

Neuropathic agents in the management of pruritus in burn injuries – Supplementary material 4: Risk of Bias and GRADE Assessment

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Cochrane Database Search Strategy

Date Run: 07/01/2020 14:23:05

#1 (burn):ti,ab,kw 3694

#2 MeSH descriptor: [Burns] explode all trees 1620

#3 (thermal inj*):ti,ab,kw 962

#4 {or #1-#3} 4935

#5 MeSH descriptor: [Pain] explode all trees 45940

#6 (pain):ti,ab,kw 165847

#7 MeSH descriptor: [Chronic Pain] explode all trees 2044

#8 MeSH descriptor: [Neuralgia] explode all trees 1500

#9 (neuralgia):ti,ab,kw 2692

#10 MeSH descriptor: [Neuralgia] explode all trees 1500

#11 (neuralgia):ti,ab,kw 2692

#12 MeSH descriptor: [Neuralgia] explode all trees 1500

#13 (neuropathic):ti,ab,kw 3992

#14 MeSH descriptor: [Pruritus] explode all trees 1448

#15 (pruritis):ti,ab,kw 365

#16 (itch):ti,ab,kw 1385

#17 {or #5-#16} 174719

#18 MeSH descriptor: [Anticonvulsants] explode all trees 2342

#19 (anticonvuls*):ti,ab,kw 4069

#20 (antiepilept*):ti,ab,kw 2725

#21 MeSH descriptor: [Gabapentin] explode all trees 763

#22 (gabapentin*):ti,ab,kw 2311

#23 MeSH descriptor: [Pregabalin] explode all trees 698

#24 (pregabalin):ti,ab,kw 1924

#25 MeSH descriptor: [Carbamazepine] explode all trees 802

#26 (carbamazepine):ti,ab,kw 2131

#27 MeSH descriptor: [Oxcarbazepine] explode all trees 133

#28 (oxcarbazepine):ti,ab,kw 500

#29 MeSH descriptor: [Lamotrigine] explode all trees 421

#30 (lamotrigine):ti,ab,kw 1255

#31 MeSH descriptor: [Antidepressive Agents] explode all trees 5574

- #32 (antidepress*):ti,ab,kw 15527
- #33 MeSH descriptor: [Duloxetine Hydrochloride] explode all trees 445
- #34 (duloxetine):ti,ab,kw 1293
- #35 MeSH descriptor: [Amitriptyline] explode all trees 1159
- #36 (amitriptyline):ti,ab,kw 2549
- #37 MeSH descriptor: [Nortriptyline] explode all trees 435
- #38 (nortriptyline):ti,ab,kw 843
- #39 MeSH descriptor: [Venlafaxine Hydrochloride] explode all trees 625
- #40 (venlafaxine):ti,ab,kw 1798
- #41 MeSH descriptor: [Milnacipran] explode all trees 122
- #42 (milnacipran):ti,ab,kw 296
- #43 (serotonin NEAR inhibitor):ti,ab,kw 2558
- #44 MeSH descriptor: [Capsaicin] explode all trees 573
- #45 (capsaicin):ti,ab,kw 1246
- #46 MeSH descriptor: [Lidocaine] explode all trees 5568
- #47 (lidocaine):ti,ab,kw 11702
- #48 (lignocaine):ti,ab,kw 1624
- #49 MeSH descriptor: [Anesthesia] explode all trees 18751
- #50 MeSH descriptor: [Anesthesia, Local] explode all trees 2076
- #51 (anaesth*):ti,ab,kw 24993
- #52 (anesth*):ti,ab,kw 66849
- #53 MeSH descriptor: [Ketamine] explode all trees 1942
- #54 (neuropath* NEAR drug):ti,ab,kw 2110
- #55 (neuropath* NEAR agent):ti,ab,kw 47
- #56 {or #18-#55} 113368
- #57 #4 and #17 and #56 33

EMBASE search strategy

1. exp burn/
2. burn*.tw.
3. exp thermal injury/
4. (thermal adj3 injur*).tw.
5. 1 or 2 or 3 or 4
6. exp pain/
7. pain.tw.
8. exp chronic pain/
9. chronic pain.tw.
10. exp neuralgia/
11. neuralgia.tw.
12. exp neuropathic pain/
13. exp pruritus/
14. pruritis.tw.
15. itch*.tw.
16. or/6-15
17. exp anticonvulsive agent/
18. anticonvuls*.mp.
19. antiepilept*.mp.
20. exp gabapentin/
21. gabapentin*.mp.
22. exp pregabalin/
23. pregabalin.mp.
24. exp carbamazepine/
25. carbamazepine.mp.
26. exp oxcarbazepine/
27. Oxcarbazepine.mp.
28. exp lamotrigine/
29. lamotrigine.mp.
30. exp antidepressant agent/
31. antidepressant.mp.
32. exp duloxetine/

33. duloxetine.mp.
34. exp amitriptyline/
35. amitriptyline.mp.
36. exp nortriptyline/
37. nortriptyline.mp.
38. exp venlafaxine/
39. venlafaxine.mp.
40. exp milnacipran/
41. Milnacipran.mp.
42. (serotonin adj5 inhibitor).mp.
43. exp capsaicin/
44. capsaicin.mp.
45. exp lidocaine/
46. lidocaine.mp.
47. lignocaine.mp.
48. exp regional anesthesia/
49. exp local anesthesia/
50. anaesth*.mp.
51. anesth*.mp.
52. exp ketamine/
53. ketamine.mp.
54. (neuropath* adj3 drug).mp.
55. (neuropath* adj3 agent).mp.
56. or/17-55
57. 5 and 16 and 56

MEDLINE search strategy

1. exp burn/
2. burn*.tw.
3. (thermal adj3 injur*).tw.
4. 1 or 2 or 3
5. exp pain/
6. pain.tw.
7. exp chronic pain/
8. chronic pain.tw.
9. exp neuralgia/
10. neuralgia.tw.
11. exp neuropathic pain/
12. exp pruritus/
13. pruritis.tw.
14. itch*.tw.
15. or/5-14
16. exp anticonvulsive agent/
17. anticonvuls*.mp.
18. antiepilept*.mp.
19. exp gabapentin/
20. gabapentin*.mp.
21. exp pregabalin/
22. pregabalin.mp.
23. exp carbamazepine/
24. carbamazepine.mp.
25. exp oxcarbazepine/
26. Oxcarbazepine.mp.
27. exp lamotrigine/
28. lamotrigine.mp.
29. antidepressant.mp.
30. exp duloxetine/
31. duloxetine.mp.
32. exp amitriptyline/

33. amitriptyline.mp.
34. exp nortriptyline/
35. nortriptyline.mp.
36. exp venlafaxine
37. venlafaxine.mp.
38. exp milnacipran/
39. Milnacipran.mp.
40. (serotonin adj5 inhibitor).mp.
41. exp capsaicin/
42. capsaicin.mp.
43. exp lidocaine/
44. lidocaine.mp.
45. lignocaine.mp.
46. exp regional anesthesia/
47. exp local anesthesia/
48. anaesth*.mp.
49. anesth*.mp.
50. exp ketamine/
51. ketamine.mp.
52. (neuropath* adj3 drug).mp.
53. (neuropath* adj3 agent).mp.
54. exp Antidepressive Agents/
55. or/16-54
56. 4 and 15 and 55

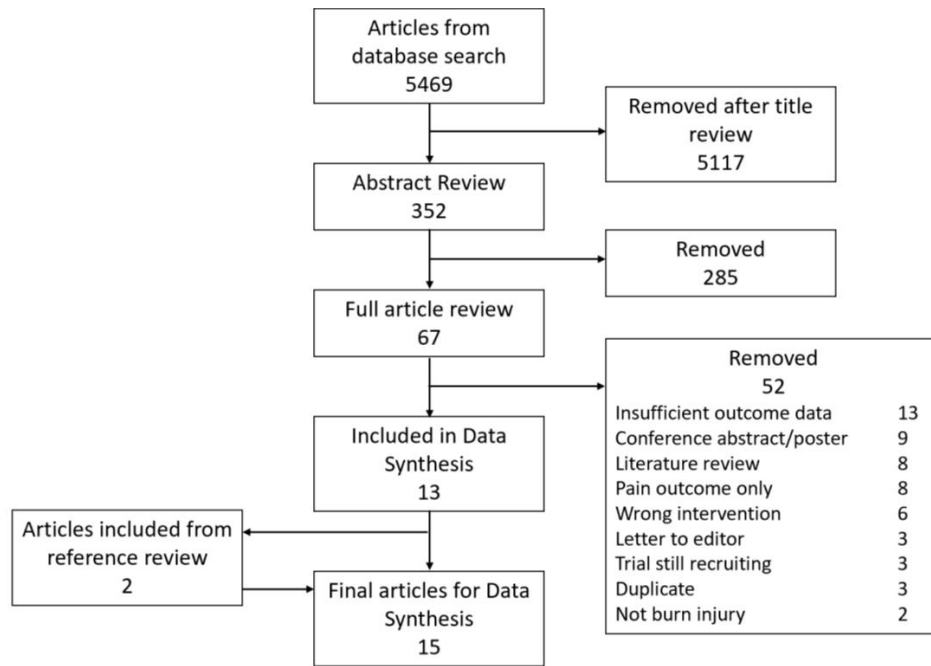


Figure S1 PRISMA flowchart

Paper	Randomisation Process	Deviations from intended intervention	Missing outcome data	Measurement of the Outcome	Selection of Reported Results	Overall
Ahuja 2011	Low	Some concern	Low	Some concern	Some concern	Some concern
Ahuja 2013	Low	Some concern	Some concern	Some concern	Low	Some concern
Demling 2002	Some concern	High risk	Low	High risk	Low	High risk
Demling 2003	Some concern	High risk	Low	High risk	low	High risk
Gray 2011	Low	Low	Low	Low	Low	Low
Jones 2019	Some concern	Low	Some concern	Low	Low	Some concern
Kwa 2019	Low	Low	Some concern	Low	Low	Some concern
Kwa 2020	Low	Low	Low	Low	Low	Low
Zheng 2015	Some concern	Some concern	Low	Low	Low	Some concern

Table S1. Risk of Bias assessment using the RoB2 (Cochrane risk of bias tool) for randomised control trials.

Paper	Confounding	Patient Selection	Classification of Intervention	Deviations from Intervention	Missing Data	Measurement of Outcome	Selection of Reported Results	Overall
Goutos 2010	Low	Moderate	Low	Low	Low	Serious	Moderate	Serious
Kaul 2018	Low	Moderate	Low	Low	Low	Serious	Low	Serious
Kneib 2019	Low	Low	Low	Low	Low	Low	Low	Low
Kopecky 2001	Low	Moderate	Low	Low	Low	Serious	Low	Serious
Mendham 2004	Low	Low	Low	Low	Low	Serious	Serious	Serious
Nieuwendijk 2018	Moderate	Moderate	Moderate	Moderate	Low	Low	Moderate	Moderate
Orellana Silva 2013	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate
Zachariah 2012	Moderate	Low	Low	Low	Low	Moderate	Moderate	Moderate

Table S2. Risk of bias assessment using ROBINS-I tool for non-randomised studies

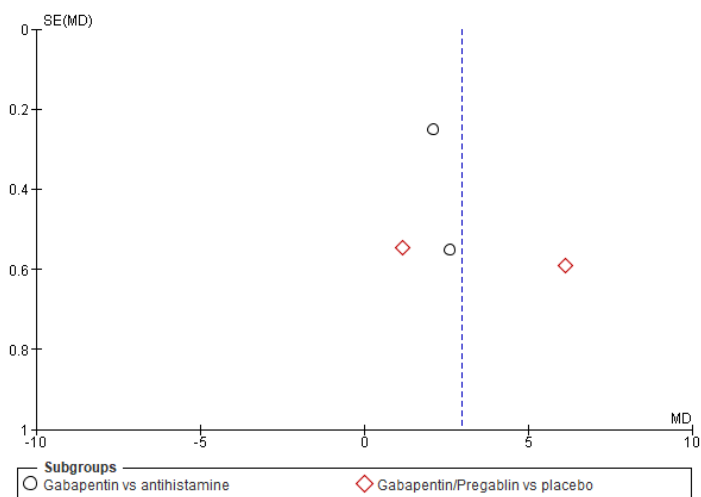


Figure S2. Funnel plot of trials included in meta-analysis of gabapentinoids for management of pruritus

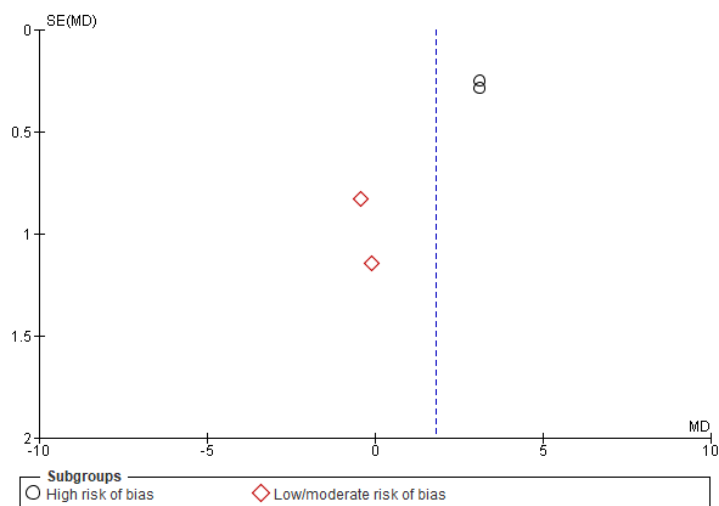


Figure S3. Funnel plot of trials included in meta-analysis of doxepin for management of pruritus

Meta-analysis	Participants (studies)	Improvement in mean VAS (95% CI)	Certainty of evidence (GRADE)
Gabapentin vs antihistamine	80 (2 studies)	2.19 (1.74-2.63)	Moderate ¹
Gabapentinoid vs placebo	128 (2 studies)	3.63 (-1.20-8.46)	Low ^{1,2,3}
Gabapentinoid vs control (All studies)	208 (4 studies)	2.96 (1.20-4.73)	Moderate ^{1,2}
Doxepin vs control (High risk bias studies)	72 (2 studies)	3.10 (2.73-3.47)	Very low ⁴
Doxepin vs control (Low/moderate risk bias studies)	61 (2 studies)	-0.32 (-1.64-0.99)	Moderate ^{1,3}
Doxepin vs control (All studies)	133 (4 studies)	1.82 (0.55-3.09)	Very low ⁴

Table S3. GRADE assessment of evidence

GRADE Working Group grades of evidence:

- High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
- Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
- Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
- Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

¹ Risk of bias - Some concerns

² Indirectness - Inclusion of participants with neuropathic pain being the primary symptom rather than pruritus

³ Imprecision - Confidence intervals cross the threshold for meaningful effect

⁴ Risk of Bias - Serious concerns, high risk of bias