Evidence-based Practice Center Systematic Review Protocol

Project Title: Effectiveness of Treatments for Diabetic Peripheral Neuropathy

Amendment: May 9, 2016

I. Background and Objectives for the Systematic Review

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 a complication of both type 1 and 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 diabetes 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 diabetic neuropathy, more than 50 percent had distal symmetric sensorimotor polyneuropathy, and other neuropathies included median mononeuropathies (25%), autonomic neuropathy (7%), and other neuropathies, including 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 will use the general usage of the term "diabetic peripheral neuropathy" (DPN) as referring to the "symmetrical sensorimotor polyneuropathy" of the hands and feet.

The signs of diabetic peripheral neuropathy are loss of vibratory sensation and altered proprioception caused by large-fiber loss, and impairment of pain, light touch, and temperature caused by loss of small fibers.[3] DPN symptoms usually start from the toes and extend upwards to the legs and hands. 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) as well as 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]

Interventions

Experimental pharmacologic interventions targeting diabetic peripheral neuropathy evaluated in recent clinical trials include aldose reductase inhibitors, such as ranirestat and epalrestat, the anti-nerve growth factor antibody fulranumab, the protein kinase C-beta inhibitor ruboxistaurin, gangliosides, and prostaglandin E1.[7] These drugs focus on reducing the impact of oxidative stress on diabetes-induced microvascular complications. A 2007 Cochrane review evaluating the effectiveness of aldose reductase inhibitors on progression of diabetic neuropathies found no evidence for effectiveness.[8] Ongoing Cochrane protocols are evaluating the effectiveness of several other classes of pharmacologic agents.[8-11] However, all of these experimental interventions have not been FDA-approved, are not used in the United States, and thus are not within the scope of our review.

***Pharmacologic treatment options to prevent the complications of diabetic peripheral neuropathy*:** The cornerstone of pharmacologic interventions to prevent complications of diabetic peripheral neuropathy is medications and strategies that improve glucose control.[12]

Key pharmacologic interventions that address comorbid conditions in patients with diabetes are statins and antihypertensives. These agents may also contribute to preventing DPN complications,[13] since co-existing peripheral vascular disease can contribute to long-term diabetic complications such as foot ulcerations.[14] 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. We will not include statins and antihypertensives in this review, because they are prescribed for other indications (hypercholesterolemia, hypertension and/or periperhal vascular disease) and not for the treatment of diabetic peripheral neuropathty.

***Non-pharmacologic treatment options to prevent the complications of diabetic peripheral neuropathy*:** 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. Advances and technologies for foot care and balance management that have been proposed but not yet tested in trials (e.g., in-shoe micro compression pumps) will not be included in this review.

***Pharmacologic treatment options to improve the symptoms of diabetic peripheral neuropathy*:** For diabetic peripheral polyneuropathy (DPN), pain is the most commonly studied symptom in the literature, although other symptoms such as paresthesias that less commonly addressed in trials are also important to patients. A variety of pharmacological approaches have been evaluated to reduce pain and improve health-related quality of life through a variety of mechanisms. These include drugs with direct impact on neurotransmitters and inhibitory pathways or binding 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 diabetic peripheral neuropathy.

For pain outcomes, there are many studies on pharmacological agents, and recent systematic reviews have identified a number of different agents with supporting evidence. However, many studies include non-diabetic peripheral neuropathy or mixed populations.

***Non-pharmacologic treatment options to <u>improve the symptoms</u> of diabetic peripheral neuropathy*:** These interventions also focus mainly on treating pain. Although there is less evidence in this area, modalities that have been evaluated specifically for diabetic peripheral neuropathy and addressed in previous reviews include acupuncture, physical therapy and exercise, electrical stimulation,[15] and surgical decompression.

Outcomes

We are considering two classes of outcomes in our review:

1- Complications of diabetic peripheral neuropathy (foot ulcers, amputation, falls, perceptions of fall risk), which can affect physical activity and health-related quality of life
2- Symptoms of diabetic peripheral neuropathy (pain, paresthesias, numbness), which can affect health-related quality of life

Complications of diabetic peripheral neuropathy (foot ulcers, falls, and perceived fall risk): DPN leads to altered proprioception and lack of sensation in the extremities. Loss of sensation increases risk for foot injury, delays treatment and can lead to foot and leg ulceration and infections. Ulcers and infections may eventually lead to amputation of the lower extremities. Altered proprioception can also increase risk of falling and fear of falling. All of these complications can affect physical activity and health-related quality of life.

Symptoms of diabetic peripheral neuropathy (pain, paresthesias, numbness): Common symptoms of DPN include pain, paresthesias and numbness, and these symptoms may significantly affect health-related quality of life. Pain is most frequently studied in the literature; paresthesias and numbness are more challenging to assess and are not generally included in clinical trials.

Available evidence and Shortcomings

Prevention of DPN complications (foot ulcers, falls and perceived fall risk)

A variety of pharmacological and non-pharmacological approaches have been evaluated for preventing complications of diabetic peripheral neuropathy. However, complications other than foot ulcers have not been comprehensively addressed in recent reviews or guidelines. For pharmacologic and lifestyle interventions, prior reviews have mainly addressed medications for glucose control [which have been evaluated in multiple Agency for Healthcare Research and Quality (AHRQ) reviews, including recent and ongoing Evidence-Based Practice Center (EPC) review 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 AHRQ EPC review Closing the Quality Gap Series.[16] A recent Cochrane review focused on the prevention of DPN included 17 randomized controlled trials.[17] 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% (95% confidence interval 0.01 to -1.17) in people with type 2 diabetes and intensive glucose control. This review is currently being updated.

For nonpharmcologic interventions, some systematic reviews have addressed specific interventions, such as exercise training or improving footwear.[18, 19] 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.[20] This review found strong evidence supporting the home monitoring of foot skin temperatures with subsequent preventative actions and the use of therapeutic footwear with demonstrated pressure-relieving effect that is 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 small. However, this review did not address amputations.

Treatment of DPN symptoms (pain, paresthesias, numbness)

Diabetic peripheral neuropathy was last covered comprehensively by an American Association of Neuromuscular and Electrodiagnostic Medicine, American Academy of Neurology, and American Academy of Physical Medicine & Rehabilitation[21] systematic review and guideline published in 2011, reviewing 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, with several other antidepressants and anticonvulsants, tramadol, and capsaicin recommended as probably effective, as well as opioids. For non-pharmacological interventions, only percutaneous electrical nerve stimulation was recommended. The review did not specifically search for interventions such as exercise or cognitive behavioral therapy for treatment (the review stated that exercise was not effective but did not state if any studies were identified).

Since this review and guideline was completed, 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,[22] clonidine,[23] cannabinoids,[24] and dextromethorphan/quinidine[25].

Newer reviews focusing on pharmacologic treatment of painful neuropathy have reported effectiveness for a number of agents, but not addressed treatment of other DNP symptoms such as of numbness and paresthesia.[26-31] 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 and also included a safety outcome, defined as adverse events and dropouts.[29] The review addresses a much broader range of pharmacotherapy for neuropathic pain in a wide range of conditions; approximately one-third were in painful diabetic peripheral neuropathy. The review assessed a broader range of interventions as moderate to high quality evidence, including serotonin-norepinephrine reuptake inhibitors (specifically, duloxetine) and gabapentin. Although the review did not report results for diabetic peripheral neuropathy specifically (separately from other causes of neuropathy), studies focusing on diabetic peripheral neuropathy are noted in the

evidence tables. Two comprehensive systematic reviews and meta-analyses focusing solely on pharmacologic interventions for painful diabetic peripheral neuropathy were published in 2014,[32] with the most recent including articles published through April 2014.[33] Other recent systematic reviews have addressed painful neuropathy more generally, not diabetes specifically,[26] or have addressed only certain classes or specific medications and interventions.[27, 28, 31, 34, 35] None of these reviews have synthesized evidence on paresthesias or health-related quality of life.

No recent reviews have comprehensively covered nonpharmacologic interventions. The most recent Cochrane review of the evidence for decompressive surgery for symmetric diabetic peripheral neuropathy, published in 2008, found eight studies, but none were eligible for inclusion in the review.[27]

Rationale for an evidence review

This review will provide a comprehensive review of available data on pharmacological and non-pharmacological intervention for the prevention of diabetic peripheral neuropathy complications and treatment of diabetic peripheral neuropathy symptoms.

The results of this review are likely to be useful to clinicians and patients in making decisions about the best available pharmacologic and non-pharmacologic treatment options to prevent the complications and to improve the symptoms of diabetic peripheral neuropathy. The results will help provide an evidence base for future practice guidelines to influence patient management. This review will also identify those area in which there is inadequate evidence.

II. The Key Questions

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

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

Key Question 2a: What are the benefits and harms of pharmacologic treatment options to improve the symptoms of diabetic peripheral neuropathy and health-related quality of life among adults age 18 or older with type 1 or type 2 diabetes mellitus?

Key Question 2b: What are the benefits and harms of non-pharmacologic treatment options (alpha-lipoic acid, acetyl-L-carnitine, acupuncture, physical therapy and exercise, cognitive behavioral therapy, electrical stimulation, surgical decompression) to improve the symptoms of diabetic peripheral neuropathy and health-related quality of life among adults age 18 or older with type 1 or type 2 diabetes mellitus?

PICOTS (patients, interventions, comparators, outcomes, timing, setting)

KQ1a and KQ1b: <u>Preventing complications</u> of diabetic peripheral neuropathy

Populations: Adults age 18 or older with type 1 or type 2 diabetes with peripheral polyneuropathy

Intervention(s):

- **Pharmacologic treatments focused on glucose control (KQ1a):**

  - Glucose-lowering strategies (single or combination agents, or an intensive control approach using multiple medications): Studies with the goal of glucose control generally include multiple agents and combinations and substitutions and specific agents are not specified. Therefore all glucose-lowering strategies will be included.

- **Non-pharmacologic and surgical interventions (KQ1b):**
  - Foot care (daily foot skin temperature measurements and consequent preventative actions, therapeutic footwear, integrated foot care, patient education, self-management)
  - Surgical interventions for foot ulcers
  - Lifestyle interventions (carbohydrate-controlled diet aimed at glucose reduction, weight loss, smoking cessation)
- Exercise or balance training or physical therapy modalities

Comparator(s): Active interventions as well as usual care/placebo

Outcome(s):

- **Benefits (KQ1a and KQ1b):**
  - Incident or recurrent foot ulcer (excluding healing of ulcer as the outcome)
  - Falls
  - Perceived fall risk
  - Amputation
  - Health-related quality of life
  - Physical activity level

- **Harms (KQ1a and KQ1b):**
  - Hypoglycemia (severe and total)
  - Gastrointestinal side effects, including nausea
  - Neuropsychiatric effects (ONLY for smoking cessation studies involving pharmacotherapy)
  - Cardiovascular events
  - Surgical harms
  - Dropouts

Timing: At least 3 months of follow-up for pharmacologic interventions and any follow up for non-pharmacologic interventions

Study design:

- Randomized controlled trials, non-randomized studies with a concurrent comparison group

Setting: Ambulatory care for all the interventions except surgical interventions

KQ2a and KQ2b: <u>Treating symptoms</u> of diabetic neuropathy

Population(s): Adults age 18 or older with type 1 or type 2 diabetes with peripheral polyneuropathy

Interventions:

- **Pharmacologic interventions focused on diabetic neuropathy (KQ2a)**

Antidepressants	Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protiptyline, trimipramine), serotonin-noradrenaline reuptake inhibitor antidepressants (desvenlafaxine, duloxetine, levomilnacipran, milnacipran, venlafaxine)
Anticonvulsants	pregabalin, gabapentin or gabapentin extended release and enacarbil, other antiepileptics (carbamazepine, lacosamide, lamotrigine, levitiracetam, oxcarbazepine, sodium valproate, tiagabine, topiramate, zonisamide)
Analgesics	Opioids (morphine, oxycodone, fentanyl, hydromorphone, methadone, oxymorphone), tramadol, tapentadol
Topical Agents	lidocaine, capsaicin, other topical treatments (clonidine, doxepin, pentoxyifylline)
Other	N-methyl-D-aspartate (NMDA) antagonists (ketamine, dextromethorphan), mexiletine, botulinum toxin A, cannabinoids

Combinations of any of the above treatments

- **Non-pharmacologic and surgical interventions (KQ2b):**
    - Supplements: alpha-lipoic acid, acetyl-L-carnitine
    - Acupuncture
    - Cognitive-behavioral therapy
    - Physical therapy or exercise
    - Electrical stimulation (transcutaneous (or percutaneous) electrical nerve stimulation (TENS) or spinal cord stimulator, frequency-modulated electromagnetic neural stimulation, patient-specific electrocutaneous nerve stimulation (Scrambler)
    - Surgical decompression

Comparator(s): Active interventions as well as treatment/placebo

Outcome(s):

- **Benefits (KQ2a and KQ2b):**
    - Pain
    - Paresthesias
    - Numbness
    - Health-related quality of life **(**Health-related quality of life is defined as measurement with instruments designed for this topic)

- **Harms (KQ2a and KQ2b):**

  Adverse effects reported in >10% of patients and all dropouts **[**10% is generally considered a threshold for common adverse effects. Adverse effects over 10% are reported in the studies and compiled in systematic reviews. Serious adverse effects (including death) are reported as dropouts due to adverse effects].

Timing: 3 weeks or more of follow up

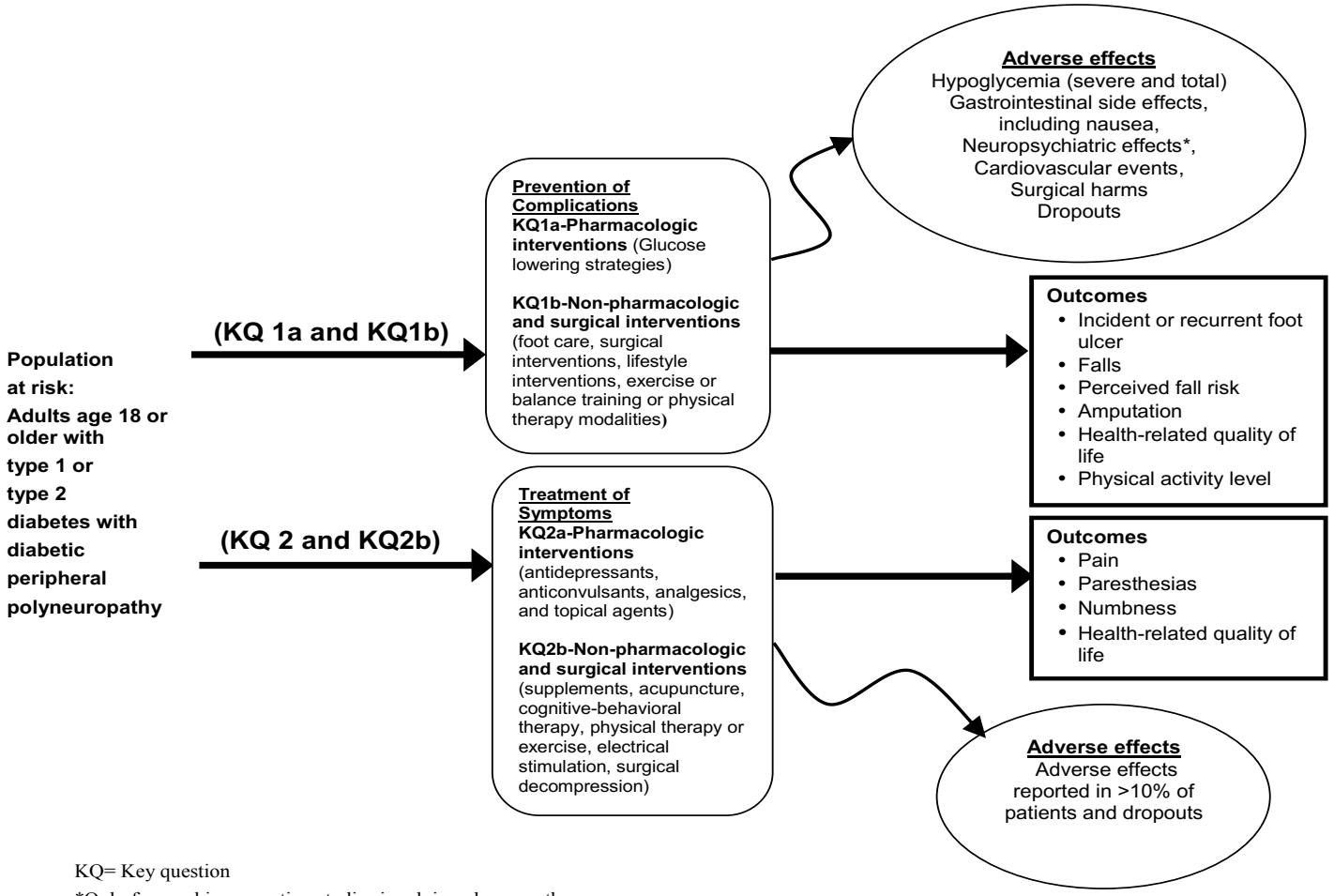
Study design:

- Parallel or crossover randomized controlled trials (must be double-blind (patient and researcher assessing the outcomes) for pharmacologic studies and others where blinding is possible, such as acupuncture)

Setting: Ambulatory care

III. Analytic Framework

Figure 1. Preliminary analytic framework for effectiveness of treatments for diabetic peripheral neuropathy



KQ= Key question

*Only for smoking cessation studies involving pharmacotherapy

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IV. Methods

A. #Criteria for Inclusion/Exclusion of Studies in the Review

Inclusion and exclusion criteria are provided in Table A, based on the PICOTS framework described above.

Table A: Inclusion/Exclusion Criteria

	KQ1a(Pharmacologic treatments) KQ1b(Non-pharmacologic treatments) For prevention of DPN Complications	KQ2a(Pharmacologic treatments) KQ2b(Non-pharmacologic treatments) For treatment of DPN Symptoms
Study design	Systematic review: We will evaluate recent systematic reviews and include those of very high quality, with updates with primary studies as needed. Randomized controlled trials, at least 10 patients, non-randomized studies with a concurrent comparison group (KQ1a &b) We will exclude crossover randomized controlled trials, case series, case reports, and meeting abstracts	Systematic review: We will evaluate recent systematic reviews and include those of very high quality, with updates with primary studies as needed. Parallel or crossover randomized controlled trials, at least 10 patients (for studies of drugs, and other studies where blinding is possible, we will exclude studies if patients and researchers assessing the outcomes are not blinded.) We will exclude non-randomized studies, case series, case reports, and meeting abstracts
Timing	Studies for KQ1a must have at least 3 months of follow-up	Studies must have 3 weeks or more of follow up
Comparisons (Pharmacological interventions)	We will include monotherapy and combination therapy comparisons (KQ1a & 2a).	
Language	Studies must be published in English	
PICOTS	Each study must address a population, intervention, comparator, and outcome listed under PICOTs in Section II of this document.	

Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions:

We will initially search for systematic reviews, and for areas where high-quality reviews exist in English, will identify and assess recent relevant (last 5 years) systematic reviews for quality using the ROBIS tool.[36] We selected 5 years since the American Academy of Neurology guideline was published in 2011. Based on this quality assessment, relevance, and availability of outcome tables, we will choose systematic reviews as the primary source for these portions of the review. We will use the data abstraction results from this review for the included studies and supplement with additional data abstraction for any outcomes not included in the systematic review. We will also hand search other recent (last 5 years) relevant reviews to identify any additional articles.

For portions of the review where we are using previous systematic reviews, we will update the searches using the search strategy from the identified SRs; our searches will also cover the year before the SR end date. If the SRs included unpublished data from websites, we will include these data and perform updated searches on those websites. We will also abstract any additional outcomes not included in the SRs (paresthesias, health-related quality of life).

For portions of the review where we are not using previous systematic reviews, we will search the following databases for primary studies: MEDLINE®, Embase®, and the Cochrane Central Register of Controlled Trials. We will develop a search strategy for MEDLINE, accessed via PubMed, based on an analysis of the medical subject headings (MeSH) terms for all potential relevant publications and text words of key articles identified a priori. We will also review the reference lists of each included article, and related systematic reviews. The search will be updated during the peer review process. Our preliminary search strategy for MEDLINE is shown in Appendix A.

Additionally, we will search clinicaltrials.gov to identify any relevant ongoing trials. We will review the Scientific Information Packets provided by the device manufacturers (Appendix B). We will use DistillerSR (Evidence Partners, 2010) to manage the screening process. DistillerSR is a web-based database management program that manages all levels of the review process. All applicable citations identified by the search strategies are uploaded to the system and reviewed in the following manner:

i. Abstract screening: Two reviewers will independently review abstracts, which will be excluded if both reviewers agree that the article meets one or more of the exclusion criteria listed in Table 1. Differences between reviewers regarding abstract eligibility will be tracked and resolved through consensus adjudication. Relevant reviews, including systematic reviews and meta-analyses, will be tagged for a references list search.

ii. Full-text screening: Citations promoted on the basis of abstract screen will undergo another independent parallel review using full-text of the articles to determine eligibility. Any differences regarding study inclusion will be tracked and resolved through consensus adjudication.

Data Abstraction and Data Management: Where possible we will use standardized forms from prior systematic reviews for data extraction. As for all forms (screening, assessment and abstraction), we will pilot test forms to identify any changes in instructions or forms needed to ensure completeness and accuracy of data collection.

Each article will undergo double review by the study investigators for data abstraction. The second reviewer will confirm the first reviewer's abstracted data for completeness and accuracy. Reviewer pairs will be formed to include personnel with both clinical and methodological expertise. A third reviewer will audit a random sample of articles to ensure consistency in the data abstraction of the articles.

Articles referring to the same study will be abstracted on a single review form if reporting the same data or on separate forms if necessary with clear information that the results should be interpreted as from the same study. We may contact the authors of the included studies for additional data, if necessary.

For all studies, reviewers will extract information on general study characteristics (e.g., study design, study period, and follow-up), 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 will also collect data on outcomes for the subgroups of interest, including age, sex, race/ethnicity, and BMI.

We will complete the data abstraction process using forms created in Excel (Microsoft, Redmond, WA). The Excel files will be used to maintain the data and to create detailed evidence tables and summary tables.

B. Assessment of Methodological Risk of Bias of Individual Studies: The assessment of risk of bias of included RCTs of treatment interventions will be conducted independently and in duplicate using the Cochrane Collaboration's Risk of Bias Tool. [37] For non-randomized studies, we will use the Cochrane Risk Of Bias Assessment Tool for Non-Randomized Studies of Interventions (ACROBAT-NRSI).[38] Differences between reviewers will be resolved through consensus adjudication. As described in Section A. we will assess systematic reviews with ROBIS and, where possible, will use the risk of bias assessment of primary studies conducted by those systematic reviews.

E. Data Synthesis: For each Key Question, we will create a set of detailed evidence tables containing all information extracted from eligible studies, including, as possible, those from the prior SRs. We will conduct meta-analyses when there are sufficient data (at least three studies) and studies are sufficiently homogenous with respect to key variables (population characteristics, study duration, and intervention). We will consider the results of individual studies included in the prior reports as well as those from newly-identified studies in this report.
Randomized controlled trials and nonrandomized studies will be analyzed separately. Statistical significance (will be set at a two sided alpha of 0.05). All studies, including those that are not amenable to pooling, will be summarized qualitatively.

We will evaluate for statistical heterogeneity among studies using an I^2 statistic, and anticipate statistical heterogeneity. A value greater than 50% will be considered to have substantial statistical heterogeneity. If we find substantial heterogeneity, we will attempt to determine potential reasons by conducting meta-regression if covariate information (e.g., age, sex) is available.

For sparse data meta-analysis we will employ the Peto Odds ratio method when event rates are less than 1 percent. When between event rates are between 5-10%, substantial differences between the N of two arms, or when effect size is large, dichotomous data will be meta-analyzed using the Mantel-Haenszel method without continuity correction. Dichotomous data with zero values in both arms will not be included in meta-analyses. All meta-analyses will be conducted using STATA (College Station, TX). For questions and outcomes where new primary studies are identified, we will make decisions about need for new meta-analyses per Robinson et al.[39]

F. ! **Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes:** At the completion of our review, two reviewers will independently grade the strength of evidence on key outcomes, including falls, pain, and health-related quality of life by adapting an evidence grading scheme recommended by the Methods Guide for Conducting Comparative Effectiveness Reviews. Conflicts will be resolved through consensus or third-party adjudication. We will consider the five required domains: study limitations, directness, consistency, precision, and reporting bias of the evidence body. Additional domains (plausible confounding, dose-response, and magnitude of effect) will be considered where applicable.
We will classify evidence pertaining to the Key Questions into four categories:
(1) "high" strength of evidence (indicating high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of the effect);

(2) “moderate” strength of evidence (indicating moderate confidence that the evidence reflects the true effect but further research could change our confidence in the estimate of the effect and may change the estimate);
(3) “low” strength of evidence (indicating low confidence that the evidence reflects the true effect and further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate); and
(4) “insufficient” strength of evidence (indicating evidence is unavailable or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion).
For questions and outcomes where new primary studies are identified, we will make decisions about need for new evidence grading per Robinson et al.[39]

G. **Assessing Applicability:** We will consider elements of the PICOTS framework when evaluating the applicability of evidence to answer our key questions as recommended in the Methods Guide for Comparative Effectiveness Reviews of Interventions. We will consider how important population characteristics (age, gender, race, ethnicity, duration and severity of diabetes), and intervention features (co-interventions) may cause heterogeneity of treatment effects and affect generalizability of the findings.

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VI. Definition of Terms

If not applicable, simply make a note to that effect.

VII. Summary of Protocol Amendments

If we need to amend this protocol, we will give the date of each amendment, describe the change and give the rationale in this section. Changes will not be incorporated into the protocol.

Date	Section	Original Protocol	Revised Protocol	Rationale
May 9th, 2016	F. Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes	At the completion of our review, two reviewers will independently grade the strength of evidence on key outcomes, including falls, pain, and health-related quality of life.	Two additional outcomes were identified as critical outcomes to be graded for the strength of evidence: foot ulcer and amputation	Based on the feedback from AE and TOO, foot ulcer and amputation outcomes have been added as critical outcomes for key question 1.

VIII. Review of Key Questions

AHRQ posted the key questions on the Effective Health Care Website for public comment. The EPC refined and finalized the key questions after review of the public comments, and input from Key Informants and the Technical Expert Panel (TEP). This input is intended to ensure that the key questions are specific and relevant.

IX. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

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

X. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

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

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published three months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than $1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder

This project was funded under Contract No. 290-2015-00006I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Appendixes

Appendix A - Search Strategy - PubMed

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

Appendix B

SIP List	
Intervention	**Manufacturer**
Tricyclic antidepressant	
Amitriptyline	Many manufacturers
Anafranil, Clofranil (Clomipramine)	Novartis
Non Pharmacologic	
TrueContour® Therapeutic Insoles	Diapedia LLC
Serotonin–norepinephrine reuptake inhibitor	
Effexor (Venlafixine)	Pfizer
Pristiq (Desvenlafaxine)	Pfizer
Cymbalta (Duloxetine)	Eli Lilly and Company
Fetzima (Levomilnacipran)	Forest Laboratories and Pierre Fabre Group
Anticonvulsants	
Lyrica (Pregabalin)	Pfizer
Neurontin (Gabapentin)	Pfizer
Tegretol (Carbamazepine)	Novartis
Vimpat (Lacosamide)	Union Chimique Belge
Lamictal (Lamotrigine)	GlaxoSmithKline
Trileptal (Oxcarbazepine)	Novartis
Topiramate	Mylan Pharmaceuticals
Valparin (Sodium Valproate)	Sanofi-Aventis
Topical Treatment	
Xylocaine (Lidocaine)	AstraZeneca
Qutenza (Capsaicin)	Acorda Therapeutics, Inc

SIP List	
Intervention	**Manufacturer**
Nexiclon (Clonidine)	Tris Pharma
Non Pharmacologic	
Scrambler Therapy with the Calmare MC5-A machine	Medical Bioengineering Research Center
Medtronic Eclipse+ Dual Channel Tens Unit Model 7723	Medtronic