TREATMENT EFFECTS OF AMITRIPTYLINE ON PAIN SYMPTOMS, QUALITY OF LIFE AND HEART RATE VARIABILITY IN BURNING MOUTH SYNDROME PATIENTS

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ผลของการรักษาด้วยยาอะมิทริปไทลีนต่ออาการปวด คุณภาพชีวิตและการผันแปรของอัตราการเต้นหัวใจในผู้ป่วยกลุ่มอาการแสบร้อนช่องปาก

น.ส.ชนิดา ชัยวร

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
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Thesis Title	TREATMENT EFFECTS OF AMITRIPTYLINE ON PAIN SYMPTOMS, QUALITY OF LIFE AND HEART RATE VARIABILITY IN BURNING MOUTH SYNDROME PATIENTS
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ชนิดา ชัยวร : ผลของการรักษาด้วยยาอะมิทริปไทลีนต่ออาการปวด คุณภาพชีวิตและการผันแปรของอัตราการเต้นหัวใจในผู้ป่วยกลุ่มอาการแสบร้อนช่องปาก. (TREATMENT EFFECTS OF AMITRIPTYLINE ON PAIN SYMPTOMS, QUALITY OF LIFE AND HEART RATE VARIABILITY IN BURNING MOUTH SYNDROME PATIENTS) อ.ที่ปรึกษาหลัก : ผศ. ทญ. ดร.กนกพร พะลัง, อ.ที่ปรึกษาร่วม : ผศ. ทพ. ดร.โจวแอล นูนู แอนดร้าครี รีคิชะ ฟีเรียระ

วัตถุประสงค์ของการศึกษานี้คือ 1) เพื่อประเมินประสิทธิภาพของการรักษาด้วยยาอะมิทริปไทลีนต่อการลดความเจ็บปวดและการเพิ่มคุณภาพชีวิตในมิติคุณภาพช่องปากในผู้ป่วยกลุ่มอาการแสบร้อนช่องปากชนิดปฐมภูมิเมื่อเปรียบเทียบกับการรักษาแบบประคับประคองด้วยน้ำยาบ้วนปากโซเดียมไบคาร์บอเนต 2) เพื่อระบุความสัมพันธ์ระหว่างการรักษาด้วยยาอะมิทริปไทลีนและการผันแปรของอัตราการเต้นหัวใจ 3) เพื่อประเมินความสัมพันธ์ระหว่างผลของอาการปวดและความผันผวนของความผันแปรของอัตราการเต้นหัวใจ การศึกษานี้ประกอบด้วยการศึกษาย้อนหลังและการศึกษาไปข้างหน้า ทำการศึกษาในผู้ป่วยกลุ่มอาการแสบร้อนช่องปากชนิดปฐมภูมิที่เข้ารับการรักษา ณ คลินิกบัณฑิตศึกษาเวชศาสตร์ช่องปาก คณะทันตแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย ในการศึกษาแบบย้อนหลังได้เก็บข้อมูลจากการสัมภาษณ์ทางโทรศัพท์โดยใช้แบบสอบถามจำนวน 3 ชนิดในผู้ป่วยเพศหญิงจำนวน 20 คน ผู้ป่วยเพศหญิงจำนวน 4 คนที่ได้รับการรักษาด้วยยาอะมิทริปไทลีนหรือน้ำยาบ้วนปากโซเดียมไบคาร์บอเนตได้เข้าร่วมในการศึกษานำร่องแบบไปข้างหน้าเพื่อเก็บข้อมูลได้แก่ อาการปวด คุณภาพชีวิตในมิติสุขภาพช่องปากและการผันแปรของอัตราการเต้นหัวใจที่จุดเริ่มต้นและติดตามที่ระยะ 3 เดือนและ 6 เดือน ผลการศึกษาย้อนหลังไม่พบความแตกต่างของความประทับใจสากลของผู้ป่วยต่อการเปลี่ยนแปลงและคุณภาพชีวิตในมิติสุขภาพช่องปากระหว่างกลุ่มอายุ การทำงาน การรักษา และลักษณะทางด้านจิตใจที่ต่างกันอย่างมีนัยสำคัญทางสถิติที่ระดับความสำคัญน้อยกว่า 0.05 ผลการศึกษาไปข้างหน้าพบว่าค่าจากมาตรวัดความเจ็บปวดด้วยสายตาของกลุ่มที่ได้รับการรักษาด้วยน้ำยาบ้วนปากโซเดียมไบคาร์บอเนตที่ระยะ 3 เดือนลดลงจากจุดเริ่มต้น ในขณะที่กลุ่มที่ได้รับการรักษาด้วยยาอะมิทริปไทลีนมีค่าจากมาตรวัดความเจ็บปวดด้วยสายตาเพิ่มขึ้นและไม่มีการเปลี่ยนแปลงของความประทับใจสากลของผู้ป่วยต่อการเปลี่ยนแปลง คุณภาพชีวิตในมิติสุขภาพช่องปากของกลุ่มที่ได้รับการรักษาด้วยยาอะมิทริปไทลีนและกลุ่มที่ได้รับน้ำยาบ้วนปากโซเดียมไบคาร์บอเนตใกล้เคียงกันที่จุดเริ่มต้นและระยะติดตามผล 6 เดือน ตัวแปรของความผันแปรของอัตราการเต้นหัวใจในกลุ่มที่ได้รับการรักษาด้วยยาอะมิทริปไทลีนสูงกว่ากลุ่มที่รักษาด้วยน้ำยาบ้วนปากโซเดียมไบคาร์บอเนต ผลการศึกษาที่พบเน้นย้ำให้เห็นความสำคัญของการนำการประเมินความประทับใจสากลของผู้ป่วยต่อการเปลี่ยนแปลงและคุณภาพชีวิตของผู้ป่วยมาปรับใช้ในการดูแลผู้ป่วยในรายบุคคล แต่อย่างไรก็ตามการศึกษานำร่องแบบไปข้างหน้านี้ควรแปลผลด้วยความรอบคอบเนื่องจากมีข้อจำกัดเรื่องขนาดตัวอย่างที่มีอย่างจำกัด ควรพิสูจน์ผลของการศึกษานี้อีกครั้งในการศึกษาในอนาคตด้วยการทดลองสุ่มตัวอย่างเปรียบเทียบทางคลินิกรวมถึงกำหนดจำนวนที่ต้องใช้ในการรักษาของผู้ป่วยที่เพียงพอจะทำให้เห็นถึงผลกระทบทางคลินิกความประทับใจสากลของผู้ป่วยต่อการเปลี่ยนแปลง

สาขาวิชา	เวชศาสตร์ช่องปาก	ลายมือชื่อนิสิต .....
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Chanida Chaiworn : TREATMENT EFFECTS OF AMITRIPTYLINE ON PAIN SYMPTOMS, QUALITY OF LIFE AND HEART RATE VARIABILITY IN BURNING MOUTH SYNDROME PATIENTS. Advisor: Asst. Prof. KANOKPORN BHALANG, D.D.S., M. S., Ph.D. Co-advisor: Asst. Prof. JOAO NUNO ANDRADE REQUICHA FERREIRA, D.D.S., M.Sc., Ph.D.

The objectives of this research project were 1) To evaluate the effectiveness of amitriptyline therapy on improving pain and the oral health-related quality of life (OHRQoL) in BMS patients when compared to palliative topical therapies (sodium bicarbonate mouthwash). 2) To determine the association between therapy of amitriptyline and heart rate variability (HRV) parameters. 3) To assess the association between pain outcomes and fluctuations in HRV parameters. This project was composed of a retrospective and a prospective study, and subjects were primary BMS patients recruited at the Oral Medicine Clinic, Faculty of Dentistry, Chulalongkorn University. In the retrospective study, 20 female participants were phone interviewed with 3 validated questionnaires and specific data was retrieved from the subject's clinical charts. Four females already taking amitriptyline or sodium bicarbonate mouthwash were then recruited into a pilot prospective study to evaluate changes on pain, OHRQoL and HRV between baseline, 3-month and 6-month follow-up visits. No significant differences on patient global impression of change (PGI-C) and OHRQoL between different age groups, working status, treatment options or psychological profile were found in the retrospective study ($p<0.05$). Regarding the prospective study, pain intensity in the sodium bicarbonate group was decreased from baseline to 3 months, while in amitriptyline group it increased and PGI-C was not changed. OHRQoL in sodium bicarbonate group and amitriptyline group were comparable at baseline and 6 months. HRV parameters in the amitriptyline group was higher than subjects in sodium bicarbonate group. These findings emphasize the value of PGI-C and OHRQoL assessments when it comes to adjust strategies during pain management in each individual with primary BMS. However, this is a pilot prospective study and must be interpreted with caution because of the limited sample size. Future investigations should be performed to confirm our findings with a randomized controlled clinical trial and also to determine the number of primary BMS patients that need to be treated (NNT) to have a clinical impact.

Field of Study:	Oral Medicine	Student's Signature .....
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		Co-advisor's Signature .....

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Chanida Chaiworn

TABLE OF CONTENTS

Page

LIST OF TABLES

Page

LIST OF FIGURES

Page

CHAPTER 1
Introduction

1.1 Background and rationale

Burning mouth syndrome (BMS) is a chronic, intractable pain condition characterized by a burning sensation or dysesthesia of the oral mucosa, without the presentation of abnormal clinical or laboratory findings (1). Pain chronicity and related disability is a major concern since complete or partial pain remissions were reported in only 50 percent of BMS patients within 6 to 7 years after onset (2). The chronicity of pain, the presence of multiple comorbidities, and unsuccessful treatments can have a negative effect on BMS patient's mood triggering psychological distress, (anxiety, depression and cancerphobia) and impairing their QoL (3).

Currently, the main proposed etiologies for primary BMS are multifactorial, involving the interaction between neurologic mechanisms and psychological factors (2, 4-6). There is an increasing evidence suggesting primary BMS is neuropathic in origin and that lesions at different levels of the peripheral or central nervous system can be present (7). Neurophysiological, psychophysical, neuropathological, and functional imaging studies concluded that several neuropathic mechanisms, contribute to the pathophysiology of primary BMS (6).

Effective therapies that target and modulate neuropathic pain mechanisms are mainly pharmacological in nature (8). Amitriptyline is widely used in Western countries and in Southeast Asia to treat chronic neuropathic pain due to the successful clinical trials and reports on its usage (9-11). This drug also commonly used in primary BMS (10) due to its analgesic action at low doses (10 mg) which is independent of its antidepressant effect at high doses (≥ 50 mg/days) (11). Routinely, palliative topical therapies are initially used to rule out saliva-based oral mucosa irritation, which include mouthwashes with sodium bicarbonate for buffering the salivary pH (12). Though, if

neuropathic mechanisms (central and peripheral) are involved, mainly neuropathic pain medications have shown promising outcomes.

Reduced heart rate variability (HRV) is associated with numerous physical and mental health disorders (13). HRV measures the balance between the autonomic sympathetic and parasympathetic nervous systems in the functional heart in different pathological conditions (14). Hence, HRV is mirroring the imbalances of the autonomic nervous system (ANS). Thus, HRV assessment has become an important diagnostic tool in the detection of ANS imbalances and can predict prognosis in several disorders, including in neuropathies (15). The anti-cholinergic properties of amitriptyline may create imbalances in the ANS. In 2012, Kulshreshtha et al. reported the effects of low-dose amitriptyline (10 mg/day) on HRV outcomes in fibromyalgia (16).

There is a lack of studies on HRV and ANS activity after amitriptyline treatment in chronic pain conditions. In addition, up to date, there are no studies assessing HRV in BMS after amitriptyline treatment. Therefore, it is essential to assess the ANS activity and potential imbalances through HRV assessment in future clinical studies.

Thus, this proposed study will fill the current gap of knowledge. This clinical study will evaluate whether amitriptyline treatment can produce pain relief, improve the quality of life (QoL) and balance ANS activity in primary BMS patients. Hence, this study aims (1) to evaluate pain symptoms and QoL improvement in BMS patients, (2) to determine the relationship between amitriptyline treatment and HRV parameters, and (3) to assess the association between pain and QoL outcomes and HRV parameters.

1.2 Research questions

1) Can treatment of amitriptyline effectively improve pain symptoms and the QoL of BMS patients when compared to palliative topical therapies (a sodium bicarbonate mouthwash)?

2) Is there a relationship between treatment of amitriptyline and HRV parameters in BMS patients?

3) Is there a relationship between pain improvement and HRV parameters in BMS patients?

1.3 Research objectives

1) To evaluate the effectiveness of amitriptyline therapy on improving pain and the QoL in BMS patients when compared to palliative topical therapies (sodium bicarbonate mouthwash).

2) To determine the association between therapy of amitriptyline and HRV parameters.

3) To assess the association between pain outcomes and fluctuations in HRV parameters.

1.4 Research hypothesis

Hypothesis A:

H_0: When compared to a sodium bicarbonate mouthwash, therapy of amitriptyline is not significantly more effective in improving pain symptoms, QoL and ANS activity in BMS patients.

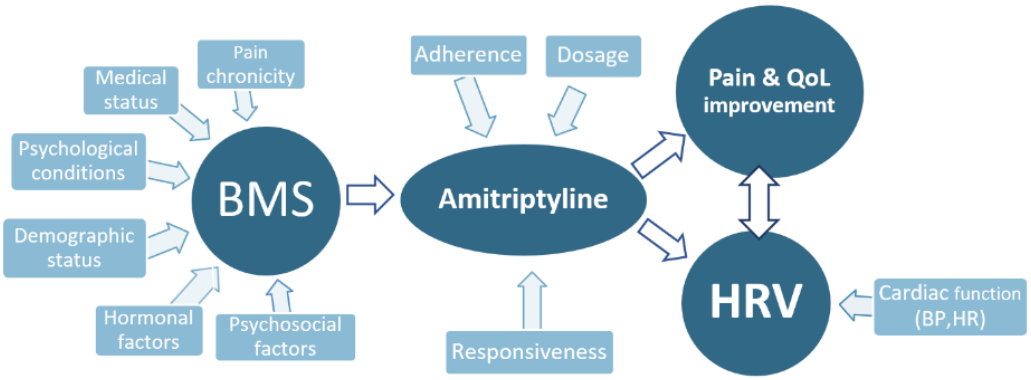
H_a: When compared to a sodium bicarbonate mouthwash, therapy of amitriptyline is significantly more effective in improving pain symptoms, QoL and ANS activity in BMS patients.

Hypothesis B:

H_0: An improvement in pain outcomes (intensity and/or chronicity) and QoL among BMS patients is not significantly associated with an increase in HRV parameters.

H_a: An improvement in pain outcomes (intensity and/or chronicity) and QoL among BMS patients is significantly associated with an increase in HRV parameters.

1.5 Conceptual framework



1.6 Study area

Oral Medicine Clinic, Faculty of Dentistry, Chulalongkorn University.

CHAPTER 2
Review literature

2.1 Burning mouth syndrome

Burning mouth syndrome (BMS) is a poorly understood, idiopathic chronic pain disorder that can be characterized by a burning sensation of the oral cavity in the absence of any identifiable organic disease. The pain is generally constant and ranges in severity from moderate to severe (17).

The American Academy of Orofacial Pain defines BMS as a burning sensation in the oral mucosa despite the absence of clinical findings and abnormalities in laboratory testing or imaging (2). The International Association for the Study of Pain defines BMS as a burning pain in the tongue or other oral mucous membrane associated with normal signs and laboratory findings lasting at least 4 months to 6 months (2). The International Headache Society in the International Classification of Headache Disorders, 3rd edition (beta version) (ICHD-3 beta) defines BMS as an intraoral burning or dysesthetic sensation, recurring daily for more than 2 hours per day over more than 3 months, without clinically evident causative lesions (2). It becomes clear that most of accepted definitions of this condition mention a lack of clinical symptoms that could provide an etiologic explanation.

The term "syndrome" refers to symptoms such as dry mouth, changes in salivary function, and taste disturbances that frequently accompany the burning sensation (17). Glossodynia, glossalgia, stomatodynia, and sore or burning tongue are some of the other terms that have been used to characterize BMS (6).

2.1.1 Clinical presentations and classifications

The clinical presentations of BMS are not consistent and vary in individual. Patients frequently report of chronic pain lasting 4 to 6 months and describe it as annoying, burning or scalding, tingling, itching, or numb at the time of presentation (17). Patients frequently report that when they eat, drink, and speak has an impact on their symptoms. Eating can reduce or eliminate symptoms briefly in some cases. Most patients avoid spicy, acidic, or hot foods, as well as alcohol, because it aggravate their symptoms (2). Some individuals report their pain worsens or becomes more notable when they are stressed or fatigued (2). The burning sensation can be continuous or intermittent, and it usually affects the anterior two-thirds of tongue (67.9%), but it can also affect other mucosal surfaces such the palate, lip, buccal mucosa, and mouth floor. The pain is more likely to occur bilaterally and symmetrically more than unilaterally (17).

In an attempt to better characterize this condition, several classifications have been proposed in the literature (6). According to Lamey and Lewis, BMS can be divided into three subgroups based on pain level fluctuations throughout a day as follow:

- BMS type 1: Burning increasing throughout the day and reaching its peak in the evening.
- BMS type 2: Characterized by the complaint of continuous sensory disturbances.
- BMS type 3: Intermittent symptoms with pain-free periods during the day.

Scala et al. recently proposed the terms "primary BMS" (idiopathic/essential condition in which no local or systemic cause for the burning can be identified) and "secondary BMS" (idiopathic/essential condition in which no local or systemic cause for the burning can be recognized) (an organic local or systemic cause for the intra-oral burning sensation is present).

2.1.2 Epidemiology

The prevalence of BMS in the general population varies from 0.7% to 15%, and appears to be dependent on the diagnostic criteria utilized (17). BMS appears to be more common in postmenopausal women, while it can also affect younger women and men. According to most reports, the female-to-male ratio is between 5:1 and 7:1. In both male and female participants, prevalence appears to rise with age (6, 17).

2.1.3 Etiology

The cause of primary BMS is mostly unknown at this time. The most reasonable explanation is that the causation is multifactorial, involving an interaction of biological (neurophysiologic mechanisms) and psychological components (2).

Over time, the pathophysiology of BMS has remained mostly unclear. It is quite likely that it occurs as a result of a combination of causes, including the interaction of psychological and neurophysiologic components (17).

2.1.3.1 Taste and Sensory System Interactions

The loss of inhibition on the trigeminal nerve as a result of injury to the chorda tympani nerve has been proposed as one etiology of BMS. Bartoshuk and colleagues (18) previously revealed the confluence of taste sensation with pain. It has been established that unilateral chorda tympani nerve injury can result in an enhanced burning sensation when capsaicin is administered on the opposite side of the damage. Bartoshuk and colleagues (18) also demonstrated that supertasters, who have a genetically defined ability to taste 6-n-propylthiouracil, have a lower acceptance of some bitter foods and experience more burn from irritants like capsaicin. This behavior appears to be linked to the density of taste receptors on the anterior tongue. This event was found more frequently in women.

2.1.3.2 Hormonal Alterations

Because BMS typically affects postmenopausal women, some researchers believe that changes in female sex hormone levels from perimenopause to postmenopause may predispose women to developing BMS. Gao and colleagues (19) found a significantly higher level of follicular stimulating hormone and a lower level of estradiol in blood test of BMS subjects compared with controls. Because both BMS and vulvodynia are more common in perimenopausal and postmenopausal women, estrogen deficiency could represent a shared etiologic mechanism for these two conditions. Estrogen receptors have been discovered in the salivary glands of the tongue and the vaginal mucosa.

Woda and colleagues recently proposed a relationship between BMS presentation and alterations in gonadal, adrenal, and neuroactive steroid levels. They suspected that prolonged anxiety or stress could cause adrenal steroid synthesis to be dysregulated and reduced. An increase in anxiety scores as well as salivary cortisol levels was found in the BMS population in a comparison study of patients and controls (17). Patients with chronic stress have been found to have higher levels of salivary cortisol. Cortisol depletion could occur if cortisol production is excessive for an extended length of time. It has been shown that both low and high doses of cortisol can be harmful to brain structures (17).

2.1.3.3 Neuropathic Considerations

Peripheral small-fiber neuropathy

Burning, tingling, and numbness are common clinical manifestations of peripheral small nerve fibers damage. In comparison to healthy control subjects, BMS patients have a lower tolerance to a painful heat stimulus near the tip of the tongue, according to Grushka (20) In BMS populations, small nerve fiber neuropathy has been observed, as well as a significant decrease in the density of small fibers in pain areas. Forssell and colleagues (21) also reported an unusual sensory threshold in the tongue in 76% of 46 BMS patients tested by quantitative sensory testing. Lauria (22) conducted superficial biopsies of the lateral aspect of the anterior two-thirds of the tongue in 12

confirmed BMS patients and reported a significant loss of epithelial and subpapillary nerve fibers in these areas.

Enhanced transient receptor potential vanilloid 1 receptors

The transient receptor potential (TRP) protein comprises calcium-permeable voltage-independent channels. Thermal sensations ranging from extreme cold to extreme heat are caused by these channels. The capsaicin receptor, also known as the TRP vanilloid 1 (TRPV1) receptor, is activated by unpleasant heat and capsaicin (17). TRPV1 fibers were up-regulated in BMS participants when compared to controls, according to Yilmaz and colleagues (23) Rectal hypersensitivity and vulvodynia have also been related to TRPV1 upregulation.

Subclinical major trigeminal neuropathy

The fifth and seventh cranial nerves have a well-known close relationship. The chorda tympani of the facial nerve and the lingual branch of the trigeminal nerve both innervate the mucosa of the tongue. These two structures proceed down the same path to the tongue. The lingual nerve fibers then terminate in fungiform papillae in the taste buds. The taste pores of the taste buds in these papillae are innervated by the chorda tympani nerve. Wang and colleagues (24) proposed an electrophysiologic interaction between these two nerves to modify the chorda tympani nerve's taste function. Other studies of neuropathic pain have shown that damage to one nerve can influence the other undamaged nerve. Minor injuries from eating too hot food or beverage, as well as common dental treatments or anesthetic injections, may cause damage. According to some estimates, around 20% to 25% of BMS cases are caused by subclinical lingual, mandibular, or trigeminal system pathology, which can be identified with a comprehensive neurophysiologic assessment (25). Masseter reflex and blink reflex and habituation in primary BMS patients has shown significant defects in the large fibers of the trigeminal nerve distribution (2).

Central pain related to deficient dopaminergic inhibition

PET studies in BMS patients showed a decrease in striatal endogenous dopamine levels, as well as a deficit in dopamine-mediated descending pain regulation in the trigeminal brainstem complex (2). These PET results are similar to those seen in the early stages of Parkinson's disease. In a case report using pramipexol, a well-known dopaminergic agonist used to treat Parkinson's disease, a 68-year-old woman shown a complete remission of BMS (17). More robust studies are needed to confirm this result in the end. Overall, it is probable that inadequate descending pain inhibition via the striatal dopamine loop is a risk factor for the development of chronic neuropathic oral and facial pains including BMS.

2.1.4 Diagnosis

It is crucial to rule out other local, systemic or psychologic causes of intraoral pain before making diagnosis. An inclusive history should be taken, focusing on the characteristics of the pain, the timing of its onset, affected location, exacerbating factors, coexisting of dry mouth, denture use, and psychologic disease such as anxiety, depression and personality disorders. Patients frequently express anxiety about the potential that their symptoms are caused by oral cancer. All patients would benefit from being asked directly about their fears of cancer. It is crucial to check for indications and clinical manifestations of parafunctional habits like clenching, tongue thrusting, and bruxism. Infections and autoimmune-mediated disease should also be evaluated.

2.1.4.1 History taking

Establishing a definitive diagnosis requires a comprehensive medical and dental history, as well as a comprehensive evaluation of current medications and a comprehensive review of systems. The descriptions of patient’s concern, as well as a history of progression, symptoms onset and a description of any previous and current treatments should be included. The intensity of the presenting pain should be assessed using proper instrument. It is essential to map out what kind of pain they are experiencing and where it is coming from. Factors that aggravate as well as those that

alleviate pain should be included in the past. Patients should be asked about any history of previous upper respiratory tract infections, middle ear disease, or surgery that may have damaged the chorda tympani nerve. Dietary habits and the use of oral care products should also be asked. To assess the presence or status of any previous or current psychosocial stresses, an appropriate psychosocial history should be examined as part of the comprehensive history (17).

2.1.4.2 Examination

Despite the fact that various local, systemic, and psychological aspects have been associated to BMS, several of these factors should be regarded as disorders that should be evaluated in the differential diagnosis of oral burning rather than as causal factors in BMS.

Local factors

Several local factors (physical, chemical, or biological) have been suggested as potential BMS causes. Some of these include (2):

- Xerostomia, a subjective sensation of dry mouth and is frequently complain by 25% of patients with BMS in addition to drug-induced xerostomia
- Hyposalivation, an objectively decrease in salivary flow rate measured by sialometry
- Taste disturbances involving an alteration in taste perception
- Oral infections: bacterial, viral, and/or fungal
- Abnormalities of oral mucosal, such as geographic tongue, scalloped or fissured tongue, and diseases such as lichen planus
- Parafunctional oral habits, such as clenching, bruxing, or tongue thrusting
- Mechanical and chemical irritations, such as galvanism and denture-related problems
- Allergic reactions

Table 1 Substances that may cause intra-oral allergic reaction (6)

Chemicals	Where it can be found
Zinc, cobalt, mercury, gold and palladium	Dental materials
Nickel sulfate	Dental materials
	Stainless steel
	Food (e.g., shrimp and chocolate milk)
Sodium lauryl sulfate	Toothpaste
Fragrance mix	Oral care products
Balsam of Peru	Oral care products
	Citrus fruits
	Spices
	Cough medicine and lozenges
Cinnamic alcohol	Cinnamon and products with cinnamon flavor

Systemic factors

Many systemic factors have been considered for explaining the cause of BMS. Some of these are **(2)**:

- Autoimmune, endocrine and gastrointestinal disorders, such as connective tissue diseases, diabetes, gastroesophageal reflux disease, and thyroid disorders
- Hormonal deficiencies and menopausal condition
- Drug-induced conditions, such as angiotensin-converting enzyme inhibitors which can induced xerostomia as the side effect
- Nutritional deficiencies involving vitamins and minerals, especially causing anemia (iron and vitamin B12 deficiency), zinc, and vitamin B complexes

Table 2 Medications that possibly cause xerostomia as a side effect (6)

Medications	Examples (generic)
Tricyclic antidepressant	Amitriptyline, nortriptyline
Antipsychotic	Carbidopa/levodopa, chlorpromazine
Antihistaminic	Phenergan
Bronchodilator (anticholinergic and β–2 agonist)	Tiotropium, formoterol
Decongestant	Oxymetazoline
Antidepressant	Venlafaxine
Skeletal muscle relaxant	Tizanidine
Antihypertensives	Furosemide, clonidine, lisinopril, verapamil
Chemotherapy	Cyclophosphamide
Protease inhibitor (for HIV)	Reyataz, Norvir, Kaletra
Opioid	Hydrocodone, oxycodone
Benzodiazepine	Diazepam
Triptan	Rizatriptan

Laboratory investigations

The desire for laboratory studies should be indicated by the data of the history and physical examination. When all clinical findings are within normal conditions, a comprehensive investigate is suggested. Recommended studies include **(17)**:

- Complete blood cell count with differential
- Fasting blood glucose
- Hemoglobin A1c
- Thyroid function (T3/T4)
- Serum iron
- Ferritin
- Total IgE
- Vitamin B6, vitamin B12, and vitamin D
- Serum antinuclear antibodies

- Anti-Sjogren's-syndrome-related antigen A and Anti-Sjogren's-syndrome related antigen B (SSA/Ro and SSB/La)
- Erythrocyte sedimentation rate (ESR)
- Serum antibodies to *Helicobacter pylori* and oral Candida
- Viral and bacterial swabs

Adjunctive testing

Imaging of the brain and brainstem via CT or MRI is recommended if pain presentation appear to be atypical of a normal presentation. This could include sensory and/or motor problems, autonomic alterations, or any other evidence of a central nervous system pathology or neurodegeneration.

The status of salivary structures may also be evaluated on proper imaging as well. Allergen patch testing may be useful in some cases. This test is usually reserved for individuals who have a lichenoid-like tissue lesion present in the oral cavity on visual inspection. To see if oral dryness is an issue, sialometry is recommended. The volume of saliva flow varies among individuals and has a poor correlation with subjective reports of dry mouth. If Sjogren syndrome is suspected, a biopsy of the small salivary glands is required to confirm the diagnosis. Psychometric evaluation may be used to examine the impact of psychological variables. A test for gastroesophageal reflux may be useful in some cases (17).

2.1.5 Prognosis

The natural history of primary BMS is poorly understood. BMS lasts about 2 to 3 years on average. However, it is known that the illness might persist for a long time. In a retrospective study of 53 participants with primary BMS, 3 percent of patients experienced complete spontaneous clinical remission within 5 years of the onset of symptoms. With or without treatment, 30 percent of the subjects showed a moderate improvement (4).

2.1.6 Management

There are few detailed suggestions for the management of patients with BMS in the literature (2). From a theoretical viewpoint, clinicians must first identify whether the patient is suffering from primary BMS or secondary BMS, in which symptoms are caused by underlying local or systemic illnesses (2). Secondary BMS requires appropriate diagnosis and treatment of the underlying causes. Clinicians currently have the option of using one of three strategies, or a combination of them, as an effective management.

2.1.6.1 Behavioral Strategies

Bergdahl et al. (26) demonstrated that cognitive behavioral therapy (CBT) can reduced the symptom intensity in BMS patients for 6 months. According to Miziara et al. (27) there was a 70% improvement in the BMS group compared to the placebo group in patients who were treated with group therapy. Patients appear to use group sessions as a support group, sharing information about their symptoms and concerns, improving their awareness of the disease, and assisting them in accepting and adhering to the provided treatment. Cognitive behavioral therapy can improve knowledge of the cause and treatments for BMS, as well as providing skills for self-monitoring the illness and introducing pain management measures. This was supported by Komiyama et al. (30), who found that the severity of pain and impairment to daily life decreased significantly from the first to the second session (28).

For BMS patients, complementary and alternative medicine (CAM) may be a valid option. In a study conducted by Lopez-Jornet et al. on 82 BMS patients, 40 (24%) already included CAM in their treatment plan. 39.3% reported it to be effective (6).

2.1.6.2 Topical Therapies

Topical therapies using the following have all been trialed, with various rates of success (2):

- Anxiolytics
- Anesthetics (lidocaine, bupivacaine)
- Antidepressants (doxepin)
- Atypical analgesics (capsaicin)
- Nonsteroidal anti-inflammatory (benzydamine)
- Antimicrobials (lysozyme, lactoperoxidase)
- Mucosal protectants (sucralfate, aloe vera, lycopene virgin oil)
- Low-level laser therapy

2.1.6.3 Systemic Therapies

Systemic approaches using a vast number of medications from various medication categories include (2):

- Antidepressants (amitriptyline, imipramine, nortriptyline, desipramine, trazodone, paroxetine, sertraline, duloxetine, milnacipran)
- Anxiolytics (clonazepam, diazepam, chlordiazepoxide)
- Anticonvulsants (gabapentin, pregabalin, topiramate)
- Antioxidants (alpha-lipoic acid)
- Histamine receptor antagonists (lafutidine; not FDA approved for use in the United States)
- Salivary stimulants (pilocarpine, cevimeline)
- Dopamine agonists (pramipexole)
- Herbal supplements (Hypericum perforatum or St John's wort, Catuama)
- Vitamin supplementation

2.2 Pharmacological treatment for burning mouth syndrome

Because there is a lack of evidence on pharmacotherapy for primary BMS. Primary BMS can be difficult to treat, and many patients do not respond well to the treatment strategies. Medical treatment can help reduce the severity of the burning clinical manifestations in many cases. Complete pain relief is not common (5).

Pharmacological therapy can be divided into systemic and topical treatment

2.2.1 Topical Therapies

2.2.1.1 Clonazepam

Clonazepam, a benzodiazepine that agonizes the GABA receptor (gamma-aminobutyric acid), efficiently lowers symptoms associated with BMS, according to a recent meta-analysis (29). Importantly, both short-term (less than 10 weeks) and long-term (more than 10 weeks) intervals of topical clonazepam administration were found to be beneficial. Xerostomia, drowsiness, and weariness were among the treatment's side effects. Patients should be informed that clonazepam might induce dependence, as symptoms may reappear if the medicine is stopped (29). Nonetheless, topical clonazepam may be a helpful alternative for treating BMS, especially for people who not willing or unable to take systemic drugs. (5).

2.2.1.2 Capsaicin

Capsaicin is an analgesic that controls neuropathic pain by acting on sensory afferent neurons (30). It binds to TRPV1 and inhibits heat-induced neuronal responses. TRPV1 is depleted after prolonged exposure to capsaicin, resulting in pain receptor desensitization. TRPVI has been linked to the development of BMS. When comparing capsaicin to a placebo in three experiments, there was a significant improvement in burning sensations (31). An increased burning sensation immediately after application of topical preparations, as well as dyspepsia, are side effects of this treatment, especially if capsaicin is taken as a capsule (32). This should be considered while prescribing capsaicin, especially for individuals with a history of gastric-related problems.

2.2.1.3 Sodium bicarbonate mouthwash

Sodium bicarbonate mouthwash has been introduced for oral care for not only promote patient comfort but also help in maintaining moisture content of the oral mucosa and decrease risk of secondary infection (33). The mouthwash such as sodium bicarbonate has no known active biological properties but has an active role as a cleansing agent because of its ability to dissolve mucus and loosen debris (34). Moreover, bicarbonate is the major determinant of buffer capacity of saliva that help maintain neutral pH level in whole saliva. Hence, the use of buffering agents like sodium bicarbonate mouthwash would be helpful to patients who have increased viscosity saliva due to diminished flow rate and pH (35).

2.2.2 Systemic Therapies

2.2.2.1 Clonazepam

There is evidence that systemic clonazepam improves pain in BMS patients significantly (36). Systemic clonazepam was most beneficial for individuals with normal salivary production, those who reported the most severe symptoms at first presentation, and those who did not take psychiatric medications, according to a study of 100 patients (37). While systemic clonazepam appears to be beneficial for pain management, preliminary research suggests that it does not enhance mood, taste impairment, or xerostomia (38). It is important to note the long-term effects of systemic clonazepam have yet to be determined and further researches are required to determine its safety and effectiveness in this context.

2.2.2.2 Alpha Lipoic Acid

Alpha lipoic acid (ALA) is an antioxidant and neuroprotective mitochondrial coenzyme that may promote the synthesis of brain development factors (31). The therapeutic advantages of ALA for BMS remain unknown. While unblinded and single-blinded trials consistently found that using systemic ALA reduced pain intensity, only two of five double-blinded studies found a change in mean pain scores when ALA was compared to a placebo. (31, 32). Headaches and stomach distress were the most commonly reported adverse effects of ALA treatment, according to one research,

however these differences were not significant when compared to placebo (32). While ALA has shown promise in the treatment of BMS, further research is needed to confirm its efficacy in this disease.

2.2.2.3 Gabapentin

Gabapentin is an anticonvulsant drug that works by acting as an agonist for GABA, an inhibitory neurotransmitter. Patients with BMS were given gabapentin, ALA, or a combination of the two in a crossover placebo-controlled study. In the gabapentin group, 50% of the participants reported improvements in pain ratings, compared to 15% in the placebo group (32). Surprisingly, when gabapentin was given in combination with ALA, 70% of patients reported less discomfort. Despite the need for more research, gabapentin is regarded to be particularly promising because it is helpful in the treatment of similar diseases including glossopharyngeal neuralgia and general neuropathic pain. (32).

2.2.2.4 Amitriptyline

Amitriptyline is a tricyclic antidepressant that also acts as an analgesic. The efficacy of amitriptyline and clonazepam in decreasing oral pain was evaluated in a recent retrospective research. Patients were evaluated six weeks and three months after therapy. At each time point, both patient groups reported less pain, and there were no significant differences between them (11). Asthenia was noted as an adverse effect in both treatment groups, and those receiving amitriptyline also felt dry mouth. The findings of this study show that amitriptyline may be a useful treatment for pain associated with BMS; nevertheless, caution should be exercised when prescribing medications that induce dry mouth in this patient population, since such treatments may cause oral discomfort when used long-term (11).

2.2.2.5 Hormonal replacement

One study of hormone replacement treatment is reported in the most current Cochrane review of BMS (39). Pisanty and colleagues compared estrone cream vs estrone and progesterone cream versus placebo in a blinded study. The trial comprised 6, 9, and 7 patients in each of the three arms. The trial's findings revealed a little impact, with no more than 25% of patients in any arm reporting relief from the burning sensation (4).

2.3 Heart rate variability

Heart rate variability (HRV) is the fluctuation in the interval between adjacent heartbeats (14). HRV is the consequence of neurocardiac activity, which is triggered by heart-brain connections and the autonomic nervous system (ANS) (14). To adaptively respond to intrinsic and external stresses, a balance between the excitatory sympathetic nervous system and the inhibitory parasympathetic nervous system of the autonomic nervous system (ANS) is necessary (13). HRV is a predictor of the ability to manage emotional reactions to stresses because this balance can be seen (13).

2.3.1 Measurement of HRV

HRV analysis can be performed in the time-domain, frequency-domain and non-linear methods (40).

The degree of variability in measures of the interbeat interval (IBI), which is the time interval between successive heartbeats, is quantified using time-domain indices of HRV. These values might be found in original data or the logarithm of primary data in order to produce a more normal distribution. The quantity of HRV detected over monitoring durations ranging from 1 minute to 24 hours is quantified using heart rate variability time-domain indices. (14). These metrics include the Standard deviation of NN intervals (SDNN), Standard deviation of RR intervals (SDRR), Standard deviation of the average NN intervals for 5 minutes (SDANN), Root mean square of successive RR interval differences (RMSSD), Number of successive RR intervals that differ by more than 50 ms (NN50), Percentage of successive RR intervals that differ by more than 50 ms (pNN50) and the Triangular Interpolation of the NN Interval Histogram (TINN) (14).

The distribution of absolute or relative power in four frequency bands is estimated using frequency-domain measurements. The Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996) divided heart rate (HR) oscillations into ultra-low-frequency (ULF) (≤0.003 Hz), very-low-frequency (VLF) (0.0033–0.04 Hz), low-frequency (LF) (0.04–0.15 Hz), and high-frequency (HF) (0.15–0.40 Hz) bands (14).

A relationship between variables that is non-linear cannot be represented as a straight line. The intricacy of the processes that govern HRV leads in non-linear

observations, which relate to the unpredictability of a time series. This section reviews S, SD1, SD2, SD1/SD2, approximate entropy (ApEn), sample entropy (SampEn), detrended fluctuation analysis (DFA) $\alpha 1$ and DFA $\alpha 2$, and D_2 non-linear measures (14).

Even though, many number HRV parameters were reported in several studies, but SDNN was recognized to demonstrated for general HRV. In chronic pain syndromes such as chronic low back pain, chronic neck–shoulder pain, fibromyalgia, complex regional pain syndrome, and phantom limb pain, several investigations have found indications of autonomic dysregulation with decreased HRV (13). Low HRV is related to several other long-term health issues, including cardiovascular disease, mental disorders, and increased morbidity (13). Chronic pain can cause ANS dysregulation, which reduces the body's ability to respond adaptively to pain. As a result, ANS dysregulation and decreased HRV have been linked to the pathophysiology of several chronic pain syndromes. Because of the diminished capacity to respond to sensory and emotional stressors, low parasympathetic tone may increase the risk of chronic pain (13).

2.3.2 Confounding variables influencing HRV

Confounding factors should be considered while interpreting HRV data. It is necessary to be aware about the confounding elements that affect HRV that can be managed. According to Laborde et al. (40), the following stable and transitory participant factors should be considered

a) Stable variables: age, gender, smoking, levels of alcohol consumption, weight, height and cardioactive medication

b) Transient variables: no extreme physical exercise the day before the experiment, no eating the last 2 hours before the experiment, and no coffee or caffeinated drinks such as energizing drinks or tea in the 2 hours before the experiment, ask if they need to use the bathroom before the experiment begins, no alcohol for 24 hours prior to the experiment.

2.4 Oral health–related quality of life and cognitive condition assessment

The World Health Organization (WHO) recognizes QoL not only as the absence of disease or infirmity but the ability of a person to lead a productive and enjoyable life. As oral health status was recalled as one part of the healthy-being, Locker et al. determined oral health–related quality of life (OHRQoL) as "the extent to which oral disorders affect functioning and psychosocial well-being (41)." QoL shows the effect of an illness on a patient. QoL is now widely acknowledged as one of the most significant outcome indicators in the assessment of any therapy or health-related intervention (41). Because QoL was associated to mental illnesses, a decrease in patients' QoL might have an impact on their psychological well-being. It was recommended that emotional disorders should be taken into consideration during the diagnosis and treatment of patients with oral mucosal disorders (42).

Psychogenic components including stress, fear, anxiety, and depression have a significant influence in pain perception and affect how patients manage with chronic pain disorders like BMS. These psychogenic components are relatively self-contained and present in BMS patients prior to the development of symptoms. Furthermore, psychogenic variables are frequently the outcome of long-term burning symptoms. (43).

Patients with chronic pain have also had cognitive aspects evaluated. Self-efficacy, pain catastrophizing, and anxiety sensitivity are all important cognitive factors in chronic pain symptoms. Self-efficacy is the perception that one is capable of performing in a certain way to achieve specific goals, and it is a key element in pain self-management. Pain catastrophizing is an excessive negative attitude toward pain that can contribute to pain aggravation. Anxiety sensitivity refers to a person's susceptibility to be afraid of anxiety symptoms. Patients with a higher sensitivity to anxiety may have a more negative emotional reaction to pain. These cognitive variables might potentially play a role in BMS patients (44).

2.4.1 Quality of life

In BMS, chronicity of pain, comorbidities, and failed therapies can impact mood, initiate or reinforce mental problems including anxiety, depression, and cancerphobia, and reduce patient's quality of life. As a result, utilizing QoL as a successful treatment outcome assessment is necessary. Addressing and evaluating clinically significant change is a concern in using QoL as an outcome measurement (45).

The Oral Health Impact Profile-14 (OHIP-14) questionnaire is a shortened version of OHIP-49 (41). It was adopted to evaluate oral QoL (46). This instrument consists of 14 items which assess various dimensions of oral function and QoL. Fourteen items of questionnaire divided into 7 different domains: functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability, handicap (42). The full score ranges from 0 to 70, higher scores indicate a lower QoL (46).

An ultra-short version of the OHIP, OHIP-5, was developed to capture the 4 dimensions of patient-perceived OHRQoL; oral function, orofacial pain, orofacial appearance and psychosocial impact (47). It was used in prosthodontic patients, temporomandibular patients and also general population subjects. OHIP-5 provides a feasible instrument to assess OHRQoL in many settings (48).

2.4.2 Anxiety and depression

Two prevalent negative emotions were anxiety and depression. Anxiety related to the patient's irritation and other emotions, whereas depression referred to the patient's negative and low emotions. In general, anxiety was commonly presented before depression. (42). Anxiety and depression were found in nearly a third of the individuals (3).

Hospital Anxiety and Depression Scale (HADs) is a 14-item self-assessment scale developed to evaluate psychological profiles and emotional distress induced by chronic pain in non-psychiatric populations (3). This instrument consists of two subscales, anxiety and depression. HAD-A evaluated anxiety and HAD-D assess depression. Each subscale has 7 items that are related to mood disorders (46). Scores

of higher than 10 on the HAD scale indicated anxiety or depression, whereas scores of 7 or less indicated no significant anxiety anxiety or depression. Finally, scores of 8 to 10 indicated borderline anxiety or depression (46).

2.4.3 Pain catastrophizing

A succession of exaggerated and negative perceptions and emotions regarding the sense of pain and pain experience is described as pain catastrophizing. There are 3 dimensions of catastrophizing: rumination (I worry all the time whether the pain will end), magnification (I wonder whether something serious might happen), and helplessness (It is awful and I feel it overwhelms me). Catastrophizing exacerbates symptoms and causes mental stress, altering the severity of pain and how patients cope with it. This is also a stronger predictor of impairment in chronic pain than other factors including pain severity, medication usage, anxiety, and depression (43).

Catastrophizing can be evaluated by Pain Catastrophizing Scale, developed by Sullivan in 1995 (49). The respondents were asked to rate the frequency of negative thoughts about pain by using 13 statements. To rate the questionnaire, subjects were stated to choose one of the following answers: 0—not at all, 1—rarely, 2—often, 3—very often, and 4—all the time. The degree of catastrophizing was determined by multiplying numerical values that corresponded to each answer. Catastrophizing (as a whole and in each of its three subcomponents) was measured in both absolute and percentage terms (43).

2.4.4 Sleep disturbance

Poor sleep quality is frequently related with mental-associated painful symptoms. Daytime drowsiness, chronic fatigue syndrome, hypertension, and cognitive disorders are consequences of sleep disturbances. Inadequate sleep quality will reduce an ability to think, handle stress, and maintain a healthy immune system. As a result, treating insomnia can help to avoid the onset of anxiety and depression. (46). Sleep disruption exacerbates pain, while pain can also induce sleep disruption. The Pittsburgh Sleep Quality Index (PSQI) is one of the validated tools used to assess sleep quality.

The PSQI is a 19-item self-administered questionnaire with 7 domains: subjective sleep quality, sleep latency, sleep length, habitual sleep efficiency, sleep disruptions, sleep medication usage, and daytime dysfunction. A score of 0–3 is assigned to each domain. A score of 0 indicates that there is no problem in this domain, while a score of 3 indicates that there is a significant problem.

CHAPTER 3

Materials and methods

3.1 Population and sample

3.1.1 Population: BMS patients from the Oral Medicine clinic at Faculty of Dentistry Chulalongkorn University

3.1.2 Sample population: BMS patients from the Oral Medicine clinic at Chulalongkorn University, who are receiving either amitriptyline or sodium bicarbonate mouthwash

3.1.3 Sample size calculation

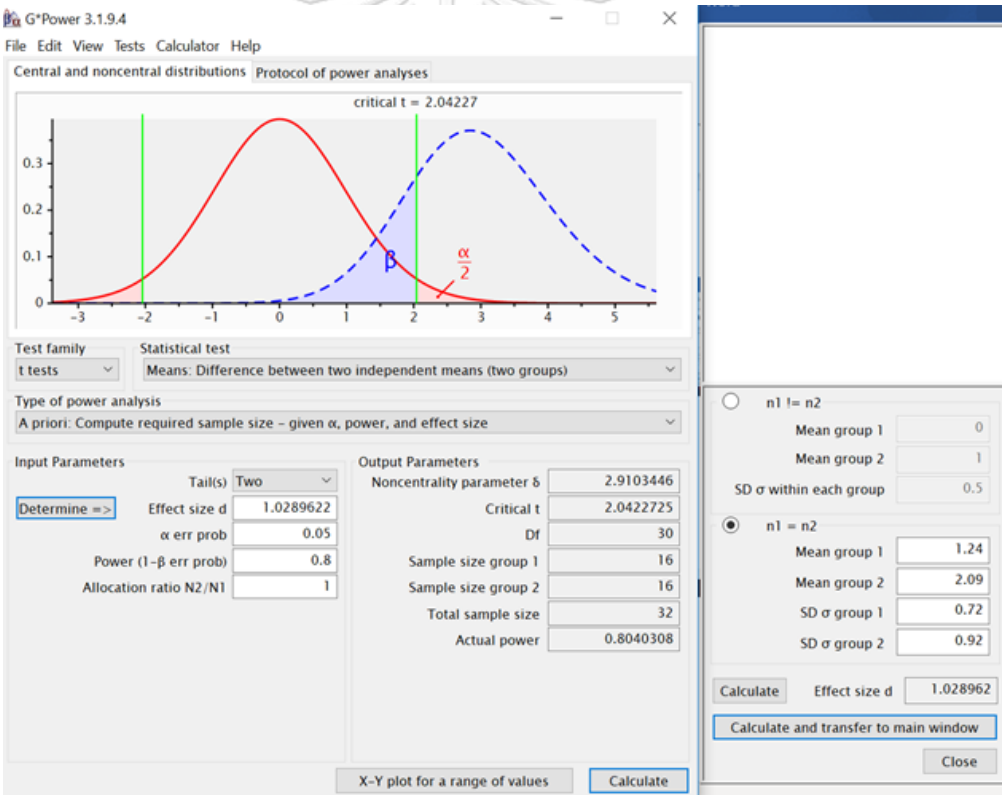


Figure 1 Sample size calculation from G*Power program

The sample size was calculated by using G*Power program version 3.1.9.4 with 80% power and 95% confidence interval level according to data from Gur et al. 2002 **(50)**. The estimated sample size is 32. To compensate for loss of participants during

follow up (attrition rate approximately 25%), we will recruit a total sample size of 40 patients (20 for each treatment arm). Clinical studies reporting long-term pain and quality of life outcomes with amitriptyline (10 mg/day) are lacking in the literature or have very limited sample size for the control/placebo group (n=5) (9).

3.2 Design

Part 1 – Retrospective study

The first stage of the study was a retrospective survey performed in primary BMS patients who attended the Oral Medicine Clinic, Faculty of Dentistry, Chulalongkorn University from January 2015 to December 2020. All data collection was done through a comprehensive phone interview. The study protocol was approved by The Human Research Ethics Committee of the Faculty of Dentistry, Chulalongkorn University. Informed consent was requested prior to enrollment in this survey. Survey was conducted in subjects that agreed to participate after inclusion criteria were met.

The inclusion criteria for this study included subjects who: (1) were previously diagnosed with primary BMS, (2) presented chronic pain in the oral mucosa for more than 3 months and (3) had minimum age of 18. Exclusion criteria were the following: (1) male, (2) unable to communicate with Thai language by phone interview, (3) non-Asian, (4) presence of poorly controlled mental illness(es).

Subjects who met the inclusion and exclusion criteria above were contacted by phone interview. All subjects were informed about the details of the study and were scheduled to give a phone interview with a maximum duration of 10 minutes. Phone interview were separated into 2 sessions if they were unable to make the interview short or if there were disruptions due to poor phone signal/connection. During the phone interview, the subject was given three questionnaires: PGI-C, OHIP-5 and Hospital anxiety and depression scale (HADS).

All data related to sociodemographics (age, working status), follow-up duration and provided BMS therapies were retrieved from the subject's clinical charts archived at the Oral Medicine Clinic.

Part 2 – Prospective study

During the second stage, all participants were screened with oral examination and laboratory investigation including complete blood count, fasting blood glucose, vitamin B12, serum ferritin, serum folate and thyroid function (by assessing T3/T4 hormones). Then, female BMS patients on amitriptyline treatment or on sodium carbonate mouthwash treatment were selected according to specific eligibility criteria (in Table 3) for the second stage of our study (prospective cohort study).

Table 3 Inclusion and exclusion criteria for subject enrollment in the prospective study (part 2)

Inclusion criteria	Exclusion criteria
1. Previously diagnosed with primary BMS, presence of chronic pain in the oral mucosa for more than 3 months with moderate to severe pain intensity (VAS ≥4) 2. Currently receiving amitriptyline (10 mg/day) or sodium bicarbonate mouthwash as a treatment for primary BMS with stable medication adherence for the past 30 days 3. Minimum age of 18 years	1. Male patients 2. Presence of local or systemic factors related to the pain symptoms 3. Uncontrolled systemic disease (e.g. hypertension stage II, diabetes, thyroid disease, cardiovascular disease) 4. Presence of abnormal laboratory findings 5. Presence of poorly controlled mental illness(es)

In this second stage, we conducted a prospective cohort study with two arms to determine the long-term effectiveness of amitriptyline treatment on improving pain symptoms, QoL and HRV in primary BMS patients (Figure 2). Amitriptyline treatment (1st treatment arm on the left) will be compared to a control group with palliative oral

topical treatment (sodium bicarbonate mouthwash only, 2nd treatment arm on the right) for BMS. The data except QoL was collected at three time points: baseline, 3 and 6 months after baseline, QoL was collected only at baseline and 6 months after baseline according to the experimental design on Figure 2 below.

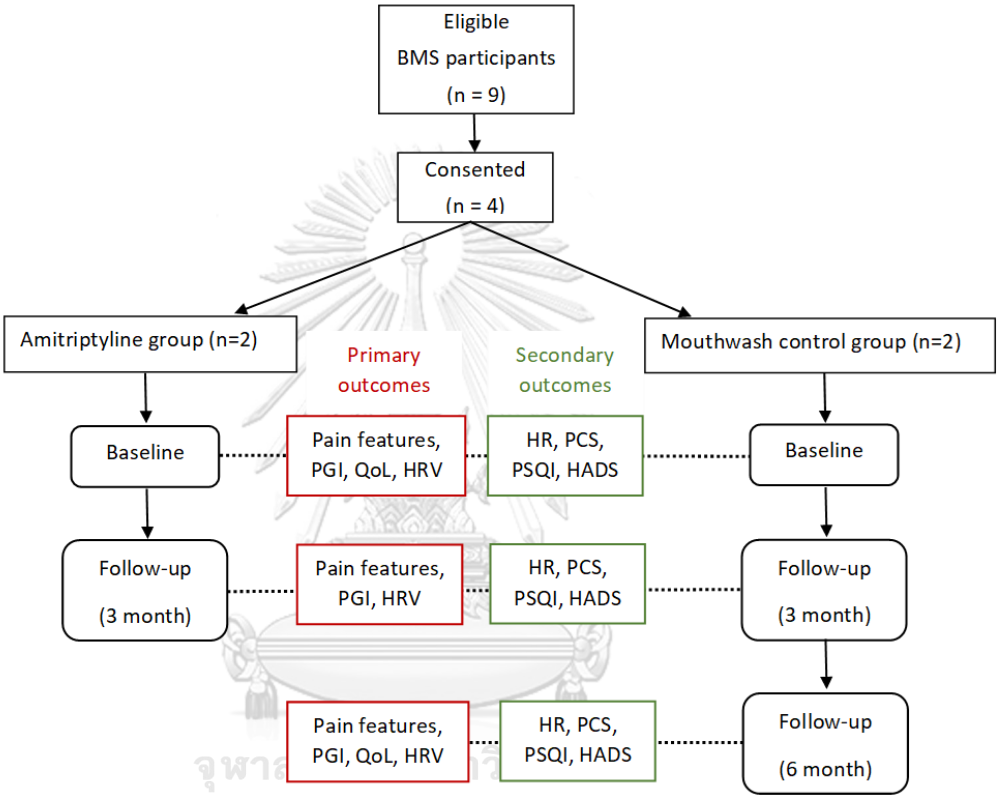


Figure 2 Flow diagram describes the design, the two treatment arms and data collection for the prospective study for primary outcomes: pain quality, intensity and chronicity, Participants' rating of global improvement (PGI-I), quality of life (QoL), and heart rate variability (HRV) and secondary outcomes: blood pressure (BP), heart rate (HR), pain catastrophizing (PCS), sleep quality (PSQI) and psychological distress (HADS).

3.3 Inclusion and exclusion criteria

The participants were recruited from patients who were given diagnosis as primary BMS according to criteria from Fortuna et al. 2013 (49) in the Oral Medicine clinic of Chulalongkorn University. Participants was selected according to the inclusion and exclusion criteria on Table 3. Either amitriptyline or sodium bicarbonate mouthwash were used as a treatment for primary BMS and this medication regimen will not be changed during the study period by the study's clinicians and researchers.

3.4 Interventions

Participants were placed into 2 arms/groups, the amitriptyline group (AMI) and the mouthwash control group (CG), according to the therapy that they are currently taking (either amitriptyline 10 mg/day or bicarbonate mouthwash 3 times a day).

3.5 Measurements

3.5.1 Primary outcomes

3.5.1.1 Pain features

Quality and intensity of subjective pain were collected by using the Thai version of short-form McGill-Melzack pain questionnaire (SF-MPQ) (51). The SF-MPQ, a shorter version of the original multidimension pain scale MPQ, consists of sensory and affective subscales. Cronbach's alpha coefficients for the total score and subscales were at alpha=0.7881.

Current pain intensity will be assessed by using a visual analog scale (VAS), a 10 cm- length line, going from "0" or "no pain at all" to "10" or "the worst pain imaginable". All participants were instructed on how to determine their pain status and mark their pain status on the VAS line. All participants will be evaluated for their pain intensity with the same dental professional, an Oral Medicine clinician.

Pain chronicity was assessed at baseline and 6 months after baseline to determine the pain duration with the following question from the Graded Chronic Pain Scale: "On how many days in the last 6 months have you had oral pain?". Participants can rate the oral pain chronicity by writing their number of days in pain.

3.5.1.2 QoL and global improvement

Participants' rating of global improvement were collected using a question from the Thai version of Patient Global Impression of Improvement (PGI-I). The Thai version was developed by Orawee Chinthakanan (52) and it has a satisfactory validity. The PGI-I use a descriptive scale where participants will self-report whether they are: very much better, much better, a little better, no change, a little worse, much worse and very much worse.

OHRQoL was measured at baseline and 6 months after baseline using the Thai version of the Oral Health Impact Profile-14 (OHIP-14) questionnaire (53). The reliability of the Thai OHIP-14 was excellent (α = 0.88) and construct validity of the questionnaires showed acceptable properties (53). Patients will be asked to answer 14 questions about the QoL, by choosing one of the most offered answers: 0 - never, 1 - almost never, 2 - sometimes, 3 - often, and 4 - very often. The score will be calculated by adding numerical values corresponding to certain answers and will be used as a measure for the quality of life.

3.5.1.3 Heart rate variability

To control unintended influence on HRV, participants were instructed to follow a normal sleep routine, refrain from eating and drinking (other than water) for 2 hours before their scheduled appointment. Upon their arrival, blood pressure will be taken.

HRV was measured using an electrocardiogram (ECG). The experimental protocol was approximately 12 minutes in duration and consisted of 3 epochs: (1) baseline (2) serial subtraction experimental stressor (3) recovery. Participant was in a supine position throughout the protocol and asked to minimize bodily movements. ECG electrodes will be placed on a chest and continuous ECG recordings was taken. During the baseline period, participants were instructed to rest and watch a slideshow of nature pictures for 10 minutes in a quiet environment room. Then, resting ECG activity was recorded for 5 minutes. After such baseline epoch an experimental stressor composed of a 2-minute of serial subtraction task will be provided. In this subtraction task, participants were instructed to subtract out loud from 400 by 7’s for 2 minutes.

The experimenter instructed participants to subtract the numbers as quickly as possible without making mistakes. In order to mimic an urgent situation, a metronome will be beeped every three seconds and participants will be told to subtract as quick or faster than the beeps. If participants made a mistake, they were told that was incorrect and the task will be back to 400 and started over again. A 5-minute recovery period was followed the experimental stressor epoch. During this recovery period participants continued to lay down on a supine position while watching a slideshow of nature pictures.

To evaluate HRV, both time-domain and frequency-domain parameters were computed. The time-domain parameters selected were the SD of the RR intervals (SDNN), NN50 and pNN50. The frequency-domain parameters, LH, HF and the LF/HF ratio were included.

3.5.2 Secondary outcomes

Secondary outcomes will be measured according to the following:

1) Blood pressure (systolic and diastolic) and heart rate parameters to evaluate for the cardiac static functional state. This was routinely measured at all time points using a calibrated OMRON device (HBP-9020). Three consecutive readings were taken to determine an average data and discard “white coat syndrome or hypertension” effects.

2) Anxiety and depression were assessed using the Thai version of the 14-item self-administered Hospital Anxiety and Depression Scale (HADS) (54). The Thai HADS had good reliability and validity for both anxiety (α = 0.8551) and depression (α = 0.8259) sub-scales. Each subscale (anxiety and depression) includes 7 items that are rated on a Likert scale of 0 = not at all to 3 = definitely/most of the time, with a potential total score on each subscale ranging from 0 to 21. Higher scores indicate higher levels of anxiety and depression.

3) Pain-related catastrophizing was assessed using the Thai version of the Pain Catastrophizing Scale (PCS) (55). Factor analysis accounted for 65.97% of variance and Cronbach’s alpha coefficients for the total score and subscales were at alpha=0.91

(55). The PCS consists of 13 items, and respondents were asked to rate the frequency with which they experienced different pain-related thoughts or feelings on a five-point Likert scale, where 0 represents “not at all” and 4 represents “all the time.”

4) Sleep disturbances was assessed using the Thai version of Pittsburgh Sleep Quality Index (56). The Thai PSQI had good reliability and validity. Cronbach’s alpha coefficients were at good levels (alpha=0.83). The sum of the 7 domains gives an overall score of 0–21. Higher scores indicated a greater sleep disturbance. A PSQI total of lesser than 5 is the cut-point for classifying subjects as a good sleep quality, while subjects with a score of greater than 5 can be indicated as a suffering. However, the PSQI was not developed to detect specific disorders (46).

3.6 Data collection

Demographic information including age, medical history, current medication, location and duration of oral pain, previous treatment(s) for BMS, presence of co-morbid (non-oral) pain conditions subjective and objective xerostomia assessments, hormonal supplementation, menstrual period and intraoral examination data were collected.

Primary and secondary outcomes assessment were done at the designated time points by one trained researcher at baseline and 3, 6 months after baseline.

3.7 Statistical analysis

In the retrospective study, descriptive statistics was used to determine the percentage and mean (95% confidence interval). Independent t-test was used to compare the outcome differences between age and follow-up duration. One-way ANOVA was used to compare the outcome differences between working and psychological status.

In the prospective study, demographic data, primary outcomes and secondary outcomes were analyzed by descriptive statistics due to the limited sample size (n=2 for each treatment arm).

The level of significance was set at 5%. All analyses were conducted using the SPSS software program version 22 (SPSS for Windows, SPSS Inc., Chicago, IL, USA).

CHAPTER 4
Results

Part 1 - Retrospective study

Characteristics of subjects

A total of 20 female subjects were enrolled in this study. Mean age of enrollment was 53.5 (95%CI 46.8, 60.3) years. According to WHO criteria, patient's age was divided into 2 groups, young adult (18-65 years) and elderly (above 65 years) (WHO, 2001). The majority of our subjects were young adults with an age range of 26-72 years. Mean follow-up duration was 27.1 months (95% CI 16.9, 37.2). More than half of the subjects (60%) had been follow-up for more than a year, but we observed no significant differences in symptom improvement and OHRQoL.

Subject's rating of global improvement

All subjects reported improvement in the PGI-C. About 60% of subjects reported "much better" improvement while 25% and 15% reported a "little better" and "very much better" improvement, respectively.

Oral health-related quality of life

Up to 95% of subjects reported oral health impact problems with a mean OHIP-5 score of 4.0 (range: 2.3 - 5.7), which are very low scores since the maximum score is 20. Therefore, the OHRQoL does not appear to be negatively impacted by BMS symptoms. However, when analyzing each of the OHIP-5 domains, orofacial pain was the most frequently impacted domain in 90% of the subjects followed by orofacial appearance (55%).

Emotional dimension

The mean anxiety and depression scores were within normal range, 4.9 (95% CI 3.8, 6.0) and 2.2 (95% CI 1.1, 3.2) respectively. BMS subjects with borderline scores for anxiety and depression had lesser BMS symptoms improvement and higher impact in OHRQoL when compared with subjects with normal HADS scores. Since a very low

number of subjects had abnormal HADS scores, one could not run statistical tests in this residual group.

Provided BMS therapy

At the time of the survey study, all BMS subjects still used at least one medication for BMS treatment. We did not perform statistical analysis on the types of provided BMS therapy because each individual received different combination of treatments and each treatment was terminated at different timings. The most commonly prescribed medication was sodium bicarbonate mouthwash (85% of subjects). The second most common treatments were systemic medication (tricyclic antidepressants, benzodiazepines, anticonvulsants) and topical agents (topical anesthetics, moisturizer, anti-inflammatory mouthwash). The less often provided treatment was occlusal polishing.

A summary of sociodemographics and other clinical features of participants against primary outcomes (PGI-C and OHRQoL) is presented in Table 4. We also examined the mean difference between each independent feature and main outcomes (PGI-C and OHRQoL). However, no significant differences on PGI-C and OHRQoL were found between different age groups, working status, treatment options and psychological status.

Table 4 Sociodemographics and clinical features of primary BMS subjects against patient global impression (PGI) and oral health-related quality of life (OHRQoL)

	Frequency N (%)	PGI-C	OHRQoL (OHIP-5)
		Mean (95%CI)	
Age			
<65	15 (75)	2.0 (1.64, 2.36)	4.1 (2.0, 6.3)
≥65	5 (25)	2.4 (1.7, 3.1)	3.6 (-0.2, 7.4)
Working status			
Yes	14 (70)	2.1 (1.7, 2.4)	4.0 (1.6, 6.4)
No	3 (15)	2.3 (1.0, 3.8)	2.7 (1.2,4.1)
Unidentified/Prefer not to answer	3 (15)	2.0 (-0.5, 4.5)	5.3 (-2.7,13.3)
Follow-up duration			
≤12 months	8 (40)	2.4 (1.9, 2.8)	5.6 (1.9, 9.3)
>12 months	12 (60)	1.9 (1.5, 2.3)	2.9 (1.2, 4.7)
Provided BMS therapies			
Sodium Bicarbonate Mouthwash	17 (85)	2.2 (1.9, 2.5)	3.4 (2.0, 4.9)
Systemic medication	9 (45)	2 (1.3,2.7)	4.3 (0.6,8)
Topical agents	7 (35)	2.0 (1.5,2.5)	3.3 (0.7, 5.8)
Nutritional supplements	3 (15)	2.3 (0.9,3.8)	2.0 (N/A)
Others	3 (15)	2.0 (N/A)	2.3 (0.9, 3.8)
Emotional dimension according to HADS score			
Anxiety			
Normal	18 (90)	2.2 (1.9,2.5)	3.6 (2.2, 4.9)
Borderline	1 (5)	1.5 (-4.9, 7.9)	8.0 (-81.0, 97.0)
Abnormal/Case	1 (5)	2	15
Depression			
Normal	18 (90)	2.2 (1.9, 2.5)	3.6 (2.3, 4.9)
Borderline	2 (10)	1.5 (-4.9,7.9)	7.5 (-87.8,102.8)
Abnormal/Case	0 (0)	-	-

PGI-C: patient global impression of change; OHRQoL: oral health-related quality of life; OHIP-5: 5-item oral health impact profile.

Part 2 – Prospective study

Two primary BMS patients who used sodium bicarbonate mouthwash and 2 patients using amitriptyline met the inclusion and exclusion criteria for the prospective cohort study. All subjects were young adult women. Mean age in this second stage of the study was 39.75 years. Subjects had age range between 26 and 53 years. The most common location of burning sensation area was the tongue, followed by the gingiva. None of the subjects were in the postmenopausal period or taking hormonal supplements. The unstimulated salivary rate was normal in all subjects and none of them reported subjective xerostomia. Subjects in sodium bicarbonate group had 20 months and 31 months follow-up period before baseline, while subjects in amitriptyline group had 1 month and 6 months follow-up period before baseline. Duration of symptoms in sodium bicarbonate group subjects were 22 months and 37 months before baseline, while subjects in amitriptyline group had 3 months and 7 months duration of symptoms. Subjects in the amitriptyline group were initially prescribed a dosage of 10 mg/day; however, one of them had the dosage increase to 20 mg/day in the last 1 month of the study. Subjects in the sodium bicarbonate group used the mouthwash 3 times/day.

Primary outcomes

Pain symptoms

The quality, intensity and chronicity of pain measurement was shown in Table 5. Subjects in sodium bicarbonate group reported a high mean affective score when compared with sensory score. Present pain intensity was mild to distressing (PPI scores 1-3). Results showed varying pain-related disability among the 4 subjects going from low to high disability (Grade 0-3). Pain intensity (VAS) in sodium bicarbonate group decreased from baseline to 3-month follow-up visit. While VAS in amitriptyline group increased from baseline to 3-month follow-up visit.

Table 5 The summary of pain symptoms, OHRQoL and HRV at baseline, 3-month and 6-month follow-up time points

	Baseline		3-month		6-month
	S	Ami	S	Ami	S
	Mean (S.D.)				
Pain dimension: SF-MPQ					
Sensory aspects	3.5 (1.5)	10.5 (6.5)	3	5.5 (1.5)	2.5 (0.5)
Affective aspects	7 (1)	4.5 (3.5)	6 (5)	5.5 (2.5)	5 (4)
Total score	10.5 (2.5)	15 (10)	9 (5)	11 (1)	7.5 (4.5)
PPI	2 (1)	2.5 (0.5)	2 (1)	2	1.5 (1.5)
VAS	26.5 (12.5)	28.5 (3.5)	22.5 (3.5)	35.5 (13.5)	43.5 (37.5)
Physical functioning: GCPS					
Pain intensity	61.7 (21.7)	52.5 (2.5)	N/A	N/A	43.3 (43.3)
Disability points	0 (0)	1.5 (1.5)	N/A	N/A	1 (1)
Grade	1.5 (0.5)	2.5 (0.5)	N/A	N/A	1 (1)
OHRQoL: OHIP-14					
Total score	31 (1)	33 (12)	N/A	N/A	31 (12)
Subject's rating of global improvement: PGI-C					
Rating	3.5 (0.5)	2.5 (0.5)	3 (1)	2.5 (5)	2.5 (1.5)
HRV parameters					
SDNN	34.8 (7.2)	51.6 (16.8)	33.2 (3.8)	72.2 (25.0)	38.7 (7.9)
RMSSD	36.3 (13.0)	74.2 (28.0)	35.9 (16.9)	99.5 (42.9)	36.9 (18.8)
NN50	56.5 (39.5)	142.5 (35.5)	64.0 (60.0)	168.5 (58.5)	63.5 (60.5)
pNN50	17.9 (13.1)	48.1 (16.4)	20.7 (19.6)	54.5 (24.6)	19.7 (18.9)
LF	509.3 (285.7)	1677.2 (826.5)	492.5 (330.1)	3528.6 (2383.9)	437.8 (281.7)
HF	514.4 (100.2)	616.1 (444.6)	411.9 (73.6)	1647.4 (758.2)	690.5 (131.9)
LF/HF ratio	1.3 (0.5)	0.3 (0.1)	1.7 (1.3)	0.6 (0.2)	2.4 (1.2)
% React	14.9 (10.3)	40.1 (19.7)	5.3 (0.5)	46.9 (19.7)	35.2 (0.8)
% Recovery	37. 7 (22.0)	86.8 (77.9)	30.3 (29.0)	69.5 (45.2)	45.1 (27.7)

S: sodium bicarbonate group; Ami: amitriptyline group; N/A: not applicable

Oral health-related quality of life and Subject's rating of global improvement

Mean score for OHIP-14 and PGI-C are shown in Table 5. A similar impact on oral health and quality of life was seen across all BMS subjects, since the mean OHIP-14 score was in the range of 31-33, when the maximum OHIP-14 score is 56. The OHIP-14 scores in sodium bicarbonate group at baseline and 6-month follow-up visit were similar. Subjects reported from "no change" in improvement to "very much better" (PGI-C score range 1-4). Only the PGI-C score of the sodium bicarbonate group showed improvement from baseline to 3-month follow-up visit and from 3-month to 6-month follow-up. The PGI-C scores of the amitriptyline group did not change through time.

Heart rate variability

Table 5 has shown that HRV parameters such as SDNN, RMSSD, NN50, pNN50, LF, HF in the amitriptyline group are higher than in subjects treated with the sodium bicarbonate mouthwash at baseline. At 3-month visit, such HRV parameters increased. In sodium bicarbonate group was found a decreasing of HRV parameters except NN50 and pNN50 at baseline to 3-month follow-up visit.

Changes in HRV parameters during the experimental stressor epoch were reduced when compared to the resting stage and increased again in recovery stage as shown in Figure 3.

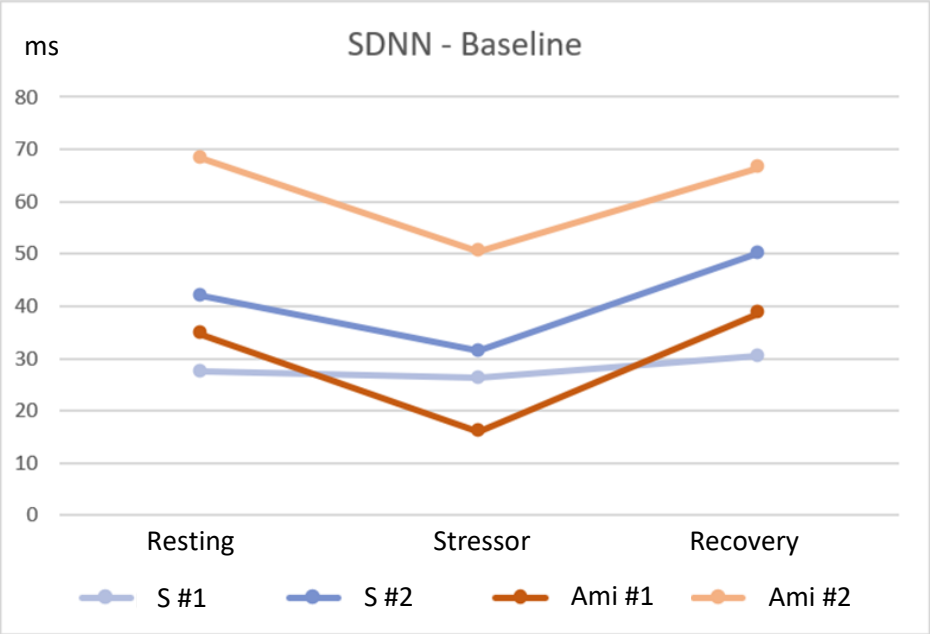


Figure 3 Changes in SDNN though resting, experiment stressor and recovery stage at baseline visit. Subjects taking sodium bicarbonate mouthwash: S #1 and S #2. Subjects taking amitriptyline: Ami #1 and Ami #2

<u>Secondary outcomes</u>

Emotional domain

Mean anxiety and depression subscales from HADS are shown in Table 6. The mean anxiety subscale score of sodium bicarbonate group was in the borderline range (score 8-10). The mean depression subscale score of both treatment groups were within a normal range (score 0-7). However, one subject in each BMS treatment group (amitriptyline and sodium bicarbonate) reported anxiety status and borderline depression. Subjects in amitriptyline group reported an improvement in anxiety and depression scores from baseline to 3-month follow-up visit. While subjects in sodium bicarbonate group reported higher depression score from baseline to 3-month follow-up visit.

Table 6 The summary of secondary outcomes at baseline, 3-month and 6-month after baseline

	Baseline		3-month		6-month
	S	Ami	S	Ami	S
	Mean (S.D.)				
Emotional domain: HADS					
Anxiety	9 3	7.5 (4.5)	8 (3)	5 (2)	8.5 (3.5)
Depression	3.5 (1.5)	5.5 (2.5)	5 (3)	3.5 (0.5)	5 (3)
Sleep disturbance: PSQI					
Total score	7.5 (1.5)	5.5 (2.5)	8 (2)	4.5 (0.5)	6.5 (2.5)
Pain catastrophizing: PCS					
Helplessness	9 (5)	7.5 (3.5)	9.5 (6.5)	7.5 (0.5)	8.5 (8.5)
Magnification	5 (2)	6 (5)	5.5 (3.5)	3	4 (4)
Rumination	10.5 (0.5)	9 (4)	7.5 (6.5)	8 (1)	10.5 (5.5)
Total score	24.5 (7.5)	22.5 (12.5)	22.5 (16.5)	18.5 (1.5)	23 (18)

S: sodium bicarbonate group; Ami: amitriptyline group; N/A: not applicable

Sleep quality

Mean score for PSQI is shown in Table 6. Subjects in the sodium bicarbonate mouthwash group reported impacted sleep problems (score of 5 and above). All BMS subjects reported a poor sleep quality at one follow-up time point at least. Subjects in the amitriptyline group reported improvement in sleep quality from baseline to 3-month follow-up visit. While subjects in sodium bicarbonate group reported lower sleep quality from baseline to 3-month follow-up visit.

Pain catastrophizing

A total PCS score and its 3 pain catastrophizing dimensions (helplessness, magnification and rumination) were comparable between the sodium bicarbonate mouthwash and amitriptyline treatment groups as shown in Table 6. The total PCS score of sodium bicarbonate and amitriptyline group decreased from baseline to 3-month follow-up visit.

CHAPTER 5
Discussion

Part 1 - Retrospective study

Because of the higher frequency of BMS in females when compared to males (ratio 5:1) (57), we excluded males from this study in order to eliminate the potential hormonal differences that can become confounders. Mean age of enrollment was slightly lower than the number 59.4 of the study in Minnesota which recruited 149 primary BMS subjects. Even though the sample size of this study was limited, the distribution was similar to previous primary BMS study (58).

The PGI main outcome analysis revealed a higher symptom improvement in BMS subjects when compared to López-Jornet et al. study who reported 40% of "little better" and 47% of "no change" in improvement (59). PGI-C has advantages in terms of overall BMS treatment comparisons according to patients' impressions of change, only 11% of BMS RCTs reported PGI-C as an outcome (60). Though, PGI-C does not take into consideration the clinicians' impressions in terms of symptom improvement as the pain management field moves to a patient-centered approach.

In this study, orofacial pain was the most commonly impacted domain by 90% of the subjects, followed by oral function (55%). Conversely, in 2008 Lopez-Jornet and colleagues (61) reported the functional limitation domain as a highest score one among all OHIP domains, while other study (62)reported psychological discomfort; however, these previous studies used OHIP-49. OHIP-5 is a brief screening and a precise instrument for assessing OHRQoL and dental-reported outcome measures (63). It was used in this study due to its suitability for our phone survey interview approach which as time constraints and also one has to avoid questionnaire fatigue; despite such advantages, OHIP-5 has never been utilized on a BMS clinical study.

In this study, the emotional dimension scores were much lower than the ones from López-Jornet et al. in 2014 (46), which reported mean anxiety and depression scores at 8.08 and 7.90, respectively.

There are certain limitations in our study that should be considered. Firstly, this was a retrospective study and some of our subjects were elderly, so the result may

have inaccurate answer from recall bias (64). Furthermore, we cannot confirm that the subject understood all of the questions. Lengthy phone interview and questionnaires could cause decision fatigue and result in irrational answer (65). The second, this study only collected the data from one-end point without comparing with baseline thus we cannot be certain of the actual improvement. Moreover, we could not conclude that the results were influenced from which rendered treatment because of the difference of combined treatments and follow-up duration.

To address these limitations, further studies should have a prospective design which can answer the etiology of primary BMS and confirm how early the treatment can provide substantial recovery and significantly decrease the symptoms. It would also be relevant to assess cost of care for primary BMS management.

Part 2 - Prospective study

The sample size of this study was limited due to the low number of eligible subjects. Moreover, some of the eligible subjects refused to participate in the study. Subjects in the amitriptyline group were able to participate only at baseline and at 3-month follow-up visit because one had to change her medication and the other was not available for the 6-month follow-up visit.

Mean age of this study was very low when compared to previous primary BMS reports (65). One of our BMS subject's age fell below the 50 years old mark and the other was below 30, and young adults rarely have primary BMS.

Pain dimension outcome had large variations because of the limited sample size. The VAS in this pilot study was slightly lower when compared to Braud and Boucher study in 2016 which reported a mean VAS of 3.6 (SD 2.4) (3). VAS and average pain intensity from GCPS were not concordant probably due to high human subjectivity when rating pain or questionnaire fatigue. High disability days reported in the GCPS confirmed the presence of pain chronicity in all our BMS subjects at baseline. However, one of the subjects in the sodium bicarbonate group reported no disability days at 6-month follow-up visit. Due to 100% attrition rate in the amitriptyline treatment group at 6-month follow-up, only GCPS scores in sodium bicarbonate group were reported.

The high OHIP-14 scores indicated negative impact in oral health in our BMS subjects which was according to the reported high disability days in pain. This study presented much poorer OHRQoL when compared to the study of Rogulj et al. in 2014 and Riordain et al. in 2009 (49, 66). The most frequently impacted domain in OHIP-14 was psychological discomfort followed by physical pain.

Regarding HRV, we collected both time-domain and frequency-domain parameters. Amitriptyline group displayed higher values for all HRV parameters when compared to the other treatment group. Conversely, two previous studies reported lower HRV parameters in subjects who took antidepressants medications when compared with non-taking depressants subjects (67, 68). However, SDNN reported in this study was much lower than the ones in temporomandibular disorder patients (147.5 ms), but RMSSD was comparable (69). Studies performing HRV analysis in BMS patients are scarce. Only one study reported frequency-domain HRV parameters and observed no differences between effective and ineffective BMS treatment groups (70). The experimental stressor was added in our ECG data collection in order to evaluate HRV fluctuations within each subject. The decreased HRV during the experimental stressor epoch was observed in this study in all subjects. In contrast, Walker et al. (71) reported a significant increase in HRV during experimental stressors in pain-free control group and subjects having functional abdominal pain. Moreover, the fluctuations in HRV in the amitriptyline group was shown to be more than sodium bicarbonate group. This finding emphasizes the anti-cholinergic effect of amitriptyline in cardiac output and HRV fluctuations upon stress responses. However, HRV confounders such as age, gender, health status and current medication should be considered when interpreting HRV fluctuations. According to other BMS reports, circadian rhythm abnormalities in BMS can lead to mood disorders like anxiety and depression (46).

The total score for pain catastrophizing and for its dimensions were comparable to the study of Rogulj et al. in 2014 (49). Subjects in this study appear to have more anxiety than depressive symptoms in the HADS, especially in the sodium bicarbonate treatment group. These findings are similar to the ones of Braud and Boucher who reported a mean HADS-anxiety score of 10 (S.D. 3.2) and HADS-depression of 6.9 (4.1) (3).

Sleep disturbance was frequently observed across all subjects. Lopez-Jornet and colleagues reported poor sleep quality in 67% of BMS patients (46). The most frequently impacted sleep domains in this study were subjective sleep quality, latency and disturbance.

Important study limitations must be considered and reflected upon. First, the sample size of this cohort study was limited (N=2 in each treatment arm) and thus we must define this study as a pilot or preliminary. Second, there were differences in the duration of onset symptoms before baseline, duration of treatment before baseline and dosage of medication in amitriptyline group during the last month of the study. Lastly, we were not able to statistically compare between the amitriptyline and sodium bicarbonate mouthwash treatments in both the short- and long-term follow-ups.

To address these limitations, future studies should have a multi-center design to recruit more BMS subjects. In addition, comparing HRV parameters with a healthy control group may reveal more substantial HRV alterations in primary BMS patients.

CHAPTER 6
Conclusion

Regarding the retrospective BMS study survey, it suggested that primary BMS patients report large to small symptoms improvement and a high quality of life status independent of the rendered BMS treatment. The symptoms improvement and quality of life in BMS patients did not vary with age, working status and follow-up durations.

The cohort study was a preliminary study in nature. This study demonstrated decreasing in pain intensity from baseline to 3-month follow-up visits in sodium bicarbonate group, while pain intensity in amitriptyline group increased from baseline to 3 months. PGI-C in sodium bicarbonate group improved from baseline to 3-month and 3-month to 6-month follow-up visit, while in amitriptyline group was not changed from baseline to 3-month follow-up visit. Comparable OHRQoL in baseline and 6-month follow-up was reported in sodium bicarbonate group and similar to OHRQoL in amitriptyline group at baseline. HRV parameters in the amitriptyline group was higher than subjects in sodium bicarbonate at baseline and 3-month follow-up visit.

This study could not establish association between long-term therapy of amitriptyline and HRV parameters, and association between pain outcomes and HRV parameters due to the limited sample size.

The findings of this study emphasize the value of patient's impression of improvement and quality of life assessments when it comes to adjust strategies during pain management in each individual with primary BMS. The application of these instruments while managing primary BMS patients may help the clinician understand how each patient perceives treatment as a patient-centered approach.

APPENDIX

APPENDIX A

Demographic record form

☐ New patient ☐ Follow-up I.D. ..... Date .....

1. ข้อมูลทั่วไป อายุ ..... ปี น้ำหนัก ..... กิโลกรัม ส่วนสูง ..... เซนติเมตร

2. โรคประจำตัว ☐ มี ☐ ไม่มี ☐ ไม่ทราบ

.....

.....

.....

3. ยา/อาหารเสริมที่ทานเป็นประจำ ☐ มี ☐ ไม่มี

.....

.....

.....

4. ตำแหน่งที่มีอาการแสบร้อนในช่องปาก

☐ ริมฝีปาก บน / ล่าง ☐ กระพุ้งแก้ม ซ้าย / ขวา ☐ ลิ้น ☐ เพดาน ☐ อื่น ๆ .....

5. ระยะเวลาตั้งแต่เริ่มมีอาการแสบร้อนในช่องปาก ..... วัน ..... สัปดาห์ ..... เดือน ..... ปี

6. การรักษาที่เคยได้รับเกี่ยวกับอาการแสบร้อนในช่องปาก ☐ เคยได้รับการรักษา ☐ ไม่เคยได้รับการรักษา

.....

.....

7. ใน 30 วันที่ผ่านมา

คุณได้ใช้ยาที่ทันตแพทย์จ่ายให้สำหรับรักษากลุ่มอาการแสบร้อนในช่องปากใช่หรือไม่ ☐ ใช่ ☐ ไม่ใช่

จำนวนวันที่ใช้ยา ..... วัน ใช้ยาครั้งละ .... เม็ด / มิลลิลิตร วันละ .... ครั้ง เช้า / กลางวัน / เย็น / ก่อนนอน

8. คุณมีอาการปากแห้งหรือไม่ ☐ มี ☐ ไม่มี Unstimulating salivary rate ..... ml/min

9. คุณมีประจำเดือนครั้งสุดท้ายเมื่อ .....

คุณมีการ ทาน / ฉีด ฮอร์โมนเพศหรือไม่ ☐ มี ☐ ไม่มี

APPENDIX B

Thai-version of short-form McGill pain questionnaire

	ไม่ปวด/ไม่รู้สึก	ปวด/รู้สึกเล็กน้อย	ปวด/รู้สึกปานกลาง ไม่รบกวนชีวิตประจำวัน	ปวด/รู้สึกมากจนทนไม่ได้ รบกวนชีวิตประจำวัน
ปวดตุ๊บ ๆ	0).....	1).....	2).....	3).....
ปวดจี๊ด	0).....	1).....	2).....	3).....
ปวดเหมือนถูกแทง	0).....	1).....	2).....	3).....
ปวดแปลบ	0).....	1).....	2).....	3).....
ปวดเกร็ง	0).....	1).....	2).....	3).....
ปวดเหมือนถูกแทะ	0).....	1).....	2).....	3).....
ปวดแสบปวดร้อน	0).....	1).....	2).....	3).....
ปวดตื้อ ๆ	0).....	1).....	2).....	3).....
ปวดหนัก ๆ	0).....	1).....	2).....	3).....
กดเจ็บ	0).....	1).....	2).....	3).....
ปวดเหมือนแตกเป็นเสี่ยง	0).....	1).....	2).....	3).....
รู้สึกเหนื่อยล้า	0).....	1).....	2).....	3).....
รู้สึกหวาดกลัวความเจ็บปวด	0).....	1).....	2).....	3).....
รู้สึกไม่สบาย	0).....	1).....	2).....	3).....
รู้สึกทรมาน	0).....	1).....	2).....	3).....

ระดับอาการปวดในขณะนี้

0 ไม่ปวด .....

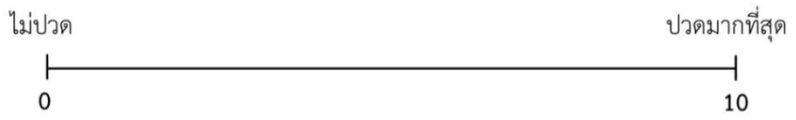
1 ปวดเล็กน้อย .....

2 ปวดพอรำคาญ .....

3 ปวดจนรู้สึกรบกวนการดำเนินชีวิต .....

4 ปวดจนทุกข์ทรมาน .....

5 ปวดมากจนทนไม่ได้ .....



APPENDIX C

Thai-version of Graded chronic pain scale (GCPS)

1. ใน**ระยะ 6 เดือนที่ผ่านมา** ท่านเคยมีอาการปวดบริเวณใบหน้าเป็นเวลากี่วัน _____วัน

2. ท่านจะให้คะแนนระดับความปวดบริเวณใบหน้าของท่านใน**ขณะนี้**เท่าไหร่ใช้ระดับคะแนนจาก 0 ถึง 10 เมื่อ 0 คือ “ไม่ปวด” และ 10 คือ “ปวดมากที่สุดเท่าที่เป็นไปได้”

ไม่ปวด										ปวดมากที่สุดเท่าที่เป็นไปได้
0	1	2	3	4	5	6	7	8	9	10

3. ใน<u>ระยะ 30 วันที่ผ่านมา</u> ท่านจะให้คะแนนความปวดบริเวณใบหน้าที่**รุนแรงมากที่สุด**ในระดับใด ใช้ระดับคะแนนเดียวกัน เมื่อ 0 คือ “ไม่ปวด” และ 10 คือ “ปวดมากที่สุดเท่าที่เป็นไปได้”

ไม่ปวด										ปวดมากที่สุดเท่าที่เป็นไปได้
0	1	2	3	4	5	6	7	8	9	10

4. ใน<u>ระยะ 30 วันที่ผ่านมา</u> ท่านจะให้คะแนนความปวดบริเวณใบหน้า**โดยเฉลี่ย**ในระดับใด ใช้ระดับคะแนนเดียวกัน เมื่อ 0 คือ “ไม่ปวด” และ 10 คือ “ปวดมากที่สุดเท่าที่เป็นไปได้” (นั่นหมายถึงความปวดของท่านที่เกิดขึ้นเป็นประจำ ขณะที่มีอาการปวด)

ไม่ปวด										ปวดมากที่สุดเท่าที่เป็นไปได้
0	1	2	3	4	5	6	7	8	9	10

5. ใน<u>ระยะ 30 วันที่ผ่านมา</u> มีประมาณกี่วัน ที่ท่านไม่สามารถทำ**กิจกรรมตามปกติ**ได้ เนื่องจากอาการปวดบริเวณใบหน้า เช่น ทำงาน ไปโรงเรียน หรือ ทำงานบ้าน

	○	○	○	○	○	○	○	○	○	○	○
วัน	ไม่มี	1	2	3	4	5	6	7	8-20	21-25	26-30
(คะแนน)	*(0)*	*(1)*	*(2)*	*(3)*	*(4)*	*(5)*	*(6)*	*(7)*	*(8)*	*(9)*	*(10)*

6. ใน<u>ระยะ 30 วันที่ผ่านมา</u> ความปวดบริเวณใบหน้าเป็นอุปสรรคต่อการทำ**กิจกรรมประจำวัน**ของท่าน มากน้อยเพียงใด ใช้ระดับคะแนน 0 ถึง 10 เมื่อ 0 คือ “ไม่เป็นอุปสรรค” และ 10 คือ “ไม่สามารถทำกิจกรรมใดๆได้”

ไม่ปวด										ไม่สามารถทำกิจกรรมใดๆได้
0	1	2	3	4	5	6	7	8	9	10

7. ในระยะ 30 วันที่ผ่านมา ความปวดบริเวณใบหน้าเป็นอุปสรรคต่อการเข้าร่วม**กิจกรรมสันทนาการ กิจกรรมทางสังคม และกิจกรรมของครอบครัว**มากน้อยเพียงใด ใช้ระดับคะแนนจาก 0 ถึง 10 เมื่อ 0 คือ “ไม่เป็นอุปสรรค” และ 10 คือ “ไม่สามารถทำกิจกรรมใดๆได้”

ไม่เป็นอุปสรรค — ไม่สามารถทำกิจกรรมใดๆได้

0 1 2 3 4 5 6 7 8 9 10

8. ในระยะ 30 วันที่ผ่านมา ความปวดบริเวณใบหน้าเป็นอุปสรรคต่อ**ความสามารถในการทำงาน**ของท่าน รวมถึงงานบ้านมากน้อยเพียงใด ใช้ระดับคะแนนเดียวกัน เมื่อ 0 คือ “ไม่เป็นอุปสรรค” และ 10 คือ “ไม่สามารถทำกิจกรรมใดๆได้”

ไม่เป็นอุปสรรค — ไม่สามารถทำกิจกรรมใดๆได้

0 1 2 3 4 5 6 7 8 9 10

APPENDIX D

Thai-version of Patient Global Impression of Change

ข้อใดต่อไปนี้อธิบายภาวะของท่าน ณ ปัจจุบัน เปรียบเทียบกับก่อนการรักษา	
ดีขึ้นมากที่สุด	1
ดีขึ้นมาก	2
ดีขึ้นเล็กน้อย	3
ไม่เปลี่ยนแปลง	4
แย่ลงเล็กน้อย	5
แย่ลงมาก	6
แย่ลงมากที่สุด	7

APPENDIX E

Thai-version of 14-item Oral Health Impact Profile (OHIP-14)

คำชี้แจง โปรดทำเครื่องหมาย ✓ ลงในช่องที่ตรงกับความเห็นของท่านมากที่สุด ในช่วง 6 เดือนที่ผ่านมา

คำถาม	ไม่เคยเลย	น้อยครั้ง	บางครั้ง	บ่อย	บ่อยมาก
1. คุณมีปัญหาในการออกเสียงคำพูดเนื่องมาจากช่องปากของคุณใช่หรือไม่					
2. คุณรู้สึกว่าการรับรสชาติอาหารของคุณแย่ลงเนื่องมาจากช่องปากของคุณใช่หรือไม่					
3. คุณมีอาการเจ็บปวดในช่องปากของคุณใช่หรือไม่					
4. คุณรู้สึกไม่สบายใจเวลารับประทานอาหารเนื่องมาจากช่องปากของคุณใช่หรือไม่					
5. คุณรู้สึกรำคาญภายในช่องปากของคุณใช่หรือไม่					
6. คุณรู้สึกอึดอัดในช่องปากของคุณใช่หรือไม่					
7. คุณรู้สึกไม่พอใจในการรับประทานอาหารเนื่องมาจากช่องปากของคุณใช่หรือไม่					
8. คุณต้องหยุดชั่วขณะระหว่างรับประทานอาหารเนื่องมาจากปัญหาช่องปากของคุณใช่หรือไม่					
9. คุณพบว่ามันยากที่จะผ่อนคลายเนื่องมาจากปัญหาช่องปากของคุณใช่หรือไม่					
10.คุณรู้สึกอายเนื่องมาจากปัญหาช่องปากของคุณใช่หรือไม่					
11.คุณรู้สึกหงุดหงิดง่ายกับผู้อื่นเนื่องมาจากปัญหาช่องปากของคุณใช่หรือไม่					
12.คุณมีความยุ่งยากขณะทำงานเนื่องมาจากปัญหาช่องปากของคุณใช่หรือไม่					
13.คุณรู้สึกไม่พอใจในการดำรงชีวิตประจำวันเนื่องมาจากปัญหาช่องปากของคุณใช่หรือไม่					
14.คุณไม่สามารถบดเคี้ยวอาหารได้เนื่องมาจากปัญหาช่องปากของคุณใช่หรือไม่					

APPENDIX F

Thai-version of Hospital Anxiety and Depression Scale (HADS)

แบบสอบถามชุดนี้มีจุดมุ่งหมายที่จะช่วยให้ผู้ดูแลรักษาท่านเข้าใจอารมณ์ความรู้สึกของท่านในขณะเจ็บป่วยได้ดีขึ้น กรุณาอ่านข้อความแต่ละข้อและทำเครื่องหมายถูกในช่องคำตอบที่ใกล้เคียงกับความรู้สึกของท่าน ในช่วง 1 สัปดาห์ที่ผ่านมา มากที่สุด และกรุณาตอบทุกข้อ

	คะแนน		**คะแนน**
1. ฉันรู้สึกตึงเครียด		2. ฉันรู้สึกเพลิดเพลินใจกับสิ่งต่างๆ ที่ฉันเคยชอบได้	
( ) เป็นส่วนใหญ่	3	( ) เหมือนเดิม	0
( ) บ่อยครั้ง	2	( ) ไม่มากเท่าแต่ก่อน	1
( ) เป็นบางครั้ง	1	( ) มีเพียงเล็กน้อย	2
( ) ไม่เป็นเลย	0	( ) เกือบไม่มีเลย	3
3. ฉันมีความรู้สึกกลัว คล้ายกับว่ากำ ลังจะมีเรื่องไม่ดีเกิดขึ้นต่างๆได้		4. ฉันสามารถหัวเราะและมีอารมณ์ขันในเรื่องต่างๆได้	
( ) มี และค่อนข้างรุนแรงด้วย	3	( ) เหมือนเดิม	0
( ) มี แต่ไม่มากนัก	2	( ) ไม่มากนัก	1
( ) มีเพียงเล็กน้อย และไม่ทำ ให้กังวลใจ	1	( ) มีน้อย	2
		( ) ไม่มีเลย	3
( ) ไม่มีเลย	0		
5. ฉันมีความคิดวิตกกังวล		6. ฉันรู้สึกแจ่มใสเบิกบาน	
( ) เป็นส่วนใหญ่	3	( ) ไม่มีเลย	3
( ) บ่อยครั้ง	2	( ) ไม่บ่อยนัก	2
( ) เป็นบางครั้ง แต่ไม่บ่อย	1	( ) เป็นบางครั้ง	1
( ) นานๆครั้ง	0	( ) เป็นส่วนใหญ่	0

7. ฉันสามารถทำ ตัวตามสบาย และรู้สึกผ่อนคลาย

( ) ได้ดีมาก 0
( ) ได้โดยทั่วไป 1
( ) ไม่บ่อยนัก 2
( ) ไม่ได้เลย 3

8. ฉันรู้สึกว่าตัวเองคิดอะไร ทำ อะไร เชื่องช้าลงกว่าเดิม

( ) เกือบตลอดเวลา 3
( ) บ่อยมาก 2
( ) เป็นบางครั้ง 1
( ) ไม่เป็นเลย 0

9. ฉันรู้สึกไม่สบายใจ จนทำ ให้ปั่นป่วนในท้อง

( ) ไม่เป็นเลย 3
( ) เป็นบางครั้ง 2
( ) ค่อนข้างบ่อย 1
( ) บ่อยมาก 0

10. ฉันปล่อยเนื้อปล่อยตัว ไม่สนใจตนเอง

( ) ใช่ 3
( ) ไม่ค่อยใส่ใจเท่าที่ควร 2
( ) ใส่ใจน้อยกว่าแต่ก่อน 1
( ) ยังใส่ใจตนเองเหมือนเดิม 0

11. ฉันรู้สึกกระสับกระส่าย เหมือนกับจะอยู่นิ่งๆ ไม่ได้

( ) เป็นมากทีเดียว 3
( ) ค่อนข้างมาก 2
( ) ไม่มากนัก 1
( ) ไม่เป็นเลย 0

12. ฉันมองสิ่งต่างๆในอนาคต ด้วยความเบิกบานใจ

( ) มากเท่าที่เคยเป็น 0
( ) ค่อนข้างน้อยกว่าที่เคยเป็น 1
( ) น้อยกว่าที่เคยเป็น 2
( ) เกือบจะไม่มีเลย 3

13. ฉันรู้สึกผวาหรือตกใจขึ้นมาอย่างกะทันหัน

( ) บ่อยมาก 3
( ) ค่อนข้างบ่อย 2
( ) ไม่บ่อยนัก 1
( ) ไม่มีเลย 0

14. ฉันรู้สึกเพลิดเพลินไปกับการอ่านหนังสือ ฟังวิทยุ หรือดูโทรทัศน์ หรือกิจกรรมอื่นๆที่เคยเพลิดเพลินได้

( ) เป็นส่วนใหญ่ 0
( ) เป็นบางครั้ง 1
( ) ไม่บ่อยนัก 2
( ) น้อยมาก 3

การคิดคะแนน

อาการวิตกกังวล คิดคะแนนข้อคี่ทั้งหมด (1, 3, 5, 7, 9, 11, 13) รวมกัน

อาการซึมเศร้า คิดคะแนนข้อคู่ทั้งหมด (2, 4, 6, 8, 10, 12, 14) รวมกัน

APPENDIX G

Thai-version of Pain Catastrophizing Scale (PCS)

ในช่วงชีวิตหนึ่ง ทุกคนเคยมีประสบการณ์ความปวด ซึ่งอาจมีตั้งแต่ ปวดศีรษะ ปวดฟัน ปวดข้อและกล้ามเนื้อ โดยส่วนใหญ่คนทั่วไปมักเผชิญกับสถานการณ์ที่อาจเป็นสาเหตุให้เกิดความปวด เช่น ภาวะเจ็บป่วย การได้รับ บาดเจ็บ การทำฟัน หรือการผ่าตัด

คณะผู้วิจัยสนใจความคิดและความรู้สึกของท่าน เมื่อท่านมีความปวด ข้อความ 13 ข้อด้านล่าง คือ ข้อความที่ อธิบายความแตกต่างของความคิดและความรู้สึกที่อาจเกี่ยวข้องกับความปวด ขอให้ท่านให้คะแนน 0 ถึง 4 คะแนนในข้อความแต่ละข้อ เพื่อบอกระดับความคิดและความรู้สึกเหล่านั้นต่อความปวด

0 –ไม่มีเลย 1-เล็กน้อย 2-ปานกลาง 3-ส่วนมาก 4-ตลอดเวลา

เมื่อฉันมีความปวด

1☐ ฉันกังวลตลอดเวลาว่าความปวดจะสิ้นสุดหรือไม่

2☐ ฉันรู้สึกว่าฉันไม่สามารถจะทำอะไรต่อไปได้

3☐ มันแย่มาก และฉันคิดว่ามันคงไม่มีทางที่จะดีขึ้น

4☐ มันเลวร้ายและทำให้ฉันรู้สึกทุกข์ทรมาน

5☐ ฉันรู้สึกว่าฉันทนไม่ได้อีกแล้ว

6☐ ฉันกลัวว่าความปวดจะรุนแรงขึ้น

7☐ ฉันคิดเกี่ยวกับเหตุการณ์ความปวดอื่นๆอยู่ตลอดเวลา

8☐ ฉันรู้สึกร้อนใจอยากให้ความปวดหายไป

9☐ ฉันไม่สามารถสลัดความคิดเกี่ยวกับความปวดออกจากใจฉันได้

10☐ ฉันคิดอยู่เสมอว่ามันเจ็บปวดมาก

11☐ ฉันคิดอยู่เสมอว่าฉันต้องการให้ความปวดสิ้นสุดลง

12☐ ฉันทำอะไรไม่ได้เลยที่จะลดความรุนแรงของความปวด

13☐ ฉันสงสัยว่าจะมีสิ่งที่ร้ายแรงเกิดขึ้น .....***รวม***

APPENDIX H

Thai-version of Pittsburgh Sleep Quality Index (PSQI)

คำแนะนำ โปรดทำเครื่องหมาย / หรือเติมข้อความในช่องว่างแต่ละข้อที่ตรงกับ การนอนหลับส่วนใหญ่ของท่าน ในระยะ 1 เดือนที่ผ่านมา (กรุณาตอบทุกข้อ)

1. ท่านมักเข้านอนเวลาประมาณ.....น.
2. ท่านต้องใช้เวลานานประมาณเท่าไร ตั้งแต่เข้านอนจนหลับไปประมาณ.....นาที
3. ปกติท่านลุกจากที่นอนเช้า เวลาประมาณ.....น.
4. ปกติท่านนอนหลับได้คืนละ.....ชั่วโมง (จำนวนชั่วโมงอาจจะแตกต่างจากจำนวนชั่วโมงตั้งแต่เริ่มเข้านอนจนถึงตื่นนอน

5. ท่านมีปัญหาเกี่ยวกับการนอนหลับเนื่องจากสาเหตุเหล่านี้บ่อยเพียงใด	ไม่เลย	<1 ครั้ง/สัปดาห์	1-2 ครั้ง/สัปดาห์	> 3 ครั้ง/สัปดาห์
5.1 นอนไม่หลับหลังจากเข้านอนไปแล้วนานกว่า 30 นาที				
5.2 ตื่นกลางดึกหรือตื่นช้ากว่าปกติ				
5.3 ตื่นเข้าห้องน้ำ				
5.4 หายใจขัด				
5.5 ไอ				
5.6 รู้สึกหนาวเกินไป				
5.7 รู้สึกร้อนเกินไป				
5.8 ฝันร้าย				
5.9 เจ็บหรือปวดตามตัว				
5.10 สาเหตุอื่น ๆ ถ้ามีระบุ.....				
6. ท่านใช้ยานอนหลับ (จะโดยแพทย์สั่งหรือซื้อเอง) เพื่อช่วยในการนอนหลับบ่อยครั้งเพียงใด				
7. ท่านรู้สึกง่วงนอนหรือเผลอหลับขณะทำกิจกรรมประจำวันเช่น กินอาหาร ทำงานบ้าน นั่งคุยกับเพื่อน เป็นต้นบ่อยเพียงใด				
	ไม่เป็นปัญหา	เป็นปัญหาบ้างเล็กน้อย	เป็นปัญหาพอสมควร	เป็นปัญหามาก
8.ท่านรู้สึกมีปัญหาเกี่ยวกับความกระตือรือร้นในการทำงานให้เสร็จลุล่วงไปด้วยดีหรือไม่อย่างไร				
	ดีมาก	ดี	ไม่ค่อยดี	ไม่ดีเลย
9. ในระยะ 1 เดือนที่ผ่านมา ท่านคิดว่าคุณภาพการนอนโดยรวมของท่านเป็นอย่างไร				

คะแนน 0 – 21 คะแนน

≤ 5 คะแนน คุณภาพการนอนดี

> 5 คะแนน คุณภาพการนอนไม่ดี

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