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Supplemental file 1. Deviations from protocol

We deviated from our pre-registered protocol (accessed from https://osf.io/mu2f5/) to improve both the clinical interpretability and comparability of the review findings.

The deviations are as follows:

- We redefined the follow-up timepoints in relation to 'post-randomisation' as opposed to 'post-treatment' to ensure comparable follow-up between trials. The follow-up timepoints are now immediate (≤ 2 weeks) and short-term (3-13 weeks).

- We redefined how the muscle relaxant medicines were grouped to better reflect clinical utility from (antispasmodic or antispastic) to (non-benzodiazepine antispasmodic, antispastic, benzodiazepine and miscellaneous).

- We conducted additional ad hoc sensitivity analyses investigating the effect of removing trials at high risk of bias, trials primarily reported as trial registry records, trials without a placebo comparison, and trials investigating the muscle relaxant medicine carisoprodol.

- We did not report the extended funnel plot following reviewer recommendations.
Supplemental file 2. Search strategy Ovid MEDLINE

Search Strategy for Ovid MEDLINE:

Part A: Generic search for randomized controlled trials
1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. comparative study.pt.
4. clinical trial.pt.
5. random*.ab,ti.
6. placebo.ab,ti.
7. drug therapy.fs.
8. trial.ab,ti.
9. groups.ab,ti.
10. or/1-9
11. (animals not (humans and animals)).sh.
12. (adolescent* or teen* or youth? or puberty or childhood or children* or p?ediatri* or preschool or pre-school or nursery or kindergarten or infant? or newborn? or neonat* or prematurity or fetal or foetal).mp.
13. 11 or 12
14. 10 not 13

Part B: Specific search for low back, sacrum and coccyx problems
15. dorsalgia.ti,ab.
16. exp Back Pain/
17. backache.ti,ab.
18. (lumbar adj pain).ti,ab.
19. coccydynia.ti,ab.
20. sciatica.ti,ab.
21. spondylosis.ti,ab.
22. lumbago.ti,ab.
23. back disorder$.ti,ab
24. or/15-23

Part C: Specific search for other spinal disorders
25. Coccyx.sh
26. Lumbar Vertebrae.sh
27. Intervertebral disc.sh
28. Sacrum.sh
29. Intervertebral disc degeneration.sh
30. (disc adj degeneration).ti,ab.
31. (disc adj prolapse).ti,ab.
32. (disc adj herniation).ti,ab.
33. spinal fusion.sh.
34. (facet adj joints).ti,ab.
35. Intervertebral Disc Displacement.sh.
36. or/25-35

Part D: Specific search for interventions of interest
37. suxamethonium.mp. or Succinylcholine/
38. exp Botulinum Toxins/
39. pancuronium/
40. Vecuronium Bromide/
41. Atracurium/
42. Rocuronium/
43. mivacurium bromide.mp.
44. cisatracurium.mp.
45. Carisoprodol/
46. Methocarbamol/
47. Chlorzoxazone/
48. Orphenadrine/
49. Baclofen/
50. tizanidine.mp.
51. Tolperisone/
52. thiocolchicoside.mp.
53. cyclobenzaprine.mp.
54. Dantrolene/
55. Clonazepam/
56. exp Diazepam/
57. Chlordiazepoxide/
58. Oxazepam/
59. Lorazepam/
60. Bromazepam/
61. Clobazam/
62. Alprazolam/
63. clotiazepam.mp.
64. Flurazepam/
65. Nitrazepam/
66. Flunitrazepam/
67. Estazolam/
68. Triazolam/
69. lormetazepam.mp.
70. Temazepam/
71. Midazolam/
72. quazepam.mp.
73. Zolpidem/
74. zaleplon.mp.
75. Eszopiclone/
76. metaxalone.mp.
77. or/37-76 (all interventions of interest)

Results
78. 24 or 36 (all back pain)
79. 77 and 78 (all back pain and all interventions of interest)
80. 14 and 79 (all RCTs of interventions of interest in back pain)
### Supplemental file 3. Search strategies for trial registries

| WHO ICTRP: Advanced search | Muscle Relaxant Medicines |
|---------------------------|--------------------------|
| Title:                   | –                        |
| Condition:               | ‘back pain’              |
| Intervention:            | 1-40                     |
| Recruitment status:      | ALL                      |
| Phases are:              | ALL                      |

| ClinicalTrials.gov: Advanced search | Muscle Relaxant Medicines |
|-------------------------------------|--------------------------|
| Study Type:                         | Interventional Studies   |
| Study Results:                      | All studies              |
| Recruitment:                        | All studies              |
| Age:                                | Adult and Senior         |
| Gender:                             | All studies              |
| Conditions:                         | ‘back pain’              |
| Interventions:                      | 1-40                     |
| Titles:                             | –                        |
| Outcome Measures:                   | –                        |
| Sponsor/Collaborators:              | –                        |
| Sponsor (Lead):                     | –                        |
| Study IDs:                          | –                        |
| Locations:                          | –                        |
| Phase:                              | –                        |
| Funder Type:                        | –                        |
| First Received:                     | –                        |
| Last Updated:                       | –                        |
| EU Clinical Trials Register: Advanced search | Muscle Relaxant Medicines |
|--------------------------------------------|--------------------------|
| **Search Term:**                           | back pain AND 'intervention' (1-40) |
| **Country:**                               | –                         |
| **Age Range:**                             | Adult and Elderly         |
| **Trial Status:**                          | –                         |
| **Trial Phase:**                           | –                         |
| **Gender:**                                | Both                      |
| **Date Range:**                            | –                         |
| **Results Status:**                        | –                         |
### Supplemental file 4. Interventions of interest

| Number | Drug name                  | ATC code | ARTG | FDA | EMA |
|--------|----------------------------|----------|------|-----|-----|
| 1      | suxamethonium              | M03AB01  | yes  | -   | yes |
| 2      | botulinum toxin            | M03AX01  | yes  | yes | yes |
| 3      | pancuronium                | M03AC01  | yes  | yes | -   |
| 4      | vecuronium                 | M03AC03  | yes  | yes | yes |
| 5      | atracurium                 | M03AC04  | -    | yes | -   |
| 6      | rocuronium bromide         | M03AC09  | -    | -   | yes |
| 7      | mivacurium bromide         | M03AC10  | yes  | -   | yes |
| 8      | cisatracurium              | M03AC11  | yes  | yes | yes |
| 9      | carisoprodol               | M03BA02  | -    | yes | -   |
| 10     | methocarbamol              | M03BA03  | -    | yes | -   |
| 11     | chlorzoxazone              | M03BB03  | -    | yes | -   |
| 12     | orphenadrine citrate       | M03BC01  | yes  | yes | -   |
| 13     | baclofen                   | M03BX01  | yes  | yes | yes |
| 14     | tizanidine                 | M03BX02  | -    | yes | yes |
| 15     | tolperisone                | M03BX04  | -    | -   | yes |
| 16     | thiocholchicoside          | M03BX05  | -    | -   | yes |
| 17     | cyclobenzaprine            | M03BX08  | -    | yes | -   |
| 18     | dantrolene                 | M03CA01  | yes  | yes | yes |
| 19     | clonazepam                 | N03AE01  | yes  | yes | yes |
| 20     | diazepam                   | N05BA01  | yes  | yes | -   |
| 21     | chlordiazepoxide           | N05BA02  | -    | yes | -   |
| 22     | oxazepam                   | N05BA04  | yes  | yes | -   |
| 23     | lorazepam                  | N05BA06  | yes  | yes | yes |
| 24     | bromazepam                 | N05BA08  | yes  | -   | yes |
| 25     | cllobazam                  | N05BA09  | yes  | yes | -   |
| 26     | alprazolam                 | N05BA12  | yes  | yes | yes |
| 27     | clotiazepam                | N05BA21  | -    | -   | yes |
| 28     | flurazepam                 | N05CD01  | -    | yes | -   |
| 29     | nitrazepam                 | N05CD02  | yes  | -   | yes |
| 30     | flunitrazepam              | N05CD03  | yes  | -   | yes |
| 31     | estazolam                  | N05CD04  | -    | yes | -   |
| 32     | triazolam                  | N05CD05  | yes  | yes | yes |
| 33     | lormetazepam               | N05CD06  | -    | -   | yes |
| 34     | temazepam                  | N05CD07  | yes  | yes | -   |
| 35     | midazolam                  | N05CD08  | yes  | yes | yes |
| 36     | quazepam                   | N05CD10  | -    | yes | -   |
| 37     | zolpidem                   | N05CF02  | yes  | yes | -   |
| 38     | zaleplon                   | N05CF03  | yes  | yes | -   |
| Number | Drug name   | ATC code | ARTG | FDA | EMA |
|--------|-------------|----------|------|-----|-----|
| 39     | eszopiclone | N05CF04  | yes  | yes | -   |
| 40     | metaxalone  | -        | -    | -   | yes | -   |
Supplemental file 5. GRADE framework

Certainty in the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group methodology. The certainty of evidence was initially classified as ‘high’ (very certain that the true effect lies close to that of the estimate of the effect) and possibly downgraded to ‘moderate’ (moderately certain 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 in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect), or ‘very low’ (very little certainty in the effect estimate: The true effect is likely to be substantially different from the estimate of effect).

We graded the evidence in the following recommended domains in the following manner:

- Risk of bias: we downgraded by one level if > 25% but < 50% of the participants in our analysis came from trials assessed as ‘high’ risk of bias, and we downgraded by two levels if > 50% of the patients came from trials assessed as ‘high’ risk of bias.
- Inconsistency: we downgraded by one level if we identified important heterogeneity. We assessed heterogeneity using the between-study variance parameter ($\tau^2$) and the proportion of study variance not due to sampling error ($I^2$).
- Indirectness: we did not consider this domain because the eligibility criteria ensures patients, interventions, and comparators were similar across studies.
- Imprecision: we downgraded by one level if the width of the confidence intervals (for continuous variables as pain intensity and disability) by crossing either the null or the threshold for a clinically meaningful effect (10 points on a 0 to 100 scale) and two levels if the interval spanned both. For dichotomous variables (like harms) we downgraded by one level if the interval spanned the null.
- Publication bias: we downgraded by only one level if we strongly detected publication bias. We assessed publication bias by visually assessing funnel plot and sensitivity analysis.

References

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2. Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence - study limitations (risk of bias). J Clin Epidemiol. 2011;64(4):407-415.
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Supplementary file 6. Calculation of effect sizes for pain intensity

| Author, year     | Muscle relaxant medicine | Outcome scale | Type of data extracted | Type of measure | Point estimate (variability) extracted | Mean (SD), converteda | Number of participants |
|------------------|--------------------------|---------------|------------------------|-----------------|----------------------------------------|---------------------|-----------------------|
| Immediate term (≤ 2 weeks) |                      |               |                        |                 |                                        |                     |                       |
| **Acute LBP**    |                          |               |                        |                 |                                        |                     |                       |
| Aparna 2018      | Thiocolchicoside        | 0-10 VAS      | Mean                   | FV              | 0.7                                    | 6.7 (30)b           | 79                    |
| Baratta 1982     | Cyclobenzaprine         | 0-10 VAS      | Mean (p-value)         | CS              | -5.5                                   | -55 (48.9)c         | 58                    |
| Friedman 2015    | Cyclobenzaprine         | 0-10 VAS      | Mean (95% CI)          | FV              | 3.6                                    | 36 (35.8)e          | 103                   |
| Friedman 2017    | Diazepam                | VRS-4         | Mean (SD)              | FV              | 1 (1)                                  | 31.7 (31.7)         | 57                    |
| Friedman 2018    | Orphenadrine            | VRS-4         | Mean (SD)              | FV              | 1.1 (1)                                | 38 (33)             | 78                    |
| Friedman 2018    | Methocarbamol           | VRS-4         | Mean (SD)              | FV              | 1.3 (1)                                | 43 (32.7)           | 80                    |
| Friedman 2019    | Baclofen                | VRS-4         | Mean (SD)              | FV              | 1.1 (1)                                | 37.7 (32)           | 79                    |
| Friedman 2019    | Metaxalone              | VRS-4         | Mean (SD)              | FV              | 1.3 (1)                                | 42 (33)             | 76                    |
| Friedman 2019    | Tizanidine              | VRS-4         | Mean (SD)              | FV              | 1.2 (1)                                | 38.7 (31.7)         | 76                    |
| Hindle 1972      | Carisoprodol            | 0-100 VAS     | Mean                   | FV              | 15.5                                   | 15.5 (30)b          | 14                    |
| Lepisto 1979     | Tizanidine              | VRS-4         | Mean                   | CS              | -1.5                                   | -51 (30)b           | 15                    |
| Pareek 2009      | Tizanidine              | 0-10 VAS      | Mean (SD)              | CS              | -5.9 (2.1)                             | -58.8 (21.4)        | 94                    |
| Ralph 2008       | Carisoprodol            | VRS-4         | Mean (SE)              | CS              | -1.9 (0.2)                             | -47 (19.5)d         | 269                   |
| Serfer 2010      | Carisoprodol A          | VRS-5         | Mean (SE)              | CS              | -1.8 (0.1)                             | -44.5 (48.4)d       | 260                   |
| Serfer 2010      | Carisoprodol B          | VRS-5         | Mean (SE)              | CS              | -1.8 (0.1)                             | -44.5 (47.5)d       | 251                   |
| NCT00671879      | Carisoprodol A          | 0-100 VAS     | Mean (SE)              | CS              | -15.5 (1.3)                            | -15.5 (22.1)d       | 271                   |
| NCT00671879      | Carisoprodol B          | 0-100 VAS     | Mean (SE)              | CS              | -16.4 (1.3)                            | -16.4 (21.4)d       | 270                   |
| NCT00671502      | Carisoprodol A          | 0-100 VAS     | Mean                   | CS              | -27.5                                  | -27.5 (30)b         | 280                   |
| NCT00671502      | Carisoprodol B          | 0-100 VAS     | Mean                   | CS              | -28                                    | -28 (30)b           | 281                   |
| **Mixed LBP**    |                          |               |                        |                 |                                        |                     |                       |
| Akhter 2017      | Thiocolchicoside        | 0-10 VAS      | Mean (SE)              | FV              | 0.94 (0.1)                             | 9.4 (11.5)d         | 144                   |

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## Short term (3-13 weeks)

| Acute LBP | 0-10 VAS | Mean (95% CI) FV | 0.6 (1) | 0.7 (1.1) | 19.3 (31.7) | 24.3 (35.3) | 108 | 107 |
|-----------|----------|------------------|---------|-----------|-------------|-------------|------|-----|
| Friedman 2015 | Cyclobenzaprine | VRS-4 | Mean (SD) FV | 0.3 (0.7) | 0.4 (0.8) | 11.3 (23) | 12.3 (25.7) | 50 | 53 |
| Friedman 2017 | Diazepam | VRS-4 | Mean (SD) FV | 0.6 (0.9) | 0.7 (1) | 21.3 (29) | 22.7 (34.7) | 70 | 34f |
| Friedman 2018 | Orphenadrine | VRS-4 | Mean (SD) FV | 0.7 (1) | 0.7 (1) | 24.7 (32) | 22.7 (34.7) | 70 | 34f |
| Friedman 2018 | Methocarbamol | VRS-4 | Mean (SD) FV | 0.6 (0.9) | 0.4 (0.7) | 18.3 (31) | 14.3 (23) | 76 | 23g |
| Friedman 2019 | Baclofen | VRS-4 | Mean (SD) FV | 0.6 (0.9) | 0.4 (0.7) | 20 (31) | 14.3 (23) | 72 | 23g |
| Friedman 2019 | Metaxalone | VRS-4 | Mean (SD) FV | 0.6 (0.9) | 0.4 (0.7) | 19.7 (29.3) | 14.3 (23) | 70 | 24f |
| Friedman 2019 | Tizanidine | VRS-4 | Mean (SD) FV | 0.6 (0.9) | 0.4 (0.7) | 19.7 (29.3) | 14.3 (23) | 70 | 24f |

| Sub-acute LBP | 0-10 VAS | Mean (p-value) CS | -2.2 | -0.3 | -22 (29.8)c | -3 (32.1)c | 13 | 15 |
|---------------|----------|-------------------|------|------|-------------|-------------|-----|-----|
| Herskowitz 2004 | Botulinum toxin A | VRS-4 | Mean (p-value) CS | -2.2 | -0.3 | -22 (29.8)c | -3 (32.1)c | 13 | 15 |

SD, standard deviation; MD, mean difference; 95% CI, 95% confidence interval; FV, Final Value; CS, Change Score; VAS, Visual Analogue Scale; VRS-4, Verbal Rating Scale 4 levels; VRS-5, Verbal Rating Scale 5 levels.

*Mean and variability measures divided by the top number of scale and multiplied by 100, e.g. 0-10 VAS score divided by 10 and multiplied by 100.

bSD imputed as variability measures not available

cSD estimated from p-value

dSD estimated from standard error

eSD estimated from 95% Confidence Interval

fSample size in the placebo group was divided by the number of groups to avoid double-counting
# Supplementary file 7. Calculation of effect sizes for disability

| Author, year | Muscle relaxant medicine | Outcome scale (range) | Type of data extracted | Type of measure | Point estimate (variability) extracted | Mean (SD), converted | Number of participants |
|--------------|--------------------------|-----------------------|------------------------|----------------|----------------------------------------|----------------------|-----------------------|
| **Immediate term (≤ 2 weeks)** | | | | | | | |
| **Acute LBP** | | | | | | | |
| Friedman 2015 | Cyclobenzaprine | 0-24 RMDQ | Mean (95% CI) | FV | 8.2 | 8.9 | 34.2 (35)\(^b\) | 108 | 107 |
| Friedman 2017 | Diazepam | 0-24 RMDQ | Mean (95% CI) | CS | -11 | -11 | -45.8 (31.4)\(^a\) | 57 | 55 |
| Friedman 2018 | Orphenadrine | 0-24 RMDQ | Mean (95% CI) | CS | -9.4 | -10.9 | -39.2 (37.9)\(^a\) | 78 | 38\(^a\) |
| Friedman 2018 | Methocarbamol | 0-24 RMDQ | Mean (95% CI) | CS | -10.6 | -11.1 | -42.1 (39.2)\(^a\) | 79 | 24\(^a\) |
| Friedman 2019 | Baclofen | 0-24 RMDQ | Mean (95% CI) | CS | -10.1 | -11.1 | -42.1 (39.2)\(^a\) | 76 | 25\(^a\) |
| Friedman 2019 | Metaxalone | 0-24 RMDQ | Mean (95% CI) | CS | -11.2 | -11.1 | -46.7 (36.5)\(^b\) | 76 | 26\(^a\) |
| Hindle 1972 | Carisoprodol | VRS-4 | Mean FV | 1.8 | 3.4 | 45 (30)\(^c\) | 14 | 14 |
| NCT00671879 2012 | Carisoprodol A | 0-24 RMDQ | Mean (SE) | CS | -5 (0.6) | -4.3 (0.7) | -20.8 (31.7)\(^d\) | 141 | 71\(^g\) |
| NCT00671879 2012 | Carisoprodol B | 0-24 RMDQ | Mean (SE) | CS | -4.2 (0.6) | -4.3 (0.7) | -17.5 (31)\(^d\) | 135 | 71\(^g\) |
| Ralph 2008 | Carisoprodol | 0-24 RMDQ | Mean (p-value) | FV | 4.1 | 6.2 | 17.1 (36.6)\(^e\) | 269 | 278 |
| Serfer 2010 | Carisoprodol A | 0-24 RMDQ | Mean (SE) | CS | -5.7 (0.3) | -4.4 (0.3) | -23.8 (21.2)\(^a\) | 269 | 133\(^a\) |
| Serfer 2010 | Carisoprodol B | 0-24 RMDQ | Mean (SE) | CS | -5.4 (0.3) | -4.4 (0.3) | -22.5 (21.5)\(^d\) | 259 | 132\(^a\) |
| **Mixed LBP** | | | | | | | |
| Aksoy 2002 | Thiocolchicoside | 0-24 RMDQ | Mean (SD) | FV | 7.2 (8.8) | 11.8 (10) | 30 (36.7) | 174 | 155 |
| **Short term (3-13 weeks)** | | | | | | | |
| **Acute LBP** | | | | | | | |
| Friedman 2015 | Cyclobenzaprine | 0-24 RMDQ | Mean (95% CI) | FV | 4.5 | 3.8 | 18.8 (31.7)\(^b\) | 108 | 107 |
| Study Year | Drug       | Time Period | Measure | Median (IQR) | FV   | CS (95% CI)   | Sample Size |
|------------|------------|-------------|---------|--------------|------|---------------|-------------|
| Friedman 2017 | Diazepam | 0-24 RMDQ | Median (IQR) | 0 (0-1) | 0 (0-6) | 1.4 (3.2) | 8.3 (19.1) | 50 | 53 |
| Friedman 2018 | Orphenadrine | 0-24 RMDQ | Mean (SD) | 5.6 (8) | 3.8 (6.7) | 23.3 (33.4) | 16 (27.7) | 69 | 34ª |
| Friedman 2018 | Methocarbamol | 0-24 RMDQ | Mean (SD) | 4.9 (7.6) | 3.8 (6.7) | 20.6 (31.5) | 16 (27.7) | 70 | 34ª |
| Goforth 2015 | Eszopiclone | 0-24 RMDQ | Mean (SD) | 6.6 (5.5) | 7.9 (7) | 27.5 (22.9) | 33.1 (29.1) | 32 | 20 |
| Zaringhalam 2010 | Baclofen A | 0-24 RMDQ | Mean (SD) | 8.8 (3.8) | 9.8 (3.9) | 36.7 (15.8) | 40.8 (16.3) | 20 | 20 |
| Zaringhalam 2010 | Baclofen B | 0-24 RMDQ | Mean (SD) | 5.7 (1.4) | 6.4 (2.9) | 23.8 (5.8) | 26.7 (12.1) | 20 | 20 |

SD, standard deviation; MD, mean difference; 95% CI, 95% confidence interval; FV, Final Value; CS, Change Score; RMDQ, Roland Morris Disability Questionnaire; VRS-4, Verbal Rating Scale 4 levels.

ªMean and variability measures divided by the top number of scale and multiplied by 100, e.g. 0-24 RMDQ score divided by 24 and multiplied by 100.

ªªSD estimated from 95% Confidence Interval
ªªªSD imputed as variability measures not available
ªªªªSD estimated from standard error
ªªªªªSD estimated from p-value
ªªªªªªSD estimated from median and IQR
ªªªªªªªSample size in the placebo group was divided by the number of groups to avoid double-counting.
### Supplemental file 8. Characteristics of included studies

| Study, Year (Reference) | Study sample | Setting | Number of relevant trial arms | Test intervention, n | Comparison intervention, n | Duration of treatment | Outcome measure (Pain, Disability) | Overall risk of Bias | Source of data |
|-------------------------|--------------|---------|-------------------------------|----------------------|---------------------------|----------------------|----------------------------------|---------------------|---------------|
| Akhter 2017¹            | 288 participants with mixed acute and subacute LBP | India   | 2                             | Oral thiocolchicoside 150mg/day + diclofenac sodium, 144 | Oral diclofenac sodium, 144 | 7 days               | 10cm VAS, NA                       | High                | Published     |
| Aksoy 2002²             | 329 participants with mixed acute and subacute LBP | Turkey  | 2                             | Oral thiocolchicoside 16mg/day + standard treatment (NSAID or another analgesic), 174 | Standard treatment (oral NSAID or another analgesic), 155 | 5-7 days           | 100mm VAS, RMDQ                  | High                | Published     |
| Aparna 2016³            | 200 participants with acute LBP | India   | 2                             | Oral thiocolchicoside 8mg/day + aceclofenac, 100 | Oral aceclofenac, 100 | 7 days               | 10cm VAS, NA                       | High                | Published     |
| Baratta 1982³           | 120 participants with acute LBP | USA     | 2                             | Oral cyclobenzaprine 30mg/day, 60 | Oral placebo, 60 | 10 days             | 10cm VAS, NA                       | High                | Published     |
| Berry (a) 1988⁴         | 105 participants with acute LBP | UK      | 2                             | Oral tizanidine 12mg/day + ibuprofen, 51 | Oral placebo + ibuprofen, 54 | 7 days               | 100mm VAS, NA                       | High                | Published     |
| Berry (b) 1988⁵         | 112 participants with acute LBP | UK      | 2                             | Oral tizanidine 12mg/day, 59 | Oral placebo, 53 | 7 days               | 100mm VAS, NA                       | High                | Published     |
| Borenstein 1990⁶        | 40 participants with acute LBP | USA     | 2                             | Oral cyclobenzaprine 30mg/day + naproxen, 20 | Oral naproxen, 20 | 14 days             | NR, VRS-4 b                       | High                | Published     |
| Study               | Participants | Age and Sex | Intervention | Comparator | Duration | Outcomes | Rating | Status  |
|---------------------|--------------|-------------|--------------|------------|----------|----------|--------|---------|
| Casale 1988*        | 20 participants with acute LBP | Italy | Oral dantrolene 25mg/day, 10 | Oral placebo, 10 | 4 days | NR, NR | Moderate | Published |
| Cogné 2017* (crossover) | 19 participants with chronic LBP | France | IM botulin toxin A 200 units, 9 | IM placebo, 10 | Single dose | 100mm VAS*, QBPDS* | High | Published |
| Dapas 1985**        | 200 participants with acute LBP | USA | Oral baclofen range 30-80mg/day, 100 | Oral placebo, 100 | 14 days | VRS-5*, NA | High | Published |
| Emrich 2015*        | 202 participants with acute LBP | Germany | Oral methocarbamol 4500mg/day, 98 | Oral placebo, 104 | 8 days | 100mm VAS, NR | High | Published |
| Fathie 1964*        | 200 participants with acute LBP | USA | Oral metamizol 3200mg/day, 101 | Oral placebo, 99 | 7 days | VRS-4*, NA | High | Published |
| Foster 2001*        | 31 participants with chronic LBP | USA | IM botulin toxin A 200 units | IM placebo | Single dose | 10cm VAS*, ODI* | Low | Published |
| Friedman 2015*      | 323 participants with acute LBP | USA | Oral cyclobenzaprine range 5-30mg/day + naproxen, 108 | Oral placebo +naproxen, 107 | 10 days | 10cm VAS, RMDQ | Low | Published |
| Study Year   | Participants | Country | Treatment | Comparator | Duration | Measure | Grade |
|--------------|--------------|---------|-----------|------------|----------|---------|-------|
| Friedman 2017 | 114          | USA     | Oral diazepam range 5-20mg/day + naproxen, 57 | Oral placebo + naproxen | 7 days   | VRS-4, RMDQ | Low   |
| Friedman 2018 | 240          | USA     | Oral orphenadrine 200mg/day + naproxen, 80 | Oral placebo + naproxen, 79 | 7 days   | VRS-4, RMDQ | Low   |
| Friedman 2019 | 320          | USA     | Oral tizanidine range 2-16mg/day + ibuprofen, 80 | Oral placebo + ibuprofen, 80 | 7 days   | VRS-4, RMDQ | Low   |
| Goforth 2014  | 58           | USA     | Oral eszopiclone 3mg/day + naproxen, 33 | Oral placebo + naproxen, 25 | 28 days  | 100mm VAS, RMDQ | Low   |
| Gold 1978     | 60           | USA     | Oral orphenadrine 200mg/day, 20 | Oral placebo, 20 | 7 days   | NR, NA     | High  |
| Herskowitz 2004 | 28         | USA     | IM botulinum toxin A 400 units, 13 | IM placebo, 15 | Single dose | 10cm VAS, NA | High  |
| Hindle 1972   | 48           | USA     | Oral carisoprodol 1400mg/day, 16 | Oral placebo, 16 | 4 days   | 100mm VAS, VRS-4 | High  |
| Study                        | Participants                                      | Country | Intervention                                                                 | Comparator                  | Duration | Pain Score | Follow-up | Study Quality |
|------------------------------|---------------------------------------------------|---------|-------------------------------------------------------------------------------|-----------------------------|----------|------------|-----------|---------------|
| Cashin et al. 2021 (/carisoprodol group 37 yrs a, butabarbital group 34.6 yrs a, placebo group 43.5 yrs a) | Entire sample 44% female                          |         |                                                                               |                             |          |            |           |               |
| Hingorani 1966 (50 participants with acute LBP) | UK       | 2       | IM diazepam 40mg + oral diazepam 8mg/day, 25                                 | IM placebo + oral placebo, 25 | 6 days   | NR, NA     |           | High          | Published     |
| Jazayeri 2011 (50 participants with chronic LBP) | Iran     | 2       | IM botulinum toxin A 200 units, 25                                           | IM placebo 25               | Single dose | 10cm VAS b, ODI b | High          | Published     |
| Ketenci 2005 (97 participants with acute LBP) | Turkey   | 3       | Oral thiocholchicoside 16mg/day, 38                                          | Oral placebo, 27            | 7 days   | 10cm VAS, NA |           | High          | Published     |
| Klinger 1988 (80 participants with acute LBP) | USA      | 2       | IV orphenadrine 60mg, 40                                                     | IV placebo, 40              | Single dose | VRS-4 b, NA |           | Low           | Published     |
| Lepisto 1979 (30 participants with acute LBP) | Finland  | 2       | Oral tizanidine 6mg/day, 15                                                  | Oral placebo, 15            | 7 days   | VRS-4, NA  |           | Moderate       | Published     |
| Machado 2016 (43 participants with chronic LBP) | USA      | 2       | IM botulinum toxin A range 500-1000 units, 21                               | IM placebo, 22              | Single injection | 10cm VAS b, ODI b | Moderate       | Published     |
| Moll 1973 (68 participants with acute LBP) | Germany  | 2       | IM diazepam 4ml + oral diazepam 40-60mg/day, 33                             | IM placebo + oral placebo, 35 | 5-10 days | NR, NA     |           | High          | Published     |
| Study | Participants | Intervention | Comparator | Duration | Outcomes | Quality | Status |
|-------|--------------|--------------|------------|----------|----------|---------|--------|
| Diazepam group | 45.8 (13.9) yrs, 39% female; placebo group 45.4 (13.3) yrs, 49% female | | | | | | |
| Pareek 2009<sup>15</sup> | 197 participants with acute LBP | tizanidine group 43.3 (12.7) yrs, 39% female; comparator group 43.5 (10.9) yrs, 40% female | India | 2 | Oral tizanidine 4mg/day + aceclofenac, 101 | 7 days | 10cm VAS, NA | High |
| Ralph 2008<sup>16</sup> | 562 participants with acute LBP | carisoprodol group 39.3 (11.8) yrs, 47% female; comparator group 41.5 (11.7) yrs, 54% female | USA | 2 | Oral carisoprodol 1000mg/day, 277 | 7 days | VRS-5, RMDQ | High |
| Salvinii 1986<sup>17</sup> | 30 participants with LBP | | Italy | 2 | Oral dantrolene 1200mg/day + ibuprofen, 15 | 8 days | VRS-4<sup>th</sup>, NA | High |
| Schliessbach 2017<sup>18</sup> (crossover) | 98 participants with chronic LBP | | Switzerland | 2 | Oral cllobazam 20mg, 49 | 2 hours | 11pt NRS, NA | Low |
| Serfer 2010<sup>19</sup> | 828 participants with acute LBP | carisoprodol (350mg) group 40.5 (12.4) yrs, 54% female; carisoprodol (250mg) group 40.9 (11.7) yrs, 51% female; placebo group 40.7 (13.1) yrs, 59% female | USA | 3 | Oral carisoprodol (350mg) 1400mg/day, 281 | 7 days | VRS-5, RMDQ | High |
| Tervo 1976<sup>20</sup> | 50 participants with acute LBP | | Finland | 2 | IM orphenadrine 60mg + oral orphenadrine 210mg/day & paracetamol, 25 | 7-10 days | NR, NR | High |
| Thompson 1983<sup>21</sup> | 76 participants with acute LBP | | UK | 2 | Oral tizanidine 6mg/day | 10 days | 100mm VAS<sup>3</sup>, NA | High |
| Tüzün 2003<sup>22</sup> | 149 participants with acute LBP | | Turkey | 2 | IM thiocholchicoside 8mg/day, 77 | 5 days | 100mm VAS, NA | High |
| Study | Participants | Location | Age and Sex | Intervention | Comparator | Duration | Outcome Measures | Status | Registry ID | Notes |
|-------|--------------|----------|-------------|--------------|------------|----------|----------------|--------|-------------|-------|
| Zaringhalam 2010<sup>27</sup> | 84 participants with chronic LBP | Iran | 4 | Oral baclofen 30mg/day, 21 Oral baclofen 30mg/day + acupuncture, 21 | No treatment, 21 Acupuncture, 21 | 35 days | 100mm VAS, RMDQ | High | Published |
| ACTRN12616000017426<sup>38</sup> | Participants with acute LBP | Australia | 2 | Oral zopiclone 7.5mg/day | Oral placebo | 14 days | NA | NA | Clinical trial registry |
| EUCTR2017-004530-29<sup>39</sup> | 134 participants with acute LBP | Greece | 2 | IM thiocolchicoside 4mg + diclofenac IM diclofenac | Single injection | NA | NA | Clinical trial registry |
| EUCTR2019-001885-14<sup>40</sup> | Participants with acute LBP and/or sciatica | Hungry | 2 | Oral tolperisone | Oral placebo | 14 days | NA | NA | Clinical trial registry |
| IRCT20111109008035N4<sup>41</sup> | 46 participants with LBP | Iran | 2 | Oral zolpidem 5mg/day | Oral placebo | 28 days | NA | NA | Clinical trial registry |
| NCT00671879<sup>42</sup> | 840 participants with acute LBP | USA | 3 | Oral carisoprodol (500mg) 1000mg/day, 279 Oral carisoprodol (700mg) 1400mg/day, 281 | Oral placebo, 280 | 14 days | 100mm VAS, RMDQ | High | Clinical trial registry |
| NCT00671502<sup>43</sup> | 840 participants with acute LBP | USA | 3 | Oral carisoprodol (500mg) 1000mg/day, 280 | Oral placebo, 279 | 14 days | 100mm VAS, RMDQ<sup>4</sup> | High | Clinical trial registry |
| Trial ID | Participants | Treatment Details | Duration | Comparator | Route | Status | Clinical Trial Registry |
|---------|--------------|------------------|----------|------------|-------|--------|------------------------|
| NCT00817986[^4] | 161 participants with acute LBP | Age and sex not reported | USA | Oral arbaclofen placarbil (20mg) 40mg/day  Oral arbaclofen placarbil (30mg) 60mg/day  Oral arbaclofen placarbil (40mg) 80mg/day | Oral placebo | 14 days | NA | NA | Clinical trial registry |
| NCT00404417[^5] | Participants with chronic LBP | (crossover, status: active not recruiting) | USA | IM botulinum toxin A | IM placebo | Single dose | NA | NA | Clinical trial registry |
| NCT00384579[^4] | Participants with acute LBP | (status: terminated) | USA | IM botulinum toxin B | IM placebo | Single dose | NA | NA | Clinical trial registry |
| NCT00384371[^4] | Participants with subacute LBP | (status: terminated) | USA | IM botulinum toxin A | IM placebo | Single dose | NA | NA | Clinical trial registry |
| NCT02887534[^4] | Participants with acute LBP | (status: withdrawn) | Not reported | Oral tizanidine  Oral SPARC1401-low dose  Oral SPARC1401-mid dose  Oral SPARC1401-high dose | Oral placebo | Not reported | NA | NA | Clinical trial registry |
| NCT01587508[^4] | Participants with acute LBP | Brazil | Oral cyclobenzaprine 20mg/day  Oral meloxicam & cyclobenzaprine | Oral placebo | 7 days | NA | NA | NA | Clinical trial registry |
Standard deviation not reported. Data not available. Abbreviations: LBP, Low Back Pain; SD, Standard Deviation; IM, Intramuscular; IV, Intravenous; NA, Not Applicable; NR Not Reported; NRS, Numerical Rating Scale; VAS, Visual Rating Scale; VRS-4, Verbal Rating Scale 4 levels; VRS-5, Verbal Rating Scale 5 levels; RMDQ, Roland Morris Disability Questionnaire; QBPDS, Quebec Back Pain Disability Scale

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## Supplemental file 9. Risk of bias assessments

| Study     | Year | Random sequence generation | Allocation concealment | Blinding (Patients) | Blinding (Care-providers) | Blinding (Outcome assessors) | Drop Outs | Intention-to-treat analysis? | Selective outcome reporting | Similarity at baseline | Co-interventions | Compliance | Timing of assessment | Other bias | Overall Risk of Bias |
|-----------|------|----------------------------|------------------------|--------------------|--------------------------|-----------------------------|-----------|-----------------------------|-----------------------------|-------------------------|-----------------|------------|---------------------|------------|---------------------|
| Fathie    | 1964 | Low risk                   | Unclear                | Low risk           | Low risk                 | Low risk                    | High risk | Low risk                    | Unclear                     | Unclear                | Unclear        | Low risk   | Unclear             | High       |
| Hingorani | 1966 | Unclear                    | Unclear                | Low risk           | Low risk                 | Low risk                    | Low risk  | Unclear                     | High risk                   | Unclear                | Unclear        | Low risk   | Unclear             | High       |
| Hindle    | 1972 | Low risk                   | Unclear                | Low risk           | Low risk                 | Low risk                    | Low risk  | High risk                   | Low risk                     | Low risk                | Unclear        | Low risk   | Unclear             | High       |
| Moll      | 1973 | Unclear                    | Unclear                | Low risk           | Low risk                 | Low risk                    | Low risk  | Unclear                     | High risk                   | High risk               | High risk     | Low risk   | Unclear             | High       |
| Tervo     | 1976 | Unclear                    | Low risk               | Low risk           | Low risk                 | Low risk                    | Unclear  | High risk                   | Unclear                     | Low risk                | Unclear        | Low risk   | Unclear             | High       |
| Gold      | 1978 | Unclear                    | Low risk               | Low risk           | Low risk                 | Low risk                    | Unclear  | Low risk                    | Unclear                     | Unclear                | Unclear        | Low risk   | Unclear             | High       |
| Lepisto   | 1979 | Unclear                    | Low risk               | Low risk           | Low risk                 | Low risk                    | Low risk  | Low risk                    | Low risk                     | Low risk                | Unclear        | Low risk   | Unclear             | Moderate   |
| Baratta   | 1982 | Low risk                   | Unclear                | Low risk           | Low risk                 | Low risk                    | High risk | Low risk                    | Unclear                     | Low risk                | Unclear        | Low risk   | Unclear             | High       |
| Thompson  | 1983 | Unclear                    | Low risk               | Low risk           | Low risk                 | Low risk                    | Unclear  | Low risk                    | Unclear                     | Unclear                | Unclear        | Low risk   | Unclear             | High       |
| Dapas     | 1985 | Unclear                    | Low risk               | Low risk           | High risk                | High risk                   | Low risk  | Unclear                     | Low risk                     | Unclear                | Unclear        | Low risk   | Unclear             | High       |
| Salvini   | 1986 | Unclear                    | High risk              | High risk          | High risk                | High risk                   | Low risk  | Unclear                     | Low risk                     | Unclear                | Unclear        | Low risk   | Unclear             | High       |
| Berry (a) | 1988 | Unclear                    | Low risk               | Low risk           | Low risk                 | Unclear                     | Low risk  | Unclear                     | Low risk                     | Unclear                | Unclear        | Low risk   | Unclear             | High       |
| Berry (b) | 1988 | Unclear                    | Low risk               | Low risk           | Low risk                 | Unclear                     | Low risk  | Unclear                     | Low risk                     | Unclear                | Unclear        | Low risk   | Unclear             | High       |
| Name       | Year | 1988 | 1990 | 2001 | 2002 | 2003 | 2004 | 2005 | 2008 | 2009 | 2010 | 2011 | 2012 | 2014 | 2015 | 2016 |
|------------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
| Casale     | 1988 | Clear| Clear| Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Clear| Moderate |
| Klinger    | 1988 | Clear| Clear| Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Clear| Low |
| Borenstein | 1990 | Clear| Clear| High | High | High | High | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Clear| High |
| Foster     | 2001 | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Clear| Low |
| Aksoy      | 2002 | Low  | Clear| High | High | High | High | Unclear| Unclear| Low  | Low  | Unclear| Low  | Low  | Low  | Clear| High |
| Tuzun      | 2003 | Clear| Clear| Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Unclear| Low  | Unclear| Clear| High |
| Herskowitz | 2004 | Clear| Clear| Low  | Low  | Low  | Low  | Low  | Unclear| Unclear| Unclear| Low  | Low  | Low  | Low  | Clear| High |
| Ketenci    | 2005 | Clear| Clear| Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | High  | Clear| Low  | Low  | Clear| High |
| Ralph      | 2008 | Clear| Clear| Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Clear| High |
| Pareek     | 2009 | Clear| Clear| Low  | Low  | Low  | Low  | Low  | Unclear| Unclear| Unclear| Low  | Low  | Low  | Low  | Clear| High |
| Serfer     | 2010 | Low  | Clear| Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | High  | Clear| Low  | Low  | Clear| High |
| Zaringhalam| 2010 | Low  | High | High | High | High | High | High | High | High | Low  | Unclear| Low  | Low  | Low  | Clear| High |
| Jazayeri   | 2011 | Clear| Clear| Low  | High | High | High | Low  | Low  | Low  | Low  | Low  | Unclear| Low  | Low  | Low  | Clear| High |
| NCT00671502| 2011 | Clear| Clear| Low  | Low  | Low  | Low  | Low  | Unclear| High  | Clear| Unclear| Clear| Clear| Clear| Clear| Clear| High |
| NCT00671879| 2012 | Clear| Clear| Low  | Low  | Low  | Low  | Low  | Unclear| Unclear| Unclear| Low  | Unclear| Low  | Unclear| Clear| Clear| High |
| Goforth    | 2014 | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Clear| Unclear| Low  | Unclear| Clear| Low |
| Emrich     | 2015 | Clear| Clear| Low  | Low  | Low  | Low  | High  | Unclear| Clear| Low  | Low  | Low  | Clear| Clear| Clear| Clear| High |
| Friedman   | 2015 | Low  | Clear| Low  | Low  | Low  | Low  | Unclear| Low  | Low  | Low  | Clear| Clear| Clear| Clear| Clear| Low |
| Aparna     | 2016 | Clear| Clear| High | High | High | High | Unclear| Unclear| Unclear| Unclear| Unclear| Low  | Low  | Low  | Low  | High |
| Study          | Year | Unclear | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear | Low risk | Unclear | Unclear | Low risk | Unclear | Unclear | Low risk | Low risk | Low risk | Moderate |
|---------------|------|---------|----------|----------|----------|----------|----------|---------|----------|---------|---------|----------|---------|---------|----------|----------|----------|----------|
| Machado       | 2016 | Unclear | Low risk | Low risk | Low risk | Low risk | Unclear  | Low risk | Unclear  | Low risk | Unclear | Unclear | Low risk | Unclear | Unclear | Low risk | Low risk | Low risk | Moderate |
| Akhter        | 2017 | Unclear | Low risk | Low risk | Low risk | Low risk | Unclear  | Low risk | Unclear  | Low risk | Unclear | Unclear | Low risk | Unclear | Unclear | Low risk | Low risk | Low risk | High     |
| Cogne         | 2017 | Low risk | Unclear  | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | High     |
| Friedman      | 2017 | Low risk | Unclear  | Low risk | Low risk | Low risk | Unclear  | Low risk | Unclear  | Low risk | Unclear | Unclear | Low risk | Unclear | Unclear | Low risk | Low risk | Low risk | Low      |
| Schliessbach  | 2017 | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear  | Low risk | Unclear  | Low risk | Unclear | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low      |
| Friedman      | 2018 | Low risk | Unclear  | Low risk | Low risk | Low risk | Unclear  | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low      |
| Friedman      | 2019 | Low risk | Unclear  | Low risk | Low risk | Low risk | Unclear  | Low risk | Low risk | Low risk | Unclear | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low      |
### Supplemental file 10. Narrative description of trials not included in meta-analysis for pain intensity (≤ 2 weeks)

| Study, Year (Reference) | Outcome (Pain intensity) |
|-------------------------|--------------------------|
| Borenstein 1990¹        | “The total pain scores, as determined by the patients daily and physicians during scheduled visits, were not significantly different.” |
| Casale 1988²            | “VAS [visual analogue scale] pain measurements during the maximal voluntary movements showed a decrease in pain rating clearly in favor of dantrolene, with a percentage variation of 50% for the drug and 8.6% for placebo. Statistical comparison between the two treatments showed dantrolene to have a higher effectiveness (p<0.001).” |
| Cogné 2017³ (crossover) | First phase crossover data was not available. The study found “no significant difference between the groups’ [botulinum toxin A vs placebo] average LBP [low back pain] during the last 8 days at Day 30 (p = 0.97)” |
| Dapas 1985⁴             | Patients were categorised into subgroups based on low back symptom severity, moderate initial pain and severe or extremely severe initial pain. “When the severity of symptoms at visits 2 and 3 [day 4 and 10] was compared with baseline values at visit 1 [day 1] within the placebo and the baclofen treatment groups, all efficacy variables [including local pain in lumbar area] showed a statistically significant (P<0.05) improvement for the severe- and moderate-pain groups.” |
| Emrich 2015⁵            | “The proportion of patients treated with methocarbamol who achieved a pain-free state rose more rapidly to over 80% and accordingly the proportion of patients who were not yet pain-free after 8 days is below 20% - in contrast to ~ 60% in the placebo group” |
| Fathie 1964⁶            | “A medically significant response was observed in 69.6% of the 46 metaxalone-treated patients who complete the course of therapy and returned for re-examination”. Compared to “17.4% of the placebo-treatment patients who completed the course of therapy [and] showed a medically significant improvement”. |
| Foster 2001⁷            | “At 3 weeks, 11 of 15 patients who received botulinum toxin (73.3%) had >50% pain relief vs four of 16 (25%) in the saline group (p < 0.012). At 8 weeks, nine of 15 (60%) in the botulinum toxin group and two of 16 (12.5%) in the saline group had relief (p < 0.009).” |
| Gold 1978⁸              | At the 48-hour evaluation, 7/20 patients treated with orphenadrine improved compared to 0/20 in the placebo group. |
| Reference          | Summary                                                                 |
|--------------------|--------------------------------------------------------------------------|
| Hingorani 1966⁹    | “Of the 25 patients in the placebo group, 18 showed improvement, 5 showed no change, and 2 were worse. Of the 25 patients in the diazepam group, 19 showed improvement, 5 showed no change, and 1 was worse. The difference would therefore seem to be marginal, patients in the treated group having almost no better results than those in the placebo group.” |
| Jazayeri 2011¹⁰   | “After 4 weeks, 76% of patients in the BoNT-A [botulinum toxin A] group reported pain relief compared to 20% in the saline group (P < 0.005). Additionally, greater pain relief was experienced by patients in the BoNT-A group at 8 weeks (64% vs. 12%; P < 0.001).” |
| Klinger 1988¹¹     | “Based on both the physicians’ evaluations of signs and symptoms and the patients’ assessments of pain, intravenous orphenadrine was highly effective compared with placebo in reducing these patients’ lumbar paravertebral muscle pain and spasm.” |
| Machado 2016¹²     | “The primary outcome of this study was the proportion of responders with a visual analogue scale (VAS) of <4 at 6 weeks. At 6 weeks, 5 subjects in the [abobotulinum toxin A] toxin group and 3 subjects in the placebo group (28% and 16%) met this criterion (p = 0.4470).” |
| Moll 1973¹³        | There was a larger overall therapeutic effect of diazepam vs placebo. Therapeutic effect was determined based on the patient’s subjective rating of improvement in pain intensity, and alterations in clinical status as determined by the examiner. |
| Salvini 1986¹⁴     | There was no significant difference between the groups dantrolene and ibuprofen vs ibuprofen for pain on movement and pain at rest at 4 and 8 days of treatment. |
| Schliessbach 2017¹⁵| First phase crossover data was not available. The study found “pain intensity in the supine position was significantly reduced by clobazam compared to active placebo (60 min: 2.9 vs. 3.5, p = 0.008; 90 min: 2.7 vs. 3.3, p = 0.024; 120 min: 2.4 vs. 3.1, p = 0.005). Pain intensity in the sitting position was not significantly different between groups.” |
| Tervo 1976¹⁶       | No statistically significant difference was observed for symptom relief from low back for orphenadrine vs saline immediately after the injection or at 7-10 days follow-up. |
| Thompson 1983¹⁷    | Tizanidine was “generally better than placebo and significantly so in respect of VAS [visual analogue scale pain intensity]” |
| ACTRN12616000017426¹⁸| Trial terminated |
| EUCTR2017-004530-29 | No data available |
|---------------------|-------------------|
| EUCTR2019-001885-14 | Trial ongoing     |
| NCT00817986        | No data available |
| NCT00404417        | Trial active but not recruiting |
| NCT00384579        | Trial terminated  |
| NCT02887534        | Trial withdrawn   |
| NCT01587508        | Trial withdrawn   |

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Supplemental file 11. Forest plot pain intensity 3-13 weeks

### Acute LBP – Non-benzodiazepine antispasmodic

| Author, Year, Medicine | Medicine N Mean SD | Control N Mean SD | MD 95% CI Weight |
|------------------------|--------------------|------------------|------------------|
| Friedman 2015 cyclobenzaprine 108 | 19.3 31.7 107 | 24.3 35.3 | -5.0 [-14.0; 4.0] 32.8% |
| Friedman 2018 orphenadrine 70 | 21.3 29.0 34 | 22.7 34.7 | -1.4 [-14.9; 12.1] 14.5% |
| Friedman 2018 methocarbamol 70 | 24.7 32.0 34 | 22.7 34.7 | 2.0 [-11.9; 15.9] 13.7% |
| Friedman 2019 meloxaline 72 | 20.0 31.0 23 | 14.3 23.0 | 5.7 [-6.1; 17.5] 18.9% |
| Friedman 2019 tizanidine 70 | 19.7 29.3 24 | 14.3 23.0 | 5.4 [-6.1; 16.9] 20.0% |
| **Overall effect** | . | . | 0.6 [-4.5; 5.7] 100.0% |

Heterogeneity: $I^2 = 0\%$; $Q^2 = 0, p = 0.56$

### Acute LBP – Antispastic

| Author, Year, Medicine | Medicine N Mean SD | Control N Mean SD | MD 95%-CI |
|------------------------|--------------------|------------------|-----------|
| Friedman 2019 baclofen 76 | 18.3 31.0 23 | 14.3 23.0 | 4.0 [-7.7; 15.7] |

### Acute LBP – Benzodiazepine

| Author, Year, Medicine | Medicine N Mean SD | Control N Mean SD | MD 95%-CI |
|------------------------|--------------------|------------------|-----------|
| Friedman 2017 diazepam 50 | 11.3 23.0 53 | 12.3 25.7 | -1.0 [-10.4; 8.4] |

### Subacute LBP – Miscellaneous

| Author, Year, Medicine | Medicine N Mean SD | Control N Mean SD | MD 95%-CI |
|------------------------|--------------------|------------------|-----------|
| Herskowitz 2004 botulinum toxin A 13 | -22.0 29.8 15 | -3.0 32.1 | -19.0 [-41.9; 3.9] |

### Chronic LBP – Antispastic

| Author, Year, Medicine | Medicine N Mean SD | Control N Mean SD | MD 95% CI Weight |
|------------------------|--------------------|------------------|-----------------|
| Zarirghalam 2010 baclofen 20 | 61.9 22.3 20 | 64.3 23.8 | -2.4 [-16.7; 11.9] 33.7% |
| Zarirghalam 2010 baclofen 20 | 40.1 13.3 20 | 47.0 19.1 | -6.9 [-17.1; 3.3] 66.3% |
| **Overall effect** | . | . | -5.4 [-13.7; 2.9] 100.0% |

Heterogeneity: $I^2 = 0\%$; $Q^2 = 0, p = 0.62$
### Chronic LBP – Miscellaneous

| Author, Year, Medicine | Medicine N | Mean | SD | Control N | Mean | SD | MD | 95%-CI |
|------------------------|------------|------|----|-----------|------|----|----|-------|
| Goforth 2014 eszopicone | 32         | 31.7 | 17.9 | 20       | 51.6 | 22.4 | -19.9 | [-31.5; -8.3] |

### Mixed LBP – Non-benzodiazepine antispasmodic

| Author, Year, Medicine | Medicine N | Mean | SD | Control N | Mean | SD | MD | 95%-CI |
|------------------------|------------|------|----|-----------|------|----|----|-------|
| Aksoy 2002 thiocolchicoside | 174         | 15.8 | 31.2 | 155       | 21.6 | 41.4 | -5.8 | [-13.8; 2.2] |

### Supplemental file 12. Forest plot disability ≤ 2 weeks

#### Acute LBP – Non-benzodiazepine antispasmodic

| Author, Year, Medicine | Medicine N | Mean | SD | Control N | Mean | SD | MD | 95% CI | Weight |
|------------------------|-----------|------|----|-----------|------|----|----|-------|--------|
| Hindle 1972 carisoprodol | 14        | 45.0| 30.0| 14        | 85.0| 30.0| -40.0[-62.2; -17.8]| 2.8% |
| Ralph 2008 carisoprodol  | 269      | 17.1| 36.6| 278       | 25.8| 37.2| -8.7[-14.9; -2.5] | 14.0% |
| Serfer 2010 carisoprodol  | 269      | -23.8| 21.2| 133       | -18.3| 21.7| -5.5[-10.0; -1.0] | 16.6% |
| Serfer 2010 carisoprodol  | 259      | -22.5| 21.5| 132       | -18.3| 21.7| -4.2[-8.7; 0.3]  | 16.5% |
| NCT00671879 2012 carisoprodol  | 141     | -20.8| 31.7| 71       | -17.9| 32.3| -2.9[-12.1; 6.3]  | 10.0% |
| NCT00671879 2012 carisoprodol  | 135     | -17.5| 31.0| 71       | -17.9| 32.3| 0.4[-8.8; 9.6]  | 10.0% |
| Friedman 2015 cyclobenzaprine | 108  | 34.2| 34.9| 107       | 37.1| 34.8| -2.9[-12.2; 6.4]  | 9.9% |
| Friedman 2018 orphenadrine  | 78       | -39.2| 37.9| 38       | -45.4| 36.5| 6.2[-8.1; 20.5]  | 5.7% |
| Friedman 2018 methocarbamol  | 80       | -33.8| 37.4| 38       | -45.4| 36.5| 11.8[-2.6; 25.8] | 5.8% |
| Friedman 2019 metaxalone | 76       | -42.1| 39.2| 26       | -46.2| 38.7| 4.1[-13.4; 21.6] | 4.2% |
| Friedman 2019 tizanidine  | 76       | -46.7| 36.5| 26       | -46.2| 38.7| -0.5[-17.5; 16.5] | 4.4% |

Overall effect: . . . -3.3[-7.3; 0.7] 100.0% Prediction interval: [-14.5; 7.9]

Heterogeneity: $I^2 = 53\% [7\%; 76\%]$, $r^2 = 20.2375$, $p = 0.02$

#### Acute LBP – Antispastic

| Author, Year, Medicine | Medicine N | Mean | SD | Control N | Mean | SD | MD | 95% CI |
|------------------------|-----------|------|----|-----------|------|----|----|-------|
| Friedman 2019 baclofen  | 79        | -44.2| 38.1| 24       | -46.2| 38.7| 2.0[-15.6; 19.6] | |

#### Acute LBP – Benzodiazepine

| Author, Year, Medicine | Medicine N | Mean | SD | Control N | Mean | SD | MD | 95% CI |
|------------------------|-----------|------|----|-----------|------|----|----|-------|
| Friedman 2017 diazepam | 57        | -45.8| 31.4| 55       | -45.8| 39.3| 0.0[-13.2; 13.2] | |

#### Mixed LBP – Non-benzodiazepine antispasmodic

| Author, Year, Medicine | Medicine N | Mean | SD | Control N | Mean | SD | MD | 95% CI |
|------------------------|-----------|------|----|-----------|------|----|----|-------|
| Aksoy 2002 thiocolchicoside | 174    | 30.0| 38.7| 156      | 49.2| 41.7| -19.2[-27.7; -10.7] | |

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Supplemental file 13. Forest plot disability 3-13 weeks

**Acute LBP – Non-benzodiazepine antispasmodic**

| Author, Year, Medicine | Medicine | Control | MD   | 95% CI | Weight |
|------------------------|----------|---------|------|--------|--------|
| Friedman 2015 cyclobenzaprine | 108 18.8 31.7 107 15.8 27.2 | 3.0 [-4.9; 10.9] | 53.8% |
| Friedman 2018 orphenadrine | 69 23.3 33.4 34 16.0 27.7 | 7.3 [-4.9; 19.5] | 22.5% |
| Friedman 2018 methocarbamol | 70 20.6 31.5 34 16.0 27.7 | 4.6 [-7.3; 16.5] | 23.7% |

**Overall effect**

Heterogeneity: $I^2 = 0\% \; [0\%; 39\%]$, $r^2 = 0$, $p = 0.84$

**Acute LBP – Benzodiazepine**

| Author, Year, Medicine | Medicine | Control | MD   | 95%-CI |
|------------------------|----------|---------|------|--------|
| Friedman 2017 diazepam | 50 1.4 3.5 53 8.3 19.1 | -6.9 [-12.1; -1.7] |

**Chronic LBP – Antispastic**

| Author, Year, Medicine | Medicine | Control | MD   | 95% CI | Weight |
|------------------------|----------|---------|------|--------|--------|
| Zaringhalm 2010 baclofen | 20 36.7 15.8 20 40.8 16.2 | -4.1 [-14.0; 5.8] | 26.0% |
| Zaringhalm 2010 baclofen | 20 23.8 5.8 20 26.7 12.1 | -2.9 [-8.8; 3.0] | 74.0% |

**Overall effect**

Heterogeneity: $I^2 = 0\%$, $r^2 = 0$, $p = 0.84$

**Chronic LBP – Miscellaneous**

| Author, Year, Medicine | Medicine | Control | MD   | 95%-CI |
|------------------------|----------|---------|------|--------|
| Goforth 2014 eszopiclone | 32 27.5 22.9 20 33.1 29.1 | -5.6 [-20.6; 9.4] |
Supplemental file 14. Forest plot acceptability

### Acute LBP – Non-benzodiazepine antispasmodic

| Author, Year, Medicine | Medicine Withdrawal N | Control Withdrawal N | RR   | 95% CI | Weight |
|------------------------|-----------------------|----------------------|------|--------|--------|
| Fathie 1964 metaxalone | 5.0 51                | 3.0 49               | 1.6  | [0.4; 6.3] | 3.3%   |
| Fathie 1964 metaxalone | 5.0 50                | 7.0 50               | 0.7  | [0.2; 2.1] | 4.9%   |
| Hindle 1972 carisoprodol | 2.0 16               | 2.0 16               | 1.0  | [0.2; 6.3] | 2.0%   |
| Lepesto 1979 tizanidine | 0.5 15               | 2.5 15               | 0.2  | [0.0; 3.8] | 0.8%   |
| Baratta 1982 cyclobenzaprine | 2.0 60         | 1.0 60               | 2.0  | [0.2; 21.5] | 1.3%   |
| Berry (a) 1988 tizanidine | 7.0 51              | 4.0 54               | 1.9  | [0.6; 6.0] | 4.4%   |
| Berry (b) 1988 tizanidine | 8.0 59              | 9.0 53               | 0.8  | [0.3; 19] | 6.5%   |
| Tuzun 2003 thiocholchicoside | 4.0 77            | 8.0 72               | 0.5  | [0.1; 1.5] | 4.4%   |
| Ketenc 2005 thiocholchicoside | 1.0 38             | 1.0 14               | 0.4  | [0.0; 5.5] | 1.0%   |
| Ketenc 2005 tizanidine   | 1.0 32              | 1.0 13               | 0.4  | [0.0; 6.0] | 1.0%   |
| Ralph 2008 carisoprodol  | 31.0 277            | 43.0 288             | 0.7  | [0.5; 1.1] | 13.0%  |
| Pareek 2009 tizanidine   | 7.0 101             | 5.0 96               | 1.3  | [0.4; 4.1] | 4.7%   |
| Serfer 2010 carisoprodol | 42.0 281            | 24.0 138             | 0.9  | [0.5; 1.4] | 12.4%  |
| Serfer 2010 carisoprodol | 26.0 271            | 24.0 138             | 0.6  | [0.3; 0.9] | 11.4%  |
| Emrich 2015 methocarbamil | 62.0 98            | 70.0 104             | 0.9  | [0.6; 1.2] | 17.1%  |
| Apama 2016 thiocholchicoside | 21.0 100          | 28.0 100             | 0.8  | [0.5; 1.3] | 11.6%  |

Overall effect: 0.8 [0.6; 1.1] 100.0%  
Prediction interval: [0.4; 1.8]  
Heterogeneity: $I^2 = 0\%$ [0\%; 32\%], $Q^2 = 0.1068, p = 0.79$

### Chronic LBP – Antispastic

| Author, Year, Medicine | Medicine Withdrawal N | Control Withdrawal N | RR   | 95% CI | Weight |
|------------------------|-----------------------|----------------------|------|--------|--------|
| Zaringhaim 2010 baclofen | 1.5 21              | 0.5 21               | 3.0  | [0.1; 69.5] | 42.8% |
| Zaringhaim 2010 baclofen | 1.0 21              | 1.0 21               | 1.0  | [0.1; 15.0] | 57.2% |

Overall effect: 1.6 [0.2; 12.9] 100.0%  
Heterogeneity: $I^2 = 0\%$, $Q^2 = 0.0717, p = 0.60$

### Chronic LBP – Miscellaneous

| Author, Year, Medicine | Medicine Withdrawal N | Control Withdrawal N | RR   | 95% CI | Weight |
|------------------------|-----------------------|----------------------|------|--------|--------|
| Goforth 2014 eszopiclone | 4 33                 | 8 25                 | 0.4  | [0.1; 1.1] | 60.7% |
| Machado 2016 botulinum toxin A | 3 21                | 3 22                 | 1.0  | [0.2; 4.6] | 39.3% |

Overall effect: 0.6 [0.2; 1.7] 100.0%  
Heterogeneity: $I^2 = 15\%$, $Q^2 = 0.1918, p = 0.28$
Supplemental file 15. Forest plot adverse events

**Acute LBP – Non-benzodiazepine antispasmodic**

| Author, Year, Medicine | Medicine | Control | Adverse Event | Adverse Event | RR     | 95% CI     | Weight |
|------------------------|----------|---------|---------------|---------------|--------|------------|--------|
| Tervo 1976 orphenadrine | 2        | 25      | 1             | 25            | 2.0    | [0.2; 20.7] | 1.0%   |
| Gold 1978 orphenadrine  | 5        | 20      | 1             | 20            | 5.0    | [0.6; 39.1] | 1.2%   |
| Lepisto 1979 tizanidine | 5        | 15      | 6             | 15            | 0.8    | [0.3; 2.1]  | 4.2%   |
| Baratta 1982 cyclobenzaprine | 25    | 58      | 17            | 59            | 1.5    | [0.9; 2.5]  | 7.9%   |
| Berry (a) 1986 tizanidine | 23     | 51      | 17            | 54            | 1.4    | [0.9; 2.4]  | 7.9%   |
| Berry (b) 1988 tizanidine | 24      | 57      | 11            | 47            | 1.8    | [1.0; 3.3]  | 6.8%   |
| Klinge 1989 orphenadrine | 8        | 40      | 3             | 40            | 2.7    | [0.8; 9.3]  | 2.8%   |
| Borenstein 1990 cyclobenzaprine | 12     | 20      | 4             | 20            | 3.0    | [1.2; 7.7]  | 4.2%   |
| Tuzun 2003 thiocolchicoside | 4        | 77      | 4             | 72            | 0.9    | [0.2; 3.6]  | 2.5%   |
| Pareek 2009 tizanidine  | 12       | 101     | 12            | 98            | 1.0    | [0.4; 2.0]  | 5.5%   |
| NCT00671502 2011 carisoprodol | 65    | 280     | 19            | 138           | 1.7    | [1.1; 2.7]  | 8.2%   |
| NCT00671502 2011 carisoprodol | 78     | 278     | 18            | 137           | 2.1    | [1.3; 3.4]  | 8.2%   |
| NCT00671879 2012 carisoprodol | 94    | 275     | 25            | 137           | 1.9    | [1.3; 2.8]  | 9.1%   |
| NCT00671879 2012 carisoprodol | 98     | 281     | 24            | 137           | 2.0    | [1.3; 3.0]  | 9.0%   |
| Emrich 2015 methocarbamol | 5        | 98      | 1             | 104           | 5.3    | [1.6; 44.6] | 1.1%   |
| Friedman 2015 cyclobenzaprine | 36    | 108     | 22            | 107           | 1.6    | [1.0; 2.6]  | 8.3%   |
| Friedman 2016 orphenadrine | 7        | 74      | 6             | 37            | 0.6    | [0.2; 1.6]  | 3.8%   |
| Friedman 2018 methocarbamol | 14      | 75      | 7             | 38            | 1.0    | [0.4; 2.3]  | 5.0%   |
| Friedman 2018 metaxalone  | 6        | 70      | 2             | 22            | 0.9    | [0.2; 4.3]  | 2.0%   |
| Friedman 2019 tizanidine | 6        | 73      | 1             | 23            | 1.9    | [0.2; 14.8] | 1.2%   |

**Overall effect**

| Prediction interval | 1.6 [1.2; 2.0] 100.0% |
|---------------------|------------------------|

Heterogeneity: $I^2 = 0\%$, $t^2 = 0.1259$, $p = 0.52$

**Acute LBP – Antispastic**

| Author, Year, Medicine | Medicine | Control | Adverse Event | Adverse Event | RR     | 95% CI     | Weight |
|------------------------|----------|---------|---------------|---------------|--------|------------|--------|
| Dapas 1985 baclofen    | 67       | 98      | 29            | 97            | 2.3    | [1.6; 3.2] | 84.3%  |
| Friedman 2019 baclofen | 7        | 73      | 2             | 22            | 1.1    | [0.2; 4.7] | 15.7%  |

**Overall effect**

| Prediction interval | 2.0 [1.1; 3.8] 100.0% |
|---------------------|------------------------|

Heterogeneity: $I^2 = 0\%$, $t^2 = 0.0983$, $p = 0.32$

**Acute LBP – Benzodiazepine**

| Author, Year, Medicine | Medicine | Control | Adverse Event | Adverse Event | RR     | 95% CI     | Weight |
|------------------------|----------|---------|---------------|---------------|--------|------------|--------|
| Hingorani 1986 diazepam | 10       | 25      | 4             | 25            | 2.5    | [0.9; 6.9] | 41.0%  |
| Friedman 2017 diazepam | 12       | 57      | 8             | 52            | 1.4    | [0.6; 3.1] | 59.0%  |

**Overall effect**

| Prediction interval | 1.8 [0.9; 3.6] 100.0% |
|---------------------|------------------------|

Heterogeneity: $I^2 = 0\%$, $t^2 = 0.0529$, $p = 0.36$

**Chronic LBP – Miscellaneous**

| Author, Year, Medicine | Medicine | Control | Adverse Event | Adverse Event | RR     | 95% CI     | Weight |
|------------------------|----------|---------|---------------|---------------|--------|------------|--------|
| Godforth 2014 eszopiclone | 2        | 32      | 1             | 20            | 1.2    | [0.1; 12.9] | 34.3%  |
| Machado 2016 botulinum toxin A | 3      | 21      | 2             | 22            | 1.6    | [0.3; 8.5]  | 65.7%  |

**Overall effect**

| Prediction interval | 1.5 [0.4; 5.7] 100.0% |
|---------------------|------------------------|

Heterogeneity: $I^2 = 0\%$, $t^2 = 0.0003$, $p = 0.88$
# Mixed LBP – Non-benzodiazepine antispasmodic

| Author, Year, Medicine | Medicine | Adverse Event N | Adverse Event N | RR 95%-CI |
|------------------------|----------|-----------------|-----------------|-----------|
| Aksoy 2002 thiocolchicoside | 11 174 | 6 155 | 1.6 [0.6; 4.3] |

0.5 1 2
### Supplemental file 16. Forest plot serious adverse events

**Acute LBP – Non-benzodiazepine antispasmodic**

| Author, Year, Medicine | Medicine | Control | RR       | 95% CI    | Weight |
|------------------------|----------|---------|----------|-----------|--------|
| NCT00671502 2011 carisoprodol | 1.5 280 | 0.5 138 | 1.5 [0.1; 36.1] | 46.2% |
| NCT00671879 2012 carisoprodol | 3.5 275 | 0.5 137 | 3.5 [0.2; 67.0] | 53.8% |

**Overall effect**

Heterogeneity: $I^2 = 0\%$, $t^2 = 0.0256$, $p = 0.70$

Overall effect: $2.3 [0.3; 20.8] 100.0\%$
### Supplemental file 17. Forest plot tolerability

#### Acute LBP – Non-benzodiazepine antispasmodic

| Author, Year, Medicine | Medicine Discontinued | Medicine N | Control Discontinued | Control N | RR  | 95% CI | Weight |
|------------------------|-----------------------|------------|-----------------------|-----------|-----|--------|--------|
| Berry (a) 1988 tizanidine | 5.0 51               | 1.0 54     |                       |           | 5.3 | [0.6; 43.8] | 12.1% |
| Berry (b) 1988 tizanidine | 5.0 57               | 1.0 47     |                       |           | 4.1 | [0.5; 34.1] | 12.1% |
| Ketco 2005 tizanidine    | 1.5 32               | 0.5 13     |                       |           | 1.2 | [0.1; 28.0] | 6.6%  |
| Ralph 2008 carisoprodol  | 8.0 277              | 5.0 284    |                       |           | 1.6 | [0.5; 5.0]  | 24.0% |
| Serfer 2010 carisoprodol | 15.0 279             | 5.0 138    |                       |           | 1.3 | [0.6; 4.0]  | 23.8% |
| Serfer 2010 carisoprodol | 3.0 271              | 5.0 138    |                       |           | 0.3 | [0.1; 1.3]  | 19.4% |

Overall effect: 1.5 [0.6; 3.5] 100.0%

Heterogeneity: $I^2 = 29\%$ [0%; 71%], $Q^2 = 0.5399$, $p = 0.22$

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#### Acute LBP – Antispastic

| Author, Year, Medicine | Medicine Discontinued | Medicine N | Control Discontinued | Control N | RR  | 95%-CI |
|------------------------|-----------------------|------------|-----------------------|-----------|-----|--------|
| Dapas 1985 baclofen     | 17.5 98               | 0.5 97     |                       |           | 34.6 | [2.1; 568] |

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Supplemental file 18. Forest plot dose subgroup analysis

Population: Acute low back pain

Medicine: Non-benzodiazepine antispasmodic

Outcome: Pain intensity

Follow-up: Immediate (≤ 2 weeks)

### Standard dose

| Author, Year, Medicine | Medicine N | Mean  | SD  | Control N | Mean  | SD  | MD    | 95% CI   | Weight |
|------------------------|------------|-------|-----|-----------|-------|-----|-------|----------|--------|
| Hindle 1972 carisoprodol | 14         | 15.5  | 30.0| 14        | 64.0  | 30.0| -48.5 | [-70.7, -26.3] | 3.2%   |
| Lepisto 1979 tizanidine  | 15         | -51.0 | 30.0| 15        | -52.7 | 30.0| -1.7  | [-19.8, 23.2]  | 3.4%   |
| Tuzun 2003 thiocolchicoside | 73        | 25.1  | 20.9| 66        | 47.4  | 19.8| -22.3 | [-29.0, -15.6] | 7.1%   |
| Ketenci 2005 thiocolchicoside | 38    | 6.3   | 11.7| 14        | 43.7  | 27.9| -37.4 | [-52.5, -22.3] | 4.8%   |
| Ketenci 2005 tizanidine   | 32         | 18.6  | 16.6| 13        | 43.7  | 27.9| -25.1 | [-41.3, -8.9]  | 4.5%   |
| Ralph 2008 carisoprodol   | 269        | -47.0 | 77.9| 278       | -30.0 | 66.7| -17.0 | [-29.2, -4.8]  | 5.6%   |
| Pareek 2009 tizanidine    | 94         | -58.8 | 21.4| 91        | -43.5 | 20.6| -15.3 | [-21.4, -9.2]  | 7.2%   |
| Serfer 2010 carisoprodol  | 260        | -44.5 | 48.4| 128       | -34.2 | 44.0| -10.3 | [-19.9, -0.7]  | 6.3%   |
| Serfer 2010 carisoprodol  | 251        | -44.5 | 47.5| 128       | -34.2 | 44.0| -10.3 | [-19.9, -0.7]  | 6.3%   |
| NCT00671502 2011 carisoprodol | 280  | 27.5  | 30.0| 140       | -28.6 | 30.0| 1.1   | [-5.0, 7.2]  | 7.2%   |
| NCT00671502 2011 carisoprodol | 281  | 28.0  | 30.0| 139       | -28.6 | 30.0| 0.6   | [-5.5, 6.7]  | 7.2%   |
| NCT00671879 2012 carisoprodol | 271 | -15.5 | 22.1| 132       | -15.2 | 21.4| -0.3  | [-4.8, 4.2]  | 7.6%   |
| NCT00671879 2012 carisoprodol | 270 | -16.4 | 21.4| 132       | -15.2 | 21.4| -1.2  | [-6.7, 3.3]  | 7.6%   |
| Friedman 2015 cyclobenzaprine | 103  | 36.0  | 35.8| 104       | 39.0  | 30.9| -3.0  | [-12.1, 6.1] | 6.4%   |
| Friedman 2018 orphenadrine | 78  | 38.0  | 33.0| 38        | 39.0  | 32.0| -1.0  | [-13.5, 11.5] | 5.5%   |
| Friedman 2019 metaxalone   | 76  | 42.0  | 33.3| 24        | 38.3  | 29.3| 3.7   | [-10.2, 17.6] | 5.1%   |
| Friedman 2019 tizanidine   | 76  | 38.7  | 31.7| 25        | 38.3  | 29.3| 0.4   | [-13.1, 13.9] | 5.2%   |

Overall effect: -9.4 [-14.5; -4.2] 100.0%

Prediction interval: [-30.0; 11.3]

Heterogeneity: $I^2 = 84\%$ [75%; 89%], $t^2 = 86.8485$, $p < 0.01$

### Above dose

| Author, Year, Medicine | Medicine N | Mean  | SD  | Control N | Mean  | SD  | MD    | 95% CI   | Weight |
|------------------------|------------|-------|-----|-----------|-------|-----|-------|----------|--------|
| Baratta 1982 cyclobenzaprine | 58       | -55.0 | 48.5| 59        | -40.0 | 48.9| -15.0 | [-32.6, 2.6] | 21.7%   |
| Berry (a) 1988 tizanidine | 46       | -29.0 | 43.3| 52        | -33.0 | 32.9| 4.0   | [-14.1, 19.4] | 26.8%   |
| Berry (b) 1988 tizanidine | 51       | 19.0  | 23.2| 45        | 19.0  | 22.9| 6.0   | [-9.2, 9.2]  | 51.4%   |

Overall effect: -2.2 [-11.4; 7.0] 100.0%

Heterogeneity: $I^2 = 30\%$ [0%; 93%], $r^2 = 20.7645$, $p = 0.24$

### Below dose

| Author, Year, Medicine | Medicine N | Mean  | SD  | Control N | Mean  | SD  | MD    | 95% CI   | Weight |
|------------------------|------------|-------|-----|-----------|-------|-----|-------|----------|--------|
| Aparna 2016 thiocolchicoside | 79       | 6.7   | 30.0| 74        | 11.5  | 30.0| -4.8  | [-14.3, 4.7] | 60.8%   |
| Friedman 2018 methocarbamol | 80       | 43.0  | 32.7| 38        | 39.0  | 32.0| 4.0   | [-8.4, 16.4] | 39.2%   |

Overall effect: -1.4 [-9.8; 7.1] 100.0%

Heterogeneity: $I^2 = 18\%$, $r^2 = 6.7860$, $p = 0.27$
Supplemental file 19. Funnel plots for all meta-analyses with ≥2 trials

Results for Egger’s regression test for funnel plot asymmetry are reported alongside funnel plots which included comparisons with 10 or more trials.  

### Acute LBP Non-benzodiazepine antispasmodics, Pain intensity ≤2 weeks

![Funnel plot for Acute LBP Non-benzodiazepine antispasmodics, Pain intensity ≤2 weeks](image)

| Intercept | Confidence Interval | t-value | p-value |
|-----------|---------------------|---------|---------|
| -1.6      | -3.7 to 0.4         | -1.5    | 0.1     |

### Acute LBP Non-benzodiazepine antispasmodics, Pain intensity 3-13 weeks

![Funnel plot for Acute LBP Non-benzodiazepine antispasmodics, Pain intensity 3-13 weeks](image)

Cashin et al. 2021
Mixed LBP Non-benzodiazepine antispasmodics, Pain intensity ≤2 weeks

Acute LBP Non-benzodiazepine antispasmodics, Disability ≤2 weeks

|                  | Intercept | Confidence Interval | t-value | p-value |
|------------------|-----------|---------------------|---------|---------|
| Egger’s test     | 0.5       | -1.3 to 2.4         | 0.6     | 0.6     |
Acute LBP Non-benzodiazepine antispasmodics, Disability 3-13 weeks

![Graph showing standard error vs mean difference]

Acute LBP Non-benzodiazepine antispasmodics, Acceptability

![Graph showing standard error vs risk ratio]

|                | Intercept | Confidence Interval | t-value | p-value |
|----------------|-----------|---------------------|---------|---------|
| Egger’s test   | -0.2      | -0.8 to 0.4         | -0.6    | 0.5     |
Chronic LBP Miscellaneous, Acceptability

Acute LBP Non-benzodiazepine antispasmodics, Adverse events

|          | Intercept | Confidence Interval | t-value | p-value |
|----------|-----------|---------------------|---------|---------|
| Egger's test | -0.3      | -1.2 to 0.7         | -0.6    | 0.6     |
Acute LBP Antispastics, Adverse events

Acute LBP Benzodiazepines, Adverse events
References

1. Sterne JAC, Sutton AJ, Ioannidis JPA, et al. Recommendations for Examining and Interpreting Funnel Plot Asymmetry in Meta-Analyses of Randomised Controlled Trials. *BMJ*. 2011;343. doi:10.1136/bmj.d4002
## Supplemental file 20. Sensitivity analyses for non-benzodiazepine antispasmodic medicines in acute LBP

| Outcome | Overall | Removed trials with an unclear definition for non-specific LBP | Removed trials measuring pain with a VRS | Removed trials where measures of variance were imputed | Removed trials for carisoprodol | Removed trials for thiocolchicoside | Removed trials at high risk of bias | Removed trials with data from trial registry record | Removed trials without a placebo comparator |
|---------|---------|-------------------------------------------------------------|---------------------------------------|---------------------------------------------------|---------------------------------|-------------------------------------|---------------------------------|-----------------------------------------------|-------------------------------------------------|
| **Pain intensity (≤ 2 weeks)** | (MD/RR [95% CI]; Tau; n) | (MD/RR [95% CI]; Tau; n) | (MD/RR [95% CI]; Tau; n) | (MD/RR [95% CI]; Tau; n) | (MD/RR [95% CI]; Tau; n) | (MD/RR [95% CI]; Tau; n) | (MD/RR [95% CI]; Tau; n) | (MD/RR [95% CI]; Tau; n) | (MD/RR [95% CI]; Tau; n) |
| Pain intensity (≤ 2 weeks) | -7.7 (-12.1 to -3.3), 76.2, n=4546 | -8.1 (-12.7 to -3.6), 79.3, n=4450 | -9.7 (-15.4 to -3.9), 92.6, n=2767 | -8.2 (-13.2 to -3.2), 77.6, n=3495 | -8 (-14.3 to -1.7), 103.9, n=1559 | -5.3 (-9.2 to -1.4), 43.8, n=4200 | 0.2 (-4.9 to 5.4), 0, n=672 | -10.2 (-15.6 to -4.7), 96.4, n=2901 | -11 (-17 to -5.1), 95.9, n=3488 |
| Change in overall effect size (%) | Increased by -0.4 (5.2%) | Increased by -2 (26%) | Increased by -0.5 (6.5%) | Increased by -0.3 (3.9%) | Increased by -0.2 (13.4%) | Increased by -0.2 (10.2%) | Increased by -2.5 (42.9%) | Increased by -3.3 (29.5%) | |
| Change in Tau² (%) | Tau² increased by 3.1 (4.1%) | Tau² increased by 16.4 (21.8%) | Tau² increased by 14.4 (1.8%) | Tau² increased by 27.2 (36.4%) | Tau² increased by 32.4 (42.5%) | Tau² reduced by 76.2 (100%) | Tau² increased by 20.2 (26.5%) | Tau² increased by 19.7 (25.9%) | |
| **Acceptability** | 0.8 (0.6 to 1.1), 0.1, n=2834 | 0.8 (0.6 to 1.1), 0, n=2520 | | | 0.9 (0.6 to 1.3), 0.2, n=1412 | 0.9 (0.6 to 1.2), 0.1, n=2433 | 0.2 (0 to 3.8), NA, n=30 | | 0.8 (0.6 to 1), 0.1, n=2332 |
| Change in overall effect size (%) | No change in acceptability | | | | Reduced by 0.1 (12.5%) | Reduced by 0.1 (12.5%) | Increased by 0.6 (75%) | No change in acceptability | No change in acceptability |
| Change in Tau² (%) | Tau² reduced by 0.1 (100%) | | | | Tau² increased by 0.1 (100%) | No change in Tau² | | | |
| **Disability (≤2 weeks)** | -3.3 (-7.3 to 0.7), 20.2, n=2438 | | | | 2.3 (-3.6 to 8.3), 0, n=652 | 2.3 (-3.6 to 8.3), 0, n=652 | -3.7 (-8.6 to 1.2), 26.7, n=2020 | -5.9 (-10.5 to -1.3), 17.5, n=1786 | |
| Change in overall effect size (%) | No change in disability | | | | | No change in disability | | | |
| Change in Tau² (%) | | | | | | Tau² reduced by 16.2 (80.2%) | | | |
| Adverse events | 1.6 (1.2 to 2), 0.1, n=3404 | - | - | - | 1.4 (1 to 2), 0.2, n=1741 | 1.6 (1.3 to 2), 0.1, n=3255 | 1.2 (0.8 to 1.9), 0.1, n=737 | 1.4 (1 to 2), 0.2, n=1741 | 1.8 (1.3 to 2.4), 0.1, n=2385 |
|----------------|-----------------------------|---|---|---|----------------------------|----------------------------|-----------------------------|----------------------------|-----------------------------|
| Change in overall effect size (%) | - | - | - | Reduced by 0.2 (12.5%) | No change in adverse events | Reduced by 0.4 (25%) | No change in adverse events | Reduced by 0.2 (12.5%) | Increased by 0.2 (12.5%) |
| Change in Tau² (%) | - | - | - | Tau² increased by 0.1 (100%) | No change in Tau² | No change in Tau² | Tau² increased by 0.1 (100%) | No change inTau² |

| Tolerability | 1.5 (0.6 to 3.5), 0.5, n=1641 | - | - | - | 3.6 (0.9 to 14.7), 0.1, n=254 | - | - | - | 1.2 (0.5 to 3), 0.4, n=1536 |
|----------------|-----------------------------|---|---|---|----------------------------|---|---|---|----------------------------|
| Change in overall effect size (%) | - | - | - | Increased by 2.1 (140%) | Tau² reduced by 0.4 (80%) | - | - | - | Reduced by 0.3 (20%) |
| Change in Tau² (%) | - | - | - | Tau² reduced by 0.1 (20%) |

LBP, Low Back Pain; MD, Mean Difference; RR, Risk Ratio; CI, Confidence Interval; VRS, Verbal Rating Scale; NA, Not Applicable