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Number xx

Effectiveness of Treatment Options for the Prevention of Complications and Treatment of Symptoms of Diabetic Peripheral Neuropathy

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

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Investigators:

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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 as well as 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 or not 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) for draft research questions and reports or to join an e-mail list to learn about new programs, products and opportunities for input.

We welcome 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.

Andrew Bindman, M.D.
Director
Agency for Healthcare Research and Quality

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

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

Aysegul Gozu, M.D., M.P.H.
Task Order Officer
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

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Key Informants

(redacted for peer review)

Technical Expert Panel

(redacted for peer review)

Peer Reviewers

(redacted for peer review)

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 MEDLINE and the Cochrane Database of Systematic Reviews for systematic reviews from January 1st, 2011 to October 12th, 2015. For questions where we did not identify high quality relevant systematic reviews, we searched for primary studies using MEDLINE, Embase®, and the Cochrane Central Register of Controlled Trials (CENTRAL) from 1966 to October 12, 2015.

Review Methods: For the prevention of DPN complications (KQ1), we included a systematic review of and primary randomized controlled trials and non-randomized studies with a concurrent comparison group. For the treatment of DPN symptoms (KQ2), we included a systematic review of and primary parallel or crossover randomized controlled trials that were blinded for interventions where blinding was possible. Two reviewers evaluated studies for eligibility, serially abstracted data using standardized forms, and 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 two systematic reviews with 95 studies and 78 additional studies, for a total of 173 studies. For prevention of DPN complications (KQ1), intensive glycemic control (as defined by each individual study) prevents lower extremity amputations more than standard control for type 2 diabetes (moderate SOE). For nonpharmacologic treatment options, specific types of therapeutic footwear (moderate SOE), home monitoring of foot skin temperature (moderate SOE), integrated foot care (low 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 reduce falls. For treatment of DPN symptoms (KQ2), the anticonvulsant pregabalin (low SOE), the serotonin-noradrenaline reuptake inhibitors duloxetine and venlafaxine (moderate SOE), the drug classes of tricyclic antidepressants (low SOE) and atypical opioids (tramadol and tapentadol) (moderate SOE), and the injectable neurotoxin botulinum toxin (moderate SOE) are more effective than placebo for reducing pain in short-term studies. Serotonin-noradrenaline reuptake inhibitors are more effective than anticonvulsants for reducing pain (moderate SOE). All oral drug classes had more than ten percent dropouts due to adverse effects. For nonpharmacologic treatments, alpha-lipoic acid is more effective than placebo (moderate SOE) and spinal cord stimulation is more effective than usual care for pain (moderate SOE), but spinal cord stimulation had risks of serious complications. No treatments improved quality of life (low 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, pregabalin, serotonin-noradrenaline reuptake inhibitors, atypical opioids, alpha-lipoic acid and spinal cord stimulation are more effective than placebo and serotonin-noradrenaline reuptake inhibitors are more effective than anticonvulsants. However, no treatments improved quality of life, studies were short-term with unclear risk of bias, all oral drugs had significant side effects, and opioids have significant long-term risks including abuse.

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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 Based upon several large studies, 30 to 50 percent of patients with diabetes will eventually develop neuropathy.² Diabetic neuropathy is nerve damage caused by either type 1 or type 2 diabetes. 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
- 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 diabetic population. In one study of people 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%).⁴ 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”.⁵ For the purposes of this review, we use the term *diabetic peripheral neuropathy* (DPN) as the *symmetrical sensorimotor polyneuropathy* of the hands and feet.

The earliest signs of DPN 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 DPN 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.⁶ Complications of DPN include secondary diseases or conditions that develop in the course of DPN, such as foot ulcers. Symptoms are defined as the subjective experience of DPN and include numbness and pain.

Interventions

Pharmacologic treatment options to prevent the complications of DPN

The cornerstone of pharmacologic interventions to prevent complications of DPN is medications and strategies that improve glucose control.⁷ Key pharmacologic interventions that address comorbid conditions in patients with diabetes are statins and antihypertensives. These agents may also contribute to preventing DPN complications,⁸ since co-existing peripheral vascular disease can contribute to long-term diabetic complications, such as foot ulcerations.⁹ Although DPN 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.

Non-pharmacologic treatment options to prevent the complications of DPN

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 the symptoms of DPN

A variety of pharmacological approaches have 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 FDA approved for DPN (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 DPN. For DPN, 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.

Non-pharmacologic treatment options to improve the symptoms of DPN

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

Available Evidence and Shortcomings

Prevention of DPN 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], lifestyle interventions, and a variety of quality improvement strategies (such as care management) previously included in the EPC review Closing the Quality Gap Series.¹⁰ A recent Cochrane review focused on the prevention of DPN included 17 randomized controlled trials.¹¹ The review reported a significantly reduced risk of developing clinical polyneuropathy among people 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% CI, 0.01 to -1.17) in people 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.^{12, 13}

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 in persons with diabetes who are at-risk for ulceration.¹⁴ This review found strong 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. However, this review did not address amputations.

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

Treatment of DPN Symptoms (Pain, Paresthesia, Numbness)

Treatments for DPN 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. The review did not include interventions such as exercise or cognitive behavioral therapy for treatment. The review stated that exercise was not effective but did not report if any studies were identified.

Since the completion of this review and guideline, new trials have been conducted on the drugs evaluated in this review and related medications, as well as trials evaluating combinations of different classes of pharmacological drugs. One additional agent has been FDA-approved for treatment of painful neuropathy: the high-dose capsaicin patch. Other agents that have recently been evaluated in trials include topical ketamine, clonidine, cannabinoids, and dextromethorphan/quinidine.

Newer reviews focusing on pharmacologic treatment of painful neuropathy have reported effectiveness for a number of agents, but they have not addressed treatment of other DPN symptoms, such as of numbness and paresthesia.¹⁵⁻²⁰ 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.¹⁸ The review assessed a broader range of interventions as moderate- to high-quality evidence, including serotonin-norepinephrine reuptake inhibitors (specifically, duloxetine) and gabapentin. Two comprehensive systematic reviews and meta-analyses focusing solely on pharmacologic interventions for painful DPN were published in 2014,²¹ with the most recent

including articles published through April 2014, and also concluded that a broader range of pharmacologic interventions were supported by sufficient evidence.²² Other recent systematic reviews have addressed painful neuropathy more generally, not diabetes specifically,²³ or have addressed only certain classes or specific medications and interventions.^{16, 17, 19, 20} None of these reviews have synthesized evidence on paresthesia or health-related quality of life. 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 DPN complications and treatment of DPN 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 (KQ):

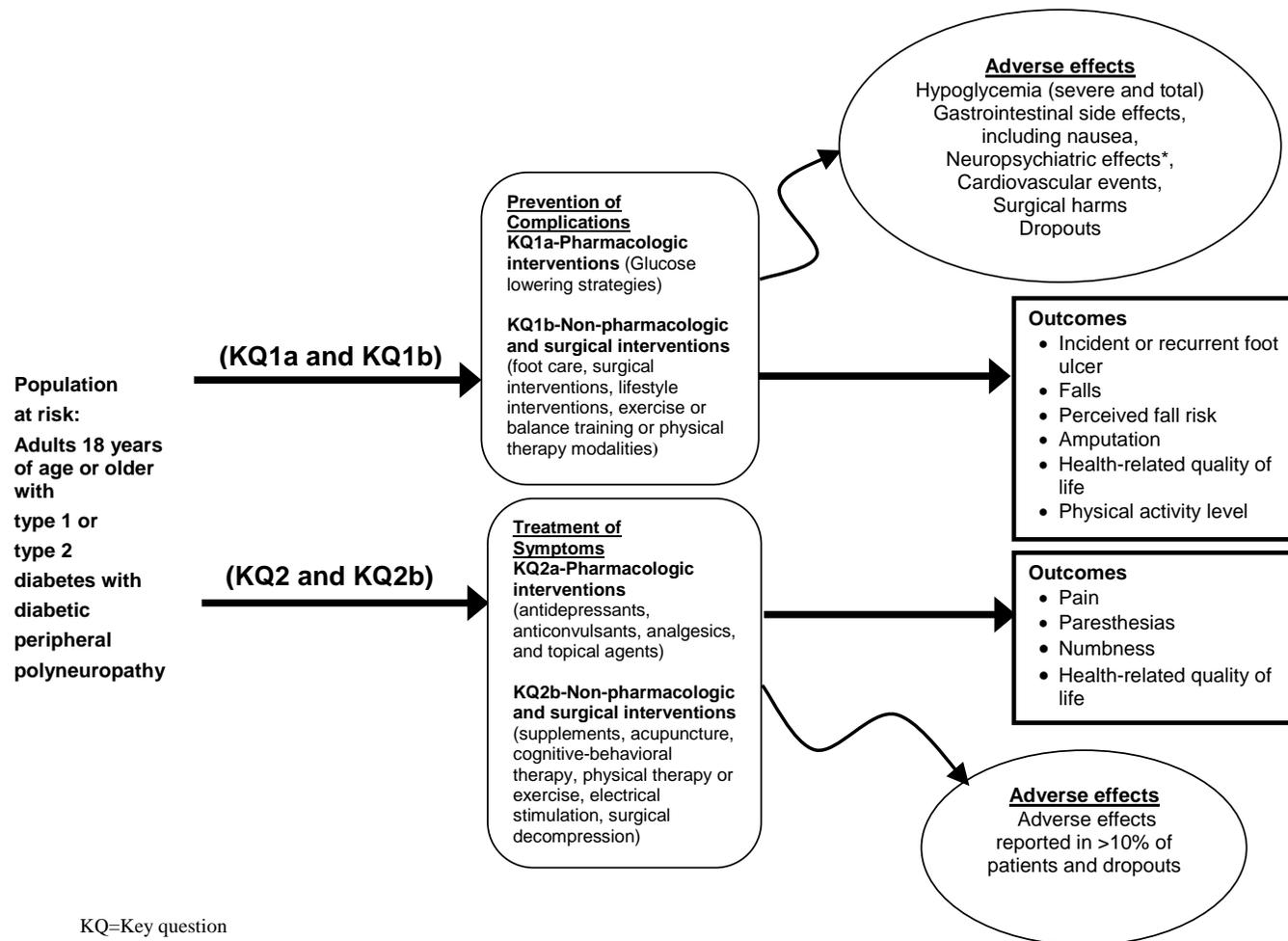
Key Question 1a: What are the benefits and harms of pharmacologic treatment options focused on glucose lowering to prevent the complications of diabetic peripheral neuropathy among adults age 18 or older with type 1 or type 2 diabetes mellitus?

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 AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews.²⁴

Protocol Development

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

Search Strategy

Systematic Reviews

We searched MEDLINE and the Cochrane Database of Systematic Reviews for systematic reviews. We chose to search from January 1st, 2011 to October 12th, 2015 because the American Academy of Neurology guideline was published in 2011.²⁵

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 KQ1b (foot ulcer) and KQ2a, we searched for publications from January 1st, 2013 to October 12th, 2015.

For questions where we did not identify high quality relevant systematic reviews, we searched for primary studies using MEDLINE, Embase®, and the Cochrane Central Register of Controlled Trials (CENTRAL) 1966 to October 12, 2015. We developed a search strategy for PubMed® based on medical subject headings (MeSH®) terms and text words of key articles (Appendix B). We plan to update the search during the peer review process. We included only studies published in English.

Study Selection

Systematic Reviews

When available, topically relevant and recent reviews were included to answer one or more of the Key Questions (intervention). 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 the quality of each review).

We did not rescreen the primary studies included in systematic reviews. Rather, we relied on the data provided in the review. For primary studies 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 2. 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 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. We used DistillerSR (Evidence Partners, 2010) to manage the screening process.

Paired investigators used the full text of articles, promoted on the basis of their abstracts, to complete additional independent screens to determine whether the articles should be included in the full data abstraction. Differences regarding citation eligibility were resolved through consensus.

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

	KQ1a and KQ1b: Preventing complications of DPN	KQ2a and KQ2b: Treating symptoms of DPN
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	<p>Pharmacologic treatments focused on glucose control (KQ1a):</p> <ul style="list-style-type: none"> - 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. <p>Non-pharmacologic and surgical interventions (KQ1b):</p> <ul style="list-style-type: none"> - 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 	<p>Pharmacologic interventions focused on DPN (KQ2a):</p> <p>Antidepressants: Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protriptyline, trimipramine), serotonin-noradrenaline reuptake inhibitor antidepressants (desvenlafaxine, duloxetine, levomilnacipran, milnacipran, venlafaxine)</p> <p>Anticonvulsants: pregabalin, gabapentin or gabapentin extended release and enacarbil, other antiepileptics (carbamazepine, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate, tiagabine, topiramate, zonisamide)</p> <p>Analgesics: Opioids (morphine, oxycodone, fentanyl, hydromorphone, methadone, oxymorphone), tramadol, tapentadol</p> <p>Topical Agents: lidocaine, capsaicin, other topical treatments (clonidine, , pentoxifylline)</p> <p>Other: N-methyl-D-aspartate (NMDA) antagonists (ketamine, dextromethorphan), mexiletine, botulinum toxin A, cannabinoids</p> <p>Combinations of any of the above treatments</p> <p>Non-pharmacologic and surgical interventions (KQ2b):</p> <ul style="list-style-type: none"> - 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

	KQ1a and KQ1b: Preventing complications of DPN	KQ2a and KQ2b: Treating symptoms of DPN
Outcomes	<p>Benefits (KQ1a and KQ1b):</p> <ul style="list-style-type: none"> - 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 <p>Harms (KQ1a and KQ1b):</p> <ul style="list-style-type: none"> - Hypoglycemia (severe and total) - Gastrointestinal side effects, including nausea - Neuropsychiatric effects (ONLY for smoking cessation studies involving pharmacotherapy) - Cardiovascular events - Surgical harms - Dropouts 	<p>Benefits (KQ2a and KQ2b):</p> <ul style="list-style-type: none"> - Pain - Paresthesia - Numbness - Health-related quality of life (Health-related quality of life is defined using measurement with instruments designed for this topic) <p>Harms (KQ2a and KQ2b):</p> <ul style="list-style-type: none"> - 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	

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

Exclusion criteria at abstract screening	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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

Data Abstraction 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, including measures of variability. We also collected data on outcomes for the subgroups of interest, including age, sex, race/ethnicity, and body mass index.

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

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

Quality (Risk of Bias) Assessment of Individual Studies Systematic Reviews

We assessed methodological quality of included systematic reviews using the ROBIS tool, which rates each systematic review with a yes, probably yes, probably no, no, no information across the four domains (study eligibility criteria; identification and selection of studies; data collection and study appraisal; and synthesis and findings).²⁶ The overall assessment of quality for each systematic review is based on a reviewer’s overall judgement given their response to the individual ROBIS items, and the assessment had 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 quality ratings or 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.²³ For non-randomized studies of treatment interventions, we used the Cochrane Risk of Bias Assessment Tool for Non-Randomized Studies of Interventions (ACROBAT-NRSI).²⁷ 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).

Strength of the Body of Evidence

We graded the strength of evidence using the scheme recommended by the EPC Methods Guide for Conducting Comparative Effectiveness Reviews.²⁴ We graded the strength of evidence for the outcomes we classified as most important or critical during protocol development, including pain, health-related quality of life, falls, foot ulcer, and amputation. We considered five domains in grading the strength of the body of evidence: study limitations, directness, consistency, precision, and reporting bias. 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 3). 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.

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 3. 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. We considered important population characteristics (age, gender, race, ethnicity, duration and severity of diabetes) and intervention features (co-interventions) that may cause heterogeneity of treatment effects and affect generalizability of the findings

Peer Review and Public Comment

The draft report will be sent to peer reviewers and will be posted on the AHRQ Web site for 4 weeks to elicit public comment. We will address all reviewer comments, revising the text as appropriate and documenting everything in a disposition of comments report that will be made available 3 months after AHRQ posts the final review on its Web site.

Organization of The Report

We first describe the results of our literature searches, followed by results for KQs, which include a list of key points, an overview of the included literature and detailed synthesis of the data and then discussion. Each section follows the format listed below:

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

Results

Discussion

References

Key Question 2a & b: What are the benefits and harms of pharmacologic treatment and non-pharmacologic 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?

Results

Discussion

References

Results for Key Questions 1a and b

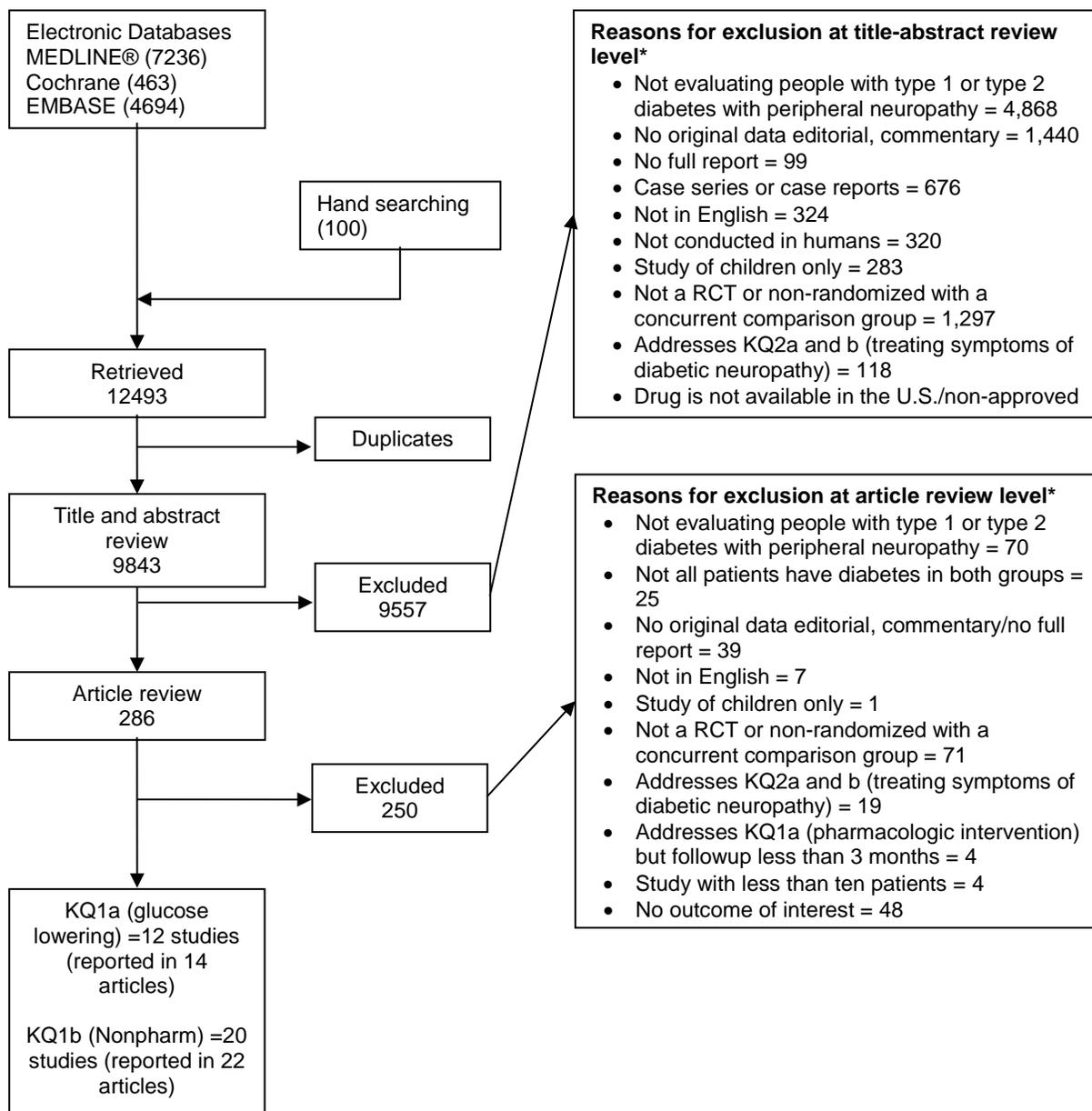
Results of the Search

We included one systematic review (30 studies) and 32 primary studies (reported in 36 articles). Figure 2 summarizes the search and selection of primary studies. The literature search identified 9843 unique citations. During the title and abstract screening, we excluded 9557 citations and 249 citations were excluded during the full-text screening. 32 studies (reported in 36 articles) were determined to meet inclusion criteria and were included. (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 RCTs and 1 cohort study);
- KQ1b - Foot care interventions - One high quality relevant systematic review (30 controlled studies) and five newly identified studies (2 RCTs and 3 cohort studies);
- KQ1b - Lifestyle interventions - One RCT;
- KQ1b - Balance interventions - Six RCTs and 1 cohort study;
- KQ1b - Exercise training interventions - Four RCTs and 1 cohort study;
- KQ1b - Physical therapy interventions - Two RCTs

Figure 2. Summary of the literature search for primary studies



* Reviewers were allowed to mark more than one reason for exclusion.

KQ1a: What are the benefits and harms of pharmacologic treatment options focused on glucose lowering to prevent the complications of diabetic peripheral neuropathy?

Key Points

- Intensive glycemic control prevented lower extremity amputations more than standard glycemic control in patients with type 2 diabetes (moderate strength of evidence).
- Strength of evidence was low or insufficient for the effect of glucose lowering strategies or specific medications on foot ulcers in patients with type 1 or type 2 diabetes.

Table 4. Summary of findings for pharmacological 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)	Two RCTs reported that intensive glycemic control prevented more foot ulcers (OR 0.25, 95% CI, 0.06 to 1.01 and 0.36, 95% CI 0.12 to 1.15), but the number of events was low despite long followup periods, and differences were not statistically significant.	Low
		Type 2 diabetes 2 RCTs (N=1326)	Two RCTs reported no difference between arms.	
	Monotherapy or combination medications	Type 1 diabetes No study	NA	Insufficient
		Type 2 diabetes 1 cohort study (N=23,395)	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.	
Lower extremity amputations	Intensive vs. standard glycemic control	Type 1 diabetes 1 RCT (N=1257)	One RCT did not show a statistically significant difference between lower extremity amputations in the intensive vs. standard glycemic control arms.	Moderate
		Type 2 diabetes 6 RCTs (N=9441)	Six RCTs reported a decreased risk of lower extremity amputations in the intensive vs. standard glycemic control arms. (Pooled OR 0.62, 95% CI 0.40 to 0.96).	
	Monotherapy- or combination medications	Type 1 diabetes None study	NA	Insufficient
		Type 2 diabetes 1 RCT (N=5238)	One RCT that compared pioglitazone versus placebo reported no difference in risk of amputations between the two arms.	
Quality of life	Mono- or combination medications	1 RCT (N=46)	One RCT reported no difference in quality of life scores between the exenatide and glargine arms.	Insufficient

Description of Included Studies

Twelve studies, reported in 14 articles, assessed the effectiveness of glycemic control and hypoglycemic medications to prevent the complications of DPN. Two studies, reported in three

articles, included patients with type 1 diabetes,²⁸⁻³⁰ and 10 studies, reported in 11 articles, included patients with type 2 diabetes.³¹⁻⁴¹

Of the 12 included studies, eleven were parallel arm RCTs^{28, 29, 31, 32, 34, 36-41} and one was a retrospective observational cohort study.³⁵ 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.^{28, 29, 31, 32, 37-41} The two other RCTs included head-to-head medication comparisons.^{34, 36} The seven RCTs^{32, 36, 37, 39, 41-43} 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) had a mean age of 72 years.³⁹ 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]³⁸) 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).^{37, 41} 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.³³

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.^{28, 29, 31, 32} The Steno-2 trial reported amputation outcomes at two time points, at the end of the trial³² and again after additional observational followup.³³ The two RCTs that included head-to-head drug comparisons were pioglitazone versus placebo³⁶ and exenatide versus glargine insulin.³⁴ The retrospective observational cohort study of over 23,000 participants compared glargine insulin versus NPH insulin.³⁵

The overall risk of bias for these studies was low for six studies, unclear for three studies and high for one study. Most of the studies (n=6) had 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.

Outcomes

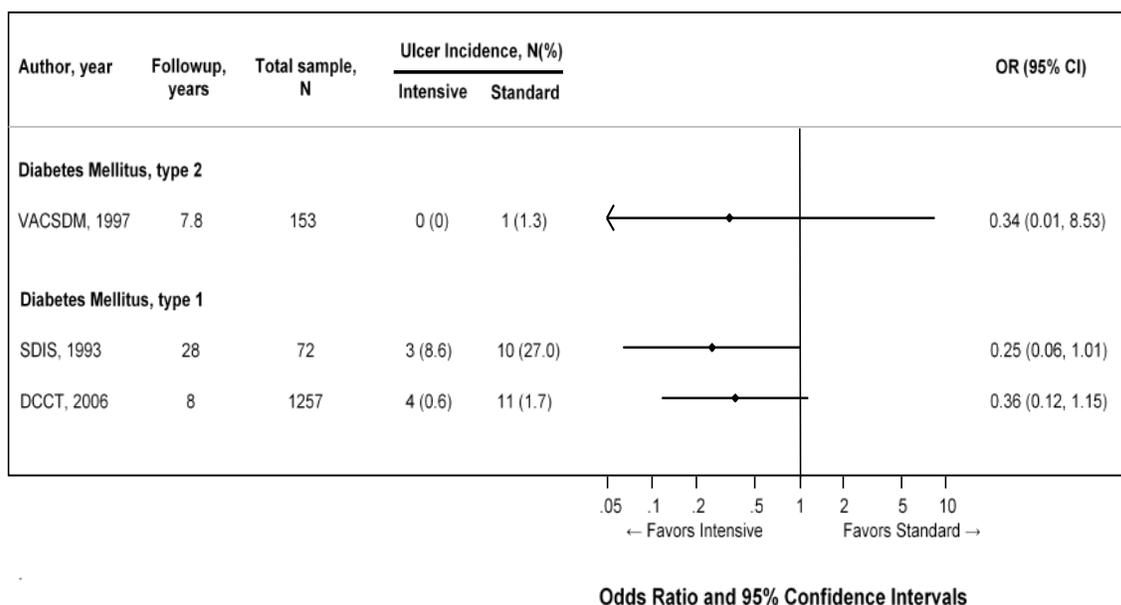
Foot Ulcer

Five studies (four RCTs and one cohort study) assessed foot ulceration.^{28, 30, 35, 38, 39} Two RCTs included patients with type 1 diabetes^{28, 29} and two included patients with type 2 diabetes,^{38, 39} comparing intensive with standard glycemic control strategies. For type 1 diabetes, the 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 odds ratio for foot ulcers in the intensive versus standard glycemic control was 0.25 (95% CI, 0.06 to 1.01).³⁰ The Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) trial had 8 years of followup, with four (0.6%) ulcerations in the intensive glycemic control treatment arm compared with 11 (1.7%) in the standard treatment arm.²⁸ The calculated odds ratio for intensive versus standard glycemic control was 0.36 (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 ulcerations in intensive versus standard glycemic

control. The differences between intensive and standard care for the prevention of foot ulcers was 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).

For type 2 diabetes, the Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes (VACS DM) and the Japanese Elderly Diabetes Intervention Trial (J-EDIT) RCTs reported foot ulcerations.^{38, 39} In the VACS DM, one ulceration occurred (in the intensive treatment arm) in the total population of 153 over 7.8 years of treatment.³⁸ In the 3-year J-EDIT RCT, 12 total ulcerations or gangrene occurred combined between the two arms and the between-arm difference was not statistically significant ($p=0.56$), but the event rates were not reported by arm³⁹. 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 ulceration rates by arm. One cohort study including patients with type 2 diabetes reported a reduced hazard ratio (HR) for foot ulceration for patients taking glargine insulin versus NPH insulin (HR 0.61; 95% CI, 0.38 to 0.98).³⁵

Figure 3. Calculated odds ratio for foot ulcers in the intensive versus standard glycemc control



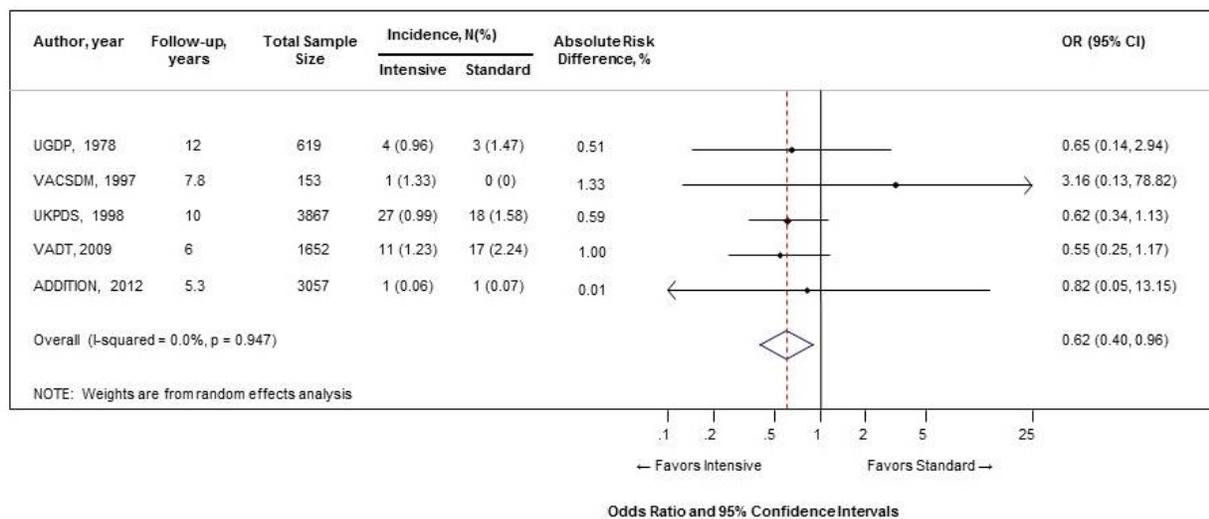
Lower Extremity Amputation

Eight RCTs reported lower extremity amputations as an outcome.^{28, 32, 36-38, 40, 41, 43} The DCCT/EDIC RCT²⁸ included patients with type 1 diabetes and the seven other RCTs included patients with type 2 diabetes.^{32, 36-38, 40, 41, 43} Six RCTs reported lower extremity amputation in patients with type 2 diabetes comparing intensive versus standard glycemc control strategies^{28, 32, 37, 38, 40, 41, 43} and one trial, the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) trial compared pioglitazone vs. placebo.³⁶ Steno-2 reported amputations at two time points, at trial end (7.8 years)³² and also after an additional mean of 5.5 years.³³ Figure 4 includes the five trials comparing intensive versus standard glycemc control. We excluded the Steno-2 from the meta-analysis because it had a mixed intervention approach³³. The calculated odds ratios for amputations ranged from 0.55 to 3.16 and were not statistically significant (Figure 4). The five trials comparing the effectiveness of intensive glycemc control versus standard treatment indicated a decreased risk of lower extremity amputations in patients with type 2 diabetes (pooled OR 0.62 [95% CI, 0.40 to 0.96]) (Figure 4). Results from the five trials comparing the effectiveness of intensive glycemc control versus standard treatment indicate the clinical benefit of decreased risk of lower extremity amputations in patients with type 2 diabetes. However, the total number of events, event rates and absolute risk differences are low despite long followup periods.

The DCCT/EDIC trial reported lower extremity amputation in patients with type 1 diabetes who received intensive glycemc control versus standard treatment with a calculated odds ratio of 0.40 (95% CI, 0.08 to 2.09), which was not statistically significant.

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 [HR 1.01 (95% CI, 0.58 to 1.73)].³⁶

Figure 4. Calculated odds ratio for lower extremity amputations in the intensive versus standard glycemic control in patients with type 2 diabetes with DPN



%=percent; CI=confidence interval; N=sample size; p=p-value; OR=odds ratio

Quality of Life

One trial assessed the quality of life using global-neuropathy-specific quality of life (NeuroQOL).³⁴ 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

Five studies reported on the risk of hypoglycemia.^{32, 34, 37, 43} 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 5).³⁴

Table 5. Studies reporting harms of glucose lowering treatments in patients with type 1 and 2 diabetes at risk for DPN

Author, Year	Arm	Harm	N for Analysis	Time Point (s)	N of Patients with Harms	% of Patients with Outcomes-harms
Jaiswal, 2015 ³⁴	Exenatide	Severe hypoglycemia	22	18 months	0	0%
	Insulin glargine		24		1	4%
	Exenatide	GI problems	22	18 months	6	27%
	Insulin glargine		24		4	17%
UKPDS*, 1998 ⁴³	Intensive glycemic control	Severe hypoglycemia	2,729	10.7 years	NR	1.2% chlorpropamide arm; 1.0% glibenclamine arm; 2.0% insulin arm
	Conventional treatment		1,138		NR	0.7% conventional 0.6% metformin arm

Author, Year	Arm	Harm	N for Analysis	Time Point (s)	N of Patients with Harms	% of Patients with Outcomes-harms
Steno-2, 2003 ³²	Intensive glycemic control	Severe hypoglycemia	80	7.8 years	12	15%
	Conventional treatment		80		5	6%
PROactive ³⁶	Pioglitazone	Hypoglycemia	2,605	34.5 months	728	28%
	Placebo		2,633		528	20%
VADT 2009 ³⁷	Intensive glycemic control	Hypoglycemia	892	6 years	76	9%
	Standard		760		28	5%
VACS DM 1995 ³⁸	Intensive	Hypoglycemia	75	7.8 years	5	6%
	Standard		78		2	2.5%

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

KQ1b: What are the benefits and harms of non-pharmacologic treatment options (foot care, surgical interventions, lifestyle interventions, exercise and balance training) to prevent complications of diabetic peripheral neuropathy?

Foot Care and Surgical Interventions for Foot Ulcers

Key Points

- Data are not consistent regarding the effect of a single session of patient education on incidence of foot ulcer with low strength of evidence. Education programs are not effective for reducing amputations with low strength of evidence.
- Integrated foot care is effective in reducing foot ulcer incidence and/or recurrence with low strength of evidence.
- Monitoring of foot skin temperature is effective for reducing foot ulcer incidence and recurrence with moderate strength of evidence.
- Specific modalities of therapeutic footwear is effective in prevention of recurrent plantar foot ulcers compared with standard-of-care therapeutic footwear with moderate strength of evidence.
- Achilles tendon lengthening, single- or pan-metatarsal head resection, and metatarsophalangeal joint arthroplasty are effective for reducing ulcer recurrence risk in selected patients with initially non-healing ulcers when compared with non-surgical treatment with low strength of evidence. However, Achilles tendon lengthening appeared to worsen physical functioning based on limited evidence.

Table 6. Summary of finding For Foot Care and Surgical Interventions

Outcomes	Comparison	Number of controlled studies (N)	Findings	Strength of Evidence

Outcomes	Comparison	Number of controlled studies (N)	Findings	Strength of Evidence
Foot ulcer	Integrated Foot Care	4 studies included Previous SR: 3 RCTs and 1 cohort Newly identified study: None (N=350)	Netten et al. reported a reduction in foot ulcer incidence or recurrence using integrated care. The reduction was ~20% across studies.	Low
	Self-management	6 studies included Previous SR: 4 RCTs Newly identified studies: 1 RCT and 1 cohort study (N=943)	<p>Self-monitoring of foot temperature: (3 RCTs from Netten et al. and 1 new RCT)</p> <ul style="list-style-type: none"> Two RCTs in Netten et al. showed reduction in foot ulcer incidence in patients using self-monitoring of foot temperature compared with standard of care. One RCT in Netten et al. reported reduction in foot ulcer recurrence in patients using self-monitoring of foot temperature compared with standard of care. One newly-identified RCT did not find statistically significant benefit. <p>Topical treatment on foot: (1 RCT from previous review and 1 cohort study)</p> <ul style="list-style-type: none"> Inconsistent findings from one RCT and one newly identified cohort study. 	Moderate
				Low
	Patient Education	4 Studies included Previous SR: 2 RCTs Newly identified studies: 1 RCT and 1 cohort study (N=16943)	Findings were inconsistent regarding the effect of a single session of patient education on the incidence of foot ulcers.	Low
	Therapeutic footwear	10 studies included Previous SR: 7 RCTs and 3 cohort studies Newly identified study: None (N=1913)	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.	Moderate
	Surgical Intervention	9 studies included Previous SR: 3 RCTs and 6 cohort studies Newly identified study: None (N=744)	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.	Low
Amputation	Integrated Foot Care	4 studies included Previous SR: 2 RCTs and 1 cohort study Newly identified study: 1 cohort (n=27840)	Findings were inconsistent regarding the effect of integrated foot care on amputations.	Low

Outcomes	Comparison	Number of controlled studies (N)	Findings	Strength of Evidence
	Self-management	1 study included Previous SR: 1 RCT Newly identified study: None (N=85)	Netten et al. reported no difference in amputations in patients who received instruction to perform structured foot inspection daily plus infrared skin thermometer vs. patients who received instruction to perform structured foot inspection daily only.	Insufficient
	Patient Education	3 studies included Previous SR: 1 RCT Newly identified studies: 1 RCT; 1 cohort study (N=16812)	There was no difference in amputation occurrence.	Low
	Therapeutic Footwear	1 study included Previous SR: 1 cohort study Newly identified study: None (N=46)	Netten et al. reported no difference in amputations in patients who accepted a prescription of orthopedic footwear and wore the footwear while being active, vs. patients who did not accept such a prescription.	Low
	Surgical Intervention	2 studies included Previous SR: 2 cohort studies Newly identified study: None (N=168)	Netten et al. reported that there were inconsistent findings from a limited number of studies.	Low
Quality of Life	Surgical Intervention	1 study included Previous SR: None Newly identified study: 1 RCT (N=28)	One newly identified study reported a worse SF-36 physical summary score after Achilles tendon lengthening compared with total contact casting only.	Insufficient

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. There were 30 controlled studies (19 RCTs and 11 non-randomized controlled studies). 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 with either 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 methodological quality of included studies and decided to assess the quality of evidence on the risk of bias of included studies, effect sizes, and expert opinion, and rate 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.²⁶ 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 controlled primary studies, as described in the Methods section. We identified five new studies: two parallel-arm RCTs^{44, 45} and three cohort studies.⁴⁶⁻⁴⁸ The cohort studies⁴⁶⁻⁴⁸ included patients with type 2 diabetes exclusively, while one RCT⁴⁴ included patients with both type 1 and type 2 diabetes and the other RCT did not specify.⁴⁷

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 fall or perceived fall risk. The outcomes are presented by interventions. The results for the outcomes are summarized by foot care intervention.

Foot Ulcer

The combination of studies included in the Netten et al. review and newly identified studies yielded 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 five controlled studies, but only five were published.⁴⁹⁻⁵² Integrated foot care provided by an endocrinologist and diabetes nurse,⁴⁹ chiropody treatment free of charge,⁵¹ or multidisciplinary foot care given at least once every three months⁵² all showed significant reductions in foot ulcer incidence or recurrence. The review by Netten et al. rated the strength of evidence as low.

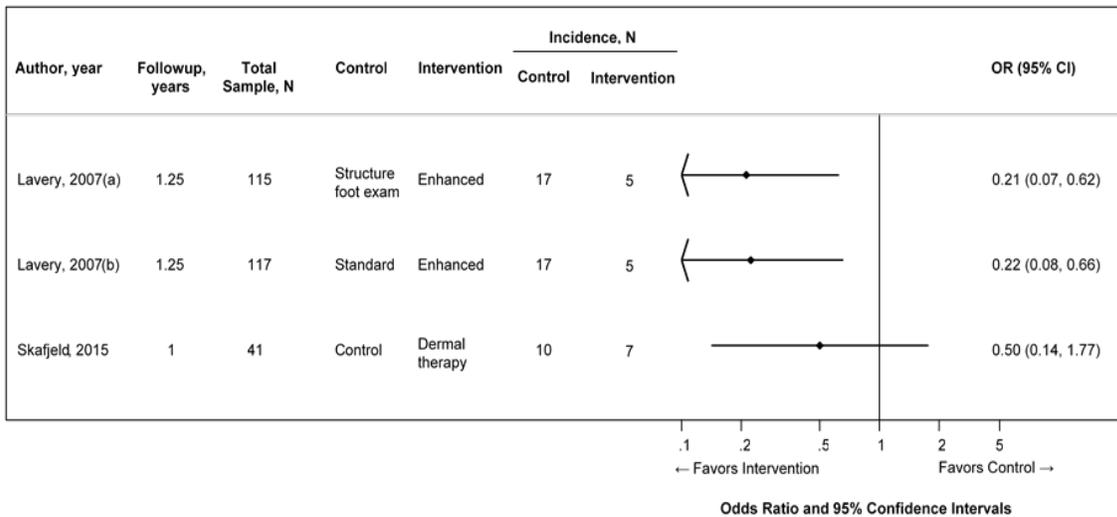
In our updated search, we did not identify any new studies that evaluated the effectiveness of integrated care for foot ulcers.

Self-Management

Four studies, three RCTs from the Netten review and one newly identified RCT, evaluated the effectiveness of self-monitoring of foot temperature on the incidence or recurrence of foot ulcers. 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.^{53, 54} 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).⁵³ Another RCT reported the foot temperature monitoring group had significantly fewer diabetic foot complications (2% vs. standard therapy group 20%, P = 0.01, odds ratio 10.3, 95% CI 1.2-85.3).

In addition, one RCT with low risk of bias included in the Netten review⁵⁵ 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 self-monitoring foot temperature on foot ulcer recurrence (7 ulcer recurrences out of 21 patients vs. 10 recurrences out of 20 patients).⁵⁵ Figure 5 summarizes results from those studies.

Figure 5. Studies show reduction in recurrence of foot ulcers in patients using self-monitoring of foot temperature



Two studies evaluated the effectiveness of topical treatments on 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, $p=0.9$).⁵⁶ We additionally identified a retrospective cohort study⁴⁸ with moderate risk of bias showing 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. There was 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 self-monitoring of the temperature of the feet was effective in lowering foot ulcer incidence. Topical application did not seem to be effective. Limited evidence supports integrated foot care or self-examination of foot.

Patient Education

Four studies evaluated the effectiveness of educational programs on diabetic foot care and its complications. The Netten et al. review concluded that there was no reduction in ulcer recurrence from single educational programs, based on two RCTs: one with high risk of bias⁵⁷ and one with low risk of bias,⁵⁸ and a low overall strength of evidence.

One newly identified RCT with high risk of bias⁴⁵ 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 16 percent increased risk (HR: 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.⁴⁶ Results are thus inconsistent on the effect of education programs on foot ulcer prevention.

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,⁵⁹ intensive footwear therapy based on a prescription algorithm,⁶⁰ shape or barefoot pressure-based custom-made insoles,⁶¹ or therapeutic shoes⁶² were effective in lowering the foot ulcer incidence. Cohort studies also reported decreased ulcer recurrence in patients wearing therapeutic sandals,⁶³ and in patients who were beneficiaries of prescribed diabetic footwear compared to those wore their own footwear.⁶⁴ However, selection bias cannot be ruled out and may be an important determinant of outcome.

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

We did not find new studies in our updated search.

Surgical Intervention

The review by Netten et al.¹⁴ included nine controlled studies, 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's authors concluded that Achilles tendon lengthening to allow a patient walking flat-footed without a bend in the knee, single- or pan-metatarsal head resection to either remove bone segments underlying the lesion or conservative treatment (i.e. relief of weight-bearing and regular dressing), and metatarsophalangeal joint arthroplasty that prevent the surfaces of the joint toe from rubbing together appear to reduce foot ulcer recurrence risk in some patients with initially non-healing foot ulcers when compared with non-surgical treatment, based on low strength of evidence. However, surgery is sometimes a last-resort approach after failed conservative treatment. Patients with diabetes who receive surgeries are often selected and at high risk of foot ulcer recurrence.

Lower Extremity Amputation Outcome

Eleven studies, five RCTs and six cohorts, reported non-pharmacologic interventions and prevention of amputation outcomes.

Integrated Foot Care

Two RCTs and one cohort study in the Netten et al. review evaluated the effect of integrated foot care on amputation outcomes. One RCT with high risk of bias⁴⁹ 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 bias⁵¹ 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.⁵² One newly identified cohort study with low risk of bias⁴⁷ 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.

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.⁶⁵ Statistical significance was not reported. In our updated search, we did not identify any studies of therapeutic footwear.

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.⁵⁴ In our updated search, we did not identify any studies of self-management.

Patient Education

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). We identified two studies evaluating effectiveness of education programs regarding diabetic foot disease and its complications. One RCT with high risk of bias did not report any amputations in either group.⁴⁵ A cohort study⁴⁶ 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.

Surgical Intervention

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.⁶⁶ Another cohort⁶⁷ 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.

Quality of Life

In our updated search, we identified one new 8-month RCT⁶⁸ 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. ATL 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 ATL 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 support the effectiveness of ATL after TCC based on one study.

Harms

The prior review¹⁴ did not assess adverse effects. Two of the five newly identified studies reported adverse effects.^{44, 46} One high risk of bias study⁴⁴ reported no dropouts in the control group and three dropouts in the intervention group. Statistical testing was not reported. Another study⁴⁶ 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.

Lifestyle Intervention

Key Point

- Strength of evidence is insufficient for the outcome of quality of life

Table 7. Summary of finding for Lifestyle intervention

Outcomes	Comparison	Number of Studies (N)	Findings	Strength of Evidence
Quality of Life	Dietary Intervention: education on plant-based diet plus Vitamin B vs. Vitamin B alone	1 RCTs (N=34)	No significant difference in total score of the Norfolk Quality of Life Questionnaire (difference of mean change: -4.0; 95% CI: -15.1 to 7.1).	Insufficient

Description of included studies

Only one 20-week pilot randomized trial assessed the effectiveness of dietary intervention using a plant-based diet and Vitamin B12 to prevent the complications of DPN.⁶⁹ 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.⁶⁹ 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 graded the strength of evidence as insufficient given only one study.

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.⁷⁰⁻⁷² 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.
- Whole body vibration improved dynamic balance and stability outcomes.

Table 8. Summary of findings for balance training and whole body vibration

Outcome	Comparison (all compared to control group)	Number of studies (N)	Findings	Strength of Evidence*
Dynamic balance and stability	Balance training	5 RCTs (reported in 6 studies) and 1 non-randomized control study (N=201)	<p>Mean change in baseline for BBS ranged from 0.2 to 2.0, direction of effect favoring intervention (calculated from 4 trials).</p> <p>Mean change in baseline for TUG ranged from -2.12 to 0.1, direction of effect favoring intervention (calculated from 4 trials).</p> <p>Mean change in baseline for FRT ranged from 0.4 to 8.97, direction of effect favoring intervention (calculated from 3 trials).</p>	NA
	Whole body vibration	2 RCTs (N=80)	<p>SMD for BBS was 1.77 (95% CI, 1.01 to 2.53), direction of effect favoring intervention (calculated from 1 trial).</p> <p>SMD for TUG ranged from -2.47 to -1.95, direction of effect favoring intervention (calculated from 2 trials).</p> <p>SMD for FRT was 1.72 (95% CI, 0.97 to 2.48), direction of effect favoring intervention (calculated from 1 trial).</p>	NA

Outcome	Comparison (all compared to control group)	Number of studies (N)	Findings	Strength of Evidence*
Physical activity	Balance training	3 RCTs (reported in 4 studies) (N=156)	Effect size for 6 minute walk test was -0.04 (95% CI, -0.52 to 0.43), reported in 1 trial. Effect size for total daily steps ranged from 0.15 to 0.16, reported in 2 trials.	NA
	Whole body vibration	None	NA	
Perceived fall risk	Balance training	3 RCTs (reported in 4 studies) and 1 non-randomized control study (N=182)	SMD for FES/FES-I ranged from -0.13 to 0 (calculated from 2 trials). SMD for Falls risk index was -1.21 (95% CI, -1.94 to -0.48), direction of effect favoring intervention (calculated from 1 trial). SMD for ABC scale was 0.42 (95% CI -0.58 to 1.41), direction of effect favoring intervention (calculated from 1 trial).	NA
	Whole body vibration	NA	NA	NA
Falls	Balance training	1 RCTs (reported in 2 studies) (N=79)	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).	Insufficient
	Whole body vibration	None	NA	NA
Foot ulcer	Balance training	None	NA	NA
	Whole body vibration	None	NA	NA
Quality of life	Balance training	1 RCT (N=39)	SMD for SF-12 physical component was 0.01 (95% CI, -0.65 to 0.68), direction of effect favoring intervention (calculated from 1 trial).	Insufficient
	Whole body vibration	None	NA	NA

We graded only critical outcomes (falls, foot ulcers, and quality of life)

For dynamic balance and stability outcomes, SMD could not be calculated for the majority of interventions due to incomplete data; data are therefore presented as a summary of the scale scores.

BBS=Berg Balance Scale (0-56), TUG= Timed Up and Go test (seconds), FRT= Functional Reach Test (distance in inches);

SMD = Standardized mean difference

NA = not applicable

Description of Included Studies

We identified seven studies (reported in 8 articles) that assessed the effect of balance training 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 also 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 studies) and non-randomized control study compared balance training with a control group⁷⁰⁻⁷⁶ (one trial also included simulation as part of the training⁷³).

Two RCTs compared whole body vibration therapy with balance training and/or a control group^{71, 77} (one trial⁷¹ included both balance training and whole body vibration arms).

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 trials studied patients with type 2 diabetes^{70, 73, 77} and one trial studied patients with both type 1 and 2 diabetes^{74, 75}. The remaining three trials did not specify the type of diabetes patients.^{71, 72, 76}

The overall risk of bias for most of the trials 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. Trials 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.^{74, 75}

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 training⁷¹⁻⁷⁷ and two trials evaluated whole body vibration.^{71, 77}

For balance training, standardized mean difference (SMD) 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.⁷¹⁻⁷⁵ 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.^{71-75, 77} Four trials, reported in five articles, compared TUG outcomes in balance training and control groups.⁷¹⁻⁷⁵ 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 trial) also reported effects on the Functional Reach Test (FRT).^{71, 72, 76} 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. Given the imprecision and inconsistency of results, we concluded that evidence was inconsistent for the effect of balance training on balance outcomes.

For whole body vibration, results are presented as SMD. One study reported effects on the Berg Balance Scale (BBS) with an SMD of 1.77 (95% CI, 1.01 to 2.53), direction of effect favoring the intervention group.⁷¹ Two studies reported effects on the Timed Up and Go Test (TUG)^{71, 77}; the SMD ranged from -2.47 to -1.95, with direction of effect favoring the intervention group (negative SMD denotes less time required to complete task). One of the studies also reported effects on the Functional Reach Test (FRT)⁷¹ with an SMD of 1.72 (95% CI, 0.967 to 2.48), with the direction of effect favoring the intervention group. Given the consistency of statistically significant results, we concluded that whole body vibration improved balance outcomes.

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.^{70, 72, 74, 75}

A RCT of balance training (reported in two articles) assessed 6-minute walk outcomes in balance training and control groups.^{74, 75} 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.⁷² The SMD 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.^{70, 74, 75} 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.⁷⁰ 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 statistically significant findings, 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 of trials^{70, 73-76} assessed perceived fall risk among participants, each study using a different scale of assessment. The heterogeneity in assessment outcomes precluded pooling of data.

Two trials, reported in three articles, evaluated the effect on the Falls Efficacy Scale (FES)^{74, 75} or FES-I (international version, modified to be more culturally and socially sensitive)⁷⁰ score between balance training and control groups.^{70, 74, 75} The SMD for FES/FES-I ranged from -0.13 to 0.

Another RCT of balance training reported the effect on the Fall Risk Index, with an SMD of -1.21 (95% CI -1.94 to -0.48), in the direction favoring the intervention group.⁷³

A prospective trial assessed the effect on the Activities-specific Balance and Confidence (ABC) scale.⁷⁶ The SMD was 0.42 (95% CI, -0.58 to 1.41) in the direction favoring the intervention group.⁷⁶ Based on the lack of statistically significant findings, 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.^{74, 75} 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).

No studies of whole body vibration evaluated falls.

Quality of Life

For balance training, one RCT reported the outcome of quality of life.⁷⁰ It reported the SF-12 physical component score; SMD was 0.012 (95% CI, -0.65 to 0.68), in the direction favoring the intervention group.

No studies of whole body vibration evaluated quality of life.

Harms

For balance training, one study reported no dropouts owing to adverse effects in either group.⁷⁰

For whole body vibration, one of the participants in the whole body vibration group dropped out owing to ankle pain.⁷⁶

Exercise Training Interventions

Definition: Exercise 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, activities considered to be a mode of fitness, 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 9. Summary of findings for exercise training interventions

Outcome	Number of studies (N)	Findings	Strength of Evidence*
Physical activity	2 RCTs (reported in 3 articles) (N=106)	Effect size for 6 minute walk test ranged from -0.04 to 0.35, reported in 2 trials. Effect size for total daily steps was 0.16 (95% CI, -0.31 to 0.63), reported in one trial.	NA
Perceived fall risk	2 RCTs (reported in 3 articles) (N=134)	Effect size for ABC score was 0.5 (95% CI not reported, p<0.05), calculated from 1 trial. SMD for FES was 0 (95% CI, -0.44 to 0.44), calculated from one trial.	NA
Falls	1 RCTs (reported in 2 articles) (N=79)	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).	Insufficient
Foot ulcer	1 RCTs (reported in 2 articles) 1 prospective cohort study (N=469)	Rate ratio of all foot ulcers was 1.24 (95% CI, 0.70 to 2.19) reported in 1 RCT. The odds ratio of incidence of foot ulcer was 0.66 (95% CI 0.36 to 1.19) in the moderately active group, and 0.36 (95% CI, 0.16 to 0.82) in the most active group, when compared against the least active group with an odds ratio of 1.0, reported in one cohort study.	Insufficient
Quality of life	1 RCT (N=87)	SMD was -4.9 (95% CI, -5.74 to -4.06), direction of effect favoring intervention.	Insufficient

*we graded only critical outcomes (falls, foot ulcers, and quality of life)

SMD=standardized mean difference, ABC Scale =Activities-specific Balance Confidence; FES =Falls Efficacy Scale; NA = not applicable

Description of Included Studies

Five studies, reported in six articles, assessed the effect of exercise training.^{74, 75, 78-81}

Exercise training interventions included treadmill training^{78, 80} and/or muscle strengthening,^{74, 78, 79} with sessions ranging from two to six times per week and up to 360 minutes total time per week.⁸⁰

Four studies, reported in five articles, were parallel arm RCTs comparing exercise training interventions with a control condition.^{74, 75, 78-80} 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).⁸¹

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.⁸¹ 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 (Table 6).^{74, 75, 78}

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.^{74, 75} Another RCT included exercise and physical therapy components but is only described in this section given overlap in outcomes.⁷⁹

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.^{74, 75, 78}

For the 6-minute walk test, the effect size ranged from -0.04 meters (95% CI, -0.52 to 0.43)⁷⁵ to 0.35 meters (95% CI not reported, but was not statistically significant).⁷⁸

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.^{74, 75} Based on the lack of statistically significant findings, 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.^{74, 75} SMD 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.⁷⁹ The calculated 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 consistently statistically significant findings, we concluded that evidence was insufficient to assess 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.^{74, 75} 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.

Foot Ulcer

One RCT (reported in 2 articles) and one prospective cohort study assessed outcomes of foot ulceration.^{74, 75, 81}

The RCT evaluated the effect of exercise training on foot ulcers.^{74, 75} 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)].⁸¹

Quality of Life

One RCT assessed the outcome of quality of life between exercise and control groups.⁸⁰ SMD was -4.9 (95% CI, -5.74 to -4.06), in the direction of effect favoring the intervention group.

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 when 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.⁸⁰

Physical Therapy Interventions

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

Key points

- Data are insufficient to assess effect of physical therapy alone on physical activity levels.

- No physical therapy intervention studies evaluated the outcome of perceived fall risk.

Table 10. Summary of finding for physical therapy interventions

Outcome	Number of studies (N)	Findings	Strength of Evidence*
Balance	1 RCT of Thai foot massage (N=60)	SMD for TUG was -0.46 (95% CI, -0.46 to -0.82), direction of effect favoring intervention	NA
Physical activity	1 RCT of weight-bearing vs non-weight-bearing activity (N=29)	SMD for average daily steps was -0.46 (95% CI, -0.46 to -0.82)1.13 (95% CI, 0.76 to 1.50), effect size of 1.0), with the direction of effect favoring the intervention group SMD for 6 minute walk test was -0.28 (95% CI, -0.452 to 1.012), with the direction of effect favoring the intervention group, calculated from one trial	NA
Perceived fall risk	None	NA	NA
Falls	None	NA	NA
Foot ulcer	1 RCT of weight-bearing vs non-weight-bearing activity (N=29)	Reported number of ulcers in weight bearing versus non-weight bearing groups: 1 vs 3 (n very small)	Insufficient
Quality of life	None	NA	NA

*we graded only the key outcomes (pain, fall, foot ulcer, amputation, and quality of life)

NA = not applicable

Description of Included Studies

Two RCTs assessed the effect of physical therapy interventions to prevent the complications of diabetic peripheral neuropathy.^{82, 83} One RCT compared two types of physical therapy exercises: weight bearing (n=15) versus non-weight bearing (n=14), each conducted in group exercise sessions supervised by a physical therapist.⁸² The other RCT assessed Thai foot massage, modified foot massage performed by traditional Thai massage therapist, (n=30) compared to a non-massage control intervention (n=30).⁸³ One trial reported followup of 12 weeks⁸², and the other trial reported a mean followup of 2 weeks⁸³ The average age of the participants was 64 years in one trial,⁸² and 58 years in the other trial.⁸³ One trial included participants with mean BMI in the obese category⁸² and one included participants with mean BMI in the overweight category.⁸³ 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.⁸³ The SMD was -0.46 (95% CI, -0.46 to -0.82), with the direction of effect favoring the intervention group⁸³.

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.⁸² The SMD was 0.66 (95% CI, -0.09 to 1.41) with the direction of effect favoring the weight-bearing group. The SMD 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.⁸²

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

Falls/Perceived Fall Risk

No data on falls or perceived fall risk reported

Foot Ulcer

One RCT assessed outcomes of foot ulceration.⁸² There was one ulcer in the weight-bearing exercise group compared with three ulcers in two participants in the non-weight-bearing exercise group.

Harms

No harms data were reported.

Discussion

Key Findings and Implications

We identified a total of 62 studies (30 studies in 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 DPN 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 DPN, including long-term complications of diabetic foot ulcers, lower extremity amputations, falls, physical activity level, perceived risk of falling, and quality of life.

For the outcome of lower extremity amputations, 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, increasing the risk for finding an effect by chance alone. Limited evidence for intensive vs. standard glycemic control exists from one large trial (DCCT/EDIC) for prevention of lower extremity amputations in patients with type 1 diabetes.⁸⁴

The outcome of diabetic foot ulcers had not been evaluated in the recent systematic reviews addressing glycemic control and DPN; therefore, we presented new findings. For diabetic foot ulcers, we found few studies that consistently showed a non-statistically significant reduction in ulcers for glycemic control over standard control for patients with type 2 diabetes but only one study in patients with type 1 diabetes. Only one RCT assessed the effectiveness of one diabetes medication over another for prevention of diabetic foot ulcers and lower extremity amputations.

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 prevention of diabetic foot ulcers. However, this approach has not been used in clinical practice. One of the reasons may be due to very limited number of studies on this intervention, which is not sufficient to be adapted in clinical recommendations.

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, the previous systematic review¹⁴ reported no benefit from an education session. The findings from newly identified studies were consistent with this previous conclusion except, evidence was not consistent regarding integrated foot care.

Only one study reported falls. The strength of evidence for physical therapy, exercise, or balance training was overall graded as low. 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. Neither exercise nor balance training improved physical activity or perceived risk of falling. Balance training had inconsistent evidence for effects on specific balance measures, but whole body vibration was shown in two studies to improve these measures of balance.

For the outcome of quality of life, we found few studies that assessed the benefits of evidence about glycemic control or foot care for improving quality of life.

Findings in relationship to what is already known

Our review confirms the conclusions from three other recent systematic reviews and meta-analyses that addressed intensive versus standard glycemic control for the prevention of lower extremity amputations in patients with type 1 and type 2 diabetes.⁸⁴⁻⁸⁶ Compared with the other 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 towards 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. Despite the few studies 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.⁸⁷ 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.⁸⁸

In our review, we updated a recent systematic review by Netten et al. on foot care interventions to prevent ulcers and lower extremity amputations.¹⁴ Evidence from this previous systematic review supports an integrated foot care program that involves podiatrist care for reducing foot ulcer recurrence.¹⁴ This is consistent with the recommendation from the Society for Vascular Surgery: patients with diabetes should undergo annual interval foot inspections by physicians (MD, DO, DPM) or advanced practice providers with training in foot care. Regarding foot care, we also showed that home-monitoring of foot skin temperature to prevent first foot ulcers was confirmed by a meta-analysis of three RCTs.⁴⁴⁻⁴⁶ We found no significant benefit from a single session of 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; 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.⁸⁷ 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.¹⁴ 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.^{52, 89} 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.⁸⁷

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 DPN.

Applicability

Our results are highly applicable to patients with type 1 and type 2 diabetes and with DPN. We selected clinical outcomes (ulcers, amputations, and quality of life) which are clinically important as well as important to patients. It is likely that diabetic foot ulcers are under-reported in our population and few studies have assessed perceived risk of falling, which is an outcome important to patients. The populations across studies consisted of participants who were older than 50 years of age, for those with type 2 diabetes, and often had diabetes-related co-morbidities. 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

The included studies were heterogeneous with regards to study design, population, intervention, outcomes reported and length of follow up. The studies addressing pharmacologic treatment did not systematically report harms of treatment, or provide references to previous publications where harms were described.

Balance training exercises adopted in these studies were diverse ranging from physical therapist guided training to computerized systems.

We did not include non-English studies (i.e., no restrictions by language in search) due to resource limitations. We do not feel that the exclusion of the non-English studies influenced our conclusions or ability to draw conclusions. We excluded studies including mixed populations with DPN and other types of neuropathy that did not report outcomes separately for DPN, which may have excluded some relevant data.

For foot care, we identified a prior relevant high-quality review meaning that we did not have to complete a new 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.

Studies evaluated various types of interventions (e.g. footwear; surgical procedures) with various comparison groups. For each intervention, the number of studies was also limited. It is difficult to provide a conclusive summary on specific interventions and conduct effectiveness evaluation.

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 DPN. In addition, we identified few studies in patients with type 1 diabetes.

The major strength of the evidence base is the 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, the limitation of the evidence is that many ulcers, and possibly also 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, and increasing the concern that our results showing a benefit from intensive (vs. standard) glycemic control could be due to chance alone. 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 for patients with diabetes and DPN, including quality of life and falls.

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.

The limitations for the 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 correlated with long-term benefits and with the patient-important outcome of falls and the ability to perform the activities of daily living.

Implications for Clinical and Policy Decision making

Our results have implications for the clinical management of patients with DPN. 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. Our review confirms existing practice for more intensive approaches to glycemic control in patients with diabetes to prevent complications associated with DPN, although the target A1c is not yet clear. Evidence supporting referrals for particular foot care programs, physical therapy modalities, or balance training is extremely limited due to concerns about intermediate measures, lower study quality and having few studies per intervention.

Future Research Needs

Future long-term studies assessing the benefits and risks of glucose lowering medications in patients with type 1 and type 2 diabetes should have protocols to systematically assess and report patient-important diabetic foot complications, foot ulcers and amputations, to strengthen our ability to combine studies and make accurate estimates of benefits. Future studies should also collect other patient-reported outcomes of falls, perceived falls, and quality of life in patients with DPN being treated with hypoglycemic agents.

Future studies assessing the benefits and risks of foot care, pharmacologic therapy, or surgical interventions in patients with type 1 or type 2 diabetes should also systematically report key outcomes of ulcers and amputations to strengthen our ability to combine studies and make accurate estimates of benefits.

DPN leads to altered proprioception and lack of sensation in the extremities. Altered proprioception can also increase risk of falling and fear of falling. In addition to the ulcers and amputations described above, these falls and the fear of falling can limit physical activity and decrease health-related quality of life. Future studies should also collect patient-reported outcomes of falls, perceived falls, and quality of life in patients with DPN who received foot care or surgical interventions. Additional studies need to be designed to address physical therapy modalities and balance training programs appropriately targeting patients with DPN to prevent falls and improve mobility, function, and quality of life. The studies we identified used a wide range of outcomes measures (e.g. sway measure, timed up and go test, and 6-minute walk test). In these studies, it was often unclear what the rationale was for the selection of these outcome measures, whether the outcome measures were correlated with deficits specific to DPN, and what the expected benefit should be. We were also uncertain whether these measures of physical activity and balance were associated with improvement in important, more distal clinical outcomes, such as falls. To strengthen the evidence-base, future studies are needed to test and

select appropriate outcome measures for patients with DPN to develop reliable core measures that have been shown to detect benefit (e.g. fewer falls, better quality of life) over time.

Conclusions

We assessed the harms and benefits for pharmacologic and non-pharmacologic interventions in patients with type 1 or type 2 diabetes to prevent complications associated with DPN. Confirming prior reviews in patients with type 2 diabetes, more intensive glycemic control was associated with reduced lower extremity amputations compared with standard glycemic control strategies, but event rates were very low limiting the strength of evidence. For foot ulcers we identified a consistently, but non-statistically significant, reduced ulcer rate for intensive vs. standard glycemic control. We identified few studies that compared mono- or combination therapies for the prevention of amputations or foot ulcers, and few studies in patients with type 1 diabetes.

Consistent with recent systematic reviews, our results support more intensive glycemic control to prevent lower extremity amputations in patients with type 2 diabetes. For foot care, the previous review suggested self-monitoring of foot skin temperatures, the use of therapeutic footwear, or integrated foot care may be effective in preventing incidence or recurrence. Our new search identified limited number of new studies; thus, the overall conclusion of the previous review was not changed.

Further studies on the intervention of whole body vibration to prevent falls are needed, as limited evidence showed that it improved intermediate measures of balance. Future treatment studies comparing monotherapy and combination pharmacotherapies in patients with type 1 and type 2 diabetes need to develop protocols to ascertain outcomes related to the complications associated with DPN: foot ulcers, lower extremity amputations, falls, and perceived risk of falling. In addition, future interventions focused on physical therapy modalities and exercise programs targeting the clinical manifestations of DPN need rigorous clinical trials with clear outcome definitions to assess falls and fall perception, as well as complications, such as ulcers and amputations.

Results and Discussion for KQ2 begin after the reference list for KQ1

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Results for Key Questions 2a and 2b

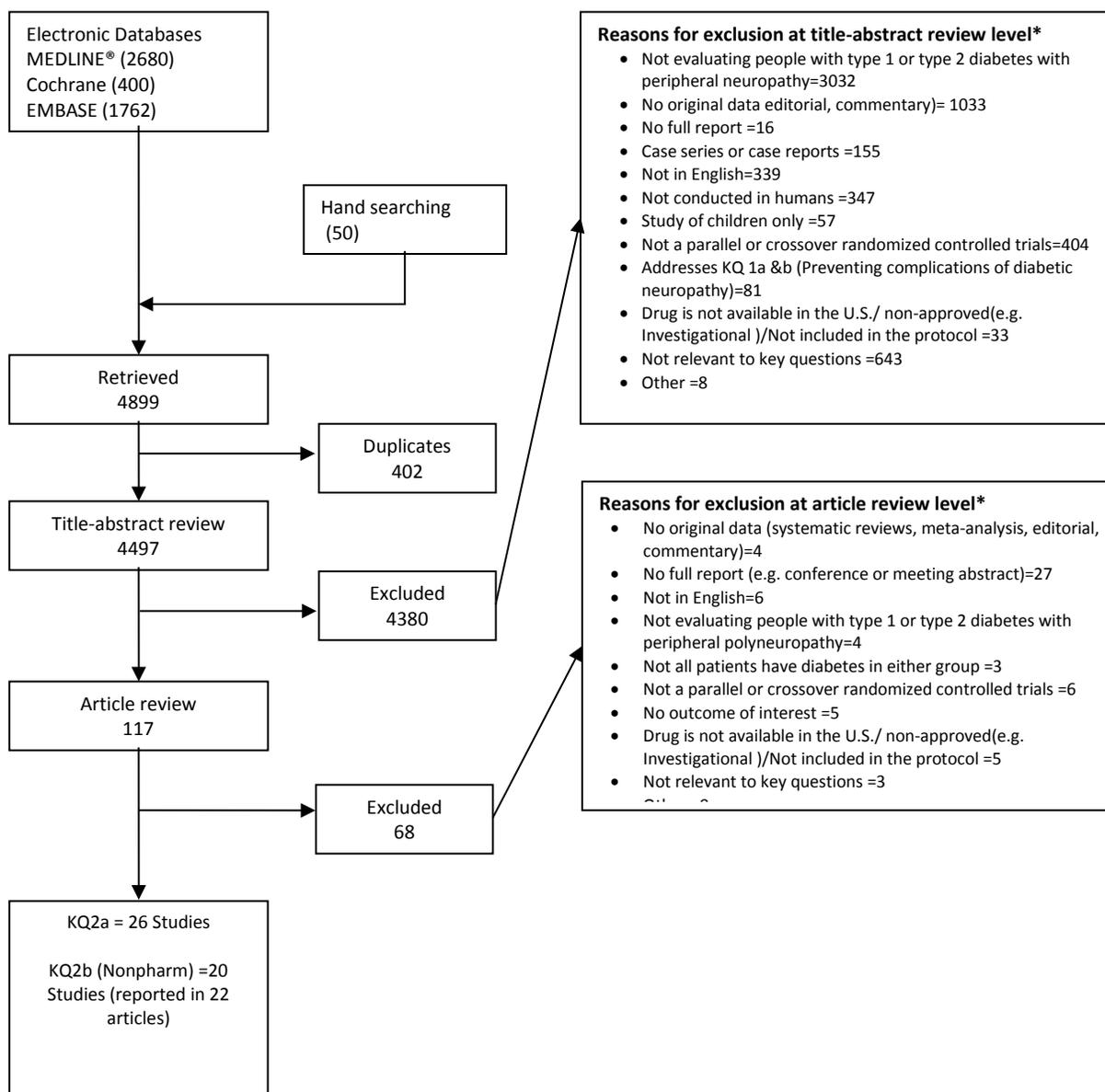
Results of the Search

We included one systematic review (65 studies) and 46 primary studies (reported in 48 articles). Figure 6 summarizes the search and selection of studies in a literature flow diagram. The literature search identified 4899 unique citations. During the title and abstract screening, we excluded 4497 citations. During the article screening, we excluded 68 citations that did not meet one or more of the inclusion criteria. (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 - One high quality relevant systematic review (65 RCTs) and 27 additional RCTs;
- 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

Figure 6. Summary of the literature search for studies



* Reviewers were allowed to mark more than one reason for exclusion.

KQ2a: What are the benefits and harms of pharmacologic treatment options to improve the symptoms of diabetic peripheral neuropathy?

Key points

- In short-term studies (<3 months), the anticonvulsant pregabalin (low SOE), the serotonin-noradrenaline reuptake inhibitors duloxetine and venlafaxine (moderate SOE), the drug classes of tricyclic antidepressants (low SOE) and atypical opioids (tramadol and tapentadol) (moderate SOE), and the intradermal neurotoxin botulinum toxin (moderate SOE) were more effective than placebo for reducing pain in diabetic peripheral neuropathy
- In short-term studies, serotonin-noradrenaline reuptake inhibitors were more effective than anticonvulsants for reducing pain in diabetic peripheral neuropathy (moderate SOE)
- No pharmacologic treatment options were more effective than placebo for improving quality of life in diabetic peripheral neuropathy
- All oral treatments had significant adverse effects, with dropout rates due to adverse effects of greater than 10 percent

Table 11. Summary of key effectiveness results for short-term studies

Outcomes*	Comparison	Number of studies reporting outcome (N)	Findings	Strength of Evidence
Pain				
Placebo-controlled comparisons				
Key anticonvulsants				
	Pregabalin vs placebo	12 studies included Previous SR: 6 RCTs Additional identified studies: 6 RCTs (N=2616)	Griebeler et al. concluded that pregabalin was more effective than placebo (SMD, -0.55 [95% CrI -0.94 to -0.15]) Additional identified RCTs were inconsistent with this finding (SMD ranged from -0.65 to 0.22). Pregabalin is more effective than placebo for reducing pain.	Low
	Gabapentin vs placebo	5 studies included Previous SR: 3 RCTs Additional identified studies: 2 RCTs, one with 2 different arms at maximum dose (N=766)	Griebeler et al. concluded that there was no difference in effectiveness of gabapentin compared to placebo (SMD, -0.58 [95% CrI, -1.54 to 0.09]). Additional identified RCTs at maximum dose were consistent with this finding (SMD were -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). There was no difference in effectiveness of gabapentin compared to placebo in reducing pain.	Low
Key serotonin- noradrenaline reuptake inhibitors				
	Duloxetine vs placebo	7 studies included Previous SR: 5 RCTs	Griebeler et al. concluded that duloxetine was more effective than placebo (SMD, -1.33 [CrI, -1.82 to -0.86]).	Moderate

Outcomes*	Comparison	Number of studies reporting outcome (N)	Findings	Strength of Evidence
		Additional identified studies: 2 RCTs (N=2141)	Additional identified RCTs were consistent with this finding (SMD -0.33 [95% CI, -0.54 to -0.12]) for the one study where this could be calculated. Duloxetine is more effective than placebo for reducing pain.	
	Venlafaxine vs placebo	2 studies included Previous SR: 2 RCTs Additional identified studies: None (N=304)	Griebeler et al. concluded that venlafaxine was more effective than placebo (SMD, -1.53 [CrI, -2.41 to -0.65]) Venlafaxine is more effective than placebo for reducing pain.	Moderate
Tricyclic antidepressants				
	Tricyclic antidepressants (TCAs) vs placebo	6 studies included Previous SR: 5 RCTs Additional identified studies: 1 RCT (N=193)	Griebeler et al. concluded that TCAs were more effective than placebo (SMD, -0.78 [CrI, -1.24 to -0.33]). Additional identified RCT was consistent with Griebeler et al. (SMD could not be calculated). TCAs are more effective than placebo for reducing pain.	Low
Opioids				
	Oxycodone vs placebo	4 studies included Previous SR: 3 RCTs Additional identified studies: 1 RCT (N = 646)	Griebeler et al. concluded that oxycodone was not more effective than placebo [SMD, -0.58 (95% CrI, -1.53 to 0.36)]. Additional identified RCT was inconsistent with Griebeler et al. [SMD, -0.24 (95% CI, -0.47 to -0.01)] Opioids are not more effective than placebo for reducing pain.	Low
	Atypical opioids (tramadol and tapentadol) vs placebo	5 studies included Previous SR: 2 RCTs Additional identified studies: 3 RCTs (N=1181)	Meta-analysis of SMDs for all 5 RCTs was -0.68 (95% CI, -0.80 to -0.56). Atypical opioids are more effective than placebo for reducing pain.	Moderate
Topical capsaicin				
	Topical capsaicin vs placebo	5 studies included Previous SR: 3 RCTs Additional identified studies: 2 RCTs (N=412)	Griebeler et al. concluded that capsaicin was more effective than placebo (SMD, -0.91 [CrI, -1.18 to -0.08]). Additional identified RCTs were inconsistent with Griebeler et al (for the one additional study where the SMD could be calculated, SMD was -0.04 (95% CI: -0.72 to 0.65). Capsaicin is not more effective than placebo for reducing pain.	Low
Dextromethorphan				

Outcomes*	Comparison	Number of studies reporting outcome (N)	Findings	Strength of Evidence
	Dextromethorphan vs placebo	3 studies included Previous SR: 2 RCTs Additional identified study: 1 RCT (N=416)	Griebeler et al. concluded that dextromethorphan was not more effective than placebo (SMD, -0.28 [95% CrI, -1.49 to 0.92]). Additional identified RCT was inconsistent with Griebeler et al. (p<0.0001 favoring dextromethorphan). Dextromethorphan is not more effective than placebo for reducing pain.	Low
Mexiletine				
	Mexiletine vs placebo	5 studies included Previous SR: 5 RCTs Additional identified studies: None (N=389)	Griebeler et al. concluded that mexiletine was not more effective than placebo (SMD, -0.29 [95% CrI, -0.91 to 0.33]). Mexiletene is not more effective than placebo for reducing pain.	Low
Botulinum toxin				
	Botulinum toxin vs placebo	2 studies included Previous SR: None Additional identified studies: 2 RCTs (N=80)	Griebeler et al. did not include this drug. For the additional identified studies, SMD ranged from -0.96 to -0.79. Botulinum toxin is more effective than placebo for reducing pain.	Moderate
Key drug-drug comparisons				
	Serotonin-noradrenaline reuptake inhibitors (SNRIs) vs anticonvulsants	3 studies included Previous SR: 2 RCTs Additional identified study: 1 RCT (N=543)	Griebeler et al. concluded that SNRIs reduced pain more than anticonvulsants (SMD, -0.69 [CrI, -1.17 to -0.21]). One additional RCT was consistent with Griebeler et al. (SMD could not be calculated, but 40.9% of those treated with duloxetine had >30% improvement in pain compared to 28.8% for pregabalin, p<0.001) SNRIs are more effective than anticonvulsants in reducing pain.	Moderate
Quality of life** - Griebeler et al did not assess this outcome				
Key anticonvulsants				
	Gabapentin vs placebo	3 RCTs included (N=579)	One of 3 RCTs reported statistically significant results in the direction favoring gabapentin (data not provided in the studies).	Low
	Pregabalin vs placebo	7 RCTs included (N=1746)	Four of 7 RCTs reported statistically significant results in the direction favoring pregabalin (data not provided in the studies).	Low
Key serotonin-noradrenaline reuptake inhibitors				
	Duloxetine vs placebo	3 RCTs included (N=996)	2 of 3 RCTs reported statistically significant results in the direction favoring duloxetine (data not provided in the studies).	Low
Opioids				
	Atypical opioids vs placebo	4 RCTs included	3 of 4 RCTs reported statistically significant results in the direction	Low

Outcomes*	Comparison	Number of studies reporting outcome (N)	Findings	Strength of Evidence
		(N =1460)	favoring atypical opioids (data not provided in many studies).	

* Only key comparison and outcomes are included in the table. Where not reported in the table, data were insufficient (only one study). Almost no studies evaluated paresthesia or numbness, so no conclusions could be drawn.

Since this is an update of a prior systematic review, for the pain outcome the Griebeler et al. 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.

** Griebeler et al. did not abstract results for quality of life outcome; these results were pulled separately. 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.

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

Description of Included Studies

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 (nine of which were head-to-head trials) that included 12,632 patients and compared 27 medications. Included trials were mostly brief (mean followup: 14 weeks); very few extended beyond 3 months. The review authors evaluated the efficacy of one outcome, pain, by standardizing the results from pain scales to estimated standard mean difference (SMD) for studies reporting less than 3 months of followup. The review authors used network meta-analysis to combine direct and indirect studies to compare drug classes and individual drugs to placebo and to each other. Key findings from their network meta-analysis are shown in Appendix D. The review authors concluded that the evidence is scant and often derived from brief trials, the majority of which had an unclear or high risk of bias.

Summary of Additional Identified Studies

We identified twenty-seven additional placebo-controlled comparisons (in twenty-six RCTs: one RCT¹ included two drugs (pregabalin and gabapentin in separate arms, both compared to placebo) not included in the Griebeler et. al review.

Followup ranged from 3 to 18 weeks, with a median of 12 weeks duration. Eighteen trials were multicenter studies. Four trials had academic funding and two did not report a funding source; the remaining twenty-one were industry funded. Trials were published between 1987 and 2015. The number of participants in the included studies ranged from 24 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.)²

Table 12: Number of included studies by drug class

Drug class	Drugs	Number of studies included in Griebeler et al.	Additional identified studies
Placebo comparisons			
Serotonin-Noradrenaline	Venlafaxine	2	0
	Duloxetine	5	2

Drug class	Drugs	Number of studies included in Griebeler et al.	Additional identified studies
Reuptake Inhibitors (SNRIs)	Desvenlafaxine	0	1
Topical Agents	Capsaicin	3	2
	Clonidine		1
Tricyclic antidepressants (TCAs)	Imipramine	2	0
	Amitriptyline	1	1
	Desipramine	2	0
Anticonvulsants	Carbamazepine	1	0
	Gabapentin	3	2
	Lamotrigine	2	0
	Valproic acid	2	0
	Topiramate	2	1
	Pregabalin	6	6
	Oxcarbazepine	3	0
	Lamotrigine	1	0
	Zonisamide	0	1
N-methyl-D-aspartate receptor antagonists	Dextromethorphan	2	1
Lacosamide	Lacosamide	4	0
Cannabinoids	Nabilone	0	1
Botulinum Toxin	Botulinum	0	2
Opiates	Oxycodone	3	1
	Tramadol/ Acetaminophen	1	1
	Tapentadol ER	1	2
Class IB antiarrhythmic	Mexiletine	5	0
Trials Comparing Medications of Different Classes	Imipramine vs. Paroxetine	1	0
	Amitriptyline vs. Topical Capsaicin 0.075%	1	0
	Amitriptyline vs. Maprotiline vs. Placebo	1	0
	Gabapentin vs. Amitriptyline	1	0
	Venlafaxine vs. Carbamazepine	1	0
	Amitriptyline vs. Lamotrigine	1	0
	Pregabalin vs. Amitriptyline	1	0
	Amitriptyline vs. Duloxetine vs. Pregabalin	1	0
	Duloxetine vs. Pregabalin	0	1

Outcomes

Pain

Placebo-Controlled Comparisons

Key Anticonvulsants

Twenty-nine studies assessed the effect of anticonvulsants compared with placebo on pain (twenty RCTs from the Griebeler et al. review and nine additional studies).

Pregabalin

Griebeler et al. (based on 6 RCTs) concluded that pregabalin was more effective than placebo (standardized mean difference (SMD), -0.55 [95% credible interval (CrI), -0.94 to -0.15]).

Additional identified RCTs were inconsistent with this finding. For five of the six additional identified pregabalin studies,^{1, 3-6} Standardized mean difference ranged from -0.65 to 0.22. Standardized mean difference could not be calculated due to incomplete crossover trial data for one additional study,⁷ but this study reported statistically insignificant findings. The results of the additional identified studies did not show effectiveness for the outcome of pain compared to placebo and were therefore not consistent with Griebeler et al. This may have been partly because the later studies, unlike the earlier ones, did not have the primary objective of evaluating the effectiveness of pregabalin for the outcome of pain. For example, some had different primary outcomes other than pain, or the primary objective was evaluating the effectiveness of a drug other than pregabalin.

Gabapentin

Griebeler et al. (based on three RCTs) concluded that gabapentin was not more effective than placebo (SMD, -0.58 [95% CrI, -1.54 to 0.09]).

An additional two gabapentin studies identified were consistent with this finding (SMD, -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).^{1, 8}

The additional identified evidence was consistent with the Griebeler et al. findings that gabapentin is not more effective than placebo for reducing pain. We graded the strength of evidence as low given inconsistency and unclear risk of bias.

Other anticonvulsants (topiramate, zonisamide, valproic acid, oxcarbazepine, lacosamide, carbamazepine, lamotrigine)

Griebeler et al. concluded (based on two RCTs) that topiramate was not more effective than placebo (SMD was -0.45 [95% CrI, -1.98 to 1.08]). One additional identified RCT of topiramate was consistent with this finding, with an SMD of -0.14 (95% CI, -0.62 to 0.34).⁹ The additional identified evidence was consistent with the Griebeler et al. findings that topiramate was not more effective than placebo. We graded the strength of evidence as low given inconsistent results and unclear risk of bias.

Griebeler et al. did not include zonisamide; we identified one additional RCT of zonisamide with an SMD of -0.63 (95% CI, -1.47 to 0.21).¹⁰ We graded the strength of evidence as insufficient given only one study.

Griebeler et al. found that all other anticonvulsants evaluated (valproic acid, oxcarbazepine, lacosamide, carbamazepine, lamotrigine) were not more effective than placebo (see Appendix D for details), and no additional RCTs were identified. We graded the strength of evidence as low for all of these anticonvulsants, given inconsistent results, except for carbamazepine, where it was inconsistent, given only one study.

Serotonin-noradrenaline reuptake inhibitor antidepressants

Ten studies assessed the effectiveness of serotonin-noradrenaline reuptake inhibitor antidepressants compared to placebo for the outcome of pain [7 RCTs from the Griebeler et al. review and 3 additional identified studies (2 for duloxetine^{11, 12} and 1 for desvenlafaxine¹³)].

Griebeler et al. concluded that serotonin-noradrenaline reuptake inhibitor antidepressants overall were more effective for the outcome of pain compared with placebo [SMD, -1.36 (95%

CrI, -1.77 to -0.95)]. 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)].

Duloxetine

Griebeler et al. concluded (based on 5 RCTs) that duloxetine was more effective than placebo (SMD, -1.33 [95% CrI, -1.82 to -0.86]).

Two additional identified RCTs were consistent with this finding (SMD -0.33 [95% CI, -0.54 to -0.12]) for the one study where this could be calculated.¹¹ For one additional RCT of duloxetine,¹² 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=0.032 in the direction favoring effectiveness of duloxetine). The additional identified evidence was consistent with the Griebeler et al. findings that duloxetine was more effective than placebo. We graded the strength of evidence as moderate, given the precision and consistency of the results with unclear risk of bias.

Venlafaxine

Griebeler et al. concluded (based on two RCTs) that venlafaxine was more effective than placebo (SMD, -1.53 [95% CrI, -2.41 to -0.65]). We identified no additional RCTs of venlafaxine. We graded the strength of evidence as moderate, given the precision and consistency of the results with unclear risk of bias.

Desvenlafaxine

Griebeler et al. did not include desvenlafaxine. We identified one additional RCT for desvenlafaxine. Standardized mean difference was -0.11 (95% CI, -0.42 to 0.21).¹³ We graded the strength of evidence as insufficient given only one study.

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.

Tricyclic antidepressants

Six studies reported pain as an outcome in assessing tricyclic antidepressants: five from Griebeler et al. and one additional identified study.¹⁴

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

The additional identified study of amitriptyline did not report sufficient data to calculate standardized mean difference, but reported that amitriptyline was statistically significantly more effective than placebo in the first part of the crossover trial only (mean difference from baseline between amitriptyline and placebo, 0.36, p<0.001).¹⁴

We graded the strength of evidence as low for the effectiveness of tricyclic antidepressants overall in reducing pain, given imprecision and inconsistency of the results and low for individual drugs desipramine and imipramine given imprecision and inconsistency, as well as for amitriptyline, given high risk of bias.

Analgesics (Opioids (Oxycodone) and Atypical Opioids (Tapentadol, Tramadol))

Four studies reported pain as an outcome in assessing opioids (all on oxycodone controlled-release), three from Griebeler et al. and one additional identified study.¹⁵

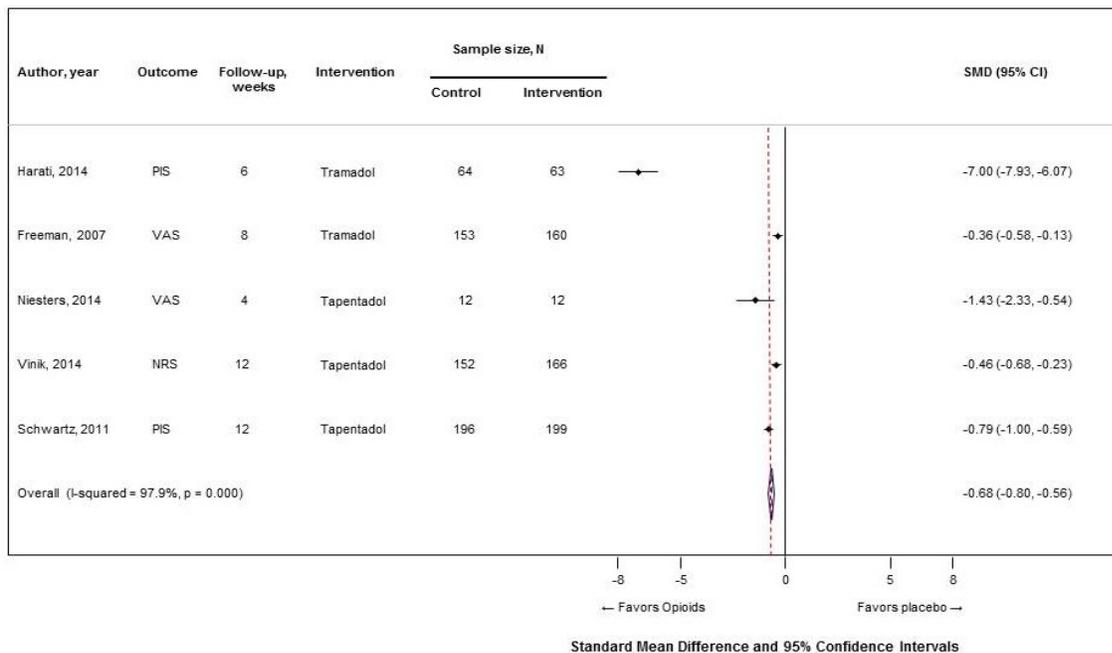
The Griebeler et al. network meta-analysis concluded that oxycodone controlled-release was not more effective than placebo [SMD, -0.58 (95% CrI, -1.53 to 0.36)]. The additional identified study¹⁵ did find that oxycodone controlled release was more effective than placebo [SMD, -0.24 (95% CI, -0.47 to -0.01)], which was inconsistent with the Griebeler et al. findings.

Five studies reported pain as an outcome in assessing atypical opioids, two from Griebeler et al. (one each with tramadol/acetaminophen and tapentadol extended-release) and three additional identified studies (two with tapentadol^{16, 17} and one with tramadol¹⁸).

Griebeler et al. did not report 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 on this drug class. Standardized mean difference ranged from -7.93 to -0.58 (from -2.32 to -0.68 for tapentadol and from -7.93 to -0.58 for tramadol). Excluding the outlier,¹⁸ 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 7).

We graded the strength of evidence as low for effectiveness of opioids in reducing pain given imprecision and inconsistency (the only drug identified was oxycodone) and moderate for atypical opioids overall given the precision and consistency of the results. For individual drugs, we graded the strength of evidence as moderate for use of tapentadol to reduce pain given precision and consistency, but low for tramadol given inconsistency and unclear risk of bias.

Figure 7. Meta-analysis of calculated standardized mean differences for studies comparing placebo vs an atypical opioid for pain outcome



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

Topical Agents

Five studies assessed topical capsaicin for pain (all 0.075% strength), three from Griebeler et al. and two additional identified studies.^{19, 20}

Griebeler et al. concluded that capsaicin was more effective than placebo (SMD, -0.91 [95% CrI, -1.18 to -0.08]). For the one additional study identified where Standardized mean difference could be calculated, standardized mean difference was -0.04 (95% CI: -0.72 to 0.65).¹⁹ The other study²⁰ 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. Capsaicin was not more effective than placebo.

We included one study for the topical version of the alpha-agonist clonidine for pain (this drug was not included in Griebeler et al);²¹ standardized mean difference was -0.50 (95% CI, -1.0 to 0.004).

We did not identify any studies of topical lidocaine that met inclusion criteria. We graded the strength of evidence as low for both clonidine and capsaicin in reducing pain, given inconsistency, imprecision and unclear risk of bias.

Other (N-methyl-D-aspartate receptor antagonists (Dextromethorphan), Cannabinoids (Nabilone), Botulinum Toxin, Mexiletine)

Three studies of dextromethorphan reported pain as an outcome (two included in Griebeler et al. and one additional identified study²²). Griebeler et al. concluded that dextromethorphan was not more effective than placebo (SMD, -0.28 [95% CrI, -1.49 to 0.92]). In the additional identified study²², 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. Dextromethorphan was not more effective than placebo.

Three additional identified studies for other drug classes that were not included in Griebeler et al., one for the cannabinoid nabilone,²³ and two for the intradermal neurotoxin botulinum toxin.^{24, 25}

One study compared the oral cannabinoid nabilone to placebo in the management of DPN,²³ with a standardized mean difference for pain of -1.02 (95% CI, -1.82 to -0.21).

Two studies compared botulinum toxin to placebo. The standardized mean difference for pain for botulinum toxin ranged from -0.96²⁵ to -0.79²⁴.

There was only one drug class analyzed in Griebeler et al. where we did not identify additional studies, for the Class IB antiarrhythmic mexiletine. Griebeler et al. concluded that mexiletine was not more effective than placebo in reducing pain (SMD, -0.29 [95% CrI, -0.91 to 0.33]).

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

We graded the strength of evidence as moderate for botulinum toxin in reducing pain given the precision and consistency of the results, and insufficient for cannabinoids (nabilone) given only one study. We graded the strength of evidence as low for mexiletine in reducing pain, given imprecision, inconsistency, and unclear risk of bias.

Drug-Drug Comparisons

Three RCTs reported pain as an outcome in comparing anticonvulsants to serotonin-noradrenaline reuptake inhibitors [2 from Griebeler et al. (1 of carbamazepine vs. venlafaxine and 1 of pregabalin vs. duloxetine) and one additional identified study of pregabalin and duloxetine]. Griebeler et al. concluded that serotonin-noradrenaline reuptake inhibitors reduced

pain more than anticonvulsants (SMD, -0.69 [95% CrI, -1.17 to -0.21]). We identified one additional study that included a comparison phase of pregabalin compared with duloxetine, which was consistent with the findings from Griebeler et al. (SMD could not be calculated, but 40.9 percent of those treated with duloxetine had more than 30 percent improvement in pain compared to 28.8 percent for pregabalin, $p < 0.001$).² Serotonin-noradrenaline reuptake inhibitors reduced pain more than anticonvulsants. 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 graded the strength of evidence as moderate for serotonin–norepinephrine reuptake inhibitors compared to anticonvulsants in reducing pain. We graded the strength of evidence as low for the outcome of pain for tricyclic antidepressants compared with anticonvulsants in studies reported in Griebeler et al., given inconsistency and unclear risk of bias, and insufficient for other drug-drug comparisons, given only one study.

Composite neuropathic symptoms score

The Griebeler et al. systematic 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,^{26, 27} with a 6-item scale including pain, paresthesia, and numbness, and 1 with mexilitine²⁸ 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 outcome²⁹⁻³¹, all addressing 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 mexilitine³² and 1 of the anticonvulsant pregabalin)³⁰ and 1 additional identified study on the atypical opioid tapentadol ER¹⁷] 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)¹⁷ 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

Griebeler et al. systematic review did not assess quality of life. Most 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 the table 13.

The most relevant quality of life subscale was abstracted in the following hierarchy for the highest therapeutic dose in each RCT: SF-36 physical function, then VAS score, then EQ-5D overall, then other QOL score, then SF-36 bodily pain, depending on what was reported.

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. Anticonvulsants are not summarized as a drug class overall, given divergent results.

One study of duloxetine vs placebo reported quality of life but not statistical significance between study arms).¹²

We graded the strength of evidence as low for all classes (anticonvulsants, serotonin-noradrenaline reuptake inhibitors, and atypical opioids) and individual drugs that reported more than one study, due to inconsistent results and unclear risk of bias (Table 13).

Table 13. Number of studies reporting the quality of life outcome

Total studies reporting quality of life and statistical significance	Number of included studies with statistically significant results	Number of included studies with statistically insignificant results
Anticonvulsants vs placebo		
Pregabalin (7 studies)	4 ^{30, 33-35}	3 ^{1, 6, 36}
Gabapentin (4 studies)	1 ³⁷	2 ^{1, 38}
Oxcarbazepine (3 studies)	1 ³⁹	2 ^{40, 41}
Topiramate (1 study)	0	1 ⁴²
Lacosamide (1 study)	1 ₄₃	0
Serotonin-noradrenaline reuptake inhibitors vs placebo)		
Duloxetine (5 studies)	1 ⁴⁴	2 ^{45, 46}
Desvenlafaxine (1 study)	0	1 ¹³
Typical opioids vs placebo		
Typical opioids (1 study)	0	1 ⁴⁷
Atypical opioids vs placebo		
Tramadol (2 studies)	1 ¹⁸	1 ⁴⁸
Tapentadol (2)	2 ^{17,49}	0

studies)		
Other drugs vs placebo		
Dextromethorphan (1 study)	1 (Sang, 2002)	0
Botulinum toxin	0	1 ²⁵
Nabilone	1 ²³	0
Drug vs drug comparisons study		
Anticonvulsant vs Serotonin–norepinephrine reuptake inhibitors vs tricyclic antidepressant	1 ⁵⁰	0

Harms

The harms results are summarize in the table 14. For drugs not reported in the table, either Griebeler et al. did not summarize harms from the study or we did not identify additional identified studies reporting harms in >10%.

Table 14: Summary of findings of harms reported in the included studies

Drugs	Findings
Tricyclic antidepressants (TCAs)	<p>Griebeler et al. reported that xerostomia was the most common anticholinergic symptom in trials of the tricyclic antidepressants (TCAs) (present in up to 89% of patients). Central nervous system symptoms associated with these drugs included somnolence (up to 69% of patients) and dizziness (5% to 16% of patients). Fatigue (11% to 34% of patients), insomnia (35% of patients), and headache (11% to 21% of patients) were also commonly described.</p> <p>Additional identified studies did not have any different or additional data about harms.</p>
Serotonin-noradrenaline reuptake inhibitors (SNRIs)	<p>Griebeler et al. reported that serotonin-noradrenaline reuptake inhibitors (SNRIs) were associated mainly with central nervous system and gastrointestinal adverse effects. Somnolence (8% to 28% of patients) and dizziness (6% to 25% of patients) were present in the serotonin-noradrenaline reuptake inhibitors trials. Nausea (10% to 32% of patients), constipation (7% to 19% of patients), and dyspepsia (9% to 18% of patients) were also common.</p> <p>Additional identified studies for serotonin-noradrenaline reuptake inhibitor antidepressants reported additional adverse effects reported in >10% of patients included dry mouth (3.3% to 13%)¹³ and vomiting (3.4% to 10.1%)¹³ in study arms for serotonin-noradrenaline reuptake inhibitor antidepressants, depending on dose.</p>
Anticonvulsants	<p>Griebeler et al. reported that patients receiving gabapentin or pregabalin frequently reported somnolence (5% to 48% of patients) and dizziness (5% to 38% of patients). Peripheral edema (4% to 17% of patients) and headache (2% to 13% of patients) were commonly seen among those receiving pregabalin.</p> <p>An additional four identified studies for anticonvulsants reported harm.</p> <p>One study of pregabalin reported a higher rate of peripheral edema (36.6%)⁵¹ and also reported weight gain in 14.6% in the intervention arm.</p> <p>A study of gabapentin reported nausea in 11%.¹</p> <p>A study of zonisamide reported higher rates in the intervention arm than in the control arm for some additional adverse effects, including cardiovascular in 25%, dermatological in 33.3%, respiratory in 33.3%, restlessness/insomnia in 25%, urinary in 25%, and weight change in 25%.</p> <p>A study of topiramate found higher rates in the intervention arm than</p>

	the control arm of additional adverse effects, including anorexia in 20%, back pain in 11%, diarrhea in 11%, paresthesia in 20%, taste perversion in 14%, and weight loss in 14%.
Topical capsaicin	Griebeler et al. reported that more than 50% of patients receiving topical capsaicin described painful burning at the application site. Additional identified studies did not have any different or additional data about harms.
Opioids	Griebeler et al. did not summarize harms of opioids. Additional identified studies reported that for oxycodone, gastrointestinal disorders (nausea, vomiting and constipation) were present in 54% of the study group and fatigue in 18%. ¹⁵ For atypical opioids, constipation was present in 22%, headache in 17 %, nausea in 16.9 to 23%, vomiting in 12.7%, and somnolence in 12%. ^{17, 18, 49}
Clonidine	This drug was not included in Griebeler et al. There were no adverse effects over 10 percent.
Nabilone	The study did not report individual adverse effects for nabilone.

Griebeler et al. did not summarize dropouts due to adverse effects. We abstracted the data from the studies included in the review and additional identified studies. The dropout results are summarized together (Table 15).

Table 15. KQ2a –Dropouts Due to Adverse Effects Reported in All Studies

Drug Class	Intervention	Dropouts Due to Adverse Effects (%)
Serotonin-noradrenaline reuptake inhibitors (SNRIs)	Venlafaxine	6 – 9.8
	Desvenlafaxine	8 - 30.4
	Duloxetine	4.3 – 19.3
Topical Agents	Capsaicin	3.6 – 8.6
	Clonidine	3
TCAs	Imipramine	Not reported
	Amitriptyline	3.6 - 38.6
	Desipramine	10 - 13
Anticonvulsants	Carbamazepine	3
	Gabapentin	8 - 21
	Lamotrigine	7.4 – 21.1
	Valproic Acid	3.4 – 4.8
	Topiramate	12 – 30.4
	Pregabalin	2.5 – 25.6
	Oxcarbazepine	10.8 – 40.9
	Zonisamide	38.5
Lacosamide	8.3 - 42.3	
N-methyl-D-aspartate Receptor Antagonists	Dextromethorphan	20.2-25.2
Cannabinoids	Nabilone	Not reported
Botulinum Toxin	Botulinum Toxin	0
Opiates and Atypical Opiates	Oxycodone	8.5 – 70
	Tramadol	8.1 - 13.8
	Tapentadol	8.1 – 16.3
Class IB Antiarrhythmics	Mexiletine	13.3

SNRI=serotonin-noradrenaline reuptake inhibitors; TCA=tricyclic antidepressants

KQ2b: 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?

Key points

- Alpha-lipoic acid was more effective than placebo and spinal cord stimulation was more effective than usual care for the outcome of pain (moderate SOE), but studies of alpha-lipoic acid were short-term and there are risks of severe complications with spinal cord stimulation.

Table 14: KQ2b Summary of finding for non-pharmacologic interventions

Outcomes*	Comparison	Number of studies reporting outcome (N)	Findings	Strength of Evidence
Pain	Supplements: Alpha-lipoic acid vs placebo	5 RCTs (N =984)	SMD for pain ranged from -2.64 to -0.54. Alpha-lipoic acid is more effective than placebo for reducing pain.	Moderate
Numbness, Paresthesia**	Supplements: Alpha-lipoic acid vs placebo	4 RCTs (N =651)	SMD ranged from -0.38 to 0.17 for numbness and from -0.47 to -0.04 for paresthesia. Alpha-lipoic acid is not more effective than placebo for improving numbness or paresthesia.	NA
Pain	Electrical stimulation: TENS vs sham	4 RCTs (N =118)	SMD ranged from -5.4 to -0.19. TENS is not more effective than sham therapy for reducing pain.	Low
Pain	Electromagnetic stimulation: Frequency-modulated electromagnetic neural stimulation vs sham	2 RCTs (N =132)	SMD ranged from -2.62 to -1.31 for short-term (<12 week) outcomes. Frequency-modulated electromagnetic neural stimulation is more effective than sham for reducing pain short-term, but not long-term.	Low
Pain	Spinal cord stimulation vs usual care	2 RCTs (N =96)	SMD ranged from -1.83 to -1.57. Spinal cord stimulation is more effective than usual care for reducing pain.	Moderate

* Where not reported in the table, data were insufficient (only one study). Almost no studies other than for alpha-lipoic acid evaluated paresthesia or numbness, so no conclusions could be drawn for other interventions.

** We did not grade this outcome, as it is not one of our pre-specified key outcomes

Supplements (alpha-lipoic acid, acetyl-L-carnitine) Description of Included Studies

Seven parallel RCTs addressed the benefits and/or harms of supplements. Six trials evaluated alpha-lipoic acid (ALA)⁵²⁻⁵⁷ and one assessed acetyl-l-carnitine.⁵⁸

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. There was generally unclear to low bias, due to poor reporting, regarding the allocation concealment, random sequence generation, assessing blinding by the outcome, incomplete outcome data, and selective outcome reporting.

Outcomes

Pain

Five RCTs reported pain as an outcome,^{53, 55-58} four of which studied alpha-lipoic acid with a study duration of 3 to 5 weeks. Three out of four RCTs of alpha-lipoic acid reported the total symptom score (TSS) subscale for lancinating pain. Standardized mean difference (SMD) between the intervention group and the control group of the difference from baseline to followup on the TSS 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 8).

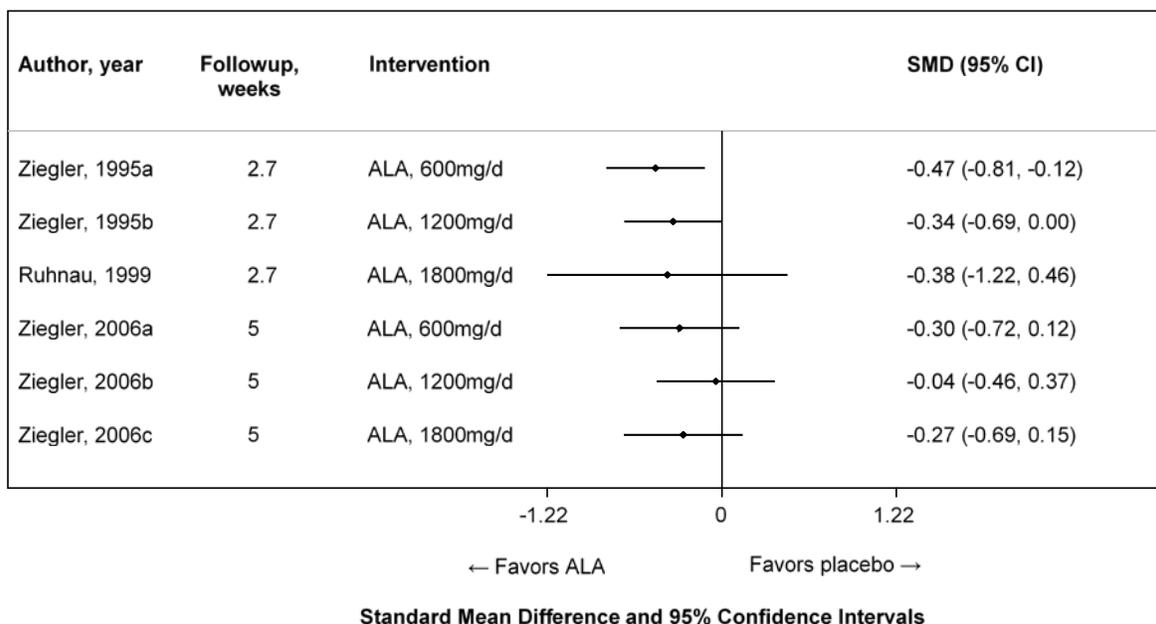
One study reported categorical outcomes only and therefore, is not shown in Figure 8. In that study, the percentage of participants with a greater than 30 percent reduction ranged from 70.8 percent to 82.5 percent in the study groups receiving alpha-lipoic acid, compared with 57.6 percent in the placebo group.⁵⁵

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, in favor of the intervention (neither the standardized mean difference nor 95% CI could be calculated, as standard deviation was not reported) ($p < 0.0001$).

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).⁵⁸

We graded the strength of evidence as low for alpha-lipoic acid in reducing pain, based on consistency of study results and unclear risk of bias, and insufficient for acetyl-L-carnitine, because there was only one study.

Figure 11. Alpha-lipoic acid (ALA): Calculated standardized mean difference for paresthesia between the intervention group and the control group of the difference from baseline to followup on the total symptom score (TSS) paresthesia score



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

Harms

Three studies, all of which used alpha-lipoic acid, reported adverse effects⁵³⁻⁵⁵. 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.⁵³

All studies reported dropouts due to adverse effects, ranging from 0 percent for 600 mg⁵³ to 13 percent for 1800 mg⁵³ in study arms. The dropout rate due to adverse effects for acetyl-L-carnitine was 6.3 percent. 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.

Acupuncture

Description of Included Studies

Only one single-blind, placebo-controlled, randomized trial with a sham arm assessed the benefits and/or harms of acupuncture to improve the symptoms of diabetic peripheral neuropathy.⁵⁹ 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 graded the strength of evidence as insufficient because there was only 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 graded the strength of evidence as insufficient because there was only one study.

Harms

There were no adverse effects occurring in more than 10 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.⁶⁰ 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.⁶⁰ 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 ($p < 0.05$ with hierarchical linear modeling for longitudinal data). We graded the strength of evidence as insufficient because there was only 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 areas⁶¹⁻⁶⁴ [of these, three used 5-70 milliamperes (mA) and one

used microcurrent (30-40 microamperes)]⁶¹. One trial used percutaneous electrical nerve stimulation (PENS), during which needles are used to deliver the electrical stimulation to affected areas (25 mA).⁶⁵ One trial used stockings with electrodes (50 microamperes).⁶⁶ And, one trial used mesodiencephalic modulation, or transcranial stimulation (4-10 mA).⁶⁷ 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 source of bias. These trials generally had a low risk of bias regarding incomplete outcome data, and selective outcome reporting.

Outcomes

Pain

All seven RCTs reported pain as an outcome. Six out of seven RCTs reported a numerical pain or visual analog scale; one (of micro- transcutaneous electrical nerve stimulation) used the Neuropathic Pain Score.⁶¹ Standardized mean difference 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 for transcutaneous electrical nerve stimulation that used a numerical pain scale. Standardized mean difference 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 12)

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 owing to study heterogeneity in intervention (micro-TENS versus TENS and modes of delivery of the electrical stimulation), outcome measures, and design (different types of run-in periods, including one with amitriptyline). We graded the strength of evidence as low for transcutaneous electrical nerve stimulation in reducing pain given the inconsistency of the evidence and insufficient for other methods of electrical stimulation because there was only one study each.

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).⁶⁵

We did not perform meta-analysis as there were only two studies and these assessed different interventions. We graded the strength of evidence as insufficient for either of these methods of electrical stimulation because there was only 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,^{68, 69} one trial evaluated pulsed electromagnetic fields,⁷⁰ and one trial evaluated repetitive transcranial magnetic stimulation⁷¹. Followup ranged from 3 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 source 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.⁶⁸ 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,⁷⁰ the standardized mean difference between the intervention arm and the control arm for the difference between baseline and followup was -0.09 (95% CI, -0.37 to 0.19). (Figure 13)

The study of repetitive transcranial magnetic stimulation⁷¹ 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).

sequence generation, and assessing blinding by the outcome. These trials generally had a low risk of bias regarding incomplete outcome data, selective outcome reporting, and other source of bias.

Outcomes

Pain

Both RCTs reported pain as an outcome; one used a visual analog scale⁷² and the other the modified Brief Pain Inventory Pain Severity Index.⁷³ Standardized mean difference between the intervention arm and the control arm on numerical pain scales ranged from -1.83 to -1.57, in the direction favoring the intervention arm. We did not perform meta-analysis because there were only two studies. We graded the strength of evidence as moderate given the consistency and precision of results and low risk of bias.

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)]⁷² 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].⁷³ We did not perform meta-analysis as there were only two studies. We graded the strength of evidence as low given the inconsistency of results.

Harms

There were no adverse effects occurring in >10% of patients. One study reported no dropouts due to adverse effects, and 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 and harms 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).^{74, 75} 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.

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 SD 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 graded the strength of evidence as insufficient because there was only 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 (92 studies) and non-pharmacologic (20 studies) approaches to improve the symptoms of DPN, mostly focusing on the outcome of pain.

For short-term followup, placebo-controlled comparisons, the following drug classes were more effective than placebo for the outcome of pain: serotonin-noradrenaline reuptake inhibitors, tricyclic antidepressants, atypical opioids, the cannabinoid nabilone (in only one study), and botulinum toxin. There was no difference in the outcome of pain with opioids, dextromethorphan, mexilitine, the anticonvulsant lacosamide, or topical clonidine.

For specific drugs within larger classes, we found the following effects for the outcome of pain: for anticonvulsants, only pregabalin and carbamazepine (in only one study) were more effective than placebo (although newer studies of pregabalin were not more effective than placebo); for serotonin-noradrenaline reuptake inhibitors, only duloxetine and venlafaxine and for tricyclic antidepressants, only amitriptyline. For drug-drug comparisons, we found the following effects: serotonin-noradrenaline reuptake inhibitors were more effective than anticonvulsants, and anticonvulsants were not different than tricyclic antidepressants.

Since values for quality of life were often not reported (only statistical significance), we counted 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. Few studies evaluated paresthesia or numbness.

For non-pharmacologic treatments, we found the following effects: for supplements, both alpha-lipoic acid and acetyl-L-carnitine (only one study) were more effective than placebo for the outcome of pain. For other interventions with more than one study, spinal cord stimulation (although there is a risk of serious complications) and frequency-modulated electrical stimulation were more effective than usual care (although not with long-term follow up); results for transcutaneous electrical nerve stimulation were inconsistent. 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.

For the outcome of pain, strength of evidence was moderate for serotonin-noradrenaline reuptake inhibitors, tricyclic antidepressants, atypical opioids, and botulinum toxin, and low for anticonvulsants, other opioids, capsaicin, clonidine, dextromethorphan and mexilitine. Evidence was insufficient for other drug classes.

For specific drugs within the anticonvulsant and antidepressant drug classes, only the anticonvulsant pregabalin and the serotonin-noradrenaline reuptake inhibitors duloxetine and venlafaxine had moderate strength of evidence, although in newer studies, pregabalin was not more effective for the outcome of pain than placebo (inconsistent with prior studies).

For the outcome of quality of life, strength of evidence was low for serotonin-noradrenaline reuptake inhibitors, anticonvulsants, and atypical opioids and insufficient for other agents. All drug classes of oral agents had at least one study with more than 10 percent dropouts owing to adverse effects.

For supplements, strength of evidence was moderate for alpha-lipoic acid and insufficient for acetyl-L-carnitine for the outcome of pain. For other interventions and the outcome of pain, strength of evidence was moderate for spinal cord stimulation; for electrical or electromagnetic

stimulation, low for transcutaneous electrical nerve stimulation and frequency-modulated electromagnetic neural stimulation and insufficient for other methods; and insufficient for acupuncture or surgical decompression.

We found no studies for exercise or physical therapy, nor studies comparing different treatments or combining treatments, and evidence was either insufficient or there were no studies for quality of life 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 sustainability or side effects.

Findings in Relationship to What Is Already Known

For pharmacotherapy, we updated the recent network meta-analysis by Griebeler et al.⁷⁶ which searched through April 2014, and identified 16 new placebo-controlled and one new drug-drug comparison. 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. Including the newer studies, our findings were consistent for the drug categories of serotonin-noradrenaline reuptake inhibitors and tricyclic antidepressants. Results were not consistent for anticonvulsants, with newer studies not showing effectiveness for the outcome of pain with low strength of evidence (including one study of gabapentin encarbil and studies of pregabalin). Given that carbamazepine and amitriptyline had only one study with high risk of bias, 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 their differences in mechanism of action from other opioids, we reanalyzed these studies separately, and found moderate strength of evidence for this drug class. 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 low strength of evidence across drug classes. 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.

The last comprehensive review including non-pharmacologic treatments⁷⁷ for DPN addressed literature through August 2008 and concluded that there were no effective non-pharmaceutical approaches. 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 Brill et al., as well as new treatments, and concluded that strength of evidence was moderate for spinal cord stimulation (although this has a risk of serious complications) and low for alpha-lipoic acid, transcutaneous electrical nerve stimulation, and frequency-modulated electromagnetic stimulation; other treatments had insufficient evidence and require more research. Another, more recent systematic review of pharmacologic treatments included open-label studies and concluded that many more drugs were effective.⁷⁸ Finally, the most recent comprehensive systematic review of pharmacologic treatments for all types of neuropathic pain (including other etiologies such as chemotherapy and trigeminal neuralgia⁷⁹) 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 neuropathy.

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 DPN, and/or be more susceptible to side effects and drug interactions. Interventions studied specifically for DPN are limited in scope, and evidence from treatments that are effective for other types of peripheral neuropathy or other chronic pain conditions (e.g. exercise, physical therapy) might also be relevant. Comparators were limited to placebo or sham, limiting our ability to compare effectiveness among treatments or appropriateness for patient selection. Outcome synthesis was limited mainly to one-time pain severity scores, 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. In particular, the review separated out long-term studies (>3 months) separately, but did not find sufficient evidence to evaluate long-term results; and 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 and because most placebo-controlled comparisons were similar. 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 that data.

There are also a number of limitations of our updated review. We excluded studies including mixed populations with DPN and other types of neuropathy that did not report outcomes separately for DPN, 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. Finally, we limited the review to pharmacologic and non-pharmacologic treatments best established in prior reviews or guidelines, 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

studies because they were not published in English this limited our scope for acupuncture, where there were many non-English studies that were excluded.

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. Although drugs are often prescribed in combination with other drugs or in combination with non-pharmacologic treatments, we identified almost 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: pregabalin, duloxetine, and venlafaxine. 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.

Studies often reported multiple assessment tools for a given outcome, which sometimes had conflicting results; however, the specific tools that were 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 not often reported separately. Other important issues, such as the impact of pain on function or quality of life, were inconsistently measured or reported. All of these factors limited our ability to conduct meta-analyses 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 3 months in duration and many were less than 1 month, despite the fact that these medications are currently 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 DPN; 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 pooling difficult. Information from the broader literature on long-term use of these medications, particularly evolving data on the long-term harms of opioids⁸⁰ in addition to the very high dropout rates identified in our review, is needed for clinical decision making on benefit/harm ratios.

Implications for Clinical and Policy Decision making

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 two drugs approved by the Food and Drug Administration for the symptom of pain in DPN: the serotonin-noradrenaline reuptake inhibitor duloxetine and the anticonvulsant pregabalin, as well as several other drug classes and agents. However, all these treatments have substantial risks of adverse effects, which may be of particular issues 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. For pregabalin, newer studies did not find that pregabalin was more effective than placebo for the outcome of pain; limited comparative studies found that duloxetine was more effective than pregabalin; and strength of evidence was low or insufficient for all other anticonvulsants and low for anticonvulsants overall. 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 of these agents exist for DPN or peripheral neuropathy more generally. This is particularly important for the atypical opioids, which were more effective than placebo for the outcome of pain in short-term studies. However, 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.⁸¹

Given the limitations of pharmacologic approaches, nonpharmacologic treatments could be of particular value. We found moderate strength of evidence for the supplement alpha-lipoic acid. Although studies were all conducted by the same investigator and studies had methodologic limitations, there were few adverse effects. For other interventions, we found moderate strength of evidence only for spinal cord stimulation, which has a risk of serious complications. Evidence on many other approaches had methodologic limitations or a limited number of studies, with small sample sizes and inconsistent results for TENS, lack of long-term effects for frequency-modulated electromagnetic stimulation, little evidence on cognitive behavioral therapy and no studies of exercise or physical therapy.

Future Research Needs

Many comparisons and outcomes that have low or insufficient evidence are future research needs. In particular, more studies are needed on many non-pharmacologic approaches, such as cognitive-behavioral therapy and exercise or physical therapy; for some, such as 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 side 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; these studies would be critical to future research, as the 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.

Conclusions

We found moderate strength of evidence for the pharmacologic drug classes of serotonin-noradrenaline reuptake inhibitors and atypical opioids for the outcome of pain compared with placebo, as well as for botulinum toxin, although almost all oral drug classes had >10% dropout rates due to adverse effects. For nonpharmacologic treatments, we found moderate strength of

evidence only for spinal cord stimulation compared with usual care, although there is a risk of serious complications. Magnitudes of effect were generally moderate and almost all studies had deficits in quality. There were few studies evaluating non-pharmacologic interventions, such as exercise or cognitive therapy, for pain. Future research should evaluate interventions using sufficient sample sizes and longer-term outcomes and, ideally, evaluate DPN more holistically, combining pharmacologic and non-pharmacologic approaches for symptoms with approaches to maximize function, such as exercise, and limit complications, such as foot ulcers and amputations.

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