Cyclobenzaprine for the treatment of myofascial pain in adults (Review)

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[Intervention Review]

Cyclobenzaprine for the treatment of myofascial pain in adults

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ABSTRACT

Background

Myofascial pain (MP) is a painful condition characterized by pain transmitted from trigger points (TP) within myofascial structures (in the muscles), local or distant from the pain. TPs can produce a characteristic pattern of irradiated pain or autonomic symptoms when stimulated. Cyclobenzaprine, a muscle relaxant that suppresses muscle spasm without interfering with muscle function, is used in clinical management of MP to improve quality of sleep and reduce pain.

Objectives

To assess efficacy and safety of cyclobenzaprine in treating MP.

Search methods

The Pain Palliative and Supportive Care Review Group's Specialised Register, CENTRAL, PubMed, EMBASE, LILACS and Scielo were searched in February 2009.

Selection criteria

All RCTs and quasi-RCTs reporting use of cyclobenzaprine for treating MP with pain assessment as a primary or secondary outcome.

Data collection and analysis

Two review authors independently screened studies identified, extracted data, assessed trial quality and analyzed results.

Main results

We identified two studies with a total of 79 participants. One study, with 41 participants, compared cyclobenzaprine with clonazepam and with placebo. Participants taking cyclobenzaprine had some improvement of pain intensity compared to those on clonazepam, mean difference (MD) -0.25 (95% CI, -0.41 to -0.09; P value 0.002) and placebo, MD -0.25 (95% CI, 0.41 to -0.09; P value 0.002). The other study, with 38 participants, compared cyclobenzaprine with lidocaine infiltration. Thirty days after treatment there were statistically non-significant differences between comparison groups, favoring lidocaine infiltration, for the mean for global pain, MD

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0.90 (95% CI -0.35 to 2.15, P value 0.16), and for the mean for pain at digital compression, MD 0.60 (95% CI -0.55 to 1.75, P value 0.30). There were no life-threatening adverse events associated with the medications.

Authors' conclusions

There was insufficient evidence to support the use of cyclobenzaprine in the treatment of MP. We identified only two small studies in which a total of 35 participants were given cyclobenzaprine, and it was not possible to estimate risks for benefits or harms. Further high quality RCTs of cyclobenzaprine for treating MP need to be conducted before firm conclusions on its effectiveness and safety can be made. Experts in this area should elect cut-off points for participants to identify whether a patient has achieved a clinically relevant reduction of pain (primary outcome), so that their results can be combined easily into future versions of this review.

PLAIN LANGUAGE SUMMARY

Cyclobenzaprine drug treatment for myofascial pain in adults

Myofascial pain (MP) is a painful condition of the muscles characterized by pain transmitted from trigger points (TP) within connective tissue surrounding and separating muscles (myofascial structures). TP can be located where the pain is felt, or can be at a distance from it. Cyclobenzaprine, one of the drugs used to treat MP, is taken as a pill. It is a muscle relaxant, particularly used to improve quality of sleep and to reduce pain. It suppresses muscle spasms - and so may prevent pain caused by MP - without interfering with muscle function. The purpose of this review was to assess how effective cyclobenzaprine is at reducing pain and improving sleep in patients with MP. We searched extensively through scientific publications and found two trials, with a total of 79 participants. These tested cyclobenzaprine against another drug called clonazepam, and fake medication (placebo), or against injections of a local anesthetic called lidocaine. A total of 35 of the 79 participants in the two trials were given cyclobenzaprine. Cyclobenzaprine was slightly better than clonazepam and placebo at reducing jaw pain, but was no better at improving sleep quality. The results from the other trial were not scientifically reliable because of the small number of participants involved, but lidocaine injections seemed to reduce pain slightly better than cyclobenzaprine pills. Despite this result, it is likely that, because it is uncomfortable to receive any form of injection, people who suffer from MP will prefer to be treated with cyclobenzaprine pills. There were no life-threatening adverse events associated with any of the medications studied. Further studies are needed to show whether cyclobenzaprine really works for treating MP, but at the moment doctors cannot say whether it is really useful.

BACKGROUND

Myofascial pain (MP) is a painful condition of the muscles characterized by pain transmitted from trigger points (TP) within myofascial structures (connective tissue surrounding and separating muscles). TP can be local to or distant from the pain (Fricton 1985; Fricton 1989; Manfredini 2006; Okeson 1998; Okeson 2006; Solberg 1986; Travell 1952). When stimulated, TP can produce a characteristic pattern of irradiated pain or autonomic symptoms (Fricton 1989; Okeson 1998; Solberg 1986). The pain can occur at rest or during function, and may be accompanied by muscle spasm. MP was initially described in 1952, although odontological and medical communities were very slow to understand it (Travell 1952). Physical examination of patients, and consideration of their medical history is required to make a diagnosis of MP, as well as the identification of the patients painful points by using digital palpation (Fricton 1985; Gerwin 1995). The face and jaw can be particularly affected by MP, and, in such temporomandibular disorders, MP can be associated with limitation of the mandibular opening (Dworkin 1992; Manfredini 2006; Okeson 2006). There are many diagnostic systems for temporomandibular disorders (TMD) of which MP is a part. Indeed, the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) was created to provide classification criteria for the condition that are universally accepted and validated. A diagnosis of MP by the RDC/TMD requires pain to be reported by the subject in response to palpation of three or more sites of the masticatory muscles (De Lucena 2006; Dworkin 1992; Manfredini 2006). Studies of prevalence show different results between Americans, Europeans and Asian populations for MP; these studies indicate that MP can occur in 21% to 93% of patients who complain of regional pain. MP shows an unusual distribution in the general population, with a predominance in females, and an age of onset ranging between 20

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and 40 years (Fishbain 1986; Gerwin 1995; Graff-Radford 1984; List 1996; List 1999; Manfredini 2006; Reitinger 1996; Schiffman 1990; Yap 2003).

The etiology (cause) of MP is complex and it is difficult to be specific about all etiological factors, however, some authors have described local (restricted to one part) and systemic (whole body) factors that seem to be associated, including: trauma, stress, emotional tension, deep pain impulse, hypovitaminosis (lack of one or more vitamins), infections, fatigue, and patients who are physically inactive and in a weak physical condition (Laskin 1969; Okeson 2006; Simons 2005).

Treatment options for MP include reassurance (patient education, self care and behavior therapy), physiotherapy (ultrasound, megapulse, short wave laser, heat exercises, biofeedback), acupuncture, splint therapy, occlusal adjustment of the teeth, dry needling (infiltration of the needle making movements, different of acupuncture), drug therapy and combined treatment (Al-Ani 2005; Koh 2003; McMillan 1997; Shi 2003; Solberg 1986). Medicines used to treat MP include analgesics, non-steroidal anti-inflammatory drugs (NSAIDS), muscle relaxants and tricyclic antidepressants such as amitriptyline (Al-Ani 2005; Koh 2003; Shi 2003).

Cyclobenzaprine, a muscle relaxant, is a centrally-acting serotonin receptor antagonist that reduces muscle tone by inhibiting serotonergic descending systems in the spinal cord (Katz 1988; Kobayashi 1996). It suppresses muscle spasms without interfering with muscle function (Basmajian 1978; Lance 1972). Cyclobenzaprine is structurally related to amitriptyline. In fact, it was initially produced as an antidepressant, and tested in clinical trials for antidepressant activity at doses above those used now for muscle relaxation (De Lee 1980). The similarity to amitriptyline has raised concerns about side effects such as drowsiness, lethargy, sinus tachycardia (rapid heartbeat), agitation, and both hypertension and hypotension (Turturro 2003), but a five-year multicenter review of its toxicity showed that cyclobenzaprine does not appear to produce life threatening cardiovascular and neurological effects (Kobayashi 1996). Also, in some trials, the incidence of troublesome side effects appears to be lower than that documented with amitriptyline (Lance 1964; Lance 1972). At present, cyclobenzaprine is used in the clinical management of MP in temporomandibular disorders to improve the quality of sleep and to reduce pain (Pertes 2005; Tofferi 2004), but its effectiveness has not been summarized in a systematic review.

OBJECTIVES

- To assess the efficacy and safety of cyclobenzaprine in the treatment of myofascial pain.
- To test the null hypothesis that there are no differences in outcomes between cyclobenzaprine versus other active treatments for treating myofascial pain.

We also sought to identify any adverse effects related to the treatment.

METHODS

Criteria for considering studies for this review

Types of studies

All randomized controlled trials (RCTs) and quasi-randomized controlled trials (quasi-RCTs) that fulfilled the criteria outlined below were included.

Types of participants

Participants of both sexes, aged over 18 years with a clinical diagnosis of MP, regardless of race, social and economical status, profession or residential location.
We excluded participants for whom cyclobenzaprine was contraindicated with conditions such as: heart problems, glaucoma, hyperthyroidism, and those who were pregnant or breastfeeding.

Types of interventions

Intervention group: cyclobenzaprine in any dose by any route.
Control group: placebo, no intervention, physiotherapy, or other control.

Types of outcome measures

Primary outcomes

Intensity, frequency and duration of pain crises recorded using validated visual analogue scales (VAS) or categorical scales (Huskisson 1983).

Secondary outcomes

- Sleep quality measured by the Pittsburg Sleep Quality Index (PSQI) (Buysse 1989; Melzack 1987).
- Adverse events, such as drowsiness, xerostomia (dryness of the mouth), pain and swelling after infiltration, lethargy, sinus tachycardia, agitation, hypertension and hypotension.
- Quality of life measured by OHIP (Slade 1994).

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Search methods for identification of studies

Electronic searches

There were no language restrictions. To identify studies we searched the Pain Palliative and Supportive Care Review Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library* 2009, Issue 1), PubMed (1966 to February 2009), EMBASE (1980 to February 2009), Literatura Latino-Americana e do Caribe em Ciências da Saúde - LILACS (1982 to February 2009), and the Scientific Electronic Library Online - Scielo (to February 2009) to identify RCTs and quasi-RCTs.

The search strategy was composed of terms for myofascial pain and cyclobenzaprine. As we searched with both subject headings and free text words, we expected to identify all studies of MP and cyclobenzaprine. The exhaustive list of synonyms for MP and cyclobenzaprine that we used can be seen in Appendix 2. Please see Appendix 3 for other bibliographic search strategies.

Searching other resources

Reference lists of the included studies were checked manually to identify any additional studies.

We contacted specialists in the field and authors of the included studies for information about unpublished data.

Data collection and analysis

Two review authors (FMGL, EJ) independently screened the studies identified by the literature search, extracted the data, assessed trial quality and analyzed the results. Other review authors were consulted when there was any disagreement or need for quality assessment of the process. If consensus was not reached, data from the studies in question were not included. The selection of titles and the methodological quality of the RCTs and quasi-RCTs were assessed by two review authors (FMGL, EJ), using the kappa test.

Quality assessment

The methodological quality of the included studies in this review were measured using the Cochrane criteria described in The Cochrane Handbook (Higgins 2006), since scales and checklists are not a reliable method to assess the validity of a primary study (Jüni 1999).

Selection bias

The following questions were asked of each study identified.

1. Was the allocation sequence adequately generated?
   i) Yes: adequate generation of allocation.
   ii) Unclear: not described, evaluator's blinding not reported, and not possible to obtain details from the authors of the primary study.
   iii) No: inadequate generation of allocation (i.e. alternate, sequential, by birth date, etc.)
2. Was allocation adequately concealed?
   i) Yes: adequate concealment of allocation.
   ii) Unclear: method of allocation concealment not described, and not possible to obtain details through contact with the authors of the primary study.
   iii) No: inadequate allocation concealment, or allocation concealment not used.

Detection bias

1. Was there a blinded assessment of outcomes?
   i) Yes: assessors unaware of the assigned treatment when collecting outcome measures.
   ii) Unclear: blinding of assessor not reported and could not be verified by contacting investigators.
   iii) No: assessors aware of the assigned treatment when collecting outcome measures.

Attrition bias

1. Were withdrawals described?
   i) Yes: less than or equal to 20% for both groups.
   ii) Unclear: not reported in paper or by authors.
   iii) No: greater than or equal to 20% for both comparison groups.

Data extraction

Two review authors (FMGL, EJ) extracted data independently. There were no discrepancies between data extractors. A standard data extraction form was used to extract the following information: characteristics of the study (design, methods of randomization); participants; interventions; outcomes (types of outcome measures, timing of outcomes pain scores - VAS, total pain scale etc, adverse events). The form was based on the recommendations made by the Pain, Palliative and Supportive Care Review Group and was used as a first step in the process of data extraction.

Data analysis

For dichotomous data, we had planned to use relative risk (RR) as the effect measure, but did not find dichotomous outcomes in the included studies. For continuous data, we used mean difference (MD).

When we found standard error of meaning (SEM) we changed it to Standard Deviation (SD), as appropriate.

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We had planned to use intention-to-treat (ITT) analysis in instances where primary studies reported their findings as dichotomous data. Participants who dropped out of trials would be assumed to be non-responders (Unnebrink 2001). ITT analysis will be used in future versions of this systematic review, where appropriate.

Heterogeneity

Inconsistency among the pooled estimates was quantified using the I^2 statistic (Higgins 2003; Higgins 2006). We used a fixed-effect model in the absence of significant heterogeneity and a random-effects model if heterogeneity were found (DerSimonian 1986).

Subgroup analysis

Subgroup by type of intervention, dosage, follow-up period, age and sex were planned. Subgroup analysis will be used in future versions of this systematic review, where appropriate.

Sensitivity analysis

If there were an adequate number of studies, a sensitivity analysis would be performed to explore causes of heterogeneity and the robustness of the results. Sensitivity analyses would evaluate the following: quality of allocation concealment (adequate, or unclear, or inadequate); method of double-blinding (adequate, or unclear, or inadequate, or not performed); rates of withdrawal for each outcome; repeating the analysis excluding unpublished studies; and different study design (parallel versus cross-over). In future versions of this systematic review, sensitivity analysis will be performed if we have an adequate number of studies.

RESULTS

Description of studies

See: Characteristics of included studies.

See 'Characteristics of included studies' table for full details of the studies included.

The search strategy identified two studies, with a total of 79 participants with MP, that were suitable for inclusion. Both studies used different diagnostic criteria. Furtado 2002 used the diagnostic criteria defined by Simons 2005 and Travell 1952, whilst Herman 2002 used those from the RDC/TMD (Dworkin 1992).

Herman 2002 included 41 participants (33 female and eight male; mean age of 27 years) with MP as defined for axis I group 1 of the RDC/TMD. One group (15 participants) received 10 mg of oral cyclobenzaprine daily, the second group (13 participants) received 0.5 mg of oral clonazepam daily, while the third group (15 participants) received placebo (lactose filler). Jaw pain intensity, sleep quality and side effects were assessed at baseline and after three weeks. While jaw pain intensity and sleep quality were measured by mean difference (endpoint and change from baseline), side effects were reported by number of participants presenting with adverse events, irrespective of type.

Furtado 2002 included 38 participants (35 female and three male; mean age of 35 years) with trapezius myofascial syndrome (shoulder pain). One group (20 participants) received 10 mg of oral cyclobenzaprine for 15 days, while the other group (18 participants) received infiltration (injection) of lidocaine (xylocaine) 1% (a local anesthetic) in a maximum of six trigger-points in the trapezius (a shoulder muscle) in a single session. Global pain, pain at digital compression and side effects were assessed at baseline, seven, 15 and 30 days after start of treatment. While global pain and pain at digital compression were measured by mean difference (endpoint) between comparison groups, side effects were reported by number of participants presenting with adverse events, irrespective of type.

Risk of bias in included studies

Both studies included in the review were described as randomized. Allocation concealment was adequate, and the methods of allocation concealment were described. Herman 2002 generated randomization by means of a randomized block design, with the blocking-variable being the current use of psychotropic medication. Furtado 2002 generated randomization by means of a draw. Furtado 2002 could not withhold knowledge of the allocated interventions, as one group received infiltration and the other received tablets. Consequently, for this trial, performance bias was not considered, since the nature of the interventions was not compatible with this element of risk of bias. Both studies had no substantial dropouts/withdrawals in the sample as a whole, or substantial differences between comparison groups. Assessors were unaware of the assigned treatment when collecting outcome measures. The study reports were free of suggestion of selective outcome reporting, and were apparently free of features that could put them at a high risk of bias. For more details about each of the included studies, see the 'Characteristics of included studies' table.

Effects of interventions

1. Cyclobenzaprine *versus* clonazepam (Herman trial)

Mean for jaw pain intensity upon awakening (endpoint)

There was a statistically non-significant difference between comparison groups for the mean for jaw pain intensity upon awakening (measured at endpoint), that favored cyclobenzaprine, as shown by the MD -0.11 (95% CI, -0.26 to 0.04; P value 0.15).

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Mean for jaw pain intensity upon awakening (change from baseline)

The mean change from baseline between comparison groups for jaw pain intensity upon awakening was statistically significant, and favored cyclobenzaprine, as shown by MD -0.25 (95% CI, -0.41 to -0.09; P value 0.002).

Sleep quality (PSQI - endpoint)

There was a statistically non-significant difference between comparison groups for sleep quality (measured by the PSQ Index at endpoint), that favored clonazepam, as shown by MD 0.84 (95% CI, -1.35 to 3.03; P value 0.45).

Sleep quality (PSQI - change from baseline)

There was a statistically non-significant difference between comparison groups for the mean change from baseline for sleep quality (measured by the PSQ index), that favored cyclobenzaprine, as shown by MD -1.53 (95% CI, -3.50 to 0.44; P value 0.13).

Side effects (irrespective of type)

There was a statistically non-significant difference between the comparison groups for the number of participants who reported side effects, that favored cyclobenzaprine, as shown by RR 1.60 (95% CI, 0.71 to 3.60; P value 0.26).

Quality of life

Neither of the included studies included quality of life as an outcome.

2. Cyclobenzaprine *versus* placebo (Herman trial)

Mean for jaw pain intensity upon awakening (endpoint)

There was a statistically non-significant difference between comparison groups for mean jaw pain intensity upon awakening (measured at endpoint), that favored cyclobenzaprine, as shown by MD -0.13 (95% CI, -0.27 to 0.01; P value 0.07).

Mean for jaw pain intensity upon awakening (change from baseline)

The mean change from baseline between comparison groups for jaw pain intensity upon awakening was statistically significant, and favored cyclobenzaprine, as shown by MD -0.25 (95% CI, 0.41 to -0.09; P value 0.002).

Sleep quality (PSQI - endpoint)

There was a statistically non-significant difference between comparison groups for sleep quality (measured by the PSQ Index at endpoint), that favored cyclobenzaprine, as shown by MD -0.48 (95% CI, -2.27 to 1.31; P value 0.60).

Sleep quality (PSQI - change from baseline)

There was a statistically non-significant difference between comparison groups for the mean change from baseline for sleep quality (measured by the PSQ index), that favored cyclobenzaprine, as shown by MD -0.95 (95% CI, -2.89 to 0.99; P value 0.34).

Side effects (irrespective of type)

There was a statistically non-significant difference between the comparison groups for the number of participants who reported side effects, that favored placebo, as shown by RR 3.08 (95% CI, 1.02 to 9.24; P value 0.05).

Quality of life

Neither of the included studies reported this outcome.

3. Cyclobenzaprine versus lidocaine infiltration (Furtado trial)

Mean for global pain after seven days (T7)

There was a statistically non-significant difference between comparison groups for the mean for global pain (measured seven days after the intervention), that favored lidocaine infiltration, as shown by MD 0.90 (95% CI, -0.70 to 2.50; P value 0.27).

Mean for global pain after 15 days (T15)

There was a statistically non-significant difference between comparison groups for the mean for global pain (measured 15 days after the intervention), that favored lidocaine infiltration, as shown by MD 0.50 (95% CI, -0.84 to 1.84; P value 0.46).

Mean for global pain after 30 days (T30)

There was a statistically non-significant difference between comparison groups for the mean for global pain (measured 30 days after the intervention), that favored lidocaine infiltration, as shown by MD 0.90 (95% CI, -0.35 to 2.15; P value 0.16).

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Mean pain at digital compression after seven days (T7)

There was a statistically non-significant difference between comparison groups for the mean for pain at digital compression (measured seven days after the intervention), that favored lidocaine infiltration, as shown by MD 0.40 (95% CI, -1.06 to 1.86; P value 0.27).

Mean pain at digital compression after 15 days (T15)

There was a statistically non-significant difference between comparison groups for the mean for pain at digital compression (measured 15 days after the intervention), that favored cyclobenzaprine, as shown by MD -0.10 (95% CI, -1.38 to 1.18; P value 0.88).

Mean pain at digital compression after 30 days (T30)

There was a statistically non-significant difference between comparison groups for the mean for pain at digital compression (measured 30 days after the intervention), that favored lidocaine infiltration, as shown by MD 0.60 (95% CI, -0.55 to 1.75; P value 0.30).

Side effects (irrespective of type)

There was a statistically non-significant difference between comparison groups for side effects, that favored lidocaine infiltration, as shown by RR 1.39 (95% CI, 0.92 to 2.10; P value 0.12).

Quality of life

None of the included studies reported this outcome.

NNT and NNH measures

It was not possible to calculate either NNT (number-needed-to-treat-to-benefit) or NNH (number-needed-to-treat-to-harm), since neither of the primary studies used dichotomous data.

DISCUSSION

Despite the prevalence of MP, and the widespread use of cyclobenzaprine, searches for evidence revealed only two RCTs that evaluated the drug for MP. The internal and external validity of the evidence provided by these studies was limited by sample sizes that were too small to detect real differences between cyclobenzaprine, clonazepam and lidocaine infiltration in people with different profiles (age range, co-morbidities, etc). The other methodological limitation was that each trial reported outcomes in different ways. Moreover, both studies included in this review used different diagnostic criteria for MP.

Although nearly all the results from the studies included in this review were statistically non-significant, generally there was a slight improvement in the participants treated with cyclobenzaprine compared to clonazepam. Although comparison of cyclobenzaprine with lidocaine produced no statistically significant results, but generally favored lidocaine, it may, nonetheless, be sensible to use cyclobenzaprine as the therapeutic option, because of the invasive nature of lidocaine infiltration. Moreover, the small amount of evidence available showed cyclobenzaprine to be clinically and statistically similar to placebo and clonazepam with regard to safety data (e.g. morning drowsiness, dry mouth, nightmares, headache, pain and swelling), but it is important to state that neither cyclobenzaprine nor clonazepam are indicated primarily for use in sleep disturbances, where a higher dose may be required to be effective, as the dosages specified for the study were intended to combat pain.

Fair-quality studies corroborate the results of this review (Basmajian 1978; De Lee 1980; Katz 1988; Tofferi 2004; Turturro 2003). Thus, there is evidence that medications that help in muscle relaxation may be effective for treating the pain of myogenic origin, and also that medications that do not allow muscle relaxation, may not offer adequate pain relief (Basmajian 1978). For example, cyclobenzaprine has been shown to be highly effective and well tolerated for the relief of muscle spasm, when compared to placebo and other drugs in trials, for patients with traumatic strains of the neck and lower back (De Lee 1980; Katz 1988). Despite this, a short-term and well-conducted study (Turturro 2003), found no difference in pain relief provided by a combination of cyclobenzaprine and ibuprofen versus ibuprofen and placebo, although this study confirmed the higher prevalence of side effects in patients receiving cyclobenzaprine. In another trial, patients with chronic musculoskeletal pain who were treated with cyclobenzaprine, reported overall improvement and moderate reductions in individual symptoms, particularly with regard to sleep (Tofferi 2004).

In agreement with the studies included in this review and previous studies, we would like to highlight the importance of a home-care regimen and patient education (cognitive-behaviour therapies) as another option to manage patients with MP (Al-Ani 2005; Herman 2002).

Future studies should elect cut-off points for participants involved to assume that a patient has or has not achieved a clinically relevant reduction of pain (primary outcome). In this way, their results can be more easily combined in future versions of this review as it will be easier to calculate sample sizes. Moreover, we would recommend that the authors of future trials compare cyclobenzaprine with other available treatment options, on its own or in combination with them (e.g. patient education, ibuprofen, clonazepam, etc).

AUTHORS' CONCLUSIONS

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Implications for practice

The limited available evidence, involving a total of 79 participants in two studies, suggests that cyclobenzaprine is similar to clonazepam and placebo for effectiveness and safety. Lidocaine infiltration showed mild superiority (not statistically significant) when compared to cyclobenzaprine, although it was associated with a higher - but not significant - number of adverse effects (pain and swelling). It is probable that the invasive characteristics of the infiltration procedure would encourage the use of cyclobenzaprine. In these circumstances, there is insufficient evidence either to support or refute the use of cyclobenzaprine for the treatment of MP.

Implications for research

The two included studies provided positive, but weak, evidence for using cyclobenzaprine to treat MP. Some methodologic flaws influenced validity and reproducibility of the conclusion. In addition, different diagnostic criteria were used in the included clinical studies. Therefore, more RCTs, especially multicenter trials with sufficient sample sizes, and more than one diagnostic criterion (in order to increase the external validity of their findings (applicability)) should be performed. Moreover, the diversity of ways of reporting estimate effects should be standardized by using clinically relevant and objective outcome variables, including quality of life. These are needed to establish cyclobenzaprine's true therapeutic effects, and, if that is shown, further studies would be required to establish the best dose and type of use of the drug.

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REFERENCES

References to studies included in this review

Furtado 2002 ***{published data only}***

Furtado RNV, Carazzato S, Farias CA, Chamlian TR, Masiero D. Myofascial syndrome: comparison between infiltration of trigger points treatment and oral medication (cyclobenzaprine) [Síndrome miofascial: comparação entre o tratamento com infiltração de trigger points e medicação oral (ciclobenzaprina)]. *Acta Fisiátrica* 2002;**9**(3):117–26. [Biblioteca Central: BR734.1]

Herman 2002 ***{published data only}***

Herman CR, Schiffman EL, Look JO. The effectiveness of adding pharmacologic treatment with clonazepam or cyclobenzaprine to patient education and self-care for the treatment of jaw pain upon awakening: A randomized clinical trial. *Journal of Orofacial Pain* 2002 Winter;**16**(1): 64–70. [PUBMED: 11889661]

Additional references

Al-Ani 2005

Al-Ani Z, Gray RJ, Davies SJ, Sloan P, Glenny AM. Stabilization splint therapy for the treatment of temporomandibular myofascial pain: a systematic review. *Journal of Dental Education* 2005;**69**(11):1242–50. [MEDLINE: 16275687]

Basmajian 1978

Basmajian JV. Cyclobenzaprine hydrochloride effect on skeletal muscle spasm in the lumbar region and neck: Two double-blind controlled clinical and laboratory studies. *Archives of Physical Medicine and Rehabilitation* 1978;**59**: 58–63.

Buysse 1989

Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Research* 1989 May;**28**(2):V. [MEDLINE: 2748771]

De Lee 1980

De Lee JC, Rockwood CA. Skeletal muscle spasm and a review of muscle relaxants. *Current Therapeutic Research* 1980;**27**(1):64–74.

De Lucena 2006

De Lucena LB, Kosminsky M, da Costa LJ, de Goes PS. Validation of the Portuguese version of the RDC/TMD Axis II questionnaire. *Pesquisa Odontológica Brasileira - Brazilian Oral Research* 2006;**20**(4):312–7. [MEDLINE: 17242791]

DerSimonian 1986

DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;**4**(3):177–88.

Dworkin 1992

Dworkin SF, LeResche L. Research diagnostic criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique. *Journal of Craniomandibular Disorders: Facial & Oral Pain* 1992;**6**(4): 301–55. [MEDLINE: 1298767]

Fishbain 1986

Fishbain DA, Goldberg M, Meagher BR, Steele R, Rosomoff H. Male and female chronic pain patients categorized by

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DSM-III psychiatric diagnostic criteria. *Pain* 1986;**26**: 181–97.

Fricton 1985

Fricton JR, Kroening R, Haley D, Siegert R. Myofascial pain syndrome of the head and neck: A review of clinical characteristics of 164 patients. *Oral Surgery, Oral Medicine, and Oral Pathology* 1985;**60**:615–23.

Fricton 1989

Fricton JR, Schiffman EL. Research in temporomandibular disorders. *Northwest Dentistry* 1989;**68**(4):29–30. [MEDLINE: 2637428]

Gerwin 1995

Gerwin RDA. Study of 96 subjects examined both for fibromyalgia and myofascial pain. *Journal of Musculoskeletal Pain* 1995;**3 (suppl 1)**:121.

Graff-Radford 1984

Graff-Radford B. Myofascial trigger-points: their importance and diagnosis in dental office. *Journal of the Dental Association in South Africa* 1984;**39**:237–40.

Higgins 2003

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analysis. *British Medical Journal* 2003;**327**:555–7.

Higgins 2006

Higgins JPT, Green S, editors. Assessment of study quality. Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 [updated September 2006]; section 6. *The Cochrane Library*. Chichester, UK: John Wiley & Sons, Ltd, 2007.

Huskisson 1983

Huskisson EC. Visual analogue scale for global pain for the trapezius region. In: Melzack R editor(s). *Visual analogue scales*. New York: Reven Press, 1983:33–7.

Jüni 1999

Jüni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. *The Journal of the American Medical Association* 1999;**282**(11):1054–60.

Katz 1988

Katz WA, Dube J. Cyclobenzaprine in the treatment of acute muscle spasm: Review of a decade of clinical experience. *Clinical Therapeutics* 1988;**10**(2):216–28.

Kobayashi 1996

Kobayashi H, Hasegawa Y, Ono H. Cyclobenzaprine, a centrally acting muscle relaxant, acts on descending serotonergic systems. *European Journal of Pharmacology* 1996;**311**(1):29–35.

Koh 2003

Koh H, Robinson PG. Occlusal adjustment for treating and preventing temporomandibular joint disorders. *Cochrane Database of Systematic Reviews* 2003, Issue 1. [DOI: 10.1002/14651858.CD003812]

Lance 1964

Lance JW, Curran DA. Treatment of chronic tension headache. *Lancet* 1964;**42**:1236–9. [MEDLINE: 14152626]

Lance 1972

Lance JW, Anthony M. Cyclobenzaprine in the treatment of chronic tension headache. *The Medical Journal of Australia* 1972;**2**(25):1409–11. [MEDLINE: 5819771]

Laskin 1969

Laskin DM. Etiology of the pain-dysfunction syndrome. *Journal of the American Dental Association* 1969;**79**(1): 147–53. [MEDLINE: 5254545]

List 1996

List T, Dworkin SF. Comparing TMD diagnoses and clinical findings at Swedish and US TMD centers using research diagnostic criteria for temporomandibular disorders. *Journal of Orofacial Pain* 1996;**10**(3):240–53. [MEDLINE: 9161229]

List 1999

List T, Wahlund K, Wenneberg B, Dworkin SF. TMD in children and adolescents: prevalence of pain, gender differences, and perceived treatment need. *Journal of Orofacial Pain* 1999;**13**(1):9–20. [MEDLINE: 10425964]

Manfredini 2006

Manfredini D, Chiappe G, Bosco M. Research diagnostic criteria for temporomandibular disorders (RDC/TMD) axis I diagnoses in an Italian patient population. *Journal of Oral Rehabilitation* 2006;**33**(8):551–8. [MEDLINE: 16856952]

McMillan 1997

McMillan AS, Nolan A, Kelly PJ. The efficacy of dry needling and procaine in the treatment of myofascial pain in the jaw muscles. *Journal of Orofacial Pain* 1997;**11**(4): 307–14. [MEDLINE: 9656906]

Melzack 1987

Melzack R. The short-form McGill Pain Questionnaire. *Pain* 1987;**30**(2):191–7.

Okeson 1998

Okeson JP. *Orofacial Pain: Guidelines for assessment, diagnosis and management*. Quintessence Publishing Co Inc, 1998.

Okeson 2006

Okeson JP. *Bell's Orofacial Pain*. 6. São Paulo: Quintessence publishing Co, Inc, 2006.

Pertes 2005

Pertes RA, Gross SG. *Clinical management of temporomandibular disorders and orofacial pain*. Quintessence Publishing Co. Inc., 2005.

Reitinger 1996

Reitinger A, Radner H, Tilscher H. Morphologic study of trigger-points. *Manuelle Medizin* 1996;**34**:256–62.

Schiffman 1990

Schiffman EL, Fricton JR, Haley DP, Shapiro BL. The prevalence and treatment needs of subjects with temporomandibular disorders. *Journal of the American Dental Association* 1990;**120**:295–303.

Shi 2003

Shi Z, Guo C, Awad M. Hyaluronate for temporomandibular joint disorders. *Cochrane Database of Systematic Reviews*

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2003, Issue 1. [DOI: 10.1002/14651858.CD002970; MEDLINE: 12535445]

Simons 2005

Simons DG, Travell JG, Simons LS. *Travell & Simons Myofascial Pain and Dysfunction: The Trigger Point Manual*. 2. Vol. **1**, Sao Paulo: ArtMed, 2005.

Slade 1994

Slade GD, Spencer AJ. Development and evaluation of the Oral Health Impact Profile. *Community Dental Health* 1994;**11**(1):3–11.

Solberg 1986

Solberg WK. Temporomandibular disorders: masticatory myalgia and its management. *British Dental Journal* 1986; **160**(10):351–6. [MEDLINE: 3459485]

Tofferi 2004

Tofferi JK, Jackson JL, O'Malley PG. Treatment of fibromyalgia with cyclobenzaprine: A meta-analysis. *Arthritis and Rheumatism (Arthritis Care and Research)* 2004; **51**(1):9–13.

Travell 1952

Travell J, Rinzler SH. The myofascial genesis of pain. *Postgraduate Medicine* 1952;**11**(5):425–34. [MEDLINE: 15509460]

Travell 1983

Travell JG, Simons DG. *Myofascial pain and dysfunction: The trigger point manual.*. Baltimore: willians and Wilkins, 1983.

Turturro 2003

Turturro MA, Frater CR, D'Amico FJ. Cyclobenzaprine with ibuprofen versus ibuprofen alone in acute myofascial strain: A randomized double-blind clinical trial. *Annals of Emergency Medicine* 2003;**41**(6):818–26.

Unnebrink 2001

Unnebrink K, Windeler J. Intention-to-treat methods for dealing with missing values in clinical trials of progressively deteriorating diseases. *Statistics in Medicine* 2001;**20**(24): 3931–46.

Yap 2003

Yap AU, Dworkin SF, Chua EK, List T, Tan KB, Tan HH. Prevalence of temporomandibular disorder subtypes, psychologic distress, and psychosocial dysfunction in Asian patients. *Journal of Orofacial Pain* 2003;**17**(1):21–8. [MEDLINE: 12756927]

* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Furtado 2002

Methods	RCT. Randomization: by draw with concealment of allocation. Design: parallel. Blindness: observer blind. Duration: 30 days. Analysis: no ITT. Location: Brazil.
Participants	Diagnosis: trapezius myofascial syndrome according to Simons & Travell (Travell 1983) . Number of participants: 38. Gender: 35 female, 3 male. Mean age: 34.6 years. Setting: clinic of physical medicine and rehabilitation of Universidade Federal de São Paulo. Participants lived at home
Interventions	Group 1. Xylocaine (lidocaine): 1% infiltration in a maximum of 6 trigger-points in the trapezius in a single session (n = 18) Group 2. Cyclobenzaprine: 10 mg at night for 15 days (n = 20)
Outcomes	A. Global pain score (VAS). B. Pain at digital compression (VAS). C. Side effects: Group 1: xerostomia and drowsiness. Group 2: pain and swelling after infiltration
Notes	No dropouts or withdrawals.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The allocation sequence was generated adequately by draw.
Allocation concealment (selection bias)	Low risk	The allocation was concealed adequately.
Blinding (performance bias and detection bias) All outcomes	High risk	There was no way to prevent the participants from having knowledge of their allocated interventions, as Group 1 received infiltration and Group 2 received tablets
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data.

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Furtado 2002 (*Continued*)

Selective reporting (reporting bias)	Low risk	The reports of the study were free of suggestion of selective outcome reporting
Other bias	Low risk	It appears that the study was free of other problems that could put it at a high risk of bias
Attrition Bias	Low risk	There were no substantial dropouts/withdrawals in the sample as a whole, or substantial differences between comparison groups
Detection Bias	Low risk	Assessors were unaware of the assigned treatment when collecting data on outcome measures

Herman 2002

Methods	RCT. Randomization: by means of a randomized block design with the blocking variable being the current use of psychotropic medication Design: parallel. Blindness: double-blind. Duration: 3 weeks. Analysis: no ITT. Location: United States of America.	
Participants	Diagnosis: myofascial pain as defined for axis I group 1 of the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) Number of participants: 41. Gender: 33 female and 8 male. Mean age: 27.06 years. Setting: not reported. Participants lived at home.	
Interventions	Group 1. Clonazepam 0.5 mg daily (n = 13). Group 2. Placebo (lactose filler) (n = 15). Group 3. Cyclobenzaprine 10 mg (n = 13).	
Outcomes	A. Jaw-pain intensity. B. Sleep quality. C. Side effects.	
Notes	No dropouts or withdrawals.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

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Herman 2002 (*Continued*)

Random sequence generation (selection bias)	Low risk	Trial report stated: "Subjects were allocated to their treatment group by means of a randomised block design with the blocking variable being the current use of psychotropic medication" Comment: probably done.
Allocation concealment (selection bias)	Low risk	The allocation was concealed adequately by pharmacy-controlled randomization
Blinding (performance bias and detection bias) All outcomes	Low risk	Trial report stated: "The capsules were formulated to have the same appearance, ... Neither the treating doctor nor the subject was aware of the treatment assignment until completion of the intervention" Comment:the allocated interventions were adequately concealed during the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Low risk	The reports of the study were free of suggestion of selective outcome reporting
Other bias	Low risk	It appears that the study was free of other problems that could put it at a high risk of bias
Attrition Bias	Low risk	Trial report stated: "The final sample consisted of 33 women and 8 men with no subject dropouts or withdrawals" Comment: there were no substantial dropouts/withdrawals in the sample as a whole, or substantial differences between comparisons groups
Detection Bias	Low risk	Trial report stated: "The capsules were formulated to have the same appearance, ... Neither the treating doctor nor the subject was aware of the treatment assignment until completion of the intervention" Comment: assessors were unaware of the assigned treatment when collecting data on outcome measures

Abbreviations
VAS = visual analogue scale

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DATA AND ANALYSES

Comparison 1. Cyclobenzaprine versus clonazepam

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean for jaw pain intensity upon awakening (endpoint)	1	26	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.26, 0.04]
2 Mean for jaw pain intensity upon awakening (change from baseline)	1	26	Mean Difference (IV, Random, 95% CI)	-0.25 [-0.41, -0.09]
3 Sleep quality (PSQI - endpoint)	1	26	Mean Difference (IV, Random, 95% CI)	0.84 [-1.35, 3.03]
4 Sleep quality (PSQI - change from baseline)	1	26	Mean Difference (IV, Random, 95% CI)	-1.53 [-3.50, 0.44]
5 Side effects (irrespective of type)	1	26	Risk Ratio (M-H, Fixed, 95% CI)	1.6 [0.71, 3.60]

Comparison 2. Cyclobenzaprine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean for jaw pain intensity upon awakening (endpoint)	1	26	Mean Difference (IV, Random, 95% CI)	-0.13 [-0.27, 0.01]
2 Mean for jaw pain intensity upon awakening (change from baseline)	1	28	Mean Difference (IV, Random, 95% CI)	-0.25 [-0.41, -0.09]
3 Sleep quality (PSQI - endpoint)	1	28	Mean Difference (IV, Random, 95% CI)	-0.48 [-2.27, 1.31]
4 Sleep quality (PSQI - change from baseline)	1	28	Mean Difference (IV, Random, 95% CI)	-0.95 [-2.89, 0.99]
5 Side effects (irrespective of type)	1	28	Risk Ratio (M-H, Fixed, 95% CI)	3.08 [1.02, 9.24]

Comparison 3. Cyclobenzaprine versus lidocaine infiltration

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean for global pain - T7	1	38	Mean Difference (IV, Random, 95% CI)	0.90 [-0.70, 2.50]
2 Mean for global pain - T15	1	38	Mean Difference (IV, Random, 95% CI)	0.5 [-0.84, 1.84]
3 Mean for global pain - T30	1	38	Mean Difference (IV, Random, 95% CI)	0.90 [-0.35, 2.15]
4 Mean pain at digital compression - T7	1	38	Mean Difference (IV, Random, 95% CI)	0.40 [-1.06, 1.86]

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5 Mean pain at digital compression - T15	1	38	Mean Difference (IV, Random, 95% CI)	-0.10 [-1.38, 1.18]
6 Mean pain at digital compression - T30	1	38	Mean Difference (IV, Random, 95% CI)	0.60 [-0.55, 1.75]
7 Side effects (irrespective of type)	1	38	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.92, 2.10]

Analysis 1.1. Comparison 1 Cyclobenzaprine versus clonazepam, Outcome 1 Mean for jaw pain intensity upon awakening (endpoint).

Review: Cyclobenzaprine for the treatment of myofascial pain in adults

Comparison: 1 Cyclobenzaprine versus clonazepam

Outcome: 1 Mean for jaw pain intensity upon awakening (endpoint)

Study or subgroup	Cyclobenzaprine N	Mean(SD)	Clonazepan N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Herman 2002	13	0.17 (0.18)	13	0.28 (0.21)		100.0 %	-0.11 [-0.26, 0.04]
Total (95% CI)	**13**		**13**			**100.0 %**	**-0.11 [-0.26, 0.04]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.43 (P = 0.15)

Test for subgroup differences: Not applicable

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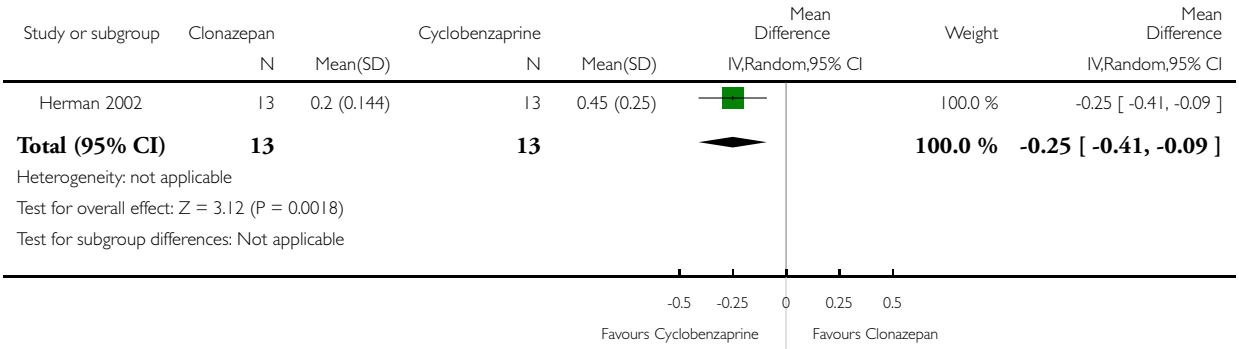
Analysis 1.2. Comparison 1 Cyclobenzaprine versus clonazepam, Outcome 2 Mean for jaw pain intensity upon awakening (change from baseline).

Review: Cyclobenzaprine for the treatment of myofascial pain in adults

Comparison: 1 Cyclobenzaprine versus clonazepam

Outcome: 2 Mean for jaw pain intensity upon awakening (change from baseline)

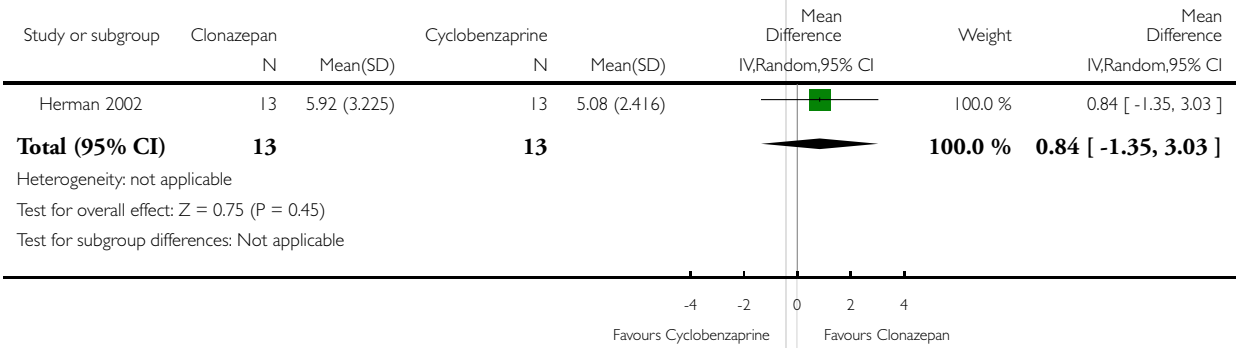


Analysis 1.3. Comparison 1 Cyclobenzaprine versus clonazepam, Outcome 3 Sleep quality (PSQI - endpoint).

Review: Cyclobenzaprine for the treatment of myofascial pain in adults

Comparison: 1 Cyclobenzaprine versus clonazepam

Outcome: 3 Sleep quality (PSQI - endpoint)



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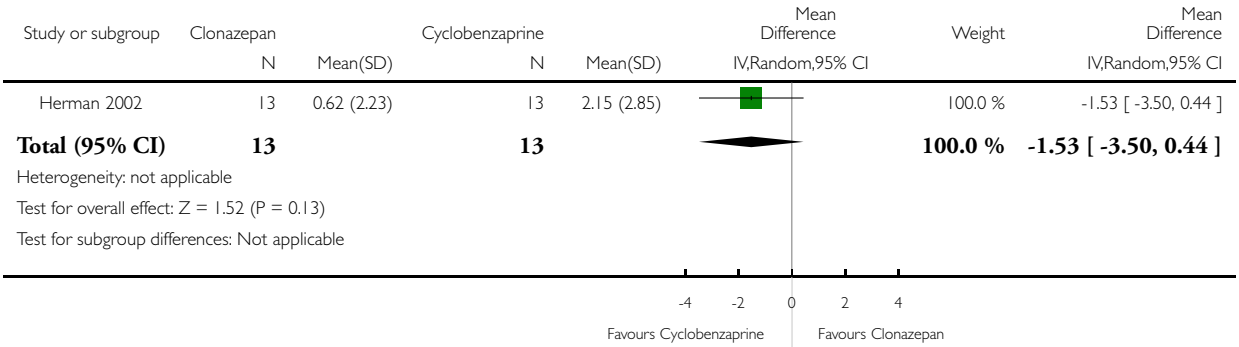
Analysis 1.4. Comparison 1 Cyclobenzaprine versus clonazepam, Outcome 4 Sleep quality (PSQI - change from baseline).

Review: Cyclobenzaprine for the treatment of myofascial pain in adults

Comparison: 1 Cyclobenzaprine versus clonazepam

Outcome: 4 Sleep quality (PSQI - change from baseline)

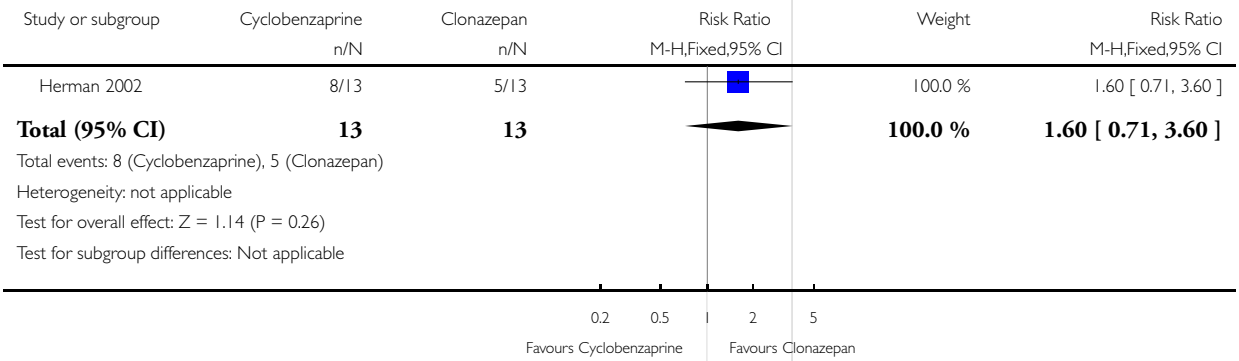


Analysis 1.5. Comparison 1 Cyclobenzaprine versus clonazepam, Outcome 5 Side effects (irrespective of type).

Review: Cyclobenzaprine for the treatment of myofascial pain in adults

Comparison: 1 Cyclobenzaprine versus clonazepam

Outcome: 5 Side effects (irrespective of type)



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Analysis 2.1. Comparison 2 Cyclobenzaprine versus placebo, Outcome 1 Mean for jaw pain intensity upon awakening (endpoint).

Review: Cyclobenzaprine for the treatment of myofascial pain in adults

Comparison: 2 Cyclobenzaprine versus placebo

Outcome: 1 Mean for jaw pain intensity upon awakening (endpoint)

Study or subgroup	Cyclobenzaprine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Herman 2002	13	0.17 (0.18)	13	0.3 (0.18)		100.0 %	-0.13 [-0.27, 0.01]
Total (95% CI)	**13**		**13**			**100.0 %**	**-0.13 [-0.27, 0.01]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.84 (P = 0.066)

Test for subgroup differences: Not applicable

Analysis 2.2. Comparison 2 Cyclobenzaprine versus placebo, Outcome 2 Mean for jaw pain intensity upon awakening (change from baseline).

Review: Cyclobenzaprine for the treatment of myofascial pain in adults

Comparison: 2 Cyclobenzaprine versus placebo

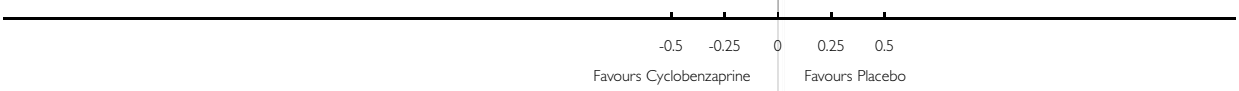
Outcome: 2 Mean for jaw pain intensity upon awakening (change from baseline)

Study or subgroup	Placebo N	Mean(SD)	Cyclobenzaprine N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Herman 2002	15	0.2 (0.15)	13	0.45 (0.25)		100.0 %	-0.25 [-0.41, -0.09]
Total (95% CI)	**15**		**13**			**100.0 %**	**-0.25 [-0.41, -0.09]**

Heterogeneity: not applicable

Test for overall effect: Z = 3.15 (P = 0.0016)

Test for subgroup differences: Not applicable



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Analysis 2.3. Comparison 2 Cyclobenzaprine versus placebo, Outcome 3 Sleep quality (PSQI - endpoint).

Review: Cyclobenzaprine for the treatment of myofascial pain in adults

Comparison: 2 Cyclobenzaprine versus placebo

Outcome: 3 Sleep quality (PSQI - endpoint)

Study or subgroup	Placebo N	Mean(SD)	Cyclobenzaprine N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Herman 2002	15	4.6 (2.401)	13	5.08 (2.416)		100.0 %	-0.48 [-2.27, 1.31]
Total (95% CI)	**15**		**13**			**100.0 %**	**-0.48 [-2.27, 1.31]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.53 (P = 0.60)

Test for subgroup differences: Not applicable

Analysis 2.4. Comparison 2 Cyclobenzaprine versus placebo, Outcome 4 Sleep quality (PSQI - change from baseline).

Review: Cyclobenzaprine for the treatment of myofascial pain in adults

Comparison: 2 Cyclobenzaprine versus placebo

Outcome: 4 Sleep quality (PSQI - change from baseline)

Study or subgroup	Placebo N	Mean(SD)	Cyclobenzaprine N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Herman 2002	15	1.2 (2.32)	13	2.15 (2.85)		100.0 %	-0.95 [-2.89, 0.99]
Total (95% CI)	**15**		**13**			**100.0 %**	**-0.95 [-2.89, 0.99]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.96 (P = 0.34)

Test for subgroup differences: Not applicable

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Analysis 2.5. Comparison 2 Cyclobenzaprine versus placebo, Outcome 5 Side effects (irrespective of type).

Review: Cyclobenzaprine for the treatment of myofascial pain in adults

Comparison: 2 Cyclobenzaprine versus placebo

Outcome: 5 Side effects (irrespective of type)

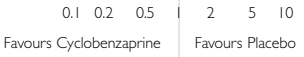
Study or subgroup	Cyclobenzaprine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Herman 2002	8/13	3/15		100.0 %	3.08 [1.02, 9.24]
Total (95% CI)	**13**	**15**		**100.0 %**	**3.08 [1.02, 9.24]**

Total events: 8 (Cyclobenzaprine), 3 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 2.00 (P = 0.045)

Test for subgroup differences: Not applicable



Analysis 3.1. Comparison 3 Cyclobenzaprine versus lidocaine infiltration, Outcome 1 Mean for global pain - T7.

Review: Cyclobenzaprine for the treatment of myofascial pain in adults

Comparison: 3 Cyclobenzaprine versus lidocaine infiltration

Outcome: 1 Mean for global pain - T7

Study or subgroup	Cyclobenzaprine N	Mean(SD)	Infiltration N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Furtado 2002	20	3.7 (2)	18	2.8 (2.9)		100.0 %	0.90 [-0.70, 2.50]
Total (95% CI)	**20**		**18**			**100.0 %**	**0.90 [-0.70, 2.50]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.10 (P = 0.27)

Test for subgroup differences: Not applicable

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Analysis 3.2. Comparison 3 Cyclobenzaprine versus lidocaine infiltration, Outcome 2 Mean for global pain - T15.

Review: Cyclobenzaprine for the treatment of myofascial pain in adults

Comparison: 3 Cyclobenzaprine versus lidocaine infiltration

Outcome: 2 Mean for global pain - T15

Study or subgroup	Cyclobenzaprine N	Mean(SD)	Infiltration N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Furtado 2002	20	2.7 (2.1)	18	2.2 (2.1)		100.0 %	0.50 [-0.84, 1.84]
Total (95% CI)	**20**		**18**			**100.0 %**	**0.50 [-0.84, 1.84]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.73 (P = 0.46)

Test for subgroup differences: Not applicable

Analysis 3.3. Comparison 3 Cyclobenzaprine versus lidocaine infiltration, Outcome 3 Mean for global pain - T30.

Review: Cyclobenzaprine for the treatment of myofascial pain in adults

Comparison: 3 Cyclobenzaprine versus lidocaine infiltration

Outcome: 3 Mean for global pain - T30

Study or subgroup	Cyclobenzaprine N	Mean(SD)	Infiltration N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Furtado 2002	20	2.6 (1.8)	18	1.7 (2.1)		100.0 %	0.90 [-0.35, 2.15]
Total (95% CI)	**20**		**18**			**100.0 %**	**0.90 [-0.35, 2.15]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.41 (P = 0.16)

Test for subgroup differences: Not applicable

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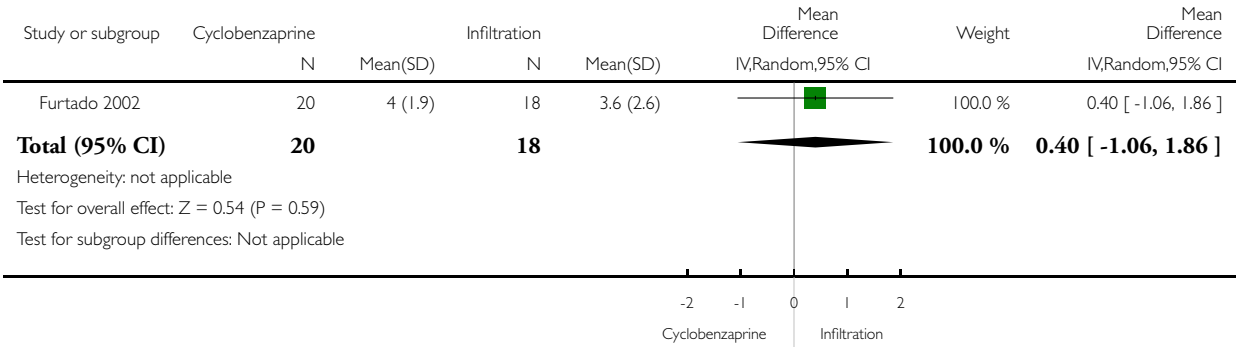
Analysis 3.4. Comparison 3 Cyclobenzaprine versus lidocaine infiltration, Outcome 4 Mean pain at digital compression - T7.

Review: Cyclobenzaprine for the treatment of myofascial pain in adults

Comparison: 3 Cyclobenzaprine versus lidocaine infiltration

Outcome: 4 Mean pain at digital compression - T7

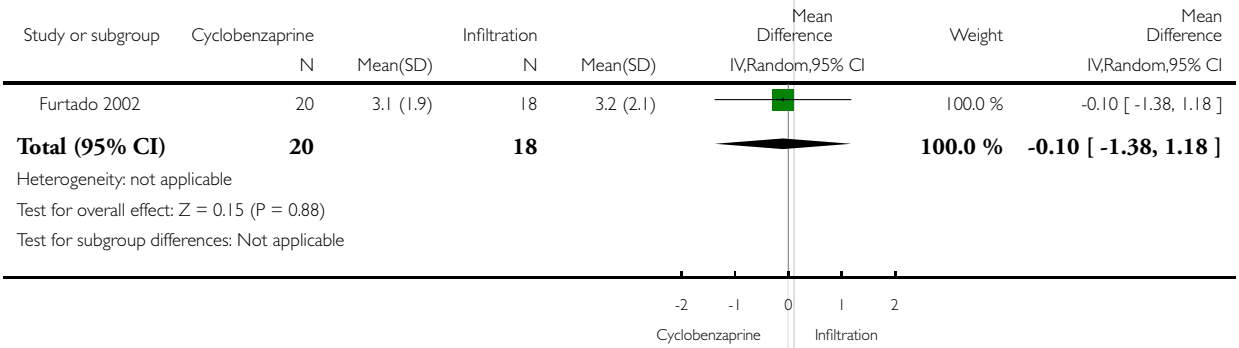


Analysis 3.5. Comparison 3 Cyclobenzaprine versus lidocaine infiltration, Outcome 5 Mean pain at digital compression - T15.

Review: Cyclobenzaprine for the treatment of myofascial pain in adults

Comparison: 3 Cyclobenzaprine versus lidocaine infiltration

Outcome: 5 Mean pain at digital compression - T15



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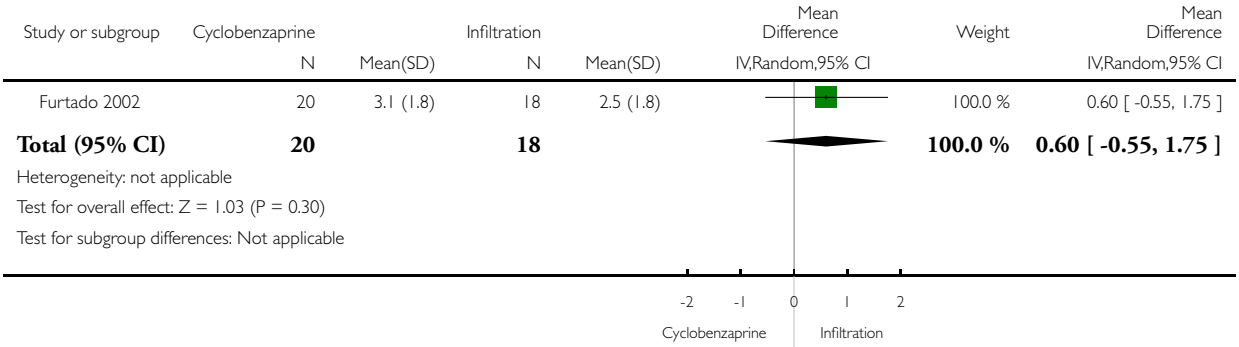
Analysis 3.6. Comparison 3 Cyclobenzaprine versus lidocaine infiltration, Outcome 6 Mean pain at digital compression - T30.

Review: Cyclobenzaprine for the treatment of myofascial pain in adults

Comparison: 3 Cyclobenzaprine versus lidocaine infiltration

Outcome: 6 Mean pain at digital compression - T30

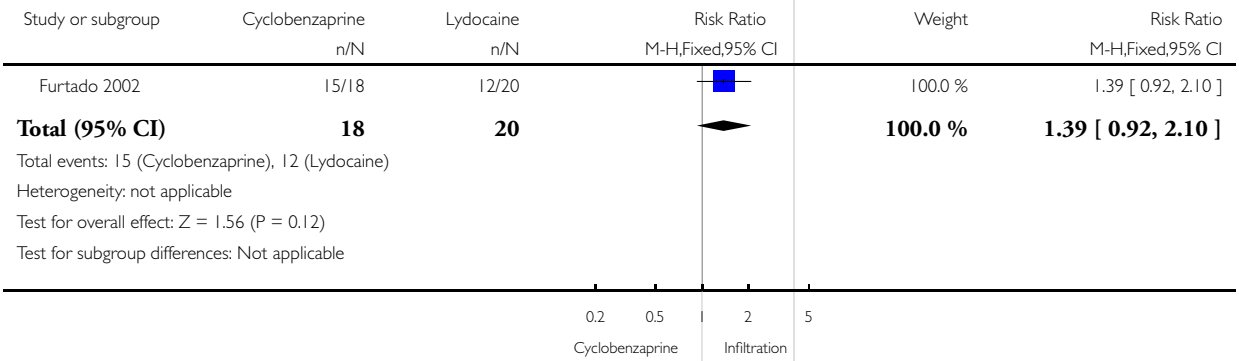


Analysis 3.7. Comparison 3 Cyclobenzaprine versus lidocaine infiltration, Outcome 7 Side effects (irrespective of type).

Review: Cyclobenzaprine for the treatment of myofascial pain in adults

Comparison: 3 Cyclobenzaprine versus lidocaine infiltration

Outcome: 7 Side effects (irrespective of type)



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APPENDICES

Appendix 1. Answer by Author of Furtado 2002

De:	"Rita Furtado"
Para:	"FREDERICO MOTA"
Assunto:	RE: Revisão Ciclobenzaprina
Data:	Wed, 27 Feb 2008 01:59:18 +0000

Olá Frederico, a minha gestação está nas últimas 4 semanas e estou pela "bola sete", louca para que acabe logo, risos... Quanto á randomização, foi feita por sorteio com sigilo de alocação. Foram colocados 40 papéis (metade ciclo, metade infiltração) em uma grande caixa e esses papéis iam sendo retirados conforme os pacientes iam sendo captados. Não foi realizada através de tábua de randomização. Um abraço, Rita.

Translation:

Dear Frederico,

My pregnancy is in the last 4 weeks. As regards to the randomization, it was done by draw with concealment of allocation. There were 40 papers (half with infiltration, half with cyclobenzaprine) in a big box and these papers were taken as the patients were captured. There was not performed board of randomization. Yours, Rita

De:	"FREDERICO MOTA"
Para:	"Rita Furtado"
Assunto:	RE: Revisão Ciclobenzaprina
Data:	Mon, 25 Feb 2008 23:57:37 -0300

Prezada Rita,
Tudo bem?
E o neném? Já está crescendo né?
Estou incluindo os dados de seu estudo em minha revisão sistemática, porém, preciso saber como foi feita a randomização para a criação dos dois grupos. Seria possível vc me informar?
Aguardo seu contato.
Devo precisar de outras informações mas somente no decorrer do trabalho.
Grande abraço e mais uma vez obrigado.
Frederico

Translation:

Dear Rita,
How is everything?
I am including the data of your study in my systematic review, but, I need to know how was the randomization done for the creation of the two groups.
I should probably need further information during the work.
With kind regards,
Frederico

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Appendix 2. Basic search strategy

((Myofascial Pain Syndromes) OR (Myofascial Pain Syndrome) OR (Myofascial Trigger PointS) OR (Myofascial Trigger Point)) AND (cyclobenzaprine OR (cyclobenzaprine hydrochloride) OR Flexeril OR Lisseril OR Dibenzocycloheptenes OR Propylamines OR (Tricyclic Antidepressive Agents) OR (Central Muscle Relaxants) OR (Tranquilizing Agents) OR Miosan OR Mirtax OR Fexmid OR Flexeril OR Flexiban OR Flexitec OR Gen-Cyclobenzaprine OR Masterelax OR Medarex OR Med Cyclobenzaprine OR Miosan OR Mirtax OR Nostaden OR Novo-Cycloprine OR Amrix OR Apo-Cyclobenzaprine OR Ciclamil OR Ratio-Cyclobenzaprine OR Reflexan OR Relexil OR Riva-Cycloprine OR Tensamox OR Tensiomax OR Tensodox OR Tonalgen OR Yuredol OR Yurelax)

Appendix 3. Search strategy for other databases

PUBMED	EMBASE	LILACS	CENTRAL
#1 MYOFASCIAL PAIN SYNDROMES [MeSH] #2 ("myofascial pain") #3 (myofascial AND ("trigger point" or trigger-point*)) #4 #1 or #2 or #3 #5 (cyclobenzaprine OR "cyclobenzaprine hydrochloride" OR Aripiprazole OR "Dorixina relax" OR Flexeril OR Lisseril OR Miosan OR Mirtax OR Fexmid OR Flexeril OR Flexiban OR Flexitec OR Gen-Cyclobenzaprine OR Masterelax OR Medarex OR Med Cyclobenzaprine OR Miosan OR Mirtax OR Nostaden OR Novo-Cycloprine OR Amrix OR Apo-Cyclobenzaprine OR Ciclamil OR Ratio-Cyclobenzaprine OR Reflexan OR Relexil OR Riva-Cycloprine OR Tensamon OR Tensamox OR Tensiomax OR Tensodox OR Tonalgen OR Yuredol OR Yurelax OR Ziclob)) #6 #4 AND #5	1. MYOFASCIAL PAIN SYNDROME [EMTREE term] 2. ("myofascial pain") 3. (myofascial AND ("trigger point$" or trigger-point$)) 4.OR/1-3 5. (cyclobenzaprine OR "cyclobenzaprine hydrochloride" OR Aripiprazole OR "Dorixina relax" OR Flexeril OR Lisseril OR Dibenzocycloheptenes OR Miosan OR Mirtax OR Fexmid OR Flexeril OR Flexiban OR Flexitec OR Gen-Cyclobenzaprine OR Masterelax OR Medarex OR Med Cyclobenzaprine OR Miosan OR Mirtax OR Nostaden OR Novo-Cycloprine OR Amrix OR Apo-Cyclobenzaprine OR Ciclamil OR Ratio-Cyclobenzaprine OR Reflexan OR Relexil OR Riva-Cycloprine OR Tensamon OR Tensamox OR Tensiomax OR Tensodox OR Tonalgen OR Yuredol OR Yurelax OR Ziclob) 6. 4 AND 5	(Mh random allocation) OR (Mh double blind method) OR (Mh single blind method) AND NOT (Ct animal) AND NOT (Ct human and Ct animal) OR (Pt clinical trial) OR (Ex E05.318.760.535$) OR (Tw clin$) AND (Tw trial$) OR (Tw ensa$) OR (Tw estud$) OR (Tw experim$) OR (Tw investiga$) OR (Tw singl$) OR (Tw simple$) OR (Tw doubl$) OR (Tw doble$) OR (Tw duplo$) OR (Tw trebl$) OR (Tw trip$) AND (Tw blind$) OR (Tw cego$) OR (Tw ciego$) OR (Tw mask$) OR (Tw mascar$) OR (Mh placebos) OR (Tw placebo$) OR (Tw random$) OR (Tw randon$) OR (Tw casual$) OR (Tw acaso$) OR (Tw azar) OR (Tw aleator$) OR (Mh research design) AND NOT (Ct animal) AND NOT (Ct human and Ct animal) OR (Ct comparative study) OR (Ex E05.337$) OR (Mh follow-up studies) OR (Mh prospective studies) OR (Tw control$) OR (Tw prospectiv$) OR (Tw volunt$) OR (Tw volunteer$) AND NOT ((Ct animal) AND NOT (Ct human and Ct animal))	#1 Exp MYOFASCIAL PAIN SYNDROMES #2 ("myofascial pain") #3 (myofascial AND ("trigger point" or trigger-point*)) #4 #1 or #2 or #3 #5 (cyclobenzaprine OR "cyclobenzaprine hydrochloride" OR Aripiprazole OR "Dorixina relax" OR Flexeril OR Lisseril OR Dibenzocycloheptenes OR Miosan OR Mirtax OR Fexmid OR Flexeril OR Flexiban OR Flexitec OR Gen-Cyclobenzaprine OR Masterelax OR Medarex OR Med Cyclobenzaprine OR Miosan OR Mirtax OR Nostaden OR Novo-Cycloprine OR Amrix OR Apo-Cyclobenzaprine OR Ciclamil OR Ratio-Cyclobenzaprine OR Reflexan OR Relexil OR Riva-Cycloprine OR Tensamon OR Tensamox OR Tensiomax OR Tensodox OR Tonalgen OR Yuredol OR Yurelax OR Ziclob) #6 #4 AND #5

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WHAT'S NEW

Last assessed as up-to-date: 19 February 2009.

Date	Event	Description
18 April 2012	Amended	The plain language summary in this review was corrected and the risk of bias tables were brought up to date for this amendment

HISTORY

Protocol first published: Issue 4, 2007

Review first published: Issue 3, 2009

Date	Event	Description
8 February 2011	Amended	Contact details updated.
9 November 2009	Amended	Contact details updated.
12 August 2009	Amended	Contact details updated.
14 March 2008	Amended	Converted to new review format.
12 February 2008	Amended	The protocol has been updated in order to broaden the scope. The use of cyclobenzaprine for the treatment of myofascial pain in temporomandibular disorders will now be analyzed as a subgroup

CONTRIBUTIONS OF AUTHORS

Conceived the review: Frederico Mota Gonçalves Leite (FMGL)

Co-ordinating the review: Álvaro Nagib Atallah (ANA)

Undertaking manual searches and screening results: FMGL and Édina da Silva (EK)

Organising retrieval of studies: FMGL and EK

Screening retrieved studies: FMGL and EK

Appraising quality of studies: FMGL and EK

Abstracting data from studies: FMGL, EJ and Regina El Dib (RED)

Writing to authors of studies for additional information: FMGL

Providing additional data about studies: FMGL, EJ and Eduardo Grossmann (EG)

Obtaining and screening data on unpublished studies: FMGL, RED, EK

Data management for the review: FMGL

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Entering data into Review Manager (RevMan 5): FMGL

RevMan statistical data: FMGL, Régis Andriolo (RA), RED

Other statistical analysis not using RevMan: FMGL, RA and RED

Double entry of data: (data entered by one person: FMGL; data entered by second person: EK)

Interpretation of data: FMGL, EK, RA and RED

Statistical analysis: FMGL, RED and ANA

Writing the review: FMGL

Performing previous research that was the foundation of the present review: FMGL

Guarantor for the review: FMGL

Responsible for reading and checking review before submission: FMGL, ANA, EK, RA, EJ and RED

Responsible for updating: FMGL, RA, RED

DECLARATIONS OF INTEREST

None known

INDEX TERMS

Medical Subject Headings (MeSH)

Amitriptyline [*analogs & derivatives; therapeutic use]; Anesthetics, Local [therapeutic use]; Clonazepam [therapeutic use]; Fascia; Lidocaine [therapeutic use]; Muscle Relaxants, Central [*therapeutic use]; Muscular Diseases [*drug therapy]; Pain [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans

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