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# Is Topical Clonazepam More Effective Than Oral Clonazepam in Treatment of Burning Mouth Syndrome (BMS)?

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# Is Topical Clonazepam More Effective than Oral Clonazepam in Treatment of Burning Mouth Syndrome (BMS)?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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INTRODUCTION

Burning mouth syndrome (BMS) is a disabling complex disorder characterized by painful and burning sensation of the oral cavity without detectable oral changes. BMS is common among women of postmenopausal age. The etiology and treatment are still being investigated; there are no specific therapy guidelines for BMS.[1,2] Many conditions are thought to be precipitating factors, such as, nutritional deficiencies, oral infections, xerostomia and peripheral neuropathies. BMS is described as a bilateral burning pain, tingling, or numbness in the oral mucosa.[3] This paper evaluates two double-blinded randomized controlled trials and one double-blinded randomized crossover trial to compare the efficacy of topical clonazepam to clonazepam PO in the treatment of BMS.

The life-time prevalence of BMS ranges from 3.7%-40% in the elderly population, and it affects primarily postmenopausal women, with a gender ratio of 7:1. Although BMS is commonly seen by the dentist it is managed by multidisciplinary teams within the scope of the physician assistant's (PA) practice. [3, 4] Since BMS is a rare chronic condition, the exact healthcare cost of BMS has not been specified; however, the cost of charges for diseases of the mouth, excluding dental care, were $25,233 in 2011.[4,5] An exact number of healthcare visits for BMS has not specified; however, the number of hospital discharges for diseases of the mouth, excluding dental care, was 21, 646 in 2011, and the average length of stay was 3.9 days in 2011.[5]

The etiology of BMS is unknown; however, it is thought to be neuropathic, associated with changes in the peripheral nervous system or central impairment suggested by neurophysiological testing, biopsies and MRI.[2, 4] There is no consensus among clinicians on the diagnostic criteria of BMS; therefore BMS is often underdiagnosed.[3]

Some therapeutic strategies commonly used to treat BMS begin with dietary guidelines that suggest avoidance of food that is known to increase burning sensations such as alcohol, spicy foods and acidic drinks. Anticonvulsants, antidepressants, analgesics and cognitive behavioral therapy have also been used in the management of BMS. According to Ducasse et al.'s review article, the anticonvulsants clonazepam and α-lipoic acid and cognitive behavioral therapy were the only treatments found to be effective in relieving symptoms.[3] Currently, no clinical guidelines exist for BMS; however, clonazepam is one of the interventions found to be effective in improving symptoms in patients with BMS.[3] The aim is to investigate whether or not topical clonazepam is more effective than clonazepam PO in the treatment of BMS.

## OBJECTIVE

The objective of this selective EBM review is to determine whether or not topical clonazepam is more effective than clonazepam PO in treatment of BMS.

## METHODS

Numerous studies were considered during the selection process for this paper. Only two double-blind randomized controlled trials and one double-blind randomized crossover trial were utilized based on the importance of the criteria for population, interventions, comparisons, and data included for patient-oriented outcomes (POEMS). The population was limited to patients with BMS with the following interventions: topical clonazepam 0.5mg and 1mg and PO clonazepam 0.5mg. Comparisons were made between the treatment group, who received either 0.5mg of topical or 0.5mg of PO clonazepam and the experimental group who received a visually matched placebo. All subjects in the randomized crossover trial received 1mg of topical clonazepam. The outcomes measured were the efficacy of topical clonazepam and PO clonazepam for the treatment of BMS analyzed by pain ratings or VAS. Patients rated the

sensation of burning pain in the mouth on a scale ranging between 0 and 10, with 0 indicating no pain and 10 indicating maximum possible pain. Pain relief was measured by using a VAS from 0 (no pain) to 10 (maximum possible pain).

A detailed search was performed through PubMed and Cochrane Library databases using the key words, "clonazepam" and "burning mouth syndrome." All three articles that were selected were published in the English language. Articles were selected based on their relevance to my clinical question and if they included POEMS. Exclusion criteria according to the three articles used were patients without BMS, patients with organic conditions which could have been a causative factor of BMS, vitamin B-12 deficiency, asthma, hepatitis, jaundice, HIV, diabetes mellitus, narrow-angle glaucoma, sleep apnea syndrome, candida infections of oral mucosa and patients with neurological conditions, to name just a few. [1, 2] Inclusion criteria for all chosen articles were studies that were randomized, controlled double-blinded crossover design with the use of topical or PO clonazepam as an intervention for BMS. The studies chosen were reported in continuous data, analysis of variance (ANOVA) F-score and change in mean from baseline, Chi square, and P-value to demonstrate statistical significance. Table 1 organizes the demographics and characteristics of all three articles discussed in this paper.

Table 1- Demographics and Characteristics of Included Studies[1, 2, 6]

| Study | Type | Pts # | Age (yrs) | Inclusion Criteria | Exclusion Criteria | W/D | Intervention |
|---|---|---|---|---|---|---|---|
| Heckmann[1] (2012) | Double-blind RCT | 20 | Experimental group 65 ± 12.4 Placebo 62.9 ± 8.7 | Idiopathic cases | Patients with the following: DM, Hepatitis, Jaundice, Inflammation and Liver malfunctions, HIV, Vitamin B-12 Deficiency, Asthma, Narrow angle glaucoma, Sleep apnea syndrome | 0 | PO clonazepam 0.5mg once daily for 9 wks |
| Gremeau-Richard[2] (2010) | Double-blind Randomized Crossover | 20 | Age over 50 years old | Presence of an isolated complaint of chronic pain in the oral mucosa. Normal clinical examination | Patients with organic conditions that was liable to be a causative factor, such as DM and anemia. Patients with neurological conditions and those who were unable to understand a pain scale | 0 | Topical clonazepam 1mg and lidocaine TID for 3wks |
| Rodriguez de Rivera Campillo[6] (2010) | Double-blind RCT | 66 | Avg age 64.9 years | Patient with BMS | Patients with disorders in the oral mucosa. | 0 | Topical clonazepam 0.5mg once daily for 6mo |

## OUTCOMES MEASURED

The outcomes measured in all three articles were those of patient-oriented evidence via pain ratings or VAS. Patients rated the sensation of burning pain in the mouth on a scale ranging between 0 and 10. Pain relief was measured by using a VAS from 0 to 10. Heckmann et al. utilized pain ratings; subjects were given a bottle of either sixty-three capsules of 0.5mg of clonazepam (Rivotril) or placebo (lactose monohydrate) to take orally once a day for nine weeks. The patients received a medication list in the form of a nine week calendar on which they had to mark off the intake and note the date each day.[1] In the Gremeau-Richard et al. study, subjects on the first visit were asked to use the VAS to score their pain intensity before injection of lidocaine or saline, then again fifteen minutes after the injection. Subjects also answered a questionnaire. On the second visit which took place one week later, subjects received injections and all subjects were prescribed 1mg of topical clonazepam (Rivotril). Subjects were instructed to suck half a tablet for three minutes without swallowing and then to expectorate saliva. This procedure had to be repeated three times a day after each meal for three weeks. The effects of clonazepam were evaluated by comparing the mean scores obtained before the study and after three weeks.[2] Lastly, Rodriguez de Rivera Campillo et al.'s subjects were given a sealed envelope containing thirty-two tablets of 0.5mg of topical clonazepam and instructed to take a single tablet in the morning, at the first sign of discomfort. Subjects were instructed to dissolve the tablet in the mouth for three minutes and, similar to the Gremeau-Richard et al. study, were instructed not to swallow and to expectorate saliva. Patients were asked to note their symptoms and instructed not to exceed four tablets a day. Burning sensation was measured by VAS during visits held at day one, then one month later and then again at six months.[6]

## RESULTS

Two of the three selected articles are double-blind randomized controlled trials while the third article is a double-blind randomized crossover trial. In all three articles clonazepam was used as an intervention for the treatment of BMS. In Heckmann et al.'s randomized controlled trial, patients were recruited to be part of the study based on the inclusion criteria restricted to idiopathic cases and exclusion criteria, such as systemic and central nervous system disease and pregnancy. During the recruitment process, patients received an examination of their oral cavity blood was drawn to screen for liver and kidney function, electrolytes and immunological parameters. The Beck Depression Inventory (BDI), Mini-Mental State Examination (MMSE), and Zerssen Mood Scale were used to screen for cognitive impairment, mood and depression disorders. After the initial examination three patients were excluded, and twenty moved on to participate in the RCT. Blinding and randomization were performed by an independent individual using RandList, a specialized software program. Ten subjects (two men and eight women) were in the placebo group and 10 subjects (five men and five women) were in the treatment group. The age range of the placebo group was 49-78years, with a mean age of 65.4 years, and the ages for the treatment group ranged from 49-89years, with a mean age of 67.5 years. With regard to age, the groups were not significantly different with a p-value of .67. The subjects were given a bottle containing 63 capsules of either 0.5mg of clonazepam (Rivotril) PO or placebo (lactose monohydrate). Patients were instructed to take one capsule on an empty stomach with approximately 200mL of water once a day. The therapy session lasted for 9 weeks, during which they had to check off the intake of their capsules and note the date to insure compliance. At the end of the therapy session, the BDI and Zerssen Mood Scale were performed to investigate any adverse effects of medications.[1] A summary of results can be seen in Table 2.

Table 2. Descriptive Statistics of Pain Ratings as Reported by Heckmann et al.[1]

| Groups | # of patients | Session 1 (mean and SD) | Session 2 (beginning of drug intake) | Session 3 | Session 4 (end of drug intake) | Session 5 | p- value |
|---|---|---|---|---|---|---|---|
| Placebo | N= 10 | 6.0 ± 2.2 | 5.0 ± 2.0 | 4.6 ± 2.0 | 4.6 ± 2.4 | 4.5 ± 1.8 | p = .011 |
| 0.5mg Clonazepam PO | N= 10 | 7.4 ± 2.4 | 4.1 ± 3.0 | 3.8 ± 3.0 | 3.9 ± 2.9 | 4.5 ± 2.4 | p < .001 |

To analyze data an ANOVA F-score and p-value were used to evaluate the change in mean from baseline. With a $p < .001$ the study demonstrated that taking 0.5mg of clonazepam PO over the span of 9 weeks has shown significant improvement in the symptom of pain in patients with BMS. The study shows that clonazepam was not only well tolerated by all participants but also effective.

Rodriguez de Rivera Campillo et al.'s randomized controlled trial assessed the efficacy of 0.5mg of topical clonazepam in the treatment of BMS. Sixty-six patients, 64 of whom were women, reported oral burning in the absence of apparent pathology. Patients with disease of the oral mucosa and those receiving treatment for BMS were excluded. Subjects taking anxiolytics or antidepressives were not rejected because of the high prevalence of BMS among patients with psychiatric disorders.[6] A table of random numbers was used to ensure randomization of participants. Patients recorded their burning sensation using a VAS from 0 to 10. Six of the following variables were recorded for each patient: age, sex, duration of disease, location of burning sensation, drug consumption and systemic disease.[6] Two groups, each containing 33 patients, were formed and received a sealed envelope containing 32 tablets of either 0.5mg of topical clonazepam or placebo (lactose tablet). Patients were advised to take a single tablet in the morning at the first sign of discomfort; if symptoms improved but then reappeared they were

allowed to take another tablet. They were instructed, however, not to exceed four tablets a day, making a total dose of 2 mg of topical clonazepam. Patients were instructed to dissolve tablets in the mouth for three minutes and then to expectorate the saliva. Patients were also asked to note their burning sensation. Patients returned after 1 week to assess adverse effects, if any. Then, patients were scheduled to return after 1 month and 6 months to monitor for adverse effects and measure VAS from 0 to 10. A summary of results can be seen in Tables 3 and 4.

Table 3. Statistical Data of the VAS Values of Patients Reported by Rodriguez de Rivera Campillo et al. [6]

| | # Pts | 1st day | 1st month | 6th month | # Anxiolytic usage | #Antidepressant usage | # Psychological disease |
|---|---|---|---|---|---|---|---|
| Topical Clonazepam | 33 | 7.69 ± 1.53 | 2.84 ± 1.69 | 3.03 ± 1.35 | 24 | 15 | 21 |
| Placebo | 33 | 7.57 ± 1.58 | 4.24 ± 1.19 | 4.42 ± 0.96 | 25 | 18 | 20 |

Table 4. Characteristic of Pain and Average Number of Tablets Taken by Patients Reported by Rodriguez de Rivera Campillo et al.[6]

| | # Burning sensation | 1st month avg # of tablets | 6th month avg # of tablets |
|---|---|---|---|
| Topical clonazepam | 33 | 70 | 62 |
| Placebo | 33 | 95 | 84 |

To analyze data, chi-square and p-value of the VAS scores were evaluated. Rodriguez de Rivera Campillo et al. demonstrated that on the first day the differences between the groups were not statistically significant; however, after 1 month, 0.5 mg of topical clonazepam had a decrease in VAS scores with a $p<.005$, whereas the decrease in the placebo group was not statistically significant. Although a number of participants consumed anxiolytics and antidepressants and had psychological diseases, according to my interpretation of the data reported by Rodriguez de Rivera Campillo et al. was not significant enough to skew results. The study also shows that the average number of tablets consumed was fewer than the number consumed by the placebo group, although not significant in those patients taking clonazepam. The study reported that after one month, 23 of 33 subjects taking clonazepam showed more than a 50% reduction in symptoms

and five subjects were cured, compared to only 4 of 33 subjects from placebo group showing improvement. After six months 23 of 33 subjects taking clonazepam improved ($p < .05$), compared to only 2 of 33 subjects from the placebo group.[6]

The Gremeau-Richard et al. crossover trial evaluated the efficacy of the use of 1mg of topical clonazepam in 20 subjects who had previously received either lidocaine or saline injections. This trial was performed to assess the mechanism of the burning pain in these subjects, thus creating two subgroups, a "peripheral" and a "central" group. The peripheral group had pain relief while the central group had no relief of pain after lidocaine injections; however, the focus of this paper is to evaluate the intervention of topical clonazepam. Inclusion criteria consisted of the presence of an isolated complaint of chronic oral pain, a normal examination, and pain present for at least 4 months. Patients with an organic condition and those who could not understand the VAS were excluded. Randomization was performed by the Clinical Investigation Centre (CIC) of Clemont-Ferrand University hospital pharmacy. On the first visit subjects completed a questionnaire and VAS scores on pain intensity before and after injections of lidocaine or saline. The questionnaire consisted of questions such as the following: Was the pain increased or decrease or same? Was there anesthesia or numbness of the tongue? On which side did the sensation change? During the second visit one week later, participants received another injection of either lidocaine or saline and completed the VAS before and after. After this visit all 20 subjects were given 1 mg of topical clonazepam (Rivotril) to take three times a day after each meal for 3 weeks. Patients were advised to suck half a tablet for 3 minutes and expectorate saliva. During the third and last visit, 3 weeks later, patients were asked to score their pain intensity using VAS. A summary of results can be seen in Table 5. [2]

Table 5. VAS Scores Before and After 3 Weeks of Topical Clonazepam Gremeau-Richard et al[2]

| | Baseline (before injections of lidocaine) (n=10) | Baseline (before injections of saline) (n= 10) | After 21 days of treatment with1 mg of topical clonazepam (n=20) | p- value after clonazepam |
|---|---|---|---|---|
| ΔVAS scores | 5.6 ± 2.8 | 5.0 ± 2.4 | 2.1 ± 2.6 | p = .002 |

An ANOVA F-score and p-value were used to evaluate the VAS scores presented by Gremeau-Richard et al. The study demonstrated that the treatment of topical clonazepam was very effective. Seven patients reported a pain intensity decrease of 2-8/10 on the VAS; six patients reported a decreased VAS score of 1-2/10, four patients experienced no pain relief and only three patients worsened. Thus, of 20 subjects, 13 subjects showed improvement. Overall, all three studies reviewed in this paper showed a significant decrease in symptoms of BMS. A summary of results from all three studies can be seen in Table 6. [2]

Table 6. Summary of p- values Reported by Heckmann et al.[1] Gremeau-Richard et al. [2] Rodriguez de Rivera Campillo et al.[6]

| | Route of clonazepam | Data measured | p -values |
|---|---|---|---|
| Heckmann et al.[1] | Oral (PO) | 9 wks | p<.001 |
| Gremeau-Richard et al. [2] | Topical | 3wks | p = .002 |
| Rodriguez de Rivera Campillo et al.[6] | Topical | 1 mo and 6 mo | p < .005, p<.05 |

DISCUSSION

All three articles showed that clonazepam, whether topical or PO, is safe, well tolerated, and significantly improves symptoms of BMS. A limitation that is apparent with all three articles, however, is the assessment of the use of clonazepam in the long-term management of BMS, because of the short duration of the trials, with the longest being 6 months reported by Rodriguez de Rivera Campillo et al. According to Gremeau-Richard et al. one factor that may

affect outcome is the pathophysiology of BMS; there may be a peripheral and/or central mechanism that plays a role in a patient's symptoms and response to treatment, specifically clonazepam. In Rodriguez de Rivera Campillo et al.'s study, 62% of subjects had psychological problems; the patients who were not suffering from psychological problems had a greater proportion of cures. Also, in this study some patients experienced sleepiness as an adverse effect. In the future, studies can be done to explore the pathophysiology of BMS, which can lead to better long-term management and clinical guidelines.

## CONCLUSION

These studies have confirmed that clonazepam whether topical or PO is effective in the treatment of BMS. In analyzing the results from the three articles, it is evident that topical clonazepam is not more effective than clonazepam PO in the treatment of BMS.