Comparative Effectiveness Review Disposition of Comments Report

Research Review Title: *Preventing Complications and Treating Symptoms of Diabetic Peripheral Neuropathy*

Draft review available for public comment from June 8, 2016, to July 7, 2016.

Research Review Citation: Dy SM, Bennett WL, Sharma R, Zhang A, Waldfogel JM, Nesbit SA, Yeh H, Chelladurai Y, Feldman D, Wilson LM, Robinson KA. Preventing Complications and Treating Symptoms of Diabetic Peripheral Neuropathy. Comparative Effectiveness Review No. 187. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. 290-2015-00006-I.) AHRQ Publication No. 17-EHC005-EF. Rockville, MD: Agency for Healthcare Research and Quality; March 2017. www.effectivehealthcare.ahrq.gov/reports/final.cfm. doi: https://doi.org/10.23970/AHRQEPCCER187.

Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

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Commentator & Affiliation	Section	Comment	Response
TEP #1	Introduction	Succinct and relevant	Thank you.
TEP #2	Introduction	Clear and concise, well written	Thank you.
TEP #2	Introduction	Page 13 (of 406) line 6: ref 23 appears to be wrong – it refers to the Cochrane Handbook.	Thank you. We have corrected the reference
Peer reviewer #1	Introduction	please see under general comments	Thank you.
TEP #3	Introduction	well written	Thank you.
Peer reviewer #3	Introduction	Well presented	Thank you.
TEP #1	Methods	Yes	Thank you.
TEP #2	Methods	This section is generally sound and comprehensive.	Thank you.
TEP #2	Methods	I would have liked some detail on what type of data were extracted and which outcomes were considered important e.g., for pain data, were both continuous and dichotomous data extracted, and were chosen outcomes based on recommendations from major pain organizations?	We have added text to clarify that we abstracted both continuous and dichotomous data. We made final choices of outcomes to report (pain and other outcomes) based input from the technical expert panel and preferentially chose patient-centered outcomes.
TEP #2	Methods	Page 15, line 21 states that the team chose to search for sys revs from 2011 onwards because the AAN guideline was published in 2011. However, this guideline only looked at treatment of painful DPN. Did the search for sys revs for other outcomes (KQ1) go back further?	We have reworded that we searched for recent systematic reviews from 2011 on and took out the wording about the AAN guideline. No, the search for systematic reviews for KQ1 did not go back further; if we did not find systematic reviews within this time frame, we did a full search for primary studies. Also, the systematic reviews included studies (and thus outcomes) earlier than 2011.
TEP #2	Methods	Page 19, line 46 “Quality (Risk of Bias) Assessment of Individual Studies”. Suggest removing “of Individual Studies”, as the following subheadings “Systematic Reviews” and “Primary Studies” show that there were different RoB assessments for sys revs vs. individual studies.	We have revised the text as suggested.
Peer reviewer #1	Methods	please see under general comments	
TEP #3	Methods	yes for all the questions	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #2	Methods	1. Need to address absence of function as a key outcome measure especially for KQ2.	We have added a definition of quality of life to clarify that we also considered function. We have added to the limitations that function was not included as an outcome in prior systematic reviews and not reported in most studies. It was addressed as an outcome only for the balance, exercise and physical therapy therapies.
Peer reviewer #2	Methods	2. Add reference to case definition for DPN: Distal symmetric polyneuropathy: a definition for clinical research: report of the American Academy of Neurology, the American Association of Electro diagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Neurology 2005; 64: 199-2007.	Thank you. We have added this reference.
Peer reviewer #2	Methods	3. For the cohort studies on surgical interventions for KQ1 please be a little more explicit as to whether the outcomes were measured by a group independent from the research team.	Yes, most cohort studies were considered as high risk of bias partly due to unblinded outcome assessment done by investigators. We have added these details to the text.
Peer reviewer #2	Methods	4. The exclusion of case series/case reports of severe adverse events is inappropriate. You may never find these outcomes in routinely conducted RCTs. Along these lines, the following report on mortality related to spinal stimulators and intrathecal pumps should be included-it is a report from the manufacturer itself: Coffey et al, Mortality associated with implantation and management of intrathecal opioid drug infusion systems to treat non cancer pain. Anesthesiology 2009; 111: 881-91. The one year mortality from SCS was 1.35%.	We appreciate this comment noting that a synthesis of safety data may consider other types of data such as case reports. Addressing the safety of these interventions overall in all types of conditions, rather than their effectiveness and safety just for diabetic peripheral neuropathy would have required a different approach in this report. We have included this point, and the reference provided, in the discussion: “Since we addressed the effectiveness of these interventions for DPN specifically, this review does not address the broader literature describing harms of these interventions in different conditions. This broader safety data, such as overall mortality from spinal cord stimulation, is therefore not included in this report.”

Commentator & Affiliation	Section	Comment	Response
Public Reviewer Susan Bergman	Methods	The analysis only goes back to 2011 and fails to consider treatments that were studied prior to that date.	The included previous systematic reviews included data prior to 2011. We also state in the methods, "for questions where we did not identify high quality relevant systematic reviews, we searched for primary studies using PubMed, Embase®, and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to May 24, 2016."
Peer reviewer #3	Methods	Well written and appropriate methodology.	Thank you.
TEP #1	Results	Would like more information about Risk of bias assessment – I know they used the Cochrane tool, and also the translation from Risk of bias assessment to strength of evidence is not clear, although the references for the methods are provided.	We have added additional information about the risk of bias and strength of evidence for the different comparisons and outcomes throughout the report. Details about how risk of bias is aggregated across studies and how strength of evidence is graded may be found in the AHRQ Methods Guidance.
TEP #2	Results - KQ1	Generally well presented, especially given the heterogeneity of the studies. KQ1a is easier to follow than 1b. KQ1a goes straight to the outcomes, whereas 1b breaks the results down further by type of intervention. I'm not sure there is a better way to present 1b, but maybe using different fonts for the subheadings or breaking down further (e.g., 1b1, 1b2) might make it read easier?	
TEP #2	Results - KQ1	It could do with a bit of cleaning up in places, e.g., Page 26, line 8 mentions seven RCTS, but it is unclear which RCTs it is referring to; Page 26, line 47, "SDIS" is not defined and is spelled out in full 8 lines later.	Thank you. We have revised it
TEP #2	Results - KQ1	I'm curious as to why ORs were used instead of RRs as they are more difficult for clinicians to interpret.	Thank you for your suggestion. We have changed all estimates to RRs.

Commentator & Affiliation	Section	Comment	Response
TEP #2	Results - KQ1	Table 4. Add a row for Harms? Even if just to mention that, the evidence was insufficient.	Thank you for this suggestion. Given the extensive detail on harms for these drugs, we were unable to summarize in a row and have therefore now included a separate table for harms, which we link to from Table 4. We have also added a summary paragraph on harms to the results. We did not grade evidence for harms, and therefore would not have been able to state that evidence was insufficient.

Commentator & Affiliation	Section	Comment	Response
TEP #2	Results – KQ2	My main concerns (specifically with Q2a) are the use of SMDs for the evaluation of efficacy, and the attempt to combine the results of individual studies with the findings of a meta-analysis, without attempting to incorporate the new studies into the meta-analysis. For SMD, it is not clear whether this is based on pain intensity or pain relief, or both. SMDs are very hard to interpret, particularly for clinical significance. Also, they are based on mean data, which may not be valid for people with pain. It is widely accepted that other outcomes, such as number of participants with at least 30% or 50% pain relief are more meaningful. When analyzing newer studies to add to the analysis of Griebeler et al, it appears that these newer studies were not added to the meta-analysis, but instead taken individually and directly compared to the overall findings of the sys rev. This makes interpretation challenging. For example, for the pregabalin studies, Table 11 states that the newer studies were inconsistent with the overall findings of the sys rev. But, it is entirely possible that the individual studies within the sys rev were also inconsistent.	We have clarified that SMD in the included meta-analysis are based on the differences between the intervention and control groups in the change in pain intensity. We appreciate the concerns about the use of SMD. The most recent high-quality meta-analysis focused on this topic chose this methodology, and in order to leverage this prior work and not complete a de novo systematic review, we adopted their methodology. We have expanded on the limitations to address the issues with interpreting SMDs, specifically as to whether the effects are meaningful. We have also added to the results and discussion the magnitude of the effect of the SMD, where appropriate. For the final comment, rather than redoing the entire meta-analysis, we chose to do focused meta-analyses just on those drugs where findings of new studies were inconsistent with those of the prior meta-analysis. This is consistent with current AHRQ EPC guidance on integrating prior systematic reviews. We originally chose not to do this for pregabalin, since later studies were not focused on pregabalin effectiveness as a primary outcome (as noted in others' comments below). However, based on comments during peer review, as well as the findings of several additional unpublished studies, we have now redone the meta-analysis for pregabalin as well (this shows that the individual studies in Griebeler et al. were consistent).

Commentator & Affiliation	Section	Comment	Response
TEP #2	Results – KQ2	I'm guessing that it was due to a lack of data, but it is not clear why studies with follow up of > 3 months were not included in the meta-analysis.	We had made this decision to be consistent with Griebeler et al. meta-analysis that we were using as it only included studies with <3 months of follow up. Given that the additional few studies we identified were 14-18 weeks in length, we have now included these studies in this section and, importantly, in the new meta-analysis for pregabalin.
TEP #2	Results – KQ2	I don't think a summary statement of opioid efficacy should be made based on results from a single opioid, i.e., oxycodone.	In contrast to Griebeler et al., we synthesized evidence on atypical opioids (tapentadol and tramadol) as a separate class. Otherwise, typical opioids are considered to be equivalent in efficacy for pain and have been treated as such in Griebeler et al. and previous meta-analyses of pharmacologic treatment of neuropathy. We therefore did not make any changes to the report.
TEP #2	Results – KQ2	Botulinum toxin SOE is assessed as moderate (Table 11, page 62). However, there are only 2 small RCTs with a total of 80 participants.	Prompted by the comments from peer reviewers we have reconsidered and carefully reexamined the evidence. Given the imprecision due to the small size of the studies, we have changed the strength of evidence to low.
TEP #2	Results – KQ2	When listing harms, only the rates and dropout rates in the active groups are listed. How did these compare with placebo rates? Similarly, were dropout rates due to lack of efficacy assessed?	We did abstract these in the evidence table provided in the appendix but did not include these in the summary tables in the text of the report. We have now done so. We assessed dropout rates due to side effects as a measure of harm, as was done in previous meta-analyses. We did not assess dropout rates due to lack of efficacy, as this would have been accounted for in the intent-to-treat analyses of the overall effectiveness of these studies.

Commentator & Affiliation	Section	Comment	Response
TEP #2	Results _KQ2	Minor points: The Griebeler sys rev should be referenced the first time it is mentioned. Figure 6, should read “Summary of the literature search for INDIVIDUAL studies” (to differentiate from the search for sys revs). Box 1 “Cochrane” should read “CENTRAL” to distinguish from the Cochrane Database of Systematic Reviews. Table 11. Suggest enlarging font for each outcome for clarity. Page 63, line 11: should “pulled” read “pooled”? Page 65, line 25: should the 95% CI read -1.1 to 0.23 (not -0.23)? Page 65, line 47: “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”. Should that read “insufficient”? Page 66, line 48: 0.36 – is that on a 0-10 scale? Page 67, line 15: SMDs are listed as ranging from 7.93 to -0.58. Shouldn’t that be -7.00 to -0.36?	We thank the reviewer for the attention to detail and have made these corrections.
TEP #2	Results – KQ2	Did no studies of the 8% capsaicin patch meet inclusion criteria?	There were no published studies that met inclusion criteria. For the final report we have incorporated results from a search of ClinicalTrials.gov and have now included one unpublished clinical trial on the 8% capsaicin patch
Peer reviewer #1	Results	please see under general comments	
TEP #3	Results	all the appropriate papers/studies reviewed. The information is adequate.	Thank you.
Peer reviewer #2	Results	1. The use of composite symptom scales (inclusion of multiple symptoms) is not in and of itself all that helpful, especially since neither function nor a definition of clinically meaningful improvement in pain is offered.	We appreciate this comment. This was not a key outcome and is thus not emphasized. However, we did include it for the sake of completeness since some studies (for alpha-lipoic acid) used this as the primary outcome and sometimes only reported this outcome.
Peer reviewer #2	Results	2. P61, Table 13: Add a new column for the significant studies that had SF-36 data 4. If ATL function outcomes are worse, then the conclusion for ATL should be "while there is low quality evidence for prevention, function outcomes are worse".	We have included all measurement instruments for quality of life and reported combined About the conclusion on ATL: Since there was only one study, we feel the evidence is insufficient to draw conclusions.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer Brian Callaghan AAN	Results - KQ2a&b:	I have several comments regarding the conclusions from these questions. 1) Botox is listed as moderate evidence despite only 2 small trials. One trial had no defined primary endpoint and no placebo response. The other study was a very small crossover study with a small placebo response. Together these studies constitute very weak evidence in support of Botox.	Given comments during peer review we re-evaluated the body of evidence and we have changed the strength of evidence to low based on the imprecision due to the small size of the studies. .
Public Reviewer Brian Callaghan AAN	Results - KQ2a&b:	2) Gabapentin was not included as a medication with supportive evidence despite multiple large studies supporting its use. The 2 newer studies were based on different long acting formulations. The SMD from Griebeler et al was almost identical to pregabalin and approached statistical significance. Moderate evidence supports a small effect of gabapentin and pregabalin.	We reanalyzed the data from Griebeler et al. to confirm their results, and the new studies are consistent with their findings. Review with our pharmacist colleagues confirm that the long acting formulations of gabapentin are pharmacologically equivalent and should be included with this drug. We have also reanalyzed the pregabalin data including unpublished results, as discussed above
Public Reviewer Brian Callaghan AAN	Results - KQ2a&b:	3) The SNRI to anticonvulsant comparison is from Griebeler et al which is quite limited because of lack of head to head trials. This evidence is very weak (see editorial on article).	Thank you for this comment. We are no longer analyzing anticonvulsants together as a drug class, but are only analyzing comparison of individual drugs.
Public Reviewer Brian Callaghan AAN	Results - KQ2a&b:	4) Spinal cord stimulator is based on 2 articles without a sham procedure with no placebo effect in the control groups. These are very weakly supportive of spinal cord stimulator placement.	We appreciate this comment. For spinal cord stimulators, we initially graded the evidence as moderate given the consistency of the results and long-term (6-month) studies. Based on comments during peer review, we re-evaluated the body of evidence, and given the small studies (and therefore some imprecision) and the use of run-in periods and no sham arm, we have revised the strength of evidence to low.
Peer reviewer #3	Results	There is almost too much detail for the average reader.	We agree that there is a lot of detail. This is an evidence review and provides details of the review for a variety of readers and stakeholders. The more detailed information on risk of bias, strength of evidence and domains (which are mostly in the appendix) is intended for clinical practice guideline developers and some other users.

Commentator & Affiliation	Section	Comment	Response
TEP #2	Discussion/ Conclusion	KQ1: Well written. Goes as far as it can, given the quality of evidence. Appropriately makes very limited definitive conclusions or recommendations.	Thank you.
TEP #2	Discussion/ Conclusion	KQ2: Again, well written and concise, and reasonable given the findings of the analysis. The findings may have been different had a different analytical method been conducted.	Thank you, we have added this to the limitations of the review process in the discussion. "Griebeler et al. also used standardized mean differences rather than a more clinically meaningful approach, and although these can be interpreted as small, moderate or large, they do not correlate with recommendations for interpretation of relative or absolute decreases in pain[77] as clinically meaningful; findings may have been different with a different analytical method."
" TEP #2	Discussion/ Conclusion	KQ2: Under "Applicability" it is stated that comparators were limited to placebo or sham, but there were some head-to-head studies in KQ2a.	Thank you, we have corrected this statement.
TEP #2	Discussion/ Conclusion	Minor point: Page 86, line 52, discussion of harms probably belongs somewhere else, i.e., not alongside the discussion of strength of evidence.	Thank you, we have revised this text as suggested.
Peer reviewer #1	Discussion/ Conclusion	please see under general comments	
TEP #3	Discussion/ Conclusion	Yes for all the questions. Future research section stated the research questions clearly.	Thank you.
Peer reviewer #2	Discussion/ Conclusion	1. If the more modern studies on pregabalin are mostly negative, why would you conclude that this drug is helpful for pain?	Thank you. We have conducted a new meta-analysis in this section, including unpublished trials.
Peer reviewer #2	Discussion/ Conclusion	2. Something should be said that it is a limitation that studies on prevention of progression to more severe neuropathy in patients with impaired glucose tolerance was not addressed in this review.	Thank you. We have added this point to the limitation section of the discussion.
Peer reviewer #2	Discussion/ Conclusion	3. With the expected low event rates for ulcers and amputations, wouldn't this add some weight to use of larger well designed observational studies?	Thank you, although well-designed observational studies can provide additional data, cohort studies are limited due to unobserved confounding factors and selection bias, e.g. why certain patients receive therapy vs. those without intervention. We have added the information to the future research section.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #2	Discussion/ Conclusion	4. P 48, Line 18: "Despite the few studies..." is inappropriate and should be deleted 5. P50, lines 15-27-integrated of care could be placed in a little better context in the overall move in the US to increase integrated/multimodal care to many aspects of chronic pain care.	Thank you for the suggestions. We have revised this text.
TEP #1	General	Robust methodology, clear, transparently stated	Thank you.
TEP #2	General	Yes to the above considerations.	Thank you.
TEP #2	General	KQ1: Overall, the authors have done a very nice job of distilling a heterogeneous and generally low quality database.	Thank you.
TEP #2	General	KQ2: There is more useful evidence for the second part of the review. The authors have done a very thorough job with a huge amount of information. I do have some concerns about the methodology, as noted below.	Thank you.
Peer reviewer #1	General	This review is greatly out of sync with my current clinical practice in diabetic peripheral neuropathy. I would like to briefly outline my experience in order to give support to my critique. I completed fellowships in clinical neurophysiology and peripheral nerve disease and have authored practice parameters for peripheral neuropathy and diabetic neuropathy. I see diabetic neuropathy patients and have practiced for 30+ years. One of the problems in these reviews is the lack of any RCTs involving old therapies. The newer pharmaceutical agents are more likely to have RCT trials since their development was during the period of the RCT becoming the gold standard. Also with older therapies there is no financial inducement for pharma to sponsor these trials. Finally, invasive procedure which are richly reimbursed by insurance payers (epidural stimulators) are again more likely to have device manufacturer sponsored trials. So in conclusion it may be the best if I can discuss as an experienced clinician my approach to my diabetic neuropathy patients by commenting on at your structured abstract.	Thank you for sharing your clinical experience with these medications. We agree that newer pharmaceutical agents and invasive procedures are more likely to have higher-quality data and this is noted in the "strengths and limitations of the evidence" in the discussion: "In addition, larger, higher-quality studies have almost all been conducted with new drugs with pharmaceutical company funding, and these were the only drugs with moderate strength of evidence: duloxetine and venlafaxine. For nonpharmacologic treatments, invasive procedures involving devices (i.e., spinal cord stimulators) are also more likely to have device manufacturer-sponsored trials and higher-quality data"

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #1	General	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).I WOULD AGREE WE TRY FOR BEST GLYCEMIC CONTROL.	Thank you for sharing your clinical experience.
Peer reviewer #1	General	For nonpharmacologic treatment options, specific types of therapeutic footwear (moderate SOE) YES WE USE FOOTWEAR IT IS RELATEIVELY INEXPENSIVE AND IS HELPFUL ,	Thank you for sharing your clinical experience.
Peer reviewer #1	General	home monitoring of foot skin temperature WE NEVER HAVE DONE THIS AND IT IS NOT GENERALLY USED (moderate SOE),	A full explanation for why this treatment is not generally used would require a different study (i.e., on practice patterns) but we have provided a few additional comments in the discussion on why this approach is not widely used.
Peer reviewer #1	General	integrated foot care (low SOE) YES THIS IS HELPFUL AND HAS PREVENTED SERIOUS PROBLEMS DUE TO NFECTION AND COMPLICATIONS	Thank you for sharing your clinical experience.
Peer reviewer #1	General	and specific types of surgical interventions (low SOE) are effective for lowering incidence and/or recurrence of foot ulcers. AGREE	Thanks for reviewing.
Peer reviewer #1	General	There is insufficient evidence to evaluate whether physical therapy, exercise or balance training reduce falls AGAIN BALANCE THERAPTY IS ALMOST UNIVERSALLY SAID BY ALL MY PATIENTS FELT TO BE HELPFUL .	Thank you for sharing your clinical experience. We have clarified the balance section and the effects on balance measures and outcomes in the discussion.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #1	General	For treatment of DPN symptoms (KQ2), the anticonvulsant pregabalin (low SOE) MOST COMMONLY USED FOR PAIN USUALLY HELPFUL , the serotonin or adrenaline reuptake inhibitors duloxetine and venlafaxine (moderate SOE) DULOXETINE HELPFUL IN CONJUNCTION WITH GABAPENITIN ALTHOUGH THERE ARE A LOT OF REPORTED PATIENT SIDE EFFECTS WITH DULOXETINE , the drug classes of tricyclic antidepressants (low SOE) THEY ARE HELPFUL PARTCULATRLY AT NIGHT WITH SLEEP PROBLEMS; THERE NEEDS TO BE SLOW TITRATION and atypical opioids (tramadol and tapentadol) (moderate SOE), NO ! THESE TEND TO BE ADDICTIVE AND TRAMADOL CAN CAUSE SEIZURES IN HIGH DOESES WE TRY NO TO USE THESE MEDICATIONS and the injectable neurotoxin botulinum toxin (moderate SOE) are more effective than placebo for reducing pain in short-term studies NO! THIS IS NOT A VIABLE THERAPUTIC OPTION FOR USE DIABETIC NEUROPATHY.	Thank you for sharing your clinical experience. We did not identify any studies of duloxetine together with gabapentin. We have also added to the limitations that there are other safety issues not addressed in this review. For tricyclic antidepressants, sleep was not an outcome of this review and we did not evaluate the rapidity of titration in the studies. For tramadol and tapentadol, we report in the abstract that "opioids have significant long-term risks including abuse" and in the discussion, that "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." Thank you for your comment on botulinum toxin; the studies on this intervention did show that it was effective for pain. Given the imprecision due to the small size of the studies and other limitations, we have changed the strength of evidence to low.
Peer reviewer #1	General	Serotonin-noradrenaline reuptake inhibitors are more effective than anticonvulsants for reducing pain (moderate SOE). NO THIS IS NOT MY OR OTHERS CLINICAL EXPERIENCE	Thank you for sharing your clinical experience. We have now taken out evaluations of anticonvulsants as a drug class since results for different anticonvulsants were heterogeneous. We now report this as comparisons with individual anticonvulsants, and we were unable to draw conclusions due to no more than one study with complete data that could be analyzed (insufficient SOE).
Peer reviewer #1	General	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) YES REASONABLE TRIALS SUGGEST BENEFIT AND IT IS INEXPENSIVE AND LOW SIDE EFFECT PROFILE	Thank you for sharing your clinical experience.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #1	General	and spinal cord stimulation is more effective than usual care for pain (moderate SOE) NO NO !!! OUR PAIN SERVICE TAKES OUT THESE ROUTNELY AND THEYR NERVER WORK! NEVER SHOULD BE USED FOR DIABETIC PN but spinal cord stimulation had risks of serious complications YES YES . No treatments improved quality of life (low SOE).	Thank you for sharing your clinical experience. We initially graded the evidence as moderate given the consistency of the results and long-term (6-month) studies. We re-evaluated the body of evidence, given the comments of the reviewers, and have revised the strength of evidence to low based on the small studies (and therefore some imprecision) and the use of run-in periods and no sham arm.
Peer reviewer #1	General	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 YES, therapeutic footwear and integrated interventions are effective for preventing incidence and/or recurrence of foot ulcers YES. For reducing pain, pregabalin, serotonin-noradrenaline reuptake inhibitors, atypical opioids NO, alpha-lipoic acid YES AS AN ADJUNCT IS NOT REALLY HELPFUL IN RELIEVIING PAIN BY ITSELF and spinal cord stimulation NO NO AGAIN NEVER USE THIS IN DIABETIC NEUROPATHY PATIENTS are more effective than placebo and serotonin-noradrenaline reuptake inhibitors are more effective than anticonvulsants THIS IS NOT REALLY THE CASE 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.	Thank you for sharing your clinical experience. We did not identify any trials evaluating alpha-lipoic acid as an adjunct. See above comment for spinal cord stimulation.
TEP #3	General	extremely meaningful, target population is well defined and questions are clearly stated	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #2	General	The key issue I have is the fact that function is not included as a key outcome for this report. While function is called out to some extent in Table 13 this is not adequate. For the areas where it would be important to call out function, such as a potentially dangerous and expensive treatment such as spinal stimulation, the conclusion should be expanded to something like, "compared to placebo pain is improved but there is not adequate data on improved function. In addition, we could not determine if the degree of improvement in pain is clinically meaningful".	We appreciate this comment. We have added to the methods that the outcomes included were decided upon with advice from the Key Informants and Technical Expert Panel. We have also added the definition of quality of life, which includes function. We also have included information on the significance of the effect sizes throughout and a reference on standards for pain studies in the discussion.
Public Reviewer Brian Callaghan AAN	General	The evidence regarding Botox and spinal cord stimulators is misleading given the very low quality articles that support their efficacy. As written, pregabalin should be favored over gabapentin when the evidence for the 2 medications is quite comparable and they are in the same class. Lack of head to head trials makes comparisons between groups, such as SNRI to anticonvulsants, difficult at best.	Thank you; we have now revised the Botox, spinal cord and SNRI to anticonvulsant comparisons and have changed the strength of evidence, based on this and other comments. For Botox, given the imprecision due to the small size of the studies, we have changed the strength of evidence to low. For spinal cord stimulators, we initially graded the evidence as moderate given the consistency of the results and long-term (6-month) studies. However, we re-evaluated this body of evidence and based on, the small studies (and therefore some imprecision) and the use of run-in periods and no sham arm, we have revised the strength of evidence to low. For head to head trials, we have now taken out evaluations of anticonvulsants as a drug class since results for different anticonvulsants were heterogeneous. We now report this as comparisons with individual anticonvulsants, and we were unable to draw conclusions due to no more than one study with complete data that could be analyzed (insufficient SOE). We have also provided extensive additional information and a new meta-analysis on pregabalin specifically.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer Susan Bergman	General	I am sorry to see that there was no evaluation of the safety or effectiveness of topical agents, particularly Lidoderm patches. Especially given the current opiate crisis and the fact that many patients with diabetic peripheral neuropathy are elderly and / or have multiple chronic conditions it would make good sense to include a relatively noninvasive and effective treatment option. Lidoderm is FDA approved for management of diabetic neuropathy. In my practice as a physiatrist I see patients with multiple chronic disabling conditions. In my patients with neuropathic pain from all causes I have seen good results with Lidoderm. In about 60% of my chronic pain patients Lidoderm produced enough pain relief that I was able to at least reduce their doses of opiates and in some cases, discontinue them entirely. Only 1 person had an adverse reaction to Lidoderm- an allergic reaction to the adhesive. Unfortunately, it is difficult to gain authorization for Lidoderm (especially from Medicare plans). Over the last several years I have had coverage for the patches repeatedly denied for patients with neuropathic pain. Insurers won't even consider approving Lidoderm unless the diagnosis is post-herpetic neuralgia or diabetic neuropathy. Even if there is only a small change in the intensity of the pain I believe that this safe and effective treatment is worth considering, especially for people on chronic opiate therapy. Not everything in medicine can be measured. While evidence based medicine is desirable, some interventions cannot be studied in a scientifically rigorous manner. There has to be a place for clinical judgment and common sense in our "brave new world" of health care.	Thank you for this comment. We did include lidocaine in the review, but identified no eligible RCTs for this treatment. We have clarified this in the results section with a separate subheading and added it in the discussion
Peer reviewer #3	General	The report is well written and contains useful information. It is very detailed and a bit hard to read for the average person, but the literature is very well reviewed and presented in detail. I have no specific comments for modification or improvements. Quality of the Report: Good	Thank you.

Commentator & Affiliation	Section	Comment	Response
TEP #2	Clarity and Usability	Yes to all of the above considerations, except where noted above for each section. Also for Reference sections (Page 52 and 92 of 406) I would suggest adding “(for KQ1)” and “(for KQ2)” after “References” so that the reader doesn’t stray onto the wrong refs for a given section.	We have made these edits.
Peer reviewer #1	Clarity and Usability	no new information and conclusions are not helpful and out of sync with clinical practice	Thank you for your comment.
TEP #3	Clarity and Usability	very well structured and organized. Conclusions are well stated. Great review for clinicians and researchers.	Thank you.
Peer reviewer #2	Clarity and Usability	Fine	Thank you.
Peer reviewer #3	Clarity and Usability	Very detailed report. May not be used much by the average clinician, but a good resourced for those doing research on DPN.	Thank you for your comment. We are writing manuscripts based on the report which will be shorter summaries of these findings.