Topical Clonazepam Solution for the Management of Burning Mouth Syndrome: A Retrospective Study

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Aims: To evaluate and compare the effectiveness of two concentrations of topical clonazepam solution in improving symptoms of burning mouth syndrome (BMS). **Methods:** A retrospective chart review was conducted of patients diagnosed with BMS and managed with topical clonazepam solution between 2008 and 2015. A 0.5-mg/mL solution was prescribed until 2012, when this was changed to a 0.1 mg/mL solution. Patients were instructed to swish with 5 mL for 5 minutes and spit two to four times daily. The efficacies of the two concentrations were compared using patient-reported outcome measures at the first follow-up, including the reported percentage of improvement in burning symptoms and the change in burning severity from baseline ranked on an 11-point numeric rating scale (NRS). Response to treatment was compared between the two concentrations using Wilcoxon rank sum test. **Results:** A total of 57 subjects were included, 32 in the 0.1-mg/mL cohort and 25 in the 0.5-mg/mL cohort, and evaluated at a median follow-up of 7 weeks. The median overall percentage improvement was 32.5% in the 0.1-mg/mL cohort and 75% in the 0.5-mg/mL cohort. The median reduction in NRS score was 0.5 points in the 0.1-mg/mL cohort and 6 points in the 0.5-mg/mL cohort. The use of either outcome measure revealed that the response to treatment with the 0.5-mg/mL solution was superior to that of the 0.1 mg/mL solution ($P < .01$). **Conclusion:** These findings suggest that a 0.5-mg/mL topical clonazepam solution is effective in the management of BMS. Future randomized clinical trials are warranted.
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Burning mouth syndrome (BMS) is a chronic pain condition characterized by an oral burning dysesthesia in the absence of any local and/or systemic causes such as candidiasis, hyposalivation, or vitamin deficiency.[1] The reported prevalence of BMS in the general population varies from 0.1% to 7.9%, with a predominance in postmenopausal females.[2–5] The burning is primarily localized to the tongue (especially the tip or anterior two-thirds), the labial mucosa, and the anterior hard palatal mucosa and is often associated with dysgeusia and xerostomia.[6] Spontaneous complete remission is rare, but up to two-thirds of patients may feel some symptomatic improvement within 6 to 7 years of onset.[7,8]

The pathophysiology of BMS is thought to be multifactorial, consisting of biologic and psychological factors.[9] Recent evidence indicates a neuropathic mechanism of disease, and symptoms appear to be peripherally mediated at least in a subset of patients.[10,11] Neuropathologic studies suggest a potential role for focal small-fiber neuropathy in the oral mucosa, presenting with decreased density of epithelial nerve fibers as well as axonal derangement.[12–14] Other studies have provided evidence for involvement of psychological elements, with a high prevalence of anxiety, depression, and somatization documented among patients. In some cases, the development of BMS appears to be

triggered by major life events and stressful or emotional situations.[15–18]

To date, results from randomized controlled trials (RCTs) assessing the efficacy of interventions for the management of BMS are controversial,[19] with a documented robust placebo response.[20] No definitive cure has been identified, and treatments focus on symptom relief.[21] Three medications have been reported to have positive outcomes: alpha-lipoic acid, capsaicin, and clonazepam.[19] Of these, low-dose clonazepam is considered first-line therapy for BMS and has been reported with various degrees of efficacy in several trials,[22–29] only two of which were placebo controlled, double blinded, and focused on classic BMS patients.[23,27]

Gremeau-Richard et al demonstrated that sucking a 1.0-mg clonazepam tablet without swallowing three times daily for 14 days led to symptomatic improvement in two-thirds of patients with no significant adverse effects.[23] Based on these findings, topical clonazepam has been used for the management of BMS at the Division of Oral Medicine and Dentistry, Brigham and Women's Hospital (BWH) since 2008. Due to considerations of taste, tolerability, and ease of use, a compounded oral solution is used rather than tablets. An initial concentration of 0.5 mg/mL was used until 2012, when this was changed to a 0.1-mg/mL solution. Both concentrations were chosen based on clinical experience and biologic plausibility, and the change to a lower concentration was devised to mitigate potential adverse effects while maintaining treatment efficacy. The sharp transition from a 0.5-mg/mL concentration to a 0.1-mg/mL concentration allows for a quasi-randomized design for comparing the effectiveness of the two solutions. The objective of this retrospective study was to evaluate and compare the effectiveness of the two concentrations of topical clonazepam solution in improving symptoms of BMS.

Materials and Methods

Patient Identification and Eligibility

Approval of the Partners' Institutional Review Board at BWH was obtained. A retrospective electronic medical chart review was conducted of all patients diagnosed with BMS and managed with topical clonazepam solution (0.1 mg/mL or 0.5 mg/mL) in the Division of Oral Medicine and Dentistry, BWH from March 2008 to February 2015. All prescriptions were filled through America's Compounding Center (ACC, http://www.accrx.com/). Subjects were identified using a database of all patients prescribed topical clonazepam solution at the practice during the study period. Due to the retrospective nature of the study, patients did not provide informed consent.

Patients were included if they presented with classic BMS symptoms, defined as a continuous, nonparoxysmal, burning pain in the oral mucosa of variable intensity with or without accompanying dysgeusia, xerostomia, or other oral dysesthesias in the absence of clinically evident causative lesions and not better accounted for by any other diagnosis.[30] All patients were instructed to swish with 5 mL of the solution for 5 minutes and spit without swallowing two to four times a day. Patients included were treated with topical clonazepam solution strictly as monotherapy. Patients treated with psychiatric medications were included only if on a stable regimen for at least 1 month. Only patients who completed at least 2 weeks of topical clonazepam therapy prior to the first follow-up evaluation were included,[23] unless an adverse reaction led to early discontinuation of treatment, in which case the withdrawal from therapy and the adverse reaction were documented.

Description of Medication

Clonazepam solution was compounded according to the following formula for 600 mL: 150 or 30 × 2 mg clonazepam tablets (active ingredient, for a 0.5 mg/mL concentration or 0.1 mg/mL concentration, respectively), 6 mL glycerin, 60 mL propylene glycol, 240 mL purified water, 6 mL bubble gum concentrate flavor, and 70% sorbitol solution to 600 mL.

Data Collection

Data abstracted from medical records included demographics, current psychiatric medication(s), concurrent treatment(s) for BMS, clinical pattern of BMS (type 1, 2, or 3),[31] intensity of burning as measured on 0–10-point numeric rating scale (NRS), burning distribution, other dysesthesias, response to topical clonazepam solution, and adverse reactions. Analysis of response to treatment was restricted to data collected from the first follow-up visits so as to minimize the risk of attrition bias and bias due to longer follow-up periods for patients receiving the 0.5-mg/mL concentration.

Outcome Measures and Statistical Analyses

The primary outcome measure was improvement in BMS symptoms from baseline to first follow-up. Response to treatment was measured using patient-reported outcome measures. Outcome measures included the overall percentage of improvement (0% to 100%) in burning symptoms as reported at the first follow-up as part of a standardized verbal questionnaire ("Overall, how much better is your oral burning sensation on a scale from 0% to 100%?"), as well as the change from baseline to the first follow-up in the worst burning severity over the week prior to evaluation ranked on a NRS (0–10) with 0 being no

Table 1 Patient Characteristics at Baseline

	0.1-mg/mL cohort (n = 32)	0.5-mg/mL cohort (n = 26)
Gender, n (%)		
Male	6 (18)	5 (19)
Female	26 (81)	21 (81)
Median age, y (range)	58.5 (22–88)	60.5 (16–84)
Burning intensity score (0–10 NRS), median (range)		
At time of visit	3.25 (0–8)	3.5 (0–9)
Worst over previous week	8.0 (3–10)	7.5 (3–10)
Clinical pattern of BMS, n (%)		
Type 1	11 (34)	9 (35)
Type 2	5 (16)	4 (15)
Type 3	3 (9)	1 (4)
Pattern not defined	13 (41)	12 (46)
Other dysesthesias,[a] n (%)		
Xerostomia	14 (44)	9 (35)
Dysgeusia	9 (28)	11 (42)
Other oral dysesthesias[b]	9 (28)	12 (46)
Current psychiatric medication(s),[c] n (%)		
Antidepressants	11 (34)	10 (38)
Anxiolytics	9 (28)	5 (19)
Sedatives	11 (34)	3 (12)
Anticonvulsants	5 (16)	3 (12)

BMS = burning mouth syndrome; NRS = numeric rating scale.
[a]More than one type of dysesthesia per patient possible.
[b]Other dysesthesias include: ageusia, sense of hypersalivation, texture changes, a sense of tissue swelling, a sense of tissue coating, and tingling/numbness.
[c]More than one psychiatric medication per patient possible.

burning at all and 10 being the worst possible burning imaginable.

For both concentrations, improvement according to the commonly used 30% and 50% cutoffs[32] was evaluated using the Wilcoxon one-sample median test, and differences in NRS were evaluated using the Wilcoxon signed-rank test. For patients who did not report the percentage improvement, the worst NRS score over the last week or, if not available, the current NRS score (at the time of the visit) were used to calculate percentage of symptomatic improvement by dividing the difference in NRS scores by the baseline score and multiplying by 100. To control for individual differences at baseline, such as the concomitant use of psychiatric medications, a stratified Wilcoxon test was used. Finally, to compare the efficacy of the two concentrations in improving burning symptoms, the sample was partitioned into two groups, according to the dosage initially prescribed. Response to treatment in both groups was compared using the Wilcoxon rank-sum test.

Results

Population Characteristics

A total of 306 BMS patients were seen at the practice and prescribed topical clonazepam solution during the study period; 58 cases met the inclusion criteria, 32 in the 0.1-mg/mL cohort and 26 in the 0.5-mg/mL cohort. The most common reasons for exclusion were missing data and loss to follow-up. Patients were evaluated at a median follow-up of 7 weeks, ranging between 3 weeks and 5.5 months, and one patient was seen at a 1-year follow-up.

At baseline, the two cohorts were balanced in terms of demographics, intensity of burning symptoms, clinical pattern of BMS, other dysesthesias experienced, and psychiatric treatment (Table 1). Most patients were female (81% in both cohorts), with a median age of 59.5 years (range 16 to 88 years). The median worst burning NRS score during the week prior to presentation was 8.0 (range 3 to 10) in the 0.1-mg/mL cohort and 7.5 (range 3 to 10) in the 0.5-mg/mL cohort. The majority of patients (44 out of 58, 76%) experienced a burning sensation in more than one site, with the most common sites affected being the tongue (51.9%), lips (16.2%), anterior palatal mucosa (11.7%), and labial mucosa (11%). Most patients (36 out of 58, 62%) reported at least one other dysesthesia aside from burning, the most common being dysgeusia and xerostomia. Of the 35 patients treated with a stable regimen of psychiatric medications, 37% (9 in the 0.1-mg/mL cohort and 4 in the 0.5-mg/mL cohort) were treated with a benzodiazepine (alprazolam or lorazepam) for management of disorders such as anxiety and insomnia. One other patient in the 0.5-mg/mL cohort was treated with a nonbenzodiazepine anxiolytic for this purpose (Table 1).

Table 2 Comparison of Percentage of Symptomatic Improvement According to Clonazepam Concentration

Percentage improvement	0.1-mg/mL cohort (n = 32)	0.5-mg/mL cohort (n = 25)
Median (25th percentile, 75th percentile)	32.5 (8.125, 55)	75 (50, 90)
P value[a]		
vs 30% cutoff	.453	< .0001
vs 50% cutoff		.0007

[a]*P* value calculated using a Wilcoxon one-sample median test.

Table 3 Comparison of Change in Patient-Reported Outcome Measures According to Concentration

	0.1-mg/mL cohort			0.5-mg/mL cohort			
	n	Median	(25th percentile, 75th percentile)	n	Median	(25th percentile, 75th percentile)	*P* value
Δ Worst NRS score	9	−0.5	(−3.5, 0)	11	−6	(−7, −4)	.003
Percentage improvement	32	32.5	(8.125, 55)	25	75	(50, 90)	.0003

NRS = numeric rating scale.
[a]*P* value calculated using Wilcoxon-Mann-Whitney test.

One of the 26 patients in the 0.5-mg/mL cohort experienced symptoms of sedation and altered mental status after 2.5 days of use, leading to early discontinuation of therapy. Thus, a total of 25 patients in the 0.5-mg/mL cohort were evaluated for response to the drug therapy. All 32 patients in the 0.1-mg/mL cohort were evaluated for response to the drug therapy.

Treatment Outcomes with the 0.1-mg/mL Solution

A total of 26 out of the 32 patients (81%) reported their improvement in symptoms at the follow-up visit. Imputation of the percentage of symptomatic improvement was performed for the remaining six patients. The median overall reported improvement in burning symptoms was 32.5%, which was not statistically significantly higher than the 30% cutoff (Table 2). An improvement equal to or higher than the 50% cutoff was reported by 41% of patients.

Nine patients reported a worst NRS score over the last week both at baseline and at follow-up, with a median reduction in NRS score of 0.5 points. Four patients had no response to treatment, and one patient reported worsening of current NRS score.

Treatment Outcomes with the 0.5-mg/mL Solution

A total of 22 out of 25 patients (88%) reported their improvement in symptoms at the follow-up visit, and values were imputed for the remaining three. The median overall reported improvement in burning symptoms was 75%, significantly higher than the 50% cutoff ($P < .01$). An improvement equal to or higher than the 50% cutoff was reported by 92% of these patients.

Eleven patients reported a worst NRS score over the last week both at baseline and at follow-up, with a median reduction in NRS score of 6 points. One patient had no response to treatment, and no patients worsened.

Comparison of Treatment Outcomes

Comparison of either percentage of improvement or change in NRS score revealed that the response to treatment with the 0.5-mg/mL solution was superior to that of the 0.1-mg/mL solution ($P < .01$, Table 3). These results remained significant after stratifying by the concomitant use of benzodiazepines or other psychiatric medications ($P < .02$).

Adverse Drug Reactions

Overall, adverse drug reactions occurred in 15.5% (9 out of 58) of patients. There was no significant difference in occurrence between the cohorts, with five patients in the 0.1-mg/mL cohort (15.6%) and four patients in the 0.5-mg/mL cohort (15.4%) reporting adverse reactions. All patients with reactions experienced sedation. Two patients in the 0.5-mg/mL cohort also experienced symptoms of altered mental status. Two patients discontinued therapy secondary to developing an adverse reaction. One patient in the 0.5-mg/mL cohort reported reactions after 2.5 days, and this led to early discontinuation of therapy (after < 2 weeks), and one in the 0.1-mg/mL cohort reported adverse reaction after 9 days, but did not discontinue therapy due to significant improvement in burning. The remaining four patients in the 0.1-mg/mL cohort continued treatment without any change, while dose reduction was required in the remaining three patients in the 0.5-mg/mL cohort. Two patients reduced the frequency of rinsing from twice a day to once daily, and this provided resolution of the adverse reactions. One patient reduced the solution concentration by half (from a total of 2.5 mg per rinse

to 1.25 mg), but still experienced adverse reactions; this prompted a switch to the 0.1-mg/mL solution at a later visit, and this new dose was well tolerated by the patient and was without sedation.

Discussion

These results have demonstrated that topical clonazepam solution is effective in the management of burning dysesthesia in patients with BMS. The 0.5-mg/mL solution (2.5 mg of clonazepam per rinse), swished and expectorated two to four times daily for a median duration of 7 weeks, was highly effective in the management of burning pain, significantly more than the 0.1-mg/mL concentration (0.5 mg of clonazepam per rinse).

Response to treatment was evaluated using two patient-reported outcome measures. The first was the reported percentage of improvement in burning symptoms. While an improvement of 30% or higher in pain intensity is thought to be associated with overall patient improvement, most clinical trials of chronic pain treatments target at least 50% reduction in pain scores from baseline, and reporting this cutoff allows comparability with published studies.[32] The current study demonstrated a marked response to treatment with topical clonazepam solution at a 0.5-mg/mL concentration, with 92% of patients reporting symptomatic improvement of at least 50% and a median improvement of 75%, significantly higher than the 50% cutoff. By comparison, only 41% of patients in the 0.1-mg/mL cohort reported an improvement of 50% or more with a median improvement of 32.5%, which was not significantly higher than the 30% cutoff. The response to the 0.5-mg/mL solution in the present study is higher than responses reported in previous studies evaluating topical therapy with clonazepam for BMS. Gremeau-Richard et al documented 50% of patients with at least 50% improvement at 2 weeks follow-up after sucking and then expectorating 1-mg clonazepam tablets three times daily.[23] A recent open-label pilot study by de Castro and Ribeiro-Rotta demonstrated the efficacy of topical clonazepam solution (1 mg/10 mL) in reducing burning intensity when the patients rinsed with the 10-mL solution three times daily, three minutes at a time prior to expectoration, for 14 days.[28] Two-thirds of the patients in that study (12 out of 18) reported improvement in their symptoms, with half experiencing symptomatic improvement greater than 50%.

The second outcome measure was the change in the worst burning severity over the week prior to evaluation, ranked on a 0–10 NRS. The median reduction in burning intensity was 6 points (mean 5.7 points) in the 0.5-mg/mL cohort. This is not only higher than the median 0.5-point reduction (mean 1.5 points) in the 0.1-mg/mL cohort, but also higher than responses to topical treatment documented in previous studies. A mean 2-point decrease in pain intensity was documented by Gremeau-Richard et al[23] and de Castro and Ribeiro-Rotta[28] (from 6 points and 5.56 points at baseline, respectively), and a mean 3-point reduction in pain scores (from 6 points at baseline) was documented in an open, nonrandomized trial[33] at 4 weeks of treatment with 0.125 to 0.25–mg clonazepam tablets, sucking and expectorating two to three times daily.

The marked effectiveness of topical clonazepam solution in the 0.5-mg/mL concentration compared to the minimal response to treatment with the 0.1-mg/mL concentration, as well as the response to topical treatment with clonazepam (dosages ranging between 0.125 mg and 1 mg) in previous studies, can be attributed to the higher concentration. Treatment with topical clonazepam solution in both concentrations was generally well tolerated with no serious adverse reactions. This is in line with the findings of Gremeau-Richard et al, who documented the development of adverse reactions in 37% of subjects (9 out of 24) in the clonazepam group, leading to the withdrawal of 2 subjects,[23] and 25% of subjects (6 out of 24) in the placebo group, leading to the withdrawal of 1 subject. While far more effective than the lower concentration, the 0.5-mg/mL solution maintains a similar safety profile. Since the majority of adverse reactions were resolved by dose adjustment, a conservative dose escalation regimen may be indicated to maximize the beneficial effects of treatment while mitigating potential adverse reactions (eg, start at two daily rinses and increase gradually up to four rinses a day over a 2-week period until the individual maintenance dose is reached).

Clonazepam is an anxiolytic/anticonvulsant that potentiates the neural inhibition mediated by gamma-aminobutyric acid ($GABA_A$). The benzodiazepine-$GABA_A$ receptor is widely distributed in the central nervous system but also in peripheral tissues, where it is likely to be accessible for local pharmacologic manipulation.[23,34] Tan et al demonstrated the presence of $GABA_A$ receptors on nerve fibers in the tongues of rats and suggested that the activation of intraoral $GABA_A$ receptors mediates analgesia, explaining the analgesic effect of topical clonazepam in BMS.[35] In this context, the formulation of a compounded solution presumably provides greater interaction with the oral mucosa as opposed to the topical use of tablets.

Due to its retrospective nature, this study had several limitations that must be emphasized. Documentation of patients' compliance with the prescribed regimen is largely incomplete or lacking, as

is the documentation of resolution of adverse drug reactions in patients who continued therapy without any change. As different regimens were employed by patients, some rinsing only twice daily and some rinsing up to four times daily, patients were exposed to different dosages per day, limiting the ability to determine an effective therapeutic dose. Blood levels of clonazepam also were not monitored, so the potential role of systemic clonazepam levels on adverse drug reactions or treatment efficacy is unclear. Additionally, the follow-up period was variable, ranging from 3 weeks to 5.5 months and in one case 1 year (median 7 weeks). The choice to avoid truncation of the follow-up period mitigated the risk of selection bias and maximized the sample size, and all results continue to hold once observations with time to follow-up longer than 9 weeks are excluded. This study was also limited by its small sample size, mostly due to missing data and loss to follow-up. However, the restrictive inclusion criteria ensured a homogenous population, and while selection bias cannot be excluded, the fact that cohorts were balanced at baseline is reassuring.

The present study was, however, characterized by a number of methodologic strengths. The sharp transition from the 0.5-mg/mL solution to the 0.1-mg/mL solution in 2012 allowed a quasi-experimental design for comparing the two concentrations. The multiplicity of outcome measures reinforced the findings and allowed comparability to published studies. Furthermore, the use of the change in worst NRS score over the week prior to evaluation as the metric for response to treatment, as opposed to change in the current NRS score at time of evaluation or change in the mean NRS score during a period of time prior to evaluation, better represented the natural history of BMS. This is best illustrated by the reporting of NRS scores at baseline, when some patients reported a current score of 0, while the reported worst score over the last week was 3 at minimum.

Finally, as high placebo response rates have been observed in trials evaluating treatments for BMS,[20] the possibility that the large effect observed in this study is due, at least in part, to a placebo effect cannot be excluded. The quasi-randomized design of the study allowed a lower bound for the effect attributed to the drug. Assuming that the 0.1-mg/mL solution is at least as effective as a placebo, the significant differences between the two concentrations can be attributed to the superior pharmacologic effect of the 0.5-mg/mL solution. Nonetheless, to validate these results and to fully evaluate drug and placebo effects in the treatment of BMS, future adequately powered, placebo-controlled randomized trials that include a third no-intervention control group,[36,37] as well as monitoring for systemic clonazepam levels, are essential.

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