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REVIEW

Oral non-benzodiazepine muscle-relaxants for people with acute and chronic primary low back pain: a systematic review with meta-analysis

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Abstract

Purpose To determine benefits and adverse effects (AE) of oral muscle-relaxants (MR) (non-benzodiazepines) for acute (< 6 weeks) and chronic (> 12 weeks) primary LBP, administered alone or combined with analgesics/NSAIDs.

Methods CENTRAL, MEDLINE, EMBASE, CINAHL were searched for pertinent randomized controlled trials. Primary outcomes comprised lack of pain relief, global efficacy and AE at 5–7 days follow-up assessed dichotomously (risk ratio, RR).

Results Fifty studies (7531 participants) were included, with data from 4775 pooled in meta-analyses. For acute LBP, non-benzodiazepine MR were associated with increased likelihood of pain relief (moderate certainty; RR: 0.53, $p < 0.0001$), global efficacy (RR: 0.49, $p = 0.0001$), muscle spasm (RR: 0.62, $p < 0.00001$), and physical outcomes (RR: 0.60, $p < 0.00001$) compared to placebo. AE were more frequent with non-benzodiazepine MR compared to placebo (low-to-moderate certainty; RR: 1.56; $p = 0.003$), and at central nervous system (CNS; RR: 2.40; $p < 0.00001$), but not at gastrointestinal (GI) level (RR: 0.77; $p = 0.62$). Combined non-benzodiazepines + analgesics/non-steroidal anti-inflammatory drugs (NSAIDs) provide a larger and clinically meaningful benefit compared to placebo + analgesics/NSAIDs for global efficacy at 5–7 days (low-certainty; RR: 0.62; $p = 0.01$). Combined therapy did not result in significant between-group differences for total AE (moderate-certainty; RR: 1.15; $p = 0.50$) and GI AE (RR: 0.63; $p = 0.08$), despite responsible for more CNS AE (low-certainty; RR: 1.91; $p = 0.002$). When comparing non-benzodiazepine MR versus placebo for chronic LBP, only data on total AE could be pooled, without between-group difference (RR: 0.93; $p = 0.69$).

Conclusions Non-benzodiazepine MR for acute LBP were associated with increased likelihood of pain relief and global efficacy compared to placebo. Combined therapy with analgesics/NSAIDs proved superior for global efficacy. Studies are needed to evaluate if non-benzodiazepine MR are of larger benefit than analgesics/NSAIDs, and if stand-alone administration provides more benefit than combined treatment. The observed AE warrant caution.

Keywords Low back pain · Muscle-relaxants · Non-benzodiazepine · Placebo

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Introduction

Non-benzodiazepines are antispasmodic muscle-relaxants (MR) used for several musculoskeletal conditions, including primary low back pain (LBP) [1]. The use of MR for LBP represents a source of controversy amongst physicians, mainly because of their effective use in clinical practice that should be balanced against their adverse effects (AE) [1]. In particular, there is a lack of high-quality research on the clinical application of these drugs, as shown during the last two decades in several narrative, systematic and meta-analytic reviews [2–4]. Another weakness relies on randomized controlled trials (RCTs) which report the effects of studies on MR through mean-derived indicators, rather than using dichotomous data, such as the rate or proportion of participants with or without pain relief. Indeed, it has been extensively demonstrated that responses to analgesic medications are not normally distributed [5]. Consequently, statistical comparisons of an analgesic versus placebo should take the non-normal distribution into account by employing appropriate statistical methods, such as non-parametric testing [5]. However, current meta-analyses tend to employ means and standard deviations from individual studies to obtain pooled estimates of effect [4, 6, 7]. This is invariably pursued via parametric statistics, implicitly assuming data are normally distributed. Because mean data inadequately describe information through non-normal distributions, combining mean group data in systematic reviews (SR) might undermine the distribution of responses to treatments. Hence, we argue that non-parametric statistical processing should be favored over mean-derived indices for data with non-normal distributions, by committing more emphasis on dichotomous data. The only systematic review that opted for analyzing dichotomous data from studies focusing on non-benzodiazepines MR for LBP was carried out by van Tulder et al. in their 2003 systematic review and meta-analysis for the Cochrane Collaboration network [8]: over a set of 11 studies, they concluded that non-benzodiazepine MR are effective in the management of acute LBP, but their AE require caution [8].

The present work was planned and executed to primarily evaluate the safety and efficacy of non-benzodiazepine MR administered as monotherapy or combined with analgesics/non-steroidal anti-inflammatory drugs (NSAIDs) in the management of acute and chronic primary LBP. To do so, we chose to align with the methodological approach of the abovementioned Cochrane review [8] by aggregating and appraising dichotomous rather than continuous data, as done in previous, even recently published knowledge synthesis works on the same topic [4, 6, 7]. In this perspective, the so-derived estimates of MR effect may contribute to portray benefits and harms of these medications in a more comprehensive and clinically usable manner.

Methods

The Preferred Reporting Items for SR and Meta-Analyses (PRISMA) guidelines were used as reporting structures for this meta-analysis [9]. The "PICO" strategy was used to assert the research question (P: primary LBP; I: non-benzodiazepines; C: placebo; placebo + analgesics/NSAIDs; O: pain).

Types of studies and participants. Published RCTs were included to incorporate the highest level of evidence in quantifying the effects of interventions [10]; adults (≥ 18 years) with LBP were involved. We excluded studies embedding mixed populations (i.e., back and neck pain, with no separate analyses), a backache due to infections, neoplasms, metastases, osteoporosis, rheumatological disorders, fractures, inflammatory process, radicular syndrome, and other diagnosable diseases. LBP was classified as acute (< 6 weeks), sub-acute (6–12 weeks) or chronic (> 12 weeks) [10].

Types of interventions. Non-benzodiazepine MR as single agent or combined with other therapeutic modalities (analgesics/NSAIDs) were included. Non-benzodiazepines incorporated in this SR were cyclobenzaprine, carisoprodol, chlorzoxazone, eperisone, ethoheptazine, flupirtine, idrocilamide, mepobramate, methocarbamol, metaxalone, orphenadrine, pridinol, promethazine, thiocolchicoside, tizanidine, and tolperisone. Discontinued MR were not considered. Baclofen was not included among the medications under scrutiny because it is an anti-spasticiy medication, not a muscle relaxant.

Main comparisons. (1) Non-benzodiazepines versus placebo for acute LBP; (2) non-benzodiazepines + analgesics/NSAIDs versus placebo + analgesics/NSAIDs for acute LBP; (3) non-benzodiazepines versus placebo for chronic LBP; (4) non-benzodiazepines + analgesics/NSAIDs versus placebo + analgesics/NSAIDs for chronic LBP.

Types of outcome measures. Data extraction and pooling were carried out on dichotomous data (events/total, i.e., the proportion of individuals not reporting a moderate or marked improvement in each outcome considered). Primary outcomes were lack of "pain relief" and "global efficacy" as assessed by the person, and AE were considered whether they involved the central nervous system (CNS) and the gastro-intestinal (GI) apparatus. Secondary outcomes were represented by muscle spasm, physical impairments (e.g., limited mobility) and generic functional conditions. Data were extracted at a 5–7-day follow-up both for primary and secondary outcomes, then entered the meta-analyses as the number of non-responders/total (e.g., number of participants with "no pain relief", "no global efficacy").

Literature searches. The following databases were searched to 30 June 2024: Cochrane Back and Neck (CBN) trials register; Cochrane Central Register of Controlled Trials; MEDLINE; EMBASE; CINAHL; ClinicalTrials.gov; World Health Organization International Clinical Trials Registry Platform. Search strategies are provided as Supplementary File 1. Additionally, we searched the reference lists of all included studies and SR pertinent to MR for LBP.

Selection of studies. Two review authors (AM and LC) performed the screening for detecting relevant records based on titles and abstracts. Three independent reviewers (LC, AM and MM) made the screening of full texts, used consensus to resolve disagreements and determine if the paper met the inclusion criteria. Finally, search results were combined in EndNote and duplicates were removed. There were no language restrictions.

Data extraction and management. Using a standardized data extraction form, two review authors (AM and LC) independently extracted data from each included study and entered the data in RevMan 5.4 by double-checked data entry.

Assessment of risk of bias. Two review authors (AM and LC) independently assessed the risk of selection, performance, detection, attrition and reporting biases for all included RCTs in two steps by employing the 13 criteria from Furlan et al. [10] and by a domain-level assessment, as follows: random sequence generation, allocation concealment, blinding of participants, care provider, and outcome assessor for each outcome measure, incomplete outcome data and other biases conforming to the methods recommended in the Cochrane Handbook [11] and by the Cochrane Back and Neck Review Group [10]. Each criterion was rated as low risk of bias, high risk of bias or unclear (either lack of information or uncertainty over the potential for bias).

Measures of treatment effect. Trials were grouped according to types of comparisons, outcomes, and assessment timepoints. A quantitative meta-analysis was conducted if studies provided sufficient dichotomous data to allow aggregation in pooled estimates. Data were pooled using the random effects model. We expressed the dichotomous data extracted as relative risks (RR) with corresponding 95% confidence intervals (95%CI). All RRs were calculated as events/total, where'event' reflects the presence/non-presence of moderate or marked improvement. For those studies reporting changes continuously, a cut-off point was set to convert continuously reported data to dichotomous data by considering a marked change in pain/global efficacy/muscle spasm to be > 16mm or > 30% decrease in Visual Analogue Scale (VAS). For an 11-points Numerical Rating Scale (NRS) this was 2 points or more [12, 13]. A RR < 1 indicated a positive effect of MR. Data entered the meta-analyses as the number of non-responders, that is: number of participants "with no pain relief", "no global improvement", "no improvement in muscle spasms". The clinical relevance of each study was assessed by two review authors (AM and LC). A clinically important treatment effect was considered for a risk ratio ≤ 0.75 [14]. We used the same cut-off for AE data. When multiple measures were reported, we extracted the most severe measure at baseline. When RCTs reported results for more than two intervention groups, we combined similar groups according to the Cochrane recommendations [11]. When data reported in a study were insufficient or unclear, we contacted the authors for further information. When authors were unavailable, we opted for analyzing only available data based on the assumption that data were missing at random [11].

Assessment of heterogeneity. Findings were tested by visual inspections of the forest plots looking at the overlap of the CI, and by the Chi^2 and inconsistency I^2 statistic tests against the conventional significance threshold ($p < 0.05$). If substantial heterogeneity was present ($I^2 > 80\%$), or when we identified clear heterogeneity by visual inspection, we downgraded for inconsistency in the quality of evidence assessment according to Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) [15]. This approach was employed to identify any additional bias.

Results

Description of studies. Figure 1 presents the flowchart of the study selection according to PRISMA. The search retrieved 2638 records. After duplicates removal, we screened 2321 records. Of these, 100 full-text articles were assessed for eligibility of which 50 were excluded (for reasons see Supplementary File 2).

Included studies. We included 50 studies in the qualitative analyses for a total of 7531 adult participants (mean age: 43.0 years; range 18–80). Of these 49.1% were men and 50.9% women. The sample sizes ranged from 18 to 806 participants. The list of all included studies is presented in Supplementary File 3. Not all the studies entered the final meta-analyses, as clearly stated in the notes of the characteristics of included studies (Table 1). As a result, the total sample was reduced to 4775 participants. RCTs that could be pooled were identified both for acute and chronic LBP, although for the latter condition the meta-analyses could be conducted only for AE. Non-benzodiazepine MR were employed as a monotherapy or in combined administration with analgesics/NSAIDs) against their respective placebos.

Interventions. The most commonly employed oral non-benzodiazepine MR was tizanidine (12 studies), followed by cyclobenzaprine (8 studies) and eperisone (7 studies) and orphenadrine (4 studies). Other, less commonly employed non-benzodiazepines were, carisoprodol, chlorzoxazone, ethoheptazine, flupirtine, idrocilamide,

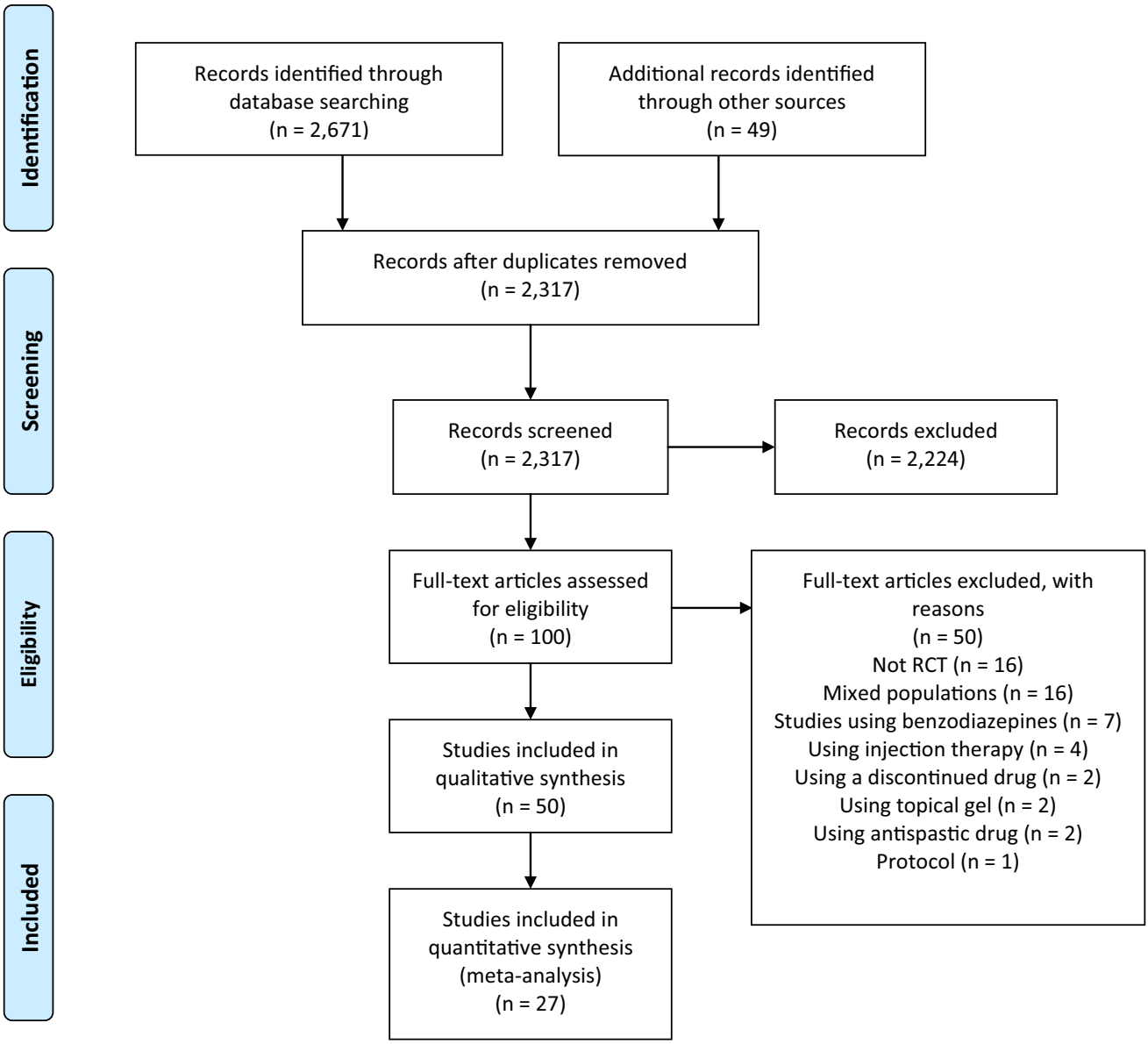


Fig. 1 Study flow diagram

mepobramate, methocarbamol, metaxalone, orphenadrine, pridinol, promethazine, thiocolchicoside, and tolperisone, with at least one study. A combination of MR plus analgesics/NSAIDs was administered in 17 studies evaluating acute LBP.

Risk of bias in included studies

Results of assessment by domain as percentages across all RCTs are in Fig. 2. Specific reasons for judgements are shown in "Characteristics of included studies" (Supplementary Material 2). High risk of bias was identified in 20 studies (40%) for intention to treat, followed by 8 studies (16%) for allocation concealment. Publication bias was assessed in a funnel plot only when a sufficient number of studies (≥ 10) could be pooled into a meta-analysis for the same outcome. This occurred only for the meta-analysis "MR (non-benzodiazepines) versus placebo for acute LBP", for the outcome "AE" (Fig. 4).

Table 1 Included studies (N = 50; 7531 participants included in qualitative review; 4775 participants included in quantitative meta-analyses)

Study	Participants	Interventions	Outcomes	Notes
Akhter 2017	N = 288 patients Male/Female (%): 47%; M: 135; F: 153 Age: 18–70 years Diagnosis: acute and sub-acute LBP	(1) Diclofenac 75 mg two times a day for 7 days (2) Diclofenac 75 mg twice daily plus Thiocolchicoside 4 mg two time a day for 7 days	Pain at base line, on day 3 and day 7 by visual analogue score (VAS) and mobility by Hand to Floor Distance Adverse events	Included in the qualitative review, not included in the meta-analysis (only continuous data)
Aksoy 2002	N = 372 enrolled. 329 patients included for the analyses Male/Female (%): 36.2%; M: 119; F: 210 Age: 18–65 years Diagnosis: Acute and subacute LBP	(I) Standard treatment (NSAID or an analgesic) + 8 mg b.i.d. of Thiocolchicoside (TCC, Muscoril)/from 5 to 7 days. N = 174 (R) Standard treatment alone (NSAID or an analgesic)/from 5 to 7 days. N = 155	Degree of improvement in the intensity of LBP between days 0 and 7, 0 and 31 and between days 7 and 31 were taken into consideration and assessed by VAS scale Adverse events	Included in the qualitative review, not included in the meta-analysis
Barrata 1982	N = 120 Male/Female (%): 59/41 Mean age: 36 (21–60) Diagnosis: Acute LBP Patients with moderate to severe degree of muscle spasm and local pain	(I) Cyclobenzaprine 10 mg t.i.d.—q.i.d./10 days. N = 58 (R) Placebo t.i.d.—q.i.d./10 days. N = 59	Proportion of patients who showed improvement (> 2 points) in pain, at days 5–7 Proportion of patients improved (> 2 points) in muscle spasm, at days 5–7 Physicians' global evaluation (5-point ordinal scale) Adverse events	Included in the meta-analysis
Basmajian 1978	N = 112 Male/Female (%): 51/49 Mean age: 41 (16–69) Diagnosis: Acute LBP	(I) Tizanidine 4 mg t.i.d./7days. N = 59 (R) Placebo t.i.d./7days. N = 53	Pain at night, at rest and on movement. Proportion of patients improved (4-point scale), on day 7 Global efficacy Adverse events	Included in the meta-analysis
Berry 1988a	N = 112 Male/Female (%): 51/49 Mean age: 41 (16–69) Diagnosis: Acute LBP	(I) Tizanidine 4 mg t.i.d./7days. N = 59 (R) Placebo t.i.d./7days. N = 53	Pain at night, at rest and on movement. Proportion of patients improved (4-point scale), on day 7 Global efficacy Adverse events	Included in the meta-analysis
Berry 1988b	N = 105 Male/Female (%): 55/45 Age: 42.5 (20–66) Diagnosis: Acute LBP	(I) Tizanidine 4 mg plus ibuprofen 400 mg t.i.d./7 days. N = 51 (R) Placebo plus ibuprofen 400 mg t.i.d./7 days. N = 54	Proportion of patients with moderate + severe pain/no pain + mild pain at rest, on day 7 Global efficacy Adverse events	Included in the meta-analysis
Bianchi 1978	N = 48 Male/Female (%): 54/46 Mean age: 46 (19–67) Diagnosis: Acute LBP (75%) or neck pain (25%). Moderate to severe muscle spasm	(I) Cyclobenzaprine 10 mg t.i.d.—q.i.d./14 days. N = 24 (R) Placebo t.i.d.—q.i.d./14 days. N = 24	Mean spontaneous pain (1–5 point scale) at baseline, day 7; Global improvement (4-point scale) on day 7 Adverse events	Included in the meta-analysis

Table 1 (continued)

Study	Participants	Interventions	Outcomes	Notes
Borenstein 1990	N = 40 Male/Female (%): 70/30 Mean age: 34.5 (20–57) Diagnosis: Acute, mild to moderate LBP	(I) Cyclobenzaprine 10 mg/8 h/14 days plus naproxen 500 mg initially, followed by 250 mg/6 h/14 days. N = 20 (R) Placebo plus naproxen 500 mg initially, followed by 250 mg /6 h/14 days. N = 20	Pain (0 to 20 NRS) Muscle spasm (0 = none to 3 = severe) Functional capacity (0–3 scale) Global efficacy (0 = poor to 4 = excellent) Adverse events	Included in the meta-analysis
Boyles 1983	N = 80 Male/Female (%): 48/52 Mean age: 39 (19–65) Diagnosis: Acute LBP	(I1) Carisoprodol 350 mg q.i.d./7 days. N = 40 (I2) Diazepam 5 mg q.i.d./7 days. N = 40	Pain (100-mm VAS) day 7—baseline Overall relief Overall improvement Adverse events	Included in the qualitative review, not included in the meta-analysis
Bragstad 1979	N = 27 Male/Female (%): not reported Mean age: 37 (21–63) Diagnosis: Acute LBP and muscle spasms of disc origin	(I1): Tizanidine 2 mg t.i.d, 7 days. N = 14 (I2): Chlorzoxazone 500 mg t.i.d, 7 days. N = 13	Difference (4-point scale) at baseline and day 7 for pain Overall effectiveness by patient Adverse events	Included in the qualitative review, not included in the meta-analysis
Cabitza 2008	N = 160 Male/Female (%): 31% M: 49; F: 111 Mean age: (I): 47.4 (10.9); (R): 48.5 (11.7) Diagnosis: Acute LBP and spasticity of spinal muscles and no Rx finding of major spinal diseases	(I) Oral eperisone 100 mg t.i.d. for 12 consecutive days. N = 80 (R) Thiocolchicoside 8 mg b.i.d. for 12 consecutive days. N = 80	Percentage of patients free from pain on movement at day 7 Percentage of patients free from pain on pressure examination at day 7 Adverse events	Included in the qualitative review, not included in the meta-analysis
Chandanwale 2011	N = 225 Male/Female (%): 47%; M: 106; F: 119 Aged: 18–60 years Diagnosis: acute musculoskeletal spasm with LBP due to spondylosis deformans, prolapsed disc or muscle sprain	(I) Eperisone t.i.d 150 mg/day for 14 days; N = 112 (R) Placebo t.i.d. for 14 days; N = 113	Pain relief Global efficacy Finger-to-floor distance Adverse events	Included in the meta-analysis
Desai 2011	N = 40 patients, (I): 20; (R): 20 Female = 25, Male = 15 Age: 18 to 55 years Diagnosis: Acute low back pain	(I) Aceclofenac 100 mg + Thiocolchicoside 4 mg b.i.d for 7 days (R) Aceclofenac 100 mg alone b.i.d for 7 days	Change in pain severity at rest was recorded using VAS Restriction of movement Adverse events	Included in the qualitative review, not included in the meta-analysis

Table 1 (continued)

Study	Participants	Interventions	Outcomes	Notes
Emrich 2015	N = 202 patients, (I): 98; (R): 104 (I) group: female = 62, male = 36; (R) group: female = 74, male = 30 Age (mean + —SD): Intervention group: 45.3 + -11 years; placebo group: 43.8 + -11.6 years Diagnosis: Acute LBP (> 50 mm on a visual analog scale (VAS) from 0 – 100 mm) due to muscular stiffness and spasms in the pelvic and lumbar region during the past 24 h and with limited flexibility (finger-floor-distance > 30 cm, lumbar flexion < 4 cm)	(I) 2 tables of Methocarbamol for maximally 8 days t.i.d. (No information on dosage) (R) 2 tables of Placebo	Global efficacy by the investigator and by the patient Restriction of motion Adverse events	Included in the meta-analysis
Friedman 2015	323 participants, N = 107 Placebo group (1); N = 108 to cyclobenzaprine group (2) and N = 108 to oxycodone/acetaminophen group (3) Sex: 165 males; 158 females Aged 21 to 64 years Diagnosis: Nontraumatic, nonradicular LBP of 2 weeks' duration or less	(1) Naproxen (20 tablets, 500 mg, b.i.d.) + 60 tablets of placebo for 10 days (2) Naproxen (20 tablets, 500 mg, b.i.d) + 5 mg of cyclobenzaprine (1 or 2 tablets every 8 h as needed) for 10 days	Improvement in Roland Morris Disability Questionnaire Adverse events	Included in the meta-analysis
Friedman 2018	N = 240 Male/Female (%): 131/109 (54.6%) Age: 18 to 69 years Diagnosis: Acute LBP	(1) Naproxen (14 tablets, 500 mg, to be used twice a day) + Placebo (2) Naproxen (14 tablets, 500 mg, to be used twice a day) + Orphenadrine (1-week supply of orphenadrine 100 mg, to be used twice a day as needed)	Improvement in Roland Morris Disability Questionnaire Adverse events	Included in the meta-analysis
Friedman 2019	N = 320 Males/Females: 187/133 Age: 38.8 (range 37–40) Eligibility: patients with non-radicular low back pain for less than or equal to 2 weeks were eligible if they had a score greater than 5 on the Roland-Morris Disability Questionnaire	(1) Ibuprofen 600 mg plus tizanidine 2 to 4 mg orally every 8 h as needed (2) Ibuprofen 600 mg plus placebo orally every 8 h as needed	Pain intensity at 1 week Improvement in Roland Morris Disability Questionnaire Adverse events	Included in the meta-analysis
Gabric 1992	N = 32 Male/Female: 20/12 females Aged: 25–57 (mean age = 41.54) Diagnosis: Chronic LBP	(I) 3 × 2 mg Tizanidine daily for 2 weeks (number of participants not disclosed) (R) 1 × 20 mg Tenoxicam daily for 2 weeks (number of participants not disclosed)	Change in pain and kinematics outcomes Adverse events	Included in the qualitative review, not included in the meta-analysis

Table 1 (continued)

Study	Participants	Interventions	Outcomes	Notes
Garcia-Filho 2006	N = 108 Male/Female: 53/55 Aged: 18 to 45 years Diagnosis: acute LBP and lumboischialgia in the last 7 days	(I) Caffeine 30 mg, carisoprodol 125 mg, sodium diclofenac 50 mg and paracetamol 300 mg, t.i.d. for a period of 7 days (N = 50) (R) Cyclobenzaprine t.i.d. for a period of 7 days (N = 48)	Pain intensity by VAS at 1 week Improvement in Roland Morris Disability Questionnaire Patient's and investigator's overall assessment of the treatment Adverse events	Included in the qualitative review, not included in the meta-analysis
Gold 1978	N = 40 Male/Female (%): not reported Mean age: not reported Diagnosis: Acute LBP and muscle spams. Limited work and daily activities	(I) Orphenadrine 100 mg b.i.d./7 days. N = 20 (R) Placebo b.i.d./7 days. N = 20	Reduction in pain Adverse events	Included in the meta-analysis
Hennies 1981	N = 30 Male/Female (%): 33/67 Mean age: 47.5 (25–70) Diagnosis: Acute spasm of back (80%) and neck (20%) muscles, actual n. of weeks of duration unknown	(I1) Tizanidine, 4 mg t.i.d., 7 days. N = 15 (I2) Diazepam 5 mg t.i.d., 7 days. N = 15	Patient self-assessment of pain (4-point scale) at baseline, and day 7 Adverse events	Included in the qualitative review, not included in the meta-analysis
Hindle 1972	N = 32 Male/Female (%): 56/44 Mean age: 38.4 (18–70) Diagnosis: Acute LBP. Farm laborers with acute lumbar strain and spasm	(I) Carisoprodol 350 mg q.i.d./4 days. N = 16 (R) Placebo q.i.d./4 days. N = 16	Change in pain and muscle spasm Number of patients with global improvement Adverse events	Included in the meta-analysis
Hingorani 1971	N = 99 Male/Female (%): 61/39 Mean age: 43.5 Diagnosis: Acute LBP of sufficient severity to require inpatient treatment	(I) Orphenadrine 35 mg + paracetamol 450 mg 2 tablets t.i.d./7 days. N = 48 (R) Aspirin 100 mg t.i.d./7 days. N = 50	Number of patients with improvement in pain (4-point scale) Adverse events	Included in the qualitative review, not included in the meta-analysis
Hoiriis 2007	N = 156 Male/Female: 89/67 Age: 41.9 ± 9.9 Diagnosis: LBP of 2 to 6 weeks' duration	(1) Muscle relaxants with sham adjustments over 2 weeks (2) Placebo with sham adjustments over 2 weeks	Pain intensity by VAS Oswestry Disability Questionnaire Adverse events	Included in the qualitative review, not included in the meta-analysis
Ketenci 2005	N = 97 patients N = 50 women; N = 47 men 38 (39.1%) received tiocolchicoside; 32 (32.9%) tizanidine and 27 (28%) placebo Age range 20–60 years; Diagnosis: Acute LBP associated with muscle spasm	(1) tiocolchicoside 8 mg capsules (morning and evening) for 5–7 consecutive days (2) Placebo capsules (morning) + tizanidine 6 mg capsules (evening) for 5–7 consecutive days (3) Placebo capsules (morning and evening) for 5–7 consecutive days	Change in pain intensity bay VAS Global efficacy Adverse events	Included in the meta-analysis

Table 1 (continued)

Study	Participants	Interventions	Outcomes	Notes
Kukushkin 2017	N = 245 Men and women: (not reported) Age 18–65 years Diagnosis: Acute LBP	(I) Tolperisone + NSAIDs (n = 124) 1–5 days: 1–2 ml tolperisone intro muscular 2/day + diclophenac 50 mg per os 3/day 6–14 days: tab tolperisone(covered) 150 ml 3/day per os + diclophenac per os if a researcher deemed necessary (C) NSAID + placebo (n = 121) 1–5 days: 1 ml placebo intro muscular 2/day + diclophenac 50 mg per os 3/day 6–14 days: tab placebo(covered) 3/day + diclophenac per os if a researcher deemed necessary	Improvement in Roland Morris Disability Questionnaire Pain assessed by VAS; Clinical Global Impression of Improvement; Patient Global Impression of Improvement; change in the range of motion Adverse events	Included in the meta-analysis
Kumar 2014	N = 100 Male/Female (%): not reported Aged: 18-55 years Diagnosis: acute LBP and muscle spasm of ≤ 7 days	(I) Fixed dose combination of thiocolchicoside (4 mg) and aceclofenac (100 mg) orally b.i.d. for 7 days (R) Chlorzoxazone (500 mg), aceclofenac (100 mg) and paracetamol (325 mg) orally b.i.d. for 7 days	Change in severity of pain on movement and at rest Change in functional outcomes Adverse events	Included in the qualitative review, not included in the meta-analysis
Lepisto 1979	N = 30 Male/Female (%): 50/50 Mean age: 42.5 (18–62) (I) and 40.8 (27–59) (R) Diagnosis: moderate to severe acute spasms due to disk prolapse in lumbar (n = 26) and thoracic (n = 4) regions	(I): Tizanidine 2 mg, t.i.d., 7 days. N = 15 (R): Placebo, t.i.d., 7 days. N = 15	Number of patients with decreased pain on day Number of patients with decreased spasm Patient's assessment of overall response Adverse events	Included in the meta-analysis
Li 2008	N = 209 Male/Female (%): 41%; M: 85; F: 124 Aged: 18–65 years; Mean age: 46 (15.1) (I) and 46.5 (15.7) (R) Diagnosis: subacute LBP lasting for at least 4 weeks	(I) Flupirtine 100 mg t.i.d. for 5–7 days (N = 105) (R) Tramadol 50 mg t.i.d. for 5–7days (N = 104)	global assessment of improvement in pain and functional capacity Adverse events	Included in the qualitative review, not included in the meta-analysis
Maaz 2016	N = 100 patients, (I): 50; (R): 50 Female = 56, Male = 44 Age: 18 to 55 years Diagnosis: Acute musculoskeletal spasm associated with LBP	(I) Eperisone 100 mg t.i.d + Paracetamol 500 mg t.i.d for 7 days (R) Thiocolchicoside 8 mg b.i.d + Paracetamol 500 mg t.i.d for 7 days	Improvement in finger to floor distance and pain, relief of spasm Adverse events	Included in the qualitative review, not included in the meta-analysis
Marcel 1990	N = 98 Male/Female (%): 62%; M: 61; F: 37 Mean age: 37.9 (9.8) (I) and 37.2 (10.3) (R) Diagnosis: acute LBP from at least 24 h	(I) Thiocolchicoside two 4 mg tablets, morning and evening, 16 mg daily, for 5 days (N = 49) (R) Placebo of identical appearance for 5 days (N = 49)	Functional status, spontaneous pain and physical outcomes Adverse events	Included in the meta-analysis

Table 1 (continued)

Study	Participants	Interventions	Outcomes	Notes
Pareek 2009	N = 197 Males/Females (%) (I) 62/39; (R) 58/38 Age range of 18–70 years Diagnosis: Acute LBP	(I) Aceclofenac 100 mg + Tizanidine 2 mg b.i.d for 7 days (N = 101) (R) Aceclofenac 100 mg alone b.i.d for 7 days (N = 96)	Pain intensity (on movement, at rest and at night) and pain relief Change in functional outcomes. Adverse events	Included in the qualitative review, not included in the meta-analysis
Pipino 1991	N = 120 Male/Female (%): 42.5/57.5 Mean age: 54.4 (20–77) (I) and 51.7 (24–76) (R) Diagnosis: chronic LBP with muscle spasm	(I1) Pridinol mesylate 4 mg IM injection b.i.d. × 3 days followed by 2 mg b.i.d. orally × 4 days. N = 60 (I2) Thiocolchicoside 4 mg IM injection b.i.d × 3 days followed by 8 mg b.i.d. orally × 4 days. N = 60	Pain intensity Patient-rated global efficacy Adverse events	Included in the qualitative review, not included in the meta-analysis
Pratzel 1996	N = 112 Male/Female (%): 78/27 Mean age: 50.8 (I) and 47.8 (R) Diagnosis: Chronic LBP with painful reflex muscle spasms	(I) Tolperisone 100 mg t.i.d., 21 days. N = 67 (R) Placebo t.i.d./ 21 days. N = 70	Clinical global impression of efficacy Number of patients with overall assessment of efficacy by the patient Adverse events	Included in the qualitative review, not included in the meta-analysis
Ralph 2008	N = 562 Male/Female (%): 48.1%; M = 263; F = 284 Mean age: 40.4 (11.8) Diagnosis: Acute, painful muscle spasm of the lower back	(I) Carisoprodol 250-mg tablets, t.i.d. for 7 days (N = 277) (R) Matching placebo tablets t.i.d. for 7 days (*N* = 285)	Patient-rated global impression of change Patient-rated pain relief Adverse events	Included in the meta-analysis
Rao 2012	N = 250 Male/Female (%): not disclosed Aged: 18 to 45 years Diagnosis: Acute LBP with spasm of spinal muscles	(I) Tolperisone 150 mg, t.i.d. for 7 days (N = 125) (R) Thiocolchicoside 8 mg, b.i.d. for 7 days (N = 125)	Improvement in pain score at rest and on movement Change in global efficacy Change in functional outcomes Adverse events	Included in the qualitative review, not included in the meta-analysis
Rollings 1983	N = 78 Male/Female (%): 53/47 Mean age: 42 (19–65) Diagnosis: Acute LBP of at least moderate intensity with muscle spasms of 7 days or less	(I1) Carisoprodol 350 mg q.i.d./7 days. N = 39 (I2) Cyclobenzaprine10 mg q.i.d./7 days. N = 39	Improvement in pain Physician's evaluation of mobility restriction and overall improvement Adverse events	Included in the qualitative review, not included in the meta-analysis
Rossi 2012	N = 60 Male/Female (%): (I) 37/63%; (R) 23.3/76.6% Mean age: 62.8 (12.1): Diagnosis: Chronic LBP	(I) Tramadol retard 100 mg o.i.d. + Eperisone 100 mg t.i.d. for 10 days. N = 30; + 10 patients Eperisone 100 mg o.i.d. for other 20 days (R) Tramadol retard 100 mg o.i.d. + Tizanidine 2 mg for 10 days. N = 30; + 10 patients Tizinadine 2 mg o.i.d. for other 20 days	Pain intensity Pain relief Adverse events	Included in the qualitative review, not included in the meta-analysis

Table 1 (continued)

Study	Participants	Interventions	Outcomes	Notes
Rusinyol 2009	N = 90 patients, (1): 30; (2): 30; (3): 30 Female = 42, Male = 48 Age: more than 18 years old Diagnosis: Acute LBP arisen over since less than 48 h, and a muscular contracture of mild to severe intensity	(1) Eperisone 50 mg t.i.d. for 7 days (2) Eperisone 100 mg t.i.d, for 7 days	Spontaneous and provoked pain, muscular contracture and its impact on working capacity Functional outcomes Adverse events	Included in the qualitative review, not included in the meta-analysis
Sakai 2008	N = 64 Males/females: Only males Mean age: (1) 44.4 (13.9); (2) 44.2 (12.2); (3) 47.9 (13.1) Diagnosis: Chronic LBP lasting more than 6 months	(1) Physical therapy only (control) (N = 25) (2) Eperisone hydrochloride (EMPP) for 4 weeks (N = 24) (3) McKenzie therapy (N = 25)	Change in pain and functional outcomes Adverse events	Included in the qualitative review, not included in the meta-analysis
Serfer 2010	N = 806 Male/Female (%): 43.7%; M = 353; F = 453 Aged: 18 to 65 years Diagnosis: Acute, painful muscle spasm of the lower back	(1) Carisoprodol 250-mg tablets four times daily for 7 days (N = 264) (2) Carisoprodol 350-mg tablets four times daily for 7 days (N = 273) (3) Placebo tablets t.i.d. (N = 269)	Patient-rated relief from starting backache and patient-rated global impression of change Adverse events	Included in the meta-analysis
Shen 2009	N = 45 Males/females: Only males Mean aged 46 years old Diagnosis: Chronic LBP lasting more than 6 months	(1) Physical therapy only (control) (N = 15); (2) Eperisone hydrochloride 50 mg t.i.d. for 4 weeks + McKenzie therapy (N = 15) (3) McKenzie therapy (N = 15)	Pain intensity by VAS Adverse events	Included in the qualitative review, not included in the meta-analysis
Sirdalud 1998	N = 405 Male/Female (%): 48/52 Mean age: 40 Diagnosis: patients with local pain syndromes (back, neck or shoulder) of recent onset and clinically discernible muscle spasms; > 50% low back	(I) Tizanidine 2 mg plus diclofenac 50 mg b.i.d./7 days. N = 185 (R): Placebo plus diclofenac 50 mg b.i.d./7 days. N = 176	Change in pain Overall assessment of efficacy Adverse events	Included in the meta-analysis
Soonawalla 2008	N = 60 (58 completed the study) Males/Females: 30/33 Aged: 18 to 65 years Diagnosis: Muscle spasm associated with LBP	(I) Thiocolchicoside 8 mg b.i.d for 7 days (N = 32) (R) Tizanidine 4 mg t.i.d for 7 days (N = 31)	Pain relief Global efficacy Adverse events	Included in the qualitative review, not included in the meta-analysis
Sweetman 1987	N = 122 Male/Female (%): 53/47 Mean age: 41.3 (?) Diagnosis: Acute LBP (1- 28 days)	Chlormezanone: excluded from this review (I) Meprobamate 150 mg plus ethoheptazine 75 mg plus aspirin 250 mg 2 tablets t.i.d./7days. N = 40 (R) Mefenamic acid 500 mg t.i.d./7 days. N = 40	Number of patients experiencing pain Patient's overall assessment Adverse events	Included in the qualitative review, not included in the meta-analysis

Table 1 (continued)

Study	Participants	Interventions	Outcomes	Notes
Tervo 1976	N = 50 Male/Female (%): 34/66 Mean age: not disclosed Diagnosis: Acute LBP. 38/50 no previous episodes. 37/50 acute onset of symptoms. 16/50 work injury	(I) Orphenadrine 60 mg (2ml) IM followed by orphenadrine (35 mg) + paracetamol (450 mg) 2 tablets t.i.d., 7 days. N = 25 (R) Saline 2ml IM followed by paracetamol (450 mg) 2 tablets t.i.d., 7 days. N = 25	Disability Subjective impression of treatments efficacy Functional outcomes Adverse events	Included in the qualitative review, not included in the meta-analysis
Tüzün 2003	N = 143 Male/Female (%): 46%; M: 66; F: 77 Aged: 18 to 65 years Diagnosis: Acute LBP with severe or moderate lumbar muscle spasm lasting less than 72 h	(I) 4 mg of Thiocolchicoside injections b.i.d. until recovery or maximum for 5 days (N = 76) (R) Placebo injections b.i.d. until recovery or maximum for 5 days (N = 67)	Pain at rest by VAS Hand-to-floor distance, muscle spasm intensity, patients' global evaluation Adverse events	Included in the meta-analysis
Uberall 2012	N = 363 (276 for the analyses) Male/Female: Female: 220 (62%) Aged: 18 to 75 years Diagnosis: Moderate to severe chronic LBP for 3 months prior to study entry	(1) Flupirtine MR 400 mg one a day (OD) in the evening over 4 weeks (N = 95) (2) Matching placebo OD in the evening over 4 weeks (N = 96)	Number of patients experiencing functional improvement Adverse events	Included in the meta-analysis
Vorobieva 2006	N = 30 Males/Females: not reported. Aged: 20 to 60 years Diagnosis: Musculoskeletal back pain	(I) Baclofen 5 mg, t.i.d for 3 days with double dose on the 4thday (30 mg daily) + Diclofenac 150 mg orally daily in three intakes (N = 14) (R) Tolperisone 150 mg t.i.d + Diclofenac 150 mg orally daily in three intakes (N = 16)	Pain intensity by VAS	Included in the qualitative review, not included in the meta-analysis
Worz 1996	N = 107 Male/Female (%): 43/57 Mean age: 49.7 Diagnosis: Chronic LBP	(I) Flupirtin 100 mg q.i.d./7 days. N = 53 (I2) Chlormezanone. Excluded from this review (R) Placebo q.i.d./7 days. N = 54	Reduction in pain intensity by 2 categories (5-point verbal scale) Reduction in muscle spasm by 2 categories (5-point verbal scale) Overall assessment by the physician Adverse events	Included in the meta-analysis

Abbreviations: b.i.d., two times a day; q.i.d., four times a day; t.i.d., three times a day; mg, milligrams; NSAID, nonsteroidal anti-inflammatory drugs; VAS, Visual analogue scale; OR, oral drug; h, hours;

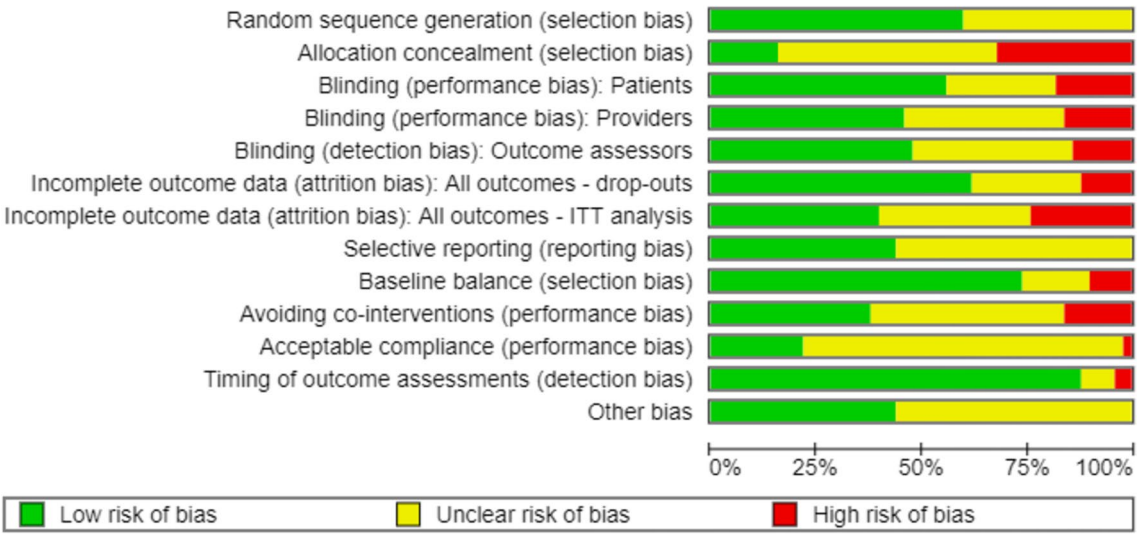


Fig. 2 Assessment of risk of bias in the included studies

Effects of non-benzodiazepine MR on LBP

Non-benzodiazepines versus *placebo for acute LBP.* Figure 3a reports the forest plots for this comparison. Based on moderate-certainty evidence from 5 studies (446 participants) [16–20], oral non-benzodiazepines demonstrated an increased likelihood of short-term (5–7 days follow-up) pain relief compared to placebo (RR: 0.53, 95% CI 0.42–0.66; absolute difference of 27%; relative difference of 47%, moderate quality; Fig. 3a) and global efficacy (RR: 0.49, 95% CI 0.35–0.70; absolute difference of 28%; relative difference of 51%; moderate quality; Fig. 3b).

Regarding secondary outcomes, we found very low-to-moderate-certainty evidence that non-benzodiazepines may reduce muscle spasm (4 studies [16, 18–20], 348 participants): RR: 0.62, 95% CI 0.51–0.75; absolute difference of 26%; relative difference of 38%; moderate quality; Fig. 3c), while low-to-moderate-certainty evidence was found for physical outcomes/limited mobility (551 participants: RR: 0.60, 95% CI 0.50–0.71; absolute difference of 24%; relative difference of 40%; moderate quality; Fig. 3d). Minimal Clinically Important Differences (MCID) (i.e., RR ≤ 0.75) at 5–7 days follow-up could be detected for pain relief, global efficacy, muscle spasm, and physical outcomes.

As for AE (Fig. 4), we found low-to-moderate-certainty evidence that total AE were more prevalent in participants receiving non-benzodiazepines (RR: 1.56, 95% CI 1.19–2.03; risk with placebo: 156/1000; risk with non-benzodiazepines: 238/1000; absolute difference of 8%; relative difference of 52%: moderate quality; Fig. 3e). The same applied to AE at the CNS level (RR: 2.40, 95% CI 1.91–3.03; risk with placebo: 86/1000; risk with non-benzodiazepines: 206/1000; absolute difference of 12%; relative difference of 140%; low quality; Fig. 3f) but not for GI AE (RR: 0.77, 95% CI 0.35–1.72; risk with placebo: 59/1000; risk with non-benzodiazepines: 46/1000; absolute difference of 1%; relative difference of 23%: low quality; Fig. 3g).

Non-benzodiazepines + analgesics/NSAIDs versus *placebo + analgesics/NSAIDs for acute LBP.* Figure 4 summarizes the results for this comparison (8 studies, 1245 participants). Eight studies were identified, 6 at low RISK OF BIAS [21–25] and 2 at high RISK OF BIAS [26, 27]. Based on low-certainty evidence from the three RCTS that could be pooled for global efficacy (704 participants) [21, 25, 27], non-benzodiazepines + analgesics/NSAIDs may provide larger benefit than placebo + analgesics/NSAIDs for global efficacy at 5–7 days follow-up (RR: 0.62, 95% CI 0.43–0.90; absolute difference of 19%; relative difference of 38%; Fig. 4a). Changes in global efficacy favoring the administration of non-benzodiazepines + analgesics/NSAIDs over placebo + analgesics/NSAIDs achieved an MCID at 5–7 days follow-up. With regard to the occurrence of AE following administration of non-benzodiazepines + analgesics/NSAIDs for acute LBP, we found moderate-certainty evidence that the combination therapy did not result in significant differences between groups for total AE (1245 participants; RR: 1.15, 95% CI 0.76–1.65; risk with placebo: 269/1000; risk with non-benzodiazepines: 301/1000; absolute difference of 3%; relative difference of 11%; moderate quality; Fig. 4b, upper panel) and GI AE (RR: 0.63, 95% CI 0.34–1.14; risk with placebo: 157/1000; risk with non-benzodiazepines: 99/1000; absolute difference of 6%; relative difference of 37%; moderate quality; Fig. 4b, lower panel), while low-certainty evidence showed that combination therapy is responsible for significantly more CNS AE than placebo (RR: 1.91, 95% CI 1.35–2.69; risk with placebo: 77/1000; ri171sk with

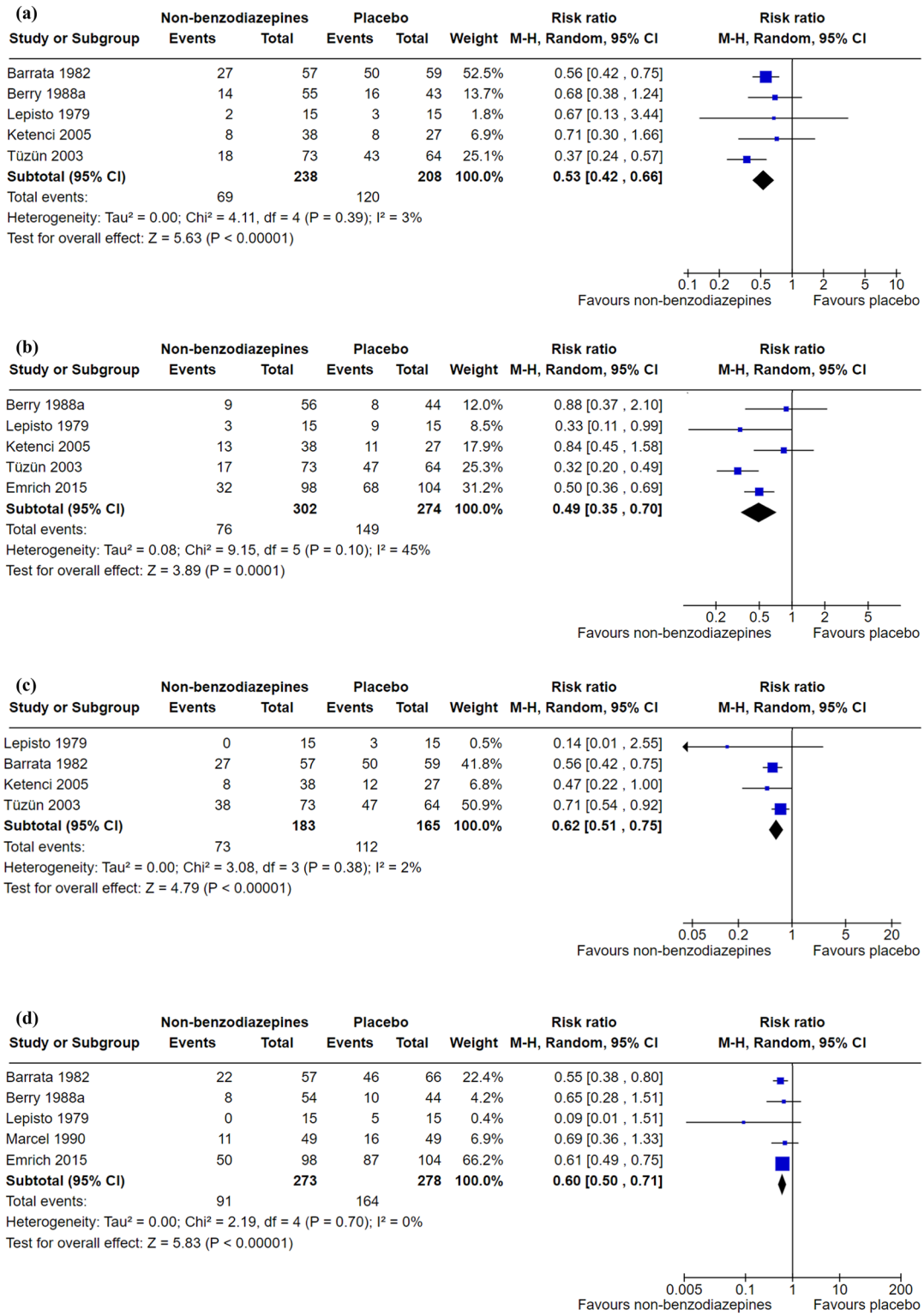
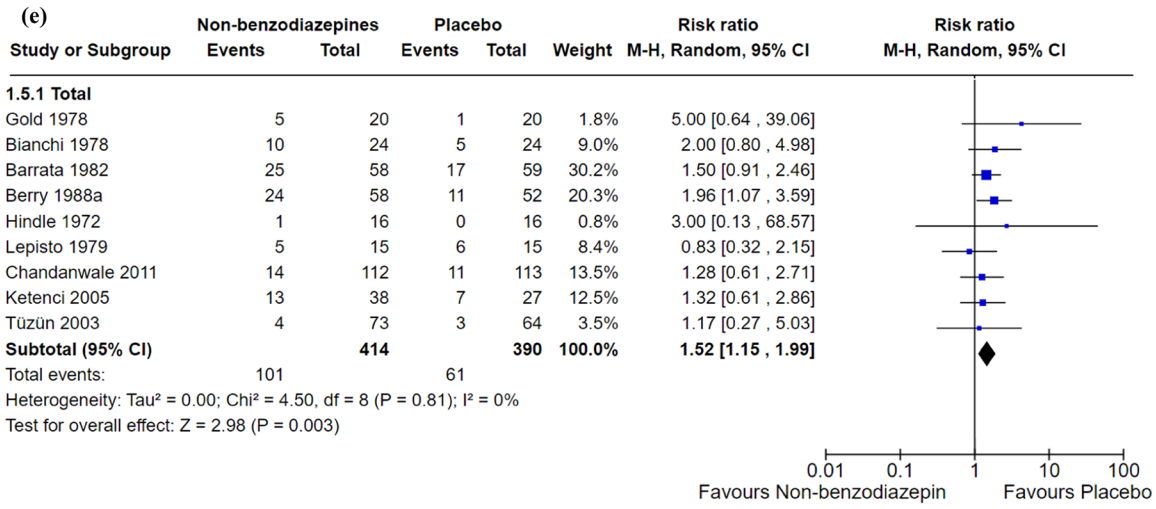
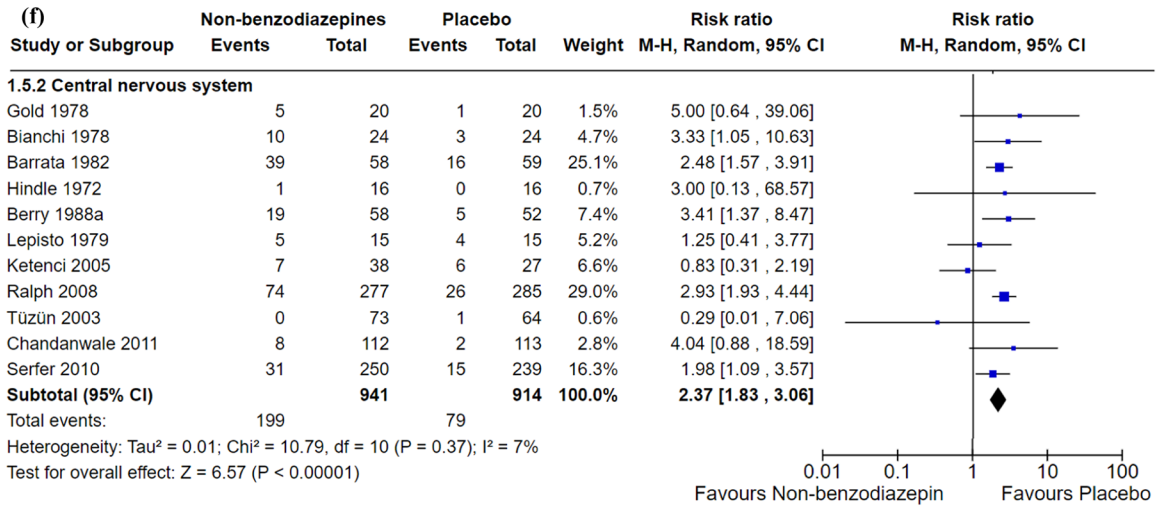


Fig. 3 **(a)** Pain relief for non-benzodiazepine muscle relaxants for acute LBP at 5–7 days follow-up 3 **(b)** Global efficacy for non-benzodiazepine muscle relaxants for acute LBP at 5–7 days follow-up **(c)** Muscle spasm for non-benzodiazepine muscle relaxants for acute LBP at 5–7 days follow-up **(d)** Physical outcomes for non-benzodiazepine muscle relaxants for acute LBP at 5–7 days follow-up **(e)** Total adverse events for non-benzodiazepine muscle relaxants for acute LBP at 5–7 days follow-up **(f)** Adverse events at the central nervous system level for non-benzodiazepine muscle relaxants for acute LBP at 5-7 days follow-up **(g)** Gastrointestinal adverse events for non-benzodiazepine muscle relaxants for acute LBP at 5–7 days follow-up





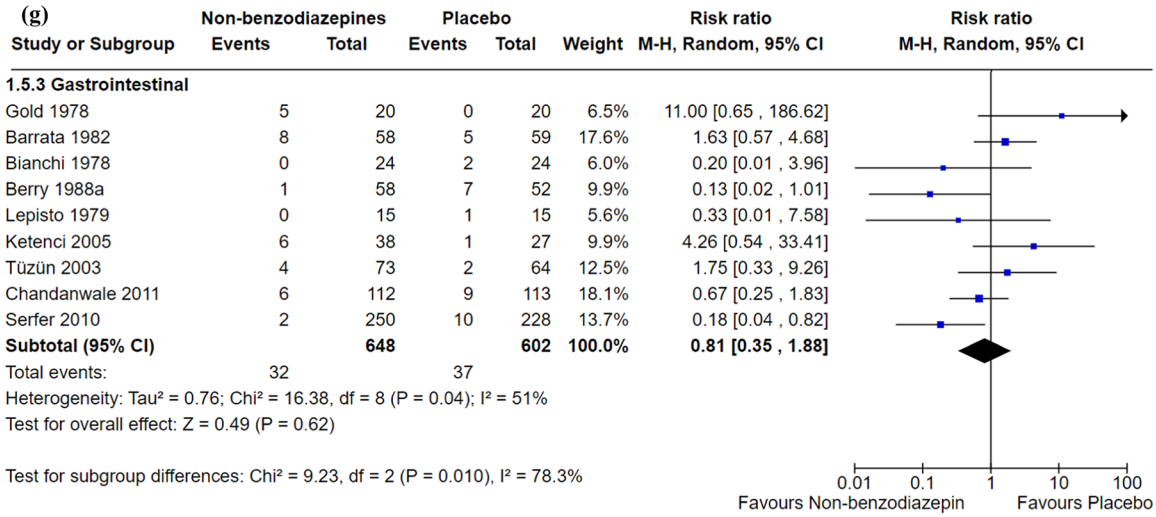


Fig. 3 (continued)

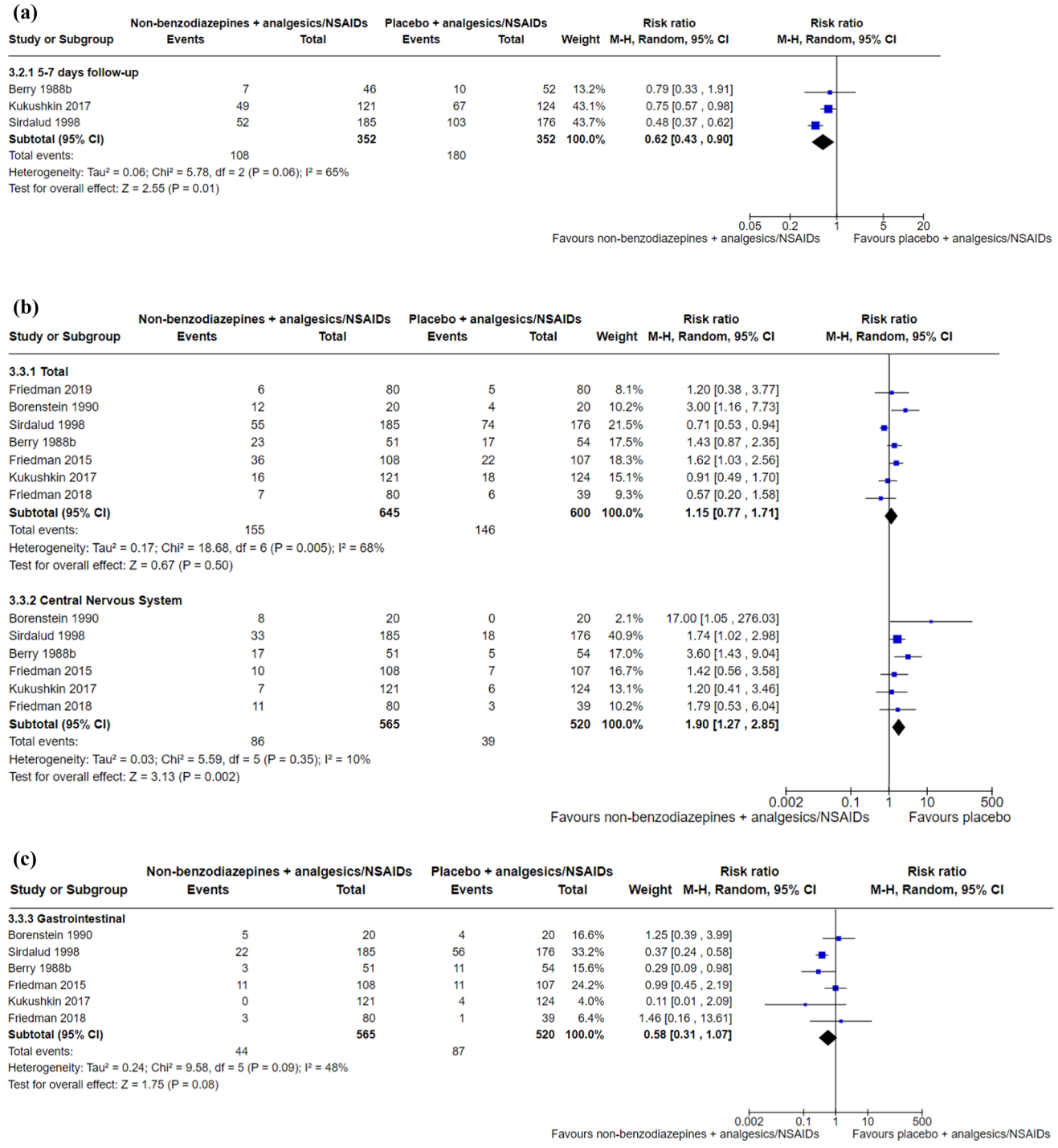


Fig. 4 **(a)** Global efficacy for non-benzodiazepine muscle relaxants + analgesics for acute LBP at 5–7 days follow-up **(b)** Total adverse events and CNS events for non-benzodiazepine MR + analgesics for acute LBP at 5–7 days follow-up **(c)** Gastrointestinal adverse events for nonbenzodiazepine MR + analgesics for acute LBP at 5–7 days followup

non-benzodiazepines: /1000; absolute difference of 9%; relative difference of 91%, low quality; Fig. 4c).

Non-benzodiazepines versus *placebo for chronic LBP.* A meta-analysis could be carried out only for AE, which revealed no significant difference in their frequency between MR (non-benzodiazepines) and placebo (3 studies, 475 participants; RR 0.93; 95% CI 0.66–1.32; low quality) [28–30] with a non-significant relative change of 7% fewer AE with MR ($p = 0.69$) (Fig. 5).

Non-benzodiazepines) + analgesics/NSAIDs versus *placebo + analgesics/NSAIDs for chronic LBP.* No RCTs were retrieved.

Discussion

The main goal of the present work was to evaluate the short-term (5–7 days) safety and efficacy of non-benzodiazepine MR given as monotherapy or in combination with analgesics/non-steroidal anti-inflammatory drugs (NSAIDs) to manage acute and chronic primary LBP. To this aim, meta-analytical aggregation of dichotomous data was chosen to synthesize the available literature quantitatively. Results showed that non-benzodiazepine MR show potential benefits versus placebo for acute LBP on very short-term pain relief, global efficacy, muscle spasm and physical outcomes. We cannot be confident that non-benzodiazepines are more useful than placebo for chronic LBP due to the paucity of RCTs sharing comparable outcomes.

Benefits on acute LBP symptoms were associated with significantly more total and CNS AE effects than placebo, but not with more GI AE. A meta-analysis of three studies did not show a difference in AE for chronic LBP. Likewise the combination of non-benzodiazepines + analgesics/NSAIDs was significantly associated with more CNS AE than placebo + analgesics/NSAIDs, with a clinically relevant difference of 91% (7 trials, 1206 participants). When appraising the AE of the scrutinized non-benzodiazepines, the results indicate CNS AE as the most prevalent, the commonest complaints being drowsiness and dizziness. Other AEs were negligible or not significantly different compared to placebo. Overall, the rate of AE suggests that non-benzodiazepines must be used with caution. While conclusions cannot be made about the risk of dependency from medications tested in the trials ultimately included in this review, there is sufficient indirect evidence from other sources that a substantial risk of dependency can develop when using non-benzodiazepines such as carisoprodol, which in the United States is a controlled substance due to addiction/abuse potential.

Evidence emerging from this SR depended on the number of aims and comparisons that could be ultimately performed. The overall evidence was qualified as "low-to-moderate", with potential external validity for the use of non-benzodiazepines for global efficacy, pain, muscle spasm and mobility. This also applies to the combined administration of non-benzodiazepines and analgesics/NSAIDs in the management of acute LBP. It should be noted that the body of literature here revised tended to focus on a relatively limited set of non-benzodiazepines, specifically tizanidine, tiocolchicoside, cyclobenzaprine, carisoprodol, methocarbamol, eperisone, and orphenadrine, which proved to be those most commonly prescribed.

Quality of evidence

The commonest methodological flaws observed were high risk of selection bias (allocation concealment), and attrition bias (ITT analysis). The randomization procedure was adequately performed in most studies. We found flaws concerning incomplete data reporting and co-intervention avoided in some studies. Considering the type of AE associated with non-benzodiazepines and the fact that most of the studies involved individuals treated outside the controlled environment of secondary care settings (i.e., outpatient or primary care settings), more attention should be devoted to compliance (clearly reported only in 18 studies), as it gives a good indication of the tolerability and acceptability of these drugs.

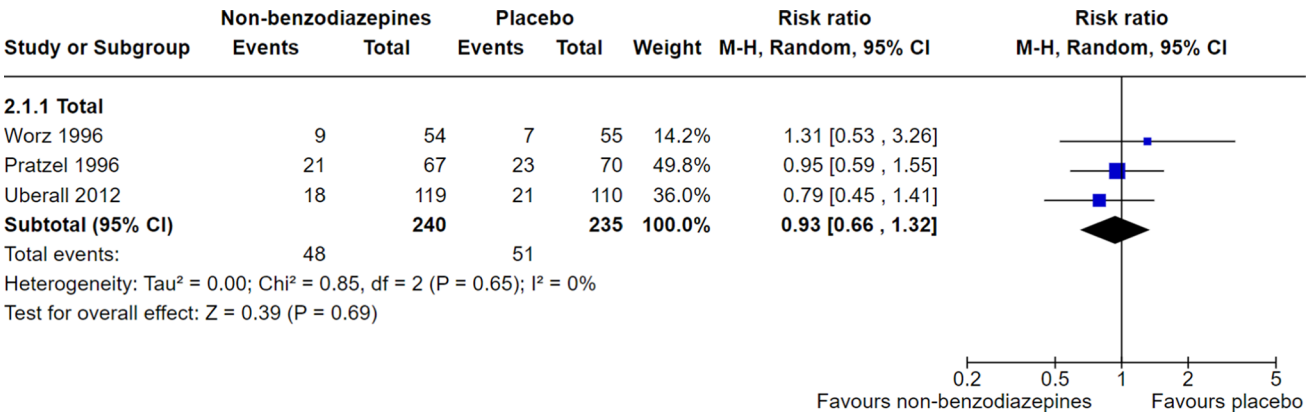


Fig. 5 Total adverse events of nonbenzodiazepine MR for chronic LBP at 5-7 days follow-up

Agreements and disagreements with other studies or reviews

The moderately positive effects of non-benzodiazepines for the management of acute LBP observed agree with a recent systematic review that evaluated the efficacy and tolerability of MR for LBP [3]. The authors identified 15 studies (3362 participants), 12 on acute LBP and 3 on chronic LBP. All the studies included were also considered in our SR; however, their meta-analyses results were presented as mean differences from pre-to post-intervention, which allowed those authors to evaluate whether the differences observed in each individual studies exceeded the cut-off thresholds for MCIDs, as suggested by Ostelo et al. [13] and Emshoff et al. [31]. As a result, a significant improvement by 21.3 mm on a pain NRS converted to the same 0–100 scale of the VAS was observed, thus exceeding the 20-point difference benchmark for a clinically meaningful change. The findings are similar in terms of AE of non-benzodiazepines for acute LBP. The results and conclusions of our SR are to be compared to those of the recent review by Cashin [4]. However, some differences between the two studies should be considered. First, our study focused on a very short follow-up period (< 2 weeks) whereas Cashin 2021 [3] reported on studies with 3–13 weeks follow-up periods. On such relatively longer follow-up, Cashin 2021 [3] reported very low- and low-certainty evidence that non-benzodiazepines (specifically, antispasmodics) might provide small, not clinically important reductions of pain intensity at or before two weeks and might increase the risk of AE in acute LBP, respectively. Conversely, we detected clinically important differences at 5–7 days follow-up (outcomes: pain relief; global efficacy) compared with placebo for non-benzodiazepines (antispasmodic and antispastic agents pooled together) given as monotherapy or in combination with NSAIDs for acute LBP. Another important issue is the nature of the outcome measures chosen as we opted for dichotomous data (e.g., proportion of patients showing improvement) whereas they employed continuous variables (e.g., mean of pain intensity before and after treatment). Hence, these SR should be viewed as complementary (as they examine different time spans and different measures of effect) rather than antithetical.

Study limitations

This review is not free of limitations. Among these, the lack of longer-term follow-up in addition to the 5–7 days span here planned. People with acute LBP may only use non-benzodiazepines for a few days or as long as 1–2 weeks, however understanding longer-term effects would be of interest for upcoming research. Moreover, while the addition of dichotomous data was done purposely to employ appropriate statistical methods that better reflect data distribution of responders to MR in studies on LBP [5], the way the efficacy outcomes were defined (i.e., dichotomously rather than using continuous measurements) may have impacted the results. The findings generated by this SR should be viewed as complimentary rather than antithetical to those reported by relatively recent reviews on the same topic [4, 6, 7].

Finally, while studies displaying high risk of bias were excluded after sensitivity analyses, articles with unclear risk of bias were maintained, provided that sensitivity analyses did not red flagged them as significant contributors to heterogeneity.

Final remarks

The results show evidence from very low to moderate certainty that non-benzodiazepines provide benefit compared to placebo for short-term pain relief, global efficacy, muscle spasm and physical outcomes (at 5–7 days follow-up) for acute LBP. The mechanism by which they induce their beneficial effects is also responsible for serious AE (drowsiness, dizziness). For clinicians, it is not only of interest whether non-benzodiazepines are more effective than placebo, but also whether they are more effective than other drugs for LBP such as NSAIDs or analgesics. Larger high-quality RCTs ensuring more robust control of bias and confounders are needed to move the field forward.

Combination of MR with analgesics/NSAIDs may be superior to analgesics/NSAIDs for overall improvement, although the quality of evidence was, again, low. It is still unknown if non-benzodiazepines offer larger benefits than analgesics/NSAIDs, because there are no RCTs that directly compare these drugs.

Another area of interest is the use of peripherally rather than centrally acting MR for LBP. These agents could induce the same beneficial effects as those acting through the CNS, but without associated AE.

In conclusion, the results of this review pointing toward some small, short-term benefits of MR on acute LBP should be interpreted against the AE associated with these medications and the number of sources of bias that affect this literature.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00586-025-08786-0.

Author contribution AM, LC and MM conceived the idea for the study. AM, LC and FS performed literature searches, study selection and assessments, and data extraction. AM and MM analyzed data. MVT and AF provided guidance and critically revised the manuscript. All authors have read and approved the submitted version of the manuscript.

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Data availability "Data is provided within the manuscript or supplementary information files".

Declarations

Conflict of interest The authors declare no competing interests.

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