Combined Topical and Systemic Clonazepam Therapy for the Management of Burning Mouth Syndrome: A Retrospective Pilot Study

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Aims: *To evaluate retrospectively the efficacy of administering an anticonvulsant medication, clonazepam, by dissolving tablets slowly orally before swallowing, for the management of burning mouth syndrome (BMS).* ***Methods:*** *A retrospective clinical records audit was performed of patients diagnosed with BMS between January 2006 and June 2009. Patients were prescribed 0.5 mg clonazepam three times daily, and changes were made to this regimen based on their individual response. Patients were asked to dissolve the tablet orally before swallowing and were reviewed over a 6-month period. Pain was assessed by patients on an 11-point numerical scale (0 to 10). A nonparametric (Spearman) two-tailed correlation matrix and a two-tailed Mann-Whitney test were performed.* ***Results:*** *A total of 36 patients (27 women, 9 men) met the criteria for inclusion. The mean (± SEM) pain score reduction between pretreatment and final appointment was 4.7 ± 0.4 points. A large percentage (80%) of patients obtained more than a 50% reduction in pain over the treatment period. One patient reported no reduction in pain symptoms, and one third of the patients had complete pain resolution. Approximately one third of patients experienced side effects that were transient and mild.* ***Conclusion:*** *This pilot study provides preliminary evidence that the novel protocol of combined topical and systemic clonazepam administration provides an effective BMS management tool.* J OROFAC PAIN 2011;25:125–130

Key words: burning, clonazepam, oral, systemic, topical

Burning mouth syndrome (BMS) is a condition that is diagnosed based on the presence of an oral burning or similar dysesthesia in the absence of other dental or medical causes.[1] Prevalence estimates range from 0.7% to 15%,[2,3] a variation that is likely to be attributed to the controversy surrounding the diagnostic criteria for this condition and to the different populations reviewed.[4] BMS predominantly affects postmenopausal women and has been associated with anxiety, depression, and personality disorders in affected patients.[1] BMS may be accompanied by other oral symptoms, including xerostomia and taste disturbances.[5–7] Spontaneous complete remission is uncommon, with just 3% of patients experiencing this within 5 years from the onset of BMS.[8]

There are very few therapeutic modalities that have demonstrated sound efficacy in the management of BMS. A systematic review of the available literature in 2005 found that trials using antidepressants, analgesics, and hormone replacement therapy produced no relief of symptoms associated with BMS.[1] A further review, conducted in 2007, found suitable evidence to support topical clonazepam and cognitive behavioral therapy and expressed interest in the potential

of alpha lipoic acid (ALA) for the management of BMS.[9] More recently, a meta-analysis of the existing research in this field concluded that "the current evidence does not support the efficacy of ALA for treatment of BMS."[10] In light of these findings, topically administered clonazepam is the only type of drug therapy that has demonstrated a reduction of BMS symptoms validated by a randomized controlled trial (RCT) of sufficient design quality to provide strongly validated conclusions.[1,4]

Clonazepam (Paxam Alphapharm Pty) is an anticonvulsant medication that is typically used for the management of epilepsy at adult doses of 4 mg to 8 mg per day.[11] This medication has also demonstrated an alternative use at lower doses for the management of orofacial pain.[4,12,13] Several studies utilizing this medication have demonstrated a reduction in BMS symptoms. One RCT[4] and one open-label trial[14] showed that sucking a clonazepam tablet for 3 minutes and then expectorating saliva was effective in reducing symptoms associated with BMS. It was also found that a systemically delivered clonazepam dose was effective in reducing symptoms associated with BMS.[15,16]

Although research in this field is frequently marred by low cohort numbers and study design challenges, there is sound preliminary evidence that systemic administration and topical administration may independently be valid modes of clonazepam delivery in the context of BMS management.[4,14–16] Based on this evidence, in 2006, one of the authors (CSF) began using a combined systemic and topical administration method using low-dose clonazepam for the treatment of BMS. In 2009, the clinical records of patients treated with this administration method were reviewed to form a preliminary assessment of the efficacy of this management modality. The working hypothesis of this pilot study was that clonazepam, when orally dissolved and then swallowed, leads to a significant reduction of pain in patients with BMS. Therefore, the aim of this study was to evaluate retrospectively the efficacy of administering an anticonvulsant medication, clonazepam, by dissolving tablets slowly orally before swallowing, for the management of BMS.

Materials and Methods

Patients and Selection Criteria

Clinical records of patients diagnosed and managed for BMS between January 2006 and June 2009 in the oral medicine practice of the authors were retrospectively assessed. The study was approved by the Human Ethics Committee of the University of Queensland, Australia. Patient selection began with a key word search through electronic records of the terms "BMS; burning mouth; burning tongue; burning; glossodynia; stomatodynia; scalded." Records were then selected to include only patients diagnosed with BMS during this period based on the presence of an intraoral burning sensation in the absence of other medical causes, such as mucosal abnormalities or concurrent oral pathology (including candidiasis, lichen planus, or erythema migrans) and abnormal hematological parameters (including nutritional deficiencies or diabetes). Patients were not excluded based on the presence of diagnosed psychological disease, but they were excluded if they had started counseling or experienced changes in central nervous system (CNS) depressant or psychoactive medication during the clonazepam treatment period. To be included, patients must have attended at least one review appointment and must have been taking clonazepam as instructed by the clinician. Verbal pain scores were recorded at initial consultation and at review on an 11-point numerical scale. Figure 1 summarizes the method of chart selection for analysis as well as exclusion factors.

Information collected from clinical records as part of this study included age, gender, description, and location of dysesthesia(s), concurrent oral symptoms, medical history information, past treatment attempted, and all appointment details including appointment dates, dosage regimen, pain, and side effect assessments.

Dosage Regimen

Patients were instructed to take their clonazepam dose only after food and were advised not to eat or drink for at least 30 minutes afterwards. All patients were advised to dissolve the clonazepam tablet orally until fully dissolved before swallowing. The clonazepam dose was escalated slowly over a 3-week period. Patients began by dissolving the tablet orally, then swallowing only one 0.5-mg tablet nightly for the first week, then twice daily (morning and night) for the second week, then three times daily (morning, afternoon, and night) for the third week with subsequent review by the clinician and modification of dose where necessary. If patients experienced side effects or were achieving relief and were eager to reduce their reliance on the medication, the dose was reduced. If patients were tolerating the medication well but not achieving complete resolution of symptoms, the dose was escalated. Review of patients by the clinician occurred at 1 month, 3 months, and 6 months following commencement of the therapy.

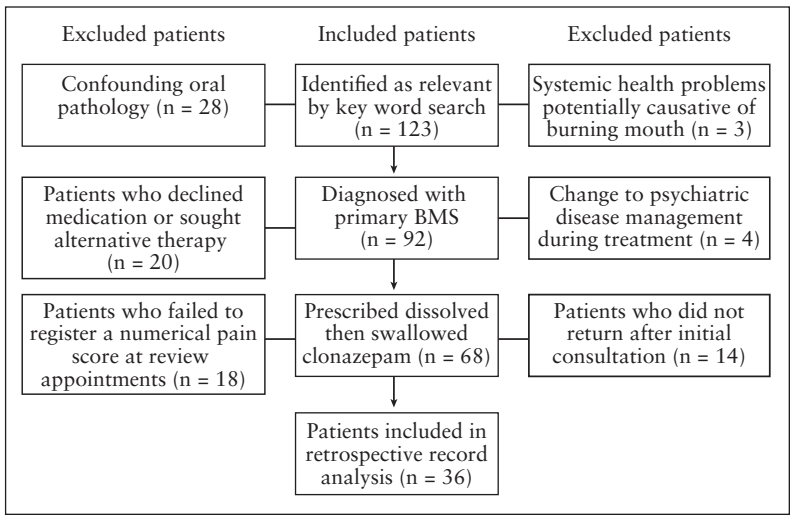

Fig 1 Method of selection of clinical records, as well as exclusion factors, for retrospective efficacy analysis.

Outcome Assessment

Patients were asked to verbally assign a pain score out of 10 on a numerical scale (with the anchors of 0 being no pain and 10 the worst pain imaginable) before beginning clonazepam therapy, and then again at each review appointment throughout treatment. Patients were responsible for dictating the time of day at which they attended their appointments, although most of these occurred before noon. Improvement of 50% was set as a discriminator of partial versus marked pain reduction to meet common chronic pain resolution aims[1] and afford ease of comparison with existing quality research in this field.[4]

Data Analysis

The efficacy of this mode of administration was primarily assessed based on the difference in pain from the first to the final appointment, although changes noted at the first review were also tested for significance by the use of a two-tailed Mann-Whitney analysis ($P < .05$). Patients were categorized into four distinct groups according to their pain changes; *(1)* no relief, *(2)* partial reduction, *(3)* marked reduction, and *(4)* complete resolution.

Prism 5.0 software (GraphPad) was used to analyze the data obtained. A nonparametric (Spearman) two-tailed correlation matrix with 95% confidence intervals was used to assess the predictive power of age, gender, number of practitioners consulted before presentation, symptom duration before presentation, number of medications concurrently taken, number of psychoactive or CNS depressant medications concurrently taken, and pretreatment pain severity on the overall pain resolution achieved. A two-tailed Mann-Whitney test was also used to detect significant differences in the presenting characteristics of separate response groups. Values of $P < .05$ were considered statistically significant. All values are expressed as mean ± SEM unless otherwise specified.

Results

Population Characteristics

Of the 36 patients who met the inclusion criteria of this study, 27 were female and 9 were male. The mean age of patients at the time of presentation was 56.7 ± 2.1 years. Pain duration before presentation ranged from 1 month to 12.5 years; however, most patients had been suffering for approximately 1 year (12.9 ± 4.5 months) before presenting to the specialist clinic. Fifteen patients experienced pain in multiple sites. The tongue was the most common site affected (n = 27), and 16 patients specified the anterior aspect of the tongue specifically as the source of their pain. Other sites frequently affected included the palate (n = 10) and the labial mucosa (n = 9). Twenty-one patients had tried other treatment options previously to address their oral pain.

Ten patients reported anxiety, depression, or significant stress as part of their medical history. Twelve patients were taking psychoactive medications (sedatives, hypnotics, antidepressants, or antianxiety agents) and two patients were taking other CNS depressant medications (movement disorder medication, narcotic analgesics, or antimigraine preparations).

Table 1 Daily Clonazepam Doses Prescribed

Dose (mg/day)	Frequency of prescription	Percentage of total prescriptions (n/169)
0.50	5	6.85%
0.75	2	2.74%
1.00	7	9.59%
1.25	1	1.37%
1.50	51	69.86%
2.00	6	8.22%
2.25	1	1.37%

Table 2 Summary of Pain Scores Recorded During Treatment

Pain scores	Mean	SEM	Range	Significant change*
Pretreatment	6.86	0.26	3–7	NA
First review	3.01	0.37	0–10	Yes
Final review	2.13	0.31	0–7	Yes

*Mann-Whitney test ($P < .05$) comparing pretreatment pain scores with those noted during review. Mean of first review was 10 weeks, and that of final review was 24 weeks.

Treatment Duration and Dosage Regimen

The mean duration from the first appointment to the final appointment was 23.9 ± 3.4 weeks, with 3.3 ± 0.2 appointments per patient on average. Daily dosage of clonazepam ranged from 0.5 mg to 2.25 mg per day (Table 1). The median daily dose of clonazepam used was 1.5 mg, which was most commonly divided into three 0.5-mg doses each day.

Pain Evaluation

The mean pretreatment pain score recorded was 6.9 ± 0.3 points out of 10. Other key pain scores are summarized in Table 2. Mean pain score reduction was 3.8 ± 0.4 points (range 0 to 10) between initial consultation and the first review appointment (10.0 ± 2.4 weeks after the initial appointment). The mean reduction observed from the first to final appointment pain score was 4.7 ± 0.4 points (median 5, range 0 to 10), representing a combined mean pain reduction of 69.2% ± 0.1%. When the categories of absolute pain score resolution forwarded by Gremeau-Richard et al[4] were used, 4 patients had less than 2 points reduction, 9 patients had 2- to 3-points reduction, 14 patients had 4- to 7-points reduction, and 7 patients experienced a pain reduction of 8 to 10 points over the course of treatment. With 50% set as a discriminator of partial versus marked relief, 16.7% of patients (n = 6) experienced only partial relief, 47% (n = 17) of patients had marked relief, and 33.3% (n = 12) obtained complete resolution of symptoms.

Correlation

A nonparametric (Spearman) two-tailed correlation matrix revealed no significant correlation between dosage regimen and degree of pain intensity. A significant relationship was detected between patient age and pain reduction ($P = .031$) and between pretreatment pain score and the overall reduction in pain ($P = .022$). No significant relationship was detected between the duration of BMS pain reported before treatment and the reduction in pain observed. Comparison of patient groups according to treatment response did not reveal any significant differences in presenting characteristics, with the exception that patients with complete pain resolution were significantly younger than patients with marked pain reduction ($P = .045$) or only partial pain reduction ($P = .008$).

Side Effects

Thirty-three percent of patients (n = 12) noted side effects during the course of treatment. These effects were transient and/or mild for 11 patients and involved initial drowsiness or tiredness (n = 6), dizziness (n = 2), changes in mood (n = 1), forgetfulness (n = 1), vivid dreams (n = 1), and transient unpleasant taste (n = 1). One patient noted more severe side effects (slurred speech and loss of balance) associated with beginning clonazepam therapy. No correlation was detected between clonazepam dosage and the occurrence of side effects.

Withdrawal

Two patients actively withdrew from clonazepam treatment, although they were not instructed to cease therapy. Lack of resolution and adverse effects were the reasons for withdrawal cited by these patients. Twenty-two patients were still taking clonazepam at their last review appointment within the 6-month period preceding June 2009.

Discussion

The cohort of patients included in this pilot study reflected BMS population features documented in the literature in terms of patient age, female gender predominance, main sites affected, onset stimuli, related symptoms, pain severity prior to treatment, and concurrent psychological disease.[1,4–6,14] The results of this study confirm the research hypothesis that the administration of orally dissolved then swallowed low-dose clonazepam does lead to significant reduction of pain in patients with BMS. The mean pain decrease of 4.7 observed over the course of treatment is a significant finding in the context of BMS management and is higher than changes documented in previous research,[4,14] but must be interpreted in light of the retrospective uncontrolled nature of this analysis. While it is clear that the combined administration protocol provides significant relief for some patients, it is not possible to draw firm conclusions about the mechanism of activity. It may be that topical and systemic effects are confounding, synergistic, or independent. Recent research by Gremeau-Richard et al[17] highlights the possibility that the relative topical and systemic (peripheral and central) contributions to an individual's BMS profile and, therefore, their susceptibility to the mode of activity of clonazepam may differ from one individual to another. A further confounding factor in the present study may be the positioning of the tablet within the mouth when dissolving (eg, through sublingual exposure), and the time taken to dissolve the tablet orally, which could have led to different relative topical and systemic activity in individual patients.

The finding that dose did not correlate with the degree of pain relief may reflect the significance of the topical effect, individual variation in therapeutic thresholds, or that the increments used due to the availability of the drug doses were insufficiently small to distinguish a more precise minimum effective dose. The predictive role of age in the response to clonazepam has been noted in previous research,[15] whereas the relevance of pretreatment pain intensity on pain resolution is a novel observation.

Side effects associated with the administration method were limited to transient and mild effects in all but one case. It is impossible, however, to state the statistical effect of patient drop-out (patients who did not take medication or did not return for review) on this and other findings and the authors advocate discretion in this regard.

Similarly, the "placebo effect" for this mode of administration cannot yet be quantified. Gremeau-Richard et al[4] attributed just 10.7% of the change in pain intensity observed from clonazepam use to a placebo effect when assessing topical clonazepam administration. The addition of a systemic component, however, may lead to a different and, perhaps, more important placebo effect. The opportunity for drug interactions that were not accounted for is also a consideration. An attempt was made to exclude patients with changes to their psychiatric treatment or potentially interacting medications during the course of clonazepam administration. While no relationship between the presence of medication or psychological disease and pain response was observed, it is possible that drug interactions or changes to psychological status that were not accounted for may have confounded the results.

The authors acknowledge that there are inherent limitations associated with research based on a clinical records audit that include recordkeeping and practitioner-dependent standardization, and that must be considered when interpreting the results presented. Individual titration of dosage and verbal pain assessment are practical methods to be used in a clinical setting, but they are less conducive to formal research methodologies and conclusions than available alternatives such as the use of a visual analog scale. A further limitation was the lack of a nonactive control arm in the study, which, for practical clinical and ethical reasons, was not possible.

Although this clinical record audit is unlikely to cover the full spectrum of patient responses to low-dose clonazepam when dissolved orally and then swallowed, the double administration method, long observation period, and relevance of age and pretreatment pain variables afford the opportunity for this study to further the limited existing knowledge in this field. Given the research that now supports the use of clonazepam for the treatment of BMS, and the lack of well-founded alternatives, a randomized prospective trial that seeks to compare different modes (independent topical and systemic methods, combined administration and placebo therapy) and establish guidelines for appropriate administration in terms of dosage range and serum thresholds seems warranted. The method of dissolving clonazepam tablets orally before swallowing appears to be a promising management option based on the preliminary findings outlined in this article and is a valid candidate for future research in this field.

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