Pharmacotherapy for diabetic peripheral neuropathy pain and quality of life

A systematic review

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ABSTRACT

Objective: To systematically assess the effect of pharmacologic treatments of diabetic peripheral neuropathy (DPN) on pain and quality of life.

Methods: We searched PubMed and Cochrane Database of Systematic Reviews for systematic reviews from 2011 to October 12, 2015, and PubMed, Embase, and the Cochrane Central Register of Controlled Trials for primary studies from January 1, 2013, to May 24, 2016. We searched Clinicaltrials.gov on March 9, 2016. Two reviewers independently evaluated studies for eligibility, serially abstracted data, and independently evaluated risk of bias and graded strength of evidence (SOE).

Results: We updated a recently completed systematic review of 57 eligible studies with 24 additional published studies and 25 unpublished studies. For reducing neuropathy-related pain, the serotonin-norepinephrine reuptake inhibitors duloxetine and venlafaxine (moderate SOE), the anticonvulsants pregabalin and oxcarbazepine (low SOE), the drug classes tricyclic antidepressants (low SOE) and atypical opioids (low SOE), and botulinum toxin (low SOE) were more effective than placebo. We could not draw conclusions about quality of life due to incomplete reporting. All studies were short-term (less than 6 months), and all effective drugs had more than 9% dropouts from adverse effects.

Conclusions: For reducing pain, duloxetine and venlafaxine, pregabalin and oxcarbazepine, tricyclic antidepressants, atypical opioids, and botulinum toxin were more effective than placebo. However, quality of life was poorly reported, studies were short-term, drugs had substantial dropout rates, and opioids have significant risks. Future studies should evaluate longer-term outcomes, use methods and measures recommended by pain organizations, and assess patients' quality of life. *Neurology*® 2017;88:1–10

GLOSSARY

CI = confidence interval; **CrI** = credible interval; **DPN** = diabetic peripheral neuropathy; **FDA** = Food and Drug Administration; **QOL** = quality of life; **RCT** = randomized controlled trial; **ROBIS** = Risk of Bias in Systematic Reviews; **SF-36** = Short Form-36; **SMD** = standardized mean differences; **SNRI** = serotonin and norepinephrine reuptake inhibitor; **SOE** = strength of evidence; **TCA** = tricyclic antidepressant.

According to estimates from the Centers for Disease Control and Prevention, 29.1 million people, or 9.3% of the US population, have diabetes and 30% to 50% of them eventually develop diabetic peripheral neuropathy (DPN), often with symptoms of pain, numbness, and paresthesia.[1,2] 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.[3] That guideline recommended pregabalin as an effective treatment and noted venlafaxine, duloxetine, amitriptyline, gabapentin, valproate, tramadol, capsaicin, and opioids as probably effective.

Supplemental data at Neurology.org

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The most recent systematic review of randomized controlled trials (RCTs) of pharmacologic interventions for painful DPN was published in 2014.[4] However, this review did not include some newer pharmacologic agents and did not synthesize evidence on other patient-reported outcomes such as health-related quality of life (QOL). It also did not include some studies identified by other comprehensive systematic reviews[3–5] or search for results from unpublished studies, now available with the advent of the ClinicalTrials.gov reporting requirements.[6]

We conducted an updated systematic review to address the benefits and harms of pharmacologic treatment options to improve the pain of DPN as well as health-related QOL, including unpublished studies reported on ClinicalTrials.gov.

METHODS We report relevant results on pain and QOL from a broader systematic review on DPN. Full details on methods and additional results on other symptoms such as paresthesia and numbness are available from the evidence report.[7] We developed the study protocol via an open process involving multiple stakeholder groups and posted on the Agency for Healthcare Research and Quality web site for public comment.

We searched PubMed and the Cochrane Database of Systematic Reviews for systematic reviews from January 1, 2011, to October 12, 2015, as the American Academy of Neurology guideline was published in 2011. We chose the most relevant, recent, and high-quality systematic review and updated the search of the review by using its search strategy, including the year before the end date of its search (2014). As a result, we searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials from January 1, 2013, through May 24, 2016. We supplemented the results of the selected review's search by searching the references of 3 other recent, relevant systematic reviews.[3–5] We also searched ClinicalTrials.gov for relevant studies using the following terms: diabetic peripheral neuropathy [disease] and "interventional" [study-types] and not ("not yet recruiting" or "terminated" or "withdrawn") [overall-status] (search Date March 9, 2016) (figure e-1 at Neurology.org).

Paired investigators independently screened articles to assess eligibility using predefined criteria (table e-1) to identify parallel or crossover RCTs. Paired investigators abstracted data sequentially on study characteristics and the outcomes of pain intensity (continuous and categorical findings, using the methods of the prior systematic review), health-related QOL, adverse effects, and dropouts due to adverse effects. For studies summarized in the prior systematic review, we did not reabstract data on pain intensity and adverse effects reported in that review, but instead used the data from that review. Two reviewers assessed risk of bias of relevant systematic reviews using the Risk of Bias in Systematic Reviews (ROBIS) tool.[8] For the additional studies, 2 reviewers assessed risk of bias using the Cochrane Collaboration's tool for assessing the risk of bias of RCTs.[9] We resolved differences between reviewers through consensus.

For QOL, we abstracted the most relevant subscale using the following hierarchy for the highest therapeutic dose in each RCT: Short Form–36 (SF-36) physical function, then Visual Analogue Scale QOL, then EuroQol–5D overall, then other QOL score, then SF-36 bodily pain. Given that many studies did not report values, but only whether or not results were statistically significant, and often reported QOL scale results differently, we could only count studies with statistical significance.

We summarized results qualitatively and quantitatively. As in the prior review's methods, we used calculated standardized mean differences (SMD), which we classified into small (Cohen $d <$ 0.5), moderate ($>$0.5 to $<$0.8), and large ($>$0.8) effect sizes. When possible, for studies that did not report variability measures, we calculated the standard deviation of change in mean using a correlation coefficient of 0.5, in accordance with methods provided in Fu et al.[10] When there were at least 3 sufficiently clinically homogenous new studies and SMD could be calculated, we conducted new meta-analyses using the DerSimonian and Laird estimate[11] for a random effects model for outcome using STATA 12.1 (College Station, TX). We conducted a sensitivity analysis using the profile likelihood estimate when there was high statistical heterogeneity (i.e., $I^2 > 50\%$).[12] We graded strength of evidence as recommended by the Methods Guide for Conducting Comparative Effectiveness Reviews.[13]

RESULTS We included 106 RCTs: 57 from an existing systematic review, with 24 additional published RCTs incorporating 25 different comparisons (table 1); and 25 studies from ClinicalTrials.gov (table e-2). The recently completed, high-quality (using ROBIS) systematic review by Griebeler et al.[1] identified RCTs through April 2014 on oral and topical analgesics for the outcome of pain for painful DPN. The 57 RCTs from this review that met eligibility for our review compared 21 medications in 10,639 patients (table e-3). Few studies extended beyond 3 months (mean follow-up was 8.8 weeks with a maximum of 22 weeks). Griebeler et al.[1] evaluated the main outcome of pain by standardizing results from pain intensity scales to estimated SMD. They then conducted network meta-analyses among studies with less than 3 months of follow-up and among studies with greater than 3 months of follow-up to compare drug classes and individual drugs to placebo and to each other.

Our updated literature search identified 25 additional published head-to-head comparisons in 24 RCTs that had not been included in Griebeler et al. One study[14] included separate arms for pregabalin and gabapentin, both compared to placebo. Follow-up duration ranged from 3 to 18 weeks (we included all additional studies in the update and did not separate studies by length of follow-up), with a mean of 10.5 weeks of duration. Seventeen were multicenter studies. Four studies had academic funding and 1 did not report a funding source; the remaining 19 were industry-funded. Trials were

Table 1 Key placebo-controlled effectiveness results for pain

Comparison	No. of RCTs (total no. of patients)	Findings	Conclusion	Strength of evidence
Key anticonvulsants				
Pregabalin	16 RCTs (n = 4,017)	Updated direct meta-analysis of 15 RCTs (SMD −0.34 [95% CI −0.50 to −0.18])	Effective	Low
Gabapentin	5 RCTs (n = 766)	Griebeler et al. network meta-analysis (SMD −0.73 [95% CrI −1.54 to 0.09]); additional identified RCTs were consistent with this finding (SMD −0.65 [95% CI −1.1 to −0.23], −0.2 [95% CI −0.67 to 0.14], and −0.20 [95% CI −0.46 to 0.06])	Not effective	Low
Oxcarbazepine	3 RCTs (n = 634)	Griebeler et al. network meta-analysis (SMD −0.45 [CrI −0.68 to −0.21])	Effective	Low
Key serotonin-noradrenaline reuptake inhibitors				
Duloxetine	7 RCTs (n = 2,203)	Griebeler et al. network meta-analysis (SMD −1.33 [CrI −1.82 to −0.86]); 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)	Effective	Moderate
Venlafaxine	2 RCTs (n = 304)	Griebeler et al. network meta-analysis (SMD −1.53 [CrI −2.41 to −0.65])	Effective	Moderate
Tricyclic antidepressants	4 RCTs (n = 81)	Griebeler et al. network meta-analysis (SMD −0.78 [CrI −1.24 to −0.33])	Effective	Low
Opioids				
Typical opioids (oxycodone)	4 RCTs (n = 583)	Griebeler et al. network meta-analysis (SMD −0.58 [95% CrI −1.53 to 0.36]); additional identified RCTs were generally consistent with this finding (SMD −0.24 [95% CI −0.47 to −0.01] and −0.06 [95% CI −0.46 to 0.34])	Not effective	Low
Atypical opioids (tramadol and tapentadol)	5 RCTs (n = 1,177)	Updated direct meta-analysis of 5 RCTs (SMD −0.68 [95% CI −0.80 to −0.56])	Effective	Low
Key topical agents				
Topical capsaicin 0.075%	5 RCTs (n = 432)	Updated direct meta-analysis of 3 RCTs (SMD −0.46 [95% CI −0.95 to 0.03])	Not effective	Low
Other key agents				
Dextromethorphan	3 RCTs (n = 416)	Griebeler et al. network meta-analysis (SMD −0.28 [95% CrI −1.49 to 0.92]); SMD could not be calculated for the additional identified RCT	Not effective	Low
Mexiletine	5 RCTs (n = 389)	Griebeler et al. network meta-analysis (SMD −0.29 [95% CrI −0.91 to 0.33])	Not effective	Low
Botulinum toxin	2 RCTs (n = 60)	SMD ranged from −0.96 to −0.79	Effective	Low

Abbreviations: CI = confidence interval; CrI = credible interval; RCT = randomized controlled trial; SMD = standardized mean differences; SR = systematic review.

Only key comparisons are included in the table. Since this is an update of a prior systematic review, the results are generally reported as (1) results from the Griebeler et al. network meta-analysis, (2) whether results from additional identified studies are consistent or inconsistent with Griebeler et al., and (3) specific results from these additional studies. In addition, a new direct meta-analysis was conducted for pregabalin, atypical opioids, and topical 0.075% capsaicin, given a substantial number of new studies with inconsistent results with Griebeler et al. with results that could be pooled. Based on the results from all findings, we then concluded whether each drug or drug class was effective or not effective or if a conclusion could not be drawn, and graded the strength of evidence for the conclusion.

published between 1990 and 2015. The number of participants ranged from 20 to 804. All trials were placebo-controlled except for one comparing duloxetine, pregabalin, and combination therapy (only the duloxetine and pregabalin comparison was abstractable and reported here).[15]

We found an additional 25 trials in ClinicalTrials.gov for which we were unable to identify a publication, 18 of which were identified as completed. Seven of the 18 completed studies (39%) reported results in ClinicalTrials.gov and are included in these results (table e-2). Only the treatments of pregabalin and the 8% capsaicin patch had more than 1 completed trial found in ClinicalTrials.gov.

Outcomes: Pain. ***Anticonvulsants vs placebo.*** Griebeler et al. concluded from 6 RCTs that pregabalin was more effective than placebo for reducing pain (SMD −0.55; 95% confidence interval [CI] −0.94 to −0.15). Our updated search identified 6 additional published RCTs as well as 4 unpublished RCTs with results. SMD could not be calculated for one of the new studies,[16] which reported statistically insignificant findings. In a meta-analysis of 15

trials for which a SMD could be calculated, pregabalin was effective (SMD −0.34; 95% CI −0.50 to −0.18) (figure 1).[14,17–26] This was a reduction in effect compared to the previous Griebeler meta-analysis and an overall small effect size with significant heterogeneity in the findings. Reporting bias was a particular concern, due to the high number of unpublished studies. We graded the strength of evidence (SOE) as low.

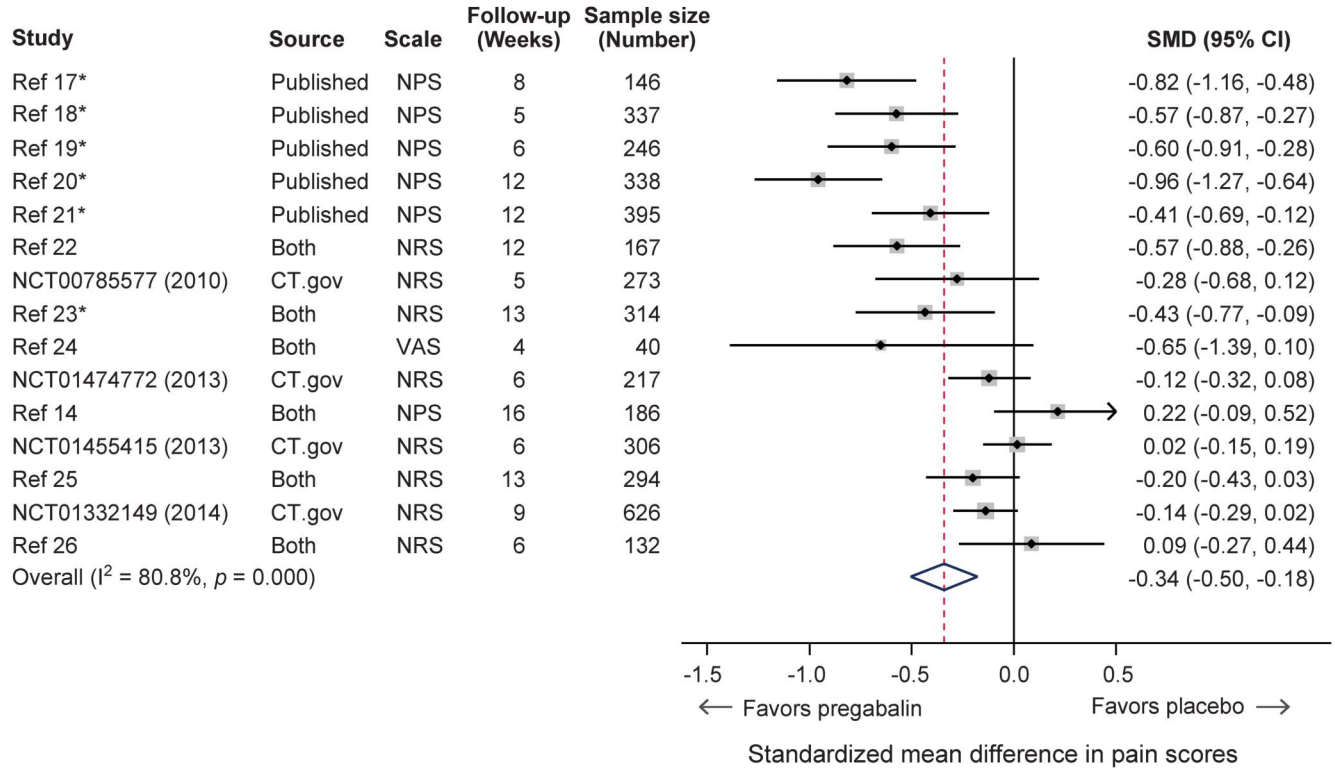
Griebeler et al. concluded that gabapentin was not more effective compared with placebo in treating pain (SMD −0.73; 95% credible interval [CrI] −1.54 to 0.09) (3 RCTs). Two RCTs from the updated search, including results from 2 different doses of gabapentin from one study, were consistent with this finding (SMD −0.65, 95% CI −1.1 to −0.23; SMD −0.27, 95% CI −0.67 to 0.14; and SMD −0.20, 95% CI −0.46 to 0.06).[14,27] We concluded that gabapentin was ineffective with low SOE.

Griebeler et al. concluded that oxcarbazepine (3 RCTs) was more effective than placebo in treating pain (SMD −0.45; 95% CrI −0.68 to −0.21) (small effect size, low SOE). In the updated search, we found no additional studies that addressed oxcarbazepine. Griebeler et al. concluded that most other anticonvulsants were ineffective (topiramate, valproic acid, lacosamide, lamotrigine) (low SOE). Zonisamide and carbamazepine had only one study each and we could not draw conclusions (insufficient SOE).

Antidepressants vs placebo. For serotonin-norepinephrine reuptake inhibitors (SNRIs), the review by Griebeler et al. included 7 RCTs in a drug class network meta-analysis with a pooled SMD of −1.36 (95% CrI −1.77 to −0.95) indicating a large effect size. Two additional RCTs identified in the updated search were consistent with this finding (SMD −0.33; 95% CI −0.54 to −0.12 and −0.11; 95% CI −0.42 to 0.21).[28,29] We concluded that the SNRI drug class was effective (moderate SOE) for pain treatment in DPN.

For specific SNRIs, the meta-analysis of duloxetine vs placebo included 5 RCTs and the pooled SMD was −1.33 (95% CrI −1.82 to −0.86), reflecting a large effect. Our update identified 2 additional RCTs that compared duloxetine vs placebo. One RCT reported a SMD of −0.33 (95% CI −0.54 to −0.12)[29] and the other RCT also found that duloxetine was significantly more effective than placebo, although SMD could not be calculated.[30] We concluded that duloxetine was more effective than placebo at reducing pain (moderate SOE).

Figure 1 Meta-analysis of calculated standardized mean differences (SMD) for studies comparing pregabalin with placebo for pain outcome



*Studies from the Griebeler et al. systematic review. Both = studies retrieved as a publication and from ClinicalTrials.gov; CT.gov = studies retrieved from ClinicalTrials.gov; Published = studies retrieved as a publication. CI = confidence interval; NPS = Neuropathic Pain Scale; NRS = Numeric Rating Scale; VAS = Visual Analog Scale.

The review by Griebeler et al. included 2 RCTs comparing venlafaxine vs placebo. Venlafaxine was more effective than placebo (SMD −1.53; 95% CrI −2.41 to −0.65) in reducing DPN-associated pain. We identified no additional studies on venlafaxine. We concluded that venlafaxine was more effective than placebo at reducing pain (large effect size, moderate SOE). Only one study evaluated desvenlafaxine, and we could not draw conclusions (insufficient SOE).

For tricyclic antidepressants (TCAs), Griebeler et al. concluded the drug class was effective based on a network meta-analysis of 4 RCTs (SMD −0.78; 95% CrI −1.24 to −0.33). We did not identify any additional studies addressing TCAs and concluded that TCAs were more effective than placebo at reducing pain (moderate effect size, low SOE). For individual TCAs, only imipramine had 2 studies, so we concluded that it was effective (low SOE). We were unable to draw conclusions for desipramine or amitriptyline (insufficient SOE).

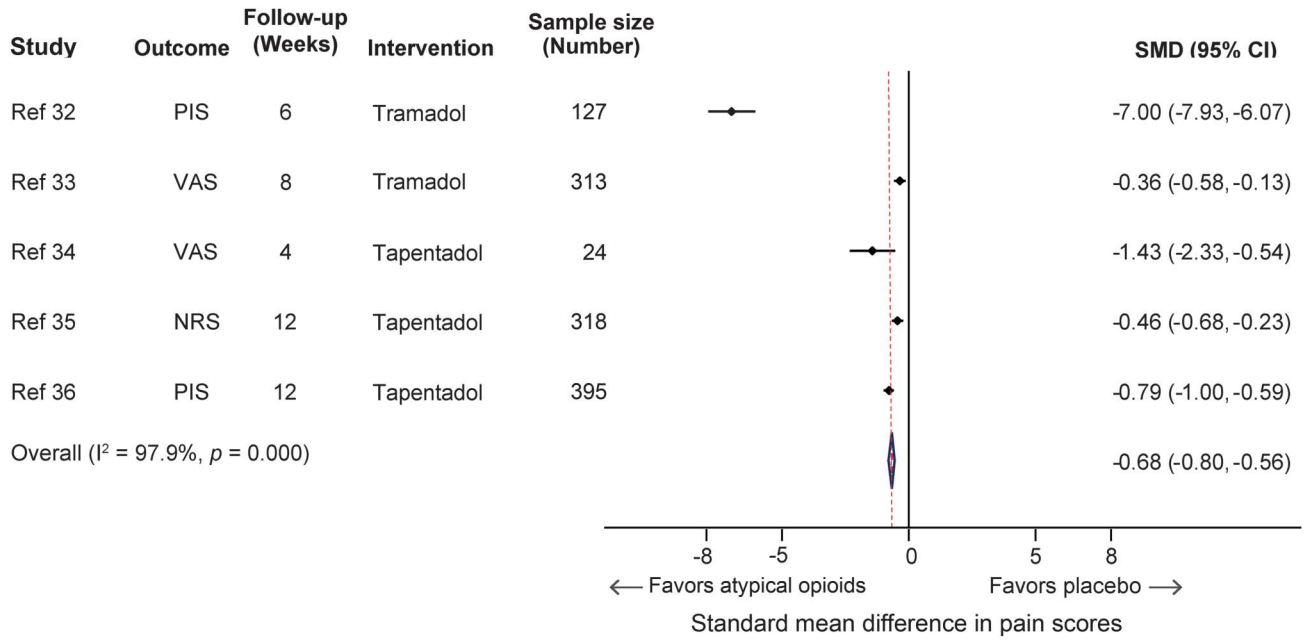
Opioids vs placebo. The systematic review by Griebeler et al. included 4 RCTs in a drug class network meta-analysis indicating opioids were not more effective than placebo (SMD −0.44; 95% CrI −1.15 to 0.25). In that analysis, Griebeler et al. pooled studies of both typical opioids (oxycodone) and atypical opioids (tramadol, tapentadol) that have activity as norepinephrine reuptake inhibitors as well as mu agonists. Considering this dual mechanism of atypical opioids, we analyzed typical and atypical opioids separately.

For typical opioids, oxycodone in 2 RCTs was not more effective compared with placebo in the Griebeler et al. analysis (SMD −0.58; 95% CrI −1.53 to 0.36). In the updated search, we identified 1 additional published RCT (SMD −0.24; 95% CI −0.47 to −0.01)[31] and 1 unpublished RCT of oxycodone vs placebo (SMD −0.06; 95% CI −0.46 to 0.34) (NCT00944697). We did not pool studies due to high statistical heterogeneity. We concluded that typical opioids were ineffective for pain treatment for DPN (low SOE).

Atypical opioid (tapentadol, tramadol) SMDs ranged from −7.0 to −0.36 (from −1.43 to −0.46 for tapentadol and from −7.0 to −0.36 for tramadol). The pooled SMD from the meta-analysis of all 5 studies (2 RCTs from Griebeler et al., and 3 additional identified RCTs) was −0.68 (95% CI −0.80 to −0.56) (figure 2).[32–36] We concluded that atypical opioids overall and both tramadol and tapentadol specifically were more effective at reducing pain compared to placebo (moderate effect size, low SOE).

Topical agents vs placebo. The review by Griebeler et al. reported a meta-analysis of 0.075% capsaicin compared to placebo, and found a pooled SMD of −0.91 (95% CrI −1.18 to −0.08). We calculated the SMD for one newly identified additional RCT (0.04; 95% CI −0.65 to 0.72)[37] and could not calculate a SMD for another,[38] although it reported no statistically significant difference. In a pooled

Figure 2 **Meta-analysis of calculated standardized mean differences (SMD) for studies comparing an atypical opioid with placebo for pain outcome**



CI = confidence interval; NRS = Numeric Rating Scale; PIS = Philadelphia Pain Intensity Scale; VAS = Visual Analog Scale.

meta-analysis of the 3 studies where a SMD could be calculated (including 1 new study), topical capsaicin 0.075% was ineffective (SMD −0.46; 95% CI −0.95 to 0.03) (figure 3).[37,39,40] We concluded that 0.075% capsaicin was not more effective than placebo at reducing pain for DPN (low SOE). We identified only one unpublished study (NCT01533428) from ClinicalTrials.gov that reported results on the 8% capsaicin patch, and so could not draw a conclusion (insufficient SOE). One study[41] reported results on topical clonidine, and we were unable to draw conclusions on its effectiveness (insufficient SOE). We identified no eligible studies of topical lidocaine.

Other agents vs placebo. For dextromethorphan, the Griebeler et al. meta-analysis of 2 RCTs reported a pooled SMD of −0.28 (95% CrI −1.49 to 0.92). We could not calculate an SMD for an additional study identified in the updated search. We concluded that dextromethorphan was ineffective (low SOE). We identified only one study each for the cannabinoids nabilone and nabiximols, so could not draw a conclusion (insufficient SOE). Griebeler et al. included 5 RCTs of mexiletine in the network meta-analysis and concluded it was not effective for pain control (SMD −0.29; 95% CrI −0.91 to 0.33) compared with placebo (low SOE). We identified no additional studies in the updated search. We identified no eligible studies of ketamine.

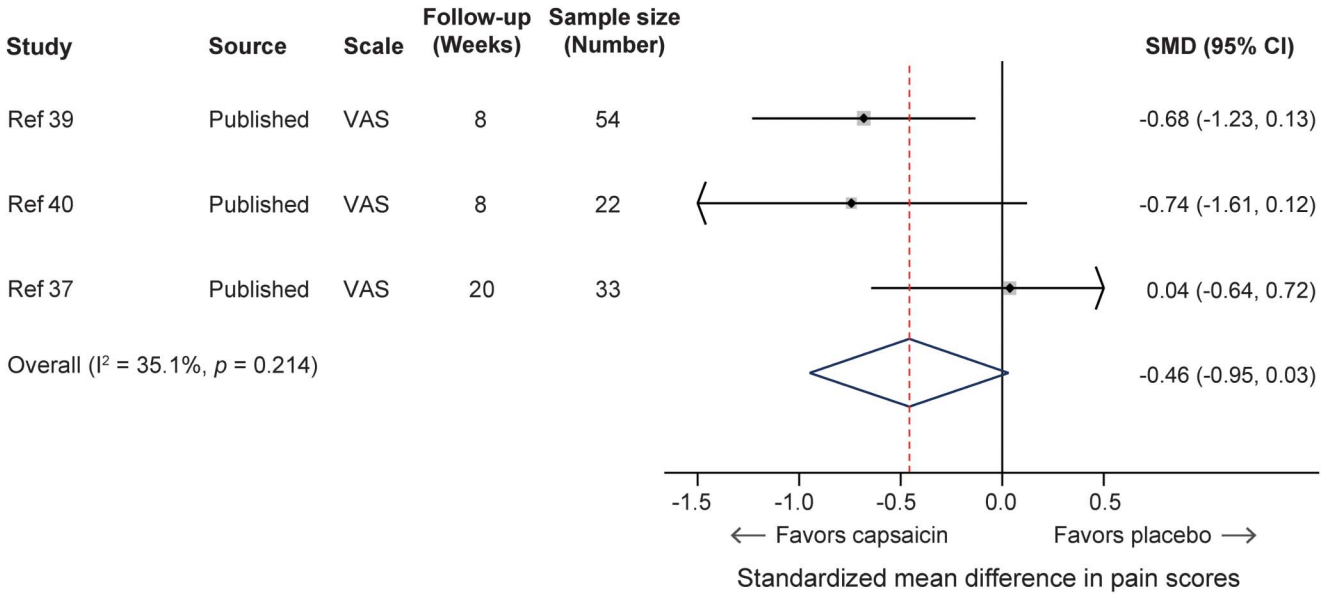
In the updated search, we identified 2 RCTs comparing botulinum toxin vs placebo, which were not included in the review by Griebeler et al. The SMDs ranged from −0.96[42] to −0.79[43] in these 2 trials. We concluded that botulinum toxin was effective at reducing pain vs placebo (moderate to large effect size, low SOE).

Drug–drug comparisons. No individual drug–drug comparisons had more than one study with analyzable results, so we could not draw conclusions on drug–drug comparisons (insufficient SOE) (table e-2).

Quality of life. We identified 32 studies that reported QOL (table e-4). Of note, many studies did not report specific QOL values, but only whether or not results were statistically significant. As a result, we could only count the number of studies with statistically significant results. Pregabalin had the highest number of studies reporting QOL (10 RCTs) with 4 showing statistically significant results and 6 showing insignificant results. Sorted by drug class, anticonvulsants had 7 of 18 studies with statistically significant results, SNRIs had 1 of 4 studies, and atypical opioids 3 of 4 studies. Given incomplete reporting, we could not draw conclusions for QOL (insufficient SOE for all comparisons).

Harms. Types of harms reported in more than 10% of participants varied by drug class (table 2). Studies of SNRIs and anticonvulsants most commonly reported dizziness, nausea, and somnolence, while studies of TCAs reported xerostomia, somnolence, and insomnia. For both opioids and atypical opioids, the most common adverse effects were constipation, nausea, and somnolence. Dropout rates due to adverse effects varied widely from 2.5% up to 70% for oral agents.

Figure 3 Meta-analysis of calculated standardized mean differences (SMD) for studies comparing topical capsaicin 0.075% with placebo for pain outcome



CI = confidence interval; VAS = Visual Analog Scale.

Table 2 Findings of harms for major drug classes and drugs

Adverse effects	Intervention, %	Placebo/drug comparison, %
Anticonvulsants		
Anorexia	10.9–20	0–0.9
Back pain	9–11	2.8–6
Cardiovascular	25	8.3
Dermatologic	8–33.3	9–25
Diarrhea	10.7–12.3	3.7–8.6
Dizziness	2.5–52.5	0–18
Fatigue	4–16	2–11
Headache	4.4–36.6	3.7–38
Nausea	2.4–41	0–16
Paresthesia	12–20	5–9
Peripheral edema	8–17	0–31.8
Respiratory	33.3	25
Restlessness/ insomnia	25	0
Somnolence	3–40	0–16.7
Taste perversion	14	0
Urinary	25	0
Weight change	25	8.3
Weight gain	14.6	1.2
Weight loss	14	6
Serotonin-norepinephrine reuptake inhibitors		
Constipation	7–19	2–8
Dizziness	1.6–26.1	6–11
Dry mouth	3.2–13	2.2
Dyspepsia	9–10	1
Nausea	10–32	2–12
Somnolence	8–28	1–8
Vomiting	2.9–10.1	2.2
Tricyclic antidepressants		
Dizziness	8–16	3
Insomnia	35	15
Somnolence	4–69	12–40
Xerostomia	26–89	8–45
Oxycodone		
Constipation	45–59	14–17
Fatigue	18	8
Nausea	36–73	8–36
Somnolence	40–41	1–47
Atypical opioids		
Constipation	6–22	1–5
Dizziness	6.3–7.2	1.3–2
Headache	2.4–5	5–5.3
Nausea	11.9–23	3–9.9
Somnolence	6–12	0.7–6
Vomiting	12.7	4.6
Topical capsaicin 0.075%		
Burning pain at the application site	13.98–63	2.7–19

For nonoral agents, dropouts were less frequent, ranging from 0% to 8.6% (table 3).

DISCUSSION We identified a substantial body of evidence (106 studies, 49 of which were in addition to the prior systematic review[1]) on the effectiveness of pharmacologic approaches to improve pain and QOL for adults with DPN. The anticonvulsants pregabalin and oxcarbazepine (low strength of evidence), the SNRIs duloxetine and venlafaxine (moderate strength of evidence), the drug classes of TCAs (low strength of evidence) and atypical opioids (low strength of evidence), and botulinum toxin (low strength of evidence) were all more effective than placebo. While most effect sizes were moderate (Cohen $d > 0.5$) or large (>0.8),[44] those for pregabalin and oxcarbazepine were small (<0.5). Of note, pregabalin has a similar mechanism of action to gabapentin, and the 2 agents are often used interchangeably in clinical care; however, Griebeler et al. and our updated review found that gabapentin was not more effective than placebo. We were unable to draw conclusions for any head-to-head drug comparisons due to insufficient evidence.

Strength of evidence was insufficient for many comparisons owing to few studies for many agents. We frequently downgraded trials in risk of bias assessment for not reporting blinding by outcome assessors and for incomplete outcome reporting. Reporting bias was a particular concern for pregabalin, due to the high number of unpublished studies, which all had negative results, and 6 additional studies on ClinicalTrials.gov without any results reported. And for many studies, particularly studies of tapentadol, study methodology was inconsistent with standards for pain trials,[45] including using nonstandard primary pain outcomes and withdrawal study methodology (of concern for studies of opioids, where withdrawal causes additional symptoms).

Since values for QOL were often not reported (only whether results were statistically significant) or reported inconsistently, we were limited to counting

Table 3 Dropouts due to adverse effects reported in all the studies

Drug class	Intervention	Dropouts due to adverse effects, %
Anticonvulsants	Carbamazepine	3
	Gabapentin	8–21
	Lacosamide	8.3–42.3
	Lamotrigine	7.4–21.1
	Oxcarbazepine	10.8–40.9
	Pregabalin	2.5–25.6
	Topiramate	12–30.4
	Valproic acid	3.4–4.8
	Zonisamide	38.5
Serotonin-noradrenaline reuptake inhibitors	Desvenlafaxine	8–30.4
	Duloxetine	4.3–19.3
	Venlafaxine	6–9.8
Tricyclic antidepressants	Amitriptyline	3.6–38.6
	Desipramine	10–13
	Imipramine	Not reported
Opiates and atypical opiates	Oxycodone	3–70
	Tapentadol	8.1–16.3
	Tramadol	8.1–13.8
Topical agents	Capsaicin	0–8.6
	Clonidine	3
NMDA receptor antagonists	Dextromethorphan	20.2–25.2
Class IB antiarrhythmics	Mexiletine	13.3
Botulinum toxin	Botulinum toxin	0
Cannabinoids	Nabilone	Not reported

the number of statistically significant studies for the most relevant QOL measures. As a result, we were unable to draw conclusions about the effects of treatments for DPN on QOL due to insufficient strength of evidence.

Frequent harms for SNRIs and anticonvulsants included dizziness, nausea, and somnolence, while studies of TCAs reported xerostomia, somnolence, and insomnia. For both opioids and atypical opioids, adverse effects were most frequently constipation, nausea, and somnolence. Dropout rates due to adverse effects varied widely from 2.5% up to 70% for oral agents and for nonoral agents from 0% to 8.6%.

Our review and the body of evidence have many limitations. We excluded studies including mixed populations of those with DPN and other types of neuropathy, which may have excluded some relevant data. Studies often reported multiple assessment tools for pain, sometimes with conflicting results, and our choices of tools may have affected findings. For pain, many different types of scales and composite tools were used, and pain severity was sometimes not reported separately. 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. We could not evaluate QOL due to incomplete reporting of results in many studies. And although we conducted risk of bias and strength of evidence assessments, these tools can only reflect what is reported in the published article and may not include all possible limitations on study quality that may be considered when evaluating these results for use in clinical care.

The evidence was also limited owing to the short duration of most studies. Most RCTs were less than 3 months in duration, although in clinical practice these are used as long-term medications. We could not assess long-term clinical outcomes and harms, including continued effectiveness with progression of DPN, long-term side effects, or long-term effect on function or diabetic complications. This is particularly important for atypical opioids, which we found were effective in short-term studies, as new guidelines and position papers now recommend against the use of opioids for chronic pain conditions given lack of evidence for long-term benefit and increasing evidence of serious risks, particularly abuse, misuse, and overdose.[46]

Our findings generally support the effectiveness of the 3 drugs approved by the Food and Drug Administration (FDA) for the treatment of pain in DPN: duloxetine, pregabalin, and tapentadol, although there was evidence of reporting bias for pregabalin. The results also suggest that other, non-FDA-approved agents may also be effective (oxcarbazepine, venlafaxine, TCAs, tramadol, and botulinum toxin). All these treatments also have substantial risks of adverse effects. Additional studies evaluating longer-term outcomes are needed to better inform clinical decision-making, patient choice, and clinical practice guidelines.

AUTHOR CONTRIBUTIONS

J.M. Waldfogel: acquisition of data, analysis and interpretation of data, drafting/revising the manuscript for content. S.A. Nesbit: acquisition of data, analysis or interpretation of data, drafting/revising the manuscript for content. S.M. Dy: study concept/design, acquisition of data, analysis and interpretation of data, drafting/revising the manuscript for content. R. Sharma: acquisition of data, study concept or design, analysis and interpretation of data, drafting/revising the manuscript for content, study supervision or coordination. A. Zhang: acquisition of data, statistical analysis, analysis and interpretation of data, drafting/revising the manuscript for content. L.M. Wilson: acquisition of data, statistical analysis, drafting/revising the manuscript for content. W.L. Bennett: study concept/design, acquisition of data, drafting/revising the manuscript for content. H.-C. Yeh: study concept/design, acquisition of data, drafting/revising

the manuscript for content. Y. Chelladurai: acquisition of data, analysis and interpretation of data, drafting/revising the manuscript for content. D. Feldman: acquisition of data, analysis and interpretation of data, drafting/revising the manuscript for content. K.A. Robinson: study concept/design, acquisition of data, drafting/revising the manuscript for content.

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DISCLAIMER

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 US Department of Health and Human Services.

DISCLOSURE

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