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Pharmacologic Interventions for Painful Diabetic Neuropathy

An Umbrella Systematic Review and Comparative Effectiveness Network Meta-analysis

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Background: Multiple treatments for painful diabetic peripheral neuropathy are available.

Purpose: To evaluate the comparative effectiveness of oral and topical analgesics for diabetic neuropathy.

Data Sources: Multiple electronic databases between January 2007 and April 2014, without language restriction.

Study Selection: Parallel or crossover randomized, controlled trials that evaluated pharmacologic treatments for adults with painful diabetic peripheral neuropathy.

Data Extraction: Duplicate extraction of study data and assessment of risk of bias.

Data Synthesis: 65 randomized, controlled trials involving 12 632 patients evaluated 27 pharmacologic interventions. Approximately one half of these studies had high or unclear risk of bias. Nine head-to-head trials showed greater pain reduction associated with serotonin–norepinephrine reuptake inhibitors (SNRIs) than anticonvulsants (standardized mean difference [SMD], −0.34 [95% credible interval {CrI}, −0.63 to −0.05]) and with tricyclic antidepressants (TCAs) than topical capsaicin 0.075%. Network meta-analysis showed that SNRIs (SMD, −1.36 [CrI, −1.77 to −0.95]), topical capsaicin (SMD, −0.91 [CrI, −1.18 to −0.08]), TCAs (SMD, −0.78 [CrI, −1.24 to −0.33]), and anticonvulsants (SMD, −0.67 [CrI, −0.97 to −0.37]) were better than placebo for short-term pain control. Specifically, carbamazepine (SMD, −1.57 [CrI, −2.83 to −0.31]), venlafaxine (SMD, −1.53 [CrI, −2.41 to −0.65]), duloxetine (SMD, −1.33 [CrI, −1.82 to −0.86]), and amitriptyline (SMD, −0.72 [CrI, −1.35 to −0.08]) were more effective than placebo. Adverse effects included somnolence and dizziness with TCAs, SNRIs, and anticonvulsants; xerostomia with TCAs; and peripheral edema and burning sensation with pregabalin and capsaicin.

Limitation: Confidence in findings was limited because most evidence came from indirect comparisons of trials with short (≤3 months) follow-up and unclear or high risk of bias.

Conclusion: Several medications may be effective for short-term management of painful diabetic neuropathy, although their comparative effectiveness is unclear.

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Diabetic peripheral neuropathy is a common long-term complication of diabetes mellitus that can affect the function and quality of life of affected persons (1). Several types of diabetic neuropathies have been identified, the most common of which is distal symmetric sensorimotor polyneuropathy. The associated neuropathic pain is estimated to affect up to 30% to 50% of persons with diabetes (2–6).

The first step in the management of painful diabetic neuropathy is optimizing glycemic control (3); however, patients also often need pharmacologic agents to relieve pain. Agents frequently used are tricyclic antidepressants (TCAs) (for example, amitriptyline), anticonvulsants (for example, gabapentin or pregabalin), serotonin–norepinephrine reuptake inhibitors (SNRIs) (for example, duloxetine or venlafaxine), opioids, opioid-like substances, and topical medications (for example, capsaicin cream) (2, 5, 6).

Evidence-based guidance about the selection of analgesic agents for painful diabetic neuropathy is not definitive. Stepwise approaches and algorithms may be used; however, the comparative effectiveness of treatment regimens that include stepwise approaches is unclear, partially because of the scarcity of direct head-to-head trials. We did a systematic review and network meta-analysis to summarize and appraise the totality of evidence from randomized, controlled trials (RCTs) about the efficacy of the most commonly used oral and topical analgesics for painful diabetic neuropathy.

Methods

Data Sources and Searches

We followed a published protocol (4) and, when reporting the review, adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Statement (7). We used an "umbrella" approach (8, 9) to identify relevant systematic reviews and RCTs. We identified systematic reviews that compared available therapeutic options for painful diabetic neuropathy with placebo or any other active comparator and compiled a list of relevant RCTs from these systematic reviews.

We did a comprehensive literature search for systematic reviews published between January 2007 and April 2014 and a search for all RCTs published between January 2012 and April 2014. We searched Ovid MEDLINE,

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Ovid EMBASE, and the Cochrane Database of Systematic Reviews. Two study investigators with experience in systematic reviews and an expert reference librarian developed the search strategy by using a combination of controlled vocabulary (Medical Subject Heading terms) and keywords for the concepts of treatment of neuralgia or diabetic neuropathy. Two reviewers working independently identified all systematic reviews on treatment of diabetic neuropathy by title and abstract.

Study Selection

On the basis of recommendations of the 2 study investigators with expertise in diabetes care and information in the American Diabetes Association statement (3), we developed a list of drugs commonly used in the United States and Europe for diabetic neuropathy, minimum effective doses, and therapeutic range (**Supplement 1**, available at www.annals.org). For a trial to be included, the intervention dose had to be at least the minimum effective dose. We chose this approach to reduce the risk of bias associated with comparing an agent with an ineffective dose of a competitor. When more than 1 dose was evaluated in the same RCT, we extracted data for the highest dose tested within the drug's therapeutic range.

Pairs of reviewers working independently identified parallel or crossover randomized trials that enrolled adults (aged ≥18 years) with painful diabetic neuropathy without imposing restrictions based on the language of publication, number of patients, or type of diabetes mellitus. We excluded studies investigating combinations of drugs. Disagreement was solved by consensus or arbitrated by a third reviewer, if necessary. We assessed chance-adjusted agreement (κ statistic) for each step requiring judgment.

The main outcome was pain relief, which was assessed as a dichotomous (the proportion of patients whose pain decreased ≥30%) and continuous (the standardized mean difference [SMD] on a pain scale) variable. When both forms were reported, they were collected and analyzed separately. If upper- and lower-extremity pain was reported, only data on the lower extremities were evaluated. When a trial reported results for several pain domains, we extracted data for the most relevant domain on the basis of a predefined hierarchy (intensity, overall pain, quality, duration, and timing in decreasing order of relevance) (4). If pain was reported at multiple time points, we assessed efficacy at the furthest time point within 3 months (short-term effect), longer than 3 months (long-term effect), or both.

Data Extraction and Quality Assessment

Independent reviewers extracted data from RCTs in duplicate using a standardized, piloted, Web-based data extraction form. We extracted data on patient demographic characteristics, diabetes baseline characteristics (for example, disease duration and hemoglobin A_{1c} level), study design, sample size, type of intervention and pain scale, and adverse effects of the medications. We requested missing or additional data for the primary outcome through e-mail contact with the corresponding authors. If the requested data could not be retrieved, we did not include the study in the primary outcome analysis. We also noted which agents were approved by the U.S. Food and Drug Administration for treatment of diabetic neuropathy and reviewed Micromedex 2.0 (Truven Health Analytics; www.micromedex.com) and Lexicomp (Wolters Kluwer Health; www.lexi.com) to supplement information about possible adverse effects.

We used the Cochrane Collaboration's risk-of-bias tool to evaluate the methodological quality of the RCTs (8). Two reviewers working independently assessed the risk of bias for random-sequence generation; allocation concealment; blinding of patients, caregivers, or outcome assessors; incomplete outcome data; selective reporting; and other biases (funding source and nature). Disagreements were resolved by discussion or arbitrated by a third reviewer. We summarized the risk of bias for all domains to produce an overall risk of bias for every trial (8). Risk of bias was considered to be high if there was concern for bias in any key domain (allocation concealment or blinding of patients), low if risk of bias was low for all key domains, and unclear in all other cases. We chose a priori to consider allocation concealment and blinding as key quality domains because of their relative importance for preventing selection bias and bias in the assessment of subjective outcomes, such as pain.

Data Synthesis and Analysis

We standardized the pain scales used in studies by estimating SMDs using the Cohen *d* method and 95% credible intervals (CrIs) (10). Because a few studies reported dichotomized outcomes, we converted the logarithm of odds ratios from those trials into SMDs by dividing by 1.81 using the Chinn method (11). To include trials that did not report variability measures, we also contacted the authors for missing data (12). When these steps were unsuccessful, we imputed SDs using the "leaving-1-out" method (13), which was used in pairwise and Bayesian network meta-analyses. Crossover trials were analyzed according to the recommendations of the Cochrane Collaboration (8).

Network Meta-analysis

Network meta-analyses were done to combine direct and indirect evidence of class and agent comparisons using the Bayesian Markov-chain Monte Carlo method. Traditional meta-analyses compare 1 intervention with another one at a time and combine evidence directly from head-to-head clinical trials if such trials exist. A network meta-analysis combines effect sizes for all possible pairwise comparisons (direct and indirect), regardless of whether they have been compared in trials. It allows researchers to compare several interventions simultaneously and evaluate relative effectiveness (14).

A random-effects model was fitted because of the potential for heterogeneity among included trials. The poste-

rior distribution of all parameters was estimated using noninformative priors for results to be represented solely by the included data. Results were based on 100 000 iterations after a burn-in of 50 000 iterations. We evaluated appropriateness of model fit by using the residual deviance, in which good model fit is represented by the residual deviance value approximating the number of unconstrained data points.

Random-effects metaregression was used to quantify the differences between subgroups and to test for statistically significant interactions among subgroups. We also did subgroup analyses on the basis of risk of bias (low vs. unclear and high risk).

Sensitivity Analysis

To evaluate the robustness of our imputations, we compared the results by including and excluding studies in which imputations were made for measures of dispersion (that is, SDs). We also compared the findings in a Bayesian network using different vague priors (uniform distributions, normal distributions, and gamma distributions with different means and variances).

We used the I^2 statistic and the Cochran Q test to assess heterogeneity for direct comparisons, in which I^2 is greater than 50% and/or the P value for heterogeneity is less than 0.10, which suggests substantial heterogeneity. Inconsistency of network meta-analyses was evaluated by comparing the estimates from direct comparisons with those from indirect comparisons for the magnitude and direction of effect. Our planned evaluation for publication bias was not possible because of the few studies included in each drug class ($n < 10$) and large heterogeneity (10). WinBUGS 1.4.3 was used to fit Bayesian Markov chain Monte Carlo models. Other statistical analyses were conducted using STATA, version 12.0 (StataCorp).

Role of the Funding Source

This study was funded by the Mayo Foundation for Medical Education and Research. The funding source played no role in the study design, conduct, or analysis or the decision to submit the manuscript for publication.

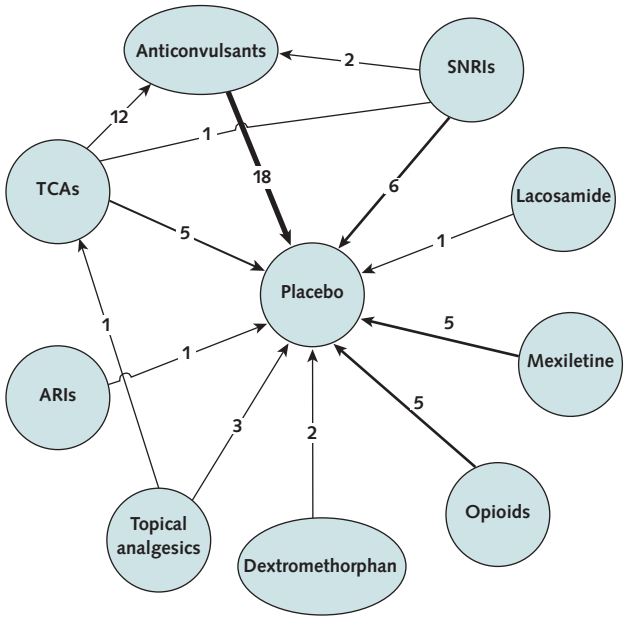
RESULTS

Search Results

We found 65 RCTs (15–79) that included 12 632 patients and compared 27 medications (**Appendix Figure 1**, available at www.annals.org). Nine head-to-head trials were identified, including 8 RCTs comparing medications of different pharmacologic classes. **Supplement 2** (available at www.annals.org) presents selected characteristics of the individual RCTs. In general, trials were brief (mean follow-up, 14 weeks) and enrolled mostly middle-aged men who had type 1 or 2 diabetes for more than 5 years.

Figure 1 and **Supplement 3** (available at www.annals.org) show the patterns of comparisons among the different treatments for short-term pain relief by drug class and individual drugs. Both networks have a star geometry, with placebo acting as the common comparator. Among all analgesics, amitriptyline was most commonly compared with other active agents (**Supplement 3**).

Figure 1. **Network of RCTs evaluating painful diabetic neuropathy within 3 mo, by drug class.**



Width of the lines is proportional to the number of trials for that comparison. ARI = aldose reductase inhibitor; RCT = randomized, controlled trial; SNRI = serotonin–norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant.

Thirty of the 65 included RCTs were considered to have a low risk of bias. Risk of bias in the remaining studies was considered to be high or unclear because of concerns about random-sequence generation, allocation concealment, blinding, incomplete outcome data, and selective reporting. Random-sequence generation and allocation concealment were appropriately described in 41 and 25, respectively, of the 65 RCTs.

Forty-eight RCTs described the blinding process clearly (**Appendix Figure 2**, available at www.annals.org). Forty-four RCTs had a large amount of missing data or a high proportion of loss to follow-up, and 58 had selective reporting problems. Seventeen trials used a crossover design, and some did not clearly report the existence or duration of a washout period. The included studies were substantially heterogeneous in most class comparisons. However, the residual deviance value approximating the number of unconstrained data points suggested good fit of the model in the network of direct and indirect comparisons.

Subgroup analysis by risk of bias (low vs. unclear and high risk) (**Supplement 4**, available at www.annals.org) suggested that RCTs at low risk of bias produced estimates

Table 1. **Comparative Analgesic Effect of Agents, by Class***

Class and Comparator	SMD From Direct Comparisons (95% CrI)	SMD From Network Meta-analyses (95% CrI)†
Opioids		
Placebo	**−0.36 (−0.55 to −0.18)**	−0.44 (−1.15 to 0.25)
ARIs		−0.11 (−2.01 to 1.76)
Anticonvulsants		0.23 (−0.54 to 0.99)
Lacosamide		−0.16 (−1.89 to 1.57)
SNRIs		0.92 (0.09 to 1.72)
Topical capsaicin		0.46 (−0.62 to 1.57)
TCAs		0.34 (−0.51 to 1.17)
Dextromethorphan		−0.17 (−1.57 to 1.22)
Mexiletine		−0.16 (−1.09 to 0.77)
ARIs		
Placebo	−0.34 (−1.19 to 0.52)	−0.33 (−2.08 to 1.42)
Opioids		0.11 (−1.76 to 2.01)
Anticonvulsants		0.34 (−1.41 to 2.13)
Lacosamide		−0.04 (−2.38 to 2.33)
SNRIs		1.02 (−0.75 to 2.85)
Topical capsaicin		0.58 (−1.34 to 2.54)
TCAs		0.45 (−1.34 to 2.27)
Dextromethorphan		−0.05 (−2.15 to 2.09)
Mexiletine		−0.04 (−1.87 to 1.83)
Anticonvulsants		
Placebo	**−0.79 (−1.01 to −0.57)**	−0.67 (−0.97 to −0.37)
Opioids		−0.23 (−0.99 to 0.54)
ARIs		−0.34 (−2.13 to 1.41)
Lacosamide		−0.38 (−1.98 to 1.22)
SNRIs	**0.34 (0.05 to 0.63)**	0.69 (0.21 to 1.17)
Topical capsaicin		0.24 (−0.63 to 1.12)
TCAs	0.00 (−0.17 to 0.17)	0.11 (−0.34 to 0.56)
Dextromethorphan		−0.39 (−1.64 to 0.84)
Mexiletine		−0.38 (−1.06 to 0.30)
Lacosamide		
Placebo	−0.29 (−0.65 to 0.07)	−0.29 (−1.87 to 1.28)
Opioids		0.16 (−1.57 to 1.89)
ARIs		0.04 (−2.33 to 2.38)
Anticonvulsants		0.38 (−1.22 to 1.98)
SNRIs		1.06 (−0.53 to 2.71)
Topical capsaicin		0.62 (−1.14 to 2.41)
TCAs		0.49 (−1.13 to 2.13)
Dextromethorphan		−0.02 (−1.98 to 1.97)
Mexiletine		0.01 (1.67 to −1.69)
SNRIs		
Placebo	**−2.10 (−3.41 to −0.79)**	**−1.36 (−1.77 to −0.95)**
Opioids		**−0.92 (−1.72 to −0.09)**
ARIs		−1.02 (−2.85 to 0.75)
Anticonvulsants	**−0.34 (−0.63 to −0.05)**	−0.69 (−1.17 to −0.21)
Lacosamide		−1.06 (−2.71 to 0.53)
Topical capsaicin		−0.45 (−1.36 to 0.49)
TCAs	−0.25 (−0.78 to 0.28)	−0.58 (−1.16 to 0.01)
Dextromethorphan		−1.08 (−2.36 to 0.19)
Mexiletine		**−1.07 (−1.81 to −0.33)**
Topical capsaicin		
Placebo	**−1.44 (−2.84 to −0.03)**	−0.91 (−1.18 to −0.08)
Opioids		−0.46 (−1.57 to 0.62)
ARIs		−0.58 (−2.54 to 1.34)
Anticonvulsants		−0.24 (−1.12 to 0.63)
Lacosamide		−0.62 (−2.41 to 1.14)
SNRIs		0.45 (−0.49 to 1.36)
TCAs	**1.02 (0.75 to 1.29)**	−0.13 (−1.03 to 0.74)
Dextromethorphan		−0.63 (−2.12 to 0.82)
Mexiletine		−0.63 (−1.67 to 0.40)
TCAs		
Placebo	**−0.55 (−0.99 to −0.11)**	−0.78 (−1.24 to −0.33)
Opioids		−0.34 (−1.17 to 0.51)
ARIs		−0.45 (−2.27 to 1.34)
Anticonvulsants	0.00 (−0.17 to 0.17)	−0.11 (−0.56 to 0.34)
Lacosamide		−0.49 (−2.13 to 1.13)
SNRIs		0.58 (−0.01 to 1.16)
Topical capsaicin	**−1.02 (−1.29 to −0.75)**	0.13 (−0.74 to 1.03)
Dextromethorphan		−0.50 (−1.78 to 0.78)
Mexiletine		−0.49 (−1.26 to 0.27)
Dextromethorphan		
Placebo	−0.25 (−0.77 to 0.28)	−0.28 (−1.49 to 0.92)
Opioids		0.17 (−1.22 to 1.57)
ARIs		0.05 (−2.09 to 2.15)
Anticonvulsants		0.39 (−0.84 to 1.64)
Lacosamide		0.02 (−1.97 to 1.98)
SNRIs		1.08 (−0.19 to 2.36)
Topical capsaicin		0.63 (−0.82 to 2.12)
TCAs		0.50 (−0.78 to 1.78)
Mexiletine		0.01 (−1.34 to 1.36)
Mexiletine		
Placebo	**−0.46 (−0.83 to −0.09)**	−0.29 (−0.91 to 0.33)
Opioids		0.16 (−0.77 to 1.09)
ARIs		0.04 (−1.83 to 1.87)
Anticonvulsants		0.38 (−0.30 to 1.06)
Lacosamide		−0.01 (−1.69 to 1.67)
SNRIs		**1.07 (0.33 to 1.81)**
Topical capsaicin		0.63 (−0.40 to 1.67)
TCAs		0.49 (−0.27 to 1.26)
Dextromethorphan		−0.01 (−1.36 to 1.34)

ARI = aldose reductase inhibitor; CrI = credible interval; SMD = standardized mean difference; SNRI = serotonin–norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant.
* Statistically significant values are in boldface.
† From direct and indirect comparisons.

of weaker effect; however, the CrIs of the estimates overlap. Therefore, although the evidence is insufficient to include or exclude differential effect estimates on the basis of the risk of bias, bias may partially explain heterogeneity.

Meta-analysis by Drug Class

This network geometry was an asymmetrical star, with most studies comparing anticonvulsants or SNRIs with placebo (**Figure 1**). Most head-to-head trials compared anticonvulsants with TCAs. The missing links between active interventions reflect the scarcity of direct comparisons.

Network meta-analysis of drugs by class that combined estimates from direct and indirect comparisons showed that, within 3 months of treatment, SNRIs (SMD, −1.36 [95% CrI, −1.77 to −0.95]), topical capsaicin 0.075% (SMD, −0.91 [CrI, −1.18 to −0.08]), TCAs (SMD, −0.78 [CrI, −1.24 to −0.33]), and anticonvulsants (SMD, −0.67 [CrI, −0.97 to −0.37]) all resulted in larger and statistically significant reductions in pain compared with placebo (**Table 1** and **Figure 2**). Opioids, aldose reductase inhibitors, dextromethorphan, the class IB antiarrhythmic mexiletine, and the new antiepileptic drug

lacosamide did not show a statistically significant difference (**Table 1**). Serotonin–norepinephrine reuptake inhibitors as a group reduced pain more than anticonvulsants (SMD, −0.69 [CrI, −1.17 to −0.21]) and opioids (SMD, −0.92 [CrI, −1.72 to −0.09]). Head-to-head trials showed that SNRIs and TCAs reduce pain more than anticonvulsants (SMD, −0.34 [CrI, −0.63 to −0.05]) and topical capsaicin, respectively.

The analysis of the long-term (>3 months) analgesic effect was limited by the scarcity of data. Some of the trials that studied aldose reductase inhibitors had the longest periods of intervention and follow-up among the included RCTs (**Supplement 2**). Compared with placebo, aldose reductase inhibitors (SMD, −0.86 [CrI, −1.58 to −0.14]) and anticonvulsants (SMD, −0.23 [CrI, −0.65 to −0.18]) had beneficial long-term analgesic effects that were statistically significant (**Supplement 5**, available at www.annals.org). We could not infer the long-term analgesic efficacy of topical capsaicin, TCAs, opioids, dextromethorphan, or mexiletine because of lack of studies measuring their effect for periods longer than 3 months.

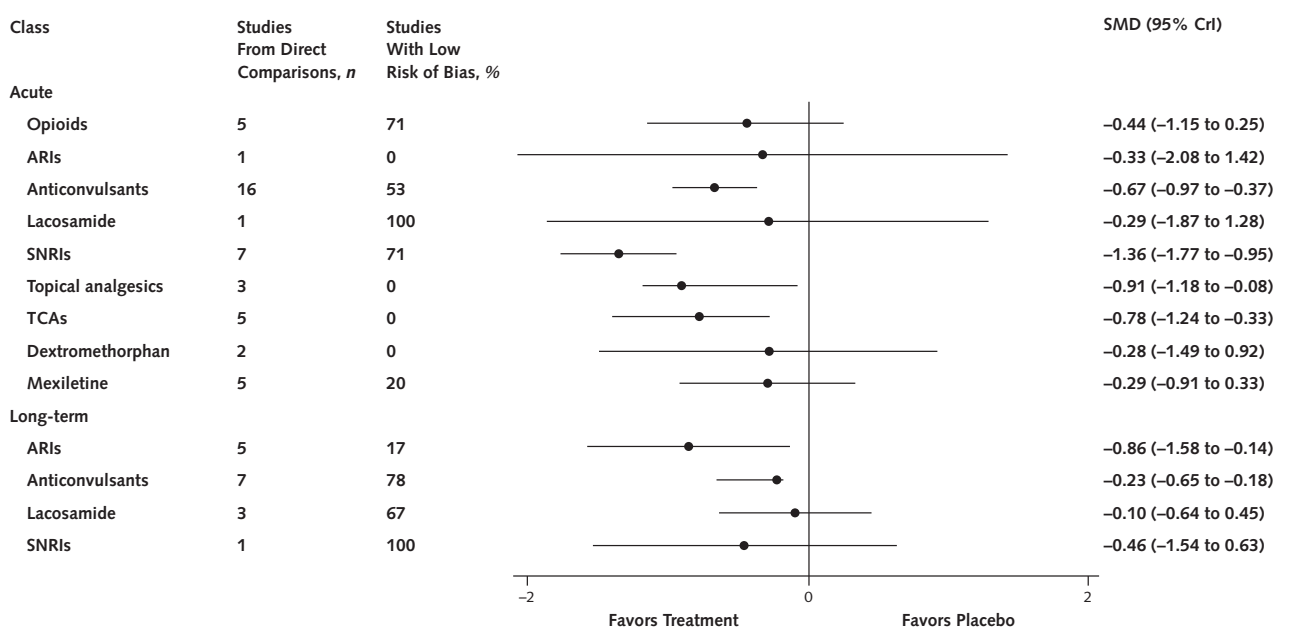
Meta-analysis by Individual Drugs

This network of evidence comparing several drugs with placebo had a radiating, star-like configuration and an overall small number of studies contributing to the direct and indirect comparisons across the specific agents (**Supplement 3**). Network meta-analysis combining results from direct and indirect comparisons revealed significantly better pain control than placebo within 3 months of treatment for carbamazepine (SMD, −1.57 [CrI, −2.83 to −0.31]), venlafaxine (SMD, −1.53 [CrI, −2.41 to −0.65]), duloxetine (SMD, −1.33 [CrI, −1.82 to −0.86]), and amitriptyline (SMD, −0.72 [CrI, −1.35 to −0.08]) (**Supplement 6**, available at www.annals.org). Most clinically relevant comparisons between individual drugs showed nonsignificant statistical differences, although pregabalin was inferior to venlafaxine (SMD, 0.99 [CrI, 0.02 to 1.96]) and duloxetine (SMD, 0.79 [CrI, 0.20 to 1.38]). Data from the few available studies that evaluated the long-term efficacy of analgesics for painful diabetic neuropathy suggest that the aldose reductase inhibitor fidarestat (SMD, −4.00 [CrI, −4.59 to −3.41]), duloxetine (SMD, −0.46 [CrI, −0.81 to −0.10]), and oxcarbazepine (SMD, −0.45 [CrI, −0.68 to −0.21]) are all more effective than placebo (**Supplement 6**).

Adverse Effects

Table 2 and **Supplement 7** (available at www.annals.org) show the most frequent adverse effects and treatment intolerance reported in the analyzed RCTs. **Table 2** also shows which drugs are approved by the U.S. Food and Drug Administration for treatment of diabetic neuropathy and lists contraindications and additional adverse effects of drugs reported in Micromedex and Lexicomp. Xerostomia was the most commonly reported anticholinergic symptom of the TCAs reported in trials (present in up to 89% of patients). Central nervous system symptoms associated with these drugs included somnolence (up to 69% of pa-

Figure 2. **Agents for treatment of diabetic peripheral neuropathy compared with placebo, by class.**



Combined direct and indirect estimates. ARI = aldose reductase inhibitor; CrI = credible interval; SMD = standardized mean difference; SNRI = serotonin–norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant.

Table 2. **Adverse Effects and Contraindications of Selected Medications Used to Treat Painful Diabetic Peripheral Neuropathy***

Medication	Common Adverse Effects	Possible Serious Adverse Effects	Contraindications	Comments
TCAs				
Amitriptyline, desipramine, imipramine	**Xerostomia** (2%–89%), **somnolence** (4%–69%), **fatigue** (11%–34%), **headache** (11%–21%), **dizziness** (5%–16%), **insomnia** (35%), orthostatic hypotension, anorexia, nausea, urinary retention, constipation, blurred vision, accommodation disturbance and mydriasis, weight gain	Hypersensitivity reactions, delirium, cardiac arrhythmias and conduction abnormalities, myocardial infarction, heart failure exacerbation, stroke, seizures, hepatotoxicity, bone marrow suppression, worsening depression, suicidal thoughts and behavior, shift to mania in bipolar disorder, the neuroleptic malignant syndrome, the serotonin syndrome, severe hyponatremia, fragility bone fractures	Hypersensitivity to drugs of similar chemical class, coadministration with an MAOI or use within 14 d of discontinuing therapy with an MAOI, acute recovery phase after myocardial infarction	Other potential adverse effects include hyponatremia, SIADH, forgetfulness, anxiety, ataxia, tremors, extrapyramidal symptoms, nightmares, paresthesia, increased intraocular pressure, hypertension, photosensitization, modest hyperglycemia, breast enlargement, galactorrhea, gynecomastia, black tongue, parotid swelling, loss or increased libido, testicular swelling, and drug withdrawal symptoms (e.g., nausea, headache, irritability, restlessness, and sleep disturbances).
SNRIs				
Duloxetine†, paroxetine‡, venlafaxine	**Nausea** (10%–32%), **somnolence** (8%–28%), **dizziness** (6%–25%), **constipation** (7%–19%), **dyspepsia** (9%–18%), diarrhea, xerostomia, anorexia, headache, diaphoresis, insomnia, fatigue, decreased libido	Hypersensitivity reactions, **the Stevens–Johnson syndrome**, hepatotoxicity, hypertensive crisis, gastrointestinal hemorrhage, abnormal bleeding, delirium, myocardial infarction, cardiac arrhythmias, **glaucoma**, worsening depression, suicidal thoughts and behavior, shift to mania in patients with bipolar disorder, seizures, severe hyponatremia, fragility bone fractures, the serotonin syndrome, the neuroleptic malignant syndrome	Hypersensitivity to drugs of similar chemical class, coadministration with an MAOI or use within 14 d of discontinuing therapy with an MAOI, concomitant use with thioridazine or pimozide, narrow-angle glaucoma	Other potential adverse effects include nervousness, anxiety, agitation, akathisia, abnormal dreams, lack of concentration, palpitations, flushing, hypertension, weakness, myalgia, muscle spasms, tremors, extra-pyramidal symptoms, **the restless legs syndrome**, paresthesia, vertigo, orthostatic hypotension, syncope, hyponatremia, SIADH, modest hyperglycemia, hyper-cholesterolemia, cholestatic jaundice, abdominal pain, vomiting, weight loss, flatulence, urinary hesitation, **urinary retention**, **erectile dysfunction**, priapism, **ejaculatory disorder**, **orgasm disorder**, **yawning**, nasopharyngitis, **blurred vision**, photosensitivity, galactorrhea, and withdrawal symptoms (e.g., nausea, vomiting, diarrhea, headache, lightheadedness, anxiety, diaphoresis, insomnia, and vivid dreams). Use with caution in hepatic or severe renal impairment (creatinine clearance <30 mL/min/1.73 m^2); a lower dose or less frequent dosing may be required.
Anticonvulsants				
Pregabalin†	**Somnolence** (5%–40%), **dizziness** (5%–38%), **peripheral edema** (4%–17%), **headache** (2%–13%), ataxia, fatigue, xerostomia, weight gain	Hypersensitivity reactions, angioedema, hepatotoxicity, rhabdomyolysis, suicidal thoughts and behavior, seizures after rapid discontinuation	Hypersensitivity to pregabalin	Other potential adverse effects include difficulty with attention or concentration, euphoria, amnesia, confusion, insomnia, muscle spasms, tremors, myoclonus, incoordination, **muscle weakness**, vertigo, balance impairment, speech disorder, blurred vision, diplopia, decreased visual acuity, myalgia, arthralgia, increased appetite, flatulence, nausea, constipation, **elevated liver enzyme levels**, **elevated creatine kinase levels**, thrombocytopenia, nasopharyngitis, sinusitis, flu-like syndrome, and withdrawal after rapid discontinuation (e.g., insomnia, nausea, headache, anxiety, diaphoresis, and diarrhea). Renal dosage adjustment required when the creatinine clearance is <60 mL/min/1.73 m^2.

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Table 2—**Continued**

Medication	Common Adverse Effects	Possible Serious Adverse Effects	Contraindications	Comments
Gabapentin	**Somnolence** (22%–48%), **dizziness** (22%–28%), ataxia, fatigue	Hypersensitivity reactions, the Stevens–Johnson syndrome, drug reaction with eosinophilia and systemic symptoms, suicidal thoughts and behavior, seizures after rapid discontinuation	Hypersensitivity to gabapentin	Other potential adverse effects include peripheral edema, weight gain, **headache** (11%–12%), nystagmus, blurred vision, diplopia, dysarthria, tremors, incoordination, hyperactive behavior, hyperkinesia, restlessness, hyperactivity, hostile behavior, concentration problems, emotional lability, mood swings, nervousness, amnesia, xerostomia, **diarrhea** (11%–12%), nausea, vomiting, constipation, abdominal pain, dyspepsia, flatulence, myalgia, viral respiratory tract infections, and withdrawal symptoms (e.g., anxiety, insomnia, nausea, pain, and sweating). Renal dosage adjustment required when the creatinine clearance is $<$60 mL/min/1.73 m^2.
Carbamazepine	**Dizziness** (10%–53%), **somnolence** (14%), **vomiting** (10%), headache, ataxia, nausea, constipation	Hypersensitivity reactions, the Stevens–Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, angioedema, eosinophilic myocarditis, cardiac arrhythmias and conduction abnormalities, congestive heart failure, agranulocytosis, aplastic anemia, bone marrow depression, pancytopenia, hepatotoxicity, liver failure, the vanishing bile duct syndrome, pancreatitis, severe hyponatremia, the water intoxication syndrome, delirium, acute intermittent porphyria, tubulointerstitial nephritis, renal failure, pulmonary hypersensitivity, suicidal thoughts and behavior, the neuroleptic malignant syndrome, seizures after rapid discontinuation	Hypersensitivity to carbamazepine or TCAs, history of bone marrow depression, concomitant use of an MAOI or use within 14 d of discontinuing therapy with an MAOI, concomitant use of nefazodone or delavirdine or other nonnucleoside reverse transcriptase inhibitors	Other potential adverse effects include pruritus, skin rash, xerostomia, anorexia, abdominal pain, diarrhea, glossitis, stomatitis, erythema multiforme, mycosis fungoides–like lesions, skin photosensitivity, anemia, neutropenia, leukopenia, thrombocytopenia, eosinophilia, leukocytosis, hypertension, aggravation of coronary artery disease, hypotension, syncope, abnormal results on liver function tests, thrombophlebitis, lymphadenopathy, carbamazepine-induced systemic lupus erythematosus syndrome, muscle weakness, myalgia, arthralgia, leg cramps, tremor, twitching, paresthesia, speech disturbance, vertigo, abnormality in thinking, nystagmus, blurred vision, **hyperacusis**, **psychomotor agitation**, psychotic disorder, urinary retention, azotemia, erectile dysfunction, hypocalcemia, hypophosphatemia, hyponatremia, and SIADH.
Topical analgesics				
Capsaicin 0.075%	**Burning pain at the application site** (54%–63%), erythema at the application site	Chemical burns (e.g., first- to third-degree) at the application site, transient increases in blood pressure due to treatment-related pain	Not determined	Other potential adverse effects include pruritus at the application site, rash, dryness, papules or swelling, nausea, and nasopharyngitis. This agent should not be applied to the face, the scalp, or broken or irritated skin. Contact with the eyes or mucous membranes should not be allowed. The treated area should not be exposed to heat or direct sunlight. Inhalation of airborne capsaicin when patches are rapidly removed may result in coughing, sneezing, or shortness of breath.

MAOI = monoamine oxidase inhibitor; SIADH = syndrome of inappropriate antidiuretic hormone secretion; SNRI = serotonin–norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant.

* Data not obtained from the meta-analyses are from Micromedex 2.0 (Truven Health Analytics; www.micromedex com) and Lexicomp (Wolters Kluwer Health; www.lexi.com). Frequently reported adverse effects in the studies included in the systematic review are in boldface.

† Approved by the U.S. Food and Drug Administration for the treatment of diabetic peripheral neuropathy.

‡ A selective serotonin reuptake inhibitor.

tients) and dizziness (5% to 16%). Fatigue (11% to 34%), insomnia (35%), and headache (11% to 21%) were also commonly described. Serotonin–norepinephrine reuptake inhibitors were associated mainly with central nervous system and gastrointestinal adverse effects. Somnolence and dizziness were present in 8% to 28% and 6% to 25% of patients in the SNRI trials, respectively. Nausea (10% to 32%), constipation (7% to 19%), and dyspepsia (9% to 18%) were also common. Patients receiving gabapentin or pregabalin frequently reported somnolence (5% to 48%) and dizziness (5% to 38%). Peripheral edema (4% to 17%) and headache (2% to 13%) were commonly seen among those receiving pregabalin. More than 50% of patients receiving topical capsaicin described painful burning at the application site.

Discussion

Our systematic review and network meta-analysis of RCTs shows that several analgesics may be effective for the short-term treatment of painful diabetic neuropathy. Selective serotonin reuptake inhibitors, topical capsaicin, TCAs, and anticonvulsants were associated with statistically significant reductions in pain. Network meta-analysis combining direct and indirect comparisons supports the effectiveness of carbamazepine, venlafaxine, duloxetine, and amitriptyline. As a group, SNRIs had a greater effect on pain control than anticonvulsants and opioids.

Patients receiving TCAs, SNRIs, and most anticonvulsants frequently reported somnolence and dizziness. Xerostomia was the most common anticholinergic effect of TCAs. Nausea, constipation, and dyspepsia were prevalent among those receiving SNRIs. Patients receiving pregabalin reported peripheral edema as a common adverse effect, whereas topical capsaicin was frequently associated with burning at the application site.

A comprehensive literature search for RCTs and previous reviews published up to April 2014 identified relevant systematic reviews on this topic. These studies provided important insights about the comparative effectiveness of pharmacologic interventions for painful diabetic neuropathy (6, 80–82). Wong and colleagues (6) investigated studies that compared paracetamol, antidepressants, opioids, nonsteroidal anti-inflammatory drugs, *N*-methyl-D-aspartic acid antagonists, tramadol, capsaicin, and anticonvulsants with placebo but excluded head-to-head trials comparing different classes of analgesics. They found better odds for pain relief with anticonvulsants and TCAs than with placebo. Quilici and associates (80) analyzed studies comparing duloxetine, pregabalin, and gabapentin and found no major differences in the analgesic effectiveness of these agents. Chou and coworkers (81) identified RCTs that compared gabapentin with TCAs for the treatment of diabetic neuropathic pain or postherpetic neuralgia and found no substantial differences.

Snedecor and colleagues (82) reported a network meta-analysis of pharmacologic interventions for painful diabetic neuropathy. In contrast with our study, this review excluded trials lasting less than 4 weeks and included other agents (for example, nabiximols and intravenous α-lipoic acid). Overall, a relative equivalence among available treatments was found. Compared with placebo, pain reduction on an 11-point (0 to 10) numerical rating scale ranged from −3.29 for sodium valproate to −0.39 for duloxetine (82).

Our review adds to these previous efforts by providing a more complete understanding of the current body of evidence on comparative effectiveness of analgesic interventions for painful diabetic neuropathy. A star-shaped network was identified, with placebo as the most common comparator. The few head-to-head trials, heterogeneity of results, and substantial proportion of trials at high or uncertain risk of bias warrant caution in our confidence in the estimates of comparative effectiveness among these agents. We also found limited data about the effect of analgesics for diabetic neuropathy beyond 3 months of treatment.

Varying recommendations for the management of painful diabetic neuropathy have been proposed (83–85). The European Federation of Neurological Societies recommended that TCAs, gabapentin, pregabalin, and SNRIs (including duloxetine and venlafaxine) should be used as first-line agents. Tramadol or stronger opioids are considered as second- or third-line medications (83). In 2011, the International Toronto Expert Panel on Diabetic Neuropathy proposed similar recommendations (84). The American Academy of Neurology recommends offering pregabalin as a first-line option, whereas venlafaxine, duloxetine, amitriptyline, gabapentin, valproate, opioids (morphine sulfate, tramadol, and controlled-release oxycodone), and capsaicin should be considered later (85).

Currently, only duloxetine and pregabalin are approved by the U.S. Food and Drug Administration and the European Medicines Agency to treat neuropathic pain in diabetes (84). The results of our review support the use of these analgesics but also show that many other interventions (for example, capsaicin cream or TCAs) are reasonable options. Our systematic review also provides data about the frequency of the most common adverse effects of these medications and can be used as a reference for estimating risk–benefit assessments on individual patients. It should be noted, however, that our systematic review is limited to the evaluation of RCTs and therefore lacks data from observational studies that may provide better evidence for rare but serious adverse effects. Furthermore, our review did not evaluate information on costs.

We believe that our network meta-analysis clearly shows the limitations of the current evidence about the comparative effectiveness of pharmacologic interventions for painful diabetic neuropathy. Evidence is scant, mostly indirect, and often derived from brief trials with an unclear or high risk of bias. Our network meta-analysis therefore

has implications for future research efforts and highlights the need for properly designed RCTs and more head-to-head comparisons of the most commonly used medications for painful diabetic neuropathy (that is, amitriptyline, gabapentin, pregabalin, and duloxetine).

In conclusion, several analgesics from different pharmacologic classes seem to be effective for the short-term management of painful diabetic neuropathy. The comparative effectiveness of these agents warrants limited confidence because of the few head-to-head RCTs of adequate duration and at low risk of bias.

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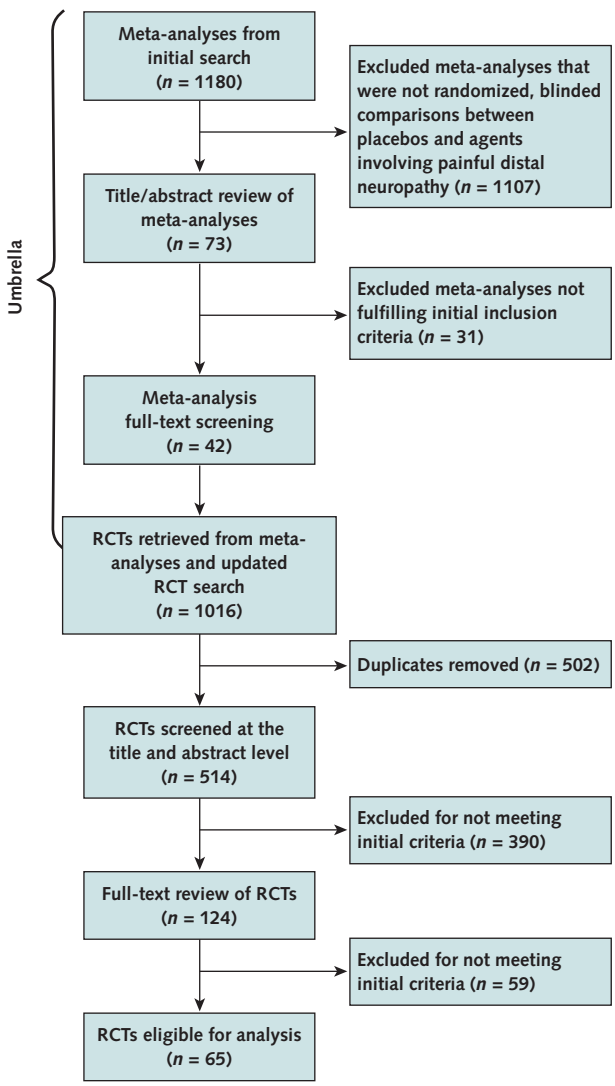
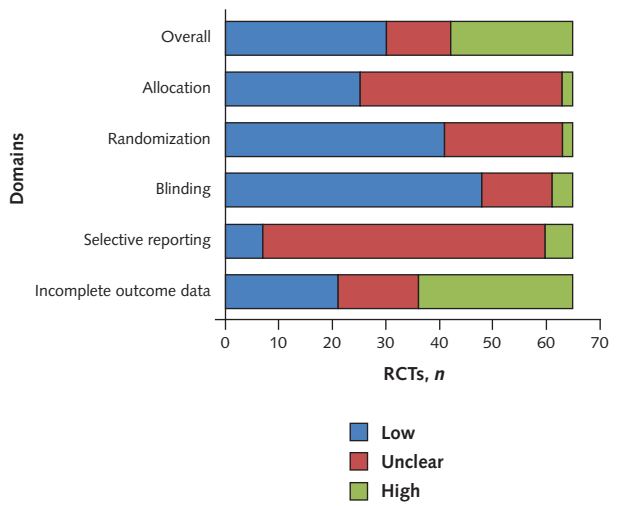
Appendix Figure 1. **Summary of evidence search and selection.**



RCT = randomized, controlled trial.

Appendix Figure 2. **Summarized risk of bias, by domains in the included RCTs.**



RCT = randomized, controlled trial.