported; SCS = spinal cord stimulation

Evidence Table D-103. Spinal cord stimulation intervention - pain continuous outcomes (KQ2b)

Author, year	Arm	Instrument Name	Baseline N, Mean, SD	Time point(s)	At time point(s), N Mean SD:	Within arm comparison	Between arm comparison
de Vos, 2014[96]	Arm 1 – Control - Control	VAS: 0-100 scale	N: 20, Mean: 67, SD: 18	3 months	N: 20, Mean: 70.6, SD: 14.2	NR	NR
de Vos, 2014[96]	Arm 2 - Spinal cord stimulation (SCS)	VAS: 0-100 scale	N: 40, Mean: 73, SD: 16	3 months	N: 40, Mean: 28.9, SD: 57.8	NR	NR
de Vos, 2014[96]	Arm 1 – Control - Control	VAS: 0-100 scale	N: 20, Mean: 67, SD: 18	6 months	N: 20, Mean: 67, SD: 21	Mean change from baseline: 0, SD: 20,p: NS	NR
de Vos, 2014[96]	Arm 2 - Spinal cord stimulation (SCS)	VAS: 0-100 scale	N: 40, Mean: 73, SD: 16	6 months	N: 40, Mean: 31, SD: 28	Mean change from baseline: 42, SD: 31, p: <0.001	Mean change from baseline: , Comparator arm: placebo, p: <0.001
Slangen, 2014[97]	Arm 1 - Control- Best medical treatment (BMT)(Control)	Modified Brief Pain Inventory, Pain Severity Index-	N: 14, Mean: 6.3, SD: 1.8	6 months	N: 14, Mean: 6.5, SD: 2.1	NR	NR
Slangen, 2014[97]	Arm 2 - Best medical treatment + Spinal Cord Stimulation (SCS)	Modified Brief Pain Inventory, Pain Severity Index-	N: 22, Mean: 7.1, SD: 1.5	6 months	N: 19, Mean: 4, SD: 2.8	NR	Mean change from baseline: , Comparator arm: BMT, p: <0.001
Slangen, 2014[97]	Arm 1 – Control - Best medical treatment (BMT)(Control)	Neuropathic Pain Scale (NPS), intensity-	N: 14, Mean: 7.6, SD: 1.5	6 months	N: 14, Mean: 7.3, SD: 2	NR	NR
Slangen, 2014[97]	Arm 2 - Best medical treatment + Spinal Cord Stimulation (SCS)	Neuropathic Pain Scale (NPS), intensity-	N: 22, Mean: 8.2, SD: 1.5	6 months	N: 19, Mean: 4.3, SD: 3	NR	Mean change from baseline: , Comparator arm: BMT, p: <0.001

BMT = best medical treatment; N = sample size; NPS = Neuropathic Pain Scale; NR = not reported; NS = not significant; p = p-value; SCS = spinal cord stimulation; SD = standatd deviation; VAS = Visual Analogue Scale

Evidence Table D-104. Spinal cord stimulation intervention - pain categorical outcomes (KQ2b)

Author, year	Arm	N for analysis	Instrument Name	Time point	n (%) of PATIENTS with outcomes	Between arm comparison
de Vos, 2014[96]	Arm 1 - Control	20	VAS, >50% pain reduction	6 months	1 (5)	NR
de Vos, 2014[96]	Arm 2 - Spinal cord stimulation (SCS)	40	VAS, >50% pain reduction	6 month	25 (60)	% change from baseline, comparator arm: control, p: <0.001
Slangen, 2014[97]	Arm 1 – Control - Best medical treatment (BMT)(Control)	14	Numeric rating scale (NRS), ≥50% reduction day	6 months	0 (0)	NR
Slangen, 2014[97]	Arm 2 - Best medical treatment + Spinal Cord Stimulation (SCS)	19	Numeric rating scale (NRS), ≥50% reduction day	6 months	9 (41)	% change from baseline, comparator arm: BMT, p: <0.001

BMT = best medical treatment; N = sample size; NR = not reported; NRS = Numeric Rating Scale; NS = not significant; p = p-value; SCS = spinal cord stimulation; SD = standatd deviation; VAS = Visual Analogue Scale

Evidence Table D-105. Spinal cord stimulation intervention - quality of life (KQ2b)

Author, year	Arm	Instrument		Baseline N, Mean SD	Time point(s)	At time point(s), N Mean SD	Within arm comparison	Between arm comparison
de Vos, 2014[96]	Arm 1 - Control-Control	MPQ Quality of Life score		N: 20, Mean: 15, SD: 6	6 months	N: 20, Mean: 14, SD: 6	Mean difference from baseline: , p: NS	NR
de Vos, 2014[96]	Arm 2 - Spinal cord stimulation (SCS)	MPQ Quality of Life score		N: 40, Mean: 16, SD: 5	6 months	N: 40, Mean: 8, SD: 7	Mean difference from baseline:, p: <0.001	Mean difference from baseline, Comparator arm: control, p: <0.001
de Vos, 2014[96]	Arm 1 – Control - Control	EQ-5D		N: 20, Mean: 46, SD: 17	6 months	N: 20, Mean: 41, SD: 20	Mean difference from baseline: , p: NS	NR
de Vos, 2014[96]	Arm 2 - Spinal cord stimulation (SCS)	EQ-5D		N: 40, Mean: 50, SD: 19	6 months	N: 40, Mean: 61, SD: 22	Mean difference from baseline: , p: <0.05	Mean difference from baseline, Comparator arm: control, p: <0.01
Slangen, 2014[97]	Arm 1 – Control - Best medical treatment (BMT)(Control)	EQ-5D, current health0-100		N: 14, Mean: 54.6, SD: 16.7	6 months	N: 14, Mean: 56.5, SD: 14.2	NR	NR
Slangen, 2014[97]	Arm 2 - Best medical treatment + Spinal Cord Stimulation (SCS)	EQ-5D, current health0-100		N: 22, Mean: 53.9, SD: 18.5	6 months	N: 19, Mean: 57.6, SD: 24.3	NR	Mean difference from baseline, Comparator arm: BMT, p: NS
Slangen, 2014[97]	Arm 1 – Control - Best medical treatment (BMT)(Control)	SF-36, physical component		N: 14, Mean: 31.7, SD: 7.9	6 months	N: 14, Mean: 30.5, SD: 7.4	NR	NR
Slangen, 2014[97]	Arm 2 - Best medical treatment + Spinal Cord Stimulation (SCS)	SF-36, physical component		N: 22, Mean: 27.9, SD: 7.5	6 months	N: 19, Mean: 32.3, SD: 10.5	NR	Mean difference from baseline, Comparator arm: BMT, p: NS

BMT = best medical treatment; EQ-5D = EuroQol; MPQ-QOL = McGill Pain Questionnaire; N = sample size; NR = not reported; NS = not significant; p = p-value; SCS = spinal cord stimulation; SD = standard deviation; SF-36 = 36 item Short Form Survey;

Evidence Table D-106. Spinal cord stimulation intervention - dropouts (KQ2b)

Author, year	Select Arm	Dropouts due to adverse effects, N	Dropouts due to adverse effects, %	Comments
Slangen, 2014[97]	Arm 1 - Best medical treatment (BMT)(Control)	NR	0	
Slangen, 2014[97]	Arm 2 - Best medical treatment + Spinal Cord Stimulation (SCS)	NR	1	Infection; also one patient died from dural puncture

% = percent; BMT = best medical treatment; N = sample size; NR = not reported; SCS = spinal cord stimulation

Evidence Table D-107. Risk of bias for RCTs (KQ2a)

Author, year	Random sequence generation	Allocation concealment	Blinding of personnel	Blinding of outcome assessors	Incomplete outcome data	Selective reporting of outcomes	Other sources of bias	Overall quality
Harati, 1998[10]	Low	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear
Ziegler, 2015[25]	Low	Low	Low	Unclear	Unclear	Unclear	Unclear	Unclear
Gao, 2015[7]	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear	Unclear
Karmakar, 2014[12]	Low	Unclear	Low	Unclear	Low	Unclear	Unclear	Unclear
Allen, 2014[1]	Low	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Ghasemi, 2014[8]	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Unclear
Niesters, 2014[14]	Low	Low	Low	Low	Unclear	Unclear	Unclear	Unclear
Tesfaye, 2013[21]	Low	Low	Low	Unclear	High	Unclear	Unclear	High
Rauck, 2013[16]	Low	Unclear	Low	Unclear	Low	Unclear	Unclear	Unclear
Toth, 2012[22]	Low	Low	Low	Low	Low	Unclear	Unclear	Unclear
Campbell, 2012[4]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Vinik, 2014[23]	Low	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Unclear
Arezzo, 2008[2]	Low	Low	Low	Unclear	Low	Unclear	Unclear	Unclear
Freeman, 2007[6]	Low	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Unclear
Atli, 2005[3]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Chad, 1990[5]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Hanna, 2008[9]	Unclear	Low	Low	Low	Low	Low	Low	Low
Jiang, 2011[11]	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Unclear
Kulkantrakorn, 2013[13]	Low	Low	Low	Unclear	Low	Unclear	Unclear	Low
Raskin, 2014[15]	Low	Unclear	Unclear	Unclear	Low	Low	Unclear	Unclear
Rowbotham, 2012[17]	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Sandercock, 2012[18]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Shaibani, 2012[20]	High	Unclear	Low	Unclear	Low	Low	Unclear	Unclear
Yuan, 2009[24]	Unclear	Unclear	Unclear	Low	Low	Unclear	Unclear	Unclear

Evidence Table D-108. Risk of bias for RCTs (KQ2b)

Author, year	Random sequence generation	Allocation concealment	Blinding of personnel	Blinding of outcome assessors	Assessing blinding by outcome: outcome assessor blinded by critical outcomes	Incomplete outcome data	Selective reporting of outcomes	Other sources of bias	Overall quality
Electrical Stimulation									
Lacigova, 2013[83]	Unclear	Unclear	Low	Unclear	Unclear	Low	Low	Low	Unclear
Gossrau, 2011[84]	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Forst, 2004[85]	Low	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Hamza, 2000[86]	Unclear	Unclear	Unclear	Low	Low	Low	Low	Low	Low
Oyibo, 2004[87]	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	High	Unclear
Kumar, 1998[88]	Unclear	Unclear	Unclear	Low	Low	Low	Low	Low	Low
Kumar, 1997[89]	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Low
Spinal Cord									
de Vos[96]	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Slangen, 2014[97]	Low	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Low
FREMS									
Bosi, 2013[90]	Low	Low	Low	Low	Unclear	Low	Unclear	Low	Low
Bosi, 2005[91]	Unclear	Unclear	Low	Low	Unclear	Low	Unclear	Low	Low
Onesti, 2013[92]	Low	Unclear	Low	Low	Unclear	Low	Unclear	Low	Low
Weintraub, 2009[93]	Unclear	Low	Low	Low	Unclear	Low	Unclear	Low	Low
Supplements									
Ziegler, 1996[77]	Low	Unclear	Low	Unclear	Unclear	High	Low	Unclear	Unclear
Ziegler, 1999[76]	Low	Unclear	Low	Unclear	Unclear	Low	Unclear	Unclear	Unclear
Ruhnau, 1999[79]	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High	Low	Unclear
Ametov, 2003[78]	Unclear	Unclear	Low	Unclear	Unclear	Low	Low	Low	Unclear
Ziegler, 2006[75]	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Ziegler, 2011[74]	Low	Low	Unclear	Unclear	Unclear	High	Unclear	Low	High
De Grandis, 2002[80]	Low	Low	Unclear	Unclear	Unclear	High	Low	Low	Unclear
Acupuncture									
Garrow, 2014[81]	Low	Low	Low	Unclear	Unclear	Unclear	Low	Low	Low
Cognitive									
Otis, 2013[82]	Low	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	Unclear
Surgical Decompression									
Macare van Maurik, 2015[94]	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear

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Appendix E. Strength of Evidence

Table E-1. Strength of evidence domains for pharmacologic treatment for the prevention of diabetic foot ulcers and lower extremity amputations (KQ1a)

Key Outcomes	Study Design: No. Studies (N)[a]	Study Limitation	Directness	Consistency	Precision	Reporting Bias	Other Issues	Key Findings	Strength of Evidence
Foot ulcer									
Intensive vs. standard glycemic control	2 RCTs in patients with **Type 1 DM** n=1,329	Moderate[a]	Direct	Consistent	Imprecise	Unsuspected	Few event rates.	Two RCTs reported no significant differences between intensive vs standard glycemic control for prevention of foot ulcers (RR 0.32, 95% CI, 0.10 to 1.06 and 0.37, 95% CI 0.12 to 1.15), but the number of events was low despite long followup periods	Low
Intensive vs. standard glycemic control	2 RCTs in patients with **Type 2 DM** n=1,326	Moderate[a]	Direct	Consistent	Imprecise	Unsuspected	None	Two RCTs reported no significant difference between arms.	Low
Monotherapy or combination medications	1 cohort study in patients with **Type 2 DM** n=23,395	High[b]	Direct	Unknown	Imprecise	Unsuspected	None	A cohort study reported reduced hazard ratio (HR: 0.6, 95% CI: 0.38 to 0.98) for foot ulcers for patients taking glargine insulin versus NPH insulin.	Insufficient

Key Outcomes	Study Design: No. Studies (N)[a]	Study Limitation	Directness	Consistency	Precision	Reporting Bias	Other Issues	Key Findings	Strength of Evidence
Lower extremity amputations									
Intensive vs. standard glycemic control	1 RCT in patients with **Type 1 DM** n=1,257	Low	Direct	Unknown	Imprecise	Unsuspected	None	One RCT did not show a statistically significant differences between lower extremity amputations in the intensive vs. standard glycemic control arms in patients with Type 1 diabetes.	Low
Intensive vs. standard glycemic control	5 RCTs in patients with **Type 2 DM** n=9,348	Low	Direct	Consistent	Imprecise	Unsuspected	None	Five RCTs reported a decreased risk of lower extremity amputations in the intensive vs. standard glycemic control arms. (Pooled RR 0.63, 95% CI 0.40 to 0.96).	Moderate
Comparisons of monotherapy or combination medications	1 RCT in patients with **Type 2 DM** n=5,238	Low	Direct	Unknown	Imprecise	Unsuspected	None	One RCT that compared pioglitazone versus placebo reported no significant difference in risk of amputations between the two arms.	Low

a. Moderate because of studies' lack of clarity about how outcomes assessed and ascertained for foot ulcers

b. High limitations because of study design as single observational study. Non-randomized design contributes significant risk of bias and limitations.

CI=Confidence Interval; DM=Diabetes Mellitus; N=sample size; OR=odds ratio; RCT=Randomized Controlled Trial

Table E-2. Strength of evidence domains for non-pharmacologic treatment for the prevention of diabetic foot ulcers (KQ1b)

Key Outcomes	Study Design: No. Studies (N)	Study Limitation	Directness	Consistency	Precision	Reporting Bias	Other Issues	Key Findings	Strength of Evidence
Diabetic foot ulcers									
Integrated foot care	3 RCTs and 1 cohort n=350	Medium	Direct	Consistent	Precise	Unsuspected	None	Netten et al. reported a reduction in foot ulcer incidence or recurrence using integrated care. The reduction was ~20% across studies. We did not identify new studies in our updated search	Low
Self-management: home monitoring of foot temperature	4 RCTs n=583	Low	Direct	Consistent	Precise	Unsuspected	None	3 RCTs from Netten et al. showed reduction in incident foot ulcers in patients using self-monitoring of foot temperature compared with standard of care. One newly identified RCT was consistent with Netten et al.	Moderate
Self-management: Topical treatment on foot	1 RCT and 1 cohort n=360	High	Direct	Inconsistent	Imprecise	Unsuspected	None	Inconsistent findings from one RCT from Netten et al. and one newly identified cohort study	Insufficient
Patient Education	3 RCTs and 1 cohort n=16,943	Medium	Direct	Inconsistent	Imprecise	Unsuspected	None	Netten et al. review concluded that there was no reduction in ulcer recurrence from one time educational programs, based on two RCTs 2 newly identified studies (1 RCT and 1 cohort) did not change this finding	Low

Key Outcomes	Study Design: No. Studies (N)	Study Limitation	Directness	Consistency	Precision	Reporting Bias	Other Issues	Key Findings	Strength of Evidence
Diabetic foot ulcers (continued)									
Therapeutic footwear	7 RCTs and 3 cohorts n=1,913	Medium	Direct	Inconsistent	Imprecise	Unsuspected	None	Netten et al. concluded that specific modalities of therapeutic footwear could be effective in the prevention of a recurrent plantar foot ulcer compared with more standard-of-care therapeutic footwear. The risk reduction ranged from 4% to 45% across studies. We did not identify new studies in our updated search	Moderate
Surgical Intervention	3 RCTs and 6 cohort n=744	high	Direct	Inconsistent	Imprecise	Unsuspected	None	Netten et al. concluded that surgical interventions (Achilles tendon lengthening, single or pan-metatarsal head resection and metatarsophalangeal joint arthroplasty) appear to reduce ulcer recurrence risk in a range from 24% to 43% in some patients with initially non-healing ulcers when compared with non-surgical treatment. We did not identify new studies in our updated search	Low

Key Outcomes	Study Design: No. Studies (N)[a]	Study Limitation	Directness	Consistency	Precision	Reporting Bias	Other Issues	Key Findings	Strength of Evidence
Lower extremity amputations									
Integrated Foot Care	2 RCTs and 2 cohorts n=27,840	Medium	Direct	Inconsistent	Imprecise	Unsuspected	None	We are unable to draw any conclusions.	Insufficient
Self-management	1 RCT n=85	High	Direct	Unknown	Imprecise	Unsuspected	None	We are unable to draw any conclusions.	Insufficient
Patient Education:	2 RCTs and 1 cohort n=16,812	Medium	Direct	Consistent	Precise	Unsuspected	None	1 RCT from Netten et al. reported no benefit from a single educational session about amputation (RR 1.0; 95% CI, 0.91 to 1.11). 2 newly identified studies (1 RCT and 1 cohort study) did not report any benefit from a single education session. Results from all three studies suggested that education programs did not change the occurrence of amputation.	Low
Therapeutic Footwear	1 cohort n=46	High	Direct	Consistent	Precise	Unsuspected	None	We are unable to draw any conclusions.	Insufficient
Surgical Intervention	2 cohorts n=168	High	Direct	Inconsistent	Imprecise	Unsuspected	None	We are unable to draw any conclusions.	Insufficient
Quality of life									
Home-monitoring of foot temperature	1 RCT N=85	High	Direct	Unknown	Imprecise	Unsuspected	None	We are unable to draw any conclusions.	Insufficient
Surgical interventions	1 RCT N=28	High	Direct	Unknown	Imprecise	Unsuspected	None	We are unable to draw any conclusions.	Insufficient

CI=Confidence Interval; DM=Diabetes Mellitus; N=sample size; OR=odds ratio; RCT=Randomized Controlled Trial

Table E-3. Strength of evidence domains for balance training intervention on outcomes of falls, foot ulcer and quality of life (KQ1b)

Key Outcomes	Study Design: No. Studies (N)	Study Limitation	Directness	Consistency	Precision	Reporting Bias	Other Issues	Key Findings	Strength of Evidence
Falls									
Balance training vs. control*	1 RCT (reported in 2 studies) n= 79	Low	Direct	Unknown	Imprecise	Unsuspected	None	One RCT reported no statistically significant difference in falls between the balance training group and the control group (2.06 versus 2.02 falls/1000 person-days, respectively) and differences were not statistically significant. We were unable to draw any conclusions.	Insufficient
Exercise training vs. control*	1 RCT (reported in 2 studies) n= 79	Low	Direct	Unknown	Imprecise	Unsuspected	None	One RCT reported no statistically significant difference in falls between the balance training group and the control group (2.06 versus 2.02 falls/1000 person-days, respectively) and differences were not statistically significant. We were unable to draw any conclusions.	Insufficient
Foot ulcer									
Exercise training vs. control*	1 RCTs (reported in 2 studies) 1 prospective cohort study n=469	Moderate	Direct	Consistent	Imprecise	Unsuspected	None	Rate Ratio of all foot ulcers is 1.24; 95% CI, 0.70 to 2.19 reported in 1 RCT Another prospective study showed incidence of re-ulceration 16.5% in the least active group, 13.4% in the moderately active group, and 13% in the most active group We were unable to draw any conclusions.	Insufficient
Physical therapy vs. control	1 RCT n=29	Low	Direct	Unknown	Imprecise	Unsuspected	None	Reported number of ulcers in weight bearing versus non-weight bearing groups: 1 vs 3 We were unable to draw any conclusions.	Insufficient

Key Outcomes	Study Design: No. Studies (N)	Study Limitation	Directness	Consistency	Precision	Reporting Bias	Other Issues	Key Findings	Strength of Evidence
Quality of Life									
Balance training vs. control	1 RCT n= 39	Low	Direct	Unknown	Imprecise	Unsuspected	None	The difference between the study arms in the mean difference from baseline was 0.29, in the direction favoring the intervention group, not statistically significantly different. We were unable to draw any conclusions.	Insufficient
Exercise training vs. control*	1 RCT n=87	Low	Direct	Unknown	Imprecise	Unsuspected	None	% change from baseline for intervention and control was 28.40 in the direction favoring the intervention group, p<0.001). We were unable to draw any conclusions.	Insufficient

CI = confidence interval; DM = diabetes mellitus; N = sample size; p = p-value; RCT = randomized controlled trial

High limitations because of study design as single observational study. Non-randomized design contributes significant risk of bias and limitations.
*Same study included under both interventions

Table E-4. Strength of evidence domains for studies comparing individual drugs with placebo in terms of pain and quality of life among adults with diabetic peripheral neuropathy (KQ2a)

Source	Key Outcomes	Study Design: No. Studies (N)	Study Limitation	Consistency	Directness	Precision	Reporting Bias	Other Issues	Key Findings	Strength of Evidence
Gabapentin vs. Placebo										
Published literature + CT.gov	Pain	5 RCTs n=833	Unclear	Inconsistent	Direct	Precise	Suspected	Newest studies did not find evidence of effectiveness.	Gabapentin does not improve pain more than placebo.	Low
Published literature + CT.gov	Quality of life	3 RCTs n=646	Unclear	Inconsistent	Direct	Could not be evaluated	Suspected		Given incomplete reporting of results, we were unable to draw any conclusions.	Insufficient
Pregabalin vs. Placebo										
Published literature + CT.gov	Pain	16 RCTs n=4,712	Unclear	Inconsistent	Direct	Precise	Suspected	Newer and unpublished studies did not find evidence of effectiveness	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.	Low
Published literature + CT.gov	Quality of life	10 RCTs n=3,513	Unclear	Inconsistent	Direct	Could not be evaluated	Suspected		Given incomplete reporting of results, we were unable to draw any conclusions.	Insufficient

Source	Key Outcomes	Study Design: No. Studies (N)	Study Limitation	Consistency	Directness	Precision	Reporting Bias	Other Issues	Key Findings	Strength of Evidence
Oxcarbazepine vs. Placebo										
Published literature	Pain	3 RCTs n=634	Unclear	Inconsistent	Direct	Imprecise	Suspected	Studies were only 16 weeks in duration.	Oxcarbazepine is more effective than placebo at reducing pain, but data was incompletely reported.	Low
Published literature	Quality of life	3 RCTs n=634	Unclear	Inconsistent	Direct	Could not be evaluated	Suspected		Given incomplete reporting of results, we were unable to draw any conclusions.	Insufficient
Lacosamide vs. Placebo*										
Published literature + CT.gov	Pain	4 RCTs n=1,626	Unclear	Inconsistent	Direct	Imprecise	Suspected		Lacosamide is not more effective than placebo at reducing pain.	Low
Published literature + CT.gov	Quality of life	1 RCT n=119	Unclear	NA	Direct	Could not be evaluated	Suspected*		We are unable to draw a conclusion.	Insufficient
Oxycodone vs. Placebo										
Published literature + CT.gov	Pain	4 RCTs n=638	Unclear	Inconsistent	Direct	Imprecise	Suspected		Opioids are not more effective than placebo for reducing pain.	Low
Duloxetine vs. Placebo										
Published literature	Pain	7 RCTs n= ,2203	Unclear	Consistent	Direct	Precise	Unsuspected		Duloxetine reduced pain more than placebo	Moderate
Published literature	Quality of life	4 RCTs n=1,112	Unclear	Inconsistent	Direct	Could not be evaluated	Suspected		Given incomplete reporting of results, we were unable to draw any conclusions.	Insufficient

Source	Key Outcomes	Study Design: No. Studies (N)	Study Limitation	Consistency	Directness	Precision	Reporting Bias	Other Issues	Key Findings	Strength of Evidence
Venlafaxine vs. Placebo										
Published literature	Pain	2 RCTs n=304	Unclear	Consistent	Direct	Precise	Unsuspected		Venlafaxine reduced pain more than placebo.	Moderate
Capsaicin 0.075% vs. Placebo										
Published literature + CT.gov	Pain	5 RCTs n= 411	Unclear	Inconsistent	Direct	Imprecise	Suspected		Capsaicin is not more effective than placebo for reducing pain.	Low
Capsaicin 8% vs. Placebo										
Published literature + CT.gov	Pain	1 RCT n=369	Unclear	Unknown	Direct	Imprecise	Suspected	Study was not published	We are unable to draw a conclusion.	Insufficient
Published literature + CT.gov	Quality of life	1 RCT n=369	Unclear	Unknown	Direct	Imprecise	Suspected		We are unable to draw a conclusion.	Insufficient
Clonidine vs. Placebo										
Published literature + CT.gov	Pain	1 RCT n= 369	Unclear	Unknown	Direct	Imprecise	Suspected	Study was not published	We are unable to draw a conclusion.	Insufficient
Nabilone vs. Placebo										
Published literature + CT.gov	Pain	1 RCT n= 60	Unclear	Unknown	Direct	Imprecise	Unsuspected		We are unable to draw a conclusion.	Insufficient
Published literature + CT.gov	Quality of life	1RCT n= 60	Unclear	Unknown	Direct	Imprecise	Unsuspected		We are unable to draw a conclusion.	Insufficient
Nabiximols vs. Placebo										
Published literature + CT.gov	Pain	1 RCT n= 297	Unclear	Unknown	Direct	Imprecise	Suspected		We are unable to draw a conclusion.	Insufficient
Published literature + CT.gov	Quality of life	1 RCT n= 297	Unclear	Unknown	Direct	Imprecise	Suspected		We are unable to draw a conclusion.	Insufficient

Source	Key Outcomes	Study Design: No. Studies (N)	Study Limitation	Consistency	Directness	Precision	Reporting Bias	Other Issues	Key Findings	Strength of Evidence
Tramadol vs. Placebo										
Published literature	Pain	RCTs: 2 n=444	Unclear	Inconsistent	Direct	Precise	Unsuspected		Tramadol reduced pain more than placebo.	Low
Published literature	Quality of Life	RCTs: 2 n=444	Unclear	Inconsistent	Direct	Could not be evaluated	Suspected		Given incomplete reporting of results, we were unable to draw any conclusions.	Insufficient
Tapentadol vs. Placebo										
Published literature	Pain	RCTs: 3 n=737	Unclear	Consistent	Direct	Precise	Unsuspected		Tapentadol reduced pain more than placebo.	Low
Published literature	Quality of Life	RCTs: 2 n=342	Unclear	Inconsistent	Direct	Could not be evaluated	Suspected		Given incomplete reporting of results, we were unable to draw any conclusions.	Insufficient
Botulinum vs. Placebo										
Published literature	Pain	RCTs: 2 n=80	Unclear	Inconsistent	Direct	imprecise	suspected		Botulinum toxin reduced pain more than placebo	Low
Dextromethorphan vs. Placebo										
Published literature	Pain	RCTs: 3 n=416	Unclear	Inconsistent	Direct	Imprecise	Unsuspected		Dextromethorphan did not reduce pain more than placebo	Low
Mexiletine vs. Placebo										
Published literature	Pain	RCTs: 5 n=389	Unclear	Inconsistent	Direct	Imprecise	Unsuspected		Mexiletine did not reduce pain more than placebo	Low

Source	Key Outcomes	Study Design: No. Studies (N)	Study Limitation	Consistency	Directness	Precision	Reporting Bias	Other Issues	Key Findings	Strength of Evidence
Duloxetine vs. Pregabalin										
Published literature	Pain	RCTs: 2 n=411	Unclear	Consistent	Direct	Could not be evaluated	Suspected		Given incomplete reporting of results, we were unable to draw any conclusions..	Insufficient

CT.gov = ClinicalTrials.gov; N = sample size; NA = not available; RCT = randomized controlled trial; vs = versus

*All four of the studies for lacosamide vs placebo 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.
†Note that only key individual drug comparisons are listed in these tables; others were included as part of drug classes or were insufficient.

Table E-5. Strength of evidence for studies comparing drug classes with placebo in terms of pain and quality of life among adults with diabetic peripheral neuropathy (KQ2a)

Key Outcomes	Study Design: No. Studies (N)	Study Limitation	Directness	Consistency	Precision	Reporting Bias	Other Issues	Key Findings	Strength of Evidence
Serotonin-noradrenaline reuptake inhibitors vs. Placebo									
Pain	RCT: 10 n=2,507	Unclear	Direct	Consistent	Precise	Unsuspected		SNRIs reduced pain more than placebo	Moderate
Quality of Life	RCT: 6 n=1,925	Unclear	Direct	Inconsistent	Could not be evaluated	Unsuspected		Given incomplete reporting of results, we were unable to draw any conclusions.	Insufficient
Tricyclic antidepressants vs. Placebo									
Pain	RCT: 4 n=(81)	High	Direct	Inconsistent	Imprecise	Unsuspected		Tricyclic antidepressants reduced pain more than placebo	Low
Atypical Opioids vs. Placebo									
Pain	RCT: 5 n=1,181	Unclear	Direct	Consistent	Precise	Unsuspected	Methodology inconsistent with pain trial standards	Atypical opioids reduced pain more than placebo	Low
Quality of Life	RCT: 4 n=786	Unclear	Direct	Inconsistent	Could not be evaluated	Unsuspected		Given incomplete reporting of results, we were unable to draw any conclusions.	Insufficient
Opioids vs. Placebo									
Pain	RCT: 4 n=638	Unclear	Direct	Inconsistent	Imprecise	Suspected		Opioids did not reduce pain more than placebo	Low

N=sample size; RCT=randomized controlled trial; vs=versus

*For quality of life, evidence was insufficient for opioids (oxycodone), Where results are not reported above for quality of life, there were no studies that evaluated this outcome for the drug class compared with placebo (e.g., tricyclic antidepressants).

Table E-6. Strength of evidence domain for the non-pharmacologic interventions (KQ2b)

Key Outcomes	Study Design: No. Studies (N)	Study Limitation	Directness	Consistency	Precision	Reporting Bias	Other Issues	Key Findings	Strength of Evidence
Alpha-lipoic acid vs. placebo									
Pain	RCT: 5 n=984	Unclear	Direct	Consistent	Precise	Suspected; not all studies reported on pain subscale separately (although onluded in the composite score)	Dose-response: absent; Strength of association: medium	Alpha lipoic acid reduced pain scores moderately more than placebo, but studies were limited by inconsistent outcome reporting and other bias	Low
Transcutaneous electrical nerve stimulation vs. sham									
Pain	RCT: 4 n=118	Unclear	Direct	Inconsistent	Imprecise	Unsuspected	Dose-response: absent	Transcutaneous electrical nerve stimulation did not reduce pain scores more than sham, although studies were small	Low
Frequency-modulated electromagnetic stimulation vs. sham									
Pain	RCT: 2 n=132	Unclear	Direct	Inconsistent	Imprecise	Unsuspected	Intervention effects did not last long-term	Frequency-modulated electromagnetic stimulation reduced pain short-term more than placebo, but not long-term	Low
Spinal cord stimulation vs. usual care									
Pain	RCT: 2 n=96	Low	Direct	Consistent	Precise	Unsuspected	Strength of association: large; Trial run-in period, no sham arm	Spinal cord stimulation reduced pain scores more than usual care	Low
Quality of Life	RCT: 2 n=96	Unclear	Direct	Inconsistent	Imprecise	Unsuspected	Run-in period, no sham arm	Standardized mean difference could not be calculated given incomplete data, but one study found a statistically significant difference and one did not. Spinal cord stimulation is not more effective than usual care for improving quality of life.	Insufficient

N=sample size; RCT=randomized controlled trial; vs=versus

*Note that other interventions or outcomes had only one small size study, and strength of evidence was therefore insufficient