# Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis

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See Comment page 129

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## Summary

**Background** New drug treatments, clinical trials, and standards of quality for assessment of evidence justify an update of evidence-based recommendations for the pharmacological treatment of neuropathic pain. Using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE), we revised the Special Interest Group on Neuropathic Pain (NeuPSIG) recommendations for the pharmacotherapy of neuropathic pain based on the results of a systematic review and meta-analysis.

**Methods** Between April, 2013, and January, 2014, NeuPSIG of the International Association for the Study of Pain did a systematic review and meta-analysis of randomised, double-blind studies of oral and topical pharmacotherapy for neuropathic pain, including studies published in peer-reviewed journals since January, 1966, and unpublished trials retrieved from ClinicalTrials.gov and websites of pharmaceutical companies. We used number needed to treat (NNT) for 50% pain relief as a primary measure and assessed publication bias; NNT was calculated with the fixed-effects Mantel-Haenszel method.

**Findings** 229 studies were included in the meta-analysis. Analysis of publication bias suggested a 10% overstatement of treatment effects. Studies published in peer-reviewed journals reported greater effects than did unpublished studies ($r^2$ 9·3%, p=0·009). Trial outcomes were generally modest: in particular, combined NNTs were 6·4 (95% CI 5·2–8·4) for serotonin-noradrenaline reuptake inhibitors, mainly including duloxetine (nine of 14 studies); 7·7 (6·5–9·4) for pregabalin; 7·2 (5·9–9·21) for gabapentin, including gabapentin extended release and enacarbil; and 10·6 (7·4–19·0) for capsaicin high-concentration patches. NNTs were lower for tricyclic antidepressants, strong opioids, tramadol, and botulinum toxin A, and undetermined for lidocaine patches. Based on GRADE, final quality of evidence was moderate or high for all treatments apart from lidocaine patches; tolerability and safety, and values and preferences were higher for topical drugs; and cost was lower for tricyclic antidepressants and tramadol. These findings permitted a strong recommendation for use and proposal as first-line treatment in neuropathic pain for tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitors, pregabalin, and gabapentin; a weak recommendation for use and proposal as second line for lidocaine patches, capsaicin high-concentration patches, and tramadol; and a weak recommendation for use and proposal as third line for strong opioids and botulinum toxin A. Topical agents and botulinum toxin A are recommended for peripheral neuropathic pain only.

**Interpretation** Our results support a revision of the NeuPSIG recommendations for the pharmacotherapy of neuropathic pain. Inadequate response to drug treatments constitutes a substantial unmet need in patients with neuropathic pain. Modest efficacy, large placebo responses, heterogeneous diagnostic criteria, and poor phenotypic profiling probably account for moderate trial outcomes and should be taken into account in future studies.

**Funding** NeuPSIG of the International Association for the Study of Pain.

## Introduction

Neuropathic pain, caused by a lesion or disease affecting the somatosensory nervous system,[1] has a substantial effect on quality of life and is associated with a high economic burden for the individual and society.[2–4] It is now regarded as a distinct clinical entity despite a large variety of causes.[5]

Epidemiological surveys have shown that many patients with neuropathic pain do not receive appropriate treatment.[2,6,7] The reasons might be low diagnostic accuracy and ineffective drugs, and perhaps also insufficient knowledge about effective drugs and their appropriate use in clinical practice.[8] Evidence-based recommendations for the pharmacotherapy of neuropathic pain are therefore essential.

Over the past 10 years, a few recommendations have been proposed for the pharmacotherapy of neuropathic pain[9–11] or specific neuropathic pain disorders, particularly painful diabetic neuropathies and post-herpetic neuralgia.[12–14] Meanwhile, new pharmacological therapies have been developed and high-quality clinical trials have been done. Previously undisclosed and unpublished large trials can now be identified online (ClinicalTrials.gov and pharmaceutical industry websites), which, together with an analysis of publication bias, might reduce the risk of bias in reporting data. Furthermore,

there were some discrepancies in previous recommendations due to inconsistencies in methods used to assess the quality of evidence.[13,15,16] To address these inconsistencies, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) was introduced in 2000[17,18] and received widespread international acceptance. Together, these reasons justify an update of the evidence-based recommendations for the pharmacotherapy of neuropathic pain.

We did a systematic review and meta-analysis of randomised controlled trials of all drug treatments for neuropathic pain published since 1966 and of unpublished trials with available results, and assessed publication bias. We used GRADE to rate the quality of evidence and the strength of recommendations.[17,18] On the basis of the updated review and meta-analysis, we revised the recommendations of the Special Interest Group on Neuropathic Pain (NeuPSIG) of the International Association for the Study of Pain for the systemic and topical pharmacological treatment of neuropathic pain.[19] Non-pharmacological management strategies such as neurostimulation techniques were beyond the scope of this work.[20]

## Methods

### Search strategy and selection criteria

We followed the 23-item Appraisal of Guidelines for Research and Evaluation (AGREE II) for developing and reporting recommendations.[21] For details of the working group, criteria for eligibility of studies for the analysis, search methods, reporting, and statistical analysis, see the appendix.

The systematic review of the literature complied with the PRISMA statement.[22] We used a standardised review and data extraction protocol (unpublished, appendix). The full reports of randomised, controlled, double-blind studies published in peer-reviewed journals between January, 1966, and April, 2013, were identified with searches of PubMed, Medline, the Cochrane Central Register of Controlled Trials, and Embase. Additional papers were identified from published reviews and the reference lists of selected papers. Studies reporting results were searched in all primary registries in the WHO Registry Network and in registries approved by the International Committee of Medical Journal Editors in April, 2013 (appendix). Only ClinicalTrials.gov had relevant data. An additional search up to Jan 31, 2014, retrieved papers from PubMed and the ClinicalTrials.gov website. Data from a search in May, 2009, of the Pharmaceutical Research and Manufacturers of America (PhRMA) clinical study results website were also included.[23]

The target population was patients of any age with neuropathic pain according to the International Association for the Study of Pain definition (ie, pain caused by a lesion or disease of the somatosensory nervous system):[1] post-herpetic neuralgia, diabetic and non-diabetic painful polyneuropathy, post-amputation pain, post-traumatic or post-surgical neuropathic pain including plexus avulsion and complex regional pain syndrome type 2 (which was generally subsumed into post-traumatic or post-surgical neuropathic pain), central post-stroke pain, spinal cord injury pain, and multiple-sclerosis-associated pain. Neuropathic pain pertaining to different causes was also included. Neuropathic pain associated with nociceptive components (eg, neuropathic cancer-related pain and radiculopathy) was included if the primary outcome of the study was related to neuropathic pain. Disorders such as complex regional pain syndrome type 1, low back pain without radicular pain, fibromyalgia, and atypical facial pain were not included because they do not meet the current definition of neuropathic pain.[1] Trigeminal neuralgia was assessed separately because the response to drug treatment was generally distinct from other neuropathic pain.[10,24]

The interventions were systemic or topical treatments (oral, sublingual, oropharyngeal, intranasal, topical, subcutaneous, intradermal, and smoking) with at least 3 weeks of treatment. Single-administration treatments with long-term efficacy (high-concentration capsaicin patches and botulinum toxin) were included if there was a minimum follow-up of 3 weeks. Studies in which intramuscular, intravenous, or neuroaxial routes of administration were used and those of pre-emptive analgesia were excluded (for details, see Dworkin and colleagues[20]).

We included randomised, double-blind, placebo-controlled studies with parallel group or crossover study designs that had at least ten patients per group. We separately summarised enriched-enrolment, randomised withdrawal trials. We excluded studies published only as abstracts and included double-blind, active comparator trials of drugs generally proposed as first-line or second-line treatments.[23] The study outcome (positive or negative) was based on the effect on the primary outcome measure—eg, neuropathic pain intensity. We excluded studies in which the primary outcome included a composite score of pain and paraesthesia or paraesthesia only.

Five investigators (SH, EM, KL, NBF, and NA) assessed studies for methodological quality by using the five-point Oxford Quality Scale (appendix).[25] A minimum score of 2 of 5 (randomised and double-blind study) was required for inclusion.[25] We also assessed the serious risk of bias relating to absence of allocation concealment, incomplete accounting of outcome events, selective outcome reporting, stopping early for benefit, use of invalidated outcome measures, and carryover effects in crossover trials.

### Evidence summary and reporting

The GRADE classification was used to assess recommendations based on the results from a group of randomised controlled trials of the same drug or drug class when relevant (eg, tricyclic antidepressants),[17,18] with final quality of evidence rated as strong or weak for the

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For more on the **Special Interest Group on Neuropathic Pain of the International Association for the Study of Pain** see http://www.neupsig.org

See Online for appendix

treatment, strong or weak against the treatment, or inconclusive (the last category was added because of the large number of inconsistent results in randomised controlled trials). We did not do a new health economic analysis of costs,[16] but estimated three levels of drug costs in various countries in relation to the average price of oral drugs for each country using price data for the daily dose as defined by WHO (appendix). The mean of these percentages for the countries was calculated, and the cost was rated as low if it was less than 67%, moderate if 67–300%, and high if more than 300% of the mean across all drugs. The final recommendations were agreed on by consensus of the authors.

### Statistical analysis

Number needed to treat (NNT) for 50% pain intensity reduction (or 30% pain reduction or at least moderate pain relief) was the primary effect measure, and the number needed to harm (NNH) was calculated as the number of patients who needed to be treated for one patient to drop out because of adverse effects. The 95% CIs for NNT and NNH were calculated as the reciprocal values of the 95% CIs for the absolute risk difference by use of the normal approximation. In dose-finding studies, data from subgroups treated with low doses (eg, pregabalin 150 mg) were not included in the meta-analysis. Difference in pain intensity was a secondary outcome. Serious and common (>10% incidence) adverse events were recorded on the data extraction form (appendix).

We used funnel plots,[26] Egger's regression,[27] and Duval and Tweedie's non-parametric trim-and-fill approach[28] to assess publication bias (appendix). Additionally, we estimated the susceptibility to bias for individual drug classes.[29,30] The extent to which the variability (heterogeneity) in treatment effects is explained by publication in a peer-reviewed journal was assessed with meta-regression. Heterogeneity in trials was presented as a L'Abbé plot[31] and as the $I^2$ statistic.

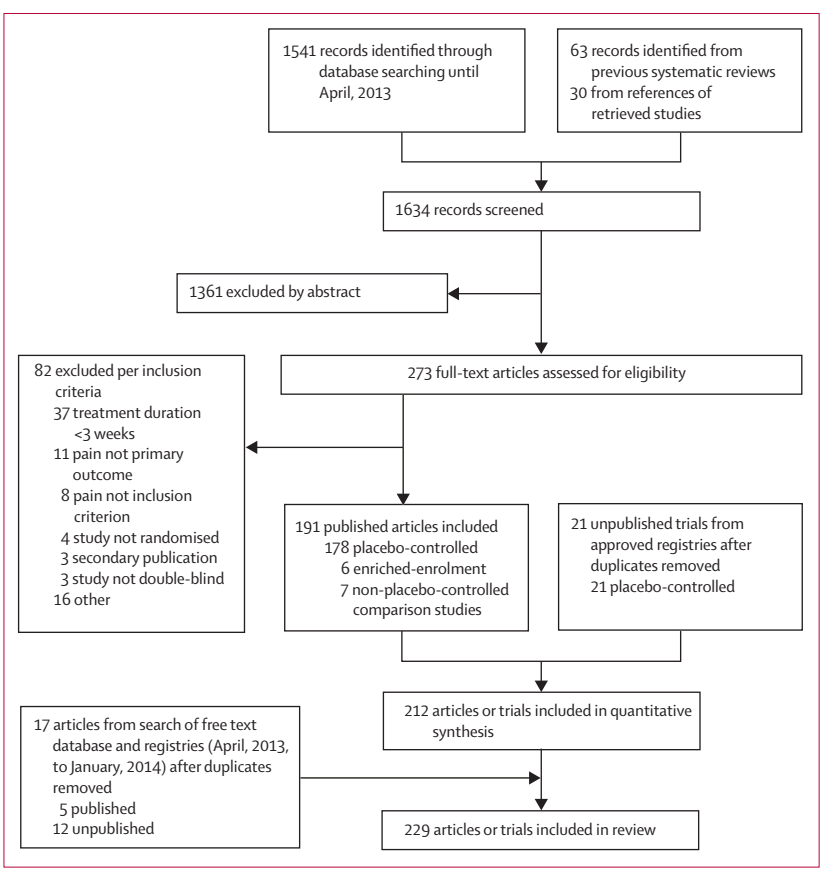


*Figure 1:* **Flow chart of study selection**

### Role of the funding source

NA, NBF, PRK, RB, ASCR, MH, SNR, and BHS are members of the NeuPSIG management committee and had a role in study design, data gathering, data analysis, data interpretation, and the writing of the report. The corresponding author and all co-authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

Figure 1 shows the results of the database and registry search. 191 published reports and 21 unpublished studies were included in the quantitative synthesis. Study characteristics are summarised in the appendix. Additionally, five published and 12 unpublished studies were retrieved between April, 2013, and January, 2014. Thus, a total of 229 reports or studies were included (see appendix for details of the references).

In studies eligible for inclusion in the meta-analysis, the following drugs were investigated: tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitor antidepressants, other antidepressants, pregabalin, gabapentin or gabapentin extended release and enacarbil, other antiepileptics, tramadol, opioids, cannabinoids, lidocaine 5% patch, capsaicin high-concentration patch and cream, botulinum toxin A, NMDA antagonists, mexiletine, miscellaneous topical treatments, newer systemic drugs, and combination therapies. 127 (55%) of 229 trials were done in patients with diabetic painful polyneuropathy or post-herpetic neuralgia. NNT and NNH could be calculated in 176 (77%) of 229 published placebo-controlled trials.

The Oxford Quality Scale (Jadad) scores for individual trials are presented in the appendix. The mean score was 4·1 (SD 0·87, range 2–5). It was lower for older studies of tricyclic antidepressants and capsaicin (3–4) and higher for more recent studies of pregabalin, gabapentin, serotonin-noradrenaline reuptake inhibitors, opioids, and capsaicin high-concentration patches (>4). Detailed descriptions of the limitations of individual studies are available from the corresponding authors on request.

Figures 2 and 3 show the NNT for individual studies for drugs with strong recommendation for use (see

appendix for other drugs) and the appendix shows the heterogeneity and the L'Abbé plot. Heterogeneity, particularly that which was not easily explained by differences in drug dose, diagnosis, and size of placebo response, was included in the GRADE recommendation.

165 published or unpublished trials with dichotomous data were analysed for publication bias. The funnel plot showed asymmetry, which was confirmed by use of Egger's regression test (figure 4A and B). The trim-and-fill method suggested 34 theoretical missing studies (figure 4C) and we adjusted our effect size from an odds ratio of 1·8 (95% CI 1·7–1·9) to 1·6 (1·5–1·7). This suggests about a 10% overstatement of treatment effects. Table 1 provides a summary of the analysis of

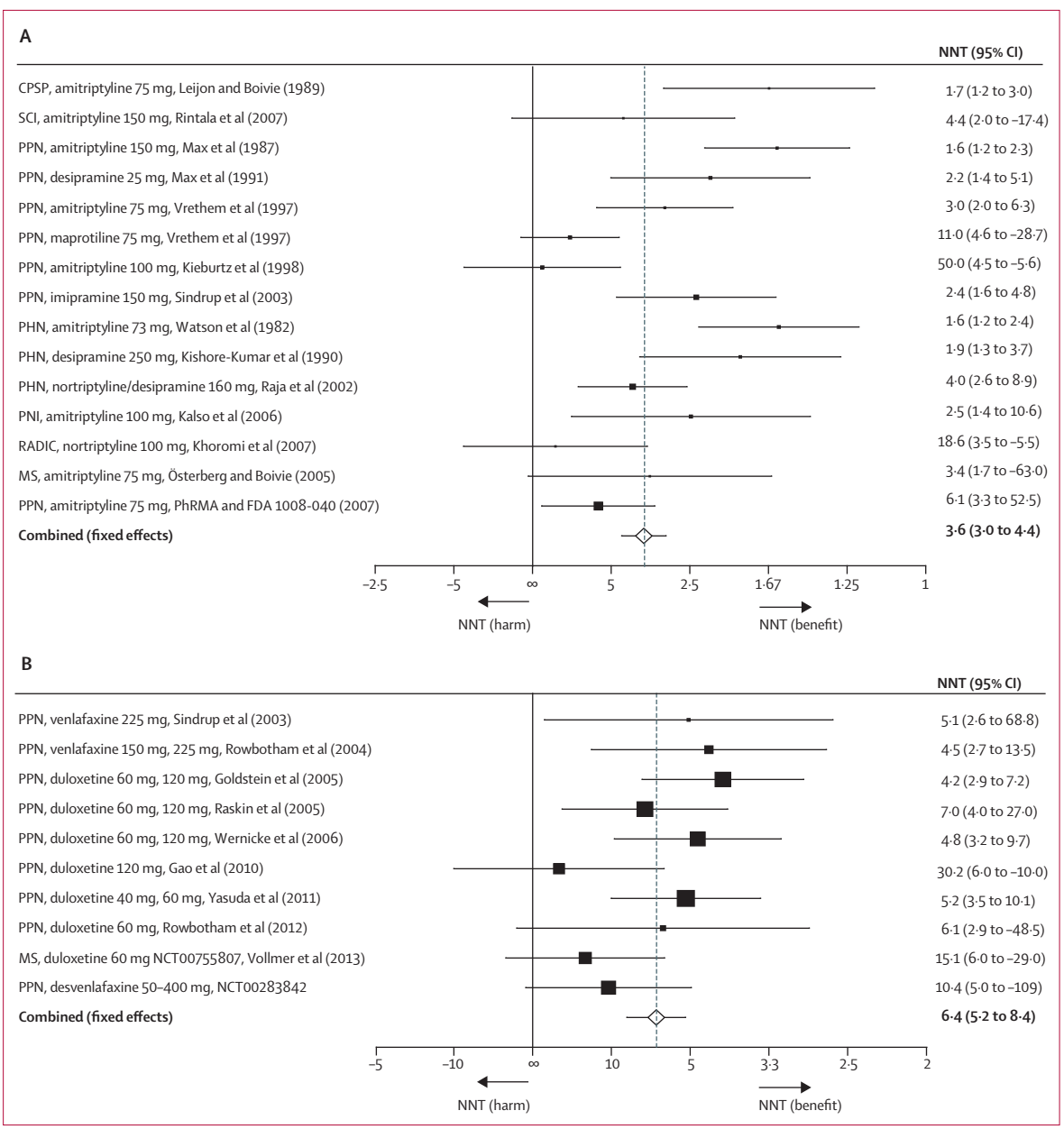


***Figure 2:*** **Forest plot of data for tricyclic antidepressants (A) and serotonin-noradrenaline reuptake inhibitors (B) included in the meta-analysis**
NNTs with 95% CI are shown for each trial and for the overall estimate (fixed effects, Mantel-Haenszel) for first-line drugs. The size of the square represents the Mantel-Haenszel weight that the study exerts in the meta-analysis. The solid line indicates the NNT of infinity, corresponding to an absolute risk difference of zero (no effect). A positive NNT indicates benefit of the drug over placebo and a negative NNT indicates that pain intensity is higher during drug treatment than during placebo treatment (harm). The dotted line represents the overall estimate. References for the studies are provided in the appendix. NNT=number needed to treat. CPSP=central post-stroke pain. SCI=spinal cord injury pain. PPN=painful polyneuropathy. FDA=US Food and Drug Administration. PHN=post-herpetic neuralgia. PNI=peripheral nerve injury. RADIC=painful radiculopathy. MS=multiple sclerosis. PhRMA= Pharmaceutical Research and Manufacturers of America.

the susceptibility to publication bias in individual drug classes. Only the estimated effect size of capsaicin 8% patches showed susceptibility to change to a clinical non-significant effect if studies with no effect were published. Using meta-regression, we identified that for studies published in peer-reviewed journals the

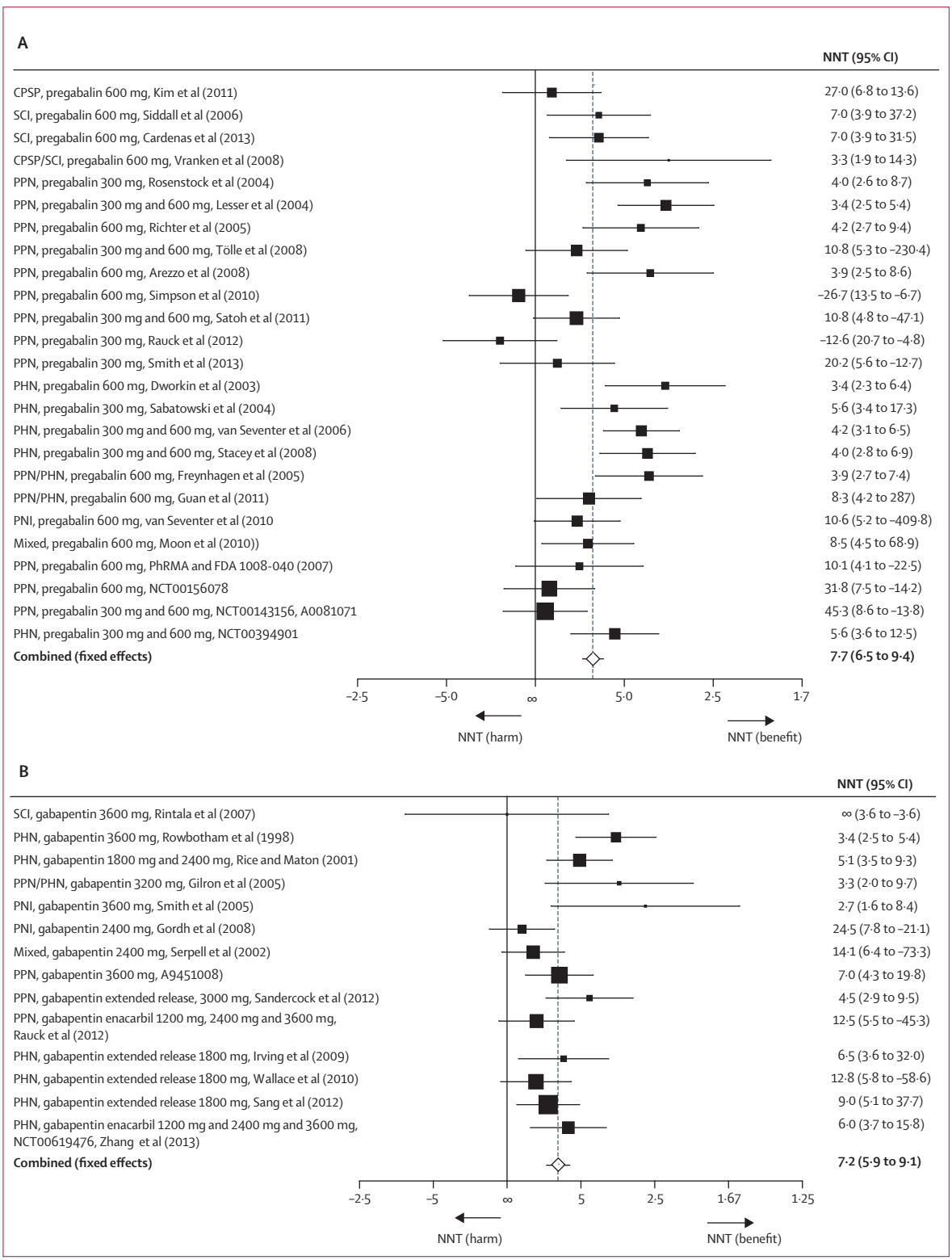


***Figure 3:*** **Forest plot of data for pregabalin (A) and gabapentin including extended release and enacarbil (B) included in the meta-analysis**

NNTs with 95% CI are shown for each trial and for the overall estimate (fixed effects, Mantel-Haenszel) for first-line drugs. The size of the square represents the Mantel-Haenszel weight that the study exerts in the meta-analysis. The solid line indicates the NNT of infinity, corresponding to an absolute risk difference of zero (no effect). A positive NNT indicates benefit of the drug over placebo and a negative NNT indicates that pain intensity is higher during drug treatment than during placebo treatment (harm). The dotted line represents the overall estimate. References for the studies are provided in the appendix. NNT=number needed to treat. CPSP=central post-stroke pain. SCI=spinal cord injury pain. PPN=painful polyneuropathy. FDA=US Food and Drug Administration. PHN=post-herpetic neuralgia. PNI=peripheral nerve injury. PhRMA= Pharmaceutical Research and Manufacturers of America.

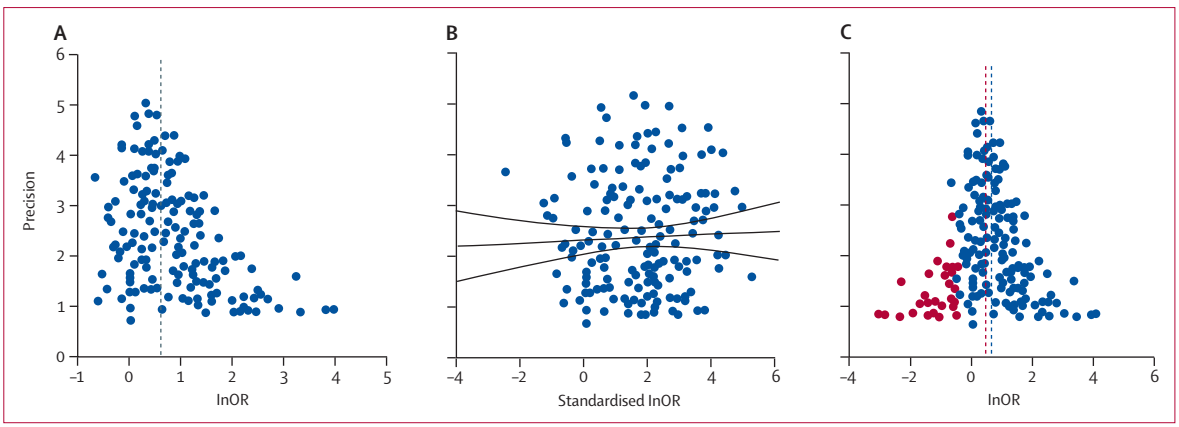


***Figure 4:*** **Evidence of publication (reporting) bias**
(A) Funnel plot showing the precision (inverse of SE) against the effect size; in the absence of bias the points should resemble a symmetrical inverted funnel. (B) Egger's regression showing the precision plotted against the standardised effect size; the 95% CIs of the regression line do not include the origin, suggesting funnel plot asymmetry. (C) Funnel plot showing the additional missing studies imputed by trim and fill in red; the red vertical line indicates the possible summary if the theoretical missing studies were to be included. InOR=natural log of the odds ratio.

reported treatment effects were greater (2·2, 1·5–3·0, n=153; adjusted $r^2$ 9·3%, p=0·009) than were those for studies identified through online repositories (1·4, 1·0–1·9, n=17).

The results of individual and combined NNT and NNH for placebo-controlled studies are presented in the appendix, along with other studies, quality of evidence, and risk differences calculated with fixed-effect and random-effects models. Generally, there was no evidence of different efficacies for most drugs in distinct neuropathic pain disorders (figures 2, 3; appendix). Few studies lasted longer than 12 weeks, with the longest lasting 24 weeks.

In 18 placebo-controlled trials (20 comparisons with placebo, of which seven comparisons had active placebos; 12 trials assessed amitriptyline [25–150 mg/day]), 16 comparisons were positive. The final quality of evidence was moderate (appendix). There was no evidence of a dose-response effect. Combined NNT for 15 studies was 3·6 (95% CI 3·0–4·4) and NNH was 13·4 (9·3–24·4).

We identified 14 studies of serotonin-noradrenaline reuptake inhibitors with available results: nine with duloxetine (20–120 mg, seven positive), four with venlafaxine (doses 150–225 mg/day, two positive, and two negative with low doses), one with desvenlafaxine (negative; appendix). The final quality of evidence was high. Combined NNT was 6·4 (5·2–8·4) and NNH was 11·8 (9·5–15·2).

18 of 25 placebo-controlled randomised trials of pregabalin (150–600 mg/day) were positive, with high final quality of evidence (appendix). There was a dose-response gradient (higher response with 600 mg daily than with 300 mg daily; data not shown). Two trials of HIV-related painful polyneuropathy with high placebo responses were negative (34% and 43% had 50% pain relief with placebo). Combined NNT was 7·7 (95% CI 6·5–9·4) and NNH was 13·9 (11·6–17·4).

| | Comparisons* | Participants† | Active pain relief | Placebo | Number needed to treat (95% CI) | Susceptibility to bias‡ |
|---|---|---|---|---|---|---|
| Tricyclic antidepressants | 15 | 948 | 217/473 | 85/475 | 3·6 (3·0–4·4) | 1973 |
| Serotonin-noradrenaline reuptake inhibitors | 10 | 2541 | 676/1559 | 278/982 | 6·4 (5·2–8·4) | 1826 |
| Pregabalin | 25 | 5940 | 1359/3530 | 578/2410 | 7·7 (6·5–9·4) | 2534 |
| Gabapentin§ | 14 | 3503 | 719/2073 | 291/1430 | 7·2 (5·9–9·1) | 1879 |
| Tramadol | 6 | 741 | 176/380 | 96/361 | 4·7 (3·6–6·7) | 982 |
| Strong opioids | 7 | 838 | 211/426 | 108/412 | 4·3 (3·4–5·8) | 1326 |
| Capsaicin 8% | 6 | 2073 | 466/1299 | 212/774 | 10·6 (7·4–18·8) | 70¶ |
| Botulinum toxin A | 4 | 137 | 42/70 | 4/67 | 1·9 (1·5–2·4) | 678 |

Data are number, unless otherwise indicated. *Number of comparisons with placebo in published trials and unpublished trials included in the meta-analysis; results from registries were included if they reported numbers of responders. †Total number of patients treated with active treatment and placebo; patients were counted twice if the study had a crossover design. ‡Number of patients needed to be treated in a new study showing no effect to make the number needed to treat (NNT) greater than 11, which is the cutoff for clinical relevance; susceptibility to publication bias implies that a new study with fewer than 400 participants with no effect might increase the NNT to greater than 11. §Including gabapentin extended release and enacarbil. ¶Susceptible to publication bias.

***Table 1:*** **Analysis of susceptibility to bias in published and unpublished trials**

We identified 14 randomised controlled trials of gabapentin (900–3600 mg/day; nine positive) and six of gabapentin extended release or gabapentin enacarbil (1200–3600 mg/day; four positive). Combined NNT was 6·3 (95% CI 5·0–8·3) for gabapentin and 8·3 (6·2–13·0) for gabapentin extended release or enacarbil. There was no evidence of a dose-response effect. Safety was good (NNH 25·6, 15·3–78·6, for gabapentin and 31·9, 17·1–230·0, for gabapentin extended release or enacarbil).

Most studies with other antiepileptic drugs were negative. Topiramate, zonisamide, and oxcarbazepine or carbamazepine had the poorest safety profiles, with a combined NNH of 6·3 (95% CI 5·1–8·0), 2·0 (1·3–4·6), and 5·5 (4·3–7·9), respectively.

Tramadol is a weak opioid agonist and a serotonin-noradrenaline reuptake inhibitor. All seven studies of tramadol (mainly tramadol extended release up to 400 mg/day) were positive, with moderate final quality of evidence (appendix). Combined NNT was 4·7 (95% CI 3·6–6·7), with the highest NNT (6·4) in the largest study (appendix). Combined NNH was 12·6 (8·4–25·3).

Tapentadol is a μ opioid agonist with noradrenaline reuptake inhibition. We identified one negative study and one positive enrichment study of tapentadol extended release; the study of the extended release formulation had potential bias (probable unmasking of the patients enrolled in the double-blind period) and high NNT (10·2, 95% CI 5·3–185·5) in 67% of the patients responding to the open phase.

We identified 13 trials of strong opioids, in which oxycodone (10–120 mg/day) and morphine (90–240 mg/day) were used mainly in peripheral neuropathic pain. The final quality of evidence was moderate. Ten trials were positive: combined NNT was 4·3 (95% CI 3·4–5·8) and NNH was 11·7 (8·4–19·3). Maximum effectiveness seemed to be associated with 180 mg morphine or equivalent (no additional benefit for higher doses; appendix).

Nabiximols (Sativex) is an oromucosally delivered spray prepared from extracts of the plant cannabis sativa with several active constituents (mainly standardised 27 mg/mL Δ-9-tetrahydrocannabinol and 25 mg/mL cannabidiol). We identified nine trials of nabiximols in neuropathic pain, of which only two were positive. One of these two studies of pain associated with multiple sclerosis was positive, whereas the other larger study had a negative primary outcome.

Based on our inclusion criteria (trials of at least 3 weeks), we identified only one small negative study of 5% lidocaine patches in post-surgical neuropathic pain and two enriched-enrolment studies in post-herpetic neuralgia. The smaller study was positive; the larger study was negative in the intention-to-treat population, but positive in the per-protocol population. However, studies of shorter duration were positive, and safety and tolerability were good in all cases.[23]

The results of five of seven studies (in patients with post-herpetic neuralgia or HIV-related painful polyneuropathy) showed sustained efficacy of a single application of high-concentration capsaicin patch (8%, better results for 60 min application in post-herpetic neuralgia and 30 min in HIV neuropathy) compared with a low-concentration patch (0·04%, to minimise the risk of unmasking related to the burning sensation of capsaicin).

| | Total daily dose and dose regimen | Recommendations |
|---|---|---|
| **Strong recommendations for use** | | |
| Gapabentin | 1200–3600 mg, in three divided doses | First line |
| Gabapentin extended release or enacarbil | 1200–3600 mg, in two divided doses | First line |
| Pregabalin | 300–600 mg, in two divided doses | First line |
| Serotonin-noradrenaline reuptake inhibitors duloxetine or venlafaxine* | 60–120 mg, once a day (duloxetine); 150–225 mg, once a day (venlafaxine extended release) | First line |
| Tricyclic antidepressants | 25–150 mg, once a day or in two divided doses | First line† |
| **Weak recommendations for use** | | |
| Capsaicin 8% patches | One to four patches to the painful area for 30-60 min every 3 months | Second line ( peripheral neuropathic pain)‡ |
| Lidocaine patches | One to three patches to the region of pain once a day for up to 12 h | Second line ( peripheral neuropathic pain) |
| Tramadol | 200–400 mg, in two (tramadol extended release) or three divided doses | Second line |
| Botulinum toxin A (subcutaneously) | 50–200 units to the painful area every 3 months | Third line; specialist use (peripheral neuropathic pain) |
| Strong opioids | Individual titration | Third line§ |

GRADE=Grading of Recommendations Assessment, Development, and Evaluation (see appendix for details about the GRADE classification). *Duloxetine is the most studied, and therefore recommended, of the serotonin-noradrenaline reuptake inhibitors. †Tricyclic antidepressants generally have similar efficacy (appendix); tertiary amine tricyclic antidepressants (amitriptyline, imipramine, and clomipramine) are not recommended at doses greater than 75 mg/day in adults aged 65 years and older because of major anticholinergic and sedative side-effects and potential risk of falls;[33] an increased risk of sudden cardiac death has been reported with tricyclic antidepressants at doses greater than 100 mg daily.[34] ‡The long-term safety of repeated applications of high-concentration capsaicin patches in patients has not been clearly established, particularly with respect to degeneration of epidermal nerve fibres, which might be a cause for concern in progressive neuropathy. §Sustained release oxycodone and morphine have been the most studied opioids (maximum doses of 120 mg/day and 240 mg/day, respectively, in clinical trials; appendix); long-term opioid use might be associated with abuse, particularly at high doses, cognitive impairment, and endocrine and immunological changes.[35-37]

***Table 2:*** **Drugs or drug classes with strong or weak recommendations for use based on the GRADE classification**

***Panel:*** **Drugs or drug classes with inconclusive recommendations for use or recommendations against use based on the GRADE classification**

**Inconclusive recommendations**

- Combination therapy
- Capsaicin cream
- Carbamazepine
- Clonidine topical
- Lacosamide
- Lamotrigine
- NMDA antagonists
- Oxcarbazepine
- SSRI antidepressants
- Tapentadol
- Topiramate
- Zonisamide

**Weak recommendations against use**

- Cannabinoids
- Valproate

**Strong recommendations against use**

- Levetiracetam
- Mexiletine

GRADE=Grading of Recommendations Assessment, Development, and Evaluation (see appendix for details about the GRADE classification).

The final quality of evidence was high. Combined NNT was 10·6 (95% CI 7·4–18·8). Results for the secondary outcomes were inconsistent (data not shown).

Six randomised controlled trials to assess the efficacy of a single administration of botulinum toxin A (50–200 units, subcutaneously, in the region of pain) in peripheral neuropathic pain were identified. The smaller studies had a positive primary outcome (NNT 1·9, 95% CI 1·5–2·4, for four studies) with a low placebo effect, but one large, unpublished study was negative. Safety was generally good (appendix).

Results for other drugs (selective serotonin reuptake inhibitor antidepressants, capsaicin cream, NMDA antagonists, Δ-9-tetrahydrocannabinol, mexiletine, and newer topical or oral drugs) are reported in the appendix. There were no randomised controlled trials with conventional non-opioid analgesics (non-steroidal anti-inflammatory drugs or acetaminophen).

Of seven randomised controlled trials of various combination therapies in neuropathic pain (appendix), the results of two showed that gabapentin combined with morphine or nortriptyline was superior to drugs given as monotherapies (and placebo in one study) at reduced doses, with no more side-effects. However, the results of the largest study (not placebo controlled) showed no difference in efficacy or side-effects between pregabalin combined with duloxetine at moderate doses (300 mg/day and 60 mg/day, respectively) and pregabalin and duloxetine monotherapies at high doses (600 mg/day and 120 mg/day, respectively) in patients unresponsive to monotherapy at moderate doses.

We identified seven comparative randomised controlled trials without placebo (appendix). Neither individual studies nor their statistical combination showed significant differences in efficacy or safety between drugs. Despite small sample sizes and unknown assay sensitivity because of the absence of a placebo, results suggested similar efficacy for first-line and most second-line recommended treatments.

There was generally no evidence of efficacy for particular drugs in specific disorders. Therefore, these recommendations apply to neuropathic pain in general. However, they might not be applicable to trigeminal neuralgia, for which we could extract only one study complying with our inclusion criteria. We therefore recommend referring to previous specific guidelines for this disorder.[10,24] Few studies included cancer-related neuropathic pain; the recommendations for the use of opioids might be different in certain cancer populations. Similarly, these recommendations do not apply to acute pain or acute pain exacerbation. Treatment of neuropathic pain in children is neglected.[32] None of the studies assessed paediatric neuropathic pain and therefore the current guidelines only apply to adults.

Details of the GRADE recommendations and practical use are provided in table 2, the panel, table 3, and the appendix. A few relevant trials have been reported since our meta-analysis, but none affected the recommendations (appendix). Based mainly on moderate or high quality of evidence and efficacy in most trials, tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitor antidepressants (particularly duloxetine), pregabalin, gabapentin, gabapentin extended release and enacarbil have strong GRADE recommendations for use in neuropathic pain and are proposed as first-line treatments, with caution recommended for several tricyclic antidepressants at high doses (table 2). Tramadol, lidocaine patches, and high-concentration capsaicin patches have weak GRADE recommendations for use and are proposed as generally second line because of lower tolerability or safety (tramadol), and low effect sizes but high values or preferences and tolerability or safety (topical agents). Topical treatments are recommended for peripheral neuropathic pain with presumed local pain

| | First-line drugs | | | Second-line drugs | | | Third-line drugs | |
|---|---|---|---|---|---|---|---|---|
| | Serotonin-noradrenaline reuptake inhibitors duloxetine and venlafaxine | Tricyclic antidepressants | Pregabalin, gabapentin, gabapentin extended release or enacarbil | Tramadol | Capsaicin 8% patches | Lidocaine patches | Strong opioids | Botulinum toxin A |
| Quality of evidence | High | Moderate | High | Moderate | High | Low | Moderate | Moderate |
| Balance between desirable and undesirable effects | | | | | | | | |
| Effect size | Moderate | Moderate | Moderate | Moderate | Low | Unknown | Moderate | Moderate |
| Tolerability and safety* | Moderate | Low-moderate | Moderate-high | Low-moderate | Moderate-high | High | Low-moderate | High |
| Values and preferences | Low-moderate | Low-moderate | Low-moderate | Low-moderate | High | High | Low-moderate | High |
| Cost and resource allocation | Low-moderate | Low | Low-moderate | Low | Moderate-high | Moderate-high | Low-moderate | Moderate-high |
| Strength of recommendation | Strong | Strong | Strong | Weak | Weak | Weak | Weak | Weak |
| Neuropathic pain conditions | All | All | All | All | Peripheral | Peripheral | All | Peripheral |

GRADE=Grading of Recommendations Assessment, Development, and Evaluation (see appendix for details about the GRADE classification). *Common side-effects: antidepressants: somnolence, constipation, dry mouth (particularly with tricyclic antidepressants), and nausea (particularly duloxetine); pregabalin or gabapentin: somnolence, dizziness, and weight gain; opioids (including tramadol): constipation, nausea, vomiting, tiredness, somnolence, dizziness, dry mouth, and itch; lidocaine patches: local irritation; capsaicin patches: local pain, oedema, and erythema; botulinum toxin A: local pain; see the appendix for further information about safety issues.

***Table 3:*** **Summary of GRADE recommendations**

generator, such as post-herpetic neuralgia, post-traumatic painful neuropathies, and painful polyneuropathies. In some circumstances—eg, when there are concerns because of side-effects or safety of first-line treatments, particularly in frail and elderly patients—lidocaine patches might be a first-line option.

Strong opioids (particularly oxycodone and morphine) and botulinum toxin A (specialist use for peripheral neuropathic pain with presumed local pain generator) have weak GRADE recommendations for use and are recommended as third line mainly because of safety concerns (opioids) or weak quality of evidence (botulinum toxin A). Prescription of strong opioids should be strictly monitored, particularly for patients requiring high doses (including tracking the dose in morphine equivalence, use of risk assessment methods and treatment agreements).[38,39]

The GRADE recommendations for tapentadol, other antiepileptics, capsaicin cream, topical clonidine, selective serotonin reuptake inhibitor antidepressants, NMDA antagonists, and combination therapy[40–42] are inconclusive mainly because of discrepant findings. However, the combination of pregabalin or gabapentin and duloxetine or tricyclic antidepressants might be an alternative option to increasing doses of monotherapy for patients unresponsive to moderate doses of monotherapy (see appendix for details).

Cannabinoids and valproate have weak recommendations against their use in neuropathic pain and levetiracetam and mexiletine have strong recommendations against their use because of generally negative trials or safety concerns, or both (see appendix for details).

| | NeuPSIG recommendation for future trials in neuropathic pain |
|---|---|
| **Patient population (appendix)** | |
| All randomised controlled trials were in adults | Do more studies in the paediatric population |
| Absence of validated diagnostic criteria and algorithms for neuropathic pain | Use NeuPSIG diagnostic criteria for probable or definite neuropathic pain and validated screening tools to confirm diagnosis* |
| Classification of patients is generally based on the cause of the pain | Classification should be based on sensory phenotypes rather than merely on the cause of the pain† |
| **Characteristics of the trials (appendix)** | |
| Trial duration is 12 weeks or less in 81% of the trials | Consider longer trial duration |
| High placebo response, particularly in recent trials | Exclude patients with low pain intensity and high variability of pain at baseline[44] |

NeuPSIG=Special Interest Group on Neuropathic Pain. *Criteria for neuropathic pain diagnosis were not available before the development of the screening methods and of diagnostic algorithms for neuropathic pain (2008);[49,50] less than 10% of clinical trials conducted over the past decade have used screening methods or diagnostic algorithms for neuropathic pain (detailed descriptions of the individual studies are available on request). †Results of recent clinical trials[51,52] and post-hoc analyses of recent clinical trials[53] that could not be included in the present meta-analysis lend support to this recommendation; the results of some trials suggested that drugs such as oxcarbazepine or topical clonidine might be significantly more effective in subgroups of patients with preserved nociceptive function compared with those without this phenotype,[54,49] but these individual trials need to be replicated and do not change the current level of recommendation for these drug treatments.

***Table 4:*** **Limitations of clinical trials in neuropathic pain included in the present systematic review and meta-analysis, and NeuPSIG recommendations for implementation of future clinical trials in neuropathic pain**

## Discussion

In accordance with previous reports,[23] results of our meta-analysis show that the efficacy of systemic drug treatments is generally not dependent on the cause of the underlying disorder (appendix). Side-effects might, however, to some degree depend on the cause—eg, drugs with CNS-related side-effects might be tolerated less well in patients with CNS lesions.[43] Pain due to HIV-related painful polyneuropathy and radiculopathy seems more refractory than other types of pain in our meta-analysis. This difference might be due to large placebo responses in HIV-related neuropathy trials,[44] a distinct clinical phenotype in subgroups of patients with radiculopathy,[45] or psychological or psychosocial comorbidities, often neglected in large trials. Topical agents have no known relevance for use in central pain, and this is clearly stated in our recommendations.

The strengths of this systematic review and meta-analysis include the analysis of publication bias[29] and unpublished trials. Publication bias can occur if studies with positive results are published whereas those with no data or negative results are not.[29] It might lead to a major overestimation of efficacy in therapeutic studies.[46] Our results show that the effect sizes estimated from studies published in peer-reviewed journals were higher than those estimated from studies available in open databases. This finding emphasises the need to search these databases in systematic reviews. Analysis of further publication bias (eg, studies that are unpublished or show no results in open trial registries) suggested a small overstatement of overall efficacy of drug treatments (by about 10%), although available methods to assess publication bias have limitations.[47] Here, we found that high-concentration capsaicin patches were the most susceptible to publication bias—ie, a new study with fewer than 400 participants with no effect can increase the NNT to an unacceptable level. This finding lends support to the robustness of a meta-analysis that includes unpublished trials and suggests that effect sizes were overestimated in previous meta-analyses of pharmacotherapy for neuropathic pain.

Results of quantitative data for individual drugs, showing NNT for 50% pain relief ranging from about 4 to 10 for most positive trials, emphasise the modest overall study outcomes in neuropathic pain. Inadequate response to drug therapy constitutes a substantial unmet need in patients with neuropathic pain and might have important consequences in terms of psychological or social adjustment.[48] However, our results might also indicate insufficient assay sensitivity in clinical trials of neuropathic pain (table 4).[55] One major issue is the placebo response, which seems to have increased in recent trials of neuropathic pain and can lead to an underestimation of drug effects.[56] Placebo response was higher in HIV-related neuropathies,[44] and in patients with low or variable pain scores at inclusion.[54] Conversely, it seems to be lower in post-herpetic neuralgia.[44] Another issue is the

heterogeneous diagnostic criteria for neuropathic pain in several trials (detailed descriptions of the individual studies are available on request). The use of diagnostic algorithms[49] and screening methods[50] should contribute to a reduction in diagnostic heterogeneity (table 4). Additionally, a largely debated issue is the heterogeneity of patients' phenotypes in clinical trials, which might indicate various underlying mechanisms.[57–59] The results of some recent trials or post-hoc analyses of recent trials suggest that some drugs might be differentially effective in patients classified according to their sensory phenotypes.[51–53]

Like previous NeuPSIG recommendations,[19] the current recommendations are determined by drug treatments rather than by the cause of pain. Our updated therapeutic algorithm for neuropathic pain based on GRADE differs in several ways from previous therapeutic recommendations. The previous recommendations generally proposed tricyclic antidepressants, pregabalin, gabapentin, and lidocaine patches as first line for neuropathic pain.[9–13,15–16,19,60] We now also recommend gabapentin extended release or enacarbil, and duloxetine as first line based on strong GRADE recommendations for use. We no longer propose lidocaine patches as first line because of weak quality of evidence. However, because of the excellent safety profile, high values and preferences, and initial positive short-term studies, we propose lidocaine as a second-line treatment for peripheral neuropathic pain. Strong opioids are now recommended as third line, contrasting with several previous recommendations in which they were generally thought of as first or second line.[19,60] This stems mainly from the consideration of potential risk of abuse, particularly with high doses,[35] and concerns about a recent increase in prescription-opioid-associated overdose mortality, diversion, misuse, and other opioid-related morbidity particularly in the USA, Canada, and the UK.[61–63] High-concentration capsaicin patches and cannabinoids are considered for the first time in therapeutic recommendations for neuropathic pain. Capsaicin patches are proposed as second line for peripheral neuropathic pain because of high quality of evidence, but small effect size, training requirement, and potential safety concerns on sensation with long-term use.[64] We provide a weak recommendation against the use of cannabinoids in neuropathic pain, mainly because of negative results, potential misuse, diversion, and long-term mental health risks of cannabis particularly in susceptible individuals.[65–70]

One important issue when proposing recommendations is the extent to which they are applied by practitioners and the question of whether the use of recommendations can contribute to improvements in practice. Few studies have investigated the real-life effect of evidence-based recommendations on physicians' practices. It has recently been reported that the drug treatment of post-herpetic neuralgia by primary care physicians was roughly consistent with the US recommendations issued some years before.[6] By contrast, a recent large study of general practitioners' adherence to current French recommendations noted a paucity of appropriate recall of first-line drugs.[8] It will be important to facilitate the dissemination of the present recommendations and subsequently to assess their real-life implementation in various countries.[7]

#### Contributors

NA, NBF, PRK, RB, ASCR, MH, SNR, and BHS are members of the NeuPSIG management committee. NA, NBF, SH, KL, and EM did the search and extracted data. NBF performed the meta-analysis. ES did the analysis of publication bias. NA and NBF drafted the report and the tables. PH, MR, PS, and MW were external advisers who reviewed the NeuPSIG recommendations before publication. All authors contributed to the guidelines in formulating the recommendations, and revising and editing the final text. All authors contributed to the final version of the report.

#### Declaration of interests

NA has served on advisory boards or speakers panels for Astellas Pharma, Adir Servier, Eli Lilly, Grünenthal, Johnson & Johnson, Sanofi Pasteur Merieux, and Pfizer, and has been an investigator in studies sponsored by Astellas, Grünenthal, and AstraZeneca. RB has received grant or research support from Pfizer, Genzyme, Grünenthal, German Federal Ministry of Education and Research, German Research Network on Neuropathic Pain, NoPain System Biology, and German Research Foundation; he has received speaker's honoraria from Pfizer, Genzyme, Grünenthal, Mundipharma, Sanofi Pasteur, Medtronic, Eisai, Eli Lilly, Boehringer Ingelheim, Astellas, Desitin, Teva Pharma, Bayer-Schering, and Merck Sharp & Dohme, and has served as a consultant for Pfizer, Genzyme, Grünenthal, Mundipharma, Allergan, Sanofi Pasteur, Medtronic, Eisai, Eli Lilly, Boehringer Ingelheim, Astellas, Novartis, Bristol-Myers Squibb, Biogenidec, AstraZeneca, Merck, and Abbvie. RHD has received research grants from the US Food and Drug Administration and US National Institutes of Health, and compensation for activities involving clinical trial research methods from Acorda, Adynxx, Allergan, Analgesic Solutions, Anika, Astellas, AstraZeneca, Avanir, Axsome, Bayer, Biogen, Bioness, Bristol-Myers Squibb, Cardiome, Centrexion, Charleston, Chromocell, Collegium, Concert, Daiichi Sankyo, Depomed, Depuy, Eli Lilly, Epicept, Flexion, Genzyme, Glenmark, Inhibitex, Johnson & Johnson, Lpath, Medicinova, Merck, Metys, MMS Holdings, Nektar, Neura, NeurogesX, Olatec, Ono, Periphagen, Pfizer, Phillips, Phosphagenics, Prolong, Q-Med, QRxPharma, Regenesis, Relmada, Sanofi-Aventis, Salix, Smith & Nephew, Sorrento, Spinifex, Takeda, Taris, Teva, Theravance, and Xenon. NBF has received speaker's honoraria from Pfizer, Grünenthal, and Norpharma, a research grant from Grünenthal, and consultancy fees from Astellas. MH has received honoraria from Eli Lilly, Janssen-Cilag, Merck Sharp & Dohme, Mundipharma, Orion, and Sanofi-Aventis for lectures, honoraria from Pfizer, Allergan, and Astellas for lectures and consulting, and honoraria from Abbvie for consulting. TSJ has received grants or honoraria, as a speaker and advisory board participant, from Pfizer, Grünenthal, Astellas, Orion, and Sanofi Pasteur. PRK has served on an advisory board for Reckitt Benckizer and has received speaker's honoraria from Pfizer. KL has received travel grants from Pfizer and Astellas. EM received grants from the Richard Saltonstall Charitable Foundation, USA, during the study. AM has received speaker's honoraria from Pfizer, speaker's honoraria and consultancy fees from Eli Lilly and Grünenthal, and a research grant from Grünenthal. SNR has served on advisory boards of Purdue Pharma, QRxPharma, Salix Pharmaceuticals, and Shionogi. ASCR has share options in Spinifex Pharmaceuticals; he undertakes consulting for Imperial College Consultants, and has received fees from Spinifex Pharmaceuticals, Astellas, Servier, Allergan, Asahi Kasei, and Medivir. Through Europain, ASCR's laboratory has received funding for research studentships from Pfizer and Astellas; other recent or current grant or studentship funding for ASCR's laboratory is from the Wellcome Trust (London Pain Consortium), Dunhill Medical Trust, National Centre for the Replacement Refinement & Reduction of Animals in Research, Westminster Medical School Research Trust, International Association for the Study of Pain, National Institute of Academic Anaesthesia, Derek Butler Trust, Medical Research Council Industrial, Biotechnology and Biological Sciences Research Council, and Pfizer-Christian-Albrechts

University of Kiel (Neuropain). ASCR is a member of the England and Wales Joint Committee on Vaccination and Immunisation (varicella subgroup). MR reports personal fees, stock options, or stock ownership from Afferent Pharmaceuticals, Centrexion, Xenoport, Nektar Therapeutics, ViroBay, Chromocell, Adynxx, Lilly, Zalicus, and Biogen IDEC outside the submitted work. PS has a patent for a system and method for detecting pain and its components using magnetic resonance spectroscopy (US patent 08755862). BHS has consulted for Pfizer and Napp, and received unconditional educational grants from Pfizer to support epidemiological research. MW reports personal fees from Boston Scientific, Jazz Pharmaceutical, Spinal Modulations, Depomed, and Inergetics. RB, NBF, KL, TSJ, and ASCR are members of the Innovative Medicines Initiative Europain collaboration, the industry members of which are AstraZeneca, Pfizer, Esteve, UCB-Pharma, Sanofi-Aventis, Grünenthal, Eli Lilly, Boehringer Ingelheim, Astellas, Abbott, and Lundbeck. The other authors declare no competing interests. No author was paid to write this report by a pharmaceutical company or other agency.

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# Informed drug choices for neuropathic pain

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See Articles page 162

Neuropathic pain affects 7–8% of people and will become increasingly common because of the ageing population, increasing incidence of diabetes, and improved survival from cancer. Unfortunately, neuropathic pain is undertreated and has a large detrimental effect on quality of life, partly because of low treatment efficacy, but also because of ignorance about how best to use available drugs.[1–3] This issue can hopefully be addressed with accessible evidence-based guidelines. The past decade has not seen any transformational change in management of neuropathic pain, although new treatments have been introduced, existing treatments have been delivered in new ways (eg, topical lidocaine plasters), and studies have tested the efficacy of combined versus single drug treatments. The report[4] in *The Lancet Neurology* by Nanna B Finnerup and colleagues (on behalf of the Neuropathic Pain Special Interest Group [NeuPSIG]) provides a timely reappraisal of the evidence base for the pharmacological management of neuropathic pain and generates some pragmatic recommendations.

The meta-analysis[4] includes randomised, double-blind, placebo-controlled studies of oral or topical analgesic therapy in disorders conforming to the present International Association for the Study of Pain definition of neuropathic pain.[5] Strengths of the methods used include estimation of publication bias and the assessment of trial data that are available online but not in peer-reviewed journals (constituting almost 10% of included studies). Perhaps unsurprisingly, studies in peer-reviewed journals showed a greater treatment effect than did unpublished studies available online. Finnerup and colleagues estimated that publication bias leads to a 10% overstatement of treatment effect (which, with the possible exception of the 8% capsaicin patch, was not predicted to be clinically significant).

Some general conclusions can be drawn: the number needed to treat to achieve 50% pain relief was high (between 4 and 10 in positive trials) and most drugs showed efficacy across a range of neuropathic pain disorders rather than for specific causes. Although combined drug therapy is intellectually appealing as a means to enhance efficacy and reduce side-effects,[6] most studies on this topic have been of relatively small size and one large study did not find a significant difference in efficacy comparing high-dose monotherapy (pregabalin or duloxetine) with combined therapy for painful diabetic neuropathy.[7] Because so many patients in clinical practice are on more than one analgesic, more studies are needed in this area. Overall, present options are far from ideal and new and more efficacious treatments than exist at present are needed for neuropathic pain.

The recommendations confirm expectations in relation to first-line treatments, including tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitors, gabapentin, gabapentin enacarbil, and pregabalin. The use of topical agents is an emerging theme in neuropathic pain of peripheral origin because they are well tolerated and both lidocaine and high-dose capsaicin patches are recommended as second-line agents along with tramadol. Botulinum toxin A and strong opiates have a weaker recommendation and are considered third-line treatment options. Such recommendations are helpful in prioritisation of treatment choice and I predict that use of strong opiates in neuropathic pain will decline because, although some efficacy is noted, a growing concern exists over the potential for misuse.

The analysis emphasises some of the challenges facing drug trials in the field of neuropathic pain, including the strong placebo response in pain studies. Several mechanisms are likely to contribute to the generation and maintenance of neuropathic pain—for example, ectopic activity in injured primary afferents, amplification of nociceptive processing within the spinal cord, microglial activation, and aberrant function of endogenous pain modulatory systems.[8] A key question for the pain field therefore is whether the predominant pathophysiological driver of neuropathic pain can be identified in an individual to allow treatment to be targeted appropriately. This task is challenging. Pathophysiological processes can coexist, their relative importance can change over time, and key outcome measures are needed (eg, assessment of the microglial response in human spinal cord is currently not possible). As a surrogate measure, patients with neuropathic pain can be grouped according to somatosensory phenotype defined by symptoms and sensory testing.[9] Such groupings will partly relate to

underlying pathophysiological mechanisms and the fact that these groups can be noted across different aetiologies of neuropathic pain points to common mechanisms whatever the original cause.

Therefore, a strong argument suggests that in future trials patients should be stratified by sensory phenotype so that such groupings can be related to treatment response. Demant and colleagues[10] used such an approach and showed that oxcarbazepine had greater efficacy in those patients with evidence of gain of sensory function termed the irritable nociceptor than did those patients with predominant loss of sensory function. Although personalised therapy for neuropathic pain is still an aspiration rather than reality, these new NeuPSIG guidelines will help to inform treatment choices, including within the primary care setting, where most patients with neuropathic pain are seen.

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# Friedreich's ataxia: the European consortium

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See Articles page 174

Often, the development of therapeutic approaches for rare disease lags behind that of other disorders not because of poor understanding of the basic pathophysiology, but because of a paucity of systematic clinical information. The ideal way to address this scarcity of clinical knowledge and to facilitate therapeutic advancement is through controlled assessment of large numbers of patients in natural history studies across several institutions. In *The Lancet Neurology*, Kathrin Reetz and collegues[1] report a cross-sectional analysis of baseline data for European patients with Friedreich's ataxia. Termed the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS) cohort, this initiative could provide a template for clinical research in rare diseases in the upcoming years.

The investigators have created a collaboration of 11 institutions across seven countries. In this report they present the primary characterisation of the neurological features of 592 patients with Friedreich's ataxia enrolled between Sept 15, 2010, and Apr 30, 2013, as assessed by examination-based scales (Scale for the Assessment and Rating of Ataxia; SARA), performance measures and composites, compilations of non-ataxic features, and quality-of-life measures. Using cross-sectional analysis, they produce estimates of progression for each of these measures, which, as expected, are most sensitive for the objective tests, particularly SARA. Interestingly, patients with early-onset disease progressed fastest, followed by those with intermediate-onset disease, with patients who had late–onset disease progressing more slowly. Such data agree very well with findings from other large cohorts of patients with Friedreich's ataxia, such as the American, Canadian, and Australian FACOMS cohort of more than 750 patients.[2–6] All of these studies represent