Clinics in Surgery

Research Article
Published: 10 Aug, 2021

Cyclobenzaprine as a Medication to Manage Pain and Improve Sleep Quality in Patients with Myofascial Pain: A Systematic Review and Meta-Analysis

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Abstract

Purposes: To assess the efficacy of cyclobenzaprine in the management of pain intensity and sleep quality in patients diagnosed with orofacial myofascial pain.

Methods: PubMed, Scopus, Web of Science, the Cochrane Library, LILACS, BBO and Embase was searched based on the guidelines for each database, and it was updated until July 2021. Randomized clinical trials, cohort studies, and case-control studies evaluating the use of cyclobenzaprine in the management of myofascial pain were included, with a minimal follow up of three weeks. Two authors carried out data extraction from the studies, and the risk of bias was assessed according to the Cochrane Collaboration's tool for assessing the risk of bias in randomized clinical trials.

Results: One hundred and seventy two studies were identified, whereby only three studies met the inclusion criteria. After a sensitive analysis, two studies comprising 86 participants were selected for the meta-analysis. The primary outcome was the change in pain intensity between initial and final measurements, which was significantly higher for the cyclobenzaprine group (95% CI, 0.027 to 0.283). A secondary outcome was the change in sleep quality between pre- and post-treatment that showed higher statistical significance for the cyclobenzaprine group (95% CI, 0.618 to 2.05). The risk of bias was considered low for five of six domains. Blinding in the management phase was considered unclear, and the small number of participants generated imprecision.

Conclusion: Evidence supports the effectiveness of cyclobenzaprine in the management of myofascial pain in short-terms, resulting in an improvement in pain and sleep quality.

Keywords: Cyclobenzaprine; Facial pain; Myofascial pain syndromes; Meta-analysis

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Received Date: *14 Jul 2021*

Accepted Date: *27 Jul 2021*

Published Date: *10 Aug 2021*

Citation:

Uemoto L, Ramos do Nascimento R, Masterson D, Trindade Mattos C, de Alencar FGP, de Vasconcellos Vilella O. Cyclobenzaprine as a Medication to Manage Pain and Improve Sleep Quality in Patients with Myofascial Pain: A Systematic Review and Meta-Analysis. Clin Surg. 2021; 6: 3279.

Introduction

Rationale

Myofascial Pain (MFP) is a regional disorder, well-characterized by the presence of hypersensitive points or trigger points localized in a taut band of muscles [1]. According to the Diagnostic Criteria for Temporomandibular Disorder (DC/TMD), myofascial pain might be classified as with or without referral. In both of them pain is present during muscle palpation, but in myofascial pain without referral there is spreading (but not referred) pain with muscle palpation. In myofascial pain with referral, on the other hand, there is pain referred to distant locations, such as teeth, head and orofacial regions [2]. When these trigger points arise in the head and neck region, MFP can be classified as a subtype of Temporomandibular Disorder (TMD). Patients with MFP often experience psychological disturbances, such as anxiety, depression, and poor sleep quality [3-6]. Several modalities of therapy have been compared in the treatment of MFP, such as trigger point injections [7-9], dry and wet needling [8], ischemic compression [10], myofascial manipulation, laser therapy, transcutaneous electrical nerve stimulation, acupuncture and magnet therapy [11]. Additionally, several medications, such as antidepressants [12,13], muscle relaxants [14,15], analgesic, and anti-inflammatory agents [16], have been tested for MFP. When MFP is associated with migraine and poor sleep, specific medication for those conditions has been used [17-21].

Cyclobenzaprine was synthesized in 1960, and it was initially being utilized as an antidepressant

drug due to its structural and pharmacological similarity to amitriptyline. At that time, it showed relatively mild antidepressant activity compared with other concurrent drugs [22,23]. Cyclobenzaprine acts as increasing brainstem norepinephrine-mediated inhibition of ventral motor neurons of the spinal cord [24]. The usual dose is 20 mg to 40 mg, administered two to four times daily in the short-term to treat muscle spasms with acute pain and musculoskeletal etiology, such as lower-back pain, torticollis, fibromyalgia, scapulohumeral periarthritis, and cervicobrachialgia. Some studies have investigated the effect of cyclobenzaprine in the treatment of chronic pain using a single dose of 10 mg before bed as a preventive medication [7,18,19], aiming to improve sleep quality and reduce the central sensitization of pain [18]. However, an important aspect to highlight is related to side effects confirmed by works assessing the use of cyclobenzaprine in patients with acute MFP [18,19,24], such as dry mouth, fatigue, drowsiness, and nausea.

Objectives

Aiming to investigate the effectiveness of cyclobenzaprine in the management of MFP, the present systematic review aimed to assemble scientific evidence related to the efficacy of cyclobenzaprine in reducing acute pain in MFP and improving sleep quality, updating the already published systematic review [25].

Material and Methods

Protocol

The methods of analysis and the inclusion criteria for the present study were previously specified and documented in a protocol in the PROSPERO database. The present review followed the guidelines of the PRISMA Statement [26].

Eligibility criteria

The following inclusion criteria were adopted to select studies: Randomized Clinical Trials (RCTs), case-control studies, and cohort studies evaluating the efficacy of cyclobenzaprine in decreasing MFP in adult patients. Studies assessing general chronic pain or general TMD, case reports, case series, review articles, editorials, reviews, and books were excluded.

Search strategy

The search strategy, research question, and null hypothesis were defined according to the PICO format [27]:

1. P - Population: adults of both genders with a clinical diagnosis of MFP;

2. I - Intervention: treatment with cyclobenzaprine alone or cyclobenzaprine associated with another therapy, independent of dose and dose regimen;

3. C - Comparison: with other therapies for myofascial pain, including placebo or non-intervention;

4. O - Outcomes: the primary outcome was the difference in the mean value of jaw pain between pre- and post-treatment, as assessed by Numeric Rating Scales (NRS) from 0 to 1. The secondary outcome was the change in sleep quality;

5. Null hypothesis: Cyclobenzaprine is not effective in reducing MFP and improving sleep quality.

6. Question: Is cyclobenzaprine effective in improving MFP symptoms and sleep quality?

An electronic search was performed by two authors (LU and RRN) to identify eligible studies, in the following electronic databases: MEDLINE *via* PubMed, Scopus, Web of Science, Latin American and Caribbean Health Sciences Literature (LILACS), BBO (BVS), The Cochrane Library and Embase, from the inception until July 2021. An experienced librarian in the health research area (DM) helped to develop search strategies according to the tutorial for each database (Table 1). No restrictions were made on the language or year of the studies. Experts were contacted to identify potentially relevant studies. Unpublished and ongoing trials were also searched in Current Controlled Trials (www.controlled-trials.com), the International Clinical Trials registry platform (http://apps.who.int/trialsearch/), ClinicalTrials.gov (www.clinicaltrials.gov), Rebec (www.rebec.gov.br), and the EU Clinical Trials Register (https://www.clinicaltrialsregister.eu).

Study selection and risk of bias

After the exclusion of the duplicated studies, two authors (LU and RRN) independently performed a selection identifying the studies related to the topic based on the eligibility criteria by considering titles and abstracts. A second analysis excluded articles that did not fully meet the inclusion criteria. The remaining studies were obtained in full text, and it was read. Interexaminer conflicts were solved by a third author (OVV) in a consensus meeting. Data extraction from the studies was carried out by two authors (LU and CTM). Due to the characteristics of the included articles, the risk of bias was assessed according to the Cochrane Collaboration's tool for assessing the risk of bias in RCTs [28] (http://handbook.cochrane.org).

Process of data collection

Meta-analysis was carried out by two reviewers (LU and CTM) using the Comprehensive Meta-Analysis software (version 3.2.00089, Biostat, Inc., Englewood, NJ, USA). The primary outcome was the difference in the mean value of jaw pain between pre- and post-treatment, as assessed by NRS from 0 (no pain) to 1 (worst pain imaginable). The secondary outcome was the mean difference in sleep quality between pre- and post-treatment. The effect size is presented in forest plots using the random-effects model. Heterogeneity was tested using the Q-value, I2 index, and Tau2.

Results

Study selection

The electronic database search identified 172 titles and abstracts. Duplicated articles (73) were removed. All remaining titles and abstracts (99) were analyzed; 87 were considered unrelated to the topic and were subsequently excluded. Figure 1 shows the selection process. The full texts of 12 studies were evaluated, and finally, three prospective, double-blind, randomized controlled trials were selected for the present review [7,18,19].

Risk of bias

The risk of bias was assessed according to the six domains of a modified Cochrane Collaboration's tool for assessing the risk of bias in RCTs [28] (Figure 2). Within each domain, assessments were made for one or more items, covering different aspects of the domain or outcomes, 'yes' (+) indicating low risk of bias, 'no' (-) indicating high risk of bias, and 'unclear' (?) indicating lack of information or uncertainty over potential for bias. For the three studies [7,18,19], random-sequence generation and allocation concealment were considered adequate, described as randomization by block design

Table 1: Electronic search strategy according to each database.

Pubmed **#1 AND #2**			
#1		#2	
("Myofascial pain"[tiab] OR "Myofascial pain syndrome*"[tiab])		("cyclobenzaprine"[Supplementary Concept] OR Cyclobenzaprine[tiab] OR Flexeril[tiab] OR "Cyclobenzaprine hydrochloride"[tiab])	
Scopus **#1 AND #2 AND #3 AND #4**			
#1	#2	#3	#4
(TITLE-ABS-KEY (“Myofascial pain” OR “Myofascial pain syndrome*” OR “Pain syndrome myofascial*” OR “Syndrome myofascial pain*” OR “Trigger Point Pain Myofascial”)	TITLE-ABS-KEY (cyclobenzaprine OR flexeril OR lisseril OR “Cyclobenzaprine hydrochloride”))	DOCTYPE (ar OR re)	SUBJAREA (mult OR medi OR nurs OR vete OR dente OR heal)
Web of Science **#1 AND #2**			
#1		#2	
TS= (“Myofascial pain” OR “Myofascial pain syndrome*” OR “Pain syndrome myofascial*” OR “Syndrome myofascial pain*” OR “Trigger Point Pain Myofascial”)		TS=(Cyclobenzaprine OR Flexeril OR Lisseril OR “Cyclobenzaprine hydrochloride”)	
BBO (BVS) **#1 AND #2**			
#1		#2	
(tw:(Myofascial pain OR Pain syndrome myofascial* OR Syndrome myofascial pain* OR Trigger Point Pain Myofascial)) OR (tw:(MH: Myofascial pain syndrome*))		(tw:(Cyclobenzaprine OR Flexeril OR Lisseril OR Cyclobenzaprine hydrochloride))	
Lilacs (BVS) **#1 AND #2**			
#1		#2	
(tw:(Dor miofascial OR MH:síndromes da dor miofascial OR síndrome miofascial OR pontos-gatilho da dor miofascial OR myofascial pain OR MH:Myofascial pain syndrome* OR Myofascial pain syndrome* OR Pain syndrome myofascial* OR Syndrome myofascial pain* OR Trigger Point PainMyofascial OR síndromes del Dolor Miofascial OR puntos disparadores))		(tw:(Cyclobenzaprine OR Flexeril OR Lisseril OR Cyclobenzaprine hydrochloride))	
The Cochrane Library **#13= #7 and #12**			
#7		#12	
#1"Myofascial pain": ti,ab,kw (Word variations have been searched)		#8Cyclobenzaprine: ti,ab,kw (Word variations have been searched)	
#2"Myofascial pain syndrome*": ti,ab,kw (Word variations have been searched)		#9Flexeril: ti,ab,kw (Word variations have been searched)	
#3MeSH descriptor: [Myofascial Pain Syndromes] explode all trees		#10Lisseril: ti,ab,kw (Word variations have been searched)	
#4"Pain syndrome myofascial*": ti,ab,kw (Word variations have been searched)		#11"Cyclobenzaprine hydrochloride": ti,ab,kw (Word variations have been searched)	
#5"Syndrome myofascial pain*": ti,ab,kw (Word variations have been searched)		**#12= #8 or #9 or #10 or #11**	
#6"Trigger Point Pain Myofascial": ti,ab,kw (Word variations have been searched)			
#7= #1 or #2 or #3 or #4 or #5 or #6			
Embase #1 ('myofascial pain': ti,ab,kw OR 'myofascial pain syndrome': ti,ab,kw OR 'pain syndrome myofascial': ti,ab,kw OR 'syndrome myofascial pain': ti,ab,kw OR 'trigger point pain myofascial': ti,ab,kw) AND (cyclobenzaprine: ti,ab,kw OR flexeril: ti,ab,kw OR lisseril: ti,ab,kw OR 'cyclobenzaprine hydrochloride': ti,ab,kw)			

[19], stratification [18], and draw [7].

Study characteristics

The selected studies [7,18,19] compared the use of cyclobenzaprine with a placebo, clonazepam, and tizanidine, and two articles included changes in sleep quality in their investigations [18,19]. The follow-up of the selected studies ranged from three [18,19] to four [7] weeks. Two studies were double-blinded [18,19], and in the other one, the measure was blinded [7]. All three studies reported that the diagnosis of MFP was based on the chief complaint of pain occurring a minimum of two [18,19] days per week or for at least one month [7], which could be reproduced by muscle palpation on a trigger point. One study [7] included participants with at least one active trigger point in the cervical or trapezius region and had had pain symptoms for more than one month. Two studies [18,19] included participants with jaw pain upon awakening, occurring a minimum of 2 days per week, reproduced during the muscle digital palpation examination in the masseter muscle. All the three studies [7,18,19] used one capsule of 10 mg of cyclobenzaprine before bedtime. Only two studies specified the time to take it: 1 h before bedtime [19], and 2 h before bedtime [18]. The period of treatment was 15 days [7] and three weeks [18,19], and the follow-up was three weeks [18,19] and four weeks [7]. The selected studies [7,18,19] reported that their treatment protocols included patient education regarding the etiology of TMD and MFP for the three groups, including both written and verbal instructions. One study [7] compared the use of cyclobenzaprine with the effects of the infiltration of Trigger Points (TgP injections) with 1% lidocaine in the short-term treatment of trapezius MFP. Pain symptoms were evaluated according to self-report questionnaires: the Symptom Severity Index (SSI) [17], the modified Symptom Severity Index (mod SSI) [37] for jaw pain [18], and the Short-Form McGill Pain Questionnaire (SF-MPQ) [7]. The SSI and mod SSI provide Numeric Rating Scales (NRS) to assess pain intensity in two works [18,19], and the mod SSI includes subscales to measure pain intensity, frequency, and duration at only one of these [18]. In both studies [18,19], subjects presenting a self-report of pain intensity in the previous week of at least 0.4 on average on an NRS of 0 (no pain)

Table 2: Characteristics of the selected studies.

Author/year	Study design	Clinical Setting Period of recruitment	Placebo Group N (Gender) Mean age* (SD) Dose	Alternative therapy Group N (Gender) Mean age*(SD) Dose	Cyclobenzaprine Group N (Gender) Mean age* (SD) Dose	Tools for measure pain intensity	Tools for measure sleep quality	Follow-up (weeks)
Herman et al. (2002)	RCT PS Double-Blinded	University of Minnesota School of Dentistry TMJ/ Orofacial Pain Clinic HealthPartners Medical Center TMD Clinic, St. Paul, MN nr	15 (14F, 1M) 24.0(4.8) (one capsule daily)	Clonazepam 13 (11F, 2M) 26.9(10.1) 0.5 mg (one capsule daily)	13 (8F, 5M) 30.3(8.6) 10 mg (one capsule daily)	SSI	PSQI	3
Furtado et al. (2002)	RCT PS Blinded	Ambulatórios de Medicina e Reabilitação Universidade Federal de São Paulo São Paulo, Brazil February-December 2001	NA	Injections in TrP 18 (17F, 1M) 35	20 (18F, 2M) 34.2 10 mg (one capsule daily)	SF-MPQ/ VAS	NA	4
Alencar et al. (2014)	RCT PS Double Blinded	Clínica de Disfunção Temporomandibular e Dor Orofacial, Escola de Odontologia de Araraquara Universidade de São Paulo, Araraquara, Brazil nr	15 (14F, 1M) 37.1 (one capsule daily)	Tizanidine 15 (15F) 36.5 4 mg (one capsule daily)	15 (14F,1M) 36.9 10 mg (one capsule daily)	modSSI	PSQI	3

Mean age*= years; RCT: Randomized Clinical Trial; PS: Prospective Study; F: Female; M: Male; TgP: trigger Points; nr: not reported; SSI: Symptom Severity Index (NRS included); mod SSI: modified Symptom Severity Index (NRS included); NRS: Numeric Rating Scale; PSQI: Pittsburgh Sleep Quality Index; SF-MPQ= Short-Form Mcgill Pain Questionnaire; NA: Not Applicable

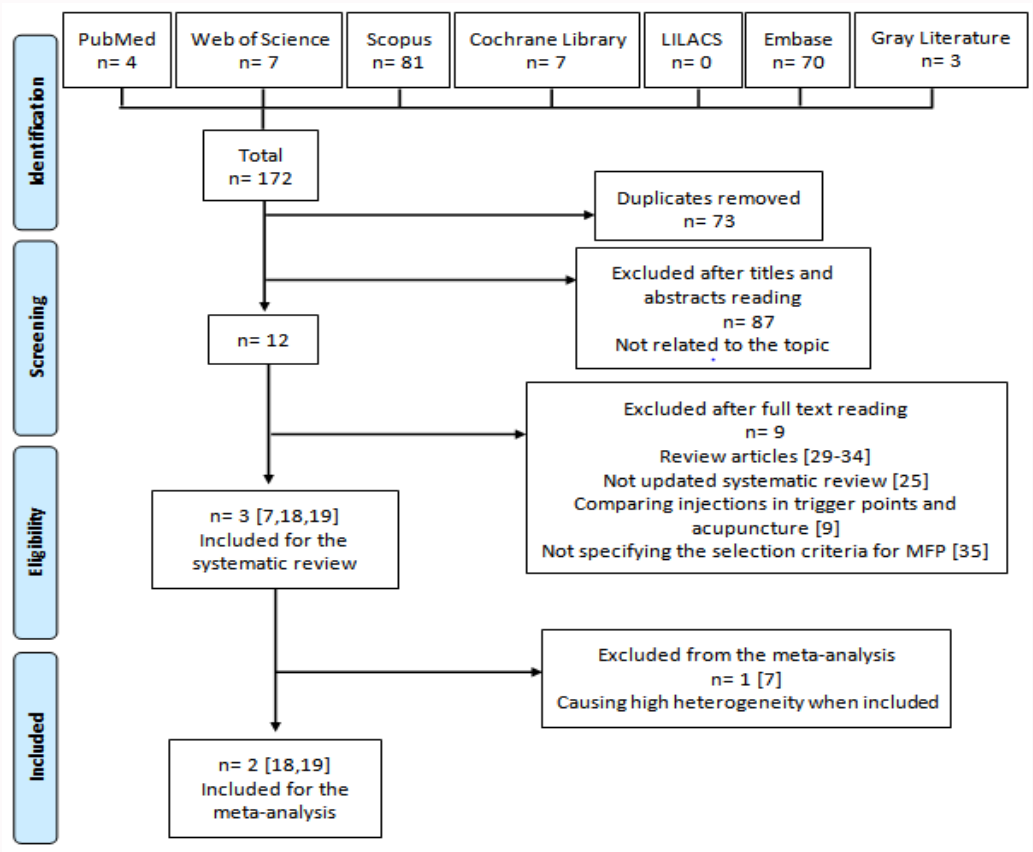

Figure 1: PRISMA flow diagram of the selected studies.

to 1 (worst pain imaginable) were included. One study [7] utilized a modified NRS to evaluate pain intensity. Only two studies [18,19] evaluated sleep quality. A total of 124 adult patients were included in this systematic review, although only 86 were finally included in the meta-analysis after sensitivity analysis. Information regarding the characteristics of the selected studies is shown in Table 2. The primary outcome was the difference in changes (from pre- to post-treatment) in pain intensity due to cyclobenzaprine compared to control. No statistically significant differences were reported among groups in the pretreatment pain intensity in any of the three studies [7,18,19], which confirm the similarity between the groups in the pretreatment. During the post-treatment evaluation at the end of the follow-up, in two studies [7,18] the decrease in pain intensity was noticeable in all groups assessed with no differences between the groups, which means

Table 3: Comparison of the initial and final variables of the selected studies.

Variable	Author/year	Pretreatment Mean (SD)			Comparison between groups	Posttreatment Mean (SD)			Comparison between groups
MFP intensity (NRS)		Group I*	Group II*	Group III*		Group I*	Group II*	Group III*	
	Herman et al. (2002)	0.48(0.05)	0.50(0.04)	0.62(0.04)	I vs III ns II vs III ns	0.28(0.06)	0.30(0.05)	0.17(0.05)	All contrasts P>0.06
		Group I**	Group II**			Group I**	Group II**		
	Furtado et al. (2002)	4.8(2.1)	4.6(2.5)		ns	1.7(2.1)	2.6(1.8)		ns
		Group I***	Group II***	Group III***		Group I***	Group II***	Group III***	
	Alencar et al. (2014)	0.69(0.07)	0.65(0.05)	0.84(0.05)	ns	0.48(0.08)	0.47(0.06)	0.55(0.07)	ns
Sleep quality (PSQI)		Group I*	Group II*	Group III*		Group I*	Group II*	Group III*	
	Herman et al. (2002)	6.54(0.97)	5.80(0.89)	7.23(0.89)	All contrasts P>0.2	5.92(0.90)	4.60(0.62)	5.08(0.67)	All contrasts P>0.2
		Group I***	Group II***	Group III***		Group I***	Group II***	Group III***	
	Alencar et al. (2014)	11.33(0.90)	12.33(0.79)	11.73(0.97)	ns	7.27(0.67)	8.47(1.30)	6.47(1.08)	ns

NRS: Numeric Rating Scale; PSQI: Pittsburgh Sleep Quality Index; ns: non-significant; NR: Not Reported; n/a: not applicable; Group I*: Clonazepam Group; Group II*: Placebo Group; Group III*: Cyclobenzaprine Group; Group I**: Lidocaine Infiltration Group; Group II**: Cyclobenzaprine Group; Group I***: Tizanidine Group; Group II***: Placebo Group; Group III***: Cyclobenzaprine Group

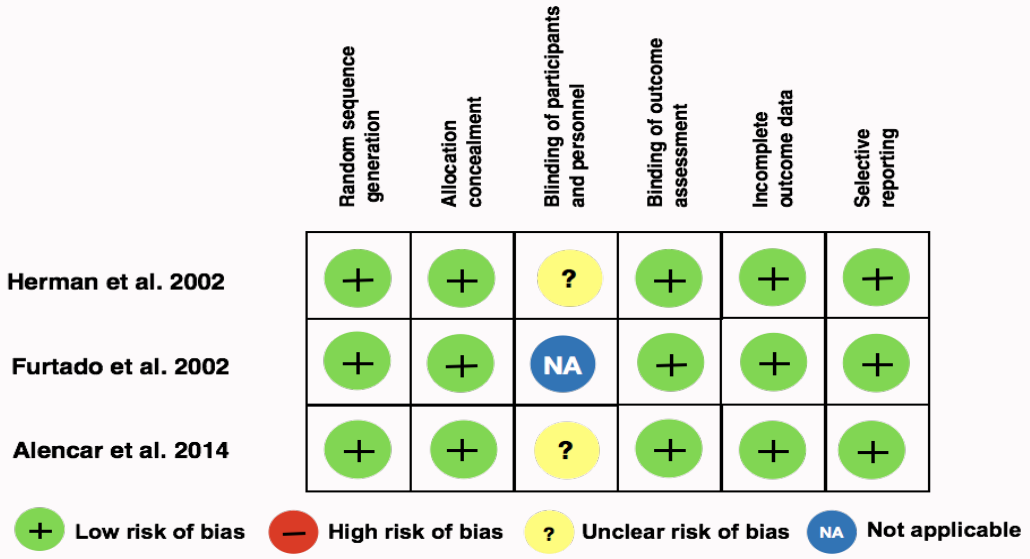

Figure 2: Summary of the risk of bias assessment according to the Cochrane Collaboration's tool for assessing the risk of bias in RCTs [28].

that all treatments were effective. In one study [19], the decrease in pain intensity was statistically significant for all three groups. Besides, the magnitude of the mean change in the cyclobenzaprine group was significantly higher than in the other groups. The secondary outcome in two works [18,19] was the difference in sleep quality, according to the Pittsburgh Sleep Quality Index (PSQI), a self-rated questionnaire that assesses sleep quality and disturbances. One study [19] reported that cyclobenzaprine was effective in improving sleep quality. The other study [18] showed similar results between groups. Table 3 shows the results of the pre- and post-treatment assessments of the selected studies for this systematic review. The side effects most commonly reported in the selected studies for cyclobenzaprine were dry mouth and morning drowsiness [7,18,19]. Nightmares [19] and fatigue [18] were also reported. In one study [7], these effects were considered important enough to halve the dose of this medication.

Quality of evidence

The quality of evidence of the selected studies for the meta-analysis was evaluated according to an adapted Grading of Recommendations Assessment, Development, and Evaluation (GRADE) [30] for systematic reviews and meta-analysis (Table 4). Our meta-analysis included two studies [18,19] investigating the effects of cyclobenzaprine in improving MFP and sleep quality. Their measurements and results were considered consistent with being phase 2 explanatory research. Both studies showed similar design, with 3-years randomized clinical trials with 30 adult participants each one, and found a significant statistical improvement in pain intensity ($P<0.001$ [18], $P<0.01$ [19]), and sleep quality ($P<0.001$ [18], and $P<0.5$ [19]), favoring the cyclobenzaprine group. They also were judged, presenting no serious limitations across the studies for all six items of GRADE [30] in analyzing the results of the effects of cyclobenzaprine on improving pain intensity and sleep quality.

Data Synthesis

The heterogeneity (I^2) in the meta-analysis was 83.47% for the pain assessment when the three studies were included [7,18,19]. A sensitivity analysis was performed, removing one study [7], which had a different methodology than the other two, since the authors

Table 4: Quality of evidence of the included studies according to an adapted Grading of Recommendations Assessment, Development and Evaluation (GRADE) [30] for systematic reviews and meta-analysis.

Outcome:												
					GRADE factors							
Prognostic factors	Number of participants	Number of studies	Number of cohorts	Estimated effect size Mean difference [95% CI] P	Phase	Study limitation	Inconsistency	Indirectness	Imprecision	Publication bias	Moderate/ Large effect size	Overall quality
MFP intensity		[18,19]	2	0.155 [0.027, 0.283] 0.018	2	X	✓	✓	UNCLEAR	✓	✓	++
Sleep quality		[18,19]	2	1.337 [0.027, 0.283] 0	2	✓	✓	✓	UNCLEAR	✓	✓	+++

Phase: Phase of investigation.
For GRADE factors: ✓: No Serious Limitations; x: Serious Limitations (or not present for moderate/large effect size); xx: Very Serious Limitations; unclear: Unable to rate item based on available information
For overall quality of evidence: +: very low; ++: low; +++: moderate; ++++: high
SD: Standard Deviation

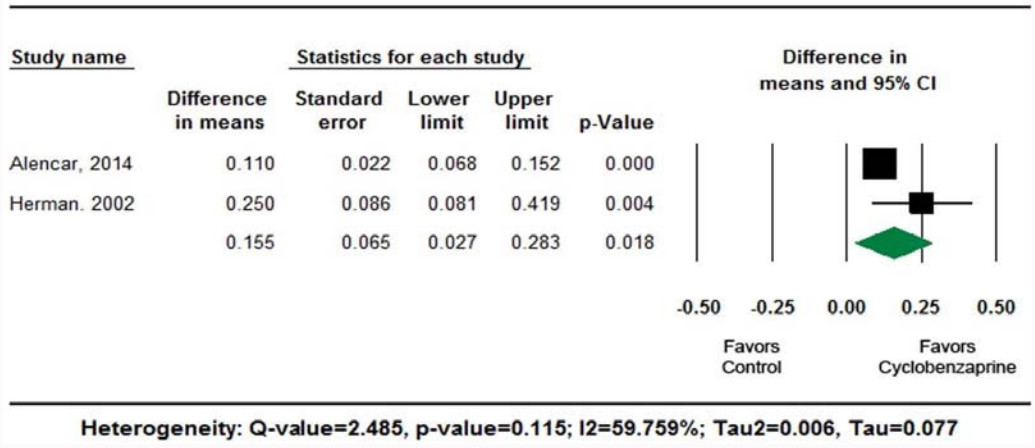

Figure 3: Forest plot of the pre- and post-treatment efficacy (21 days follow-up) of cyclobenzaprine for MFP using a Numeric Rating Scale (NRS).

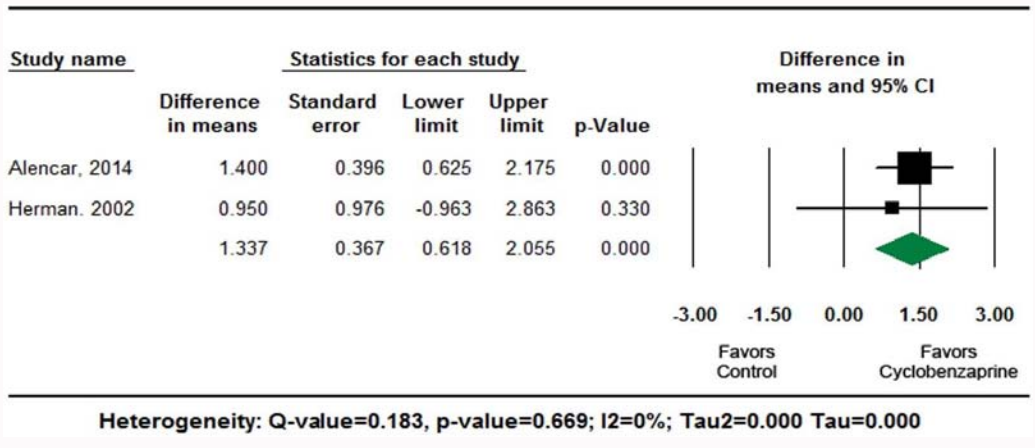

Figure 4: Forest plot of sleep quality pre- and post-treatment (21 days follow-up) evaluated using the Pittsburg Sleep Quality Index (PSQI).

did not apply patient education or included a placebo group. The heterogeneity was reduced to moderate (I^2=59.75%), which made the results more reliable. The heterogeneity for sleep quality was considered low (I^2=0%). Eighty six participants were divided into the placebo [18,19] (n=30), clonazepam [19] (n=13), tizanidine [18] (n=15) and cyclobenzaprine [18,19] (n=28) groups. In the meta-analysis, it was only possible to compare the cyclobenzaprine and the placebo groups. The effect size was presented trough the difference in means, with positive values indicating better results for the cyclobenzaprine group. Figure 3 shows that the efficacy of cyclobenzaprine in reducing MFP was 0.155 greater than the control group (on a scale of 0 to 10), and the difference was statistically

significant (95% CI, 0.027 to 0.283). Sleep quality was assessed using the PSQI, which showed a statistically significant improvement (1.337 greater on a scale of 0 to 21) in the cyclobenzaprine group (95% CI, 0.618 to 2.05), as shown in Figure 4.

Discussion

MFP is a frequent complaint reported in the literature as chronic pain, recognized as a medical and a socioeconomic problem [29]. Different pains, such as headaches, jaw pain, and nonspecific neck pain, have been reported to affect 54.6% [40] to 93.75% [29] of patients with complaints of chronic headache and neck pain, respectively. Clinical trials involving therapies for MFP typically assess pain intensity by using self-report questionnaires, since it is considered a reliably method [32,33]. Therefore, the use of the SSI with included NRS provides a recognized assessment of MFP [31-35].

Several studies have tested medication in the treatment of MFP [12-17,20,21]. A recent study [36] evaluated studies comparing local anesthetics to dry needling, analgesics, and anti-inflammatory drugs. Notwithstanding the strict protocol followed by our review to assess the efficacy of cyclobenzaprine in reducing myofascial pain, only three randomized clinical trials [7,18,19], and one systematic review [25] were found in the literature. Although it was well-conducted, Leite et al. [25] did not update their review, and it was excluded from the present research. Furtado et al. [7] compared two different interventions and did not include a placebo group in their trial. It resulted in a different way of reporting the outcomes, increasing the heterogeneity between the selected studies (I^2=83.47%). Due to their similar methodology, only two studies [18,19] were included in the meta-analysis.

Despite their small sample sizes, the studies selected to perform the meta-analysis [18,19] were well-conducted and considered as presenting a low risk for five of the six domains in the assessment of the risk of bias. They presented similar diagnostic criteria for MFP, and the measurements and results across the studies were consistent. When comparing the placebo [18,19], clonazepam [19], and tizanidine [18] groups with the cyclobenzaprine group [18,19], a mean difference of 0.15 was observed on a NRS of 0 (no pain) to 1 (the worst pain). The meta-analysis showed statistically significant relief in MFP, favoring cyclobenzaprine (95% CI, 0.027 to 0.283). At the end of follow-up, Herman et al. [19] observed that the cyclobenzaprine group experienced a higher level of improvement (72.7% decrease in MFP, mean change of 0.45) as compared with the clonazepam and placebo groups (40% decrease, mean changes of 0.20 and 0.20, respectively).

The intragroup changes in the mean scores from pre- to post-treatment were statistically significant in all three groups [18,19], and the outcome associated with the cyclobenzaprine group was higher and differed significantly from the other post-treatment values. The results of the present meta-analysis are consistent with those found in the literature [37,38].

For sleep quality, the meta-analysis showed a statistically significant decrease in means between the groups, favoring cyclobenzaprine, as shown by the mean difference of 1.337 measured using the PSQI (95% CI, 0.618 to 2.05). A meta-analysis conducted by Tofferi et al. [38], to evaluate the effectiveness of cyclobenzaprine in the treatment of fibromyalgia, concluded that patients treated with cyclobenzaprine were three times more likely to report global improvements and moderate reductions in other symptoms particularly sleep. These works are in agreement with the results of the present review.

A longitudinal study with a large sample [39] and another well-conducted study [40] concluded that a relationship between sleep quality and pain might exist, implying that a greater length of time would be required to assess significant changes in sleep quality. An important aspect to highlight is related to side effects reported by the participants, such as dry mouth, fatigue, drowsiness, and nausea. Browning et al. [37] reported that the effect of cyclobenzaprine is most significant in the first four days of treatment, and it comes at the price of significant adverse effects. Two studies [40,41] evaluating the effects of the addition of cyclobenzaprine to ibuprofen treatment in patients with acute myofascial strain confirmed the higher prevalence of adverse effects. These authors suggested that shorter courses may be better for treating the acute phase of pain. When cyclobenzaprine is indicated as a muscle relaxant, the dosage is higher than in preventive use, which consequently increases the collateral effects. Both studies included in the present meta-analysis [18,19] used a single daily dose of 10 mg of cyclobenzaprine [42] as a preventive medication, and our results confirmed that this dosage was effective in enhancing sleep quality. Therefore, no higher dosage would be necessary for that purpose.

Finally, in the two studies [18,19] included in this meta-analysis, all groups received self-care management and patient education, and improvements in pain intensity and sleep quality were also found in the placebo groups, highlighting the importance of cognitive-behavioral therapy in the treatment of the MFP.

Implications for practice

The estimated impact of the efficacy of cyclobenzaprine as a preventive medication in MFP varies from one study to another, and the cost-effectiveness of interventions to improve MFP has also been controversial. The two studies involving 86 participants selected in the present meta-analysis confirmed moderate evidence that the use of cyclobenzaprine presents an association with the relief of MFP. An improvement in sleep quality was observed during the follow-up period of three weeks, favoring cyclobenzaprine. Although only two studies were used in this meta-analysis, we concluded that cyclobenzaprine was statistically significant in reducing pain and improving sleep quality in MFP.

Implications for research

There are some limitations related to the present review. According to GRADE [30], a small number of participants generated imprecision, which downgraded the overall quality of the included studies? The number of participants could have been not large enough to detect clinically significant differences between the treatment arms. Additionally, the authors did not cite if a sample size calculation or a pilot study was performed, and it was unclear if there was blinding in the management phase of the selected studies, which increases the risk of bias, according to The Cochrane Collaboration's tool for assessing the risk of bias in RCTs [28]. However, the studies were well-conducted, presenting similar diagnostic criteria for MFP, and the measurements and results across the studies were consistent, which made it feasible to perform a meta-analysis. Hence, we considered that an exposure-response gradient exists between the studies since the same methodology was used to assess the variables and outcomes. It made it feasible to perform the meta-analysis, which favored cyclobenzaprine for the treatment of MFP and improving sleep quality. Future studies would focus on prospective more extensive controlled trials, with an appropriate sample size, to

increase their applicability and their effects in clinical practice with enough statistical power. These are necessary to standardize the cyclobenzaprine best therapeutic and dose, minimizing its side effects when using as a medication in the MFP therapy.

Conclusion

· Although the small number of studies used in this systematic review and meta-analysis, we concluded that there is moderate evidence of an association between the use of cyclobenzaprine and the relief of MFP.

· Concerning sleep quality, an improvement was observed during the follow-up period of three weeks, also favoring cyclobenzaprine.

Acknowledgment

We thank the Coordination of Improvement for Higher Education Personnel (CAPES) from the Brazilian Ministry of Education for the scholarship supporting the first author's PhD degree during the development of the present study.

Contributions of Authors Statement

We declare that all authors (Luciana Uemoto, Rizomar Ramos do Nascimento, Danielle Masterson, Claudia Trindade Mattos, Francisco Guedes Pereira de Alencar Jr and Oswaldo de Vasconcellos Vilella participated in the concept and design, analysis, and interpretation of data, drafting and revising the manuscript, and are responsible for the reported research.

References

1. Simons DG, Travell JG, Simons LS. Myofascial pain and dysfunction: The trigger point manual, Ed. 2, Williams & Wilkins, Baltimore, Introduction, p.18.
2. Ohrbach R, Gonzalez Y, List T, Michelotti A, Schiffman E. Diagnostic criteria for Temporomandibular disorders (DC/TMD) clinical examination protocol: version 02 June 2013.
3. Lucchetti G, Oliveira AB, Mercante JPP, Peres MFP. Anxiety and fear-avoidance in musculoskeletal pain. Curr Pain Headache Rep. 2012;16(5):399-406.
4. Andrews G, Hobbs MJ, Borkovec TD, Beesdo K, Craske MG, Heimberg RG, et al. Generalized worry disorder: A review of DSM-IV generalized anxiety disorder and options for DSM-V. Depress Anxiety. 2010;27(2):134-47.
5. Means-Christensen AJ, Roy-Byrne PP, Sherbourne CD, Craske MG, Stein MB. Relationships among pain, anxiety, and depression in primary care. Depress Anxiety. 2008;25(7):593-600.
6. Karakurum B, Soylu O, Karataş M, Giray S, Tan M, Arlier Z, et al. Personality, depression, and anxiety as risk factors for chronic migraine. Int J Neurosci. 2004;114(11):1391-9.
7. Furtado RNV, Carazzato S, Farias CA, Chamlian TR, Masiero D. Myofascial syndrome: Comparison between infiltration of trigger points treatment and oral medication (cyclobenzaprine). Acta Fisiátrica. 2002;9(3):117-26.
8. Liu L, Huang QM, Liu QG, Ye G, Bo CZ, Chen MJ, et al. Effectiveness of dry needling for myofascial trigger points associated with neck and shoulder pain: A systematic review and meta-analysis. Arch Phys Med Rehabil. 2015;96(5):944-55.
9. Gazi MCB, Issy AM, Avila IP, Sakata RK. Comparison of acupuncture to injection for myofascial triggers point pain. Pain Pract. 2011;11(2):132-8.
10. Cagnie B, Castelein B, Pollie F, Steelant L, Verhoeyen H, Cools A. Evidence for the use of ischemic compression and dry needling in the management of trigger points of the upper trapezius in patients with neck pain: A systematic review. Am J Phys Med Rehabil. 2015;94(7):573-83.
11. Vernon H, Schneider M. Chiropractic management of myofascial trigger points and myofascial pain syndrome: A systematic review of the literature. J Manipulative Physiol Ther. 2009;32(1):14-24.
12. Plesh O, Curtis D, Levine J, McCall WD. Amitriptyline treatment of chronic pain in patients with temporomandibular disorders. J Oral Rehabil. 2000;27(10):834-41.
13. Bendtsen L, Jensen R. Amitriptyline reduces myofascial tenderness in patients with chronic tension-type headache. Cephalalgia. 2000;20(6):603-10.
14. Alpaslan C, Kahraman AS, Durmuslar C, Cula S. Comparative efficacy of four muscle relaxants on signs and symptoms of the myofascial pain syndrome associated with temporomandibular disorders: A randomized clinical trial. J Musculoskelet Pain. 20:310-316.
15. Naikmasur V, Bhargava P, Guttal K, Burde K. Soft occlusal splint therapy in the management of myofascial pain dysfunction syndrome: A follow-up study. Indian J Dent Res. 2008;19(3):196-203.
16. Khalighi HR, Mortazavi H, Mojahedi SM, Azari-Marhabi S, Abbasabadi FM. Low level laser therapy versus pharmacotherapy in improving myofascial pain disorder syndrome. J Lasers Med Sci. 2016;7(1):45-50.
17. Dao TTT, Lund JP, Rémillard G, Lavigne GJ. Is myofascial pain of the temporal muscles relieved by oral sumatriptan? A cross-over pilot study. Pain. 1995;62(2):241-4.
18. Alencar FGP, Viana PG, Zamperini C, Becker A. Patient education and self-care for the management of jaw pain upon awakening: A randomized controlled clinical trial comparing the effectiveness of adding pharmacologic treatment with cyclobenzaprine or tizanidine. J Oral Facial Pain Headache. Spring. 2014;28(2):119-27.
19. Herman CR, Schiffman EL, Look JO, Rindal DB. 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. J Orofac Pain. 2002;16(1):64-70.
20. Vidor LP, Torres ILS, de Souza ICC, Fregni F, Caumo W. Analgesic and sedative effects of melatonin in temporomandibular disorders: A double-blind, randomized, parallel-group, placebo-controlled study. J Pain Symptom Manage. 2013;46(3):422-32.
21. Harkins S, Linford J, Cohen J, Kramer T, Cueva L. Administration of clonazepam in the treatment of TMD and associated myofascial pain: A double-blind pilot study. J Craniomandib Disord. 1991;5(3):179-86.
22. Linden CH, Mitchiner JC, Lindzon RD, Rumack BH. Cyclobenzaprine overdosage. J Toxicol Clin Toxicol. 1983;20(3):281-8.
23. Vinar O, Grof P. Proheptatriene in depression (extensive study). Act Nerv Super (Praha). 1965;7(3):290.
24. Turturro MA, Frater CR, D'Amico FJ. Cyclobenzaprine with ibuprofen versus ibuprofen alone in acute myofascial strain: A randomized, double-blind clinical trial. Ann Emerg Med. 2003;41(6):818-26.
25. Leite FMG, Atallah AN, Dib RE, Grossmann E, Januzzi E, Andriolo RB, et al. Cyclobenzaprine for the treatment of myofascial pain in adults. Cochrane Database Syst Rev. 2009;2009(3):CD006830.
26. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analysis of studies that evaluate health care interventions: Explanation and elaboration. J Clin Epidemiol. 2009;62(10):e1-34.
27. Schardt C, Adams MB, Owens T, Keitz S, Fontelo P. Utilization of the PICO framework to improve searching PubMed for clinical questions. BMC Med Inform Decis Mak. 2007;7:16.
28. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The cochrane collaboration's tool for assessing risk of bias in randomized trials. BMJ. 2011;343:d5928.

29. Cerezo-Téllez E, Torres-Lacomba M, Moral OMD, Sánchez-Sánchez B, Dommerholt J, Gutiérrez-Ortega C. Prevalence of myofascial pain syndrome in chronic non-specific neck pain: A population-based cross-sectional descriptive study. Pain Med. 2016;17(12):2369-77.

30. Huguet A, Hayden JA, Stinson J, McGrath PJ, Chambers CT, Tougas ME, et al. Judging the quality of evidence in reviews of prognostic factor research: adapting the GRADE framework. Syst Rev. 2013;2:71.

31. Fricton JR. Musculoskeletal measures of orofacial pain. Anesth Prog. 1990;37(2-3):136-43.

32. Nixdorf DR, John MT, Wall MM, Fricton JR, Schiffman EL. Psychometric properties of the modified Symptom Severity Index (SSI). J Oral Rehabil. 2010;37(1):11-20.

33. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain. 2005;113(1-2):9-19.

34. 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 Surg Oral Med Oral Pathol. 1985;60(6):615-23.

35. Elenbaas JK. Centrally acting oral skeletal muscle relaxants. Am J Hosp Pharm. 1980;37(10):1313-23.

36. Nouged E, Dajani J, Ku B, Al-Eryani K, Padilla M, Enciso R. Local anesthetic injections for the short-term treatment of head and neck myofascial pain syndrome: A systematic review with meta-analysis. J Oral Facial Pain Headache. 2019;33(2):183-98.

37. Browning R, Jackson JL, O'Malley PG. Cyclobenzaprine and back pain: A meta-analysis. Arch Intern Med. 2001;161(13):1613-20.

38. Tofferi JK, Jackson JL, O'Malley PG. Treatment of fibromyalgia with cyclobenzaprine: A meta-analysis. Arthritis Rheum. 2004;51(1):9-13.

39. Bigatti SM, Hernandez AM, Cronan TA, Rand KL. Sleep disturbances in fibromyalgia syndrome: Relationship to pain and depression. Arthritis Rheum. 2008;59(7):961-7.

40. Childers MK, Borenstein D, Brown RL, Gershon S, Hale ME, Petri M, et al. Low-dose cyclobenzaprine versus combination therapy with ibuprofen for acute neck or back pain with muscle spasm: A randomized trial. Curr Med Res Opin. 2005;21(9):1485-93.

41. Borenstein DG, Korn S. Efficacy of a low-dose regimen of cyclobenzaprine hydrochloride in acute skeletal muscle spasm: Results of two placebo-controlled trials. Clin Ther. 2003;25(4):1056-73.

42. Ağargün MY, Tekeoğlu I, Güneş A, Adak B, Kara H, Ercan M. Sleep quality and pain threshold in patients with fibromyalgia. Compr Psychiatry. 1999;40(3):226-8.