Neuropathic
Review

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A systematic review and meta-analysis of randomized controlled head-to-head trials of recommended drugs for neuropathic pain

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Abstract

Neuropathic pain is a challenging chronic pain condition. Limited knowledge exists regarding the relative effectiveness of pharmacological treatments, and differences in trial design and impact of the placebo response preclude indirect comparisons of efficacy between drug classes. The purpose of this systematic review and meta-analysis of head-to-head trials was to compare the efficacy and tolerability of drugs recommended for neuropathic pain. We conducted a systematic review and meta-analysis of direct-comparison double-blind randomized trials. Primary outcomes were mean change in pain intensity and number of responders with a 50% reduction in pain intensity. Secondary outcomes encompassed quality of life, sleep, emotional functioning, and number of dropouts because of adverse events. We included 30 trials (4087 patients), comprising 16 crossover and 14 parallel-group design studies. All studies were conducted in adults, and the majority were investigator-initiated trials. We found moderate-quality evidence for equivalence (no clinically relevant difference) between tricyclic antidepressants (TCA) and gabapentin/pregabalin with a combined mean difference in pain score of 0.10 (95% CI −0.13 to 0.32). We could not document differences between TCA and serotonin–noradrenaline reuptake inhibitors (SNRI), between SNRI and gabapentin/pregabalin, or between opioids and TCA (low quality of evidence). We found more dropouts because of adverse events with SNRI and opioids compared with TCA (low quality of evidence). We did not identify any studies that included topical treatments. This systematic review of direct-comparison studies found evidence for equivalence between TCA and gabapentin/pregabalin and fewer dropouts with TCA than SNRI and opioids.

Keywords: Neuropathic pain, Systematic review, Pharmacotherapy, Randomized controlled trial, Comparative

1. Introduction

Neuropathic pain is a common and challenging chronic pain condition.[47,59] Despite posing a significant human and economic burden, effective pain relief remains an unmet global need.

As for all chronic pain conditions, treatment of neuropathic pain should follow a multidisciplinary approach. However, in this review, we only consider pharmacological treatments. The current international recommendation for pharmacotherapy in neuropathic pain, as outlined by the Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain (IASP) from 2015, included 8 different drug types.[13] First-line treatments are tricyclic antidepressants (TCA), serotonin–noradrenaline reuptake inhibitors (SNRI), pregabalin, and gabapentin, second-line treatments lidocaine patches, capsaicin high-concentration patches, and tramadol, and third-line treatments strong opioids and botulinum toxin type A (BTX-A). The recommendations are based on placebo-controlled randomized trials, with efficacy assessed through numbers needed to treat (NNT) and tolerability using numbers needed to harm (NNH) and the certainty of evidence assessed according to the Grading of

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Recommendations Assessment, Development, and Evaluation (GRADE) criteria.

The relative treatment effect of recommended drugs for neuropathic pain cannot be estimated reliably from indirect treatment comparisons of effect sizes or network meta-analysis. Several factors contribute to this challenge. First, differences in study design preclude a direct comparison. As an example, most studies assessing TCA are small crossover studies with per-protocol analyses, which may overestimate treatment effect compared with studies assessing pregabalin that are most often larger and parallel-design studies with ITT analyses.[13] Second, emerging evidence suggests that the effect size cannot be reliably estimated by subtracting the placebo response from the active treatment response.[14,32] Notably, studies with high placebo responses may underestimate the true treatment effect.[24,25,29,34] Consequently, if there exists an interaction between the placebo and drug effect, network meta-analyses become inadequate for inferring relative effectiveness and tolerability.

Although the NeuPSIG review included active comparator trials of first- and second-line drugs,[13] it did not include third-line drugs and has not been updated since the search was conducted in April 2013 and did not include other outcomes than NNT and NNH. Therefore, the purpose of this systematic review was to compare the efficacy and tolerability of first-, second-, and third-line drugs for neuropathic pain through head-to-head trials. The aim is to complement the work in progress by NeuPSIG to update the 2015 guidelines as these only consider placebo-controlled trials.

2. Methods

This review adhered to guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.[39] The protocol for this systematic review was registered in Prospero (ID: CRD42022364481) before the conduct of the review. There was 1 deviation from the protocol: In the protocol, our search in clinical trials registers was limited to clinicaltrialsregister.eu, but we also included clinicaltrials.gov in the search for unpublished studies with results.

2.1. Eligibility criteria

2.1.1. Design

We included comparative, double-blind randomized controlled trials (RCTs) with parallel-group or crossover study designs that investigated the analgesic effect of at least 2 first-, second-, and third-line drugs for neuropathic pain.[13] We only included double-blind RCTs to reduce the risk of bias. Studies were required to examine neuropathic pain as the primary target condition. As in the NeuPSIG systematic review,[13] studies with a treatment duration of at least 21 days (or a follow-up for at least 21 days in case of single treatment) and with at least 10 patients per group were eligible for inclusion. Randomized controlled trials without an active comparison group, single case reports, clinical observations, and studies published only as abstracts were excluded.

2.1.2. Population

Studies eligible for inclusion included patients of any age with neuropathic pain, as defined by the IASP definition (ie, pain caused by a lesion or disease of the somatosensory nervous system) and the current *ICD-11*.[26,52] This included, but was not restricted to, diabetic, chemotherapy-induced and other painful polyneuropathies, postherpetic neuralgia, postamputation pain, post-traumatic or postsurgical neuropathic pain, painful radiculopathy, central poststroke pain, spinal cord injury pain, and mixed neuropathic pain. Conditions not considered neuropathic according to the current definitions, such as complex regional pain syndrome and fibromyalgia, were not included.

2.1.3. Interventions and comparators

We considered studies examining at least 2 pharmacological treatments recommended by the current NeuPSIG treatment recommendation of 2015[13]: TCA, SNRI, pregabalin, gabapentin (including gabapentin extended release and enacarbil), lidocaine patches, capsaicin high-concentration patches, tramadol, strong opioids, and BTX-A. A placebo treatment was not required.

2.1.4. Outcomes

We grouped the outcomes of interest into primary and secondary outcomes. Primary outcomes measured the effectiveness of interventions and included (1) mean change from baseline to the last week of treatment in pain intensity scales (eg, using a numerical rating scale or visual analogue scale) and (2) number of responders defined as the proportion of patients with 50% reduction in pain intensity. If this information was unavailable, we considered a 30% pain reduction or alternatively at least moderate pain relief.

Secondary outcomes were Patient Global Impression of Change (PGIC), quality of life (QoL), sleep duration and quality, emotional functioning (eg, anxiety and depression), number of withdrawals during active treatment, number of dropouts because of adverse events, and adverse events.

2.2. Search methods and study selection

We adhered to the PRISMA for Searching (PRISMA-S) extension.[46] We conducted a literature search for available trials until July 2023 in the electronic databases PubMed, Embase, Cochrane central, clinicaltrial.gov, clinicaltrialsregister.eu, FDA, and EMEA websites. Only studies published in English were searched for and included. Search strategies are available in the supplementary. Record management was conducted using the Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). Two review authors (A.A.S. and N.L.G.) independently screened titles and abstracts, accessing the full text of articles that met the a priori inclusion criteria specified in the protocol. Disagreements were resolved through reviewer re-examination and discussion of the article or by consulting an independent third reviewer (N.B.F.).

2.3. Data extraction

Two authors (A.A.S. and N.L.G.) independently extracted data from included studies. A third author (N.B.F.) resolved disagreements. We extracted details on the patient, interventions, comparisons, outcomes, and study design of each study, including sample size, age, sex, neuropathic pain condition, primary and secondary outcomes at baseline and at the end of follow-up, type and dose of treatment, route of administration, comparator type, add-on therapy, study year, and design. If studies reported multiple analyses (eg, ITT or per-protocol), we extracted the more conservative data with a preference for ITT analyses.

2.4. Data synthesis

We combined data in meta-analyses where sufficient data were available using Review Manager (RevMan) version 5.4. All analyses were conducted using a random-effect model because of substantial differences in methodology and scales within the included studies and varying levels of heterogeneity observed in most of our analyses. Pain outcomes measured on continuous scales were expressed as mean differences (MD) with a 95% CI, whereas risk difference (RD) was used for dichotomous outcomes. Secondary outcomes measured on continuous scales were expressed as standardized mean differences (SMDs) with a 95% CI when studies examined the same outcome assessed with different scales. An SMD of 0.2 represented a small effect, 0.5 a moderate effect, and 0.8 a large effect.[54] For studies that reported partial pain outcomes (eg, mean values without SDs), we calculated outcomes as needed based on other available information. We planned to conduct meta-analysis for all the outcomes of this review, and studies with available outcome data were included in the meta-analysis. Studies were grouped by the intervention type/drug group. Studies that investigated subtherapeutic drug doses, including pregabalin $<$ 150 mg, gabapentin $<$ 900 mg, TCA $<$ 50 mg, and duloxetine $<$ 60 mg,[13] were not included in the meta-analysis. Heterogeneity between studies was examined using a χ^2 test and the I^2 statistic.

2.5. Assessment of risk of bias

Using the Cochrane risk-of-bias[20] for randomized trials, methodological quality was independently assessed by 2 reviewers (A.A.S. and N.L.G.). We assessed the following 6 risk-of-bias categories: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome reporting, and selective reporting. Each category was classified as low, unclear, or high risk of bias. Disagreements between reviewers were resolved through discussion or by consulting a third reviewer (N.B.F.).

2.6. Quality of evidence

The GRADE approach was used to assess the quality of evidence. The quality of evidence was rated from very low to high.[19] The certainty began with high quality but could be downgraded because of study limitations, inconsistency, imprecision, and indirectness.

3. Results

The combined searches resulted in 7900 records. After removing duplicates, 5626 records were screened for title and abstract. We reviewed 171 full-text articles and subsequently excluded 141 studies. In total, 30 publications were eligible and included in the review (**Fig. 1**).

3.1. Included studies

We included 30 comparative, double-blind RCTs with parallel-group or crossover study designs comprising a total of 4087 patients.[1,2,6,8,11,15–17,21,27,28,30,35–38,41–45,48–51,55,57,58,60,62] Sixteen of these were also included in the NeuPSIG review (Appendix 5b).[13] Fourteen of the included studies were classified as parallel-group trials, with 4 of these including a placebo group. Sixteen of the included studies had a crossover study design, of which 8 also had a placebo group. Characteristics of included studies are provided in **Table 1**, and assessment scales used are presented in supplementary table S1, http://links.lww.com/PR9/A220. All trials were conducted in adults, and no trials included children or adolescents younger than 18 years. Of the 25 studies reporting inclusion criteria for age, 13 had an upper limit between 65 and 89 years, whereas 12 had no upper age limit. Most studies included both men and women with numbers reasonably representative for the respective pain conditions. Studies were conducted in Europe, United States, Canada, Iran, India, Japan, and Australia. Of the 26 studies that reported funding, 5 were company-sponsored trials, and 21 were investigator-initiated trials, of which 9 had drugs provided free by a company and 2 received company funding. All studies investigated measures of neuropathic pain as primary outcome. Pain conditions included diabetic painful polyneuropathy (D-PPN) (n = 15), postherpetic neuralgia (PHN) (n = 4), mixed peripheral neuropathic pain (PNP) (n = 4), D-PPN and PHN (n = 2), chemotherapy-induced painful polyneuropathy (C-PPN) (n = 1), chronic lumbar root pain (CLRP) (n = 2), cancer neuropathic pain (n = 1), and spinal cord injury neuropathic pain (SCI-NP) (n = 1).

3.2. Risk of bias

A summary table for risk-of-bias judgments for included studies is shown in **Figure 2**. Risk-of-bias assessments for individual studies are included in **Figure 3**. Details of risk-of-bias assessment are included in the supplementary.

3.3. Outcomes

Results related to change in pain intensity are presented in **Figure 3A–D**, treatment responders in **Figure 4A–D** with L'Abbé plots in supplementary Figure S1, http://links.lww.com/PR9/A220, and dropouts because of adverse events in **Figure 5A–D**. QoL, sleep, emotional functioning, and dropouts are presented in the supplementary.

3.3.1. Tricyclic antidepressants vs pregabalin/gabapentin

3.3.1.1. Mean change in pain intensity

We identified 10 studies (920 patients) that evaluated the effect of TCA and pregabalin or gabapentin on neuropathic pain through head-to-head comparisons. The pooled effect showed no difference between TCA and pregabalin/gabapentin in pain reduction (MD 0.10, 95% CI −0.13 to 0.32, $P = 0.39$) (**Fig. 3A**).

3.3.1.2. Treatment responders

Eight studies (849 patients) reported either 50%, 30%, or at least moderate pain relief and were eligible for inclusion in the meta-analysis for treatment responders (**Figure 4A** and Supplementary Figure S1a, http://links.lww.com/PR9/A220). The combined effect showed a non-significant trend, suggesting superiority of TCA compared with pregabalin/gabapentin (RD 0.06, 95% CI −0.01 to 0.12, $P = 0.08$).

3.3.1.3. Secondary outcomes

We did not find any studies reporting PGIC. No differences were found in QoL or sleep scores (Supplementary Figures S2 and S3, http://links.lww.com/PR9/A220). We found 9 studies that investigated the treatment effect on emotional functioning by using different depression scales (Supplementary table S1, http://links.lww.com/PR9/A220). None of these studies reported a significant difference between the treatment groups, and meta-analysis of the 2 studies that reported extractable data also showed no difference (Supplementary Figure

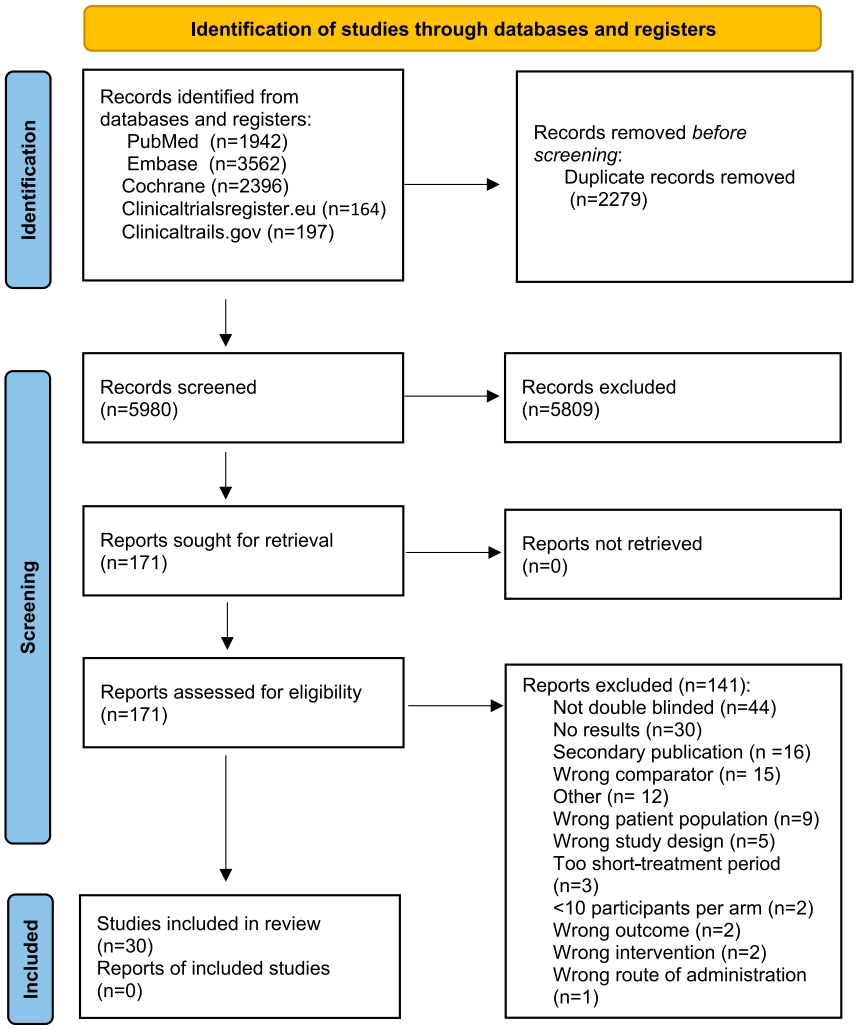

Figure 1. PRISMA flowchart showing the study selection process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

S4, http://links.lww.com/PR9/A220). We found no significant difference in number of patients who withdrew during active treatment (Supplementary Figure S5, http://links.lww.com/PR9/A220) or number of dropouts because of adverse events (RD 0.02, 95% CI −0.03 to 0.07, $P = 0.50$) (**Fig. 5A**). Most frequent adverse events were dry mouth and dizziness during TCA treatment and somnolence and dizziness during pregabalin/gabapentin treatment.

3.3.2. Serotonin–noradrenaline reuptake inhibitors vs pregabalin/gabapentin

3.3.2.1. Mean change in pain intensity

We found 8 studies that investigated the effect of SNRI compared with pregabalin or gabapentin. Five studies (1495 patients) reported pain reduction by change in pain intensity scales and were included in meta-analysis (**Fig. 3B**). The pooled effect size showed higher pain reduction in the SNRI group compared with pregabalin or gabapentin groups (MD 0.36, 95% CI 0.01–0.70, $P = 0.04$).

3.3.2.2. Treatment responders

Three studies (1312 patients) reported extractable data for 50%, 30%, or at least moderate pain reduction and were included in the meta-analysis (**Figure 4B** and Supplementary Figure S1b, http://links.lww.com/PR9/A220). The combined effect showed no difference between the SNRI group compared with pregabalin or gabapentin (RD 0.03, 95% CI −0.08 to 0.14, $P = 0.59$).

3.3.2.3. Secondary outcomes

We did not find any studies reporting PGIC. No differences were found in QoL, sleep, or depression outcomes (Supplementary Figure S2, S3, S4, http://links.lww.com/PR9/A220). We found no significant difference in number of patients who withdrew during active treatment (Supplementary Figure S5, http://links.lww.com/PR9/A220) and number of dropouts because of adverse events (RD 0.03, 95% CI −0.03 to 0.10, $P = 0.34$) (**Fig. 5B**). Considering adverse events, nausea was more common during SNRI treatment compared with pregabalin or gabapentin, and dizziness was more common during pregabalin/gabapentin treatment.

3.3.3. Tricyclic antidepressants vs serotonin–noradrenaline reuptake inhibitors

3.3.3.1. Mean change in pain intensity

We found 6 studies that investigated the effect of TCA compared with SNRI. Four studies (432 patients) reported on change in pain from baseline using numeric rating scales (**Fig. 3C**). No difference was found between TCA and SNRI treatment groups (MD 0.33, 95% CI −0.44 to 1.10, $P = 0.40$).

Table 1

Characteristics of included studies.

Study Year	Design	Randomized N	Intervention	Condition	Treatment length (d)	Minimal pain intensity	Age Inclusion criteria	Age	Sex % Female	Funding	Country/ ethnicity
1008-040. 2007[1]	P	256	Amitriptyline 75 mg Pregabalin 600 mg	D-PPN	56	≥4/10	NA	NA	37.8	Pfizer	Europe Australia South Africa
Bansal et al. 2009[2]	C	51	Amitriptyline 50 mg Pregabalin 600 mg	D-PPN	35	≥5/10	18–75	Median 54.5 Range 48–61	56.8	Inv. Init. Drugs	India
Boyle et al. 2012[6]	P	83	Amitriptyline 75 mg Duloxetine 120 mg Pregabalin 600 mg	D-PPN	28	NA	≥18	64.2 (9.6)	31.3	Inv. Init. (Pfizer)	United Kingdom/ 100% Anglo-American
Chandra et al. 2006[8]	P	76	Gabapentin 2700 mg Nortriptyline 150 mg	PHN	56	≥4/10	≥18	55.6 (13.5) 52.5 (10.6)	51.4	Inv. Init. (Pfizer)	India
Enomoto et al. 2018[11]	P	303	Pregabalin 600 mg Duloxetine 60 mg	D-PPN	84	≥4/10	20–80	60.0 (9.8) 59.3 (8.2)	27.4	Eli Lilly	Japan
Gilron et al. 2005[16]	C	57	Morphine 120 mg Gabapentin 3200 mg	D-PPN+ PHN	28	≥Moderate severity	18–89	Range 40–81	43.9	Inv. Init. Drugs	Canada/ 97% White
Gilron et al. 2009[15]	C	56	Gabapentin 3600 mg Nortriptyline 100 mg	D-PPN+ PHN	31	≥4/10	18–89	Range 53–73	37.5	Inv. Init Drugs	Canada/ 100% White
Gilron et al. 2015[17]	C	52	Morphine 100 mg Nortriptyline 100 mg	Mixed PNP	31	≥3/10	18–89	Median 66 Range 49–80	26.9	Inv. Init. Drugs	Canada/ 100% Anglo-American
Holbech et al. 2015[21]	C	73	Pregabalin 600 mg Imipramine 75 mg	Mixed PNP	35	≥4/10	20–85	59.3 range 29–82	40.6	Inv. Init. Drugs	Denmark
Joharchi et al. 2019[27]	P	180	Pregabalin 300 mg Duloxetine 60 mg	D-PPN	84	≥4/10	40–65	54.0 (4.5) 54.9 (3.7)	61.1	Inv. Init.	Iran
Kaur et al. 2011[28]	C	65	Amitriptyline 50 mg Duloxetine 60 mg	D-PPN	42	≥5/10	18–75	Median 52.5 IQR 48.2–62	53.4	Inv. Init. Drugs	India
Khoromi et al. 2007[30]	C	55	Morphine 90 mg Nortriptyline 100 mg	CLRP	49	≥4/10	18–65	Median 52.5 Range 30–64	83.3	Inv. Init. Drugs	United States
Majdinasab et al. 2019[35]	P	104	Gabapentin 900 mg Duloxetine 60 mg	D-PPN	56	≥4/10	18–75	60.7 (5.7) 59.7 (5.6)	56.7	Inv. Init.	Iran
Max et al. 1992[36]	C	54	Amitriptyline 150 mg Desipramine 150 mg	D-PPN	42	≥ Moderate severity	NA	Median 58 Range 20–84	38.9	Merck Sharp and Dohme; Eli Lilly	United States
Mishra et al. 2012[37]	P	120	Gabapentin 1800 mg Amitriptyline 100 mg Pregabalin 600 mg	Cancer NP	28	NA	NA	NA	NA	Inv. Init.	India
Mohammadali Bayani et al. 2021[38]	P	66	Nortriptyline 25 mg Duloxetine 20 mg	D-PPN	35	NA	≥30	57.6 (7.1) 57.0 (6.5)	94.5	Inv. Init.	Iran
Morello et al. 1999[41]	C	25	Gabapentin 1800 mg Amitriptyline 75 mg	D-PPN	42	NA	≥18	60.4 (10.8)	4.0	NA	United States/ 92% White 8% African American
Panerai et al. 1990[42]	C	39	Chlorimipramine 100 mg Nortriptyline 100 mg	Mixed PNP	21	NA	18–80	49	43.6	Inv. Init. Drugs	Italy
Raja et al. 2002[43]	C	76	Morphine/ methadone 240 mg Nortriptyline/ desipramine 160 mg	PHN	42	≥4/10	>18	71.0 (12.0)	55.3	Inv. Init.	United States/ 88% White 11% African American

(*continued on next page*)

Table 1 (*continued*)

Characteristics of included studies.

Study Year	Design	Randomized N	Intervention	Condition	Treatment length (d)	Minimal pain intensity	Age Inclusion criteria	Age	Sex % Female	Funding	Country/ ethnicity
Rauck et al. 2013[44]	P	421	Gabapentin Enacarbil 1.200, 2.400, 3600 mg Pregabalin 300 mg	D-PPN	91	≥4/10	≥18	Range 32–79	40.7	Glaxo SmithKline	United States/ 80% White ?% African American
Razazian et al. 2014[45]	P	257	Pregabalin 150 mg Venlafaxine 150 mg	D-PPN	35	≥4/10	NA	55.1 (9.6)	60.7	NA	Iran
Rintala et al. 2007[48]	C	38	Gabapentin 3600 mg Amitriptyline 150 mg	SCI NP	56	≥5/10	18–70	42.6 (12.6)	5.3	Inv. Init.	United States/ 45% White 18% Black 14% Hispanic
Robertson et al. 2019[49]	C	18	Gabapentin 2400 mg Pregabalin 600 mg	CLRP	56	NA	≥18	57.0 (16.5)	38.9	Inv. Init.	Australia
Rowbotham et al. 2005[50]	P	47	Amitriptyline 150 mg Desipramine 150 mg	PHN	42	NA	>40	71.7 (40-84) 69.4 (40-84)	57.4	Inv. Init.	United States
Salehifar et al. 2020[51]	P	82	Pregabalin 150 mg Duloxetine 60 mg	C-PPN	42	≥4/10	≥18	49.4 (9.7) 48.7 (9.6)	100	Inv. Init.	Iran
Sindrup et al. 2003[55]	C	40	Amitriptyline 150 mg Venlafaxine 225 mg	Mixed PNP	28	≥4/10	20–70	26 (31-69)	28.1	Inv. Init. Drugs	Denmark
Tesfaye et al. 2013[58]	P	804	Pregabalin 300 mg Duloxetine 60 mg	D-PPN	56	≥4/10	≥18	61.9 (11.0) 61.5 (10.6)	44.3	Eli Lilly	United Kingdom/ 82% White 9% American Indian or Alaska native 9% Asian
Tesfaye et al. 2022[57]	C	140	Amitriptyline 75 mg Duloxetine 120 mg Pregabalin 600 mg	D-PPN	42	≥4/10	≥18	61.8 (11.0)	26.2	Inv. Init.	United Kingdom/ 94% White 4% Asian 2% Black
Watson et al. 1998[60]	C	33	Amitriptyline 100 mg Nortriptyline 150 mg	PHN	35	≥Moderate severity	NA	NA	NA	NA	Canada
Zakerkish et al. 2017[61]	P	134	Nortriptyline 75 mg Duloxetine 60 mg	D-PPN	42	≥4/10	>18	53.4 (8.6)	58.2	NA	Iran

Funding is reported as company-sponsored ("company name"), investigator-initiated (Inv. Init.), investigator initiated with company-provided drugs (Inv. Init. Drugs), or investigator initiated with funding from company (Inv. Init. "company name").

C, crossover; CLRP, chronic lumbar loot pain; C-PPN, chemotherapy-induced painful polyneuropathy; D-PPN, diabetic painful polyneuropathy; NA, not available; NS, not significant; P, parallel; PHN, postherpetic neuralgia; PNP, peripheral neuropathic pain; S, significant; SCI NP, spinal cord injury neuropathic pain.

3.3.3.2. Treatment responders

The pooled effect showed no difference between TCA and SNRI treatment groups in the number of treatment responders (4 studies, 505 patients) (RD −0.04, 95% CI −0.25 to 0.18, $P = 0.73$) (**Figure 4C** and Supplementary Figure S1c, http://links.lww.com/PR9/A220).

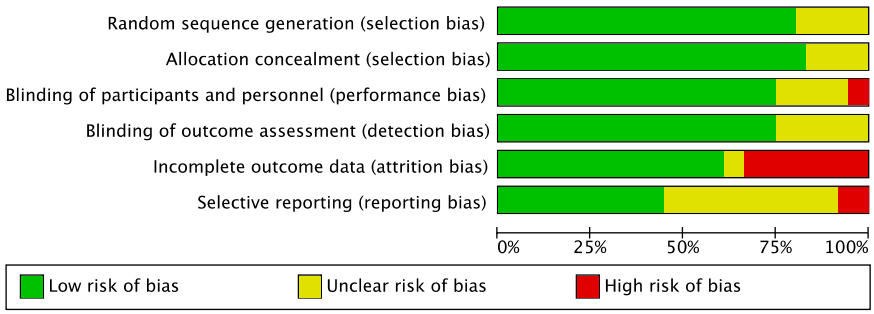

Figure 2. Risk-of-bias graph: review authors' judgements about each risk-of-bias item presented as percentages across all included studies.

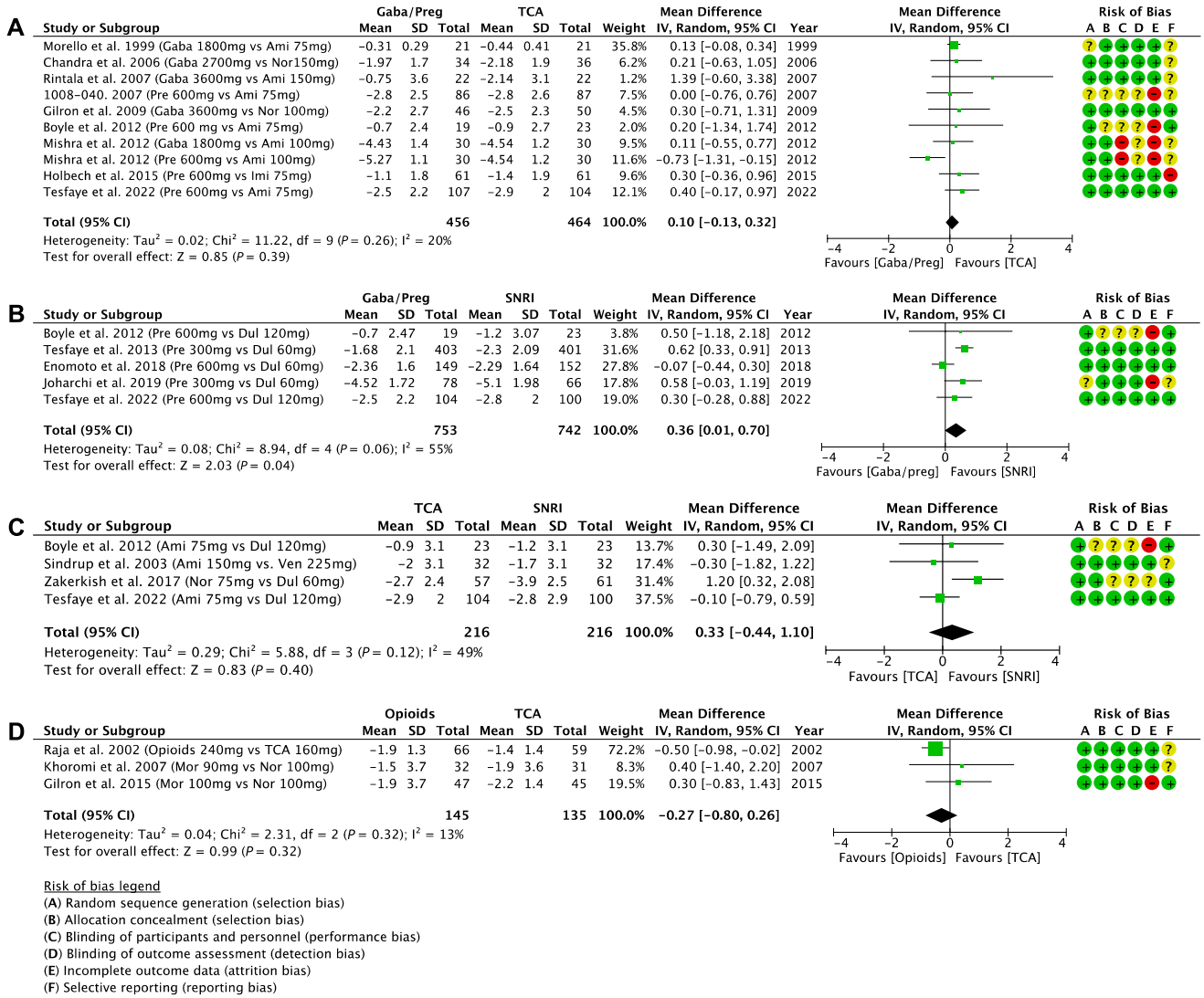

Figure 3. Forest plots of mean change in pain intensity (0-10 numeric rating scale) of trials comparing gabapentin/pregabalin with TCA (A), gabapentin/pregabalin with SNRI (B), TCA with SNRI (C), and opioids with TCA (D). SNRI, serotonin–noradrenaline reuptake inhibitors; TCA, tricyclic antidepressants.

3.3.3.3. Secondary outcomes

We did not find any studies reporting on PGIC. There were no differences in QoL (SMD −0.05, 95% CI −0.30 to 0.19, $P = 0.67$) or sleep scores (SMD 0.19, 95% CI −0.05 to 0.44, $P = 0.12$) (Supplementary Figure S2 and S3, http://links.lww.com/PR9/A220). One study compared the effect of amitriptyline and duloxetine on depressive symptoms and concluded no significant difference between treatment groups.[57] We found no significant difference in number of patients who withdrew during active treatment (Supplementary Figure S5, http://links.lww.com/PR9/A220), but significantly, more people dropped out because of adverse events in SNRI groups compared with TCA (RD −0.07, 95% CI −0.13 to −0.01, $P = 0.03$) (**Fig. 5C**). Considering adverse events, dry mouth was more frequent in TCA treatment groups, and somnolence was more common in SNRI groups.

3.3.4. Opioids vs tricyclic antidepressants/gabapentin

3.3.4.1. Mean change in pain intensity

We found 3 studies (280 patients) that investigated the effect of opioids compared with TCA and one with gabapentin. The pooled effect showed no difference between opioids and TCA in pain reduction (MD −0.27, 95% CI −0.80 to 0.26, $P = 0.32$) (**Fig. 3D**), and 1 study showed no statistically significant difference between gabapentin and opioids (MD −0.45, 95% CI −1.58 to 0.68, $P = 0.43$).[16]

3.3.4.2. Treatment responders

The pooled effect showed no difference in the number of responders between opioids and TCA (RD 0.03, 95% CI −0.16 to 0.22, $P = 0.77$) (**Figure 4D** and Supplementary Figure S1d, http://links.lww.com/PR9/A220) or between opioids and gabapentin (RD 0.18, 95% CI −0.01 to 0.37, $P = 0.06$).

3.3.4.3. Secondary outcomes

We did not find any studies reporting on PGIC. There were no differences in QoL, sleep, or depressive symptoms between TCA and opioids or between gabapentin and opioids (Supplementary Figures S2, S3, S4, http://links.lww.com/PR9/A220). Studies showed that significantly more people withdrew during opioid

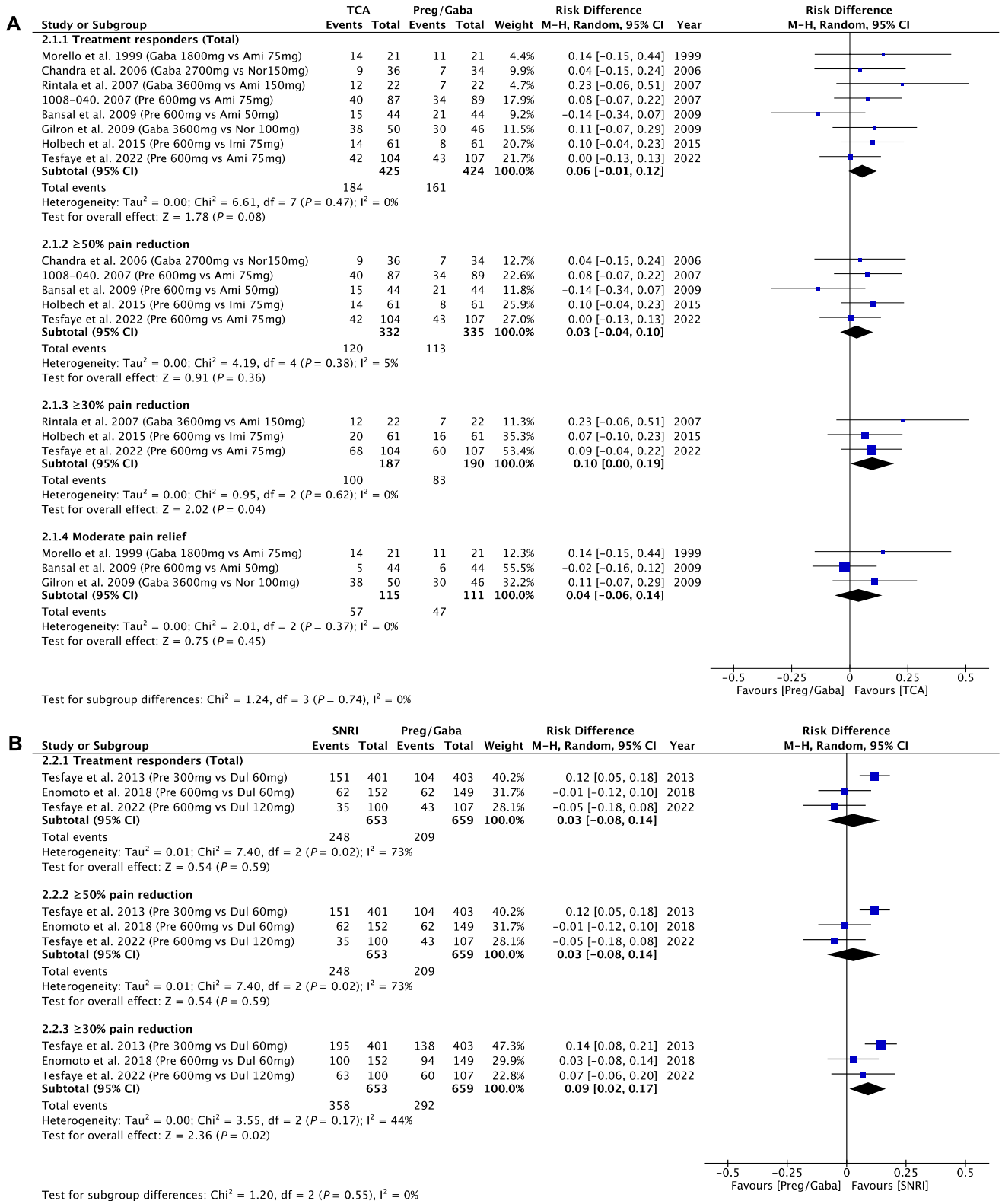

Figure 4. Forest plots of treatment responders, of trials comparing gabapentin/pregabalin with TCA (A), gabapentin/pregabalin with SNRI (B), TCA with SNRI (C), and opioids with TCA (D). A responder was defined as a patient with at least 50% pain reduction (if not available 30% pain reduction or at least moderate pain relief). SNRI, serotonin–noradrenaline reuptake inhibitors; TCA, tricyclic antidepressants.

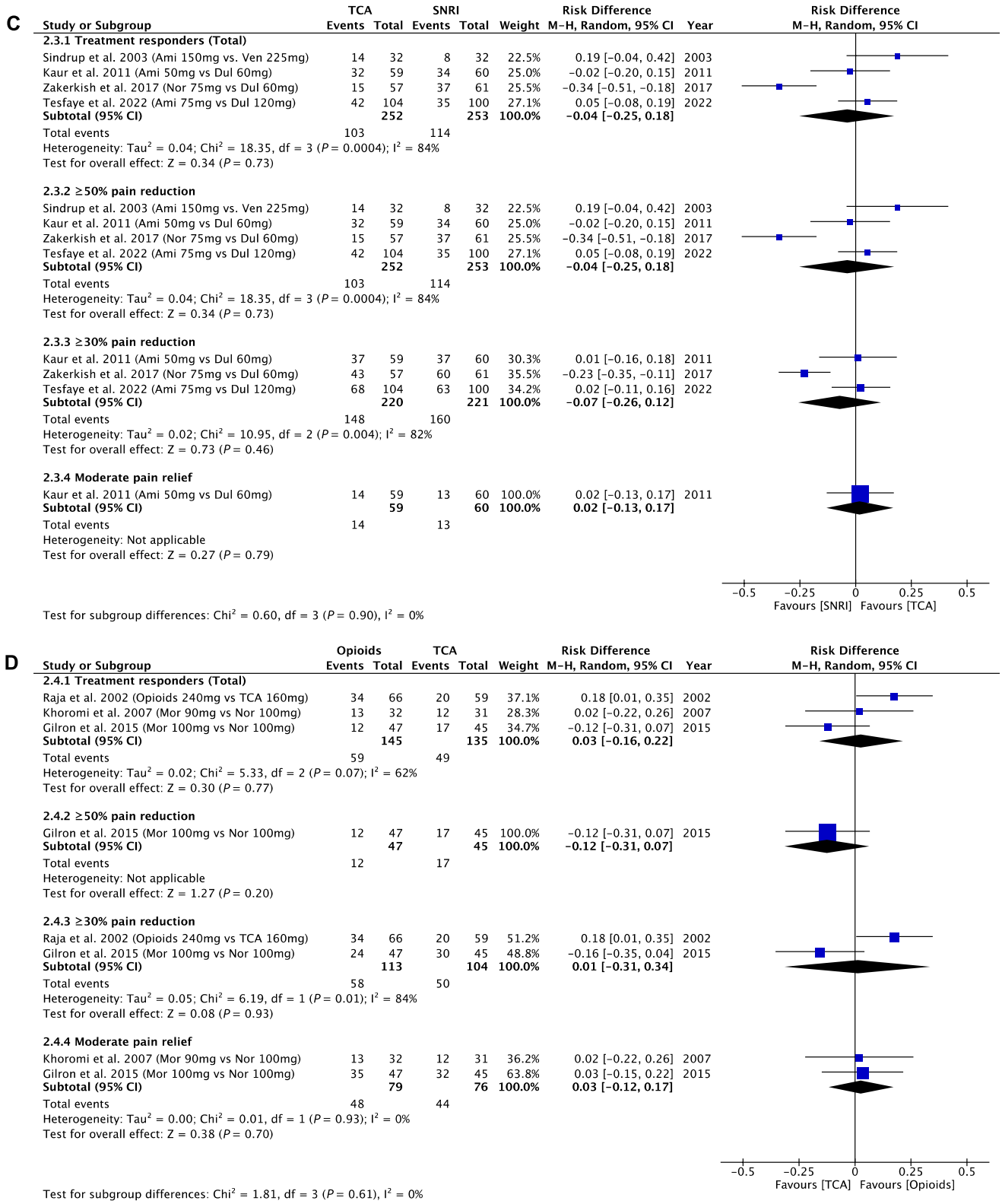

Figure 4. Continued.

treatment (RD 0.16, 95% CI 0.07–0.24, $P = 0.0002$) (Supplementary Figure S5, http://links.lww.com/PR9/A220) and significantly more people dropped out because of adverse events (RD 0.09, 95% CI 0.03–0.15, $P = 0.006$) compared with TCA treatment (**Fig. 5D**). Considering adverse event, constipation was more frequent during opioid treatment, and dry mouth was more common during TCA treatment.

3.3.5. Comparison of different tricyclic antidepressants

We found 4 studies that compared the treatment effect of 2 different TCA drugs. Two small studies compared the treatment effect of amitriptyline vs desipramine and found no difference between the 2 drugs,[36] but more responders with desipramine than amitriptyline in 1 study.[50] Dry mouth was more frequent in the amitriptyline group, and constipation was more common in the desipramine group. One study compared amitriptyline with nortriptyline, and no difference was found between the treatments, beside more intolerable side effects with amitriptyline compared with nortriptyline.[60] One small study found a significantly better pain relief with chlorimipramine compared with nortriptyline with similar tolerability.[42]

3.3.6. Gabapentin vs pregabalin

We found 3 studies that compared the treatment effects of gabapentin and pregabalin. One study reported significantly more pain relief with pregabalin 600 mg than gabapentin 1800 mg (MD −0.84, 95% CI −1.45 to −0.22, $P = 0.042$),[37] and one found more pain reduction with gabapentin 2400 mg than pregabalin 600 mg, $P = 0.035$ and significantly more adverse events associated with pregabalin than gabapentin (31 [81%] vs 7 [19%], $P = 0.002$).[49] The third study compared pregabalin with gabapentin-enacarbil, and no significant differences were found between the treatments.[44]

3.4. Summary and quality of evidence

The quality was rated from low to moderate (Supplementary table S2, http://links.lww.com/PR9/A220). We identified 10 trials including in total 918 patients comparing TCA with gabapentin/pregabalin. There was moderate-quality evidence for equivalence, ie, that there is not a clinically relevant difference in efficacy or tolerability. Although most trials were numerically in favor of TCA, the combined mean difference in pain score was 0.10 with a 95% CI from −0.13 to 0.32, suggesting no clinically relevant difference between these drug classes. We identified 8 trials comparing SNRI with gabapentin/pregabalin with 3 trials not included because of suboptimal doses, and 1495 patients were included in the meta-analysis. We found no evidence for superiority of 1 drug class (low quality of evidence). Data on one of the 2 primary outcomes suggested better efficacy of duloxetine 60 to 120 mg over pregabalin 300 to 600 mg but no difference in

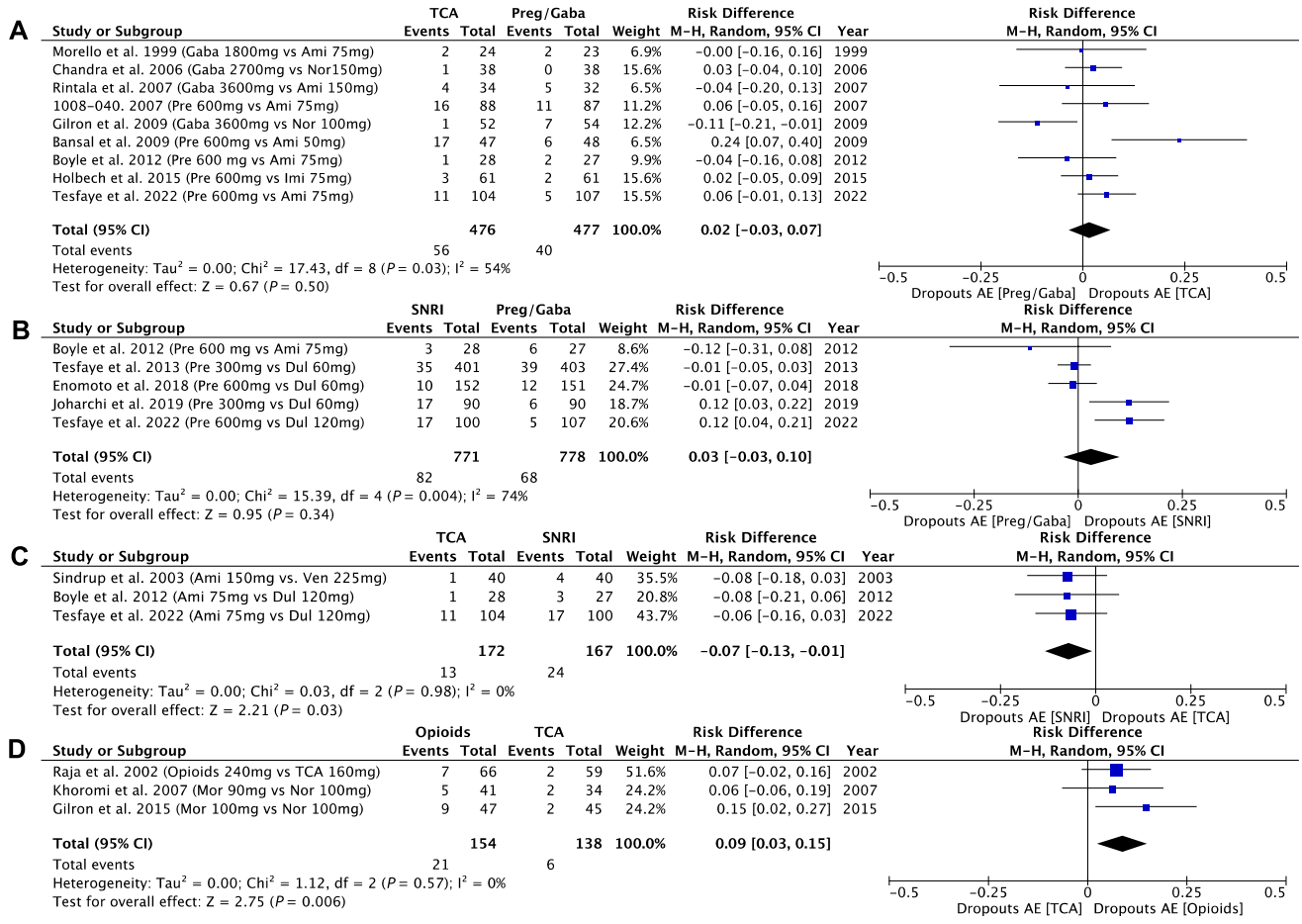

Figure 5. Forest plots of number of dropouts because of adverse events of trials comparing gabapentin/pregabalin with TCA (A), gabapentin/pregabalin with SNRI (B), TCA with SNRI (C), and opioids with TCA (D). The distribution indicates more dropouts with the drug. SNRI, serotonin–noradrenaline reuptake inhibitors; TCA, tricyclic antidepressants.

other outcomes. We identified 6 trials comparing SNRI with TCA of which 1 trial used suboptimal doses and was not included, and 462 patients were included in meta-analysis. We could not document consistent better efficacy of 1 drug class, but the 95% CI was wide, and we cannot exclude a clinically significant difference (low quality of evidence). There were significantly more dropouts with SNRI than TCA treatment. We identified 4 trials comparing opioids with either TCA or gabapentin, with no evidence for difference in efficacy, but more patients dropped out to side effects with opioids than TCA (low quality of evidence). There was inconclusive evidence for comparison within the drug classes. We did not identify any studies that included topical treatments.

4. Discussion

In this review, we compared efficacy and tolerability of drugs recommended for neuropathic pain using randomized controlled head-to-head trials. We found moderate-quality evidence for equivalence (no clinically relevant difference) between TCAs and gabapentin/pregabalin. We could not document differences between TCA and SNRI, between SNRI and gabapentin/pregabalin, or between opioids and the other drug classes (low quality of evidence). There were no studies comparing lidocaine and capsaicin patches and BTX-A. The results are in agreement with the current NeuPSIG recommendations from 2015 with TCA, SNRI, gabapentin, and pregabalin as first-line drugs.[13] Opioids were considered third-line drugs in the NeuPSIG recommendations because of risk of abuse, misuse, and opioid-associated mortality consistent with the IASP opioid statement,[22] and we also found more dropouts with opioids.

We did not find evidence for superior effect of 1 drug class on quality of life, sleep, or mood, but few studies provided data for comparisons. In addition, there were no differences in dropouts because of side effects, except for more patients dropping out because of SNRI and opioids than TCA treatment (low quality of evidence). The NeuPSIG review with data extracted up to 2013 included 16 of the 30 direct-comparison studies included in this review, and the NNT results suggested similar efficacy for first-line drugs. A previous qualitative study from 2010 also compared head-to-head trials of oral pharmacological treatments for neuropathic pain.[61] This study included 27 trials of which 13 were also included in our trial, whereas the remaining trials included nonrecommended treatments or did not fulfill our inclusion criteria such as at least 3 weeks of treatment. The review indicated modest efficacy of antidepressants, opioids, and gabapentinoids.

Direct-comparison studies are important to include in treatment guidelines and when considering evidence. First, there are a limited number of placebo-controlled double-blind trials in the field of neuropathic pain, warranting inclusion of all evidence. Second, it is the best way to compare relative effectiveness of drugs. Placebo-controlled trials have shown lower numbers needed to treat (NNT) with TCA than SNRI and gabapentin/pregabalin, but this may be explained by differences in trial design such as crossover vs parallel-group design and per-protocol vs ITT analyses.[13] In addition, because drug and placebo responses are not additive and estimated treatment effects dependent on the placebo response, indirect comparisons between trials, including network meta-analyses, can be misleading. Comparing efficacy between drugs within the same trial overcomes these restraints. As pointed out previously,[61] head-to-head trials may also provide information on pain mechanisms if particular phenotypes respond to one and not another drug; however, subgroup analyses were not performed in this study.

Of particular importance is the comparison of TCA with SNRI and gabapentin/pregabalin. Systematic reviews using the Cochrane risk-of-bias tools and the GRADE report moderate-quality evidence for SNRI and pregabalin but low-quality or no evidence for TCA for neuropathic pain.[4,12,40] These reviews often put emphasis of the small study size of TCA trials, despite similar results across multiple small trials. The information size for a meta-analysis should take into account the combined number of patients and trials and not the size of single trials.[7] The risk of random error is high in single small trials, but the size itself is not a bias and "small study effects" are likely explained by per-protocol analysis rather than ITT in crossover trials, methodological bias and publication bias, more homogeneous populations, and less inflation of baseline pain (and thus lower placebo responses).[9,31] In the absence of such bias, multiple small trials may provide similar or better estimates of effect size than single large trials.[3,5,23,33,53,56] The requirement now for trial registration will allow us to estimate publication bias, and thus, small clinical trials may in the future provide faster and possible more correct evidence for or against a specific treatment. Dismissing small investigator-initiated studies carries the risk of favoring expensive drugs that are of interest to drug companies because scarce funding sources for academia limit the possibility to do investigator-initiated large multinational trials.[10,18] Pharmaceutical companies also often do not have the incentive to perform direct-comparison studies, emphasizing the need to support investigator-initiated trials.

Our review had the advantage of incorporating a search for unpublished studies and gray literature. The studies included in our analysis encompassed patients with diverse age groups, gender distribution, ethnic backgrounds, and various neuropathic pain conditions, although we did not identify any studies in children. Most trials were investigator-initiated. However, there are several limitations to our review. We did not include comparisons with a placebo group; as result, the studies cannot document an effect of the treatments and ascertain the sensitivity of the trials. However, we restricted the inclusion criteria to drugs recommended for neuropathic pain based on evidence from placebo-controlled trials.[13] The studies we included used varying maximum doses, raising the possibility that we may not have compared equivalent doses. To mitigate this issue, we excluded studies from the meta-analysis if the doses used were deemed subtherapeutic.[13] Additional limitations include variations in the specific drugs within each drug class, the utilization of different scales for measuring secondary outcomes and different study designs, lack of a minimum criteria for pain intensity, and the absence of long-term follow-up data in the included trials. Also, we did not assess different pain phenotypes, and there were not enough studies in individual pain conditions to identify possible etiology or phenotype-specific differences. In future trials that compare 2 active treatments, both of which have previous evidence of efficacy, it is advisable to design them as noninferiority trials with sufficient statistical power. However, we acknowledge that such trials can be expensive and challenging to conduct. Including a placebo arm in these trials may prove useful in confirming assay sensitivity.

5. Conclusion

This systematic review and meta-analysis of head-to-head trials indicate comparable effectiveness between TCA and gabapentin/pregabalin, with no evidence supporting differences between these drugs and SNRIs.

Disclosures

Outside the submitted word, N.B.F. has received consultancy fees from Vertex, Novartis Pharma, NeuroPN, Nanobiotix, Neurvati, and Samiona and has undertaken consultancy work for Aarhus University with remunerated work for Biogen, Merz, and Confo Therapeutics. She has received grants from IMI2-PainCare an EU IMI 2 (Innovative Medicines Initiative) public-private consortium, and the companies involved are Grunenthal, Bayer, Eli Lilly, Esteve, and Teva, outside the submitted work. A.A.S. and N.L.G. declare no conflicts of interest.

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