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pharmacotherapy for neuropathic pain, including studies published in peer-reviewed journals since January, 1966, and unpublished trials retrieved from ClinicalTrials.gov and websites of pharmaceutical companies.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 Studies published in peer-reviewed journals reported greater effects than did unpublished studies (I² 9·3%, p=0·009).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 (5·9–9·2) 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.
there were some discrepancies in previous recommendations due to inconsistencies in methods used to assess the quality of evidence. To address these inconsistencies, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) was introduced in 2000 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. 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. Non-pharmacological management strategies such as neurostimulation techniques were beyond the scope of this work.

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. 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. 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 International Committee of Medical Journal Editors in Registry Network and in registries approved by the reference lists of selected papers. Studies reporting results Register of Controlled Trials, and Embase. Additional January, 1966, and April, 2013, were identified with full reports of randomised, controlled, double-blind and data extraction protocol (unpublished, appendix). The the PRISMA statement. We used a standardised review and data extraction protocol (unpublished, appendix).

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), with final quality of evidence rated as strong or weak for the pharmacotherapy of neuropathic pain.

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)

Five investigators (SH, EM, KL, NBF, and NA) assessed studies for methodological quality by using the five-point Oxford Quality Scale (appendix). A minimum score of 2 of 5 (randomised and double-blind study) was required for inclusion. 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), with final quality of evidence rated as strong or weak for the pharmacotherapy of neuropathic pain.
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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

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 (e.g., 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,⁶⁶ Egger’s regression,²⁷ and Duval and Tweedie’s non-parametric trim-and-fill approach⁸ to assess publication bias (appendix). Additionally, we estimated the susceptibility to bias for individual drug classes.⁸⁰–⁸³ 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 plot⁸⁴ and as the I² 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. 150 mg of pregabalin 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.

Figure 1: Flow chart of study selection

![Flow chart of study selection](image-url)
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.

163 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](image)

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.

**Table 1**

<table>
<thead>
<tr>
<th>Drug Description</th>
<th>NNT (95% CI)</th>
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<tr>
<td>CPSP, amitriptyline 75 mg, Lejon and Boivie (1989)</td>
<td>1·7 (1·2 to 3·0)</td>
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<td>SCL, amitriptyline 150 mg, Ilntala et al (2007)</td>
<td>4·4 (2·0 to 12·4)</td>
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<td>PPN, amitriptyline 150 mg, Max et al (1987)</td>
<td>1·6 (1·2 to 2·3)</td>
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<td>PPN, desipramine 25 mg, Max et al (1991)</td>
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<td>PPN, amitriptyline 75 mg, Vrethem et al (1997)</td>
<td>3·0 (2·0 to 6·3)</td>
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<td>PPN, maprotiline 75 mg, Vrethem et al (1997)</td>
<td>11·0 (4·6 to 28·7)</td>
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<td>PPN, amitriptyline 100 mg, Kieburtz et al (1998)</td>
<td>50·0 (45·0 to 55·6)</td>
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<td>PPN, imipramine 150 mg, Sindrup et al (2003)</td>
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<td>PHN, nortriptiline/desipramine 160 mg, Raja et al (2002)</td>
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<td>RADIC, nortriptiline 100 mg, Khoromi et al (2007)</td>
<td>18·6 (13·5 to 55·5)</td>
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<td>MS, amitriptyline 75 mg, Österberg and Boivie (2005)</td>
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<td>PPN, amitriptyline 75 mg, PhRMA and FDA 1008-040 (2007)</td>
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<td>PPN, duloxetine 60 mg, 120 mg, Goldstein et al (2005)</td>
<td>4·2 (2·9 to 7·2)</td>
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<td>PPN, duloxetine 60 mg, 120 mg, Raskin et al (2005)</td>
<td>7·0 (4·0 to 27·0)</td>
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<td>PPN, duloxetine 60 mg, 120 mg, Wernicke et al (2006)</td>
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<td>PPN, desvenlafaxine 50–400 mg, NCT00283842</td>
<td>10·4 (5·0 to 109)</td>
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<td><strong>Combined (fixed effects)</strong></td>
<td><strong>6·4 (5·2 to 8·4)</strong></td>
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the susceptibility to publication bias in individual drug classes. Only the estimated effect size of capsaicin 8% patches showed susceptibility to change to a 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.
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 (95% CI 5·2–8·4) and NNH was 11·8 (9·5–15·2).

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).

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.

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).

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
- Memantine

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 7–18). 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, A-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. 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. 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

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<th>First-line drugs</th>
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<th>Third-line drugs</th>
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<tr>
<td>Serotonin-noradrenaline reuptake inhibitors</td>
<td>Tricyclic antidepressants</td>
<td>Pregabalin, gabapentin, gabapentin extended release or enacarbil</td>
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<tr>
<td>Tramadol</td>
<td>Capsaicin 8% patches</td>
<td>Lidocaine patches</td>
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<tr>
<td>Strong opioids</td>
<td>Botulinum toxin A</td>
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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).10,19

The GRADE recommendations for tapentadol, other antiepileptics, capsaicin cream, topical clonidine, selective serotonin reuptake inhibitor antidepressants, NMDA antagonists, and combination therapy46–48 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,5,9 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.6 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,6 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 bias9 and unpublished trials. Publication bias can occur if studies with positive results are published whereas those with no data or negative results are not.6 It might lead to a major overestimation of efficacy in therapeutic studies.6 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.6 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.6 However, our results might also indicate insufficient assay sensitivity in clinical trials of neuropathic pain (table 4).6 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.6 Placebo response was higher in HIV-related neuropathies,6 and in patients with low or variable pain scores at inclusion.6 Conversely, it seems to be lower in post-herpetic neuralgia.6 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 algorithms66 and screening methods68 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.7-11 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.7-11

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.9-11,15-16,19,60 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 recommendations in which they were generally thought of as first or second line.10,14 This stems mainly from the consideration of potential risk of abuse, particularly with high doses,15 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.11-14 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.16 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.11-13

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.17 By contrast, a recent large study of general practitioners’ adherence to current French recommendations noted a paucity of appropriate recall of first-line drugs.18 It will be important to facilitate the dissemination of the present recommendations and subsequently to assess their real-life implementation in various countries.17

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 final manuscript. 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, Analytika Solutions, Anika, Astellas, AstraZeneca, Avanir, Axonmed, 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, Periphragen, Pfizer, Phillip’s, Phosphagenics, Prolong, Q-Med, QRxPharma, Regenerex, Remoda, 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 Benckiser and has received speaker’s honoraria from Pfizer. KL has received travel grants from Pfizer and Astellas. EM has 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
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