Supplementary

Table S1. Outcome assessment scales

Study Year	Pain intensity	Quality of life	Sleep	Emotional functioning
1008-040 2007	11-point Likert scale	NA	Sleep interference score (0-10)	HADS-depression scale
Bansal et al. 2009	VAS (0-100)	NA	NA	Hamilton-depression scale
Boyle et al. 2012	Brief Pain Inventory (0-10)	SF-36 score (0-100)	Sleep interference score (0-10)	NA
Chandra et al. 2006	11-point Likert scale	NA	VAS (0-100)	NA
Enomoto et al. 2018	11-point NRS	EQ-5D -VAS score	Sleep interference score (0-10)	Beck-depression scale
Gilron et al. 2005	NRS (0-10)	SF-36 score (0-100)	Pain interference items (NRS 0-10)	Beck-depression scale
Gilron et al. 2009	NRS (0-10)	SF-36 score (0-100)	Pain interference items (NRS 0-10)	Beck-depression scale
Gilron et al. 2015	NRS (0-10)	SF-36 score (0-100)	Pain interference items (NRS 0-10)	Beck-depression scale
Holbech et al. 2015	NRS (0-10)	SF-36 score (0-100)	Sleep disturbance (NRS 0–10)	Major-depression scale
Joharchi et al. 2019	VAS (0-100)	NA	NA	NA
Kaur et al. 2011	VAS (0-100)	NA	NA	Hamilton-depression scale
Khoromi et al. 2007	NRS (0-10)	SF-36 score (0-100)	NA	Beck-depression scale
Majdinasab et al. 2019	VAS (0-100)	NA	Sleep interference score (0-10)	NA
Max et al. 1992	Global pain scale	NA	NA	NA
Mishra et al. 2012	VAS (0-100)	NA	NA	NA
Mohammadali Bayani et al. 2021	VAS (1-10)	NA	NA	NA
Morello et al. 1999	NRS (0-10)	NA	NA	NA
Panerai et al. 1990	VAS (0-100)	NA	NA	Hamilton-depression scale
Raja et al. 2002	NRS (0-10)	NA	Multidimensional Pain Inventory (0-6)	Beck-depression scale
Rauck et al. 2013	NRS (0-10)	SF-36 score (0-100)	Sleep interference score (0-10)	POMS- depression scale
Razazian et al. 2014	VAS (0-100)	NA	Sleep interference score (0-10)	Mood interference depression scale
Rintala et al. 2007	VAS (0-100)	NA	NA	CES-Depression scale
Robertson et al. 2018	VAS (0-10)	NA	NA	NA
Rowbotham et al. 2005	VAS (0-100)	NA	NA	Beck-depression scale
Salehifar et al. 2020	VAS (0-100)	NA	NA	NA
Sindrup et al. 2003	NRS (0-10)	NA	NA	NA

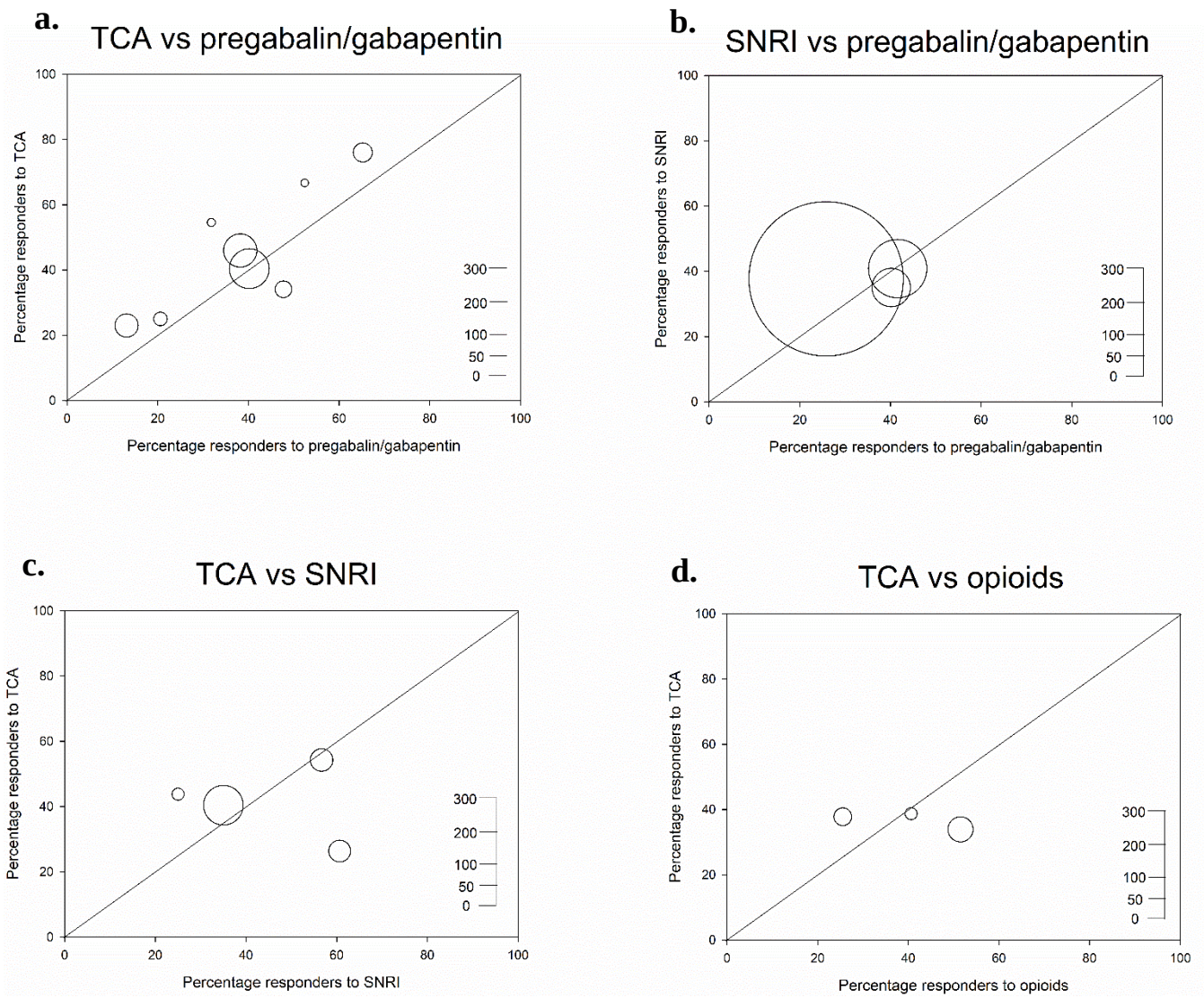
Tesfaye et al. 2013	BPI-MSF (0-10)	NA	Sleep interference score (0-10)	HADS-depression scale
Tesfaye et al. 2022	NRS (0-10)	SF-36 score (0-100)	Insomnia Severity Index (0-28)	HADS-depression scale
Watson et al. 1998	VAS (0-10)	NA	VAS (0-10)	Beck-depression scale
Zakerkish et al. 2017	VAS (0-100)	NA	NA	NA

VAS; Visual Analog Scale, NRS; Numerical Rating Scale, BPI-MSF; Brief Pain Inventory Modified Short Form, HADS; Hospital Anxiety and Depression Scale

Risk of bias assessment

Regarding random sequence generation and allocation concealment categories, most studies were assessed as having a low risk of bias. The remaining studies were rated as having an unclear risk because they did not provide a method for randomization and failed to describe how they concealed allocation. Considering blinding of participants and personnel, studies were judged as having an unclear risk of bias due to lack of a clear statement of blinding, and as having a high risk when the blinding were attempted but likely to be broken. Most studies had a low risk of bias for blinding the outcome assessors. Regarding incomplete outcome data, most studies had a low risk of bias due to either few dropouts during treatment or the use of baseline observation carried forward. Concerning selective reporting, studies that had a pre-registered protocol and reported all prespecified outcomes were rated as having a low risk. Studies that did not pre-register a protocol were rated as having an unclear risk, and studies that pre-registered their protocol but did not report all outcomes in the trial or included additional outcomes in the trials were considered as having a high risk of bias.

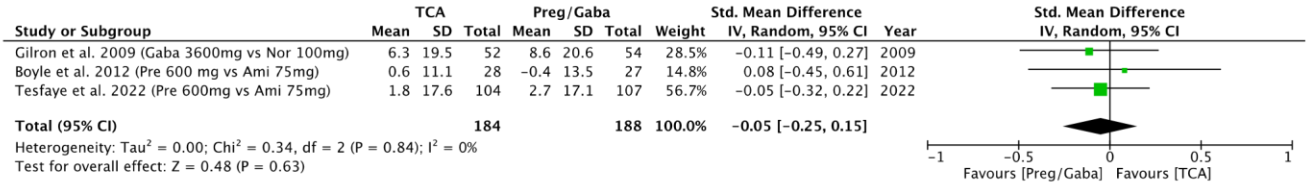
Figure S1. L'Abbé plots



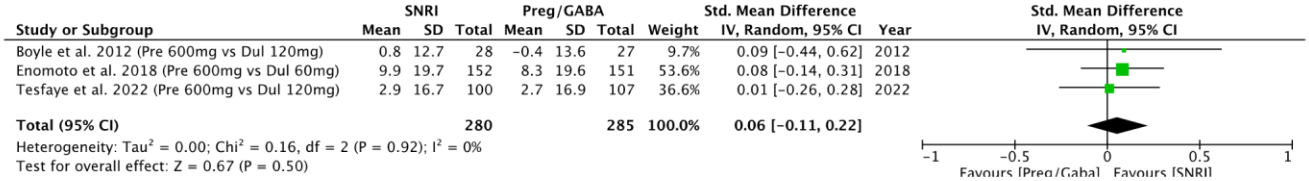
Circle sizes indicate number of patients treated with each drug

Figure S2. Forest plots of mean change in quality-of-life assessment scales

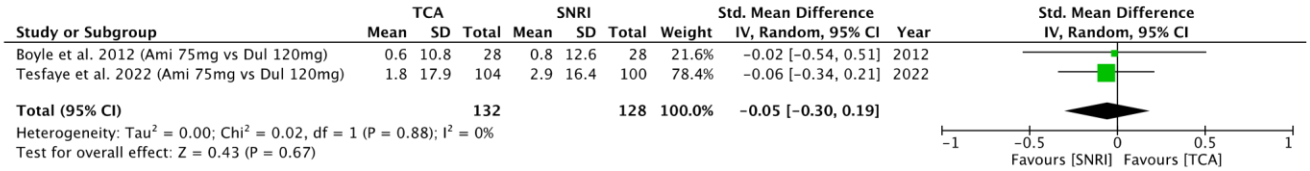
a.



b.



c.



d.

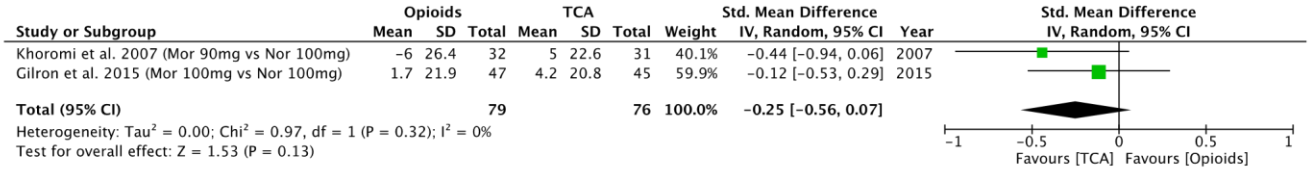
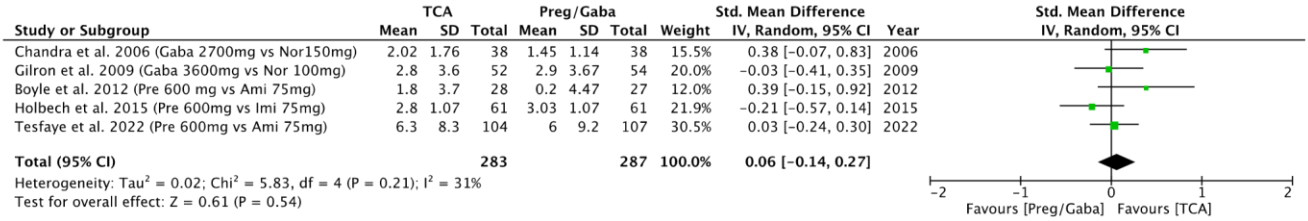
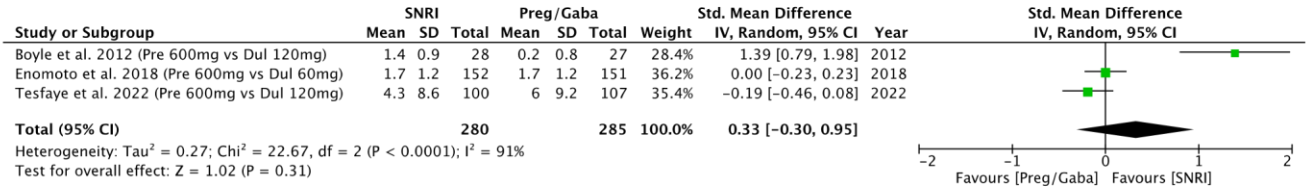


Figure S3. Forest plots of mean change in sleep assessment scales

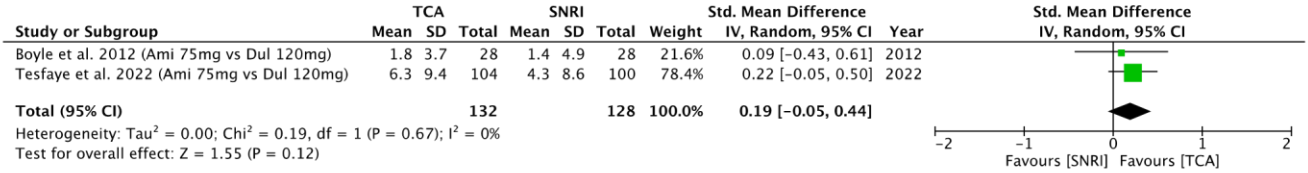
a.



b.



c.



d.

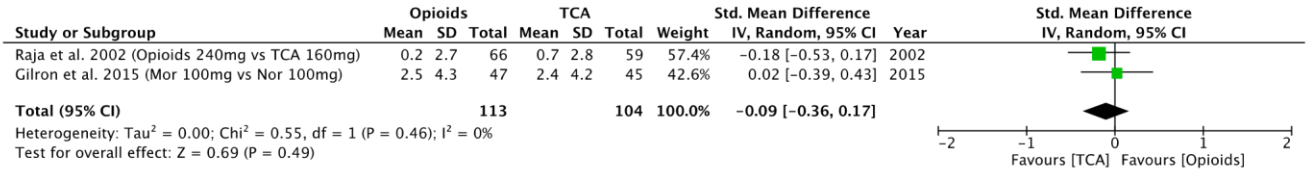
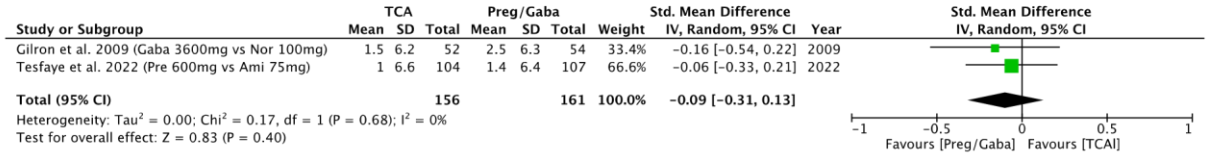
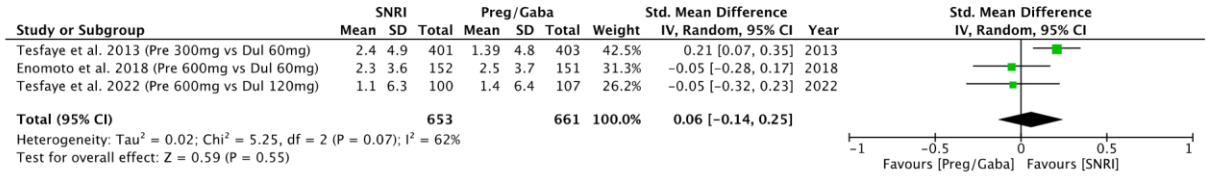


Figure S4. Forest plots of mean change in emotional functioning (depression scales)

a.



b.



c.

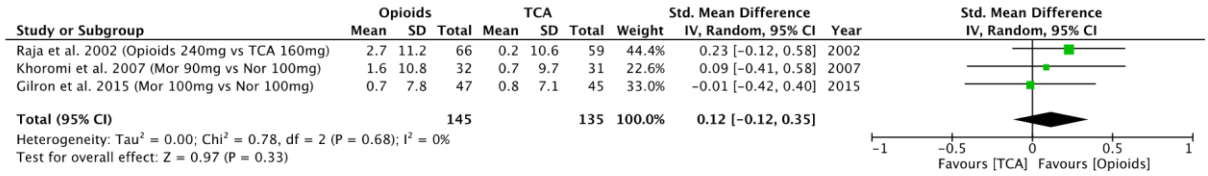
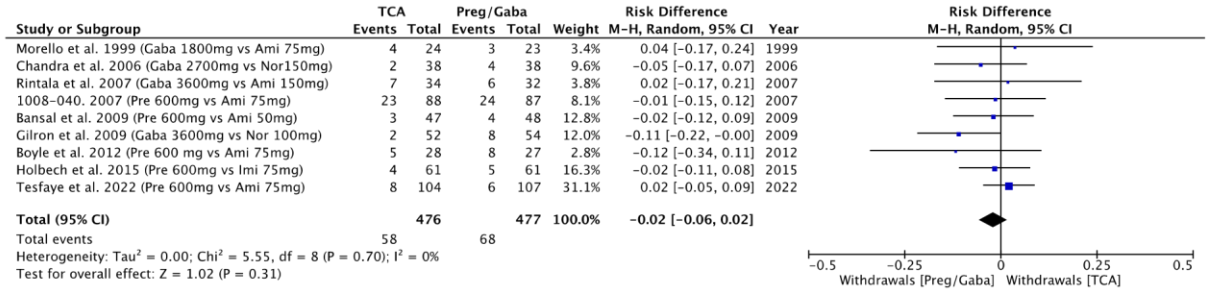
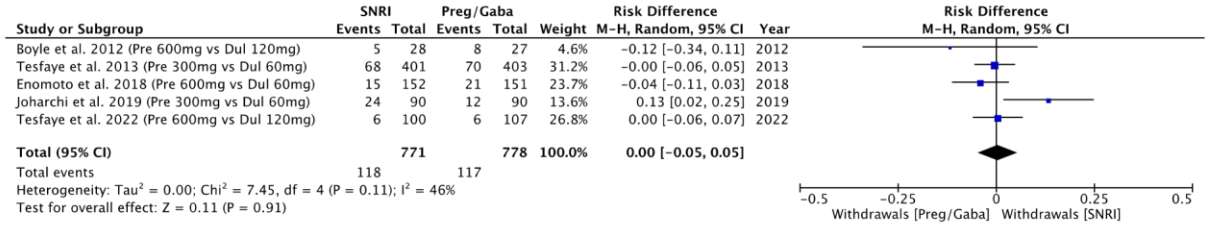


Figure S5. Withdrawals during active treatment

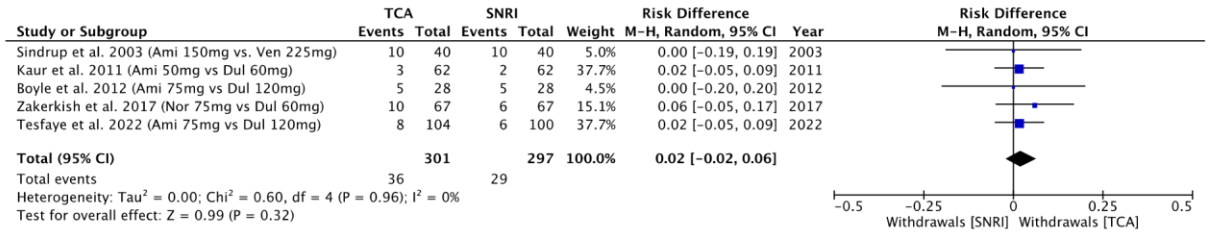
a.



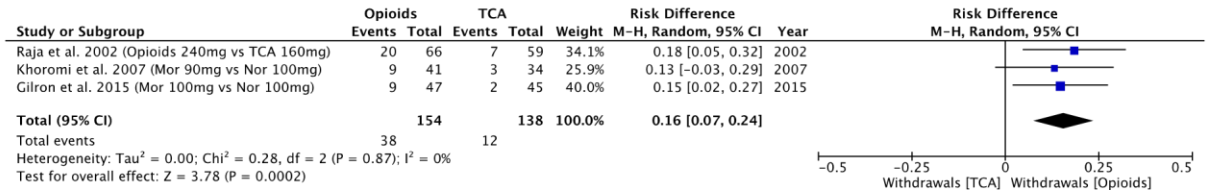
b.



c.



d.



The distribution indicates more withdrawal with the drug.

Table S2. Grading of quality of evidence

	Initial quality	**Risk of bias**	**Inconsistency between trials***	**Imprecision**	**Indirectness**	**Final quality of evidence**
TCA vs gabapentin/ pregabalin	High	Low	I^2=20%/0%/54% Different doses Downgraded	No	Mixed central and peripheral neuropathic pain conditions	Moderate
SNRI vs gabapentin/ pregabalin	High	Low	I^2=55%/73%/74% Different doses Downgraded	Wide CI and inconsistency between outcomes Downgraded	Neuropathic pain due to polyneuropathy	Low
TCA vs SNRI	High	Low	I^2=49%/86%/0% Different doses Downgraded	Wide CI Downgraded	Mixed peripheral neuropathic pain conditions	Low
Opioids vs TCA/ gabapentin	High	Low	I^2=0%/57%/0% Different doses Downgraded	Wide CI Downgraded	Mixed peripheral neuropathic pain conditions	Low
Studies were not downgraded for indirectness since all studies included patients with neuropathic pain as defined in the ICD 11. Publication bias was not assessed but the search included two trials registries for trials with results. *I^2 presented for the two primary outcomes for efficacy and harm (withdrawals due to side effects).						

Search strategies:

We employed a combination of controlled terms (subject headings), such as MeSH, and free-text terms (keywords). Results were limited to randomized double-blind trials. We also searched gray literature (references in relevant published systematic reviews and included studies).

PubMed/Medline - Date; 03.10.2022

("Randomized Controlled Trial"[pt] OR "Controlled Clinical Trial"[pt] OR "Pragmatic Clinical Trial"[pt] OR "Equivalence Trial"[pt] OR "Clinical Trial, Phase III"[pt] OR "Randomized Controlled Trials as Topic"[mh] OR "Controlled Clinical Trials as Topic"[mh] OR "Random Allocation"[mh] OR "Double-Blind Method"[mh] OR "Single-Blind Method"[mh] OR Placebos[Mesh:NoExp] OR "Control Groups"[mh] OR (random*[tiab] OR sham[tiab] OR placebo*[tiab]) OR ((singl*[tiab] OR doubl*[tiab]) AND (blind*[tiab] OR dumm*[tiab] OR mask*[tiab])) OR ((tripl*[tiab] OR trebl*[tiab]) AND (blind*[tiab] OR dumm*[tiab] OR mask*[tiab])) OR (control*[tiab] AND (study[tiab] OR studies[tiab] OR trial*[tiab] OR group*[tiab])) OR (Nonrandom*[tiab] OR "non random*"[tiab] OR "non-random*"[tiab] OR "quasi-random*"[tiab] OR quasirandom*[tiab]) OR allocated[tiab] OR (("open label"[tiab] OR "open-label"[tiab]) AND (study[tiab] OR studies[tiab] OR trial*[tiab])) OR ((equivalence[tiab] OR superiority[tiab] OR "non-inferiority"[tiab] OR noninferiority[tiab]) AND (study[tiab] OR studies[tiab] OR trial*[tiab])) OR ("pragmatic study"[tiab] OR "pragmatic studies"[tiab]) OR

((pragmatic[tiab] OR practical[tiab]) AND trial*[tiab]) OR ((quasiexperimental[tiab] OR "quasiexperimental"[tiab]) AND (study[tiab] OR studies[tiab] OR trial*[tiab])) OR (phase[ti] AND (III[ti] OR 3[ti]) AND (study[ti] OR studies[ti] OR trial*[ti])) OR (phase[ot] AND (III[ot] OR 3[ot]) AND (study[ot] OR studies[ot] OR trial*[ot]))) AND ((((((((((((opioid*[Title/Abstract]) OR (botulinum toxin a[Title/Abstract])) OR (tramadol[Title/Abstract])) OR (lidocaine patch*[Title/Abstract])) OR (Tricyclic antidepressant*[Title/Abstract])) OR (Capsaicin patch*[Title/Abstract])) OR (venlafaxine[Title/Abstract])) OR (Duloxetine[Title/Abstract])) OR (SNRI[Title/Abstract])) OR (serotonin-noradrenaline reuptake inhibitors[Title/Abstract])) OR (pregabalin[Title/Abstract])) OR (enacarbil[Title/Abstract])) OR (gabapentin[Title/Abstract])) OR ((((((("Amitriptyline"[Mesh]) OR "Antidepressive Agents, Tricyclic" [Pharmacological Action]) OR ((((("Gabapentin"[Mesh]) OR "Pregabalin"[Mesh]) OR "1 (((alphaisobutanoyloxyethoxy)carbonyl)aminomethyl)-1-cyclohexaneacetic acid" [Supplementary Concept]) OR "Serotonin and Noradrenaline Reuptake Inhibitors"[Mesh] OR ("Serotonin and Noradrenaline Reuptake Inhibitors" [Pharmacological Action]))) OR (("Duloxetine Hydrochloride"[Mesh]) OR "Venlafaxine Hydrochloride"[Mesh])) OR ((("Capsaicin"[Mesh]) OR "Lidocaine"[Mesh]) OR "Tramadol"[Mesh])) OR (("Botulinum Toxins, Type A"[Mesh]) OR ("Analgesics, Opioid"[Mesh] OR "Analgesics, Opioid" [Pharmacological Action])))) AND ((("Peripheral Nervous System Diseases"[Mesh]) AND ("Pain"[Mesh])) OR (((((("phantom pain"[Title/Abstract]) OR (Neuralgia[Title/Abstract])) OR (neuropath* pain[Title/Abstract])) OR ((("Neuralgia"[Mesh]) OR "Trigeminal Neuralgia"[Mesh]) OR "Neuralgia, Postherpetic"[Mesh])))) NOT (("Animals"[Mesh]) NOT ("Humans"[Mesh])) NOT (("Systematic Review" [Publication Type]) OR "Review" [Publication Type])

1941 hits

Embase - Date; 03.10.2022

('gabapentin'/exp OR 'gabapentin enacarbil'/exp OR 'pregabalin'/exp OR 'serotonin noradrenalin reuptake inhibitor'/exp OR 'tricyclic antidepressant agent'/exp OR 'capsaicin'/exp OR 'lidocaine'/exp OR 'tramadol'/exp OR 'botulinum toxin a'/exp OR 'opiate'/exp OR gabapentin OR gabapentin:ab,ti OR enacarbil:ab,ti OR pregabalin:ab,ti OR ('serotonin noradrenaline' AND reuptake AND inhibitor:ab,ti) OR duloxetine:ab,ti OR venlafaxine:ab,ti OR (tricyclic AND antidepressant*:ab,ti) OR capsaicin:ab,ti OR (capsaicin AND patch*:ab,ti) OR (lidocaine AND patch*:ab,ti) OR tramadol:ab,ti OR (botulinum AND toxin AND a:ab,ti) OR opioid:ab,ti) AND ('neuralgia'/exp OR (neuropath*:ab,ti AND pain:ab,ti) OR neuralgia:ab,ti OR 'phantom pain':ab,ti OR ('neuropathy'/exp AND 'pain'/exp)) AND ('article'/it OR 'article in press'/it OR 'erratum'/it OR 'preprint'/it) AND ('randomized controlled trial'/de OR 'controlled clinical trial'/de OR random*:ti,ab,tt OR 'randomization'/de OR 'intermethod comparison'/de OR placebo:ti,ab,tt OR compare:ti,tt OR compared:ti,tt OR comparison:ti,tt OR ((evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab)) OR ((open NEXT/1 label):ti,ab,tt) OR (((double OR single OR doubly OR singly) NEXT/1 (blind OR blinded OR blindly)):ti,ab,tt) OR 'double blind procedure'/de OR ((parallel NEXT/1 group*):ti,ab,tt) OR crossover:ti,ab,tt OR 'crossover':ti,ab,tt OR (((assign* OR match OR matched OR allocation) NEAR/6 (alternate OR group OR groups OR intervention OR interventions OR patient OR patients OR subject OR subjects OR participant OR participants)):ti,ab,tt) OR assigned:ti,ab,tt OR allocated:ti,ab,tt OR ((controlled NEAR/8 (study OR design OR trial)):ti,ab,tt) OR volunteer:ti,ab,tt OR volunteers:ti,ab,tt OR 'human experiment'/de OR trial:ti,tt) NOT (((random* NEXT/1 sampl* NEAR/8 ('cross section*' OR questionnaire* OR survey OR surveys

OR database OR databases)):ti,ab,tt) NOT ('comparative study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'randomly assigned':ti,ab,tt) OR ('cross-sectional study' NOT ('randomized controlled trial'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'control group':ti,ab,tt OR 'control groups':ti,ab,tt)) OR ('case control*':ti,ab,tt AND random*:ti,ab,tt NOT ('randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt)) OR ('systematic review':ti,tt NOT (trial:ti,tt OR study:ti,tt)) OR (nonrandom*:ti,ab,tt NOT random*:ti,ab,tt) OR 'random field*':ti,ab,tt OR (('random cluster' NEAR/4 sampl*):ti,ab,tt) OR (review:ab AND review:it NOT trial:ti,tt) OR ('we searched':ab AND (review:ti,tt OR review:it)) OR 'update review':ab OR ((databases NEAR/5 searched):ab) OR ((rat:ti,tt OR rats:ti,tt OR mouse:ti,tt OR mice:ti,tt OR swine:ti,tt OR porcine:ti,tt OR murine:ti,tt OR sheep:ti,tt OR lambs:ti,tt OR pigs:ti,tt OR piglets:ti,tt OR rabbit:ti,tt OR rabbits:ti,tt OR cat:ti,tt OR cats:ti,tt OR dog:ti,tt OR dogs:ti,tt OR cattle:ti,tt OR bovine:ti,tt OR monkey:ti,tt OR monkeys:ti,tt OR trout:ti,tt OR marmoset*:ti,tt) AND 'animal experiment'/de) OR ('animal experiment'/de NOT ('human experiment'/de OR 'human'/de)))

3562 Hits

Cochrane - Date; 03.10.2022

(opioid* OR botulinum toxin a OR tramadol OR lidocaine patch* OR Tricyclic antidepressant* OR Capsaicin patch* OR venlafaxine OR Duloxetine OR SNRI OR serotonin-noradrenaline reuptake inhibitors OR pregabalin OR enacarbil OR gabapentin)

AND

("phantom pain" OR Neuralgia OR (neuropath* pain))

2396 Hits

Clinicaltrialsregister.eu - Date; 10.07.2023

“Neuropathic pain”, “with results”

164 Hits

Clinicaltrial.gov - Date; 10.07.2023

“Neuropathic pain”, “Neuralgias”, “Painful”, “with results”

197 Hits