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

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Aims: *To compare the relative effectiveness of a benzodiazepine (clonazepam), a muscle relaxant (cyclobenzaprine), and a placebo for the treatment of jaw pain upon awakening, when each is combined with the recommended nonpharmacological components of initial medical management.* ***Methods:*** *Forty-one subjects were recruited with a diagnosis of myofascial pain based on the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD). All subjects were given education about TMD and a self-care program. Subjects were randomized into 1 of 3 groups: clonazepam (0.5 mg/night), cyclobenzaprine (10 mg/night), or placebo. The primary outcome measure was the subjects' average intensity of jaw pain upon awakening over the prior week. This was recorded with a visual analog scale at pretreatment and at the completion of the 3-week trial. A secondary outcome measure was sleep quality based on the Pittsburgh Sleep Quality Index.* ***Results:*** *Within-group changes showed a statistically significant ($P < .001$) decrease in jaw pain upon awakening for all 3 groups. Between-group differences demonstrated a statistically significant difference ($P < .016$) between cyclobenzaprine and placebo, and between cyclobenzaprine and clonazepam. There was no significant effect on sleep quality in any group.* ***Conclusion:*** *This study suggests that cyclobenzaprine is statistically superior to either placebo or clonazepam when added to self-care and education for the management of jaw pain upon awakening. Based on the subjects' report of sleep quality, these medications failed to significantly improve sleep in the short term.*

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Temporomandibular disorders (TMD) are musculoskeletal disorders affecting the temporomandibular joints (TMJ) and/or the muscles of mastication, as well as contiguous tissue components.[1] Commonly associated with TMD is myofascial pain (MFP), which involves muscle, tendon, and fascia, and is clinically characterized by distinct trigger points that when palpated produce regional referred pain.[2] Other symptoms that frequently accompany myofascial pain include psychological disturbances (eg, anxiety and depression) and difficulties with sleep.[3] One study estimated that 25% of TMD sufferers meet the criteria for myalgia or for MFP.[4] In a study of 20- to 40-year-old student nurses, 50% exhibited symptoms of MFP in association with their masticatory

muscles.[5] A report on a TMD clinic population revealed that MFP was the most common cause of pain, accounting for 54.6% of chronic head and neck pain in these patients.[6]

Initial medical management is the recommended treatment for patients with symptomatic TMD, and is similar to other musculoskeletal disorders affecting the body. The National Institutes of Health Technology Assessment Conference Statement on the Management of Temporomandibular Disorders recommends that initial attention should be given to the issue of patient education and home-care, including the elimination of oral habits.[1] It also suggests that medications may be a useful initial aid. However, there is a lack of controlled clinical trials to determine the effectiveness of pharmacologic interventions as an adjunct to nonpharmacologic management of symptomatic TMD.

One medication employed for treatment of TMD is clonazepam (Klonopin, Roche Laboratories), a benzodiazepine which is classified as an anticonvulsant and has a pharmacologic profile similar to other anxiolytic/sedative benzodiazepines. The effect of these drugs has been attributed to their interaction with the γ-aminobutyric acid (GABA) and, more specifically, the $GABA_A$ receptor subtypes complex.[7] Clinically, clonazepam is used not only to control seizures, but also as a mean to control motor or movement disorders (ie, restless leg syndrome), as an anxiolytic, and as a sedative to aid in sleep.

Another medication used in the treatment of TMD is cyclobenzaprine (Flexeril, Merck & Co.), a centrally acting skeletal muscle relaxant that is closely related in structure to the tricyclic antidepressants and that was originally tested as an antidepressant.[8] It acts primarily within the central nervous system at the brainstem level through a poorly defined mechanism.[9] Recent studies suggest that cyclobenzaprine is a serotonin ($5\text{-}HT^2$) receptor antagonist that exerts its muscle relaxant effects due to a central inhibition of serotonergic descending systems.[10] Clinically, cyclobenzaprine has been widely used to treat fibromyalgia syndrome,[11,12] chronic tension type headaches,[13] and muscle spasm of the cervical and lumbar region.[14] Only 1 study has compared cyclobenzaprine with a benzodiazepine (diazepam) and a placebo.[14] Clinical improvement in signs and symptoms of chronic muscle spasm was observed for both medications as well as the placebo, but there was no statistical difference between the 3 treatment groups.

The aim of this study was to compare the relative effectiveness of clonazepam, cyclobenzaprine, and a placebo for the treatment of jaw pain upon awakening, when each is combined with the recommended nonpharmacological components of initial medical management.

Materials and Methods

Study Sample

Subjects were recruited at the University of Minnesota School of Dentistry TMJ/Orofacial Pain Clinic, HealthPartners Medical Center TMD Clinic, St. Paul, MN, a private practice (ELS), and by advertisement in the *University of Minnesota Daily*.

Criteria for inclusion of subjects included: *(1)* jaw pain upon awakening, occurring a minimum of 2 days per week; *(2)* a diagnosis of myofascial pain as defined for axis 1 group I of the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD).[15] Concurrent diagnoses of TMJ arthralgia and disc displacement with reduction were allowed; *(3)* a self-report of an average jaw pain intensity in the past week of at least 4 on a visual analog scale (VAS) of 0 (no pain) to 1.0 (worst pain imaginable); *(4)* a self-report of psychological stability (subjects taking antidepressants were considered stable if they reported no current depression, and had been on a stable regimen of psychotropic medications for 3 months); *(5)* an age range between 18 and 65 years.

Criteria for exclusion of subjects included: *(1)* any dental, orofacial problem or TMD not meeting the definition of myofascial pain as defined by the *RDC/TMD*; *(2)* a self-report of persistent depression or an unstable regimen of psychotropic medication of less than 3 months as indicated by their history; *(3)* jaw pain of potential systemic origin as identified by their history (specifically, subjects were asked if they had been diagnosed with fibromyalgia, or if they had widespread pain); *(4)* clinical or radiographic evidence of osseous, odontogenic, or TMJ pathology; *(5)* a report of liver dysfunction, alcoholism, glaucoma, history of seizures, impaired renal function, use of monoamine oxidase inhibitors, acute recovery phase of myocardial infarction, arrhythmia, heart block or conduction disturbances, congestive heart failure, hyperthyroidism, pregnancy, or any other contraindications to clonazepam or cyclobenzaprine (including drug allergies).

Prior to the recruitment of subjects, the first 3 authors underwent a calibration exercise and demonstrated adequate reliability for the relevant clinical examination items necessary to make a

Table 1 Selected Characteristics of Study Subjects by Treatment Group

Variable	Clonazepam	Placebo	Cyclobenzaprine	*P* value for between-group differences
Sample Size (n) – Dx of MFP	13	15	13	
Mean age (SD)	26.9 (10.1)	24.0 (4.8)	30.3 (8.6)	$P > .122$
Sex	2 male 11 female	1 male 14 female	5 male 8 female	$P > .14$
Diagnosis of TMJ arthralgia	4	5	5	$P > .6$
Use of psychotropic medication	1	1	1	$P = 1.0$
Mean frequency of jaw pain upon awakening (SEM)	5.5 (0.4)	4.8 (0.4)	5.9 (0.3)	$P > .17$

RDC/TMD diagnosis for myofascial pain. Their 3 pairwise kappa statistics ranged from 0.81 to 1.0. Out of 47 subjects meeting the criteria for inclusion, 41 consented to participate, including 33 women and 8 men. Table 1 shows by treatment group the age distributions, sex distributions, concurrent TMJ diagnoses, concurrent use of psychotropic medications, and days/week that jaw pain was experienced upon awakening. Subjects were paid a nominal compensation for their participation. This study was reviewed and approved by the Institutional Review Board: Human Subjects Committee, University of Minnesota, Minneapolis, MN and the Institutional Review Board for the HealthPartners Research Foundation.

Study Design

The study design was a double-blind, placebo-controlled, randomized clinical trial to evaluate the relative effectiveness of adding either cyclobenzaprine or clonazepam to patient education and a self-care program in the management of jaw pain upon awakening. The primary outcome measure was the average intensity of jaw pain upon awakening. The secondary outcome measure was change in sleep quality.

All subjects, including the placebo group, received patient education consisting of explanations of TMD and MFP, and a self-care program administrated by 1 of the first 3 authors. The latter included both written and verbal instructions relative to self-care for masticatory muscle pain.[16]

Subjects were allocated to their treatment group by means of a randomized block design with the blocking variable being the current use of psychotropic medications. Study dosage was consistent with common clinical practice: Group 1 received 0.5 mg of clonazepam daily, group 2 received a placebo consisting of lactose filler, and group 3 received 10 mg of cyclobenzaprine daily. The capsules were formulated to have the same appearance, and all subjects took 1 capsule 1 hour before bedtime during the 3-week intervention. Neither the treating doctor nor the subject was aware of the treatment assignment until completion of the intervention.

Data Collection

Data collection was performed at baseline and at the 3-week follow-up by means of 2 standardized self-report questionnaires: (1) Symptom Severity Index (SSI) for jaw pain, TMJ pain, and temple pain, which is a valid and reliable self-report questionnaire,[17,19,20] and (2) the Pittsburgh Sleep Quality Index (PSQI),[18] a 19-item self-report questionnaire used to assess sleep quality and disturbances. The primary outcome measure in this study was the pain sensory intensity VAS, 1 of 5 VAS included in the SSI. In addition, a record was kept for each subject consisting of any reported side effects from their assigned medication, as well as whether they felt a need for further treatment at the end of their 3-week intervention.

Data Analysis

The data analysis for jaw pain sensory intensity and sleep quality included an unadjusted analysis for within-group changes over time (paired *t* test), and between-group differences as to mean change from baseline (2-sample independent *t* test). Alpha was set at 0.05/3 = 0.017 to reduce the likelihood

Table 2 Pretreatment, Posttreatment, and Change from Baseline Means for Jaw Pain Intensity upon Awakening and Pittsburgh Sleep Quality Index (PSQI) by Treatment Group

	Pretreatment mean (SEM)	Posttreatment mean (SEM)	Change from baseline mean (SEM)	*P* value for within-group differences
Jaw pain intensity				
Group I (n = 13) Clonazepam	0.48 (0.05)	0.28 (0.06)	0.20 (0.04)	$P = .0007$
Group II (n = 15) Placebo	0.50 (0.04)	0.30 (0.05)	0.20 (0.04)	$P = .0003$
Group III (n = 13) Cyclobenzaprine	0.62 (0.04)	0.17 (0.05)	0.45 (0.07)	$P = .0001$
P-value for pairwise contrasts between groups	I vs III – $P < .054$ II vs III – $P < .061$	All contrasts $P > .06$	I vs III – $P < .004$ II vs III – $P < .004$	
PSQ Index				
Group I (n = 13) Clonazepam	6.54 (0.97)	5.92 (0.90)	0.62 (0.62)	$P > .3$
Group II (n = 15) Placebo	5.80 (0.89)	4.60 (0.62)	1.20 (0.60)	$P > .06$
Group III (n = 13) Cyclobenzaprine	7.23 (0.89)	5.08 (0.67)	2.15 (0.79)	$P < .02$
P value for pairwise contrasts between groups	All contrasts $P > .2$	All contrasts $P > .2$	All contrasts $P > .1$	

of a Type I error. A trend toward statistical significance was defined as $.017 < P < .05$. The adjusted analysis was performed with Proc GLM (SAS Institute) to control for age, sex, and between-subject differences for the outcome variable at baseline.

Results

The final sample consisted of 33 women and 8 men with no subject dropouts or withdrawals. As shown in Table 1, there was no statistically significant baseline difference in terms of age, sex distributions, concurrent diagnoses of TMJ arthralgia, concurrent use of psychotropic medications, or for days/week with jaw pain upon awakening. In each group, just 1 subject was being treated concurrently with a psychotropic drug for depression. As shown in Table 1, the mean frequency of jaw pain upon awakening varied between 4.8 and 5.9 days per week. Despite the randomization process, there were differences at baseline for jaw pain intensity upon awakening that tended toward significance. As shown in Table 2, the difference between the clonazepam group (0.48) and cyclobenzaprine group (0.62) had a *P* value < .054, and the difference between the placebo group (0.50) and the cyclobenzaprine group (0.62) showed $P < .061$.

Within-group changes over the 3-week intervention were statistically significant for all 3 groups (Table 2). Patients in group 3 who received cyclobenzaprine in addition to patient education and the self-care program experienced a decrease in jaw pain from a baseline mean score of 0.62 to 0.17, or a 72.7% decrease. Patients in group 1 who received clonazepam in addition to the nonpharmacologic intervention decreased from a mean jaw pain of 0.48 to 0.28, or a 40.1 % decrease. Patients in group 2 who received the placebo performed similarly, decreasing from a mean jaw pain of 0.50 to 0.30, a 40.2% improvement. The magnitude of mean change from baseline for the cyclobenzaprine group (0.45) was significantly greater than for either the placebo group (0.20) or the clonazepam group (0.20). The improvements observed within groups and the differences between groups are depicted in Figure 1.

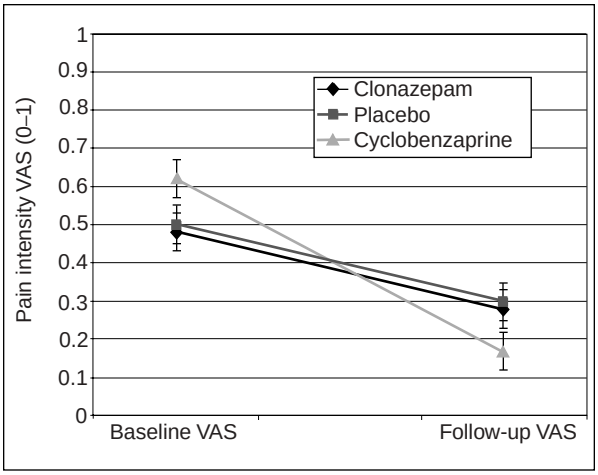

Fig 1 Change in intensity of jaw pain upon awakening (unadjusted means and standard error measure by treatment group).

Although the observed decreases over time in jaw pain intensity differed statistically between treatment groups, the 3 treatment groups were relatively grouped together with respect to their observed posttreatment means for jaw pain intensity. There was no statistical difference ($P > .1$) between a mean score of 0.30 for placebo, 0.28 for clonazepam, and 0.17 for cyclobenzaprine. However, an adjusted analysis was performed to control for baseline differences in the intensity of jaw pain upon awakening as well as differences in the age and sex distribution. After this adjustment, the least squares post-treatment estimates and SEM were 0.32 (0.04) for the clonazepam group, 0.34 (0.05) for the placebo group, and 0.12 (0.05) for the cyclobenzaprine group. The adjusted outcome associated with the cyclobenzaprine was statistically superior to that associated with either clonazepam or the placebo ($P < .016$).

The PSQI, having a possible score range of 0 to 21, was used to measure sleep quality. Participant baseline scores ranged from 1 to 17. The results show that participants who received cyclobenzaprine had a mean baseline score of 7.23 and a mean decrease of 2.15 that tended toward statistical significance ($P < .02$). The group that received clonazepam had a baseline mean of 6.54 with a nonsignificant mean decrease of 0.62 ($P > .3$), while the group that received placebo had a baseline mean of 5.80 with a nonsignificant mean decrease of 1.20 ($P > .06$). Sixty-six percent (27 out of 41) of participants had a global PSQI score of >5 at baseline that, according to Buysse et al,[18] suggests poor sleep quality. Following the intervention period, 61% (25 out of 41) of participants obtained a PSQI score of >5, indicating that poor sleep quality had not been relieved by the intervention.

Subjects for all 3 groups reported side effects from their assigned medications. Eight subjects (62%) of those receiving cyclobenzaprine reported side effects including morning drowsiness, dry mouth, and nightmares, while 5 subjects (40%) receiving clonazepam reported side effects including morning drowsiness and headache. Three subjects, or 20%, who received placebo in addition to education and self-care, reported side effects including drowsiness, dry mouth, and an increase in premenstrual symptoms. The frequencies of subjects reporting side effects were not statistically different (chi-square = 1.42; $P > .23$). No subjects reported side effects that interfered with their daily routine, or required a need to decrease their medication dosage.

All participants reported being compliant with taking their prescribed capsules. All participants reportedly made some effort to implement a self-care regimen. This ranged from watching daytime oral habits to discontinuing gum chewing, eating a "pain-free" diet, and modifying sleep position. The range of unused study medication at closure was from 0–4 capsules/subject.

Following completion of the intervention period, 7 out of 13 subjects in the clonazepam group felt a need for further treatment. By way of comparison, 6 out of 15 subjects in the placebo group and 3 out of 13 in the cyclobenzaprine group felt likewise. The difference in these proportions was not statistically significant (chi-square = 2.52; $P > .11$).

Discussion

This study is the first randomized clinical trial assessing cyclobenzaprine in a TMD population with a primary muscular disorder. The results of this study show that cyclobenzaprine is more effective ($P < .016$) than clonazepam or a placebo when given in addition to patient education and a home self-care program for the management of jaw pain upon awakening.

It is reasonable to question whether the statistically significant mean improvement for all 3 of the treatment groups should also be considered to be clinically significant. Unpublished data from the TMJ/Orofacial Pain division at the University of Minnesota indicate that a difference in jaw pain intensity of 2 points (0.2 in the SSI score) is the minimum difference that may be clinically meaningful to subjects. This would suggest that, on average, subjects in the placebo and clonazepam groups would likely be aware of a meaningful improvement; in fact, approximately half of them felt that further treatment was not necessary after just a 3-week intervention. Furthermore, the average improvement reported by the cyclobenzaprine group was more than twice that of both the clonazepam and placebo groups. This improvement was again illustrated when only 3 subjects in the cyclobenzaprine group felt a need for further treatment.

In the present study, all subjects reported that palpation of their muscles duplicated their jaw pain complaints, and pointed to their masseter muscles as the source of their primary pain. Within the limits of this examination technique, one can conclude that their pain was primarily muscular in origin. The rationale for treating such patients with cyclobenzaprine has been discussed in the literature as well as the possible mechanisms by which it may affect myofascial pain and the resul-

tant symptoms of jaw pain upon awakening. According to Ellenbaas,[20] cyclobenzaprine relieves skeletal muscle spasm of local origin without interfering with muscle function. It has been demonstrated to be an effective skeletal muscle relaxant whose major site of action is supraspinal.[8,10,21] In addition, pharmacologic studies in animals have shown a similarity between the effects of cyclobenzaprine and its structural analog, the tricyclic antidepressants. These effects include norepinephrine potentiation, potent peripheral and central anticholinergic effects, and sedation.[9] However, this study was of 3-weeks' duration and as such did not evaluate the effects of long-term use of these medications. In addition, the effects of long-term use of these medications are unknown. In the long-term management of persons with chronic jaw pain upon awakening, other treatment options should be considered that include intraoral appliances and physical and cognitive behavioral therapy.

This study failed to find the benzodiazepine (clonazepam) to be more effective than a placebo. As such, this finding appears to be in conflict with past clinical research. One study found that diazepam, another benzodiazepine, is effective for chronic orofacial pain of myogenic origin.[22,23] These investigators compared diazepam, ibuprofen, and a combination of diazepam and ibuprofen to placebo in a 4-week, double-blind trial. The decrease in orofacial pain, as measured on a VAS, was significantly greater for both diazepam groups than for the ibuprofen and placebo groups. Additional clinical research has led to recommendations for a 2- to 4-week course of benzodiazepines, including clonazepam, for patients whose pain appears to be of musculoskeletal origin.[24] One double-blind randomized clinical trial tested clonazepam in subjects with TMJ disc dislocations, TMJ arthralgia, and concurrent myofascial pain.[25] Self-reports revealed a reduction in pain at all sites assessed, with several areas reaching significance despite the small sample size of 10.

It must be noted that clonazepam's primary indication is for controlling seizures. Because of its sedating properties, it has also been used for sleep disturbances. Unlike clonazepam, diazepam is a proven skeletal muscle relaxant, as is cyclobenzaprine.[14,26] Herein may lie the answer as to why cyclobenzaprine was observed to be more effective than clonazepam in the treatment of jaw pain upon awakening. Based on the results of this and previous studies,[14,22,23,26,27] there is evidence that medications which aid in muscle relaxation and sedation may be effective for treating the symptoms of masticatory pain of myogenic origin. This study also suggests that medications that do not allow for relaxation of the muscles may not offer adequate pain relief under these conditions. In agreement with previous studies,[28,29] the pain improvements seen for all 3 groups reinforce the importance of patient education and a home self-care regimen for the management of myofascial pain.

The subjects in this study with jaw pain upon awakening had a significantly higher global PSQI score when compared to healthy pain-free controls without sleep complaints.[18] This is consistent with findings of other studies evaluating sleep disturbances in persons with musculoskeletal disorders.[30] Even though the mean sleep quality for the subjects in this study improved, the average sleep quality was still close to the range of poor sleep (> 5) at study closure. Clearly, complex interactions appear to exist between sleep and musculoskeletal pain conditions. Clarification of the exact mechanism by which sleep is disturbed in people with jaw pain upon awakening represents an important area for future research.

There may be several possible explanations as to why sleep quality as measured by the PSQI failed to improve more for the subjects of this study. Neither cyclobenzaprine nor clonazepam is primarily indicated for use in sleep disturbances. Moreover, the dosages specified for this study were intended to affect pain, but a higher dose may be required to be effective for sleep problems. It might also be that a greater length of time would be required to see significant improvement in sleep, since some improvement was observed over the duration of this intervention. Finally, the use of a subjective sleep measure relies on memory, and thus is subject to a recall bias that could be associated with a pattern of poor sleep.

While this study clearly suggests that cyclobenzaprine may be an effective adjunct for the management of jaw pain upon awakening, several limitations should be considered when interpreting the results. First, this is the initial clinical trial evaluating this specific application of cyclobenzaprine, and as such it should be repeated, preferably with the addition of a no-treatment group for comparison. Second, most of the study population (73%, or 30 of 41) was drawn from responders to a newspaper advertisement, and may not represent actual patient populations. Third, subjective self-report measures cannot be objectively verified for accuracy, although subjective reports may be the most important outcome measure in pain management. As retrospective measures, these measures would also be subject to recall bias, and may vary

with respect to both prospective and objective findings. Finally, it is not clear what symptoms or signs other than jaw pain upon awakening were affected by these medications. Future studies might utilize objective polysomnographic sleep data to evaluate which of these medications may have an effect on nocturnal parafunctional activity as well as sleep architecture.

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