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. pruritus.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. pruritus.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/
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/
41. exp capsaiacin/
42. capsaiacin.mp.
43. exp lidocaine/
44. lidocaine.mp.
45. lignocaine.mp.
46. exp regional anesthesia/
47. exp local anesthesia/
48. anaest*.mp.
49. anest*.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
<table>
<thead>
<tr>
<th>Paper</th>
<th>Randomisation Process</th>
<th>Deviations from intended intervention</th>
<th>Missing outcome data</th>
<th>Measurement of the Outcome</th>
<th>Selection of Reported Results</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahuja</td>
<td>Low</td>
<td>Some concern</td>
<td>Low</td>
<td>Some concern</td>
<td>Some concern</td>
<td>Some concern</td>
</tr>
<tr>
<td>Ahuja</td>
<td>Low</td>
<td>Some concern</td>
<td>Some concern</td>
<td>Some concern</td>
<td>Low</td>
<td>Some concern</td>
</tr>
<tr>
<td>Demling</td>
<td>Some concern</td>
<td>High risk</td>
<td>Low</td>
<td>High risk</td>
<td>Low</td>
<td>High risk</td>
</tr>
<tr>
<td>Demling</td>
<td>Some concern</td>
<td>High risk</td>
<td>Low</td>
<td>High risk</td>
<td>Low</td>
<td>High risk</td>
</tr>
<tr>
<td>Gray</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Jones</td>
<td>Some concern</td>
<td>Low</td>
<td>Some concern</td>
<td>Low</td>
<td>Low</td>
<td>Some concern</td>
</tr>
<tr>
<td>Kwa</td>
<td>Low</td>
<td>Low</td>
<td>Some concern</td>
<td>Low</td>
<td>Low</td>
<td>Some concern</td>
</tr>
<tr>
<td>Kwa</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Zheng</td>
<td>Some concern</td>
<td>Some concern</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Some concern</td>
</tr>
</tbody>
</table>

Table S1. Risk of Bias assessment using the RoB2 (Cochrane risk of bias tool) for randomised control trials.
<table>
<thead>
<tr>
<th>Paper</th>
<th>Confounding</th>
<th>Patient Selection</th>
<th>Classification of Intervention</th>
<th>Deviations from Interventions</th>
<th>Missing Data</th>
<th>Measurement of Outcome</th>
<th>Selection of Reported Results</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goutos 2010</td>
<td>Low</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Serious</td>
<td>Moderate</td>
<td>Serious</td>
</tr>
<tr>
<td>Kaul 2018</td>
<td>Low</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Serious</td>
<td>Low</td>
<td>Serious</td>
</tr>
<tr>
<td>Kneib 2019</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Kopecky 2001</td>
<td>Low</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Serious</td>
<td>Low</td>
<td>Serious</td>
</tr>
<tr>
<td>Mendham 2004</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Serious</td>
<td>Serious</td>
<td>Serious</td>
</tr>
<tr>
<td>Nieuwendijk 2018</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Orellana Silva 2013</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
<td>Moderate</td>
</tr>
<tr>
<td>Zachariah 2012</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

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
<table>
<thead>
<tr>
<th>Meta-analysis</th>
<th>Participants (studies)</th>
<th>Improvement in mean VAS (95% CI)</th>
<th>Certainty of evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin vs antihistamine</td>
<td>80 (2 studies)</td>
<td>2.19 (1.74-2.63)</td>
<td>Moderate¹</td>
</tr>
<tr>
<td>Gabapentinoid vs placebo</td>
<td>128 (2 studies)</td>
<td>3.63 (-1.20-8.46)</td>
<td>Low¹,²,³</td>
</tr>
<tr>
<td>Gabapentinoid vs control (All studies)</td>
<td>208 (4 studies)</td>
<td>2.96 (1.20-4.73)</td>
<td>Moderate¹</td>
</tr>
<tr>
<td>Doxepin vs control (High risk bias studies)</td>
<td>72 (2 studies)</td>
<td>3.10 (2.73-3.47)</td>
<td>Very low⁴</td>
</tr>
<tr>
<td>Doxepin vs control (Low/moderate risk bias studies)</td>
<td>61 (2 studies)</td>
<td>-0.32 (-1.64-0.99)</td>
<td>Moderate¹,²,³</td>
</tr>
<tr>
<td>Doxepin vs control (All studies)</td>
<td>133 (4 studies)</td>
<td>1.82 (0.55-3.09)</td>
<td>Very low⁴</td>
</tr>
</tbody>
</table>

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 the 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