The Efficacy and Safety of Muscle Relaxants in Inflammatory Arthritis: A Cochrane Systematic Review

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ABSTRACT. ***Objective***. To determine the efficacy and safety of muscle relaxants in pain management in patients with inflammatory arthritis (IA).

Methods. We searched the Cochrane Central Register of Controlled Trials, Medline, Embase, and PsychINFO for randomized controlled trials in adults with IA that compared any muscle relaxant (administered via any route) to another analgesic intervention or placebo. We also searched the 2008-2009 American College of Rheumatology and European League Against Rheumatism abstracts and performed a hand search of reference lists of relevant articles. Primary outcomes were patient-reported pain relief ≥ 30% and withdrawals due to adverse events. Two authors independently assessed methodological quality and extracted data.

Results. Six trials (126 participants) were included in this review. All trials were deemed to have a high risk of bias. Five crossover trials evaluated benzodiazepine; 4 assessed diazepam (n = 71), and one assessed triazolam (n = 15). The sixth trial, a parallel-group study, evaluated zopiclone (non-benzodiazepine, n = 40). No trial was longer than 2 weeks and 3 single-dose trials assessed outcomes at 24 hours only. Overall, the included trials failed to find evidence of a beneficial effect of muscle relaxants over placebo (at 24 hours, 1 week, or 2 weeks) or in addition to nonsteroidal antiiflammatory drugs (at 24 hours) on pain intensity, function, or quality of life. Data from 2 trials of longer than 24-hour duration (diazepam and zopiclone, n = 74) found that participants who received a muscle relaxant had significantly more adverse events compared with those who received placebo [number needed to harm (NNTH) 3, 95% CI 2 to 7]. These were predominantly central nervous system side effects including dizziness and drowsiness (NNTH 3, 95% CI 2 to 11).

Conclusion. Based upon the currently available evidence in patients with IA, benzodiazepines (diazepam and triazolam) do not appear to be beneficial in improving pain over 24 hours or 1 week. The non-benzodiazepine agent zopiclone also did not significantly reduce pain over 2 weeks. However, even short-term muscle relaxant use (24 hours to 2 weeks) is associated with significant adverse events, predominantly drowsiness and dizziness. (J Rheumatol Suppl. 2012 Sept;90:34–9; doi:10.3899/jrheum.120340)

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Despite the significant advances in treatments over the past few decades, pain management remains a significant issue for many patients with inflammatory arthritis (IA)[1]. Progressive disease is often characterized by synovial tissue proliferation and persistent inflammation, with resultant cartilage degradation, bone erosion, and damage to adjacent soft tissue and neural structures[2]. In the early stages of IA, pain is the result of the nociceptive effects of local inflammation[3]. Over time, however, the sources of pain become more numerous[4] and are often compounded by associated poor sleep, psychological comorbidity, and muscle spasm[5].

Sleep disturbance, independent of mood status, has also been associated with fatigue, exhaustion, irritability, poor function, and a cycle of greater pain[6]. There is also literature to suggest that elevated levels of anxiety seen in patients with RA are associated with higher levels of pain[7,8,9,10]. As muscle relaxants are widely prescribed in the management of insomnia, anxiety, and muscle spasm, in theory, they may therefore be useful adjuvant agents in the management of pain in patients with IA.

The term "muscle relaxant" is very broad and includes a wide range of drugs with different indications and mechanisms of action. Muscle relaxants can be divided into 2 main categories: antispasticity and antispasmodic medications. Antispasticity medications are used to reduce spasticity that interferes with therapy or function. Examples of such agents include baclofen and dantrolene.

The antispasmodic agents are further subclassified into the benzodiazepines and the non-benzodiazepines. Since the introduction of chlordiazepoxide (Librium®) in 1960[11] and diazepam (Valium®) in 1962[12], the benzodiazepines have been widely prescribed for a variety of medical and psychiatric indications. Non-benzodiazepines include a variety of drugs that can act at the brain stem or spinal cord level. Examples include carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol, tizanidine, and orphenadrine. All antispasmodic agents can cause significant drowsiness, dizziness, confusion, nausea, and vomiting. While these agents have been used for the treatment of painful musculoskeletal conditions associated with muscle spasm, such as acute low back pain and muscle strains[13], their use in IA is less well described.

Our review is part of the 3e (Evidence, Expertise, Exchange) Initiative on Pain Management by Pharmaco-therapy in Inflammatory Arthritis[14]. The objective was to systematically review the literature concerning one of 10 selected questions as an evidence base for generating the recommendations. The question addressed was: "What is the effectiveness, safety, and role of (antidepressants), muscle relaxants (and neuromodulators) in inflammatory arthritis, and how should they be administered (i.e., interval, safety, and route)?" This article is a modified version of a Cochrane Review that specifically focused on rheumatoid arthritis (RA)[15].

METHODS

The systematic literature review was carried out in several steps in accordance with the methods recommended by the Cochrane Collaboration[16].

Rephrasing the research question. The clinical question posed by the expert clinicians was rephrased to enable epidemiological enquiry using the PICO (Patient, Intervention, Comparator, Outcome) method[17]. Patients were defined as adults with RA, psoriatic arthritis, ankylosing spondylitis, or spondyloarthritis. The intervention was defined as treatment with any formulation or dose of a muscle relaxant as either monotherapy or in combination. Comparators included placebo or any other pharmacological [excluding disease modifying antirheumatic drugs (DMARD)] or nonpharmacological analgesic modalities. The primary outcomes of interest were pain and withdrawals due to adverse events (AE), including mortality. The literature search was limited to randomized controlled trials (RCT), including trials where treatment was allocated via a quasirandom method.

Systematic literature search. A literature search for articles published between 1950 and May 2010 was performed in Medline, Embase, and the Cochrane Central Register of Controlled Trials. For details on the search strategy, which was developed in collaboration with an experienced librarian, see the online Appendix available from www.3epain.com. In addition, a search was conducted of abstracts from the European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) scientific meetings in 2008 and 2009. Review articles were also retrieved for identifying additional references via hand search.

Selection of articles. The titles and abstracts of all studies identified by the search strategy were screened and all potentially eligible studies were reviewed in full text by 2 authors (BR and SW). Studies were excluded if they contained a mixed population where the data of those with IA could not be extracted separately, or if they were written in languages that could not be translated by one of the members of the 3e Initiative multinational panel. Drugs that had been withdrawn from the market due to safety concerns were excluded from the review. Any disagreement in study selection was resolved by consensus or by discussion with a third reviewer (RB).

Data extraction and quality appraisal. Raw data were extracted from the included studies by 2 authors (SW and BR), using predetermined forms. Differences in data extraction were resolved by referring back to the original articles and establishing a consensus. A third reviewer (RB) was consulted to help resolve differences as necessary. Two authors (SW, BR) independently assessed risk of bias for all included studies for the following items: random sequence generation, allocation concealment, blinding of participants, care provider, outcome assessor for each outcome measure, incomplete outcome data, and other biases, conforming to the methods recommended by the Cochrane Collaboration[16]. To determine the risk of bias of a study, each criterion was rated as Yes (low risk of bias), No (high risk of bias), or Unclear (either lack of information or uncertainty over the potential for bias).

Data analysis. For continuous data, results were analyzed as mean differences (MD) between the intervention and comparator group with 95% confidence intervals (CI). However, when different scales were used to measure the same conceptual outcome (e.g., pain), standardized mean differences (SMD) were calculated instead. For dichotomous data, a relative risk (RR) with corresponding 95% CI was calculated. In cases where individuals were missing from the reported results, we assumed the missing values to have a poor outcome. Prior to metaanalysis, we assessed studies for clinical homogeneity with respect to type of therapy, control group, and outcomes. Where studies were sufficiently homogeneous that it remained clinically meaningful for them to be pooled, metaanalysis was performed using a random-effects model. Statistical heterogeneity was assessed using the I^2 statistic[18]. In addition to the absolute and relative magnitude of effect, for dichotomous outcomes, the number needed to treat (NNT) to benefit or the number needed to treat to harm (NNTH) were calculated from the control group event rate and the relative risk using the Visual Rx NNT calculator, available from: http://www.nntonline.net/visualrx/). Analysis was performed using Review Manager 5.

RESULTS

Study characteristics. A total of 174 references were identified with the systematic search strategy. After title and abstract screening, 25 articles were retrieved for full-text review, of which 6 trials (n = 126 participants) fulfilled the inclusion criteria. No further relevant studies were identified from searching the 2008-2009 ACR and EULAR abstracts or article references (Figure 1). A detailed list of the excluded references is included in the online appendices available from www.3epain.com.

Characteristics of the included studies are summarized in Table 1. The majority of studies were published in the late 1970s, and no studies were identified that involved subjects with an inflammatory arthropathy other than RA. Three studies evaluated inpatients[19,20,21] and 3 studies included outpatients[22,23,24]. Most participants were women (83%), in accordance with the epidemiology of RA, and all patients had active disease, with 56% of patients hospitalized at the time of study. Only 17% (22/127) of patients were receiving corticosteroids and 30% (38/127) were receiving DMARD (only 5/38 methotrexate). No patients were receiving biological

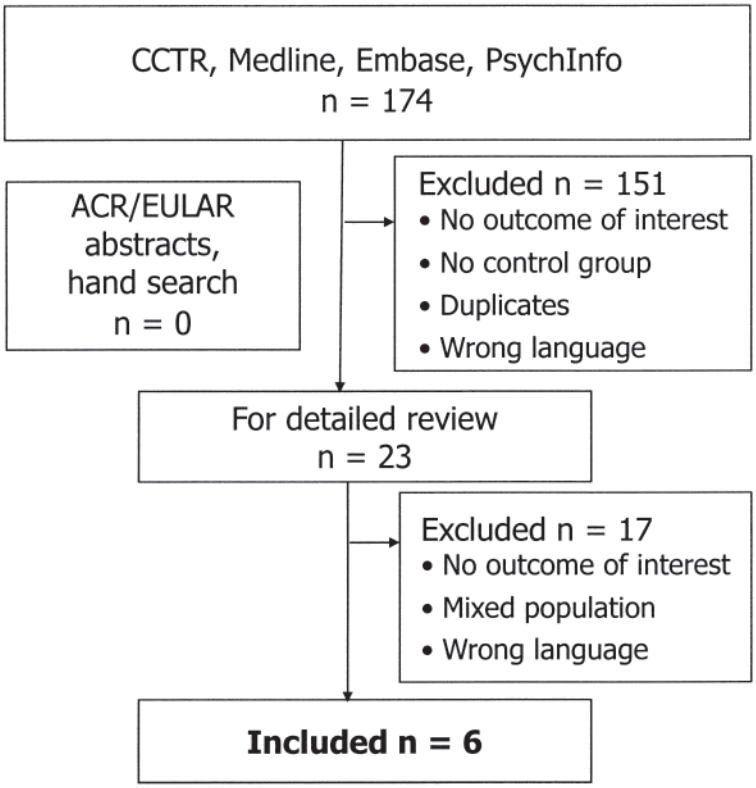

Figure 1. Literature search from which 23 articles were selected for detailed review. Six articles met the inclusion criteria.

Study	Population	Intervention	Comparator(s)	Outcome(s)	Study Design
Bayley 1976[19]	18 inpatients with active RA Age 18-75 yrs, disease duration 3 months-25 yrs. Exclusion: any patient taking corticosteroids or indomethacin > 75 mg/day, known hypersensitivity to study drugs	Diazepam 10 mg	Indomethacin 100 mg or placebo	Primary: 1. Sleep, 2. Night pain, 3.EMS , 4. Adverse events Secondary: Patient preference	Cross over trial, double blind, single dose over 3 consecutive nights
Hobkirk 1977[20]	18 inpatients with active RA Age 43-77 yrs, disease duration 4 mo to 22 yrs. Exclusion: Corticosteroid use, > 75 mg indomethacin daily, allergy to study drugs	Diazepam 10 mg + Indomethacin 100 mg	Indomethacin 100 mg or placebo	Primary: 1. Sleep, 2. Night pain, 3. EMS, 4. Adverse events Secondary: Patient preference	Crossover trial, double blind, single dose over 3 consecutive nights
Sharma 1978[21]	18 inpatients with active RA 2 Age 24-68 yrs. Exclusion: Corticosteroid use, > 75 mg indomethacin daily, allergy to study drugs	Indomethacin 100 mg + diazepam 10 mg	Sulindac 200 mg or Sulindac 200 mg + 10 mg diazepam	Primary: 1. Sleep, 2. Night pain, 3. EMS, 4. Adverse events Secondary: Patient preference	Cross over trial, double blind, single dose over, 3 consecutive nights
Vince 1973[22]	17 outpatients with RA, mean age 47 yrs (31-73), disease duration 5.8 yrs (2-20), 15/17 Steinbroker III, 5/24 receiving < 10 mg oral corticosteroids, all receiving NSAID. Exclusion: nil specified	Diazepam 15 mg daily	Placebo	Primary: 1. Pain, 2. Disease Activity 3. Adverse events. 4. Patient and doctor global assessment	Cross over trial, double blind, 1 week
Walsh 1996[23]	15 outpatients with RA and subjective complaint of daytime fatigue and sleepiness, mean age 53.5 yrs, disease duration 12.1 yrs, duration sleep complaint 6.5 yrs, EMS 76.1 min, 10/15 patients receiving prednisone. Exclusion: sleep apnea, sedating medications, significant psychopathology	Triazolam 0.25-0.125 mg*	Placebo	Primary: 1. Daytime somnolescence, Insomnia Secondary: 1. Pain 2. Sleep, 3. Disease activity, 4. Mood	Cross over study, double blind, 1 week
Drewes 1998[24]	41 outpatients with RA, mean age 51 yrs. Exclusion: Fibromyalgia	Zopiclone 7.5 mg	vs placebo	Primary: 1. Sleep (polysomnography, subjective sleep assessments) Secondary: 1. RA disease activity, 2. Pain, 3. adverse events	RCT, double-blind, 2 weeks

** Triazolam 0.25 mg first 2 nights (age 30-59 yrs) or 0.125 mg (age 60-70 yrs). Dose doubled after second night if poor clinical response. EMS: early morning stiffness; RCT: randomized controlled trial.

agents. No studies reported any specific information about the type of pain affecting participants or whether they had depression.

Five trials assessed a benzodiazepine[19,20,21,22,23] and 1 trial assessed the non-benzodiazepine agent zopiclone (n = 40)[24]. Of the benzodiazepine studies, 4 evaluated diazepam (n =

71)[19,20,21,22] and 1 evaluated triazolam (n = 15)[23]. Five trials included a placebo control[19,20,22,23,24], 1 compared diazepam with a nonsteroidal antiinflammatory drug (NSAID)[19], and 2 studies assessed whether diazepam in combination with an NSAID was superior to an NSAID alone[20,21].

Five trials used a crossover design[19,20,21,22,23], and of these, only 1 included a washout period[23]. The remaining study used a parallel-group design[24]. No trial was longer than 2 weeks' duration, with 50% of the included trials being single-dose studies.

All trials were deemed to have a high risk of bias (Figure 2), with the major flaws being that they were too small and of too short duration to be able to detect a clinically significant difference. The most common methodological flaws included failure to describe randomization, allocation concealment, and blinding of study participants and personnel. All studies described the use of a "placebo" but did not provide specific information about the characteristics of the placebo and in particular whether the placebo was identical or not to the active treatment. There was no evaluation of a carryover period effect in any of the crossover trials, with 3 trials failing to have a washout period. No study recorded the use of any analgesic cointerventions.

Effects of Interventions

Efficacy. No study reported the primary outcome measure of patient-reported pain relief ≥ 30%. Available pain data were confined in all trials to mean pain visual analog scale (VAS) or means of ordinal outcomes. When pooled, the short-term single-dose studies assessing diazepam (52 participants)[19,20,21] showed no benefit in mean night pain VAS (0–10 cm) scores over the control arm (SMD –0.22, 95%CI –1.02 to 0.58). The other 3 studies of between 1 and 2 weeks' duration[22,23,24] also showed no significant improvement in mean pain over control (SMD –0.20, 95% CI –0.59 to 0.18).

Three studies assessed the efficacy and safety of a benzodiazepine versus placebo on pain intensity[19,22,23]. Two small crossover trials[19,22] compared diazepam with placebo at different timepoints and reported conflicting results (2 trials, 35 people). Bayley and Haslock[19] reported that a single dose of diazepam was superior to placebo in relieving night pain (mean improvement 0.9 cm, 95% CI –1.77 to –0.03, on a 10-cm VAS); while Vince and Kremer[22] reported no difference in mean pain scores between diazepam and placebo after 1 week.

Two studies compared different benzodiazepines with placebo over 1 to 2 weeks' duration[22,23]. After 2 weeks, Vince and Kremer[22] again found no significant difference in mean pain scores between diazepam and placebo. Walsh, *et al*[23] compared triazolam with placebo in patients with RA and sleep disturbance and also found no significant difference in pain outcomes after 2 weeks. Pooling these 2 studies of 1 week duration using a random-effects model yielded the same result (SMD –0.19, 95% CI –0.68 to 0.30).

One small study (1 trial, 41 patients) found no benefit of zopiclone over placebo over 2 weeks on either present pain intensity (MD –0.20, 95% CI –0.77 to 0.37) or total pain rating index (MD –6.60, 95% CI –16.25 to 3.05)[24].

Two small crossover trials (2 trials, 35 people) evaluated whether there was any benefit in the addition of diazepam to an NSAID over taking an NSAID alone[20,21]. Both trials were small and were 3 consecutive-night trials of inpatients with

	Bayley 1976	Drewes 1998	Hobkirk 1977	Sharma 1978	Vince 1973	Walsh 1996
Adequate sequence generation?	?	?	?	?	?	?
Allocation concealment?	?	?	?	?	?	?
Blinding?	✓	?	✓	✓	?	?
Incomplete outcome data addressed?	✓	✓	✓	✓	x	✓
Free of selective reporting?	✓	✓	✓	✓	✓	✓
Compliance?	✓	?	✓	✓	?	?
Cointerventions?	?	?	✓	✓	?	?
Were Baseline Characteristics similar?	?	✓	?	?	x	✓
Was an intention to treat analysis performed	✓	x	x	x	?	x
Was there a high drop out rate?	✓	✓	✓	x	x	✓
Summary Assessment of Bias	x	x	x	x	x	x
	x: high risk of bias, ✓: low risk of bias, ?: unclear risk of bias.					

Figure 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

active disease. Neither trial found additional benefit of the combination in terms of pain reduction compared with NSAID alone. SD were estimated from a conservative estimate of the p values in each of the trials; when data were pooled, the results were the same (SMD –0.14, 95% CI –1.65 to 1.36).

Safety outcomes. There was a paucity of data available regarding withdrawals due to AE, with 3 trials having event rates of "0"[19,22,24]. Overall there was a trend towards more withdrawals in patients receiving a muscle relaxant but this did not receive statistical significance (RR 2.84, 95% CI 0.31 to 26.08). In the 1 study of the non-benzodiazepine agent zopiclone versus placebo there were no withdrawals due to AE at the end of the 2-week trial[24].

Overall, 34% of patients receiving an intervention and 22% of patients in the control group suffered an adverse event. When pooled over all time periods, there was only a trend towards an increase in AE in patients receiving muscle relaxants (RR 1.40, 95% CI 0.58 to 3.41). Not surprisingly, the rate of AE for diazepam varied greatly between the single-dose trials (11%–28%) and the 2-week study (71%).

In the single crossover studies (3 trials, 106 people) evaluating short-term outcomes (24 hours) of diazepam versus placebo, there was no significant increase in the total number of AE (RR 0.78, 95% CI 0.41 to 1.48)[19,20,21]. However, in the longer 1-week or 2-week trials, there were significantly more AE (RR 4.03, 95% CI 1.08 to 15.10)[22,24]. When data from the trials of more than 24 hours' duration were pooled, there were significantly more AE (NNTH 3, 95% CI 2 to 8). Consistent with the literature, these were predominantly central nervous system side effects including dizziness and drowsiness (NNTH 3, 95% CI 2 to 11). In the 1 small trial of zopiclone, 32% suffered an adverse event, with 14% of events related to dizziness and drowsiness[24]. Given the small sample size there was a trend only towards significance (RR 14.04, 95% CI 0.87 to 227.89).

DISCUSSION

Our systematic review assesses the existing literature regarding the efficacy and safety of muscle relaxants for treating pain in patients with IA. The results of this review served as an evidence base for one of 10 recommendations regarding pain management by pharmacotherapy that were generated by a multinational panel of rheumatologists as part of the 3e Initiative. A detailed description of all final recommendations can be found elsewhere[14].

There is currently weak evidence that benzodiazepines (diazepam and triazolam) do not improve pain by any clinically significant difference over 24 hours or 1 week in patients with RA. There is also weak evidence that there is no short-term benefit of diazepam over indomethacin, and no change in pain score with addition of diazepam to an NSAID over an NSAID alone.

No reliable conclusions can be made from these data regarding withdrawals due to AE. There was no significant increase in the total number of AE over 24 hours; however, AE were significantly increased when the trials were of 1 or 2 weeks' duration. The predominant side effects in patients receiving muscle relaxants were dizziness and drowsiness, with 1 adverse event occurring in every 3 people, on average. The 1 small non-benzodiazepine trial identified found no benefit of zopiclone over placebo in outpatients over 2 weeks. Physicians are also often concerned about the potential problem of addiction and withdrawal associated with these agents; however, no study addressed these outcomes so no conclusions can be made in regard to this in this patient population.

There are several limitations in the interpretation of the results of our review. There were no large trials or limited head-to-head trials, and no studies longer than 2 weeks' duration. All included trials had a high risk of bias, and there were no data on any patients with IA other than RA. In addition, the populations included in this review are also not reflective of current patients with RA. More than half the included trial participants were inpatients, who were hospitalized with poorly controlled disease. Many were receiving only NSAID, or occasionally low-dose corticosteroids or DMARD, reflective of practice at the time. No patients were receiving biologic agents. The nature and duration of the patient's pain or whether any other analgesics were being used (or were no longer needed) was not described in any of the studies. Given the significant advances in disease-modifying strategies for patients with IA, the applicability of these results is limited.

Data are also lacking on many commonly used benzodiazepine agents (alprazolam, clonazepam, lorazopam, oxazepam, etc.); moreover, there are no data available on any of the skeletal muscle relaxants including baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, dantrolene, metaxalone, methocarbamol, orphenadrine, and tizanidine. There was substantial heterogeneity in the outcome measures used in the included trials.

Safety and efficacy data are limited to a maximum of 1 week for the benzodiazepines and 2 weeks for the only non-benzodiazepine included in this review (zopiclone). Reliable conclusions about withdrawal due to AE and total AE rates can therefore not be drawn from these short trials. Although not identified in our review, chlorzoxazone has been implicated in causing serious (including fatal) hepatocellular toxicity. Chlormezanone has also been implicated in causing Stevens-Johnson syndrome and toxic epidermal necrolysis.

Based upon the currently available evidence in patients with IA, benzodiazepines (diazepam and triazolam) do not appear to be beneficial in improving pain over 24 hours or 1 week, and longer treatment periods are not evaluated. Although conclusions cannot be made about the risk of dependency from the trials included in this review, there is sufficient indirect evidence from other sources that a substantial risk of dependency can develop when using muscle relaxants. Until better evidence is available regarding their differential efficacy or safety, these agents should be used

with caution, particularly in patients who are prone to addiction.

To better assess the efficacy and safety of muscle relaxants in patients with RA, large double-blind placebo-controlled and head-to-head RCT with homogeneous RA populations who have pain despite optimal DMARD and/or biological DMARD therapy are required.

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