# Topical Clonazepam and Placebo Effect in Burning Mouth Syndrome

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Topical Clonazepam and Placebo Effect in Burning Mouth Syndrome

A Thesis Presented by

*Michal Ahuva Kuten-Shorrer, DMD*

To

The Faculty of Medicine

In partial fulfillment of the requirements for the degree of

Doctor of Medical Sciences

*Research Mentors: Nathaniel Treister, DMD, DMSc¹, Alessandro Villa, DDS, PhD, MPH¹, and John Kelley, PhD²*

¹Harvard School of Dental Medicine and Brigham and Women’s Hospital

²Endicott College

Boston, Massachusetts

March 2016
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ACKNOWLEDGEMENTS

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ABSTRACT

Burning mouth syndrome (BMS) is a chronic pain condition reported to affect up to 7.9% of the general population, with associated detrimental impact on patients’ quality of life. Currently employed treatment regimens follow therapy for other neuropathic pain conditions. Very few placebo-controlled randomized trials (RCTs) have been conducted to evaluate the efficacy of these regimens, with a wide range of placebo responses documented. Low-dose clonazepam is considered first-line therapy for BMS, either in a topical or systemic mode of administration. An innovative formulation of topical clonazepam in the form of a compounded oral solution has been used at the Division of Oral Medicine and Dentistry at Brigham and Women’s Hospital (DOM-BWH) since 2008 for the management of BMS and other oral dysesthesias. An initial concentration of 0.5 mg/mL was used until 2012, when this was changed to a 0.1 mg/mL solution.

The objectives of this project were to 1) quantify the magnitude of placebo response in BMS, 2) evaluate the tolerability, safety, and efficacy of the two concentrations of topical clonazepam solution for the management of BMS, and 3) compare their effectiveness in improving burning symptoms.

We first conducted a systematic review of published randomized, blinded, placebo-controlled trials of therapies for BMS and evaluated the magnitude of the placebo response compared with the response to the treatment. Twelve RCTs were included. Ten studies (83%) reported at least some improvement in the symptomatology of patients receiving active treatment compared with baseline. In six of these studies (60%), there was also a positive response to placebo. On average, treatment with placebos produced a response that was 72% as large as the response to active drugs.

Next, we conducted a retrospective chart review of all patients with oral dysesthesia, including BMS, managed with topical clonazepam solution (0.1 mg/mL or 0.5 mg/mL) in DOM-BWH from 2008 to 2015. The relative safety of the two concentrations of the solution was evaluated in terms of occurrence of adverse drug reactions (ADRs) and occurrence of change to treatment plan secondary to ADRs. A total of 541 charts were reviewed. 162 subjects met the
inclusion criteria, 84 patients in the 0.1 mg/mL cohort and 78 in the 0.5 mg/mL cohort, evaluated at a median follow-up of 6 weeks. Thirty-eight (23%) patients developed ADRs. The most frequently reported ADR was sedation (62% of ADRs), followed by altered mental status and dizziness (7% each). In total, dose adjustments were required in nine patients (6%), and treatment was discontinued in 13 patients (8%). ADRs were more frequently reported in the 0.5 mg/mL cohort, but no significant difference was found between the two concentrations, either in terms of occurrence of ADRs or change to treatment secondary to ADRs, or in terms of types of ADRs (p>0.05).

Finally, we conducted a retrospective chart review of all patients diagnosed specifically with BMS and managed with topical clonazepam solution (0.1 mg/mL or 0.5 mg/mL) from 2008 to 2015. The efficacy of the two concentrations in improving burning symptoms was compared using patient-reported outcome measures, including the percentage improvement in burning symptoms as reported at first follow-up, and the change from baseline to first follow-up in the worst burning severity over the week prior to evaluation, ranked on an 11-point numeric rating scale (NRS). The study included 57 subjects, with 32 patients in the 0.1 mg/mL cohort and 25 patients in the 0.5 mg/mL cohort, who were evaluated at a median follow-up of 7 weeks. The median overall percentage improvement associated with the 0.1 mg/mL solution was 32.5% (range 0-100%), not significantly higher than the commonly used 30% cut-off. Treatment with the 0.5 mg/mL solution was associated with median overall percentage improvement of 75% (range 0-100%), significantly higher than the more conservative 50% cut-off (p<0.01). The median reduction in NRS score was 6 points in the 0.5 mg/mL concentration, and 0.5 points in the 0.1 mg/mL concentration. Using either outcome measure, response to treatment with the 0.5 mg/mL solution was superior to that associated with the 0.1 mg/mL solution (p<0.01).

This thesis is the first to suggest a potentially considerable role for placebo effect in treatments for BMS. Our results suggest that treatment with topical clonazepam solution is generally safe and well-tolerated, with a similar safety profile for both concentrations. A 0.5 mg/mL concentration is highly effective in the management of burning dysesthesia in patients with BMS, significantly more than a 0.1 mg/mL concentration.
INTRODUCTION AND REVIEW OF THE LITERATURE

I. Clinical Features and Epidemiology of Burning Mouth Syndrome

Oral dysesthesia, a subset of paresthesia, is defined as an unpleasant abnormal sensation involving the oral cavity. Burning mouth syndrome (BMS) is a chronic neuropathic condition that manifests as a burning dysesthesia in the oral cavity, generally localized to the anterior tongue, inner aspect of the lips and anterior hard palate (Grushka, 1987). BMS is defined by the absence of any local or systemic contributing etiologies such as candidiasis, hyposalivation, nutritional deficiencies or uncontrolled diabetes mellitus. Additional associated features include xerostomia (sensation of oral dryness), dysgeusia (altered sensation of taste), and other oral dysesthesias (Patton et al., 2007).

The prevalence of BMS increases with age and is seen more frequently in peri- and post-menopausal females. In the absence of universally accepted diagnostic criteria, the epidemiologic data on BMS are poor, with reported prevalence rates in the general population varying from 0.1 – 7.9% (Tammiala-Salonen et al., 1993, Lipton et al., 1993, Bergdahl & Bergdahl, 1999, Kohorst et al., 2015). In many cases patients go undiagnosed and untreated for months to years and often see multiple medical and dental practitioners before referral to an appropriate specialist (Mignogna et al., 2005).

II. Pathophysiology of BMS

The pathophysiology of BMS is poorly understood and likely involves interactions among local, systemic, and/or psychogenic factors (Patton et al., 2007).

a. Peripheral Component

A role for focal peripheral neuropathy in the pathophysiology of BMS was first suggested by Grushka et al. who utilized quantitative sensory testing (QST) methods to investigate the differences in thermal and tactile sensory modalities between BMS patients and healthy controls (Grushka et al., 1987). Thermal pain tolerance was found to be significantly reduced among the BMS subjects at the tip of tongue, a site of clinical burning pain in approximately 85% of the subjects tested. In a later study, BMS patients were found to perceive significantly more pain
from mechanical stimulation on the tongue, which also lasted longer compared with controls (Ito et al., 2002). Studies evaluating the effects of topical anesthesia and lingual nerve blocks on BMS symptoms demonstrated heterogeneous results, suggesting that at least in a subset of patients the symptoms appear to be peripherally mediated (Formaker et al., 1998, Gremeau-Richard et al., 2010). In neuropathological studies, biopsies obtained from the oral mucosa of BMS patients demonstrated decreased density of epithelial nerve fibers as well as axonal derangement, indicating a potential role for focal small fiber neuropathy of the oral mucosa (Lauria et al., 2005, Yilmaz et al., 2007, Puhakka et al., 2016). Finally, immunohistochemical stainings of tongue mucosal biopsies revealed significant increases in the expression of the heat and capsaicin receptor TRPV1 and its regulator nerve growth factor (NGF) within the surviving subepithelial nerve fibers of BMS patients (Yilmaz et al., 2007). As up-regulation of these factors has been associated with neuropathic pain symptoms and hypersensitivity states, they may also play a role in the development and maintenance of the burning dysesthesia in BMS.

b. Central Component

Several brain imaging studies provide evidence supporting the involvement of central neuropathic mechanisms in the pathophysiology of BMS, alongside or independent of focal peripheral neuropathy. A functional magnetic resonance (fMRI) study measuring brain activation in response to painful thermal stimuli revealed hypoactivity of the entire brain, and more specifically, of the thalamus, among BMS patients compared to pain-free controls (Albuquerque et al., 2006). Thalamic stimulation has been shown to increase activity in areas of the brainstem linked with descending inhibition, leading to the hypothesis that the hypofunctional thalamus does not allow for adequate descending inhibition of pain in BMS. Positron emission tomography (PET) studies demonstrated presynaptic dysfunction of the dopaminergic system within the basal ganglia in BMS patients, indicating a possible decline in endogenous dopamine levels. As previous data suggests that dopaminergic pathways participate in pain perception and in modulation of nociceptive information, the hypofunction of the dopaminergic system and subsequent deficient descending inhibition may be a contributing factor to BMS symptomatology (Jaaskelainen et al., 2001, Hagelberg et al., 2003).
c. Psychosocial Component

Other studies provide evidence for psychological elements in the etiology of BMS, with a high prevalence of anxiety, depression, and somatization documented among patients (Amenabar et al., 2008, Schiavone et al., 2012, de Souza et al., 2012). It is difficult, however, to link cause and effect, as any long-term illness, let alone one like BMS that adversely affects quality of life (Lopez-Jornet et al., 2008), can produce psychological disturbances. The term “vulnerability factors” was proposed by Lamey et al. as to link between early life experiences and subsequent susceptibility to develop BMS (Lamey et al., 2005). In their multicenter study comparing BMS patients and healthy controls, patients were found to have significantly higher adverse life experiences (e.g. recent bereavements and maternal depression), as well as higher scores for depression and anxiety. BMS patients were also characterized by cancer phobia, recurrent gastrointestinal problems, backache, disturbed sleep and chronic fatigue. The authors hypothesized that the “vulnerabilities” associated with early life events may sensitize the individual to react physically to current stressful life events. More evidence for components of psychosocial origin in BMS is provided by the observation that reassurance alone has a beneficial effect, resulting in a remission or resolution of oral symptoms in 24% of patients (Trombelli et al., 1994).

III. Current Evidence on Treatments for BMS

To date, evidence from RCTs as to the efficacy of interventions for the management of BMS is mixed, and no definitive cure has been identified (de Moraes et al., 2012). Furthermore, a wide range of placebo responses have been documented, with patients in the control arm responding positively to an inert substance that has a similar appearance to the studied treatment. In general, treatments for BMS focus on symptom relief, and regimens follow therapy for other neuropathic pain conditions (Grushka et al., 2002). Three particular substances have been reported to have positive outcomes, namely alpha-lipoic acid, capsaicin and clonazepam (de Moraes et al., 2012).

IV. Clonazepam

Clonazepam is a benzodiazepine derivative, and possesses both anticonvulsant and anxiolytic properties (Pinder et al., 1976). As such, it is indicated for the treatment of seizure disorders and panic disorder (Klonopin® [package insert]. Roche; 2009). While the exact mechanism of action
is unknown, it is believed to be related to the ability of clonazepam to potentiate neural inhibition mediated by gamma-aminobutyric acid (GABA) by increasing the GABA$_A$ receptor affinity for GABA. Once GABA binds to this receptor, ion channels open for chloride ions to enter the neuron, leading to hyperpolarization and rendering the cell less responsive to excitatory signals.

Clonazepam is rapidly absorbed after oral administration, reaching maximum plasma concentrations within 2-4 hours. It undergoes extensive hepatic metabolism and is excreted mainly in the urine. The half-life for elimination of clonazepam from plasma is typically 30-40 hours. Wide variation exists in maximum plasma concentrations of clonazepam between individuals, making it difficult to define a lower limit for therapeutic effect or an upper limit at which adverse effects may appear. For this reason, maintenance dosage must be individualized for each patient depending upon response, with a maximum recommended daily dose of 20 mg for the treatment of seizure disorders and 0.1-0.2 mg/kg of body weight for the treatment of panic disorder (Klonopin® [package insert]. Roche; 2009).

The principle adverse effects associated with clonazepam therapy are attributed to central nervous system depression, with symptoms of drowsiness, somnolence, fatigue and lethargy most frequently reported. These adverse effects are typically transient and self-limiting, however, at times they can be sufficiently severe to warrant dosage reduction or discontinuation of therapy (Pinder et al., 1976). In order to minimize the occurrence of adverse effects, it is recommended to increase the daily dose progressively, usually after 2-4 weeks of therapy, until the maintenance dose suited for the individual patient is reached.

a. Clonazepam for Management of BMS

The GABA$_A$ receptor is widely distributed, not only in the central nervous system, but also in peripheral tissues (Anholt et al., 1985, Gremeau-Richard et al., 2004, Tan et al., 2014). Activation of GABA$_A$ receptor is thought to mediate analgesia (Enna & McCarson, 2006), explaining the analgesic effect of clonazepam in BMS. Low-dose clonazepam is considered first-line therapy for BMS and has been reported with various degrees of efficacy in several trials (Grushka et al., 1998, Gremeau-Richard et al., 2004, Amos et al., 2011, Heckmann et al., 2012), only two of which were placebo-controlled and double-blind (Gremeau-Richard et al., 2004, Heckmann et al., 2012).
Heckmann et al. evaluated the efficacy of low dose systemic clonazepam in 20 patients with BMS (Heckmann et al., 2012). Patients were given either 0.5 mg of clonazepam or placebo once daily for 9 weeks. Statistically significant improvement in pain ratings were observed in both groups compared to baseline, but the improvement was more pronounced in the clonazepam group.

Gremeau-Richard et al. evaluated the efficacy of topical clonazepam in 48 patients with BMS (Gremeau-Richard et al., 2004). Patients were instructed to dissolve a 1.0 mg tablet of either clonazepam or placebo in the mouth for three minutes and spit out without swallowing, three times daily for 14 days. There was a statistically significant decrease of pain score compared with placebo, with two-thirds of patients reporting a significant improvement, and adverse reactions were not significantly more frequent in the clonazepam group. Specifically, reported adverse reactions included drowsiness (4/24 [16.7%] patients and 3/24 [12.5%] patients in the clonazepam and placebo groups, respectively), burning increase (2/24 [8.3%] patients in both groups), dry mouth, spasmophilia and euphoric behavior (one patient in the clonazepam group only [4.2%]), and led to the drop-out of 2/24 patients and 1/24 patients in the clonazepam and placebo groups, respectively. The efficacy of the treatment was also measured in an open manner for a longer time. Over half of the patients who felt improvement after the 14 days treatment reported residual partial improvement at a 6 months follow-up visit.

b. Topical clonazepam in the Form of a Compounded Oral Solution

Based on the data by Gremeau-Richard et al. (Gremeau-Richard et al., 2004), topical clonazepam for management of BMS and other oral dysesthesias has been used at the Division of Oral Medicine and Dentistry at Brigham and Women’s Hospital since 2008. Due to considerations of taste, tolerability, and ease of use, a compounded oral solution is used rather than the topical use of 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 solution concentrations were chosen for use based on clinical experience and biological plausibility, and the change from a 0.5 mg/mL solution to a 0.1 mg/mL solution was devised in order to mitigate potential adverse effects while maintaining treatment efficacy. While a short period of overlap between the two concentrations occurred during the months of January 2012 until November 2012, only a handful of patients were prescribed either
one during this time. All prescriptions have been filled through America’s Compounding Center (Newton, MA, USA, http://www.accrx.com/). Clonazepam solution was compounded according to the following formulary for 600 mL: 150 x 2 mg clonazepam tablets (active ingredient), 6 mL glycerin, 60 mL propylene glycol, 240 mL purified water, 6 mL bubble gum concentrate flavor, and 70% sorbitol solution to 600 mL.

V. Placebo Analgesia

Placebo analgesia is defined as a positive response to the administration of a substance known to be non-analgesic, but which the patient strongly believes is a potent pain killer (Greene et al., 2009). The placebo intervention is thus designed to simulate a therapeutic context, which affects the patient’s brain, body and behavior (Finniss et al., 2009).

Recent advances from behavioral, psychophysiological and neuroimaging methods demonstrate that the placebo effect is a 'real' neurobiological phenomenon, and that the altered pain experience during placebo analgesia results from active inhibition of nociceptive activity (Meissner et al., 2011). Specifically, placebo analgesia is thought to be regulated, at least in part, by endogenous opioid mechanisms. The involvement of opioid mechanisms was first suggested in a clinical study of post-operative pain in patients undergoing third molar tooth extraction (Levine et al., 1978). The authors observed that naloxone, an opioid antagonist, interfered with placebo analgesia and hypothesized that this effect was due to its interfering with the endogenous opioid system.

The involvement of the opioid system in placebo analgesia has since been confirmed by data obtained from brain imaging techniques such as PET and fMRI (Greene et al., 2009, Finniss et al., 2010, Meissner et al., 2011), where similar brain activation patterns among patients taking a strong opioid medication and those taking a placebo were observed (Petrovic et al., 2002). The analgesic effect has been shown to occur in three different phases of pain processing (Kong et al., 2007): influencing the anticipation of pain relief (pre-painful stimulus phase), altering the perception of pain (during administration of painful stimulus), and modifying the reporting of pain (post-painful stimulus phase).
VI. The Role of Placebo Effect in Treatment Response

RCTs are currently considered the gold standard in clinical pharmacological research for establishing treatment efficacy. A treatment is considered legitimate if it proves to be superior to a placebo, an inert substance given as a control (Kaptchuk, 1998). The drug effect is measured as the difference between the drug and placebo responses, and the placebo response, in turn, is comprised of the genuine placebo effect and any changes due to regression to the mean and the natural history of the disorder. Thus, the magnitude of the placebo response depends, among other factors, on the condition being treated. Evidence suggests that placebo effects are primarily observed in subjective outcomes (Wechsler et al., 2011). Substantial placebo responses have been documented in the treatment of conditions such as depression and irritable bowel syndrome (IBS) (Walsh et al., 2002, Patel et al., 2005), with the fraction of drug response duplicated by placebo being 60% in major depressive disorder and 74% in IBS. Given the subjective nature of BMS symptoms with the subsequent reliance on patient-reported outcomes, similar findings may be expected in BMS.
HYPOTHESES AND SPECIFIC AIMS

I. Hypotheses

1. Patients being treated for BMS are especially sensitive to favorable treatment outcomes associated with a placebo effect, similar to other chronic pain disorders.
2. Topical clonazepam solution, when swished with 5 mL for 5 minutes and expectorated two to four times daily, is generally well-tolerated, but associated with potential adverse reactions; and a 0.1 mg/mL concentration is associated with fewer and less severe adverse reactions than a 0.5 mg/mL concentration.
3. Topical clonazepam solution, when swished with 5 mL for 5 minutes and expectorated two to four times daily, is effective in the management of BMS; and a 0.1 mg/mL concentration is as effective as a 0.5 mg/mL concentration.

II. Specific Aims

1. To quantify the extent of placebo response in BMS.
2. To determine the absolute and relative safety of treatment with topical clonazepam solution (0.1 mg/mL compared to 0.5 mg/mL) for oral dysesthesia and the associated adverse reaction profile.
3. To determine the relative extent of improvement in patient-reported outcome measures achieved by treatment of BMS with two different concentrations of topical clonazepam solution (0.1 mg/mL compared to 0.5 mg/mL).
SIGNIFICANCE

BMS has a negative impact on the general and psychological well-being of patients, and is associated with poor quality of life (Lopez-Jornet et al., 2008, Ni Riordain et al., 2010, Souza et al., 2011). Spontaneous complete remission is rare, but between one half and two-thirds of patients may feel some improvement in their symptoms within 6 to 7 years of onset (Sardella et al., 2006, Patton et al., 2007). Nevertheless, most patients continue to need substantial healthcare resources, resulting in a significant social and economic burden.

Numerous therapies for palliating BMS symptoms have been proposed and tested. These treatments differ in their degree of effectiveness as well as in the range and frequency of adverse events (de Moraes et al., 2012). Given the chronic nature and prevalence of BMS, alongside the deleterious impact on patients’ general and psychological well-being, the need to identify a safe and effective mode of treatment for patients is vital. In light of the wide range of placebo responses documented in trials evaluating different treatments for BMS, a better understanding of the placebo effect in BMS is critical in the assessment of treatment response and in the design of future RCTs. Furthermore, because placebo and drug effects are usually additive, a better understanding of the placebo effect in BMS can be harnessed in the clinical setting to enhance the treatment response.
SPECIFIC AIM 1. A SYSTEMATIC REVIEW OF PLACEBO RESPONSE IN BURNING MOUTH SYNDROME

I. Materials and Methods

A systematic literature search was conducted using the PubMed/Medline database to identify English language published randomized controlled clinical trials of therapies for BMS. The search was conducted using the following terms: burning mouth syndrome, BMS and stomatodynia crossed with treatment and therapy. Articles published up to June 2012 were included.

a. Inclusion Criteria

Any randomized, blinded and placebo-controlled studies evaluating effectiveness of a medication compared to placebo were included. Studies were only included if they strictly evaluated patients with BMS, i.e. excluded patients with oral mucosal lesions or abnormal laboratory findings that could be causative for their oral burning symptoms, such as iron deficiency anemia and vitamin deficiencies. Only English language articles were included, for reasons of feasibility. Potential studies were first screened at the level of titles and abstracts for placebo-controlled RCTs. The full articles of selected studies were then screened to confirm eligibility. Extracted data included details of blinding, design (parallel or cross-over), sample size and subjects’ demographics, treatment(s) and placebo evaluated, study duration, outcome measures, and duration of follow-up period.

b. Data Analysis

Clinical outcomes of both the placebo arm and treatment arm(s) were extracted from all included studies. The fraction of active treatment response duplicated by placebo was calculated and averaged across all studies, in order to evaluate the magnitude of the placebo effect compared with that of the active treatment. This is a common metric used in meta-analyses examining the placebo effect in RCTs (Kirsch et al., 2008). A conservative decision rule was selected for

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studies with multiple time points or multiple active treatments. The longest follow-up period and
the most effective active treatment were used in the calculation, with the purpose of minimizing
the fraction of the active response duplicated by placebo. In the case of cross-over trials, only the
first period (prior to the cross-over) was used in calculation.

II. Results

A total of 422 studies were identified. These included randomized active-controlled trials, review
articles, case reports, repeated articles, and other studies that did not meet the eligibility criteria.
Twelve studies met the inclusion criteria and were reviewed (Table 1). The number of
participants ranged from 20 to 120, with the majority being female. Eleven studies were double-
blind, randomized, and placebo-controlled trials. One was a single-blind trial (Marino et al.,
2010). The intensity of pain was assessed in the majority of studies (11/12) using visual analog
scales (VAS). A single study used a unique 5 point (0-4) categorical scale (Lopez-D’alessandro
& Escovich, 2011). The median duration of therapy in all trials was 8 weeks (range 1-12).

a. Placebo Arm in Included Studies

The placebo was administered in the same manner as the active treatment in all studies, however
its composition was only specified in seven studies (58%). Petruzzi et al. emphasized that the
placebo was matched with the treatment with respect to shape, taste, smell and color (Petruzzi et
al., 2004), while in three other trials the authors simply stated that the placebo was identical
looking to the treatment (Tammiala-Salonen & Forssell, 1999, Gremeau-Richard et al., 2004,
Sardella et al., 2008). In the seven trials in which placebo composition was specified, the most
commonly used placebo was cellulose starch in the form of oral pills (4/7 studies). Other placebo
formulations included cellulose as a primary ingredient, with dicalcium phosphate,
 microcrystalline cellulose, hydroxipropylmethyl cellulose, silicon dioxide, vegetal magnesium
stearate, shellac and stearic acid (Carbone et al., 2009). Other placebos used were lactose
monohydrate (Heckmann et al., 2012) and mouthwash of boric acid (Marino et al., 2010). A
boric acid mouthwash was compared with three different therapies administered in different
regimens, two of which were also topical in the form of a mouthwash. None of the studies
included a no-treatment control.
Table 1. Randomized, placebo-controlled trials in burning mouth syndrome

<table>
<thead>
<tr>
<th>Authors</th>
<th>Evaluable patients (n)</th>
<th>Gender (M/F)</th>
<th>Mean age (years)</th>
<th>Treatment (n)</th>
<th>Placebo (n)</th>
<th>Treatment duration (weeks)</th>
<th>Pain scale</th>
<th>Follow-up</th>
</tr>
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<tbody>
<tr>
<td>Heckmann et al 2012</td>
<td>20</td>
<td>7/13</td>
<td>66.45</td>
<td>clonazepam 0.5 mg/day (10)</td>
<td>lactose monohydrate (10)</td>
<td>9</td>
<td>VAS</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Silvestre et al 2012</td>
<td>23</td>
<td>4/19</td>
<td>72.65 ± 12.10</td>
<td>capsaicin oral rinse (0.02%) x 3/day (12)</td>
<td>N/A, x 3/day (11)</td>
<td>1</td>
<td>VAS</td>
<td>N/A</td>
</tr>
<tr>
<td>López-D’alessandro and Escovich 2011</td>
<td>120</td>
<td>26/94</td>
<td>57.5 ± 14.1</td>
<td>ALA 600 mg/day (20); GABA 300 mg/day (20); ALA+GABA (20)</td>
<td>cellulose starch 100 mg/day (60)</td>
<td>8</td>
<td>Numerical (unique system)</td>
<td>N/A</td>
</tr>
<tr>
<td>Marino et al 2010</td>
<td>56</td>
<td>10/46</td>
<td>62 ± 9.8</td>
<td>capsaicin oral rinse x 3/day (14); ALA 400 mg x 2/day (14); LLP oral rinse x 5/day (14)</td>
<td>boric acid 0.05 g/100 ml mouthwash x 3/day (14)</td>
<td>8</td>
<td>VAS</td>
<td>8 weeks</td>
</tr>
<tr>
<td>López-Jornet et al 2009</td>
<td>60</td>
<td>6/54</td>
<td>64.37 ± 11.61</td>
<td>ALA 800 mg/day (30)</td>
<td>cellulose tablets 800 mg/day (30)</td>
<td>8</td>
<td>VAS</td>
<td>N/A</td>
</tr>
<tr>
<td>Cavalcanti and da Silveira 2009</td>
<td>31</td>
<td>4/29</td>
<td>62.9*</td>
<td>ALA 200 mg x 3/day</td>
<td>cellulose starch capsules 100 mg x 3/day</td>
<td>4</td>
<td>VAS, GPE</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Carbone et al 2009</td>
<td>52</td>
<td>9/43</td>
<td>67.3 ± 11.9</td>
<td>ALA 400 mg + multi-vitamins complex x 2/day (18); ALA 400 mg x 2/day (14)</td>
<td>cellulose tablets, x2/day (20)</td>
<td>8</td>
<td>VAS, MPQ</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Sardella et al 2008</td>
<td>39</td>
<td>4/35</td>
<td>64.9 ± 4.7</td>
<td>H. perforatum extract 300 mg capsules x 3/day (19)</td>
<td>N/A, 300 mg capsules x 3/day (20)</td>
<td>12</td>
<td>VAS</td>
<td>N/A</td>
</tr>
<tr>
<td>Greemeau-Richard et al 2004</td>
<td>48</td>
<td>4/44</td>
<td>65 ± 2.1</td>
<td>topical clonazepam (24)</td>
<td>N/A, 1 mg x 3/day (24)</td>
<td>2</td>
<td>VAS</td>
<td>6 months</td>
</tr>
<tr>
<td>Petruzzi et al 2004</td>
<td>50</td>
<td>14/36</td>
<td>56.5</td>
<td>capsaicin 0.25% x 3/day (25)</td>
<td>N/A, x 3/day (25)</td>
<td>4</td>
<td>VAS</td>
<td>N/A</td>
</tr>
<tr>
<td>Femiano and Scully 2002</td>
<td>60</td>
<td>18/42</td>
<td>45*</td>
<td>ALA 200 mg x 3/day (30)</td>
<td>cellulose starch 100mg x 3/day (30)</td>
<td>8</td>
<td>VAS</td>
<td>1 year</td>
</tr>
<tr>
<td>Tammiila-Salonen and Forssell 1999</td>
<td>28</td>
<td>0/28</td>
<td>58.6</td>
<td>trazodone 200 mg daily (11)</td>
<td>N/A, x 2/day (17)</td>
<td>8</td>
<td>VAS, MPQ</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Abbreviations: M: male; F: female; ALA: Alpha-lipoic acid; GABA: gabapentin; LLP: lysozyme, lactoperoxidase; N/A: not available; VAS: visual analog scale; MPQ: McGill pain questionnaire; GPE: global perceived effect.

* Median age (mean age was not reported).
b. Outcome Assessment

In ten studies (83%) at least some improvement in the symptomatology of patients receiving active treatment as compared to baseline was reported, while in the remaining two studies (17%) there was no improvement (Sardella et al., 2008, Lopez-Jornet et al., 2009). A positive response to placebo, ranging from 15% to 74%, was explicitly documented in six of the ten studies (60%) that showed improvements in the active treatment arm (Table 2) (Cavalcanti & da Silveira, 2009, Lopez-D'alessandro & Escovich, 2011). In three of these studies, the placebo response was statistically indistinguishable from the active agent (Tammiala-Salonen & Forssell, 1999, Cavalcanti & da Silveira, 2009, Carbone et al., 2009). Cavalcanti and da Silveira tested the effectiveness of systemic alpha lipoic acid (ALA) in a cross-over study compared with cellulose starch (Cavalcanti & da Silveira, 2009). Carbone et al. evaluated the efficacy of systemic ALA alone and ALA with multi-vitamins compared with identical placebo pills containing cellulose (Carbone et al., 2009). In both trials, there was a statistically significant reduction in symptoms in both treatment and placebo arms, and there was no significant difference for ALA over the placebo. In the cross-over trial, there was also no significant difference for the sequence order. Tammiala-Salonen and Forssell evaluated the efficacy of the antidepressant trazodone compared with a non-specified placebo (Tammiala-Salonen & Forssell, 1999). Placebo arm patients responded with significant reduction in pain intensity, and the reduction in VAS scores was statistically indistinguishable from that achieved with trazodone over the 8 week treatment period.
Table 2. Clinical outcomes in randomized placebo-controlled trials in BMS documenting positive placebo effect

<table>
<thead>
<tr>
<th>Authors</th>
<th>Clinical outcome</th>
<th>Treatment vs. placebo – significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heckmann et al 2012</td>
<td>Improvement, p&lt;0.001</td>
<td>Clonazepam better than lactose monohydrate, p=0.01</td>
</tr>
<tr>
<td>Lopez-D’alessandro and Escovich 2011</td>
<td>ALA + GABA: 70% improvement or resolution; ALA: 55% improvement or resolution; GABA: 50% improvement or resolution</td>
<td>ALA+GABA 13.2 times better than cellulose starch; ALA 7 times better than cellulose starch; GABA 5.7 times better than cellulose starch p&lt;0.001</td>
</tr>
<tr>
<td>Cavalcanti and da Silveira 2009</td>
<td>71% improvement or resolution; Complete remission in 6.5% p&lt;0.001</td>
<td>NS</td>
</tr>
<tr>
<td>Carbone et al 2009</td>
<td>Improvement in both ALA and ALA + multi-vitamins groups (p=0.047 and p=0.013, respectively)</td>
<td>Improvement, p=0.030</td>
</tr>
<tr>
<td>Femiano and Scully 2002</td>
<td>97% improvement or resolution; 0 worsened</td>
<td>ALA better than cellulose starch, p&lt;0.0001</td>
</tr>
<tr>
<td>Tammiala-Salonen and Forssell 1999</td>
<td>General reduction in pain, p&lt;0.01</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: ALA: alpha-lipoic acid; GABA: gabapentin; NS: non-significant (p>0.05).

Follow-up periods were reported in six studies, ranging from two weeks (Heckmann et al., 2012) to 12 months after the end of treatment (Femiano & Scully, 2002), while in the remaining studies a follow-up was not reported. At 8 weeks after the end of drug intake, Carbone et al. recorded a continued reduction in VAS scores in both treatment and placebo arms, without any statistically significant differences between the two ALA groups and the cellulose starch placebo group (Carbone et al., 2009). In contrast, after the same period of time, Cavalcanti and da Silveira noted a relapse in most patients who reported any improvement at the end of the treatment period, regardless of treatment assignment (Cavalcanti & da Silveira, 2009). Famiano and Scully conducted the longest follow-up period of one year. All 12 placebo control patients who reported any improvement after receiving cellulose starch for two months had deteriorated
to some extent over this time. The deterioration was statistically significant compared with the 73% of patients who reported a sustained response with ALA (Femiano & Scully, 2002).

c. Overall Placebo Response

The robustness of the placebo response was compared to the drug response (Table 3). Sufficient data in order to calculate the placebo response as a fraction of the active treatment response was reported in ten studies (83%). Six of the ten studies (60%) reported means and standard deviations of VAS scores, allowing the calculation of the standardized change in symptomatology. The mean placebo response as a fraction of drug response over all ten studies was 72%, suggesting a robust placebo response.

Table 3. Changes in pain for active and placebo treatment, and fraction of active response duplicated by placebo

<table>
<thead>
<tr>
<th>Studies Reporting Means and SDs</th>
<th>Absolute Change</th>
<th>Standardized Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active</td>
<td>Placebo</td>
</tr>
<tr>
<td>Heckmann et al 2012</td>
<td>2.90</td>
<td>1.50</td>
</tr>
<tr>
<td>Marino et al 2010</td>
<td>2.90</td>
<td>-0.20</td>
</tr>
<tr>
<td>López-Jornet et al 2009</td>
<td>2.20</td>
<td>3.80</td>
</tr>
<tr>
<td>Carbone et al 2009</td>
<td>1.79</td>
<td>1.60</td>
</tr>
<tr>
<td>Sardella et al 2008</td>
<td>1.77</td>
<td>1.13</td>
</tr>
<tr>
<td>Gremeau-Richard et al 2004</td>
<td>2.50</td>
<td>0.70</td>
</tr>
</tbody>
</table>

Studies Reporting Means Only

<table>
<thead>
<tr>
<th>Studies Reporting Medians Only</th>
<th>Absolute Change</th>
<th>Standardized Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tammiali-Salonen and Forssell 1999*</td>
<td>13.90</td>
<td>12.30</td>
</tr>
</tbody>
</table>

Studies Reporting Percent of Patients Showing Any Improvement

<table>
<thead>
<tr>
<th></th>
<th>Absolute Change</th>
<th>Standardized Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>López-D’alessandro and Escovich 2011</td>
<td>0.70</td>
<td>0.15</td>
</tr>
<tr>
<td>Femiano and Scully 2002</td>
<td>0.97</td>
<td>0.40</td>
</tr>
</tbody>
</table>

Mean

<table>
<thead>
<tr>
<th></th>
<th>Absolute Change</th>
<th>Standardized Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.72</td>
<td>0.72</td>
</tr>
</tbody>
</table>

Note: Standardized change scores are the effect size known as Cohen’s d. Abbr eviation: SD:

standard deviation.

*The larger change scores for these studies occurred because they used a VAS scale with a range of 0-100, while the other studies used VAS scales with a range of 0-10.

III. Discussion

Recent evidence suggests that placebo effects are primarily observed in subjective outcomes (Wechsler et al., 2011). This highlights the importance of understanding the role of placebo
effect in BMS, where outcome assessment is based on patient reported measures, and a wide range of both placebo and treatment responses has been documented. Current clinical pharmacological research relies on the superiority of a treatment compared with a placebo in the context of an RCT. The present study is the first systematic review investigating the placebo response in RCTs evaluating treatments for BMS.

Based on this review of 12 placebo-controlled RCTs evaluating different treatments for BMS, a mean placebo response as a fraction of drug response of 72% was found. The reported placebo responses varied across trials, and half of the studies reviewed (6/12) reported a non-zero positive placebo response, ranging from 15% (Lopez-D'alessandro & Escovich, 2011) to 74% of patients classified as responders (Cavalcanti & da Silveira, 2009). In most cases, the placebo used was cellulose in the form of oral pills; and in all six studies reporting a positive placebo response, the therapy evaluated, as well as the placebo, were administered systemically. Comparable results were documented in a meta-analysis of forty-five IBS placebo-controlled RCTs, with a placebo response ranging from 16% to 71.4% and an average placebo response of 40.2% relative to a 54.1% average treatment response (Patel et al., 2005). As in BMS, symptom-based diagnostic criteria are the gold standard for the diagnosis of IBS (Moayyedi & Ford, 2011), and the prevalence of IBS has been estimated at between 2% and 15% of the general population, with slight female predominance (Choung & Locke, 2011). Similar findings were reported for RCTs evaluating therapies for postoperative pain, with an average mean placebo response as a fraction of mean treatment response of 54% (McQuay et al., 1996). In the setting of major depressive disorder (Walsh et al., 2002), the average proportion of patients responding to placebo in reviewed RCTs was 30%, with the comparable figure of 50.1% for patients receiving active treatment, and thus, the fraction of drug response duplicated by placebo was 60% (30/50.1).

Comparing and aggregating results from the studies included in this review is limited by differences in study design, including sample size, duration of therapy, definition of clinically significant outcome and placebo control. Moreover, data reporting practices differed across studies, as summarized in Table 3. Despite these limitations, the magnitude of the placebo response in BMS appears to be quite robust.
The high placebo response rates documented in this review pose a significant challenge for the design of future RCTs evaluating therapies for BMS. In order to obtain strong evidence for treatment efficacy in BMS, future adequately powered multicenter trials are essential. Such trials would benefit from including a standard protocol for providing instructions, and from evaluating treatment efficacy over an adequately long follow-up period (e.g. minimum of eight weeks) in order to discern whether the treatment is more effective than placebo. With respect to reporting of data, it is recommended that in future studies all available data will be reported, in particular means, medians and standard deviations of outcome measures, so that aggregation and comparison of data will become a simpler undertaking. In order to allow differentiation between the natural course of the symptoms or regression to the mean and the genuine placebo effect, the inclusion of a third “no treatment” waitlist control group is recommended (Conboy et al., 2006, Greene et al., 2009). The waitlist group is then regarded as an indicator of the most minimal effects of observation and attention (Hawthorne effect) in the context of an RCT.

Recent studies demonstrate that the components of the medical encounter can be delivered in a manner analogous to dose-dependence to produce clinically significant symptomatic improvement, and that the patient-practitioner relationship is the most robust component of the placebo effect (Kaptchuk et al., 2008, Kelley et al., 2009). Taking the time to interview patients and discuss their symptoms, expressing empathy and confidence in the treatment, all lead to significantly more effective outcomes. This observation may explain the findings of Trombelli et al., who demonstrated that in the case of BMS, reassurance alone can have a beneficial effect, resulting in a remission or resolution of oral symptoms in 24% of patients (Trombelli et al., 1994). Assuming a genuine placebo effect exists in BMS (which can be validated in an RCT design that includes a no-treatment group), harnessing the placebo effect in clinical practice would allow to enhance the clinical outcome.
SPECIFIC AIM 2. A RETROSPECTIVE MEDICAL CHART REVIEW OF THE ADVERSE REACTIONS ASSOCIATED WITH TOPICAL CLONAZEPAM THERAPY

I. Materials and Methods

Approval of the Partners’ Institutional Review Board at Brigham and Women’s Hospital was obtained. A retrospective electronic medical chart review was conducted of all patients with oral dysesthesia, including BMS, managed with topical clonazepam solution (0.1 mg/mL or 0.5 mg/mL) in the Division of Oral Medicine and Dentistry at BWH from 2008 to 2015. The concentration of 0.5 mg/mL was used until 2012, when this was changed to a 0.1 mg/mL solution. Subjects were identified through an output from America’s Compounding Center of all patients prescribed topical clonazepam solution at the practice during the study period. Data collected from medical records included demographics, description of oral dysesthesia(s), current psychiatric medication(s), concurrent treatment(s) for oral dysesthesia, occurrence and description of adverse drug reactions (ADR), and changes to treatment plan following ADRs. Data regarding the occurrence and nature of ADRs was collected at first follow-up visits only, as to minimize the risk of attrition bias as well as bias as a result of longer follow-up periods for patients receiving the 0.5 mg/mL concentration.

a. Inclusion Criteria

Patients were either treatment-naïve or on a stable regimen for at least one month prior to beginning topical clonazepam solution therapy. All patients had been instructed to swish with 5 mL for 5 minutes and spit, without swallowing, two to four times a day. Patients treated with psychiatric medications were included only if on a stable regimen for at least one month. Patients who swallowed one or more doses of the solution as means of systemic therapy were excluded. Finally, only patients with at least one follow-up encounter, either in person or by phone, were included.
b. Outcome Measures and Statistical Analysis

The primary outcome measure was the occurrence of ADRs in patients treated with topical clonazepam solution (0.1 mg/mL or 0.5 mg/mL). A secondary outcome measure was the occurrence of change to treatment plan secondary to ADR, i.e. dose reduction or discontinuation of topical clonazepam solution. These outcomes were evaluated using descriptive statistics. In order to evaluate the relative safety of the two concentrations of the solution in terms of occurrence of ADRs and occurrence of change to treatment plan secondary to ADRs, the sample was partitioned into two groups, according to the dosage initially prescribed. To this end, Fisher’s Exact Test was applied.

II. Results

A total of 541 charts were reviewed. Figure 1 illustrates the chart review process and patient eligibility. 162 cases met the inclusion criteria, with 84 patients in the 0.1 mg/mL cohort and 78 in the 0.5 mg/mL cohort. Patients’ characteristics are summarized in Table 4. The two cohorts were balanced at baseline with respect to gender, age, type of dysesthesia(s), and concurrent psychiatric medication(s).
Figure 1. Specific Aim 2. Chart review process and patient eligibility

Cases identified through ACC output (n=541)

0.5 mg/mL cohort (n=266)

188 excluded
64 Lost to follow-up
26 Declined treatment
39 Swallowed at least one dose
59 Prescribed concurrent therapy

N=78

0.1 mg/mL cohort (n=275)

191 excluded
87 Lost to follow-up
26 Declined treatment
24 Swallowed at least one dose
54 Prescribed concurrent therapy

N=84
a. Occurrence of Adverse Drug Reactions and Subsequent Change to Treatment Plan

Patients were evaluated at a median follow-up of 6 weeks (ranging from 3 days to 3 years). A total of thirty-eight (23%) patients developed ADRs, with dose adjustments required in 9 cases (6%), and treatment discontinuation in 13 cases (8%). Although ADRs were more frequently reported in the 0.5 mg/mL cohort, no significant difference was found between the two concentrations, either in terms of occurrence of ADRs or in terms of change to treatment plan due to ADRs (p>0.05, Fisher’s exact test), as presented in Table 5.
Table 5. Comparison of adverse reactions according to concentration

<table>
<thead>
<tr>
<th>Variable</th>
<th>N (%)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.1 mg/mL cohort (n=84)</td>
<td></td>
</tr>
<tr>
<td>ADR</td>
<td>15 (18)</td>
<td></td>
</tr>
<tr>
<td>Dose limiting ADR</td>
<td>2 (2)</td>
<td>0.09</td>
</tr>
<tr>
<td>Discontinuation of treatment due to ADR</td>
<td>5 (6)</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>0.5 mg/mL cohort (n=78)</td>
<td></td>
</tr>
<tr>
<td>ADR</td>
<td>23 (29)</td>
<td></td>
</tr>
<tr>
<td>Dose limiting ADR</td>
<td>7 (9)</td>
<td></td>
</tr>
<tr>
<td>Discontinuation of treatment due to ADR</td>
<td>8 (10)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: ADR: adverse drug reaction.

* p-value (p < 0.05) calculated using Fisher’s Exact Test.

b. Types of Adverse Drug Reactions

ADRs were further grouped into seven categories, as follows: sedation, altered mental status, dizziness, burning increase, nausea, skin reaction, and other. Sedation, manifesting with drowsiness, sleepiness, and motor incoordination was the most frequently reported ADR (accounting for 62% of ADRs), followed by altered mental status, presenting as confusion, disorientation, and concentration impairment (7%) and dizziness (7%) (Table 6). While sedation was more frequently reported in the 0.5 mg/mL cohort, the difference was not statistically significant (p>0.05, Fisher’s exact test). Specifically, 17 (22%) patients reported sedation secondary to rinsing with the topical clonazepam compared with 9 (11%) patients in the 0.1 mg/mL cohort. Most patients reported drowsiness and sleeping longer than usual at night or midday. Some patients reported having trouble walking without support. Two patients in the 0.5 mg/mL cohort were involved in motor vehicle accidents (MVAs) after initiating treatment with topical clonazepam solution. Additional information was available in these two cases, as follows: the accident occurred 10-15 minutes after first rinsing with the solution in one case, and after approximately 7 rinses (total of 4 days since initiation of treatment) in the other case. Both patients attributed their involvement in MVAs to a state of sedation secondary to the use of clonazepam. The latter was brought to an ED, where clinical and radiographic examinations were within normal limits and a toxicology screen was negative, including a negative result for traces of clonazepam.
Table 6. Types of adverse drug reactions according to concentration

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>0.1 mg/mL cohort (n=84)</th>
<th>0.5 mg/mL cohort (n=78)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation</td>
<td>9 (11)</td>
<td>17 (22)</td>
<td>0.08</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>0 (0)</td>
<td>3 (4)</td>
<td>0.12</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (1)</td>
<td>2 (3)</td>
<td>0.61</td>
</tr>
<tr>
<td>Burning increase</td>
<td>2 (2)</td>
<td>0 (0)</td>
<td>0.49</td>
</tr>
<tr>
<td>Nausea</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>0.48</td>
</tr>
<tr>
<td>Skin Reaction</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>0.48</td>
</tr>
<tr>
<td>Other §</td>
<td>4 (5)</td>
<td>2 (3)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

More than one ADR per patient possible.
* p-value (p < 0.05) calculated using Fisher’s Exact Test.
§ Other ADRs include: cough, tooth sensitivity, sense of tissue numbness, vivid dreams, oral dryness, and falling.

Table 7 replicates the analyses presented in Tables 2 and 3, concentrating on patients experiencing ADRs. No significant differences were found in terms of change to treatment plan or types of ADRs.

Table 7. Consequences and types of reactions among patients experiencing adverse drug reactions

<table>
<thead>
<tr>
<th>Variable</th>
<th>0.1 mg/mL cohort (n=15)</th>
<th>0.5 mg/mL cohort (n=23)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADRs leading to change in treatment plan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose reduction</td>
<td>2 (13)</td>
<td>7 (30)</td>
<td>0.45</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>5 (33)</td>
<td>8 (35)</td>
<td>1.0</td>
</tr>
<tr>
<td>Types of ADR§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedation</td>
<td>9 (60)</td>
<td>17 (74)</td>
<td>0.79</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>0 (0)</td>
<td>3 (13)</td>
<td>0.29</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (7)</td>
<td>2 (9)</td>
<td>1.0</td>
</tr>
<tr>
<td>Burning increase</td>
<td>2 (13)</td>
<td>0 (0)</td>
<td>0.17</td>
</tr>
<tr>
<td>Nausea</td>
<td>0 (0)</td>
<td>1 (4)</td>
<td>1.0</td>
</tr>
<tr>
<td>Skin Reaction</td>
<td>0 (0)</td>
<td>1 (4)</td>
<td>1.0</td>
</tr>
<tr>
<td>Other §</td>
<td>4 (27)</td>
<td>2 (9)</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Abbreviation: ADR: adverse drug reaction.
* p-value (p < 0.05) calculated using Fisher’s Exact Test.
§ More than one ADR per patient possible.
† More than one ADR per patient possible.
§ Other ADRs include: cough, tooth sensitivity, sense of tissue numbness, vivid dreams, oral dryness, and falling.

c. Overlap Period

As mentioned above, newly diagnosed patients with oral dysesthesia were prescribed the 0.5 mg/mL solution until the year 2012, when the concentration was changed to 0.1 mg/mL.
However, a short period of overlap between the two concentrations occurred between January 2012 to November 2012, when 7 (8%) new patients received the 0.1 mg/mL solution and 6 (8%) new patients received the 0.5 mg/mL solution. Two of these 6 patients in the 0.5 mg/mL cohort experienced ADRs, while none of the 7 patients in the 0.1 mg/mL cohort experienced ADRs. Starting in November 2012, all new patients were prescribed the 0.1 mg/mL solution. All of the results above continue to hold once the observations from the overlap period are excluded.

III. Discussion

This retrospective study is the first to collect data on the safety profile of topical clonazepam solution for the management of oral dysesthesias, including BMS. While the percentage of patients who experienced ADRs may appear high (23% [38/162]), this value is in fact smaller than the one observed by Gremeau-Richard et al. in their RCT evaluating topical clonazepam in the form of a tablet for the management of BMS (Gremeau-Richard et al., 2004), in which 37% (9/24) of patients in the clonazepam group reported an ADR, with the subsequent drop-out of 8% (2/24) of patients. Similarly, in our study, 8% (13/162) of patients required treatment discontinuation secondary to ADRs, and an additional 6% (9/162) of patients required dose reduction in order to continue treatment. By far, the most frequently reported ADR was sedation, with overall 16% (26/162) of patients reporting signs and symptoms of drowsiness, sleepiness and motor incoordination. This finding also correlates with the findings of Gremeau-Richard et al., who document drowsiness in 17% (4/24) of patients in the clonazepam group.

Serious ADRs are defined as any untoward medical occurrence that at any dose results in death, requires hospital admission or prolongation of existing hospital stay, results in persistent or significant disability/incapacity, or is life threatening (Edwards & Aronson, 2000). Out of the 162 patients included in this study, only two patients (1%) experienced serious ADRs - both reporting sedation that led to their involvement in MVAs. Although no physical harm occurred to either one of them, the mere involvement in an MVA subsequent to sedation fulfils the criteria above. All other reported ADRs associated with therapy with topical clonazepam solution were minor in nature, not meeting the criteria.
While ADRs were more frequently reported in the 0.5 mg/mL cohort, the difference was not statistically significant. There was also no statistically significant difference between the two cohorts in terms of change to treatment plan secondary to ADR. Additionally, there was no statistically significant difference between the two cohorts in terms of types of ADRs. However, serious ADRs were documented in the 0.5 mg/mL cohort only, as described above. Based on these findings, the two concentrations of topical clonazepam solution evaluated in this study, namely a higher concentration of 0.5 mg/mL and a lower concentration of 0.1 mg/mL, appear to have similar safety profiles with perhaps a tendency toward more serious ADRs with the 0.5 mg/mL solution.

The systemic nature of the various types of ADRs documented in this study suggest that some level of systemic absorption, albeit minimal, occurs while rinsing with topical clonazepam solution. Assuming that all patients followed the instructions religiously and refrained from swallowing the solution, these systemic effects could be explained by either mucosal absorption or systemic absorption when swallowing saliva with traces of clonazepam, or both. This hypothesis is supported by the findings of Gremeau-Richard et al. (Gremeau-Richard et al., 2004), who detected low plasma clonazepam concentrations, well below the therapeutic concentration threshold for anti-epileptic activity, after sucking 1 mg clonazepam tablets three times a day and expectorating, for 2 weeks. Of note, these low clonazepam levels remained unchanged compared to the baseline value that was determined after a single topical administration. In contrast, a single systemic administration of clonazepam after 2 weeks of topical therapy led to a significant increase in plasma clonazepam concentrations, measured at 30, 60, 120, and 180 minutes after administration.

In order to attribute causation of an adverse reaction to a drug with certainty, three criteria must be fulfilled (Edwards & Aronson, 2000): a) chronological plausibility in relation to drug administration, b) favorable response to withdrawal of the drug (dechallenge) that is clinically plausible, and c) a pharmacologically or phenomenologically definitive event, evaluated using a satisfactory rechallenge procedure if necessary. Due to its retrospective nature, this study is limited in the ability to determine causality with certainty. At most, the reported adverse reactions can be classified as possible ADRs, defined as clinical events occurring with reasonable time relation to the administration of the drug, but where competing explanations are
plausible and dechallenge information is lacking or unclear (Edwards & Aronson, 2000). Since the data collected is practitioner-dependent, details of adverse reactions in terms of onset, duration, recovery and any sequelae are incomplete, as no standardized questionnaires were presented to patients at time of assessment. In addition, in the majority of cases, only descriptive data in the form of signs and symptoms related to the adverse reaction is reported, without a definite diagnosis for the reaction. Another limitation of this retrospective study is that documentation of patients’ compliance with the prescribed regimen is largely incomplete or lacking. As such, it cannot be ruled out that patients may have swallowed some amount of the solution while rinsing, whether intentionally or not, leading to the occurrence of ADRs. Finally, due to the lack of placebo controls, an additional limitation is the difficulty in discerning between true ADRs and nocebo responses. These so called negative placebo responses may occur because of patients’ negative expectations and beliefs, especially in the context of information received regarding the potential side effects associated with a drug (Wells & Kaptchuk, 2012). This may be of particular importance in this study, since several providers contributed patients to the cohorts, and perhaps educated patients differently regarding the possible side effects.

With the above limitations in mind, the present study is characterized by a number of methodological strengths contributing to the robustness of the conclusions. First, the relatively abrupt transition from the 0.5 mg/mL solution to the 0.1 mg/mL solution in 2012 allows a quasi-experimental, randomized-like comparative design of the two concentrations of solution in terms of their relative safety. Second, since adverse reactions reported in this study can only be classified as possible ADRs and may not be ascertained, the estimated prevalence of ADRs could be interpreted as a conservative upper bound. Finally, the collection of data at the first follow-up encounter mitigates the risks of bias due to longer periods of follow-up for patients in the 0.5 mg/mL cohort, as well as attrition bias. Minimizing the risk of attrition bias is especially important, since patients experiencing ADRs are more likely to discontinue treatment and not return for further evaluations, compared to patients responding well to the treatment prescribed. For this reason, first follow-up encounters via telephone were also included. Nonetheless, in order to validate the results of this study, future randomized and placebo-controlled trials are necessary.
SPECIFIC AIM 3. A RETROSPECTIVE MEDICAL CHART REVIEW OF THE EFFICACY OF TOPICAL CLONAZEPAM SOLUTION FOR THE MANAGEMENT OF BURNING MOUTH SYNDROME

I. Materials and Methods

Approval of the Partners’ Institutional Review Board at Brigham and Women’s Hospital was obtained. A retrospective electronic medical chart review was conducted of all patients diagnosed specifically 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 at BWH from 2008 to 2015. The concentration of 0.5 mg/mL was used until 2012, when this was changed to a 0.1 mg/mL solution. Subjects were identified through an output from America’s Compounding Center of all patients prescribed topical clonazepam solution at the practice during the study period. Data collected from medical records included demographics, current psychiatric medication(s), concurrent treatment(s) for BMS, clinical pattern of BMS (types 1, 2, or 3) (Lamey & Lewis, 1989), intensity of burning as measured on an 11-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 first follow-up visits only, as to minimize the risk of attrition bias as well as bias as a result of longer follow-up periods for patients receiving the 0.5 mg/mL concentration.

a. Inclusion Criteria

Patients were included if they presented with classic BMS symptoms, defined as an oral mucosal continuous, non-paroxysmal, burning pain of variable intensity, with or without accompanying dysgeusia, xerostomia or other oral dysesthesias (ICHD, 2013) and in the absence of clinical evidence of a local or systemic condition that could be considered causative factors (e.g. oral candidiasis or diabetes mellitus). All patients had been instructed to swish with 5 mL 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 one month. Response to treatment is anticipated after two weeks of therapy, as described by Gremeau-Richard et al. (Gremeau-Richard et al., 2004). Only patients who completed at least two weeks of topical
clonazepam therapy prior to first follow-up evaluation were included, unless an adverse reaction led to dose reduction or early discontinuation of treatment, in which case the withdrawal from therapy and the adverse reaction were documented. Only in-person follow-up encounters were included, unless a patient experienced an adverse reaction which was reported via telephone.

b. Outcome Measures and Statistical Analysis

The primary outcome measure was improvement in oral burning dysesthesia following treatment with topical clonazepam solution (0.1 mg/mL or 0.5 mg/mL). Response to treatment was measured using patient-reported outcome measures. Outcome measures included the percentage improvement in burning symptoms as reported at first follow-up, as compared to the commonly used cutoffs of 30% and 50% symptomatic improvement (Dworkin et al., 2005), as well as the change from baseline to first follow-up in the worst burning severity over the week prior to evaluation, ranked on an 11-point NRS. For both concentrations, improvement according to 30% and 50% cutoffs 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 time of visit) were used to calculate percentage of symptomatic improvement by dividing the difference in NRS scores by the baseline NRS score and multiplying it by one-hundred. To control for individual differences at baseline, such as the concomitant use of psychiatric medications, especially systemic benzodiazepines, a stratified Wilcoxon test was used. Finally, in order 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. A Wilcoxon-Mann-Whitney test was used to compare the percentage improvement in both groups, with the goal of showing “no-inferiority” of the 0.1 mg/mL solution relative to the 0.5 mg/mL solution.

II. Results

A total of 58 subjects were included in this study, 32 patients in the 0.1 mg/mL cohort and 26 patients in the 0.5 mg/mL cohort (Figure 2), evaluated at a median follow-up of 7 weeks (ranging between 3 weeks and 1 year).
a. Population Characteristics

Patients’ characteristics are summarized in Table 8. The two cohorts were balanced at baseline with respect to these characteristics. In both cohorts 81% of patients were females, and the median age was 58.5 years in the 0.1 mg/mL cohort and 60.5 years in the 0.5 mg/mL cohort. The median worst burning NRS scores during the week prior to presentation were 8 (range 3-10) in the 0.1 mg/mL cohort, and 7.5 (range 3-10) in the 0.5 mg/mL cohort. Over half of the patients in both cohorts reported other oral dysesthesias in addition to their burning pain: 20 patients (62.5%) in the 0.1 mg/mL cohort reported at least one other dysesthesia, compared to 16 patients (61.5%) in the 0.5 mg/mL cohort. Overall, 23 patients (71.9%) in the 0.1 mg/mL cohort and 12 patients (46.2%) in the 0.5 mg/mL cohort were treated with psychiatric medications on a stable regimen at baseline. Of these, 9 patients (28%) in the 0.1 mg/mL cohort and 4 patients (15%) in the 0.5 mg/mL cohort were treated with a benzodiazepine (alprazolam or lorazepam) for management of disorders such as anxiety and insomnia.
Table 8. Specific Aim 3. Patient characteristics at baseline

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

Abbreviation: BMS: burning mouth syndrome.

† More than one type of dysesthesia per patient possible.

* Other dysesthesias include: ageusia, sense of hypersalivation, texture changes, and a sense of tissue swelling, a sense of tissue coating, and tingling /numbness.

‡ More than one psychiatric medication per patient possible.

A total of 44 patients (76%) experienced a burning sensation in more than one site (Figure 3). The tongue was the most commonly affected site (51.9%), followed by the lips (16.2%), the anterior palatal mucosa (11.7%) and the labial mucosae (11%).

Figure 3. Overall burning distribution at baseline
Out of the 26 patients included in the 0.5 mg/mL cohort, one patient experienced symptoms of sedation and altered mental status after 3 days of use, leading to early discontinuation of therapy. Thus, a total of 25 patients were evaluable for response to therapy. All 32 patients in the 0.1 mg/mL cohort were evaluable for response.

b. Treatment Outcomes

One patient in the 0.5 mg/mL cohort had no response to treatment at first follow-up, compared to 4 patients in the 0.1 mg/mL cohort. In the 0.5 mg/mL cohort, 22 (88%) patients reported the “percentage improvement” in their symptoms at the follow-up visit, and the remaining three patients reported either their “worst NRS score over the last week” (1/3) or their “current NRS score” (2/3) both at baseline and at first follow-up, allowing to calculate the percentage of symptomatic improvement. In the 0.1 mg/mL cohort, 26 (81%) patients reported the “percentage improvement” in their symptoms at the follow-up visit. Imputation of the percentage of symptomatic improvement was performed for the remaining 6 patients, using either their reported “worst NRS score over the last week” (3/6) or their “current NRS score” (3/6) at baseline and first follow-up. An improvement equal to, or higher than the commonly used 50% cut-off was reported by 92% of patients treated with topical clonazepam solution in the 0.5 mg/mL concentration. Overall, treatment with the 0.5 mg/mL solution was associated with median improvement of 75% (range 0-100%), significantly higher than the 50% cut-off.
(p<0.01, Table 9). The median improvement associated with the 0.1 mg/mL solution was 32.5% (range 0-100%), and was not significantly higher than the more permissive cut-off of 30%.

Table 9. Comparison of percentage of symptomatic improvement according to concentration

<table>
<thead>
<tr>
<th>Percentage improvement</th>
<th>0.1 mg/mL cohort (n = 32)</th>
<th>0.5 mg/mL cohort (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (25\text{th}, 75\text{th})</td>
<td>32.5 (8.125, 55)</td>
<td>75 (50, 90)</td>
</tr>
<tr>
<td>p* versus 30% cut-off</td>
<td>0.453</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>versus 50% cut-off</td>
<td></td>
<td>0.0007</td>
</tr>
</tbody>
</table>

*p-value (p < 0.05) calculated using a Wilcoxon one-sample median test.

A total of 11 patients in the 0.5 mg/mL cohort reported “worst NRS score over the last week” both at baseline and at first follow-up, compared to 9 patients in the 0.1 mg/mL cohort. The median reduction in NRS scores was 6 points in the 0.5 mg/mL concentration, and 0.5 points in the 0.1 mg/mL concentration. Using either outcome measure, percentage improvement or change in NRS score, response to treatment with the 0.5 mg/mL solution was superior to that associated with the 0.1 mg/mL solution (p<0.01, Table 10). Stratifying the response to treatment by the concomitant use of psychiatric medications, and specifically systemic benzodiazepines, all the results above remain.

Table 10. Comparison of change in patient-reported outcome measures according to concentration

<table>
<thead>
<tr>
<th></th>
<th>0.1 mg/mL cohort</th>
<th>0.5 mg/mL cohort</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ Worst NRS score</td>
<td>9</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>-0.5</td>
<td>-6</td>
<td></td>
</tr>
<tr>
<td>Median (25\text{th}, 75\text{th})</td>
<td>(-3.5,0)</td>
<td>(-7,-4)</td>
<td>0.003</td>
</tr>
<tr>
<td>Percentage improvement</td>
<td>32</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>32.5</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Median (25\text{th}, 75\text{th})</td>
<td>(8.125,55)</td>
<td>(50, 90)</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

Abbreviation: NRS: numeric rating scale.
*p-value (p < 0.05) calculated using a Wilcoxon-Mann-Whitney test.

c. Adverse Drug Reactions

Adverse drug reactions occurred in 15.4% (4/26) of patients in the 0.5 mg/mL cohort and 15.6% (5/32) of patients in the 0.1 mg/mL cohort. All patients experienced sedation, and 2 patients in the 0.5 mg/mL cohort also experienced symptoms of altered mental status. As mentioned above, one patient in the 0.5 mg/mL cohort discontinued therapy secondary to developing an ADR. Dose reduction was required in the remaining three patients in order for them to continue treatment. One patient in the 0.1 mg/mL cohort discontinued therapy secondary to developing an
ADR, and the remaining four patients continued treatment without any change. One patient reported transient drowsiness during the first week only of using the solution, another reported slight drowsiness that was tolerable, and a third patient reported sleeping longer than usual but this was not bothersome. The fourth patient experienced complete resolution of burning symptoms after approximately one month of rinsing, and discontinued therapy since it was no longer necessary.

d. Overlap Period

As previously mentioned, a short period of overlap between the two concentrations of solution occurred between January 2012 to November 2012, when 6 (19%) new patients received the 0.1 mg/mL solution and 3 (11%) new patients received the 0.5 mg/mL solution. None of these patients had no response to treatment, and one of the six patients in the 0.1 mg/mL cohort reported complete resolution of symptoms at first follow-up. All of the results above are continue to hold once the observations from the overlap period are excluded.

III. Discussion

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

Two patient-reported outcome measures were used in this study in order to evaluate response to treatment. First, the reported percentage improvement in burning symptoms, ranging from 0-100%. Following the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations (Dworkin et al., 2005), the fraction of patients reporting percentage improvement in burning symptoms of at least 30% as well as the fraction of patients reporting at least 50% improvement were reported. 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 aim for at least 50% reduction in pain scores from baseline, and reporting this cut-off allows comparability with published studies. In this context,
according to a 2005 Cochrane review of treatments for BMS, aiming for a 50% symptomatic improvement may be too high, and a 30% cut-off could be more realistic (Zakrzewska et al., 2005).

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 at least 50% improvement in burning intensity and a median improvement of 75%, significantly higher than the 50% cut-off. By comparison, the median improvement associated with the 0.1 mg/mL solution was 32.5%, not significantly higher than the 30% cut-off. The response to the 0.5 mg/mL solution in this study is higher than responses reported in previous studies evaluating topical therapy with clonazepam for BMS. Gremeau-Richard et al. (Gremeau-Richard et al., 2004) documented 49% of patients with at least 50% improvement at two weeks follow-up after sucking 1 mg clonazepam tablets three times a day and expectorating. A recent open-label pilot study demonstrated the efficacy of topical clonazepam solution (1 mg/10 mL) in reducing burning intensity in patients with BMS, when rinsed with three times daily over a period of 14 days (de Castro & Ribeiro-Rotta, 2014). Out of 18 patients in that study, 9 patients (50%) experienced symptomatic improvement greater than 50%.

The second outcome measure used in the present study was the change in the worst burning severity over the week prior to evaluation, ranked on an 11-point (0-10) NRS. Per IMMPACT recommendations, an NRS measure of pain intensity can be used as a core outcome measure in clinical trials evaluating treatments for chronic pain. Previous studies evaluating therapy with topical clonazepam asked subjects to estimate their mean NRS score over a period of time ranging between one to two weeks prior to evaluation, whereas the metric used in this study was the worst NRS score over the week prior to evaluation. While limiting the ability to compare the results of this study with those of previous studies, the present results are arguably stronger from a methodological standpoint. Providing an estimate of a mean pain score over a period of time in the past is not an intuitive undertaking, and may prove to lead to unreliable reports. The worst pain score, on the other hand, is a salient and more robust metric.

A median reduction in burning intensity of 6 points (mean 5.7 points) was found in the 0.5 mg/mL cohort. This is not only higher than the median 0.5 points reduction (mean 1.5 points)
in NRS scores in the 0.1 mg/mL cohort, but also higher than responses to topical treatment documented in previous studies. In their RCT, Gremeau-Richard et al. (Gremeau-Richard et al., 2004) documented a mean 2-point decrease in pain intensity (from a baseline of 6 points) at a two weeks follow-up after sucking 1 mg clonazepam tablets three times a day and expectorating. A mean 3-point reduction in pain scores (from a baseline of 6 points) was documented by Woda et al. in an open, prospective, non-randomized trial (Woda et al., 1998) at four weeks of treatment with 0.125-0.25 mg clonazepam tablets, sucking and expectorating between two to three times a day.

No serious adverse reactions were noted in the present study, and treatment with topical clonazepam solution in either a 0.5 mg/mL concentration or a 0.1 mg/mL concentration was generally safe and well-tolerated. While one patient discontinued treatment with the 0.1 mg/mL solution secondary to developing sedation, the other four patients who experienced sedation symptoms did not require any changes in treatment plan and found the adverse reactions to be transient and/or tolerable. A total of 4 patients experienced ADRs with the 0.5 mg/mL solution, manifesting with symptoms of sedation with or without altered mental status. Three patients required dose reduction in order to continue treatment, and one patient withdrew from treatment altogether. These results are in line with the findings of Greameu-Richard et al. who documented the development of ADRs in 9 out of 24 subjects (37%), two of whom subsequently dropped out of the trial (Gremeau-Richard et al., 2004). Of note, in their RCT, similar adverse reactions were also reported by 6 subjects in the placebo arm, leading to the withdrawal of one of them from the study.

The marked effectiveness of the topical clonazepam solution in the 0.5 mg/mL concentration for management of burning dysesthesia in BMS patients, compared to the minimal response to treatment with the 0.1 mg/mL solution and to the response to topical treatment with clonazepam in the form of tablets (ranging in dosages between 0.125 mg to 1 mg) in previous studies mentioned above, can be attributed to the higher concentration. Both solution concentrations were chosen for use at the Division of Oral Medicine and Dentistry at BWH based on clinical experience and biological plausibility. The change from a 0.5 mg/mL solution to a 0.1 mg/mL solution was devised in order to mitigate potential ADRs while maintaining treatment efficacy. However, based on the results of the current study, the higher concentration of solution is by far
more effective and associated with similar ADRs. Since the majority of ADRs can be resolved by decreasing the dose of the solution, a conservative dose escalation regimen – e.g. start at rinsing twice a day and increase gradually to three or four times a day over the course of two weeks, until the maintenance dose suited to each individual patient has been reached – may be indicated to maximize the beneficial effects of treatment while mitigating the potential adverse reactions.

Clonazepam is an anxiolytic/anticonvulsant which potentiates the neural inhibition mediated by gamma-aminobutyric acid (GABA). The benzodiazepine-GABA\textsubscript{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 (Anholt et al., 1985, Gremeau-Richard et al., 2004). In their recent study, Tan et al. demonstrated the presence of GABA\textsubscript{A} receptors on nerve fibers in rats’ tongues (Tan et al., 2014). They were furthermore able to increase the mechanical sensitivity thresholds of these nerve fibers with the topical application of muscimol, a GABA\textsubscript{A} agonist, after exposing the tongues to a nociceptive stimuli in the form of hot water. These findings suggest that the activation of intraoral GABA\textsubscript{A} receptors mediates analgesia, and may explain the analgesic effect of topical clonazepam in BMS. In this context, the formulation of a compounded solution is presumed to provide greater interaction with the oral mucosa as opposed to the probable insufficient dissolution of tablets when used topically.

The epidemiologic profile of patients included in this study correlates with data reported previously on BMS. The vast majority of patients were females (approximately 80% in both cohorts), with a median age of 59.5 years (range 16-88 years). The tongue was the most common site affected by burning dysesthesia, and a total of 21 patients (36%) specified the tip of tongue as the site affected. Other sites frequently reported were the anterior palatal mucosa and lips, and a total of 44 patients (76%) experienced a burning sensation in more than one site. Over half of the patients in both cohorts reported chronic oral burning pain accompanied by other oral dysesthesias, with xerostomia and dysgeusia the most frequently reported. A total of 35 patients (60%) were treated with psychiatric medications at baseline for management of co-morbidities such as anxiety, depression and insomnia. In this context, a possible carry-over effect may have been added to the effect of the topical clonazepam. It is important to note, however, that the
results are robust to stratification of the response to treatment in both cohorts according to use of psychiatric medications in general, and benzodiazepines in particular.

The present study, although limited by its retrospective design, is characterized by a number of methodological strengths. First, the relatively abrupt transition from the 0.5 mg/mL solution to the 0.1 mg/mL solution in 2012 allows a quasi-randomized design for comparing the two concentrations of solution in terms of their relative efficacy. Second, the use of more than one outcome measure, in line with IMMPACT recommendations for chronic pain clinical trials (Dworkin et al., 2005), reinforces the findings, maximizes the sample size given the retrospective nature of the study, and allows comparability to published studies. 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, allows for better representation of the natural history of BMS, which can be characterized by gradual increase in pain intensity throughout the day (BMS Type 1) or fluctuations in pain intensity (BMS Type 3), and not necessarily presenting with continuous pain (BMS Type 2). This is best illustrated by the reported NRS scores at baseline, when some patients reported a “current NRS score” of zero, while the reported “worst NRS score over the last week” was 3 at minimum. Another strength of the present study is the restrictive inclusion criteria that ensures a homogenous population.

Finally, as a high placebo response rate has been observed in trials evaluating treatments for BMS (see Specific Aim 1), one cannot exclude the possibility that the large effect observed in this study is due, at least in part, to a placebo effect. The quasi-randomized design of the study allows to provide a lower bound of the effect attributed to the drug. Assuming that the 0.1 mg/mL solution does at least as well as a placebo, the difference between the two concentrations could be attributed to the effect of the 0.5 mg/mL solution. Nonetheless, it is not possible to exclude the possibility that the inclusion criteria used in this study, in particular the requirement of at least one follow-up evaluation, biases the results in ways that are dealt with in RCTs by intention-to-treat analysis. Thus, in order to evaluate the genuine drug and placebo effects, future adequately powered randomized and placebo-controlled trials that include a no-intervention control group are essential.
CONCLUSIONS AND FUTURE WORK

I. Specific Aim 1

Placebo response in clinical trials evaluating treatments for BMS is considerable, with a mean placebo response as fraction of drug response of 72%, and a wide variability in reported placebo responses across trials. Future studies are required in order to differentiate between the true placebo effect and the natural course of the symptoms or regression to the mean. To this end, the inclusion of a third “no-treatment” control group in trials assessing treatments for BMS is recommended.

II. Specific Aim 2

Treatment with topical clonazepam solution (0.1 mg/mL or 0.5 mg/mL) is generally safe and well-tolerated. Among patients experiencing ADRs, the most frequently reported reaction was sedation, followed by altered mental status, and dizziness. While in some cases no change to treatment plan was required and ADRs were tolerable and/or transient, others necessitated dosage reduction or withdrawal from treatment. ADRs were more frequently reported in association with the 0.5 mg/mL concentration, but the difference was not statistically significant, and there was no statistically significant difference between the two concentrations in terms of types or severity of ADRs. Prospective studies are needed in order to attribute with certainty the causation of the observed adverse reactions to treatment with topical clonazepam solution.

III. Specific Aim 3

Topical clonazepam solution in a 0.5 mg/mL concentration is markedly effective in the management of burning dysesthesia in patients with BMS, significantly more than a 0.1 mg/mL concentration, while maintaining a similar safety profile. Together with the conclusions of Specific Aim 2, this suggests that the 0.5 mg/mL solution should be preferred in clinical practice. Future randomized and placebo-controlled trials are necessary in order to validate these results.
REFERENCES


