Pharmacotherapy and non-invasive neuromodulation for neuropathic pain: a systematic review and meta-analysis

Nadia Soliman, Xavier Moisset*, Michael C Ferraro, Daniel Ciampi de Andrade, Ralf Baron, Joletta Belton†, David L H Bennett, Margarita Calvo, Patrick Dougherty, Ian Gilron, Aki J Hietaharju, Koichi Hosomi, Peter R Kamerman, Harriet Kemp, Elena K Enax-Krumova, Ewan McNicol, Theodore J Price, Srinivasa N Raja, Andrew S C Rice, Blair H Smith, Fiona Talkington†, Andrea Truini, Jan Vollert, Nadine Attal*, Nanna B Finnerup*, Simon Haroutounian*, NeuPSIG Review Update Study Group*

Summary

Background There remains a substantial unmet need for effective and safe treatments for neuropathic pain. The Neuropathic Pain Special Interest Group aimed to update treatment recommendations, published in 2015, on the basis of new evidence from randomised controlled trials, emerging neuromodulation techniques, and advances in evidence synthesis.

Methods For this systematic review and meta-analysis, we searched Embase, PubMed, the International Clinical Trials Registry, and ClinicalTrials.gov from data inception for neuromodulation trials and from Jan 1, 2013, for pharmacological interventions until Feb 12, 2024. We included double-blind, randomised, placebo-controlled trials that evaluated pharmacological and neuromodulation treatments administered for at least 3 weeks, or if there was at least 3 weeks of follow-up, and which included at least ten participants per group. Trials included participants of any age with neuropathic pain, defined by the International Association for the Study of Pain. We excluded trials with enriched enrolment randomised withdrawal designs and those with participants with mixed aetiologies (ie, neuropathic and non-neuropathic pain) and conditions such as complex regional pain syndrome, low back pain without radicular pain, fibromyalgia, and idiopathic orofacial pain. We extracted summary data in duplicate from published reports, with discrepancies reconciled by a third independent reviewer on the platform Covidence. The primary efficacy outcome was the proportion of responders (50% or 30% reduction in baseline pain intensity or moderate pain relief). The primary safety outcome was the number of participants who withdrew from the treatment owing to adverse events. We calculated a risk difference for each comparison and did a random-effects meta-analysis. Risk differences were used to calculate the number needed to treat (NNT) and the number needed to harm (NNH) for each treatment. Risk of bias was assessed by use of the Cochrane risk of bias tool 2 and certainty of evidence assessed by use of GRADE. Recommendations were based on evidence of efficacy, adverse events, accessibility, and cost, and feedback from engaged lived experience partners. This study is registered on PROSPERO, CRD42023389375.

Findings We identified 313 trials (284 pharmacological and 29 neuromodulation studies) for inclusion in the meta-analysis. Across all studies, 48 789 adult participants were randomly assigned to trial groups (20 611 female and 25 078 male participants, where sex was reported). Estimates for the primary efficacy and safety outcomes were tricyclic antidepressants (TCAs) NNT=4·6 (95% CI 3·2–7·7), NNH=17·1 (11·4–33·6; moderate certainty of evidence), α2δ-ligands NNT=8·9 (7·4–11·10), NNH=26·2 (20·4–36·5; moderate certainty of evidence), serotonin and norepinephrine reuptake inhibitors (SNRIs) NNT=7·4 (5·6–10·9), NNH=13·9 (10·9–19·0; moderate certainty of evidence), botulinum toxin (BTX-A) NNT=2·7 (1·8–9·61), NNH=216·3 (23·5–∞; moderate certainty of evidence), capsaicin 8% patches NNT=13·2 (7·6–50·8), NNH=1129·3 (135·7–∞; moderate certainty of evidence), opioids NNT=5·9 (4·1–10·7), NNH=15·4 (10·8–24·0; low certainty of evidence), repetitive transcranial magnetic stimulation (rTMS) NNT=4·2 (2·3–28·3), NNH=651·6 (34·7–∞; low certainty of evidence), capsaicin cream NNT=6·1 (3·1–∞), NNH=18·6 (10·6–77·1; very low certainty of evidence), lidocaine 5% plasters NNT=14·5 (7·8–108·2), NNH=178·0 (23·9–∞; very low certainty of evidence). The findings provided the basis for a strong recommendation for use of TCAs, α2δ-ligands, and SNRIs as first-line treatments; a weak recommendation for capsaicin 8% patches, capsaicin cream, and lidocaine 5% plasters as second-line recommendation; and a weak recommendation for BTX-A, rTMS, and opioids as third-line treatments for neuropathic pain.

Interpretation Our results support a revision of the Neuropathic Pain Special Interest Group recommendations for the treatment of neuropathic pain. Treatment outcomes are modest and for some treatments uncertainty remains. Further large placebo-controlled or sham-controlled trials done over clinically relevant timeframes are needed.

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*Contributed equally

†Independent researcher with lived experience

‡Members listed at the end of the Article

Pain Research Group, Department of Surgery and Cancer, Imperial College London, London, UK (N Soliman PhD, H Kemp MD, Prof A S C Rice MD); **Université Clermont Auvergne, CHU Clermont-Ferrand, Inserm, Neuro-Dol, Clermont-Ferrand, France** (Prof X Moisset MD); **Centre for Pain IMPACT, Neuroscience Research Australia, Australia** (M C Ferraro BSc); **School of Health Sciences, Faculty of Medicine and Health, University of New South Wales Sydney, NSW, Australia** (M C Ferraro); **Center for Neuroplasticity and Pain, Health Science and Technology Department, Faculty of Medicine, Aalborg University, Denmark** (D Ciampi de Andrade MD); **Division of Neurological Pain Research and Therapy, Department of Neurology, Christian-Albrechts-University, Kiel, Germany** (Prof R Baron MD); **Fraser, CO, USA** (J Belton MSc); **Reading, UK** (F Talkington MSc); **The Nuffield Department of Clinical Neuroscience, University of Oxford, Oxford, UK** (Prof D L H Bennett PhD); **Faculty of Biological Sciences, Pontificia Universidad Católica de Chile, Santiago, Chile** (M Calvo MD); **Anesthesiology Division, Faculty of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile** (M Calvo); **Department of Pain Medicine, MD Anderson Cancer Center, Houston, TX, USA** (Prof P Dougherty PhD); **Department of Anesthesiology and Perioperative Medicine**

(Prof I Gilron MD); **Biomedical & Molecular Sciences** (Prof I Gilron), **Centre for Neuroscience Studies** (Prof I Gilron), **School of Policy Studies** (Prof I Gilron), **Queen's University, Kingston, ON, Canada; Kingston Health Sciences Centre, Providence Care Hospital, Kingston, ON, Canada** (Prof I Gilron); **Department of Neurology, Tampere University Hospital, Tampere, Finland** (A J Hietaharju MD); **Department of Neurosurgery, Osaka University Graduate School of Medicine, Suita, Japan** (K Hosomi MD); **Brain Function Research Group, School of Physiology, Faculty of Health Sciences, University of the Witwatersrand, South Africa** (Prof P R Kamerman PhD); **Department of Neurology, BG University Hospital Bergmannsheil, Ruhr University Bochum, Germany** (Prof E K Enax-Krumova MD); **Department of Pharmacy Practice, Massachusetts College of Pharmacy and Health Sciences, Boston, MA, USA** (E McNicol MS); **Center for Advanced Pain Studies, Richardson, TX, USA** (Prof T J Price PhD); **Department of Neuroscience, University of Texas at Dallas, School of Behavioral and Brain Sciences, Richardson, TX, USA** (Prof T J Price); **Departments of Anesthesiology and Critical Care Medicine and Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA** (Prof S N Raja MD); **Division of Population Health and Genomics, School of Medicine, University of Dundee, Dundee, UK** (Prof B H Smith MD); **Department of Human Neuroscience, Sapienza University, Rome, Italy** (A Truini MD); **Department of Clinical and Biomedical Sciences, Faculty of Health and Life Sciences, University of Exeter, Exeter, UK** (J Vollert PhD); **Inserm U987, APHP, UVSQ Paris Saclay University, Hôpital Ambroise Paré, Boulogne-Billancourt, France** (Prof N Attal MD); **Danish Pain Research Center, Department of Clinical Medicine, Aarhus University, Aarhus, Denmark** (Prof N B Finnerup MD); **Department of Anesthesiology,**

Research in context

Evidence before this study

We systematically searched PubMed, EMBASE, Clinical trials.gov, and International Clinical Trials Registry up to Feb 12, 2024. The search terms included combining terms for neuropathic pain—eg, ([neuropath* or hyperalgesia or allodynia or neuralgia] adj4 pain*).tw., with "Exp analgesia" and "neuromodul*" to ensure breadth and text words for specific pharmacological—eg, ([TCA adj2 antidepressant*] OR [SNRI adj2 antidepressant*] OR [SSRI adj2 antidepressant*] OR antiepileptic* OR opioid* OR cannabinoids OR cannabis-based medicine OR cannabis OR lidocaine OR capsaicin OR botulinum toxin type A OR NMDA antagonist OR NSAIDs OR gabapentin* OR pregabalin).tw. and neuromodulation interventions—eg, (spinal cord adj3 [stimulat* or electrostimulat*]) or (dorsal root adj3 [stimulat* or electrostimulat*]) or (percutaneous electrical nerve adj3 stimulat*) or PENS or (transcutaneous electrical nerve adj3 stimulat*) or TENS or (transcranial direct current adj4 stimulat*) or tDCS or (repetitive transcranial magnetic adj4 stimulat*) or rTMS or (epidural motor cortex adj4 [stimulat* or electrostimulat*]) or EMCS or SENZA or neuromodul*).tw, and a filter for randomised controlled trials, with no language restrictions. The last large scale systematic review and meta-analysis evaluating pharmacotherapy for neuropathic pain was done over a decade ago. Although individual studies and reviews have focused on specific interventions and specific aetiologies, there has not been a systematic evaluation comparing the effectiveness and safety of both pharmacological and neuromodulation treatments for neuropathic pain.

Added value of this study

Our systematic review and meta-analysis synthesised data from over 40 000 participants across 313 randomised controlled trials, making it one of the most comprehensive evaluations of treatments for neuropathic pain to date. Using rigorous selection criteria and current evidence synthesis methods, we provide robust pooled estimates of treatment efficacies. We assessed the certainty of evidence using GRADE methodology and did sensitivity analyses to evaluate potential biases. Our evidence-to-recommendation process included important considerations beyond efficacy, such as adverse events, accessibility, and cost, and engaged lived experience partners to align recommendations with patient priorities. Despite the inclusion of an additional 109 randomised controlled trials, the recommendations have only changed modestly since 2015. Capsaicin cream, previously considered inconclusive, is now classified as a second-line treatment with a weak recommendation. Tramadol, which was previously a second-line treatment, is now grouped with opioids and recommended as a third-line option with a weak recommendation. Additionally, rTMS, which was not evaluated in 2015, has now been assessed.

Implications of all the available evidence

This systematic review underscores the modest efficacy of many pharmacological treatments for neuropathic pain, possibly influenced by the heterogeneity of underlying mechanisms and participant phenotypes in clinical trials. Neuromodulation techniques, emerging as alternatives, demand larger sham-controlled trials to address uncertainties surrounding their long-term efficacy and safety. The recommendations highlight the need for shared decision making, prioritising patient autonomy and preferences when tailoring treatment strategies. Health-care professionals should adapt these guidelines to their specific contexts, accounting for the cost, accessibility, and feasibility of treatments. Further research, including for combination therapies, is necessary to optimise outcomes and improve the quality of life for individuals with neuropathic pain.

Introduction

Neuropathic pain, caused by a lesion or disease of the somatosensory nervous system,[1] substantially affects patients' quality of life and imposes a substantial economic burden on individuals and society.[2,3] Regardless of the aetiology of nerve damage, the treatment of neuropathic pain is challenging, requiring accurate diagnosis and biopsychosocial assessment[4] and the application of evidence-based recommendations that consider efficacy and safety of available treatments.

The Special Interest Group on Neuropathic Pain (NeuPSIG) of the International Association for the Study of Pain (IASP) published its first guidelines in 2007,[5] with an update in 2015,[6] incorporating the Grading of Recommendations Assessment, Development, and Evaluation (GRADE)[7] and unpublished trials. Since then, new pharmacological trials and neuromodulation techniques (non-implantable and implantable devices that aim to provide pain relief through targeted electrical or magnetic stimulation of the nervous system[8]) have been developed and evaluated, along with updated safety data and advances in evidence appraisal methods.

Therefore, we aimed to summarise the evidence from randomised controlled trials in people with neuropathic pain in an updated systematic review and meta-analysis. We provide estimates of the efficacy and safety related to tolerability of pharmacological treatments and neuromodulation techniques, and assessments of the risk of bias and certainty of evidence. These findings informed the updated recommendations for use of pharmacological and non-invasive neuromodulation techniques to treat neuropathic pain. The recommendations are intended for use by a broad range of health-care professionals, including by primary care physicians and other non-specialists in neuropathic pain.

Methods

Search strategy and selection criteria

For this systematic review and meta-analysis, we searched PubMed, EMBASE, Clinical Trials.gov, and the

International Clinical Trials Registry Platform, without language restriction, up to Feb 12, 2024. We restricted the search start date for pharmacological interventions to 2013 to build upon the previous recommendations,[6] without restricting the date for neuromodulation trials (search strategy in appendix pp 2–4). Study selection was done by use of the Systematic Review Facility[9] whereby two authors (from NS, XM, DCdA, RAA, ME, MF, SF, BG, DHS, PRK, HK, EKE-K, GTK, EM, JP, HP, CRP, TIP, AR, NTL, QVT, JV, JW, CQ, AZ, MDZ, NA, NBF) independently did title abstract and full text screening. Disagreements were resolved by a third independent reviewer (NS, XM, DCdA, RAA, ME, MF, SF, BG, DHS, PRK, HK, EKE-K, GTK, EM, JP, HP, CRP, TIP, AR, NTL, QVT, JV, JW, CQ, AZ, MDZ, NA, NBF). We also did reference and citation searches of included trials to identify further trials. The review protocol was co-produced with patient partners (JB and FT) and registered on PROSPERO (CRD42023389375). We report the results in accordance with PRISMA.

Inclusion and exclusion criteria and data collection

For the systematic review and meta-analysis, we included randomised, double-blind, placebo-controlled trials of either parallel or crossover design, excluding those that used enriched enrolment randomised withdrawal, which can introduce selection bias and limit generalisability.[10] Trials included participants of any age with neuropathic pain, defined by IASP[2] to include conditions such as postherpetic neuralgia, diabetic and non-diabetic painful polyneuropathy, post-traumatic or postsurgical neuropathic pain, painful radiculopathy, central post-stroke pain, spinal cord injury pain, trigeminal neuralgia, erythromelalgia, multiple sclerosis-associated neuropathic pain, and multi-aetiology neuropathic pains. We excluded trials with mixed aetiologies (eg, neuropathic and non-neuropathic pain) and conditions such as complex regional pain syndrome, low back pain without radicular pain, fibromyalgia, and idiopathic orofacial pain.[2,11] Only trials with at least 10 participants per group at the end of the treatment were included.[12]

We included any pharmacological and neuromodulation intervention if they were administered for at least 3 weeks or if after single administration there were at least 3 weeks of follow-up. Outcome data were extracted based on the trial primary endpoint. If the primary endpoint was within the first 3 weeks, then outcome data were extracted from the timepoint following week 3. Studies testing more than one type of treatment concomitantly were also included.

Data analysis

We extracted summary estimates from the published studies and reports. The primary efficacy outcome was the proportion of responders (at least 50% reduction in baseline pain intensity, alternatively 30%, or at least moderate pain relief). Where available, continuous pain outcomes were also extracted. The primary safety outcome was the number of participants who withdrew from treatment owing to adverse events. In duplicate on the Covidence platform, data were extracted (appendix p 5) and risk of bias of the primary outcome was assessed by use of the Cochrane Risk of Bias Tool 2.[13] All disagreements were resolved by a third independent reviewer.

We combined data in a meta-analysis where sufficient data were available, using both dichotomous and continuous pain-related outcomes. Risk difference and standardised mean difference (SMD) were calculated, and the random-effects model was used for pairwise meta-analyses. Risk difference was used to calculate the number needed to treat (NNT), based upon the intention to treat (ie, the number of participants randomised), and the number needed to harm (NNH), based on those who received the intervention. For dichotomous outcomes, we used the Mantel–Haenszel method to pool the results of individual studies and the unrestricted maximum likelihood mixed-effects model was used to account for study-level variability. For crossover studies, if available, we included the first phase of the study to avoid carryover and period effects. However, when such data were not available, the combined or pooled analyses were extracted (ie, the data from all phases of the trial). We did a post-hoc sensitivity analysis to evaluate the effect of potential outliers using the outlier function in R. Studies are defined as outliers if their 95% CI interval lies outside the 95% CI of the pooled effect. Studies identified as outliers were then excluded in a subsequent reanalysis, and the results compared with the primary analysis.

To minimise clinical heterogeneity, we combined studies that assessed interventions with similar mechanisms of action. Heterogeneity was assessed by use of Cochran's Q, χ^2, Tau^2, and I^2 statistics. To reduce the effect of reporting bias, we have included both published trials and results from trial registries. To detect reporting bias, we used funnel plot and Egger's regression to test for asymmetry and trim and fill analysis to impute theoretically missing trials. This method was applied to all included studies where 50% or 30% reduction in pain intensity or moderate pain relief were reported. We also did a susceptibility analysis to estimate the number of additional participants needed in studies with no treatment effect to change the NNT for all significant outcomes to a level likely to be below clinically meaningful, namely, NNT 10. Where this number is fewer than 400, we considered the results to be susceptible to reporting bias and therefore unreliable.[14]

The analyses were done with R version 4.4.1. and the packages meta (version 7.0), metafor[15] (version 4.6-0), and dmetar (version 0.1.0).[16]

Certainty of evidence

We used the GRADE[7] tool to assess the certainty of effect estimates for each drug class or category or

Washington University in St Louis School of Medicine, St Louis, MO, USA
(Prof S Haroutounian PhD)

Correspondence to:
Nadia Soliman, Pain Group, Department of Surgery and Cancer, Imperial College London, Chelsea and Westminster Hospital, London SW10 9NH, UK
n.soliman16@imperial.ac.uk

For more on **Covidence** see www.covidence.org

See **Online** for appendix

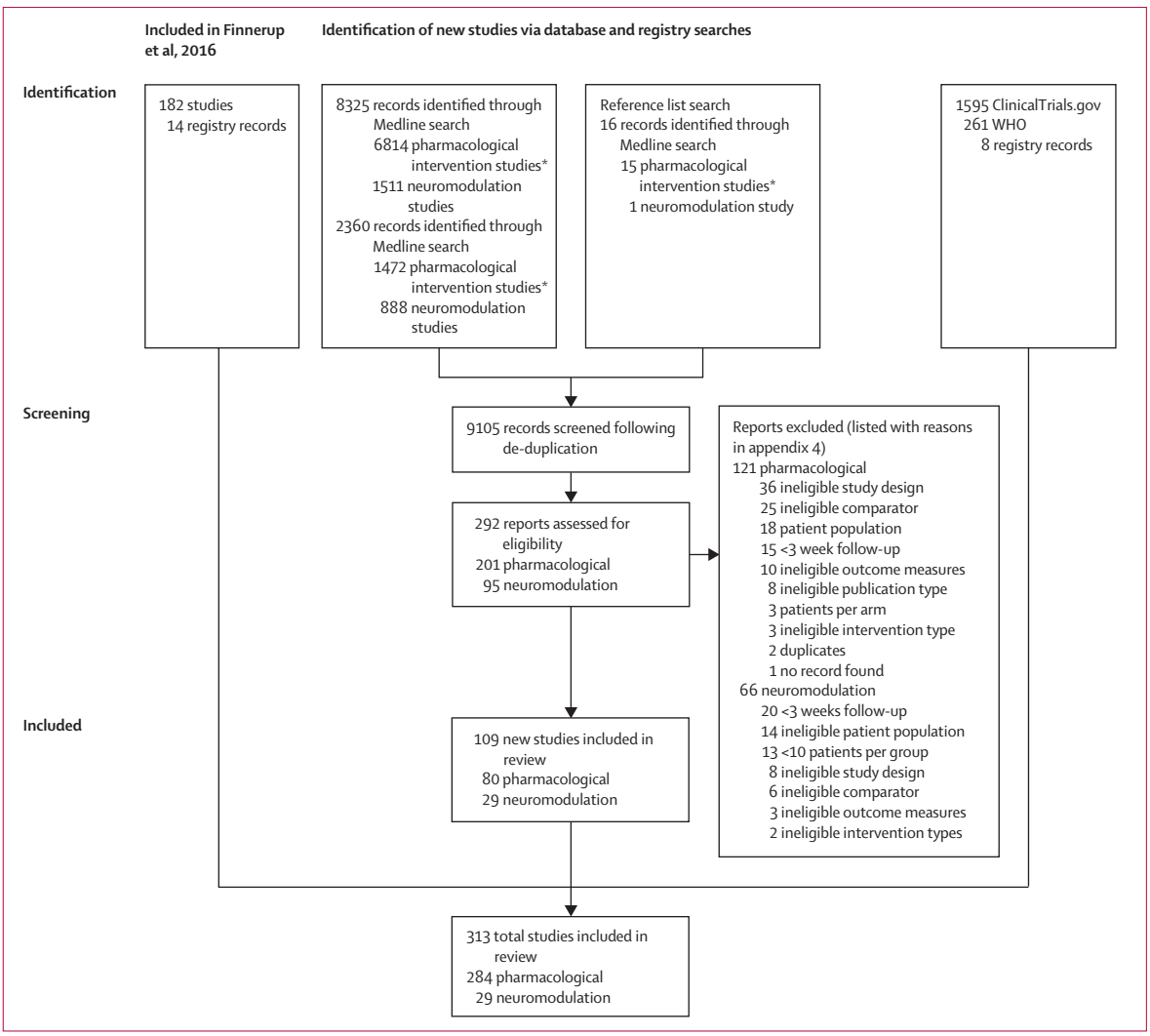


Figure 1: **PRISMA flowchart of study selection**
*Studies investigating a pharmacological intervention.

For the **essential medicine lists** see https://global.essentialmeds.org

neuromodulation intervention. Two authors independently evaluated each category, and disagreements were resolved through team discussion for consistency. GRADE assessed risk of bias, indirectness, imprecision, inconsistency, and publication bias, resulting in a certainty rating of high, moderate, low, or very low certainty (appendix pp 4–6).

Evidence to recommendations

The recommendations were developed through a series of expert consensus meetings and anonymous online voting. The group consisted of experts in basic science, clinical trials, clinical management, evidence synthesis, and with lived pain experience. We followed the GRADE framework[7] and considered certainty of evidence, effect size, cost, and harms (including frequency, severity, and prevalence from Micromedex and LexiComp, and prescribing information for each drug; appendix pp 5–7). Availability of treatments was assessed by use of the essential medicine lists for low-income and middle-income countries; appendix pp 8–11).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The database searches retrieved 10 685 studies, 9105 following de-duplication. The registry searches retrieved 1856 records. All studies included in the 2015 recommendations[8] were screened against the revised inclusion criteria and checked for retractions and any erasures or updates. Overall, 292 new studies were assessed at full text for eligibility leading to the inclusion of 80 pharmacological and 29 neuromodulation studies

	Pain responders (n responders/N total)					Treatment withdrawals (n withdrawals/N total)			
	Active	Placebo	Total patients	Number needed to treat (95% CI)	Susceptibility to bias*	Active	Placebo	Total patients	Number needed to harm (95% CI)
Recommended first-line									
α2δ-ligands	3069/9569	1423/6617	16186	8·9 (7·4–11·1)	1994	906/9319	332/6866	16185	26·2 (20·4–36·5)
Serotonin noradrenaline reuptake inhibitors	858/2207	364/1493	3700	7·4 (5·6–10·9)	1287	282/2363	61/1567	3930	13·9 (10·9 –19·0)
Tricyclic antidepressants	272/723	114/720	1443	4·6 (3·2–7·7)	1728	681/1352	23/671	2023	17·1 (11·4 –33·6)
Recommended second-line									
Capsaicin 8% patches	397/1242	214/868	2110	13·16 (7·6– 50·8)	NA	11/1288	5/893	2181	1129·3 (135·7–∞)
Capsaicin cream	111/249	68/223	472	6·1 (3·1–∞)	297†	53/495	15/479	974	18·6 (10·6 –77·1)
Lidocaine 5% plasters	62/249	33/238	487	14·5 (7·8–108·2)	NA	13/257	10/246	503	178·0 (23·9–∞)
Recommended third-line									
Botulinum toxin type A	102/202	18/171	373	2·7 (1·8–5·1)	1029	2/160	3/157	317	216·3 (23·5–∞)
Repetitive transcranial magnetic stimulation targeting–primary motor cortex	67/207	18/168	375	4·2 (2·3–28·3)	514	2/337	3/299	636	651·6 (34·7–∞)
Opioids	229/613	117/558	1171	5·9 (4·1–10·7)	838	84/781	22/745	1526	15·4 (10·8–24·0)

Data are n/N, unless stated otherwise. NA=not applicable. NNT=number needed to treat. *Refers to the number of patients in a trial who do not respond to treatment that would lead to an NNT>10, considered as the cutoff for reasonable clinical benefit. This calculation is not possible for treatments with NNT>10. The higher the numerical value, the lower the susceptibility to bias. If the susceptibility to bias is less than 400, a new study with fewer than 400 participants with no effect could change the NNT to a level that is not clinically meaningful; however a study with a susceptibility to bias score higher than 400 will not.[14] †Susceptible to reporting bias.

Table 1: **Pain response, withdrawals, and susceptibility to reporting bias based on number needed to treat**

(see appendix pp 12–19 for excluded references and reasons). In total, we identified 313 studies: 284 pharmacological and 29 neuromodulation studies for inclusion in the review (figure 1). Across the pharmacological studies included a total of 84 different drugs were assessed. The most frequently evaluated drug classes were α2δ-ligands (76 studies), tricyclic antidepressants (TCAs, 21 studies), serotonin–norepinephrine reuptake inhibitors (SNRIs, 19 studies), and opioids (19 studies). In neuromodulation studies meeting the inclusion criteria, repetitive transcranial magnetic stimulation (rTMS) was the most studied (14 studies), followed by transcranial direct current stimulation (tDCS, seven studies). Other interventions included motor cortex stimulation (two studies), percutaneous electrical nerve stimulation (two studies), peripheral nerve stimulation (two studies), transcutaneous electrical nerve stimulation (TENS, two studies), spinal cord stimulation (one study), and pulsed electromagnetic field therapy (one study).

Across all studies, 48789 participants were randomly assigned to trial groups (20611 female and 25078 male participants, where sex was reported.) We did not identify any trials including participants younger than 18 years of age. Participants were predominantly classified on the basis of aetiology and treatments were evaluated in a broad range of neuropathic pain conditions. Most trials did not report how neuropathic pain was diagnosed or did not grade its certainty.[17] The included studies were crossover (91 studies) or parallel (222 studies) design. The sample size ranged from 10 to 1269 participants; median sample size was 96 participants. The trial duration (treatment plus follow up) ranged from 3 to 24 weeks; the median duration was 8 weeks. The trials assessed 89 pharmacological interventions and nine neuromodulation interventions. 35 studies assessed more than one intervention in the same study. Concomitant medication was permitted in 147 (45%) of the 273 studies that reported this information (appendix pp 20–36).

33, 139, and 138 studies had an overall low, some concerns, and high risk of bias respectively (three unpublished trials could not be assessed because they are no longer publicly accessible). Risk of bias judgements are shown for each included study in appendix (pp 56–64).

In forest plots, we present the risk difference based on reduction in pain intensity (either 50% or 30% pain reduction or moderate pain relief), and SMD based on posttreatment mean values and standard deviations. We also present withdrawals due to adverse events from which the NNH was calculated. The nature and frequency of adverse events are shared on the Open Science Framework.

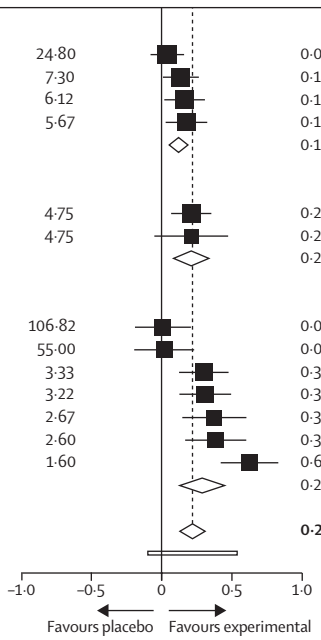
For the **Open Science Framework** see https://osf.io/kjq9u/

21 studies evaluated tricyclic antidepressants (TCAs), which predominantly evaluated amitriptyline (13 studies). The combined NNT (13 studies) was 4·6 (95% CI 3·2–7·7), and NNH (21 studies) was 17·1 (11·4–33·6; table 1, figure 2). Estimate of effect (16 comparisons) was SMD 0·7 (0·2–1·1; appendix p 65). Removal of outliers increased the NNT by 17% to 5·5 (3·99–8·64) and decreased the SMD by 23% to 0·5 (0·3–0·7). There was moderate certainty of evidence.

19 studies of serotonin and norepinephrine reuptake inhibitors (SNRIs) predominantly evaluated duloxetine (11 studies). The combined NNT (14 studies) was 7·4 (95% CI 5·6–10·9), and NNH (17 studies) was 13·9

A

	Pain condition	Drug	Dose	Events/total		Number needed to treat	Risk difference (95% CI)	Weight
				Experimental	Control			
50% pain reduction								
Dinat et al (2015)	HIV	Amitriptyline	25–50 mg/day	47/124	42/124	24·80	0·04 (−0·08 to 0·16)	9·3%
Holbech et al (2015)	Painful peripheral neuropathy	Imipramine	75 mg/day	14/73	4/73	7·30	0·14 (0·01 to 0·26)	9·1%
PhRMA 1008–40 (2007)	Diabetic peripheral neuropathy	Amitriptyline	75 mg/day	40/87	24/81	6·12	0·16 (0·02 to 0·31)	8·7%
Gillving et al (2020)	Painful peripheral neuropathy	Imipramine	30–150 mg/day	12/51	3/51	5·67	0·18 (0·03 to 0·32)	8·6%
Random-effects model							0·12 (0·05 to 0·19)	35·7%
Heterogeneity: I^2=0%, τ^2≤0·0001, p=0·44								
30% pain reduction								
Raja et al (2002)	Postherpetic neuropathy	Nortriptyline	160 mg/day	24/76	8/76	4·75	0·21 (0·07 to 0·35)	8·7%
Rintala et al (2007)	Spinal cord injury	Amitriptyline	50 mg three times a day	20/38	12/38	4·75	0·21 (−0·05 to 0·47)	5·7%
Random-effects model							0·21 (0·08 to 0·34)	14·4%
Heterogeneity: I^2=0%, τ^2=0, p=1·00								
Moderate pain relief								
Kieburtz et al (1998)	HIV	Amitriptyline	25–100 mg/day	23/47	24/50	106·82	0·01 (−0·19 to 0·21)	7·2%
Khoromi et al (2007)	Radiculopathy	Nortriptyline	100 mg	12/55	11/55	55·00	0·02 (−0·19 to 0·23)	6·9%
Sindrup et al (2003)	Painful peripheral neuropathy	Imipramine	25–75 mg/day	14/40	2/40	3·33	0·30 (0·12 to 0·48)	7·8%
Max et al (1988)	Postherpetic neuropathy	Amitriptyline	150 mg/day	27/58	9/58	3·22	0·31 (0·13 to 0·49)	7·6%
Max et al (1991)	Diabetic peripheral neuropathy	Desipramine	12·5–250 mg/day	11/24	2/24	2·67	0·38 (0·15 to 0·60)	6·5%
Kishore–Kumar et al (1990)	Postherpetic neuropathy	Desipramine	12·5–250 mg/day	12/26	2/26	2·60	0·38 (0·17 to 0·60)	6·8%
Watson et al (1982)	Postherpetic neuropathy	Amitriptyline	73 mg/day	16/24	1/24	1·60	0·62 (0·42 to 0·83)	7·1%
Rando-effects model							0·29 (0·13 to 0·45)	49·8%
Heterogeneity: I^2=76%, τ^2=0·0355, p<0·01								
Random effects model							**0·22 (0·13 to 0·31)**	**100·0%**
Prediction interval							(−0·10 to 0·54)	
Heterogeneity: I^2=69%, τ^2=0·0187, p<0·01								
Test for subgroup differences: χ^2_2=4·46, df=2 (p=0·11)								



B

	Pain condition	Drug	Dose	Events/total		Risk difference (95% CI)	Weight
				Experimental	Control		
Panerai et al (1990)	Mixed	Chlorimipramine	25 mg four times a day	0/24	1/24	−0·04 (−0·20 to 0·11)	3·4%
Sindrup et al (2003)	Painful peripheral neuropathy	Imipramine	25–75 mg/day	1/40	2/40	−0·02 (−0·13 to 0·08)	7·0%
Leijon et al (1989)	Central post-stroke pain	Amitriptyline	75 mg/day	0/15	0/15	0·00 (−0·18 to 0·18)	2·5%
Mishra et al (2012)	Cancer	Amitriptyline	50–100 mg/day	0/30	0/30	0·00 (−0·10 to 0·10)	8·6%
Raja et al (2002)	Postherpetic neuropathy	Nortriptyline	Up to 160 mg/day	2/46	1/50	0·02 (−0·06 to 0·10)	12·1%
Max et al (1988)	Postherpetic neuropathy	Amitriptyline	150 mg/day	5/34	3/25	0·03 (−0·19 to 0·24)	1·8%
Khoromi et al (2007)	Radiculopathy	Nortriptyline	100 mg	2/34	1/39	0·03 (−0·08 to 0·15)	5·9%
Panerai et al (1990)	Mixed	Nortriptyline	25 mg four times a day	2/24	1/24	0·04 (−0·12 to 0·20)	3·3%
Kieburtz et al (1998)	HIV	Amitriptyline	25–100 mg/day	3/47	1/50	0·04 (−0·05 to 0·13)	10·0%
Rintala et al (2007)	Spinal cord injury	Amitriptyline	50 mg three times a day	4/34	2/31	0·05 (−0·11 to 0·22)	3·1%
Vrethem et al (1997)	Mixed	Maprotiline	25–75 mg/day	2/37	0/37	0·05 (−0·05 to 0·16)	7·2%
Kishore–Kumar et al (1990)	Postherpetic neuropathy	Desipramine	12·5–250 mg/day	5/26	3/26	0·08 (−0·12 to 0·27)	2·2%
Vrethem et al (1997)	Mixed	Amitriptyline	25–50 mg/day	3/37	0/37	0·08 (−0·03 to 0·20)	6·0%
Max et al (1991)	Diabetic peripheral neuropathy	Desipramine	12·5–250 mg/day	2/24	0/24	0·08 (−0·05 to 0·21)	4·8%
Graff-Radford et al (2000)	Postherpetic neuropathy	Amitriptyline	200 mg/day	1/11	0/13	0·09 (−0·22 to 0·40)	0·9%
Robinson et al (2004)	Postamputation	Amitriptyline	150 mg/day	2/20	0/19	0·10 (−0·05 to 0·25)	3·4%
Osterberg et al (2005)	Multiple sclerosis	Amitriptyline	75 mg/day	7/23	4/23	0·13 (−0·16 to 0·42)	1·0%
PhRMA 100840 (2007)	Diabetic peripheral neuropathy	Amitriptyline	75mg/day	16/87	4/81	0·13 (0·03 to 0·24)	7·2%
Max et al (1987)	Diabetic peripheral neuropathy	Amitriptyline	150 mg/day	5/29	0/29	0·17 (0·03 to 0·32)	3·8%
Gillving et al (2020)	Painful peripheral neuropathy	Imipramine	150 mg/day	9/44	0/39	0·20 (0·07 to 0·34)	4·4%
Kalso et al (1995)	Chemotherapy-induced peripheral neuropathy	Amitriptyline	25–100 mg	4/15	0/15	0·27 (0·03 to 0·50)	1·5%
Random-effects model						0·06 (0·03 to 0·09)	100·0%
Heterogeneity: I^2=0%, τ^2=0·0001, p=0·49							
Random-effects model							
Prediction interval						**0·06 (0·03 to 0·09)**	**100·0%**
Heterogeneity: I^2=0%, τ^2=0·0001, p=0·49						(0·02 to 0·10)	
Test for subgroup differences: χ^2_0=0·00, df=0 (p=NA)							

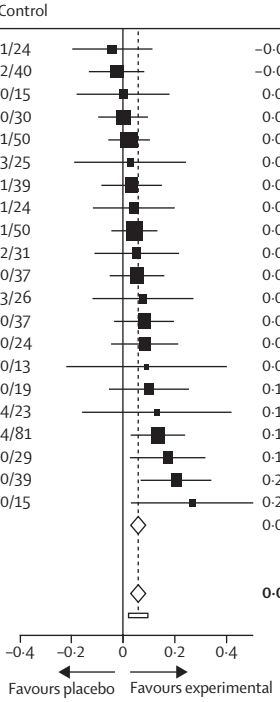


Figure 2: **Comparison of TCAs *vs* placebo**
(A) Risk difference based on participants with 50% or 30% reduction in pain intensity or moderate pain relief. (B) Risk difference based on the number of withdrawals.

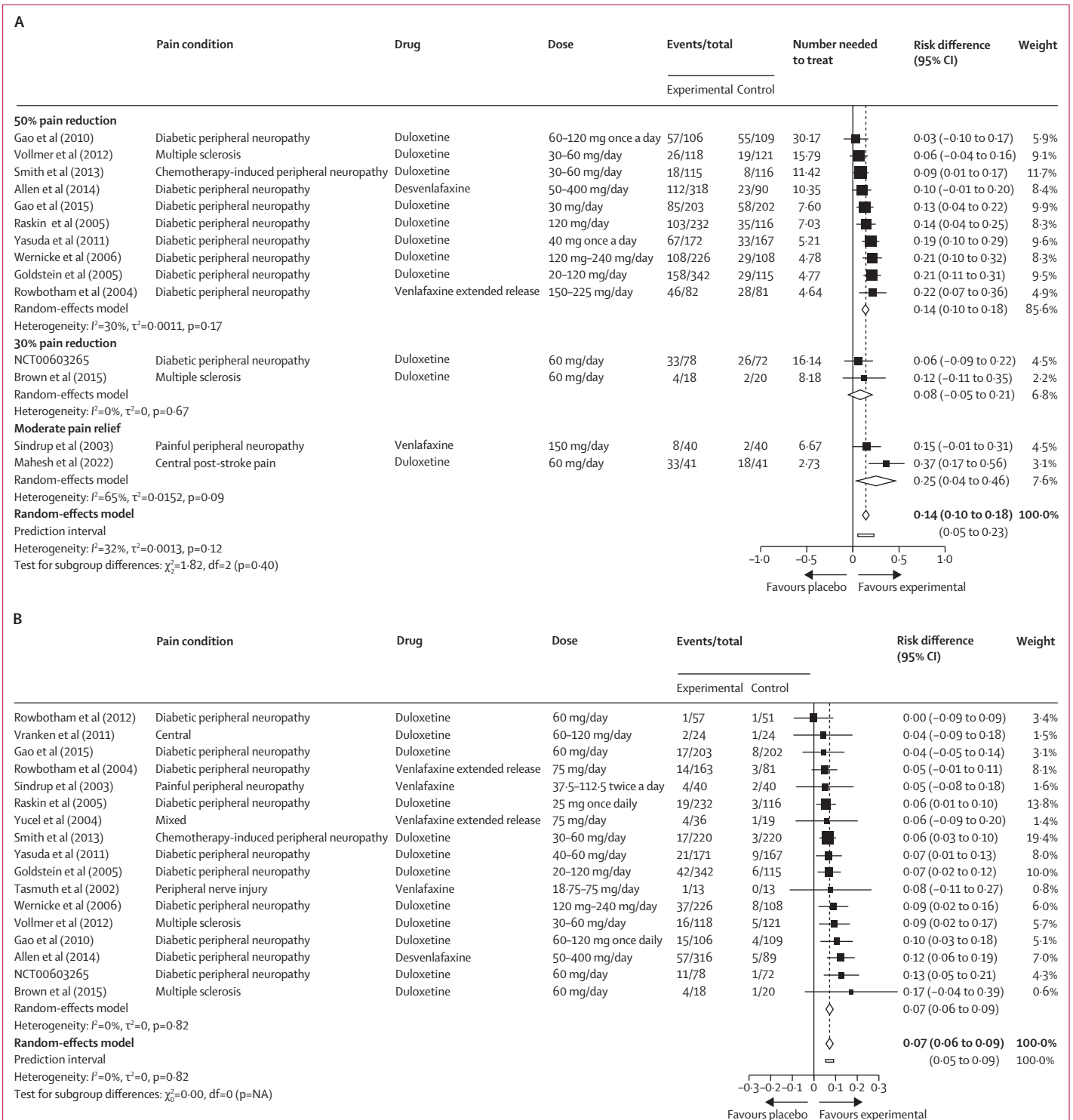


Figure 3: **Comparison of SNRIs *vs* placebo**
(A) Risk difference based on participants with 50% or 30% reduction in pain intensity or moderate pain relief and (B) risk difference based on the number of withdrawals.

(10·9–19·0; table 1, figure 3). Estimate of effect (19 comparisons) was SMD 0·4 (0·3–0·5; appendix p 65). There was a moderate certainty of evidence.

72 studies evaluated α2δ-ligands, which included pregabalin (45 studies), gabapentin (15 studies), gabapentin extended release (seven studies), and

mirogabalin (five studies). The combined NNT (56 studies) was 8·9 (95% CI 7·4–11·1) and NNH (65 studies) was 26·2 (20·4–36·5; table 1, figure 4). Estimate of effect (82 comparisons) was SMD 0·4 (0·3–0·5; appendix p 66). Removal of outliers did not change the NNT but decreased the SMD by 19% to 0·3 (0·26–0·36). There was moderate certainty of evidence.

18 studies evaluated opioids which included tramadol (six studies), oxycodone (six studies), morphine (four studies), buprenorphine (one study), and

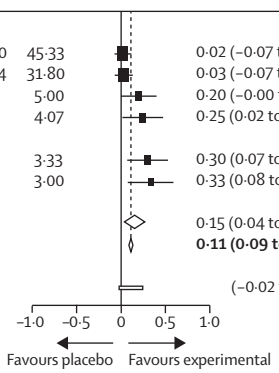
A

	Pain condition	Drug	Dose	Events/total		Number needed to treat	Risk difference (95% CI)	Weight
				Experimental	Control			
50% pain reduction								
Rauck et al (2012)	Diabetic peripheral neuropathy	Pregabalin	100 mg three times a day	14/66	35/120	−12·57	−0·08 (−0·23 to 0·07)	1·3%
Simpson et al (2014)	HIV	Pregabalin	600 mg/day	51/183	66/194	−16·26	−0·06 (−0·15 to 0·03)	2·1%
Simpson et al (2010)	HIV	Pregabalin	600 mg/day	59/151	65/151	−25·17	−0·04 (−0·15 to 0·07)	1·8%
Baba et al (2020)	Diabetic peripheral neuropathy	Pregabalin	75–150 mg twice a day	16/87	16/89	241·97	0·00 (−0·13 to 0·14)	1·5%
Ziegler et al (2015)	Diabetic peripheral neuropathy	Pregabalin	150 mg twice a day	19/70	15/62	33·91	0·03 (−0·15 to 0·21)	1·0%
Gordh et al (2007)	Mixed	Gabapentin	300–2400 mg/day	11/120	7/120	30·00	0·03 (−0·03 to 0·10)	2·5%
Kim et al (2011)	Central post-stroke pain	Pregabalin	75–300 mg twice a day	26/110	22/109	28·96	0·03 (−0·07 to 0·14)	1·8%
Raskin et al (2016)	Diabetic peripheral neuropathy	Pregabalin	30 mg twice a day	55/301	43/301	25·08	0·04 (−0·02 to 0·10)	2·6%
Markman et al (2018)	Peripheral nerve injury	Pregabalin	600 mg/day	78/275	64/267	22·76	0·04 (−0·03 to 0·12)	2·4%
Baba et al (2019)	Diabetic peripheral neuropathy	Mirogabalin	5–30 mg/day	118/500	64/334	22·53	0·04 (−0·01 to 0·10)	2·7%
Smith et al (2013)	Diabetic peripheral neuropathy	Pregabalin	150 mg/day	32/99	26/95	20·18	0·05 (−0·08 to 0·18)	1·6%
Holbech et al (2015)	Painful peripheral neuropathy	Pregabalin	300 mg/day	8/73	4/73	18·25	0·05 (−0·06 to 0·17)	1·8%
Huffman et al (2015)	Diabetic peripheral neuropathy	Pregabalin	150–300 mg/day	39/198	25/186	15·98	0·06 (−0·01 to 0·14)	2·4%
Baba et al (2020)	Diabetic peripheral neuropathy	Mirogabalin	10–30 mg/day	67/274	16/89	15·44	0·06 (−0·06 to 0·19)	1·6%
nKato et al (2019)	Postherpetic neuropathy	Mirogabalin	60 min	121/461	60/304	15·36	0·07 (0·00 to 0·13)	2·6%
Mu et al (2018)	Diabetic peripheral neuropathy	Pregabalin	300 mg /day	97/313	74/307	14·52	0·07 (−0·00 to 0·14)	2·4%
Sang et al (2013)	Postherpetic neuropathy	Gabapentin extended release	300–1800 mg/day	65/220	52/231	14·22	0·07 (−0·01 to 0·15)	2·3%
Serpell et al (2002)	Mixed	Gabapentin	300–800 mg three times a day	32/153	21/152	14·09	0·07 (−0·01 to 0·16)	2·2%
Tolle et al (2008)	Diabetic peripheral neuropathy	Pregabalin	150–600 mg/day	113/299	29/96	13·19	0·08 (−0·03 to 0·18)	1·9%
Hincker et al (2019)	Chemotherapy-induced peripheral neuropathy	Pregabalin	75–300 mg twice a day	5/26	3/26	13·00	0·08 (−0·12 to 0·27)	1·0%
Ushida et al (2022)	Spinal cord injury	Mirogabalin	10–30 mg/day	21/151	9/150	12·65	0·08 (0·01 to 0·15)	2·5%
Wallace et al (2010)	Postherpetic neuropathy	Gabapentin extended release	1800 mg/day	95/273	36/134	12·61	0·08 (−0·01 to 0·17)	2·1%
Rauck et al (2012)	Diabetic peripheral neuropathy	Gabapentin enacarbil	1200–3600 mg/day	87/234	35/120	12·48	0·08 (−0·05 to 0·21)	1·6%
Satoh et al (2010)	Diabetic peripheral neuropathy	Pregabalin	300–600 mg/day	55/179	29/135	10·82	0·09 (−0·00 to 0·19)	2·0%
PhRMA 1008–40 (2007)	Diabetic peripheral neuropathy	Pregabalin	600 mg/day	34/86	24/81	10·10	0·10 (−0·04 to 0·24)	1·4%
Moon et al (2010)	Diabetic peripheral neuropathy	Pregabalin	300 mg twice a day	42/162	11/78	8·46	0·12 (0·02 to 0·22)	1·9%
Vinik et al (2014)	Diabetic peripheral neuropathy	Pregabalin	150 mg twice a day	21/56	27/112	7·47	0·13 (−0·04 to 0·30)	1·2%
Cardenas et al (2013)	Spinal cord injury	Pregabalin	30 min	33/112	17/108	7·29	0·14 (0·03 to 0·25)	1·8%
Richter et al (2004)	Diabetic peripheral neuropathy	Pregabalin	150–600 mg/day	47/161	13/85	7·20	0·14 (0·04 to 0·24)	1·9%
Siddall et al (2006)	Spinal cord injury	Pregabalin	75–300 mg twice a day	15/70	5/67	7·16	0·14 (0·02 to 0·25)	1·8%
PhRMA A9451008 (2005)	Diabetic peripheral neuropathy	Gabapentin	3600 mg/day	75/196	45/187	7·04	0·14 (0·05 to 0·23)	2·1%
NCT00394901 (2007)	Postherpetic neuropathy	Pregabalin	150–600 mg/day	83/273	15/98	6·62	0·15 (0·06 to 0·24)	2·1%
Irving et al (2009)	Postherpetic neuropathy	Gabapentin extended release	1800 mg/day	29/107	6/51	6·52	0·15 (0·03 to 0·28)	1·7%
Vinik et al (2014)	Diabetic peripheral neuropathy	Mirogabalin	5–30 mg/day	113/284	27/112	6·38	0·16 (0·03 to 0·28)	1·6%
Zhang et al (2013)	Postherpetic neuropathy	Gabapentin enacarbil	1200–3600 mg/day	109/276	22/95	6·12	0·16 (0·06 to 0·27)	1·9%
Lesser et al (2004)	Diabetic peripheral neuropathy	Pregabalin	25 mg three times a day	94/260	17/97	5·37	0·19 (0·09 to 0·28)	2·0%
Rice et al (2001)	Postherpetic neuropathy	Gabapentin	1200–2400 mg/day	74/223	16/111	5·33	0·19 (0·10 to 0·28)	2·1%
Freynhagen et al (2005)	Mixed	Pregabalin	150–600 mg/day	86/273	8/65	5·21	0·19 (0·09 to 0·29)	2·0%
Jiang et al (2018)	Radiotherapy	Pregabalin	75 –600 mg/day	19/68	5/69	4·83	0·21 (0·08 to 0·33)	1·7%
van Seventer et al (2006)	Postherpetic neuropathy	Pregabalin	150–600 mg/day	83/275	8/93	4·63	0·22 (0·14 to 0·29)	2·3%
Sandercock et al (2012)	Diabetic peripheral neuropathy	Gabapentin gastric retentive	3000 mg/day	29/96	4/51	4·47	0·22 (0·11 to 0·34)	1·7%
Stacey et al (2008)	Postherpetic neuropathy	Pregabalin	150–600 mg/day	78/179	17/90	4·05	0·25 (0·14 to 0·36)	1·8%
Rosenstock et al (2004)	Diabetic peripheral neuropathy	Pregabalin	100 mg three times a day	30/76	10/70	3·97	0·25 (0·11 to 0·39)	1·5%
Arezzo et al (2008)	Diabetic peripheral neuropathy	Pregabalin	300 mg twice a day	40/82	20/85	3·96	0·25 (0·11 to 0·39)	1·4%
Sabatowski et al (2004)	Postherpetic neuropathy	Pregabalin	150–300 mg/day	63/157	8/81	3·31	0·30 (0·20 to 0·40)	2·0%
Dworkin et al (2003)	Postherpetic neuropathy	Pregabalin	300 or 600 mg/day	45/89	17/84	3·30	0·30 (0·17 to 0·44)	1·5%
Random-effects model							0·11 (0·09 to 0·13)	87·1%
Heterogeneity: I^2=63%, τ^2=0·0043, p<0·01								
30% pain reduction								
Rintala et al (2007)	Spinal cord injury	Gabapentin	1200 mg three times a day	8/38	12/38	−9·50	−0·11 (−0·35 to 0·14)	0·7%
Guan et al (2011)	Diabetic peripheral neuropathy	Pregabalin	300 mg twice a day	130/206	53/102	8·97	0·11 (−0·01 to 0·23)	1·7%
van Seventer et al (2010)	Peripheral nerve injury	Pregabalin	75–300 mg twice a day	50/127	32/127	7·06	0·14 (0·03 to 0·26)	1·8%
Liu et al (2015)	Postherpetic neuropathy	Pregabalin	300 mg/day	58/112	33/110	4·59	0·22 (0·09 to 0·34)	1·6%
Random-effects model							0·13 (0·06 to 0·21)	5·8%
Heterogeneity: I^2=45%, τ^2=0·0011, p=0·14								

(Figure 4 continues on next page)

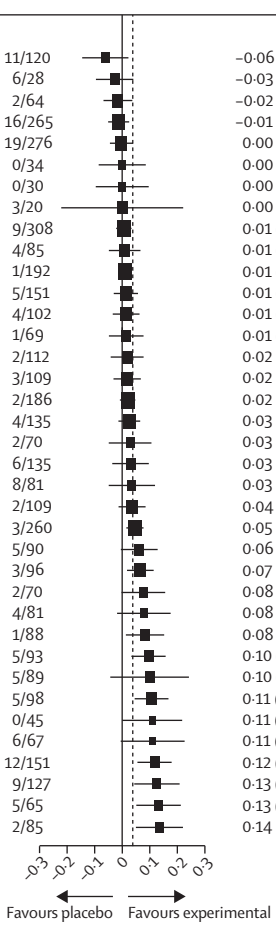
A

	Pain condition	Drug	Dose	Events/total		Number needed to treat	Risk difference (95% CI)	Weight
				Experimental	Control			
Moderate pain relief								
PhRMA A0081071 (2008)	Diabetic peripheral neuropathy	Pregabalin	600 mg/day	115/301	54/150	45·33	0·02 (−0·07 to 0·12)	2·1%
PhRMA A0081030 (2007)	Diabetic peripheral neuropathy	Pregabalin	600 mg/day	114/267	53/134	31·80	0·03 (−0·07 to 0·13)	1·9%
Gorson et al (1999)	Diabetic peripheral neuropathy	Gabapentin	300–900 mg/day	17/40	9/40	5·00	0·20 (−0·00 to 0·40)	0·9%
Gilron et al (2005)	Diabetic peripheral neuropathy and postherpetic neuropathy	Gabapentin	3200 mg/day	27/57	13/57	4·07	0·25 (0·02 to 0·47)	0·8%
Vranken et al (2008)	Central	Pregabalin	600 mg/day	7/20	1/20	3·33	0·30 (0·07 to 0·53)	0·8%
Smith et al (2005)	Phantom limb pain and residual limb pain	Gabapentin	300–3600 mg/day	13/24	5/24	3·00	0·33 (0·08 to 0·59)	0·6%
Random-effects model							0·15 (0·04 to 0·27)	7·1%
Heterogeneity: I^2=61%, τ^2=0·0120, p=0·02							**0·11 (0·09 to 0·13)**	**100·0%**
Random-effects model								
Prediction interval							(−0·02 to 0·24)	
Heterogeneity: I^2=61%, τ^2=0·0043, p=0·01								
Test for subgroup differences: χ^2_2=0·81, df=2, p=0·67								



B

	Pain condition	Drug	Dose	Events/total		Risk difference (95% CI)	Weight
				Experimental	Control		
Pregabalin							
Rauck et al (2012)	Diabetic peripheral neuropathy	Pregabalin	300 mg/day	2/66	11/120	−0·06 (−0·15–0·02)	1·2%
Moon et al (2010)	Diabetic peripheral neuropathy	Pregabalin	300 mg twice a day	8/62	6/28	−0·03 (−0·10–0·04)	1·6%
Jiang et al (2018)	Radiotherapy	Pregabalin	150 mg twice a day	1/64	2/64	−0·02 (−0·07–0·04)	2·1%
Markman et al (2018)	Peripheral nerve injury	Pregabalin	600 mg/day	13/274	16/265	−0·01 (−0·05–0·03)	2·7%
Raskin et al (2016)	Diabetic peripheral neuropathy	Pregabalin	300 mg/day	18/272	19/276	0·00 (−0·04–0·04)	2·5%
Alexander et al 2021)	Diabetic peripheral neuropathy	Pregabalin	300 mg/day	0/34	0/34	0·00 (−0·09–0·09)	1·1%
Mishra et al (2012)	Cancer	Pregabalin	150–600 mg/day	0/30	0/30	0·00 (−0·10–0·10)	1·0%
Vranken et al (2008)	Central	Pregabalin	50–600 mg/day	3/20	3/20	0·00 (−0·22–0·22)	0·2%
Mu et al (2018)	Diabetic peripheral neuropathy	Pregabalin	300 mg/day	11/313	9/308	0·01 (−0·02–0·03)	3·1%
Richter et al (2004)	Diabetic peripheral neuropathy	Pregabalin	150–600 mg/day	9/161	4/85	0·01 (−0·05–0·07)	1·9%
Simpson et al (2014)	HIV	Pregabalin	150–300 mg twice a day	3/183	1/192	0·01 (−0·01–0·03)	3·4%
Simpson et al (2010)	HIV	Pregabalin	150 mg/day	7/151	5/151	0·01 (−0·03–0·06)	2·4%
Guan et al (2011)	Diabetic peripheral neuropathy	Pregabalin	300 mg twice a day	11/206	4/102	0·01 (−0·03–0·06)	2·2%
Holbech et al (2015)	Painful peripheral neuropathy	Pregabalin	150 mg twice a day	2/69	1/69	0·01 (−0·05–0·08)	1·7%
Vinik et al (2014)	Diabetic peripheral neuropathy	Pregabalin	300 mg/day	2/56	2/112	0·02 (−0·04–0·08)	1·8%
Kim et al (2011)	Central post-stroke pain	Pregabalin	75–300 mg twice a day	5/110	3/109	0·02 (−0·03–0·07)	2·2%
Huffman et al (2015)	Diabetic peripheral neuropathy	Pregabalin	150–300 mg/day	6/198	2/186	0·02 (−0·01–0·05)	3·1%
PhRMA A0081030 (2007)	Diabetic peripheral neuropathy	Pregabalin	600 mg/day	15/271	4/135	0·03 (−0·01–0·07)	2·6%
Ziegler et al (2015)	Diabetic peripheral neuropathy	Pregabalin	150 mg twice a day	4/70	2/70	0·03 (−0·05–0·11)	1·3%
Satoh et al (2011)	Diabetic peripheral neuropathy	Pregabalin	300 mg/day	10/134	6/135	0·03 (−0·04–0·10)	1·6%
Sabatowski et al (2004)	Postherpetic neuropathy	Pregabalin	75–300 mg/day	21/157	8/81	0·03 (−0·05–0·12)	1·2%
Liu et al (2015)	Postherpetic neuropathy	Pregabalin	300 mg/day	6/111	2/109	0·04 (−0·01–0·08)	2·2%
Lesser et al (2004)	Diabetic peripheral neuropathy	Pregabalin	25–200 mg three times a day	15/260	3/260	0·05 (0·01–0·08)	3·0%
Stacey et al (2008)	Postherpetic neuropathy	Pregabalin	150–600 mg/day	21/179	5/90	0·06 (−0·01–0·13)	1·6%
Tolle et al (2008)	Diabetic peripheral neuropathy	Pregabalin	75 mg twice a day	29/299	3/96	0·07 (0·02–0·11)	2·2%
Rosenstock et al (2004)	Diabetic peripheral neuropathy	Pregabalin	100 mg three times a day	8/76	2/70	0·08 (−0·00–0·16)	1·3%
PhRMA 100840 (2007)	Diabetic peripheral neuropathy	Pregabalin	600 mg/day	11/86	4/81	0·08 (−0·02–0·18)	1·0%
Baba et al (2020)	Diabetic peripheral neuropathy	Pregabalin	300 mg/day	8/85	1/88	0·08 (0·01–0·15)	1·5%
van Seventer et al (2006)	Postherpetic neuropathy	Pregabalin	150–600 mg/day	41/275	5/93	0·10 (0·03–0·16)	1·7%
Chappell et al (2014)	Diabetic peripheral neuropathy	Pregabalin	300 mg/day	7/45	5/89	0·10 (−0·04–0·24)	0·5%
NCT00394901 (2007)	Postherpetic neuropathy	Pregabalin	150–600 mg/day	43/273	5/98	0·11 (0·05–0·17)	1·8%
McDonnell et al (2018)	Diabetic peripheral neuropathy	Pregabalin	150 mg twice a day	5/46	0/45	0·11 (−0·00–0·22)	0·8%
Siddall et al (2006)	Spinal cord injury	Pregabalin	75–300 mg twice a day	14/70	6/67	0·11 (−0·01–0·23)	0·7%
PhRMA A0081071 (2008)	Diabetic peripheral neuropathy	Pregabalin	600 mg/day	60/305	12/151	0·12 (0·06–0·18)	1·7%
van Seventer et al (2010)	Peripheral nerve injury	Pregabalin	75 –300 mg twice a day	25/127	9/127	0·13 (0·04–0·21)	1·2%
Freynhagen et al (2005)	Mixed	Pregabalin	150–600 mg/day	57/273	5/65	0·13 (0·05–0·21)	1·2%
Arezzo et al (2008)	Diabetic peripheral neuropathy	Pregabalin	300 mg twice a day	13/82	2/85	0·14 (0·05–0·22)	1·2%



(Figure 4 continues on next page)

B

	Pain condition	Drug	Dose	Events/total		Risk difference (95% CI)	Weight
				Experimental	Control		
Hincker et al (2019)	Chemotherapy-induced peripheral neuropathy	Pregabalin	75–300 mg twice a day	5/25	1/25	0·16 (−0·01 to 0·33)	0·4%
Satoh et al (2011)	Diabetic peripheral neuropathy	Pregabalin	600 mg/day	12/45	6/135	0·22 (0·08 to 0·36)	0·5%
Dworkin et al (2003)	Postherpetic neuropathy	Pregabalin	300 or 600 mg/day	28/89	4/84	0·27 (0·16 to 0·37)	0·8%
Smith et al (2013)	Diabetic peripheral neuropathy	Pregabalin	150 mg/day	10/99	8/95		0·0%
Random-effects model						0·04 (0·03 to 0·06)	66·2%
Heterogeneity: I^2=62%, τ^2=0·0017, p<0·01							
Mirogabalin							
Kato et al (2019)	Postherpetic neuropathy	Mirogabalin	15–30 mg/day	36/461	12/304	0·04 (0·01 to 0·07)	2·9%
Ushida et al (2022)	Spinal cord injury	Mirogabalin	20–40 mg/day	14/151	6/148	0·05 (−0·00 to 0·11)	1·9%
Vinik et al (2014)	Diabetic peripheral neuropathy	Mirogabalin	5–15 mg/day	20/284	2/112	0·05 (0·01 to 0·10)	2·3%
Baba et al (2020)	Diabetic peripheral neuropathy	Mirogabalin	10–30 mg/day	18/273	1/88	0·05 (0·01 to 0·10)	2·4%
Random-effects model						0·05 (0·03 to 0·07)	9·6%
Heterogeneity: I^2=0%, τ^2=0, p<0·93							
Gabapentin							
Gilron et al (2005)	Diabetic peripheral neuropathy and postherpetic neuropathy	Gabapentin	3000–3200 mg/day	1/48	1/44	0·00 (−0·09 to 0·08)	1·1%
Levendolu et al (2004)	Spinal cord injury	Gabapentin	900–3600 mg/day	0/20	0/20	0·00 (−0·09 to 0·09)	1·0%
Mishra et al (2012)	Cancer	Gabapentin	300–600 mg/day	0/30	0/30	0·00 (−0·10 to 0·10)	1·0%
Simpson et al (2001)	Diabetic peripheral neuropathy	Gabapentin	600–2700 mg/day	2/30	2/30	0·00 (−0·13 to 0·13)	0·6%
PhRMA A9451008 (2005)	Diabetic peripheral neuropathy	Gabapentin	3600 mg/day	15/200	11/189	0·02 (−0·03 to 0·07)	2·2%
Serpell et al (2002)	Mixed	Gabapentin	300–800 mg three times a day	20/153	17/152	0·02 (−0·05 to 0·09)	1·4%
Backonja et al (1998)	Diabetic peripheral neuropathy	Gabapentin	Up to 3600 mg/day	7/84	5/81	0·02 (−0·06 to 0·10)	1·3%
Gordh et al (2007)	Mixed	Gabapentin	300–2400 mg/day	7/113	4/111	0·03 (−0·03 to 0·08)	1·9%
Rowbotham et al (1998)	Postherpetic neuropathy	Gabapentin	100–1200 mg three times a day	21/113	14/116	0·07 (−0·03 to 0·16)	1·0%
Hahn et al (2004)	HIV	Gabapentin	400–2400 mg/day	1/15	0/11	0·07 (−0·12 to 0·25)	0·3%
Rice et al (2001)	Postherpetic neuropathy	Gabapentin	1200–2400 mg/day	34/223	7/111	0·09 (0·02 to 0·15)	1·6%
Rintala et al (2007)	Spinal cord injury	Gabapentin	1200 mg three times a day	5/32	2/31	0·09 (−0·08 to 0·27)	0·4%
Random-effects model						0·03 (0·01 to 0·05)	13·9%
Heterogeneity: I^2=0%, τ^2=0, p<0·85							
Gabapentin extended release							
Gewandter et al (2019)	Radiculopathy	Gabapentin extended release	1800 mg/day	0/32	4/32	−0·12 (−0·25 to −0·00)	0·6%
Wallace et al (2010)	Postherpetic neuropathy	Gabapentin extended release	1800 mg/day	31/272	15/133	0·00 (−0·06 to 0·07)	1·6%
Sandercock et al (2012)	Diabetic peripheral neuropathy	Gabapentin extended release	3000 mg/day	4/96	2/51	0·00 (−0·06 to 0·07)	1·6%
Zhang et al (2013)	Postherpetic neuropathy	Gabapentin enacarbil	1200–3600 mg/day	34/276	11/95	0·01 (−0·07 to 0·08)	1·4%
Sang et al (2013)	Postherpetic neuropathy	Gabapentin extended release	300–1800 mg/day	19/221	8/231	0·05 (0·01 to 0·10)	2·4%
Rauck et al (2012)	Diabetic peripheral neuropathy	Gabapentin enacarbil	1200 mg/day	38/234	11/120	0·07 (−0·02 to 0·16)	1·1%
Irving et al (2009)	Postherpetic neuropathy	Gabapentin extended release	1800 mg/day	10/107	1/51	0·07 (0·01 to 0·14)	1·6%
Random-effects model						0·03 (−0·01 to 0·06)	10·3%
Heterogeneity: I^2=46%, τ^2=0·0006, p<0·01							
Random-effects model						**0·04 (0·03 to 0·05)**	**100·0%**
Prediction interval						(−0·02 to 0·10)	
Heterogeneity: I^2=50%, τ^2=0·0008, p<0·01							
Test for subgroup differences: χ^2_3=2·44, df=3 (p=0·49)							

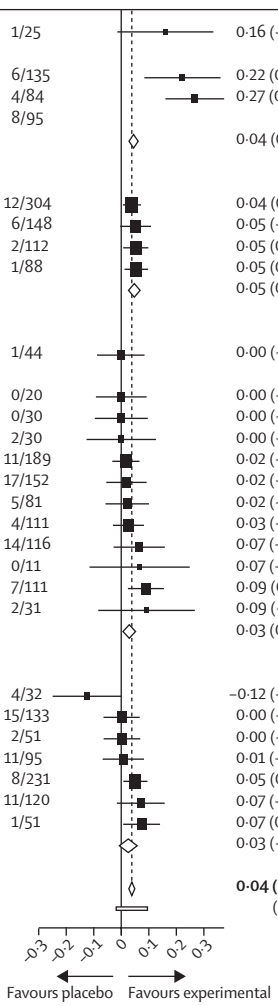


Figure 4: **Comparison of α2δ-ligands *vs* placebo**
(A) Risk difference based on participants with 50% or 30% reduction in pain intensity or moderate pain relief and (B) risk difference based on the number of withdrawals.

methadone (one study). The combined NNT for opioids (11 studies) was 5·9 (95% CI 4·1–10·7), estimate of effect (18 comparisons) SMD 0·4 (0·3–0·6), and NNH (16 studies) 15·4 (10·8–24·0; table 1; appendix pp 68–69). There was low certainty of evidence.

11 studies evaluated BTX-A, two of which were done in people with trigeminal neuralgia (and not included in the meta-analysis). The combined NNT (six studies) was 2·7 (95% CI 1·8–5·1), estimate of effect (six comparisons) SMD 0·5 (0·2–0·9), and NNH (eight studies) was 216·3 (23·5–∞). Removal of an outlier increased the NNT by 21% to 3·4 (2·3–6·1; table 1, appendix pp 70–71). There was moderate certainty of evidence.

Capsaicin (0·025–0·125% concentration) cream, capsaicin 8% patches, and lidocaine 5% plasters were evaluated in 13, 9, and 4 studies, respectively. For capsaicin cream, the combined NNT (seven studies) was 6·1 (95% CI 3·1–∞), estimate of effect (seven comparisons) SMD 0·3 (–0·1 to 0·6) and NNH (13 studies) was 18·6 (10·6–77·1; table 1; appendix pp 72–73). For capsaicin 8% patches, the combined NNT (seven studies) was 13·2 (7·6 to 50·8), an estimate of effect (12 comparisons) SMD 0·4 (0·1–0·8) and NNH (seven studies) was 1129·3 (135·7 to ∞; table 1; appendix pp 74–75). For lidocaine 5% plasters, the combined NNT (three studies) was 14·5 (7·8 to 108·2), an estimate of effect (three comparisons) SMD 0·2 (–0·2 to 0·5) and

	Daily dosages and dose regimen*	Recommendation
Strong recommendation for use		
α2δ-ligands	Gabapentin 1200–3600 mg in three divided doses Gabapentin ER 1200–3600 mg in two divided doses Pregabalin 150–600 mg in two divided doses Mirogabalin 10–30 mg in two divided doses	First line
SNRIs	Duloxetine 60–120 mg once a day Venlafaxine 150–225 mg once a day or in two divided doses	First line
Tricyclic antidepressants†	25–150 mg once a day or in two divided doses	First line
Weak recommendation for use		
Lidocaine 5% plasters‡	1–3 plasters to the painful area for up to 12 h per day	Second line for peripheral neuropathic pain
Capsaicin 8% patches‡	1–4 patches to the painful area for 30–60 min with a minimal application interval of 60 days	Second line for peripheral neuropathic pain
Capsaicin cream‡§	Usually 0·075% one to three times per day	Second line for peripheral neuropathic pain
Botulinum toxin type A‡	50–300 units to the painful area every 3 months	Third line for peripheral neuropathic pain
rTMS (10–20 Hz targeting M1)§	1200–3000 pulses per session	May be used in selected patients
Opioids§¶	Usually <120 mg morphine equivalent in two divided doses Tramadol 200–400 mg in two extended releases or three divided doses	May be used in selected patients

Drugs pertaining to the same drug class are presented in alphabetical order. ER=extended release. NA=not applicable. *Initiate systemic drugs at low doses, titrating slowly. Consult product information for precautions and contraindications. †TCAs are not recommended in older adults because of their anticholinergic and sedative side effects and increased potential risk of falls.[18] An increased risk of sudden cardiac death has been reported for doses over 100 mg/day. ‡Recommended for people living with peripheral neuropathic pain in a localised area, which can be covered by the allowed number of capsaicin 8% patches or lidocaine 5% plasters. This locally applied treatment may be appropriate as first line treatment in vulnerable patients (eg, older adults or people with multiple diseases, or in cases of polypharmacy). §Change from the 2015 recommendations: capsaicin cream, previously inconclusive, is now second-line, particularly if capsaicin 8% patches are not available, with a weak recommendation; tramadol, previously second-line, is now grouped with opioids and recommended as third-line with a weak recommendation; rTMS was not evaluated in 2015. ¶In patients who have not responded to other reasonable treatments, within the shortest possible duration of use.

Table 2: **First-line, second-line, and third-line recommendations for the drugs or drug classes or neuromodulation treatments for neuropathic pain based on the GRADE classification**

NNH (four studies) was 178·0 (23·9 to ∞; table 1; appendix p 76). Certainty was rated moderate for capsaicin 8% and very low for capsaicin cream and lidocaine 5% plasters.

15 studies evaluated rTMS at several targets, predominantly the primary motor cortex (12 studies). For rTMS at the primary motor cortex (M1), the combined NNT (six comparisons) was 4·2 (95% CI 2·3–28·3), estimate of effect (14 comparisons) SMD 0·9 (0·4–1·4) and NNH (12 comparisons) was 651·6 (34·7–∞). Removal of an outlier increased the NNT by 36% to 6·6 (3·67–31·97) and decreased SMD by 15% to 0·8 (0·3–1·3; table 1; appendix p 77). There was low certainty of evidence.

Meta-analyses of cannabinoids, carbamazepine–oxcarbazepine, lacosamide, lamotrigine, levetiracetam, NMDA receptor antagonists, mexiletine, topiramate, and transcranial direct current stimulation (tDCS) are presented in the appendix pp 79–93.

A total of 191 published or unpublished studies with dichotomous data were analysed for publication bias. Visual inspection of the funnel plot showed asymmetry, and trim and fill imputed 37 theoretically missing studies. This reduced the summary of efficacy (risk difference) from 0·12 (95% CI 0·11–0·14) to 0·08 (0·06–0·10; appendix pp 94–95). The analysis of susceptibility to bias is summarised in table 1. Only the estimated effect of capsaicin cream showed susceptibility to change to a non-significant effect. Subgroup analyses

Panel: **First-line, second-line, and third-line recommendations for the drugs or drug classes or neuromodulation treatments for neuropathic pain with inconclusive recommendations or recommendations against us based on the GRADE classification**

Inconclusive evidence for use*

- Carbamazepine–oxcarbazepine†
- Lacosamide
- Lamotrigine
- NMDA
- Selective serotonin reuptake inhibitors
- Transcranial direct current stimulation
- Transcutaneous electrical nerve stimulation
- Spinal cord stimulation
- Topiramate

Recommendations against use

- Cannabinoids
- Valproate
- Levetiracetam
- Mexiletine‡

*The remaining interventions which were assessed as inconclusive due to insufficient evidence are listed in the appendix pp 23–43. †For trigeminal neuralgia, these two drugs are recommended as first-line for long-term carbamazepine (200–1200 mg/day) or oxcarbazepine (300–1800 mg/day) in three divided doses.[19,20] ‡For the treatment of inherited erythromelalgia (300–600 mg/day in three divided doses) this drug may be of benefit.[21]

showed that overall risk of bias and trial design did not influence treatment effects (appendix pp 94–95).

The GRADE classifications and recommendations for use are summarised in table 2 and the panel, and further details are provided in the appendix (pp 96–102). The recommendations apply to neuropathic pain in general and because none of the studies assessed paediatric neuropathic pain, these guidelines only apply to adults.

Discussion

We present the revised NeuPSIG recommendations, which for the first time evaluated both pharmacological and neuromodulation treatment of people with neuropathic pain. According to existing standards to minimise errors and bias,[22] we did a comprehensive systematic review and meta-analysis of 313 double-blind, randomised controlled trials. The recommendations are based on the quality of available evidence and expert consensus, with representation from 13 countries and every continent. This updated guideline included sensitivity analyses to evaluate the effect of potential biases, and qualitatively assessed each treatment's adverse effects, cost, and accessibility. Additionally, lived experience partners were engaged from inception.

33 studies were rated as being at low risk of bias across all domains; the remaining studies were rated as having some concerns or high risk of bias in at least one domain, and typically in several domains. Our analysis also revealed evidence of publication bias, which might have led to an overestimation of effects, but we cannot rule out alternative explanations including heterogeneity and small study effects. Risks of bias, high heterogeneity in some meta-analyses, and imprecision reduced the certainty of evidence. Five treatment categories—α2δ-ligands, SNRIs, TCAs, BTX-A, and capsaicin 8% patches—were rated with moderate certainty. According to the GRADE definition,[23,24] this means that "the true effect is likely to be close to the estimate of effect but there is a possibility that it is substantially different." The remaining categories received a low or very low-certainty rating, indicating that we have little confidence in the effect estimate, and that the true effect might differ significantly from the estimate.[23,24]

The recommendations are for all neuropathic pain; the evidence in the review is not sufficient to confidently make recommendations for specific patient populations. Based on so-called strong for GRADE recommendations (moderate to high certainty of evidence), and because there is no evidence of superiority of any of these drugs in head-to-head trials,[25] we continue to propose TCAs, SNRIs, and α2δ-ligands as first-line treatments. However, we acknowledge the increased risk of TCA adverse effects in older adults, as well as an increased risk of drug-related death in people taking both α2δ-ligands and opioids[8] particularly regarding pregabalin.[26,27] Therefore, we recommend that prescribers systematically assess the applicable risks when proposing these treatments.

As second-line treatment, we recommend topical treatments for localised peripheral neuropathic pain. Capsaicin 8% patches (moderate certainty of evidence), lidocaine 5% plaster (very low), and capsaicin cream (very low), although of low effectiveness, have high safety and tolerability. These treatments might be proposed as first-line in patients who are susceptible (eg, older adults or in the presence of multiple comorbidities or medications with high risk of drug interactions). It has been suggested that suppression of peripheral inputs might be beneficial in central post-stroke pain; studies are needed to confirm the potential benefit of topical treatments for central neuropathic pain.[28]

As in previous recommendations, we recommend botulinum toxin type A injection as third-line. This recommendation balances the moderate certainty of evidence, large effect size, and good safety profile with the evidence based predominantly on small trials for refractory peripheral neuropathic pain, and restricted accessibility.

The distinction between weak and strong opioids is increasingly questioned, as the risks associated with this therapeutic class depend mainly on dose.[29] With more than 70 000 opioid overdose deaths per year in the US in recent years (20 000 of which were from prescription opioids[30]), the opioid crisis is still prevalent.[30] We recommend that the use of all opioids, including the weak opioid agonist, tramadol, should be restricted to third-line in patients with worsening pain who have not responded to other reasonable treatments, with the shortest possible duration of use, and early and ongoing review, considering the risk of misuse and abuse.[31]

Consistent with French guidelines,[32] our meta-analysis included 29 sham-controlled trials of invasive and non-invasive neuromodulation techniques, the majority (14) of which involved rTMS. Only studies of high-frequency motor cortex rTMS (and not other cortical targets or lower frequencies) were efficacious, whereas results with tDCS were inconclusive; our analysis was limited by the trials having different targets. We also were not able to assess stimulation parameters which varied across trials and might also be a source of heterogeneity. Although the effect size of M1-rTMS was greater than that of many drug treatments, we propose it as third-line owing to the low certainty of evidence, low availability, and high cost. In contrast to non-invasive brain stimulation, we found only one sham-controlled trial of spinal cord stimulation (SCS) for painful radiculopathy.[33] SCS use is increasing and is recommended by clinical guidelines and licensed in the EU, the UK,[34] and the USA; however, a systematic review and meta-analysis of implanted neuromodulation for chronic pain report "very-low certainty evidence that SCS may not provide clinically important benefit on pain intensity" compared with sham.[35] There is a need for large, double-blind, sham controlled, parallel trials over clinically relevant

timeframes to examine the relative efficacy and safety of SCS to allow for comparison with other interventions.[36,37]

Cannabinoids received a so-called weak against recommendation, and, in accordance with other meta-analyses,[38–40] are not efficacious. Other drug therapies received inconclusive recommendations although some are recommended for specific neuropathic pain conditions. For example, carbamazepine and oxcarbazepine are recommended as first line drugs for patients with trigeminal neuralgia[41] and mexiletine is commonly used for the treatment of erythromelalgia.[21]

Lastly, we were unable to draw any conclusions about drug combinations owing to the paucity of trials including a placebo group. A 2023 systematic review and meta-analysis of combinations (opioids with antidepressants or α2δ-ligands, and α2δ-ligands with antidepressants) showed no greater efficacy and found similar safety compared with each drug alone.[42] Effective combination therapy is considered a key strategy in pain management; when and how to combine might be addressed by clinical thinking (eg, partial response to the first drug tried, then add-on a second drug with a different mechanism that is not expected to compound adverse effects). However, existing evidence and evidence included in this review is insufficient to recommend any specific combination with confidence. Further research is necessary to identify optimal combinations and improve treatment outcomes.

Our recommendations prioritise patient autonomy by offering a range of treatment options, highlighting the benefits, harms, and uncertainties of each. Since neuropathic pain affects individuals differently, it is crucial to consider patient values and preferences for high-quality, patient-centred care, which may also include modalities such as psychological interventions.[43,44] Shared decision-making helps patients understand risks and benefits while expressing their concerns. Treatment choices depend on factors such as efficacy, safety, administration, and effect on daily activities, accessibility, and mental health.[45] Understanding preferences allows for personalised care, often through individual treatment trials,[46–48] enabling tailored, effective treatment.

Interpretation of these results and subsequent recommendations must account for possible limitations. Although our study was pre-registered on PROSPERO, we acknowledge that the level of detail in the registration might not fully prevent the potential for selective decision-making. However, we did the review in accordance with our protocol and have reported our methods and findings transparently, clearly documenting any deviations. Design, outcome, and reporting inconsistencies have contributed to changes in treatment effect estimates in recent studies.[49] We also observed significant variability in the characteristics of the clinical trials included in this review, which contributed to heterogeneity and reduced the precision of our meta-analyses. In line with methods from our previous review,[8] we combined 50% and 30% response rates for efficacy analyses on the basis that NNTs calculated from these endpoints are similar.[50] This approach increased the amount of data included in each analysis; however, we acknowledge that it might affect the treatment effect size. Although the crossover design, used in one-third of studies, was not shown to influence treatment effect, many trials did not report phase-by-phase data. Therefore, we included the results as reported without the ability to adjust for the paired nature of these studies. This limitation presents a potential unit of analysis issue and might overestimate the precision of the effect. A last limitation is that treatment effect cannot always be compared across drugs as there are differences in study design and placebo responses.[51,52] Many of the studies of TCAs are older, had small sample sizes, and have lower placebo response rates than, for example, newer studies of SNRIs or pregabalin. Further comparative trials are needed to study relative treatment effects.

The generally modest and decreasing estimates of effect seen in pharmacotherapy might be attributed to changes that have occurred over time, including larger study size and longer study duration.[51] Another potential source of heterogeneity is participant phenotypes, which potentially reflect different underlying mechanisms. Notably, certain drugs targeting specific mechanisms have shown greater efficacy in participants stratified by sensory phenotype, although with conflicting results.[53–56] Predictive algorithms, such as those proposed for rTMS,[57] might offer a way to personalise therapy further.

A shortage of data prevented us from analysing dose–response relationships and some trials used lower than maximum recommended doses. For example, some studies used pregabalin 300 mg/day as an active control group, which is half the maximum recommended dose.[58,59]

There was a notable lack of detail regarding how adverse events were measured and classified. Furthermore, the short-term follow-up in many trials, combined with potential under-reporting of adverse events, raised concerns about the data completeness. As a result, we also did a qualitative assessment of known harms rather than relying on the calculated NNHs alone.

Our review has highlighted that for some treatments much uncertainty remains. This can be remedied by large placebo-controlled or sham-controlled parallel trials done over clinically relevant timeframes.

It is necessary for health-care professionals to adapt these recommendations to their own contexts, to consider the cost and accessibility of each treatment, as well as individual patient values and preferences, to ensure their quality implementation in health care.

NeuPSIG Review Update Study Group
UK: R Abuukar Abdullahi, M Evans, B Gwyther, H Phillips, C Ramirez Piriz, A Rottenberg, D Hohenschurz-Schmidt, C Wang, A Zachariadis. *UK–Germany*: J D Wandrey. *Austria:* S Freigang. *Brazil:* Gabriel Taricani Kubota. *France:* J Phalip. *Indonesia:* T Istri Pramitasuri. *Philippines:* N Taule-Lim. *Vietnam:* Q V Than. *Bangladesh:* M D Zunaid.

Contributors

Conceptualisation (Protocol development): NS, XM, JB, FT, ASCR, NA, NBF, SH. Funding acquisition (in person meeting): XM. Funding acquisition (NS salary): ASCR, NS. Data curation and formal analysis: NS. Investigation: NS, XM, DCdA, RAA, M Evans, MCF, SF, BG, DH-S, PRK, HK, EKE-K, GTK, EM, JP, HP, CRP, TIP, AR, NT-L, QVT, JV, JDW,AZ, MDZ, NA, NBF. Methodology: NS, XM, JB, FT, ASCR, NA, NBF, SH. Project administration: NS. In person meeting administration: XM, NA, NS. Supervision: NS, NA, NBF, SH. Validation: NS, XM, RAA, DCdA, RB, JB, DLHB, MC, PD, ME, MCF, SF, BG, DH-S, AJH, IG, KH, PRK, HK, EKE-K, GTK, EM, JP, HP, TJP, CRP, BHS, TIP, SNR, ASCR, AR, FT, NTL, QVT, AT, JV, JDW, CW, AZ, MDZ, NA, NBF, SH. Visualisation: NS. GRADE and evidence to recommendations: NS, XM, DCdA, RB, DLHB, MC, PD, MCF, AJH, IG, KH, PRK, HK, EKE-K, EM, TJP, BHS, SNR, ASCR, AT, JV, NA, NBF, SH. Writing—original draft: NS, XM. Writing—review and editing: NS, XM, RAA, DCdA, RB, JB, DLHB, MC, PD, ME, MCF, SF, BG, DH-S, AJH, IG, KH, PRK, HK, EKE-K, GTK, EM, JP, HP, TJP, CRP, BHS, TIP, SNR, ASCR, AR, FT, NT-L, QVT, AT, JV, JDW, CW, AZ, MDZ, NA, NBF, SH. NS, XM, RAA, DCdA, RB, JB, DLHB, MC, PD, ME, MCF, SF, BG, DH-S, AJH, IG, KH, PRK, HK, EKE-K, GTK, EM, JP, HP, TJP, CRP, BHS, TIP, SNR, ASCR, AR, FT, NT-L, QVT, AT, JV, JDW, CW, AZ, MDZ, NA, NBF, and SH verified the data and accept responsibility for the decision to submit for publication.

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ASCR declares the following (last 36 months): Officer of IASP; employee of Imperial College London; consultancy for Imperial College Consultants- has included remunerated work for: Astra Zeneca, Pharmnovo, Confo, Combigene, and Shanghai SIMR Biotech & Science Practice (Wellcome Trust); inventor on patents WO 2005/079771 & EP13702262.0/ WO2013 110945. Member Joint Committee on Vaccine and Immunisation—varicella sub-committee; Analgesic Clinical Trial Translation: Innovations, Opportunities, and Networks steering committee member. Medicines and Healthcare products Regulatory Agency, Commission on Human Medicines—Neurology, Pain & Psychiatry Expert Advisory Group. 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Data Sharing

Data will be openly available on publication on the Open Science Framework DOI 10.17605/OSF.IO/KJQ9U.

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