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

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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pharmacotherapy for neuropathic pain, including studies published in peer-reviewed journals since January, 1966, and unpublished trials retrieved from ClinicalTrials.gov and websites of pharmaceutical companies.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 Studies published in peer-reviewed journals reported greater effects than did unpublished studies (r^2 9·3%, p=0·009).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.

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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
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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.

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
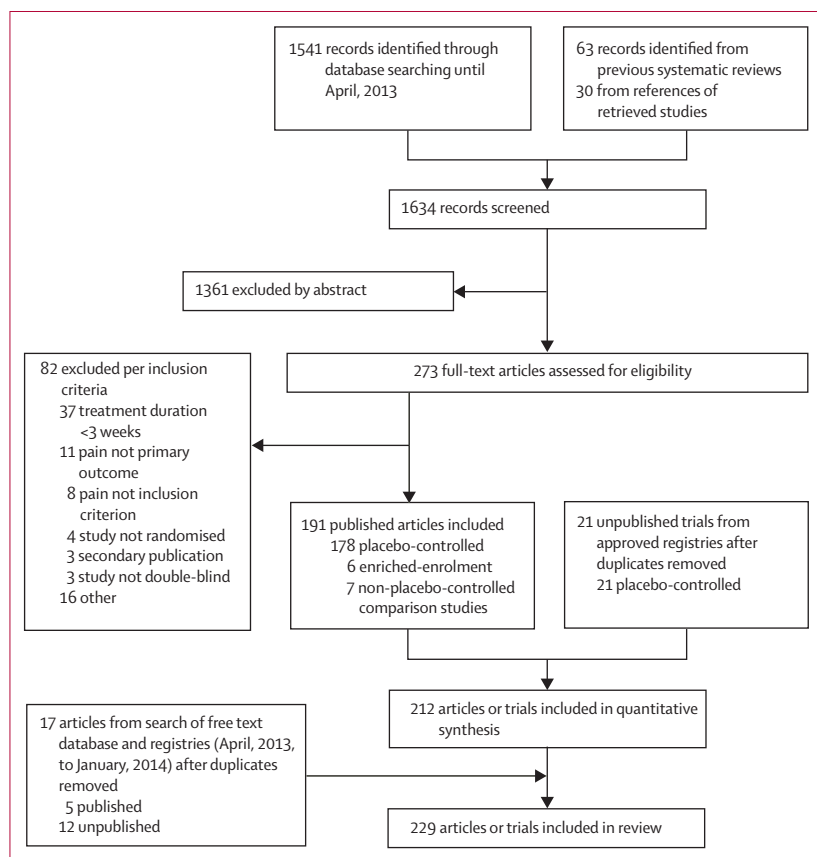

Figure 1: Flow chart of study selection

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
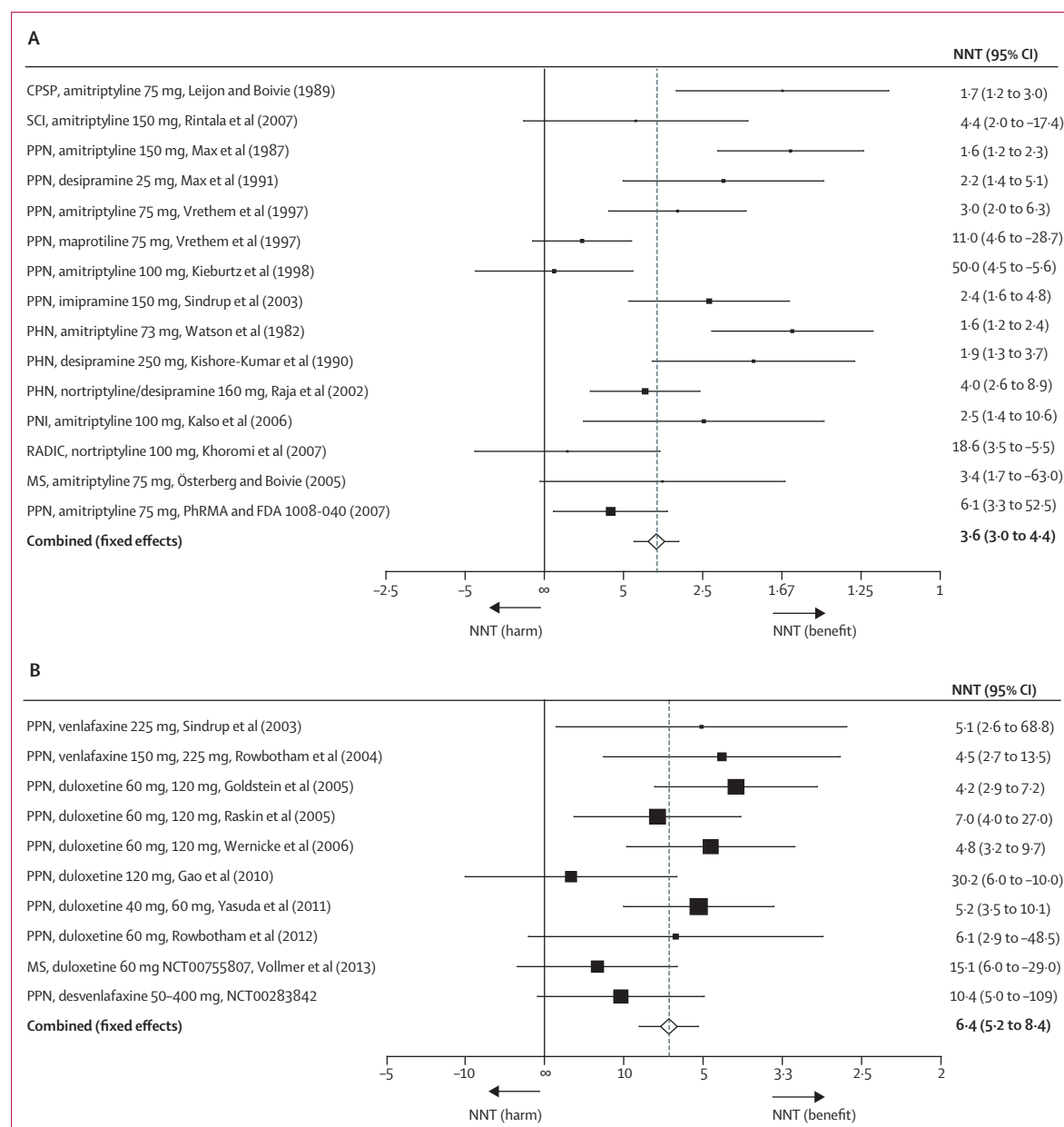

Figure 2: Forest plot of data for tricyclic antidepressants (A) and serotonin-noradrenaline reuptake inhibitors (B) included in the meta-analysis

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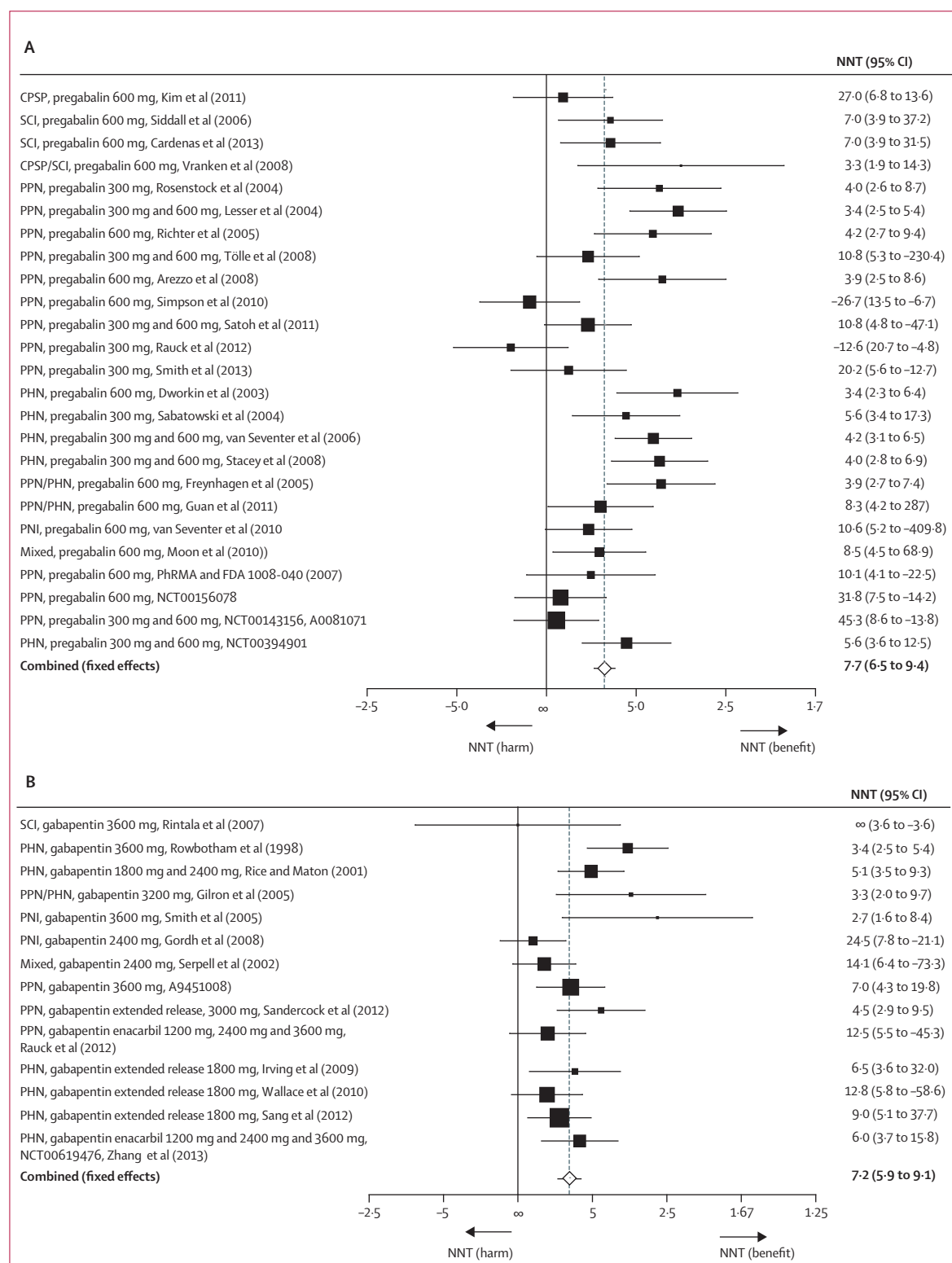
the susceptibility to publication bias in individual drug classes. Only the estimated effect size of capsaicin 8% patches showed susceptibility to change to a clinical non-significant effect if studies with no effect were published. Using meta-regression, we identified that for studies published in peer-reviewed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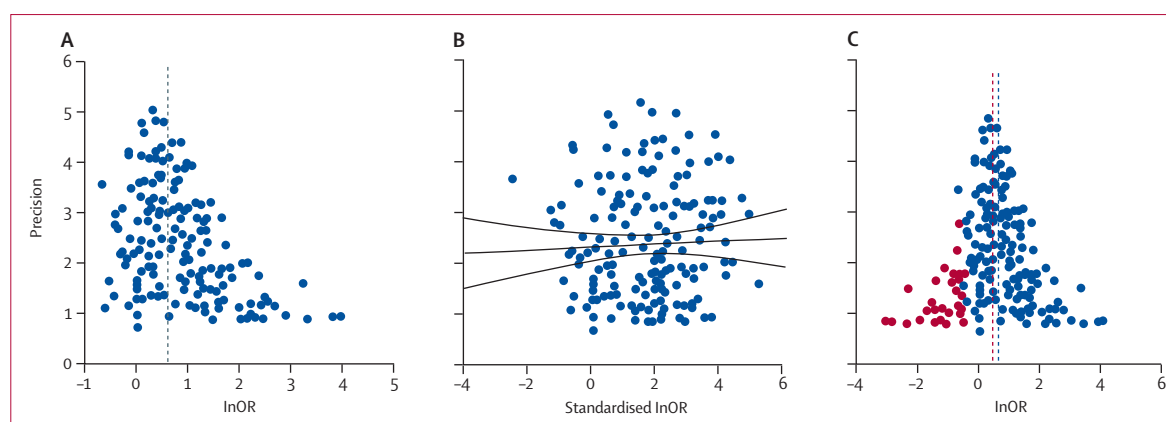
A

	NNT (95% CI)
CPSP, pregabalin 600 mg, Kim et al (2011)	27·0 (6·8 to 13·6)
SCI, pregabalin 600 mg, Siddall et al (2006)	7·0 (3·9 to 37·2)
SCI, pregabalin 600 mg, Cardenas et al (2013)	7·0 (3·9 to 31·5)
CPSP/SCI, pregabalin 600 mg, Vranken et al (2008)	3·3 (1·9 to 14·3)
PPN, pregabalin 300 mg, Rosenstock et al (2004)	4·0 (2·6 to 8·7)
PPN, pregabalin 300 mg and 600 mg, Lesser et al (2004)	3·4 (2·5 to 5·4)
PPN, pregabalin 600 mg, Richter et al (2005)	4·2 (2·7 to 9·4)
PPN, pregabalin 300 mg and 600 mg, Tölle et al (2008)	10·8 (5·3 to –230·4)
PPN, pregabalin 600 mg, Arezzo et al (2008)	3·9 (2·5 to 8·6)
PPN, pregabalin 600 mg, Simpson et al (2010)	–26·7 (13·5 to –6·7)
PPN, pregabalin 300 mg and 600 mg, Satoh et al (2011)	10·8 (4·8 to –47·1)
PPN, pregabalin 300 mg, Rauck et al (2012)	–12·6 (20·7 to –4·8)
PPN, pregabalin 300 mg, Smith et al (2013)	20·2 (5·6 to –12·7)
PHN, pregabalin 600 mg, Dworkin et al (2003)	3·4 (2·3 to 6·4)
PHN, pregabalin 300 mg, Sabatowski et al (2004)	5·6 (3·4 to 17·3)
PHN, pregabalin 300 mg and 600 mg, van Seventer et al (2006)	4·2 (3·1 to 6·5)
PHN, pregabalin 300 mg and 600 mg, Stacey et al (2008)	4·0 (2·8 to 6·9)
PPN/PHN, pregabalin 600 mg, Freynhagen et al (2005)	3·9 (2·7 to 7·4)
PPN/PHN, pregabalin 600 mg, Guan et al (2011)	8·3 (4·2 to 287)
PNI, pregabalin 600 mg, van Seventer et al (2010	10·6 (5·2 to –409·8)
Mixed, pregabalin 600 mg, Moon et al (2010))	8·5 (4·5 to 68·9)
PPN, pregabalin 600 mg, PhRMA and FDA 1008-040 (2007)	10·1 (4·1 to –22·5)
PPN, pregabalin 600 mg, NCT00156078	31·8 (7·5 to –14·2)
PPN, pregabalin 300 mg and 600 mg, NCT00143156, A0081071	45·3 (8·6 to –13·8)
PHN, pregabalin 300 mg and 600 mg, NCT00394901	5·6 (3·6 to 12·5)
Combined (fixed effects)	**7·7 (6·5 to 9·4)**

–2·5   –5·0   ∞   5·0   2·5   1·7

← NNT (harm)   NNT (benefit) →

B

	NNT (95% CI)
SCI, gabapentin 3600 mg, Rintala et al (2007)	∞ (3·6 to –3·6)
PHN, gabapentin 3600 mg, Rowbotham et al (1998)	3·4 (2·5 to 5·4)
PHN, gabapentin 1800 mg and 2400 mg, Rice and Maton (2001)	5·1 (3·5 to 9·3)
PPN/PHN, gabapentin 3200 mg, Gilron et al (2005)	3·3 (2·0 to 9·7)
PNI, gabapentin 3600 mg, Smith et al (2005)	2·7 (1·6 to 8·4)
PNI, gabapentin 2400 mg, Gordh et al (2008)	24·5 (7·8 to –21·1)
Mixed, gabapentin 2400 mg, Serpell et al (2002)	14·1 (6·4 to –73·3)
PPN, gabapentin 3600 mg, A9451008	7·0 (4·3 to 19·8)
PPN, gabapentin extended release, 3000 mg, Sandercock et al (2012)	4·5 (2·9 to 9·5)
PPN, gabapentin enacarbil 1200 mg, 2400 mg and 3600 mg, Rauck et al (2012)	12·5 (5·5 to –45·3)
PHN, gabapentin extended release 1800 mg, Irving et al (2009)	6·5 (3·6 to 32·0)
PHN, gabapentin extended release 1800 mg, Wallace et al (2010)	12·8 (5·8 to –58·6)
PHN, gabapentin extended release 1800 mg, Sang et al (2012)	9·0 (5·1 to 37·7)
PHN, gabapentin enacarbil 1200 mg and 2400 mg and 3600 mg, NCT00619476, Zhang et al (2013)	6·0 (3·7 to 15·8)
Combined (fixed effects)	**7·2 (5·9 to 9·1)**

–2·5   –5   ∞   5   2·5   1·67   1·25

← NNT (harm)   NNT (benefit) →

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. lnOR=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 poly-neuropathy) 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		
Gabapentin	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

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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).

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

	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**

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]

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