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

Francisco Guedes Pereira de Alencar Júnior, DDS, MS, MS, PhD
Assistant Professor
General Dental Sciences Department
TMD and Orofacial Pain
Marquette University School of Dentistry
Milwaukee, Wisconsin, USA

Patricia Gabriela Sabino Viana, DDS, MS, PhD
Former PhD Candidate
Department of Dental Materials and Prosthodontics
Araraquara Dental School
UNESP - Univ Estadual Paulista
Araraquara
São Paulo, Brazil

Camila Andrade Zamperini, DDS, PhD
Former PhD Candidate
Department of Dental Materials and Prosthodontics
Araraquara Dental School
UNES–Univ Estadual Paulista
Araraquara
São Paulo, Brazil

Anne Buss Becker, DDS, MS
Assistant Professor
Franciscano University Center
Santa Maria
Rio Grande do Sul, Brazil

Correspondence to:
Dr Francisco Guedes Pereira de Alencar Júnior
Marquette University School of Dentistry
TMD and Orofacial Pain
PO Box 1881
Milwaukee, WI 53201-1881
Email: francisco.alencar@mu.edu or alencardoc@gmail.com

Aims: To compare the effectiveness of adding cyclobenzaprine, tizanidine, or placebo to patient education and a self-care management program for patients with myofascial pain and specifically presenting with jaw pain upon awakening. **Methods:** Forty-five patients with a diagnosis of myofascial pain based on the guidelines of the American Academy of Orofacial Pain participated in this 3-week study. The subjects were randomly assigned into one of three groups: placebo group, TZA group (tizanidine 4 mg), or CYC group (cyclobenzaprine 10 mg). Patients were evaluated for changes in pain intensity, frequency, and duration by using the modified Severity Symptoms Index and changes in sleep quality with the use of the Pittsburgh Sleep Quality Index. Data were analyzed by ANOVA and post-hoc or nonparametric statistical tests as appropriate. **Results:** All three groups had a reduction in pain symptoms and improvement of sleep quality based on a comparison of pretreatment and treatment scores. However, no significant differences among the groups were observed at the posttreatment evaluation. **Conclusion:** The use of tizanidine or cyclobenzaprine in addition to self-care management and patient education was not more effective than placebo for the management of patients with myofascial jaw pain upon awakening. *J Oral Facial Pain Headache 2014;28:119–127. doi: 10.11607/ofph.963*

Key words: *cyclobenzaprine, myofascial pain, orofacial pain, sleep, tizanidine*

Myofascial pain is a common cause of chronic pain in the musculoskeletal system, although most of the time is not diagnosed properly. It may be induced by stimulation of hyperirritable points within bands of skeletal muscle or in the muscle fascia, known as trigger points.[1–4] Trigger points may be related to a localized or more generalized pain distribution throughout the body. They may be active when related to pain as a symptom or may be latent and not causing pain but possibly associated with muscle shortening.[3] Other symptoms that patients with myofascial pain frequently experience are psychological disturbances, such as anxiety and depression, and poor sleep quality.[2,5]

Treatment modalities used in the management of myofascial pain especially related to masticatory muscles include physical therapy, occlusal appliances, pharmacotherapy, trigger-point injections, acupuncture, behavioral modification, self-care management, and biofeedback.[2,3,6–14] These therapies accompanied by counseling/education and changes in behavioral habits are adequate for the majority of patients with this type of dysfunction.[15]

The goal of counseling is to educate the patient about the possible etiology of the disorder and provide information about the understanding of all etiologic contributing factors as well as management techniques. Also, advocating the use of bilateral mastication and a soft diet, decreased caffeine consumption, ingestion of a proper amount of water, postural adjustment, and control of daytime muscle hyperactivity such as tooth clenching will also have an important role in the improvement of the patient's health condition.[3] According to Wright and Schiffman,[3] self-care management has been considered effective in 60% to 90% of patients with myofascial pain and should be included as a standard procedure in the initial treatment plan.

Although there is little literature based on randomized clinical trials to establish the effectiveness of adding any medication in the initial treatment plan, pharmacological management has been suggested.[2] In this context, cyclobenzaprine and tizanidine are medications that could be indicated in the management of patients with myofascial pain. Cyclobenzaprine is a centrally acting skeletal muscle relaxant, pharmacologically related to tricyclic antidepressants, that reduces tonic somatic motor activity by influencing both alpha and gamma motor neurons. It is a receptor antagonist of serotonin that exerts a muscle relaxant effect by inhibiting the serotonergic descending system in the spinal cord.[7,16–18] Studies in animal models with musculoskeletal hypertonicity concluded that cyclobenzaprine has no activity at the neuromuscular junction, and also has no direct effect on the skeletal muscle.[16] This medication has been proven to be effective for the treatment of musculoskeletal pain[7,8,17,19] and can be also indicated in cases of tension-type headache, fibromyalgia, and muscular spasms in the cervical and lumbar region.[2] Herman et al[2] demonstrated the superior effectiveness of cyclobenzaprine when compared to clonazepam in the management of jaw pain upon awakening. The most common adverse effects are drowsiness and dry mouth, which are transitory and decrease in most patients within a few days.[2,16,18,20,21] Nevertheless, in a recent systematic review,[4] the authors concluded that further randomized clinical studies would be required to establish clinical evidence of the effectiveness and safety of this medication for the treatment of myofascial pain.

Tizanidine also acts as a central muscle relaxant. It has been demonstrated in animal studies that doses below those required for producing muscular relaxation have an antinociceptive effect.[22,23] Studies in humans have indicated that tizanidine was generally well tolerated by patients, although it could produce some adverse effects that ranged from slight to moderate, such as somnolence and dry mouth.[24] Tizanidine has been used in the prophylactic or preventive management of patients with tension-type headaches and migraine, confirmed by studies that have demonstrated the medication's efficacy and tolerability, although an adequate dose has not yet been established.[22,23,25–27]

Therefore, considering the therapeutic indications of these medications, as well as the need for more data about the addition of pharmacologic interventions for the management of myofascial pain, the aim of this study was to compare the effectiveness of adding cyclobenzaprine, tizanidine, or placebo to a patient education and a self-care management program for patients with myofascial pain and specifically presenting with jaw pain upon awakening.

Materials and Methods

Study Sample

The sample consisted of consecutive subjects selected on a voluntary basis from patients who were seeking treatment for chronic orofacial pain at the São Paulo State University, Araraquara Dental School, Temporomandibular Disorders and Orofacial Pain Clinic. This study was approved by the Human Research Ethics Committee of the Araraquara Dental School, São Paulo State University (Protocol No. 30/04). All individuals were first fully informed about the study design and then asked to give their free informed consent prior to participating in it. No financial compensation was given to any patient. All patients selected were diagnosed with myofascial pain with a chief complaint of jaw pain that could be reproduced by muscle palpation of a trigger point.

Patients were selected for this study based on the following inclusion and exclusion criteria.

Criteria for inclusion: *(1)* jaw pain upon awakening, occurring a minimum of 2 days per week, reproduced during the muscle digital palpation examination in the masseter muscle; *(2)* diagnosis of myofascial jaw pain based on the guidelines of the American Academy of Orofacial Pain (AAOP)[28]; *(3)* self-report of average jaw pain intensity in the past week of at least 4 on a numeric scale of 0 (no pain) to 10 (most severe pain imaginable), persisting for at least 6 months; *(4)* self-report of psychological stability (subjects taking antidepressants would be considered stable if they reported no current depression and had been on a stable regimen of medications for at least 3 months); and *(5)* age range between 18 and 65 years.

Criteria for exclusion: *(1)* systemic diseases such as fibromyalgia, rheumatoid arthritis, or lupus; *(2)* a self-report of persistent depression or an unstable regimen of medications of less than 3 months duration, as indicated by their history; *(3)* pregnancy or lactation; *(4)* history of drug or alcohol dependence; *(5)* concomitant treatment with α2-adrenergic agonists (ie, clonidine, methyldopa) or α2-adrenergic antagonists (ie, phenotiazines), or use of monoamine oxidase; *(6)* report of liver dysfunction, impaired renal function, acute recovery phase of myocardial infarction, heart block or conduction disturbances, arrhythmia, hypertension, hypotension, glaucoma, or hyperthyroidism, and use of congestive heart failure inhibitors; *(7)* history of allergic reaction to tizanidine or cyclobenzaprine, or any other contraindications to the use of these medications; and *(8)* diagnosis of temporomandibular joint (TMJ) arthralgia/osteoarthrosis or mechanical TMJ disorders (disc displacements) according to the AAOP guidelines.

Prior to the recruitment of subjects, the authors (PGSV and CAZ) underwent a calibration exercise.

The calibrated examiner palpated with a pressure of 1.5 kg and was calibrated using a pressure algometer.[28]

Patients were submitted to a clinical examination involving a history investigation and physical examination. The history investigation included questions about pain location, intensity, frequency, and duration, as well as the presence of possible etiologic factors such as sleep bruxism, daytime teeth clenching, and poor sleep quality. The physical examination consisted of digital palpation of muscles of mastication to detect trigger points that would reproduce the jaw pain (the patient's complaint) and to confirm the diagnosis of myofascial pain.[29]

Study Design

The study design was a double-blind, placebo-controlled clinical trial to evaluate the effectiveness of adding either cyclobenzaprine or tizanidine to patient education and a self-care program in the management of jaw pain upon awakening. The primary outcome measure was the decrease of pain symptoms, evaluated by the modified Severity Symptoms Index (mod SSI—average total score obtained from three subscales)[30,31] and by the pain intensity on a visual analog scale (one of three subscales included in the mod SSI).[2] The secondary outcome measure was change in sleep quality measured by means of the Pittsburgh Sleep Quality Index (PSQI).[2,32]

This study was designed according to another study[2] published in 2002, so the results obtained from the use specifically of tizanidine added to self-care and patient education could be compared, since clonazepam was shown in that study not to be superior to cyclobenzaprine.[2] There were some minor differences in the present study design, but these were not significant enough to affect the possibility of data comparison between the studies.

Out of 48 patients meeting the criteria for inclusion in the study, 45 consented to participate. All subjects were instructed to discontinue the use of any pain medication for a 1-week washout period before starting treatment. Following the washout period, the selected patients were allocated to one of three treatment groups according to a randomized process. Pain intensity data, obtained on pretreatment examination, was used as a blocking variable for stratified random sampling in such a way that the three groups presented similar pain-intensity averages. This process was performed by an author (PGSV) who was not blinded to the treatment group.

The treatment protocol used in accordance with each group was: placebo group (one capsule daily, consisting of lactose filler); TZA group (tizanidine hydrochloride 4 mg, one capsule daily); and CYC group (cyclobenzaprine hydrochloride 10 mg, one capsule daily). The subjects were instructed to take one capsule, 2 hours before bedtime, during the 3-week period. An author (PGSV) supplied the patients with medications and was responsible for the treatment instructions.

The medications were distributed free of charge and all capsules were formulated to have the same appearance; all medicine bottles had the same appearance as well. The drugs were manufactured by Pharmaceutical Sciences Faculty, UNESP, Araraquara/SP, Brazil. All subjects from all three groups received patient education consisting of explanations about the etiology of temporomandibular disorders (TMD) and myofascial pain.[2] The self-care program[3] was always administrated by the same author (PGSV), including both written and verbal instructions. These instructions were a little different from other studies[2,3] and included:

1. An explanation of possible factors involved in the etiology and perpetuation of myofascial pain, such as number of meals a day (hypoglycemia), lack of water intake (dehydration), high intake of caffeine (a central nervous system stimulator), and daytime tooth clenching.
2. Instruction in the mandibular rest position (teeth gently apart, lips slightly touching, tongue not pressing against the teeth, and jaw muscles relaxed) and the importance of it for the health of their neuromuscular system. They were also asked to watch their posture during the day as well as to avoid sleeping on their stomach and pressure on their jaws.
3. Instruction in performing simultaneous bilateral mastication but not to load the TMJs or any masticatory muscles, and to apply heat to the masseter muscles for at least 15 minutes up to three times a day and never to use cold.
4. Recommendations to eat a soft-food diet and avoid excessive mouth openings.
5. Standardization in the use of analgesics in the case of persistent pain, in order to prevent medication interaction and a confounder effect. Therefore, the patients were instructed to use ibuprofen (400 mg) as a rescue medication and to verbally inform the author responsible for the treatment (PGSV), at the final appointment, about the frequency and number of rescue medication tablets used. No other pain medication was used by the patients during the length of the study.

Evaluations and Data Collection

Subjects were followed up for 3 weeks, and the data collection was carried out by one author (CAZ) who was blinded to the treatment group. The instruments used for the outcome evaluation in this study were two standardized self-report questionnaires: *(1)* mod

SSI—pain symptoms evaluation[30,31] (primary outcome measure), and *(2)* PSQI—sleep quality and disturbances assessment[32] (secondary outcome measure).

The mod SSI is a self-report pain measure consisting of three subscales assessing three pain dimensions (intensity, frequency, and duration). This instrument has been validated and documented previously.[31] Each subscale is assessed on a scale of 28 points (bubbles) on a visual analog scale. For each of the three subscales, subjects mark 1 of 28 bubbles on an optical scanning form, as an ordinal scale, to represent their pain experience. Potential responses for pain intensity range from "zero" on the far left to "worst imaginable" on the far right. Responses for pain frequency and duration range from "never" on the far left to "constant" on the far right. Within the pain frequency and duration scales, descriptors are periodically posted between the extremes to spread the responses over the full scale. For scoring, each scale has a numeric range from 0 with the bubble on the far left to 1 with the bubble on the far right. Bubbles marked in between these extremes are rated linearly between the bounds of 0 and 1, thus producing a fraction. All three scales are then averaged to produce the overall summary score.[30,31]

The PSQI is a 19-item self-report questionnaire that generates seven component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction. The global score is a sum of these seven components.[32]

Data Analysis

A one-way analysis of variance (ANOVA) was used to test the equivalence of the three groups (placebo, TZA, and CYC) at the pretreatment assessment for the pain intensity, mod SSI, and PSQI measurements. Additionally, repeated measures ANOVA and then Scheffe test were used to evaluate the effect of treatment and time of measurement on the management of jaw pain upon awakening. Kruskal-Wallis nonparametric analysis was performed to detect differences among the groups in the use of rescue medication as well as with respect to the subjects' age. A significance level of .05 was used for all statistical tests.

Results

The final sample size consisted of 45 patients (43 women and 2 men), whose characteristics are described in Fig 1. The patients were allocated to one of the three groups, with 15 subjects in each group. During the length of the study, no patient dropped out. There was no statistically significant difference ($P > .05$) in terms of age, with an average age of 37.1 years for the placebo group, 36.5 years for the TZA group, and 36.9 years for the CYC group. Sex distribution was identical for the placebo and CYC groups, with 87% female and 13% male, while the TZA group was 100% female.

The pain-intensity data showed no significant difference among the three groups for the pain-intensity measurements at the pretreatment assessment (stratified random sampling; $P = .0579$). Significant differences were found in pain-intensity measurements from pretreatment to posttreatment for all groups ($P < .0001$); however, the posttreatment assessment revealed no differences among the groups (Table 1). There was no significant interaction effect between treatment and time of measurement.

For mod SSI measurements, the one-way ANOVA revealed that at least two of the three groups were significantly different from each other ($P = .0048$) at the pretreatment assessment, as can be seen in Table 2. There was a statistically significant difference in the pretreatment and posttreatment measurements as well in the treatments. The Scheffe test demonstrated that at posttreatment, the CYC and placebo groups were significantly different from one another ($P = .0319$), where the decrease of symptoms was significantly higher in the CYC group. At posttreatment, the TZA group did not differ significantly from the other groups. There was also no significant interaction effect between treatment and time of measurement.

With respect to PSQI evaluation, the results demonstrated equality of all groups ($P = .7274$) at the pretreatment assessment. There were also statistical differences ($P < .0001$) between the pretreatment and posttreatment PSQI scores for all groups (Table 3). However, no differences among the groups were observed. There was also no significant interaction effect between treatment and time of measurement.

The main side effects reported in this study were morning drowsiness, dry mouth, and fatigue. Morning drowsiness was reported in 13% of the patients in the placebo group, 73% of the patients in the TZA group, and 53% of the patients in the CYC group. The incidence of dry mouth was 33%, 73%, and 60% for the placebo, TZA and CYC, groups, respectively. Fatigue was a side effect reported in 7% of the patients in the placebo group, 27% of the patients in the TZA group, and 20% of the patients in the CYC group. In the TZA group, two patients related loss of appetite; in the placebo group, one patient related insomnia.

Considering the use of rescue medication, the mean number of ibuprofen tablets (400 mg/tablet) was 2.5 for the placebo group, 2.7 for the TZA group, and 3.3 for the CYC group; these values were not statistically significant among the three groups ($P = .268$).

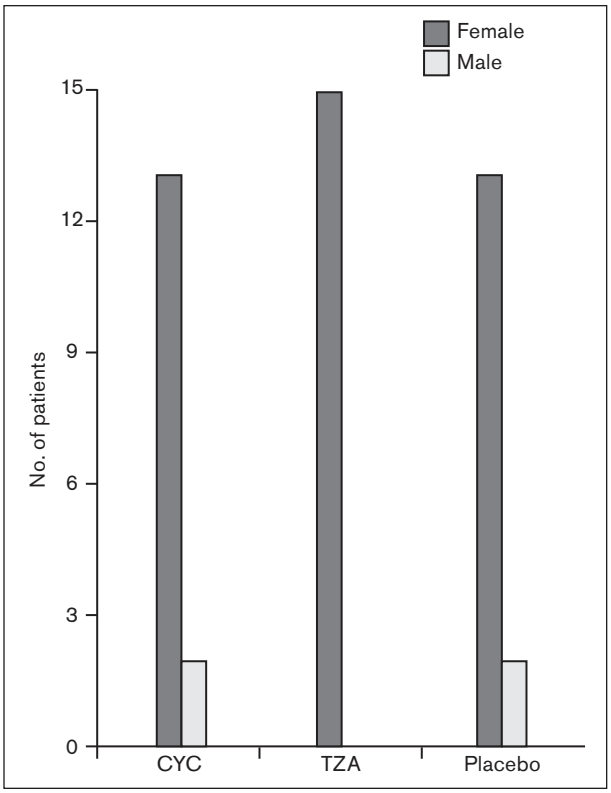

Fig 1a Sex of the patient sample in the cyclobenzaprine (CYC) group (n = 15), tizanidine (TZA) group (n = 15), and placebo group (n = 15).

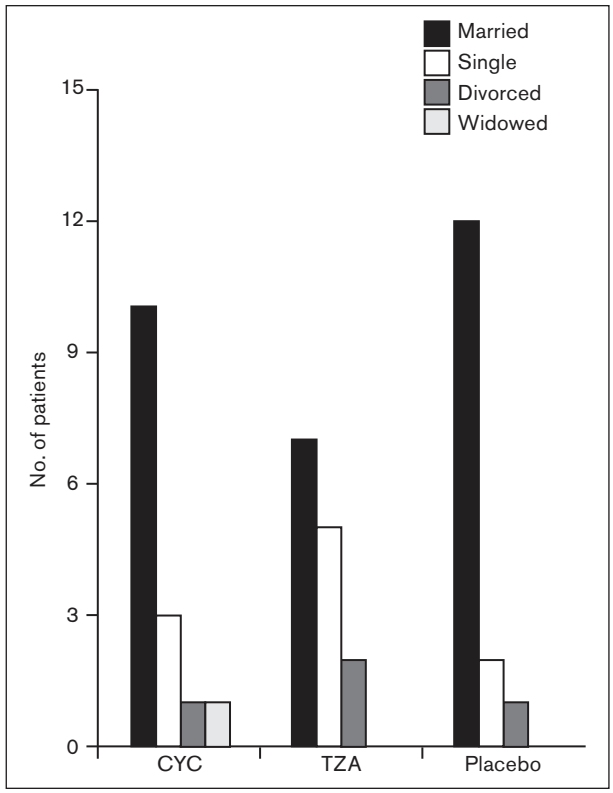

Fig 1b Civil status of the patient sample in the cyclobenzaprine (CYC) group (n = 15), tizanidine (TZA) group (n = 15), and placebo group (n = 15).

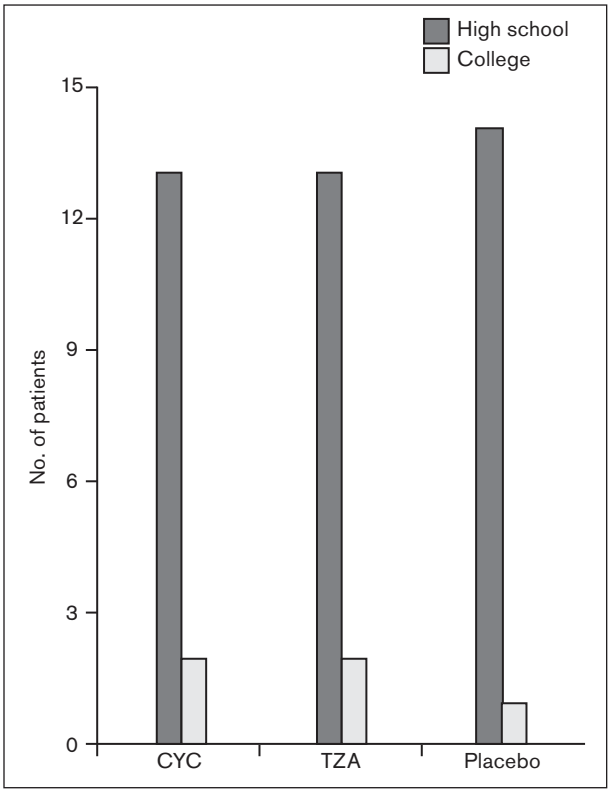

Fig 1c Education level of the patient sample in the cyclobenzaprine (CYC) group (n = 15), tizanidine (TZA) group (n = 15), and placebo group (n = 15).

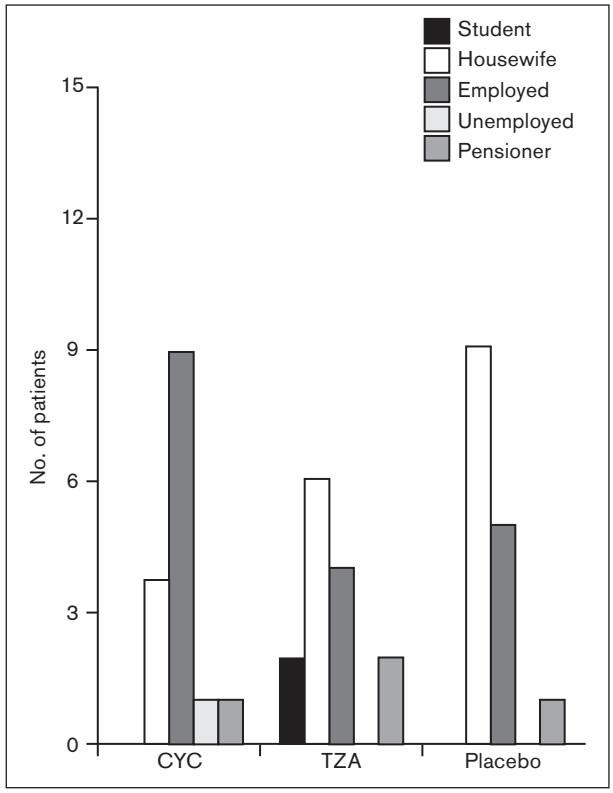

Fig 1d Occupation of the patient sample in the cyclobenzaprine (CYC) group (n = 15), tizanidine (TZA) group (n = 15), and placebo group (n = 15).

Table 1 Mean (Standard Deviation) Pretreatment and Posttreatment Pain Intensity Scores* of the Study Groups

Group	Pretreatment	Posttreatment
Placebo	0.65 (0.05)^{Aa}	0.47 (0.06)^{Bb}
Tizanidine	0.69 (0.07)^{Aa}	0.48 (0.08)^{Bb}
Cyclobenzaprine	0.84 (0.05)^{Aa}	0.55 (0.07)^{Bb}

*Measured on a visual analog scale (one of three subscales included in the modified Severity Symptoms Index.
Horizontally, means with different capital superscript letters are significantly different ($P < .05$). Vertically, means with different small superscript letters are significantly different ($P < .05$).

Table 2 Mean (Standard Deviation) Pretreatment and Posttreatment Pain Symptom (mod SSI) Scores of the Study Groups

Group	Pretreatment	Posttreatment
Placebo	0.67 (0.01)^{Aa}	0.51 (0.05)^{Ba}
Tizanidine	0.70 (0.07)^{Aa}	0.58 (0.03)^{Ba,b}
Cyclobenzaprine	0.84 (0.02)^{Ab}	0.61 (0.05)^{Bb}

mod SSI, modified Pain Severity Index.
Horizontally, means with different capital superscript letters are significantly different ($P < .05$). Vertically, means with different small superscript letters are significantly different ($P < .05$).

Table 3 Mean (Standard Deviation) Pretreatment and Posttreatment PSQI Scores of the Study Groups

Group	Pretreatment	Posttreatment
Placebo	12.33 (0.79)^{Aa}	8.47 (1.30)^{Bb}
Tizanidine	11.33 (0.90)^{Aa}	7.27 (0.67)^{Bb}
Cyclobenzaprine	11.73 (0.97)^{Aa}	6.47 (1.08)^{Bb}

PSQI, Pittsburgh Sleep Quality Index.
Horizontally, means with different capital superscript letters are significantly different ($P < .05$). Vertically, means with different small superscript letters are significantly different ($P < .05$).

Discussion

The prevalence of myofascial pain has been reported in the literature for populations with different pain complaints, such as headaches, lower back pain, and jaw pain, as well as in controls (patients without pain).[12,13] A study conducted on 269 nursing students, between the ages of 20 and 40 years, concluded that 50% of the sample exhibited symptoms of myofascial pain associated with the masticatory muscles.[33] In a report on the clinical characteristics of TMD in the population, myofascial pain was the most common dysfunction, affecting 54.6% of patients with complaints of chronic headache and neck pain.[1]

In another study[34] trying to establish the prevalence of myofascial pain trigger points in a patient population with chronic headaches, including tension-type headaches and migraines, the authors found that trigger points were present in 77% of the subjects. Active trigger points were more frequent in temporalis, occiptofrontalis, and masseter muscles.

Preventive medications used to manage myofascial pain symptoms could act by improving a patient's sleep quality and/or decreasing jaw pain. Specifically as a preventive medication for myofascial pain patients, cyclobenzaprine has been evaluated in few studies.[2]

According to Nixdorf et al,[31] a complete and accurate representation of the pain experience is essential in clinical trials involving treatment interventions for chronic pain conditions such as TMD. Among the pain-evaluation modalities, pain intensity is the outcome variable most used in these studies because it is easily conceptualized, reliably reported by study subjects, and considered a robust measure.[31,35] In agreement, the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) Statement has recommended pain intensity as a core outcome variable for assessing pain in clinical trials.[36]

However, the pain experience can vary among individuals, and it has been suggested that besides pain intensity, other aspects of pain must be evaluated, such as frequency, duration, and sensory and affective dimensions. Considering that a systematic evaluation of the multiple aspects of pain is needed for a better interpretation of clinical trial outcomes and that the mod SSI is capable of globally assessing pain,[31] the mod SSI has been used as an instrument for assessment of pain symptoms in TMD studies.[2,12,13,31,37] Hence, the pain intensity and mod SSI measurements were used in this study.

The pain-intensity data showed that there was an improvement of symptoms for all groups between pretreatment and posttreatment, but no statistically significant difference among the groups could be observed. The mod SSI results also demonstrated an improvement of symptoms for all groups between pretreatment and posttreatment. Moreover, at posttreatment, cyclobenzaprine was more effective than placebo. However, it is important to consider that there was a pretreatment difference between the groups. This fact must be taken into account, because it weakens any conclusion about the superiority of cyclobenzaprine in the present study. The absence of statistically significant differences in pain intensity also supports this view. Herman et al[2] also evaluated the effect of cyclobenzaprine on patients with jaw pain upon awakening, comparing it to clonazepam and placebo. The present study tried to minimize other possible confounders, such as inclusion of patients with Axis I diagnosis group 2 and 3 (arthralgia and disc displacements), since the pain

mechanism could be different from myofascial pain. This would be even more critical if the jaw pain upon awakening could be attributed to arthralgia (inflammation in the TMJ) causing jaw pain upon awakening.

Tizanidine, an imidazolic derivative, was not more effective compared to the medications (cyclobenzaprine, placebo) used by the other groups in this study to alleviate painful symptoms. Tizanidine has been used in Europe and Japan for several years to alleviate painful muscle spasms due to musculoskeletal disorders and spasticity of various origins.[24] The present results for tizanidine are not in agreement with the results obtained by Malanga et al[40] and Manfredini et al.[41] However, there are several differences in study designs that could explain this lack of agreement. Malanga et al[40] did not evaluate the use of tizanidine on myofascial pain with jaw pain upon awakening; they did not have a control (placebo or no treatment) group; and most importantly, they used a higher dose—patients could be titrated up to 12 mg/day and the dose maintained for 2 weeks. Although Manfredini et al[41] also evaluated tizanidine 4 mg/day, the dosage was not administered once at bedtime; instead, patients were instructed to take 2 mg in the morning and 2 mg after dinner. Patients who participated in the study had the diagnosis of myofascial pain but not specifically jaw pain upon awakening. Also, their study was not a randomized trial and they did not have a control or placebo group (not a controlled study). Finally, they did not use any kind of patient education or self-care management along with the medications. Another explanation could be that since the present study evaluated myofascial pain in the orofacial region, the pain in this area could have been complicated or aggravated by the presence of oral daytime parafunctions and sleep bruxism. Taking safety into consideration, the dose of 4 mg used in the present study has been used as the initial dose for the treatment of muscular spasms, and could be titrated up to 36 mg/day, divided in three different doses, without significant effects of toxicity in adults.[42] Most studies have evaluated the use of tizanidine as a preventive medication in headache management, and the doses varied from a single dose to three divided doses, and also patients could be titrated up to a maximum of 32 mg/day.[21] A double-blind study compared the effectiveness of tizanidine to placebo for the treatment of patients with headaches, using a total dose of 18 mg/day, divided into three doses of 6 mg each. After 1 month of treatment, the headache index was reduced by 54% in the group treated with tizanidine compared to 19% in the placebo group, with the occurrence of adverse effects reported in fewer than 10% of the patients.[25] Since a single dose of cyclobenzaprine had already been shown to be effective,[2] the present study evaluated a single dose of tizanidine. Since the patients were not titrated to the maximum dose tolerated or effective for them, future research should evaluate the effect of tizanidine in larger single daily doses (6 to 12 mg) as well as in three daily doses from 4 to 6 mg, titrating the dose as necessary.

Considering that complex interactions appear to exist between sleep and chronic pain conditions, the present study also evaluated the effect of the medications and self-care program on sleep quality. It is known that chronic pain may cause sleep disturbances, and sleep disturbances may cause or prolong chronic pain.[44] The PSQI, having a possible score range from 0 to 21 (0 being the best and 21 the worst), was used to measure sleep quality. The results of the present investigation indicate that cyclobenzaprine, tizanidine, as well as placebo associated with self-care were all effective in improving sleep quality, without significant differences among the groups.

This finding is of fundamental importance in the management of myofascial pain, since poor quality of sleep may act as an important etiologic contributing factor. In fact, it should be kept in mind that this study did not use only a placebo medication, but rather the placebo was added to the self-care management program; this may be at least one of the possible explanations why patients had better sleep quality with with placebo medication. Chronic pain can disrupt sleep architecture so that patients sleep only in the light stages of sleep, which can cause the patient to wake up feeling tired and also fatigued during the course of the day.[44] If patients can reduce their pain intensity, frequency, and duration, it may affect their sleep architecture and have a positive influence on sleep quality. Hence, as demonstrated by the present results, patients engaged in a self-care management program can obtain relief of their pain symptoms, and this can have a positive impact on their sleep quality. Therefore, it is fundamental to point out that the improvement in pain and sleep quality observed for the control group reinforces the importance of a home-care regimen and patient education to manage patients with myofascial pain.[2,3] This does not mean that patients with myofascial pain will never benefit from the use of a preventive medication such as cyclobenzaprine. Depending on the duration, frequency, and intensity of pain, and the presence of central sensitization, the use of these medications could be helpful.

The present findings in the control (placebo) group also indicate that patients with chronic orofacial pain can obtain improvement of their pain condition as well as improvement in their sleep quality not only without the use of medications, but also without the need for occlusal appliances or any other irreversible interventions such as occlusal adjustments. Therefore, the

initial treatment approach for these patients should always include self-care management and patient education.

High withdrawal rates probably indicate some combination of poor tolerability and ineffectiveness,[45] which was not observed in the present study. All reported side-effects occurred more frequently with tizanidine and cyclobenzaprine than with placebo. However, both medications were safe and well tolerated, with adverse effects similar to what have been previously reported in other studies.[24,26,40,42,46]

This study had some limitations, since only sleep quality and remission of pain were evaluated. Other signs or symptoms, such as the quality of life, sleep architecture, nocturnal parafunctional activities (especially sleep bruxism), and tenderness to digital muscle palpation, should be evaluated in future studies. Since all patients had a trigger point in the masseter muscle that may have been responsible for their jaw pain, sleep bruxism or/and daytime clenching were likely etiologic factors, but a sleep study during the time of the research would have been required to test this possibility. Moreover, studies with a longer evaluation time, such as the 3 months suggested in the guidelines for preventive medications in chronic headache management,[47] are also warranted in the future.

It could be concluded that in the short term, the use of tizanidine or cyclobenzaprine, in addition to self-care management and patient education, was not more effective than adding a placebo medication. Similarly, since there was also no significant difference among the groups in sleep quality, longer duration studies would be useful, since clinically some patients need more than 3 weeks to report improvement in their sleep quality.

The use of tizanidine with patient education and self-care management may be another option for the treatment plan, especially when patients do not tolerate or respond well to cyclobenzaprine. However, it should be evaluated in greater doses (6 to 12 mg). Most studies that have evaluated tizanidine as a preventive medication have studied it in headache patients, and it was always administrated three times a day. Cyclobenzaprine when used or indicated as a muscle relaxant is also administered three times a day. Future studies are needed to test if tizanidine may be used once a day as a preventive medication for myofascial pain patients.

Acknowledgments

The authors thank PIBIC and PROAP for financing part of this research. They also acknowledge Marquette University, specifically the General Dental Sciences Department (MUSoD), for the great support during the conclusion of this research. They also thank Jessica E. Pruszynski, PhD,, Medical College of Wisconsin, Division of Biostatistics for her important revision of the data. The authors reported no conflicts of interest related to this study.

References

1. 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: 615–623.
2. 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;16:64–70.
3. Wright EF, Schiffman EL. Treatment alternatives for patients with masticatory myofascial pain. J Am Dent Assoc 1995;126: 1030–1039.
4. Leite FM, Atallah AN, El Dib R, et al. Cyclobenzaprine for the treatment of myofascial pain in adults. Cochrane Database Syst Rev 2009;8(3):CD006830.
5. Castro MM, Daltro C. Sleep patterns and symptoms of anxiety and depression in patients with chronic pain. Arq Neuropsiquiatr 2009;67:25–28.
6. Turk DC, Zaki HS, Rudy TE. Effects of intraoral appliance and biofeedback/stress management alone and in combination in treating pain and depression in patients with temporomandibular disorders. J Prosthet Dent 1993;70:158–164.
7. Denucci DJ, Dionne RA, Dubner R. Identifying a neurobiologic basis for drug therapy in TMDs. J Am Dent Assoc 1996; 127:581–593.
8. Dionne RA. Pharmacologic treatments for temporomandibular disorders. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1997;83:134–142.
9. Konstantinovic VS, Lazic V. Occlusion splint therapy in patients with craniomandibular disorders (CMD). J Craniofac Surg 2006;17:572–578.
10. 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: 196–203.
11. Shen YF, Younger J, Goddard G, Mackey S. Randomized clinical trial of acupuncture for myofascial pain of the jaw muscles. J Orofac Pain 2009;23:353–359.
12. Venancio RA, Alencar Jr FG, Zamperini C. Different substances and dry-needling injections in patients with myofascial pain and headaches. Cranio 2008;26:96–103.
13. Venancio RA, Alencar FG Jr, Zamperini C. Botulinum toxin, lidocaine, and dry-needling injections in patients with myofascial pain and headaches. Cranio 2009;27:46–53.

14. Ay S, Evcik D, Tur BS. Comparison of injection methods in myofascial pain syndrome: A randomized controlled trial. Clin Rheumatol 2010;29:19–23.
15. Randolph CS, Greene CS, Moretti R, Forbes D, Perry HT. Conservative management of temporomandibular disorders: A posttreatment comparison between patients from a university clinic and from private practice. Am J Orthod Dentofacial Orthop 1990;98:77–82.
16. Katz WA, Dube J. Cyclobenzaprine in the treatment of acute muscle spasm: Review of a decade of clinical experience. Clin Ther 1988;10:216–228.
17. Santandrea S, Montrone F, Sarzi-Puttini P, Boccassini L, Caruso I. A double-blind crossover study of two cyclobenzaprine regimens in primary fibromyalgia syndrome. J Int Med Res 1993;21:74–80.
18. Spiller HA, Winter ML, Mann KV, Borys DJ, Muir S, Krenzelok EP. Five-year multicenter retrospective review of cyclobenzaprine toxicity. J Emerg Med 1995;13:781–785.
19. Elenbaas JK. Centrally acting oral skeletal muscle relaxants. Am J Hosp Pharm 1980;37:1313–1323.
20. Basmajian JV. Cyclobenzaprine hydrochloride effect on skeletal muscle spasm in the lumbar region and neck: Two double-blind controlled clinical and laboratory studies. Arch Phys Med Rehabil 1978;59:58–63.
21. Lance JW, Anthony M. Cyclobenzaprine in the treatment of chronic tension headache. Med J Aust 1972;2:1409–1411.
22. Murros K, Kataja M, Hedman C, et al. Modified-release formulation of tizanidine in chronic tension-type headache. Headache 2000;40:633–637.
23. Saper JR, Lake AE 3rd, Cantrell DT, Winner PK, White JR. Chronic daily headache prophylaxis with tizanidine: A double-blind controlled, multicenter outcome study. Headache 2002;42:470–482.
24. Pareek A, Chandurkar N, Chandanwale AS, Ambade R, Gupta A, Bartakke G. Aceclofenac-tizanidine in the treatment of acute low back pain: A double-blind, double-dummy, randomized, multicentric, comparative study against aceclofenac alone. Eur Spine J 2009;18:1836–1842.
25. Rapoport AM, Bigal ME. Preventive migraine therapy: What is new. Neurol Sci 2004;25:177–185.
26. Saper JR, Winner PK, Lake AE 3rd. An open-label dose-titration study of the efficacy and tolerability of tizanidine hydrochloride tablets in the prophylaxis of chronic daily headache. Headache 2001;41:357–368.
27. Smith TR. Low-dose tizanidine with nonsteroidal anti-inflammatory drugs for detoxification from analgesic rebound headache. Headache 2002;42:175–177.
28. Simons DG, Travell JG, Simons LS. Travell and Simons's Myofascial Pain and Dysfunction: The Trigger Point Manual, Vol 1 (ed 2). Baltimore: Williams & Wilkins, 1999.
29. De Leeuw R. Orofacial Pain: Guidelines for Assessment, Diagnosis, and Management, ed 4. Chicago: Quintessence, 2008.
30. Fricton JR. Musculoskeletal measures of orofacial pain. Anesth Prog 1990;37:136–143.
31. Nixdorf DR, John MT, Wall MM, Fricton JR, Schiffman EL. Psychometric properties of the modified Symptom Severity Index (SSI). J Oral Rehabil. 2010;37:11–20.
32. 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 Res 1989;28:193–213.
33. Schiffman EL, Fricton JR, Haley DP, Shapiro BL. The prevalence and treatment needs of subjects with temporomandibular disorders. J Am Dent Assoc 1990;120:295–303.
34. Sanita PV, Alencar FGP Jr. Myofascial Pain Syndrome as a contributing factor in patients with chronic headaches. J Musculosk Pain 2009;17:15–25.
35. Jensen MP, Karoly P. Self-report scales and procedures for assessing pain in adults. In: Turk DC, Melzack R (eds). Handbook of Pain Assessment, ed 2. New York: Guilford Press, 2001:15–34.
36. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 2005;113:9–19.
37. Alencar F Jr, Becker A. Evaluation of different occlusal splints and counselling in the management of myofascial pain dysfunction. J Oral Rehabil 2009;36:79–85.
38. Betucci D, Testa L, Calzoni S, Mantegazza P, Viana M, Monaco F. Combination of tizanidine and amitriptyline in the prophylaxis of chronic tension-type headache: Evaluation of efficacy and impact on quality of life. J Headache Pain 2006;7:34–36.
39. Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain 2008;9:105–121.
40. Malanga GA, Gwynn MW, Smith R, Miller D. Tizanidine is effective in the treatment of myofascial pain syndrome. Pain Physician 2002;5:422–432.
41. Manfredini D, Romagnoli M, Cantini E, Bosco M. Efficacy of tizanidine hydrochloride in the treatment of myofascial face pain. Minerva Med 2004;95:165–171.
42. Spiller HA, Bosse GM, Adamson LA. Retrospective review of tizanidine (Zanaflex) overdose. J Toxicol Clin Toxicol 2004;42:593–596.
43. Semenchuk MR, Sherman S. Effectiveness of tizanidine in neuropathic pain: An open-label study. J Pain 2000;1:285–292.
44. Merrill RL. Orofacial pain and sleep. Sleep Med Clin 2010;5:131–144.
45. Chou R, Kim P, Helfand M. Comparative efficacy and safety of skeletal muscle relaxants for spasticity and musculoskeletal conditions: A systematic review. J Pain Symptom Manage 2004;28:140–175.
46. Malanga GA, Ruoff GE, Weil AJ, Altman CA, Xie F, Borenstein DG. Cyclobenzaprine ER for muscle spasm associated with low back and neck pain: Two randomized, double-blind, placebo-controlled studies of identical design. Curr Med Res Opin 2009;25:1179–1196.
47. Silberstein S, Tfelt-Hansen P, Dodick DW, et al. Guidelines for controlled trials of prophylactic treatment of chronic migraine in adults. Cephalalgia 2008;28:484–495.