ความชุกของอาการปวดเท็มโพโรแมนดิบิวลาร์ดิสออเดอร์เรื้อรังและโรคร่วมในกลุ่มตัวอย่างผู้ป่วยไทย - การศึกษาแบบตัดขวาง

นางสาวชา ทู วิน

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
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PREVALENCE OF CHRONIC TEMPOROMANDIBULAR DISORDER PAIN AND COMORBIDITIES I N A GROUP OF THAI PATIENT: A CROSS SECTIONAL STUDY

Miss Tra Thu Nguyen

A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science Program in Occlusion and Orofacial Pain
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ชา ทู วิน : ความชุกของอาการปวดเท็มโพโรแมนดิบิวลาร์ดิสออเดอร์เรื้อรังและโรคร่วมในกลุ่มตัวอย่างผู้ป่วยไทย - การศึกษาแบบตัดขวาง (PREVALENCE OF CHRONIC TEMPOROMANDIBULAR DISORDER PAIN AND COMORBIDITIES IN A GROUP OF THAI PATIENT: A CROSS SECTIONAL STUDY) อ.ที่ปรึกษาวิทยานิพนธ์หลัก: รศ. ทญ. สุขนิภา วงศ์ทองศรี, อ.ที่ปรึกษาวิทยานิพนธ์ร่วม: ผศ. ทญ. ดร. กนกพร พะลัง, หน้า.

วัตถุประสงค์: 1. สำรวจความชุกของเท็มโพโรแมนดิบิลาร์(ทีเอ็มดี)เรื้อรังและโรคร่วมในกลุ่มผู้ป่วยไทย 2. ประเมินความสัมพันธ์ระหว่างค่าพารามิเตอร์ของความปวด (ระยะเวลาของความปวด ระดับความปวด และความถี่ของความปวด) กับจำนวนโรคร่วมและดัชนีการกระจายอาการปวดทั่วร่างกาย (ดับบลิวพีไอ) ในผู้ป่วยทีเอ็มดี และ 3. ประเมินความสัมพันธ์ระหว่างการปรากฏความเรื้อรังกับประวัติครอบครัวของผู้ป่วยทีเอ็มดี

วิธีการ: ศึกษาภาคตัดขวางในผู้ป่วยนอกจำนวน 351 คน ผู้ป่วยได้รับแบบสอบถามชนิดสัมภาษณ์ซึ่งประกอบ ด้วย 4 ส่วน (ข้อมูลพื้นฐาน ค่าพารามิเตอร์ของความปวด ค่าดับบลิวพีไอ และการวินิจฉัยโรคร่วม) การวินิจฉัยทีเอ็มดีทำตามเกณฑ์การวินิจฉัยทีเอ็มดี ใช้สัมประสิทธิ์สหสัมพันธ์แบบสเปียร์แมนและการวิเคราะห์การถดถอยเชิงเส้นและการทดสอบไคสแควร์ โดยใช้นัยสำคัญที่ระดับ $p<0.05$

ผลการศึกษา: ร้อยละ 25 มีอาการปวดเรื้อรัง ร้อยละ 82 ของผู้ป่วยปวดเรื้อรังมีอาการโรคร่วมอย่างน้อยหนึ่งอย่าง จำนวนของโรคร่วมสัมพันธ์กับระยะเวลาของความปวด ($p= 0.02$) และค่าดับบลิวพีไอสัมพันธ์กับระยะเวลาของความปวดและระดับความปวด ($p<0.001$) การปวดทีเอ็มดีเรื้อรังไม่สัมพันธ์กับประวัติครอบครัว (OR = 1.31; 95% CI= 0.78-2.21)

สรุป: การปรากฏโรคร่วมพบได้บ่อยในผู้ป่วยทีเอ็มดีเรื้อรัง ระยะเวลาของความปวดเป็นปัจจัยที่เหมาะสมในการทำนายการปรากฏโรคร่วมหรือการกระจายอาการปวด ระดับความปวดสามารถใช้ทำนายการปรากฏการกระจายความปวดได้แต่ระดับความเชื่อถือได้ยังไม่ชัดเจน

ภาควิชา ทันตกรรมบดเคี้ยว ลายมือชื่อนิสิต .....

สาขาวิชา ทันตกรรมบดเคี้ยวและความเจ็บปวดช่องปากและใบหน้า ลายมือชื่อ อ.ที่ปรึกษาหลัก .....

ลายมือชื่อ อ.ที่ปรึกษาร่วม .....

ปีการศึกษา 2560

5875810532 : MAJOR OCCLUSION AND OROFACIAL PAIN
KEYWORDS: COMORBIDITIES / CROSS-SECTIONAL STUDIES / PAIN PARAMETERS / QUESTIONNAIRES / TMD PAIN

TRA THU NGUYEN: PREVALENCE OF CHRONIC TEMPOROMANDIBULAR DISORDER PAIN AND COMORBIDITIES IN A GROUP OF THAI PATIENT: A CROSS SECTIONAL STUDY. ADVISOR: ASSOC. PROF. SUKNIPA VONGTHONGSRI, CO-ADVISOR: ASST. PROF. KANOKPORN BHALANG, Ph.D., pp.

Objectives: 1. to investigate the prevalence of chronic temporomandibular disorder (TMD) and its comorbidities in a group of Thai patients; 2. to evaluate the relationship between pain parameters (pain duration, pain intensity, and pain frequency) with the number of comorbidities and widespread pain index (WPI); 3. to assess the relationship between the presence of chronic pain with familial history in TMD pain patients. Methods: A cross-sectional study was undertaken of 351 outpatients. Patients were given an interviewer-administered questionnaire which contained four parts (demographic data, pain parameters, WPI and comorbidities diagnosis). Diagnosis was made in accordance with Diagnostic Criteria for Temporomandibular Disorder. Spearman rank correlation coefficient linear regression, and Chi-square test were used, with a significance level of $p \leq 0.05$. Results: 25% reported chronic pain. 82% of chronic pain patients had at least one comorbidity. The number of comorbidities was associated with pain duration ($p = 0.02$); WPI was related to pain duration and pain intensity ($p < 0.001$). The presence of chronic TMD pain was not related to familial history (OR = 1.31; 95% CI = 0.78 – 2.21). Conclusions: The presence of comorbidity was prevalent in chronic TMD pain patients. To predict the presence of comorbidities or spreading pain presence, pain duration is a feasible factor. Pain intensity can be used to predict the presence of spreading pain, but its reliability is not clear.

Department:	Occlusion	Student's Signature .....
Field of Study:	Occlusion and Orofacial Pain	Advisor's Signature .....
		Co-Advisor's Signature .....
Academic Year:	2017	

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CONTENTS

Page

Page

CHAPTER I: INTRODUCTION

Chronic pain is defined as the pain which lasts longer than acceptable healing time (3 to 6 months) (1). In recent years, chronic pain has been becoming one of major health problems all over the world (2). According to the National Institute of Health (NIH), approximately 25.5 million adults in the United States were facing chronic pain in 2012, and this figure increased up to 100 million in 2014 (2). Not only the pain itself but the patients with chronic pain also commonly report multiple comorbid painful diseases and spreading pain condition resulting to change of the view of chronic pain from a persistent symptom to a complex condition (3, 4). Although the number of chronic pain patient increases annually, controlling chronic pain is still a big challenge due to lack of specific effective approach. NIH recommends that discovering factors or causes which can influence the appearance of chronic pain and comorbidities can help clinicians in pain management. Predictions regarding these factors need to be based on significant discrepancies in the prevalence of chronic pain and comorbidities among strata and populations.

Among seven types of chronic pain which are classified by The International Association for the Study of Pain (namely chronic primary pain, chronic cancer pain, chronic postsurgical and posttraumatic pain, chronic headache and orofacial pain, chronic neuropathic pain, chronic musculoskeletal pain, and chronic visceral pain), chronic orofacial pain is directly related to dentistry, and temporomandibular

disorders (TMD) pain is considered to be the major cause of non-odontogenic-related orofacial pain (5).

The aims of this study were to (i) investigate the prevalence of seven comorbidities in Thai chronic TMD pain patients; (ii) assess several potential contributing factors in the relationship with the appearance of chronic pain, comorbidities, and the spreading pain.

Definition

Pain, following the IASP, is defined as an "unpleasant sensory or emotional experience associated with actual or potential tissue damage or described in terms of such damage." Orofacial pain is the pain perceived in orofacial areas (6).

Chronic pain is pain which persists at least for three months, and usually longer than the essential healing time (7).

Temporomandibular disorders, in the guideline of the American Academy of Orofacial Pain (AAOP), is defined as all functional disturbances of joints and muscles of the masticatory system (8).

Chronic temporomandibular disorder pain is chronic orofacial pain which occurs in the masticatory system and is associated with masticatory disturbance.

Sensitization is the increase in response of noxious sensory neurons with stimulations. It is represented by a reduced pain threshold or spontaneous pain (9).

Comorbidity, medically speaking, is the situation in which two or more health

problems derived from a disease in an individual (10). Studies on general chronic pain concentrate on two main types of comorbidity: physical and psychological. In this study, researchers focus on the mechanism of the progress from acute pain, to chronic pain, then spreading pain and comorbidities, so only physical comorbidities will be concerned.

Research questions

What is the prevalence of chronic TMD pain and its comorbidities in a group of patients in Thailand? Do the pain parameters influence on the development of spreading pain and comorbidities in TMD pain patients? Does the familial history with chronic pain influence on the presence chronic TMD pain?

Objectives

Objective 1: To assess the prevalence of chronic TMD pain and seven comorbidities (frequent headache, chronic fatigue syndrome, chronic low-back pain, chronic pelvic pain, irritable bowel syndrome, interstitial cystitis) in a group of Thai patients.

Objective 2: To investigate the relationship between pain parameters (pain duration, pain intensity, pain frequency) and the development of spreading pain in both chronic and acute TMD pain patients.

Hypothesis: The Widespread Pain Index (WPI) would be positively associated with pain duration, pain intensity, and pain frequency.

Objective 3: To investigate the relationship between pain parameters and the

developing of comorbidities in chronic TMD pain patients.

Hypothesis: The number of comorbidities would be positively associated with pain duration, pain intensity, and pain frequency

If pain parameters are related to WPI and the number of comorbidities, we will predict the probability of spreading pain and comorbidities in TMD pain patients.

Objective 4: To evaluate the relationship between the familial history with chronic pain and the presence of chronic TMD pain in TMD patients.

Hypothesis: The presence of chronic pain diseases is more common in the family of chronic TMD pain patients.

Expected benefit

The knowledge from this study will help clinicians to estimate the severity and complexity of TMD pain patients by reported pain parameters. Hence, the clinicians can choose appropriate therapies, and cooperate with others if necessary to provide adequate care to patients.

Research design: Cross-sectional study

CHAPTER II: LITERATURE REVIEW

Pain and chronic pain

In the past, the pain was defined as an uncomfortable sensation which is a response to injury and tissue damage (i.e., a noxious stimulation) (11). Based on this definition, when injured tissues were healed, the pain would disappear. However, in fact, the pain can persist after physical healing or occurs not associate with the appearance of tissue damage. Therefore, from 1979, the definition was replaced by International Association for the Study of Pain (IASP) to “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." This change allows the pain to occur without visible causes (7). Physiologically, pain can be considered as the physical alarm which cautions us against potential damages. Pathologically, when the pain lasts too long, it loses the physiological meaning and becomes a chronic disease that interferes patient’s functions. What are the criteria to differentiate between physiological pain and chronic pain?

According to IASP, pain is classified to three groups by duration. Acute pain is the pain that lasts within 2 weeks; subacute is the pain that lasts 2 weeks to < 3 months; and chronic pain is the pain that lasts 3 months or longer (7). Acute pain comes with specific causes, with a clear progress in quality. It can be intense in the beginning or within a week, then subsides with the reduction of the causes and eventually disappears after healing. The causes of acute pain are identifiable, include

inflammation, injury, trauma or surgery (12). Neurologically, acute pain is caused by the activation of consecutive neurons (13).

On the other hand, chronic pain tends to recur. It commonly is dull pain in quality, with worsening and remission periods present alternatively. The chronic pain usually lasts for at least 3 months, without somatic causes (7). In the past, patients who report persistent pain were ascribed with psychological problems (14). Recently, chronic pain was more likely to be related to maladaptation in the nervous system. The underlying etiology of the chronic pain is central sensitization (12).

Sensitization

Sensitization is characterized by an enhancement of neuronal response to a group of stimulation (15). In the pain field, sensitization is referred to the pain which is not evoked by the noxious stimulus (allodynia, spontaneous pain), or is much more than the level of stimulus (hyperalgesia) (9). Sensitization in pain can occur in both peripheral or central nervous system. While the inflammatory pain was related to peripheral sensitization (16), chronic pain diseases and the developing of spreading pain or comorbidities are associated with central sensitization (9).

The mechanisms of peripheral sensitization are reducing threshold of receptors through phosphorylation and increase receptor expression through protein kinase pathways. In peripheral sensitization, after receiving noxious stimulation, the free nerve endings secrete substance P and CGRP which are contained inside the vesicles in the free nerve endings. Substance P and CGRP then vasodilate adjacent

blood vessels and recruit macrophages as well as neutrophils. Substances secreted from these cell activate other nerve endings then expand the pain (16). The result of this mechanism is the neurogenic inflammation due to the local response including vasodilation and pain. The subsequence of nociceptor activation is the activation of protein kinase A (PKA) and protein kinase C (PKC) pathways in the postsynaptic neurons, leading to enhance the expression of Na^+ channels (17) and Na^+ channels phosphorylation. Phosphorylation Na^+ channel is a biochemical process which adds phosphate groups to the structure of the channels, resulting in prolonging the opening periods of the channels. This process allows more ionic currents pass into neurons and reduce the polarized condition of neurons, finally reduce threshold of Na^+ channels (18, 19) (Figure 1).

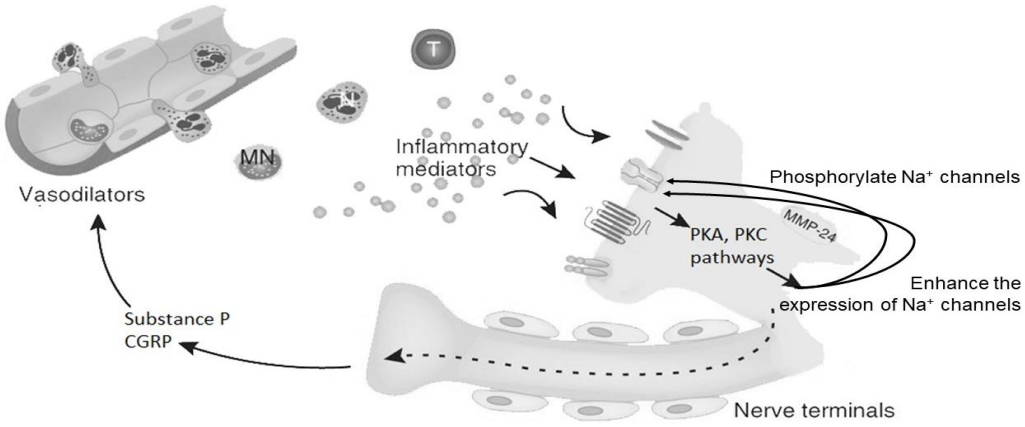


Figure 1: Inflammatory substances activate receptors:
G-couple protein receptor -> activation PKA, PKC pathway -> phosphorylate and modulate the synthesis and expression of Na^+ channels. Picture was modified from (20).

Central sensitization is defined as an amplification of neural signaling within the central nervous system and consists of three mechanisms: the anatomical connection of pain pathways, the long-term potentiation, and the activation brain areas of pain (21-24). The first mechanism is the normal anatomical characteristic of the sensory system in which the upper order neurons relay input signal from many lower neurons, leading to a poor localization toward the source of pain (23). The hyperalgesia occuring in the region not including the zone of injury is called secondary hyperalgesia (Figure 2). The secondary hyperalgesia may occur in skin, muscles, joints, or even viscera (22).

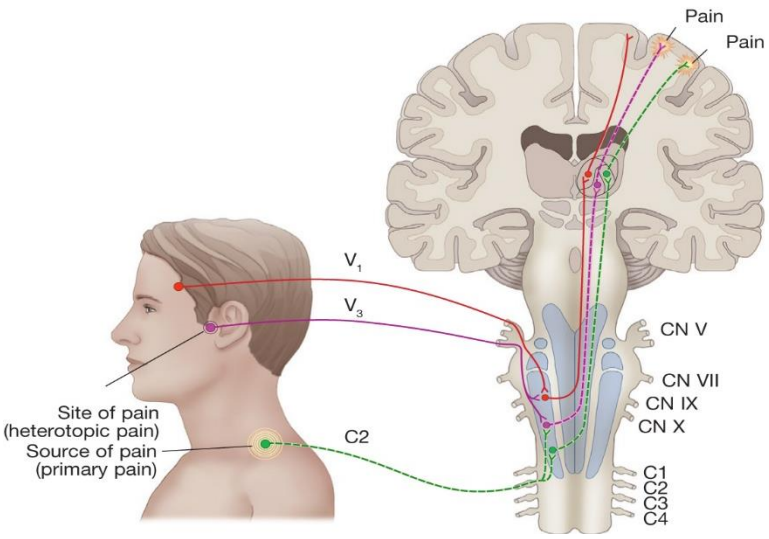


Figure 2: Anatomical connection in pain pathway leads to a poor localization toward the source of pain. Picture was adopted from (23).

The second mechanism is the long-term potentiation of NMDA receptors (15). Long-term potentiation (LTP) is one form of neuroplastic change which increases synaptic efficacy, then smoothen the response of a neuron to a particular stimulation (21). Physiologically, LTP is very common in forming memory, and contribute to the development of complex skills which require fast responses (such as movement of

fingers in playing piano, or learning a new language) (15). To induce LTP, an enough amount of stimulation (about frequency, and duration) is required (25). NMDA and AMPA are nociceptors for glutamate in pain pathway. While AMPA is selectively permeable with K^+ and Na^+ ion, NMDA is permeable to all positive charge ions including K^+, Na^+, Ca^{2+}. In resting membrane potential, NMDA receptors are blocked by Mg^{2+} ions. Glutamate released in synaptic cleft opens APMA of postsynaptic cell first, then the Na^+ influx increases the membrane potential. At the potential which is close to action potential, Mg^{2+} ions start to be expelled from NMDA and open the NMDA receptors, then allow Ca^{2+} current flows into the cell. Inside the cell, Ca^{2+} activates adenyl cyclase to synthesize cAMP. cAMP is an important secondary messenger type which activates PKA and PKC pathway (Figure 3).

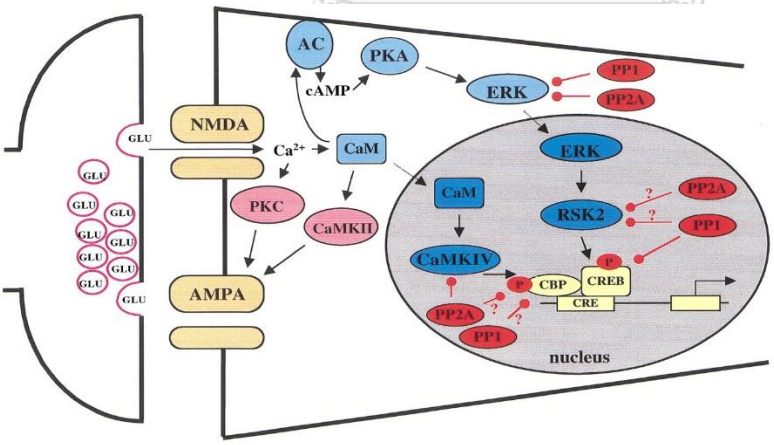


Figure 3: Ca2+ pass NMDA, and activate PKA and PKC pathway. These pathways modulate transcription and protein synthesis. Source of picture (26).

The results of PKA and PKC pathways are increasing expression of nociceptors (Figure 4), forming new dendrites (Figure 4), and phosphorylation Na+ channels (Figure 5) which prolong excitatory period and decrease threshold of neurons. Addition to activation of adenyl cyclase, activated NMDA receptors also interact with

postsynaptic density (PSD) proteins (25). PSD proteins can modulate functions of glutamate receptors and the insertion or removal cell membrane, then modulate the expression of receptors (Figure 6) (25). LTP was shown to be related to the increase of forming new dendrites connecting between cells, increase the amount of neurotransmitter released from presynaptic neurons (25). The consequences of LTP of NMDA lead to the reduction of receptor threshold, increasing of the receptor expression, expanding of the connection between neurons, and increasing neurotransmitter secretion (25).

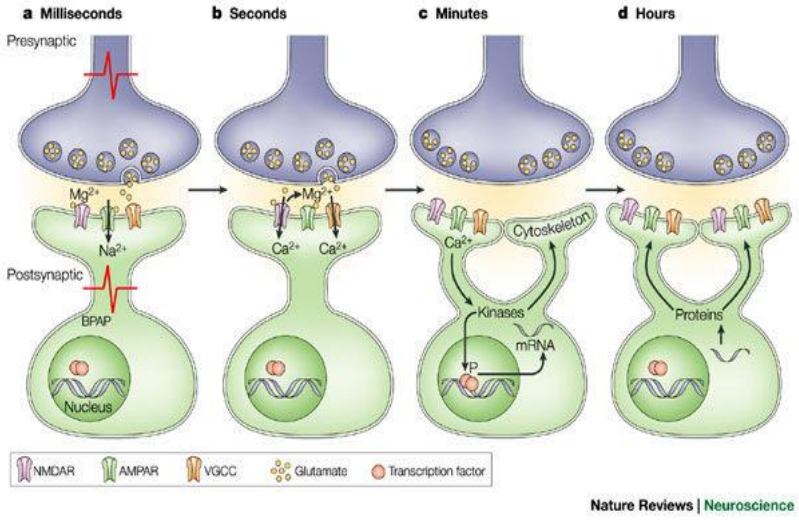


Figure 4: LTP leads to forming dendrites connecting between neurons, enhance receptor expression (27).

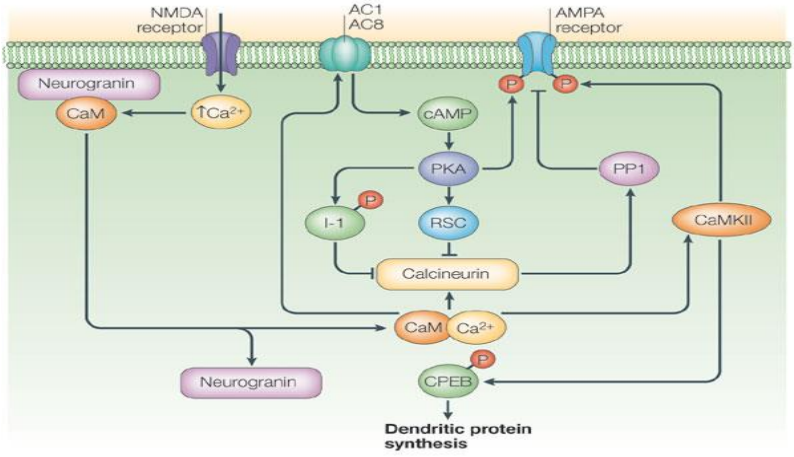


Figure 5: LTP leads to Na+(Sodium) channels phosphorylate. Source of picture (28).

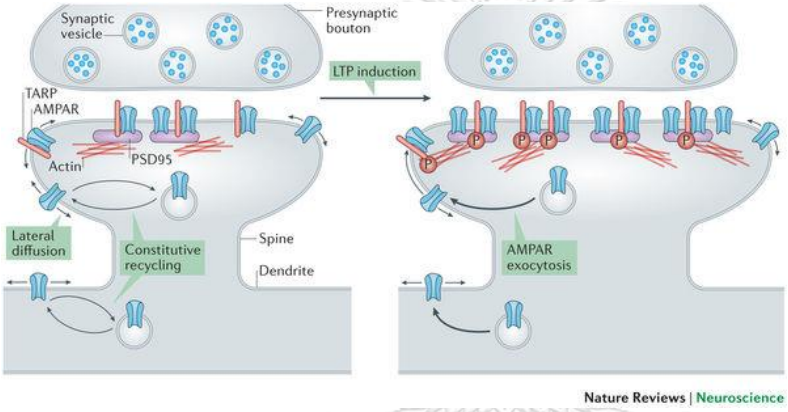


Figure 6: LTP modulates the expression of receptor through PSD protein (29).

The third mechanism is that the pain can stimulate not only sensory cortex but also other pain related to brain areas (13, 21). Pain input signal is transferred by three pathways: neo-spinothalamic tract, paleo-spinothalamic tract, and the archi-spinothalamic tract. In the neo-spinothalamic tract, pain signal is relayed in thalamus and sensory cortex which are responsible for interpretation and localization of the pain. In the paleo- spinothalamic and the archi-spinothalamic tracts, the pain signal is relayed in the cortex areas which are responsible for pain-related response including emotion, autonomic response, memory, and motor action (30). Hence, this widely activation leading to neuroplastic changes occurs not only in sensory cortex but also

in the related brain areas (13). Consequently, the result of the neuroplasticity in pain-related areas is disorders in the organs that are controlled by these areas (30-32). The neuroplastic changes may occur in the structure of the brain, or switch the way the brain response to pain (30). Specifically, there are two reviews summarized the results of imaging studies which aimed to compare the activity of the brain between acute and chronic pain patients (30, 31). The reviews summarized that, in acute pain patients, the most activated areas were primary sensory cortex (S1), secondary sensory cortex (S2), anterior cingulate cortex (ACC), insular cortex (IsC), prefrontal cortex (PFC), thalamus, and amygdala. Among these brain areas, thalamus, S1, and S2 are responsible for pain perception, while ACC, IsC, PFC, and amygdala are responsible for emotion. For the patients having pain duration of 2 months, the most activated brain areas were thalamus, ACC, IsC, PFC. For patients who have pain for 10 years, the most activated areas were ACC and PFC (30, 31). These findings showed that the brain switches the response way to pain from "sensory" to "emotion and mood." Structural changes such as the remodeling of neurons and receptors, selective death of GABAergic neurons; decrease of opioid receptors (31), the reduction of grey matter in pre-frontal cortex and insula (33, 34) lead to loss of pain modulation (Figure 7).

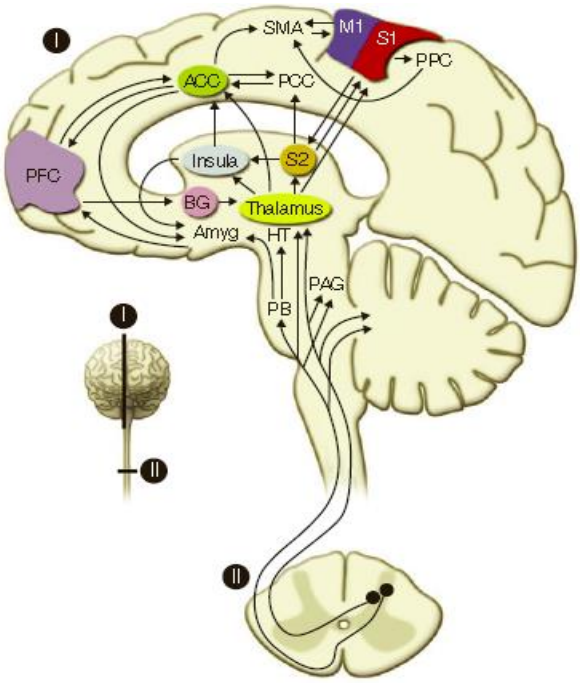


Figure 7: Brain areas receive pain signals:
Anterior cingulate cortex (ACC), amygdala, hypothalamus (HT), posterior cingulate cortex (PCC), prefrontal cortex (PFC), insula, primary (S1) and secondary (S2) somatosensory cortex, etc. Picture is adopted from (13).

Comorbidities and spreading pain in TMD pain patients

In the US, 80% of TMD pain patients had spreading pain condition (35, 36). The most frequent pain sites were neck, shoulder and back (35, 37). The spreading pain was reported in patients who experienced orofacial pain for just a week (38). Moreover, comorbidities appearance is frequently reported in chronic TMD pain patients (39). Seven common comorbidities in chronic TMD pain include frequent headache (HD), chronic low-back pain (LB), chronic pelvic pain (PV), chronic fatigue syndrome (CFS), irritable bowel syndrome (IBS), fibromyalgia (FB), and interstitial cystitis (IC) (32). Although the relationship between these comorbidities and chronic TMD pain is unclear, their relationship was supported by several epidemiological studies. Specifically, TMD pain patients have 5 to 10 times higher risk of headache, two times higher risk of back pain (40, 41). Patients with IBS have 7 times higher risk

of TMD; reversely, TMD patients have 3 times higher risk of IBS (42, 43). The prevalence CFS in TMD patients vary from 10 to 43%, compared to only 1% in general population (44). Pelvic pain, headache, back pain and fibromyalgia were considered as the potential risks of developing TMD (45-48).

Contributing factors of central sensitization

The pain itself is considered as the most important factor affecting on central sensitization. Duration, frequency, and amplitude of the stimulus are found to be positive related to the LTP mechanism (24, 25).

Pain duration: The LTP needs an adequate time to be induced. The longer stimulus exists, the more results of LTP accumulate. Consequences are more sensitized receptors leading to persistent pain sensation; more new dendrites formation leading to the spreading of pain; more neuroplastic changes leading to more disorders in other organs (24, 25).

Pain intensity and pain frequency: The higher amplitude or the higher frequency stimulus will recruit more neurons to transmit the signal; as a result, more receptors will be in LTP and more results of LTP (24, 25).

Potential factors which can affect pain, spreading pain and comorbidities

Gender: the effect of gender on central sensitization is unclear. However, females are suggested to be more susceptible to pain and usually, to be reported to have higher pain intensity (49). Females also have a higher prevalence of chronic pain disease than male (39). In a study conducted in the United States, among TMD pain

patients, females were more likely to have spreading pain than male (35, 36).

Age: Previous studies suggested that older people are more susceptible to pain (49), as well as some chronic diseases (50). The prevalence of some comorbidities in TMD patients is related to age. For example, the prevalence of headache was the highest at around age 40 and reduce at the age 50 to 60, or the prevalence of knee and neck is significantly higher in older people, around age 60 (36).

Race, culture: Culture and race were demonstrated to be related to pain intensity and the presence of some comorbidities (36, 37, 51). For example, Africans are reported to have higher pain intensity, pain-related disability than Europeans (51); TMD patients in Arabic Saudi are reported to have higher prevalence of headache than those in Sweden and Italy, but the prevalence of stomachache is higher in Italy than Saudi or Sweden (37).

Familial history: Several chronic pain diseases were suggested to be related to familial factors, such as migraine (52), familial episodic pain syndrome (53), and rheumatoid arthritis (54).

CHAPTER III: RESEARCH METHODOLOGY

1. Sampling

Samples were collected at the Occlusion Clinic at the Dental Hospital of Chulalongkorn University.

Inclusion criteria: Participants are outpatients with age from 16 to 65 years.

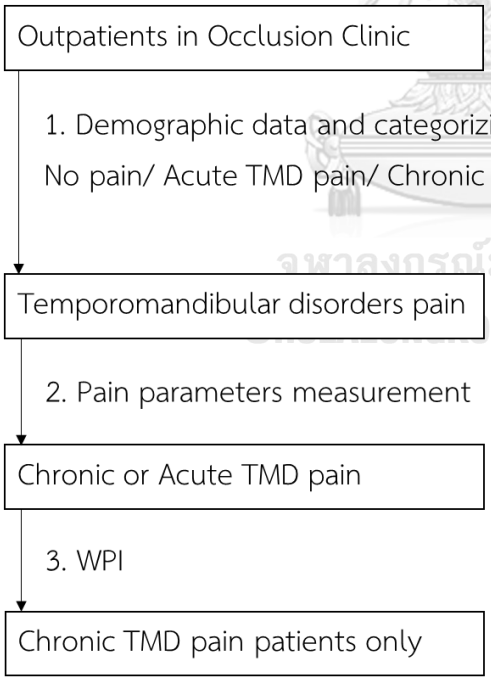
Exclusion criteria: Patients who have chronic pain with identified specific causes (i.e. neuropathic pain, diabetes, hypertension without management, autoimmune disease, cancer, after injuries, after operation) (32). Patients who cannot communicate Thai language fluently, or have mental problems which can interfere understanding ability were also excluded.

Sample size of this study was calculated by G*Power 3.1 with the "testing correlation between two quantitative variables" (55) for a linear regression model with an effect size r = 0.3, significance level α = 0.1, type II error probability β = 0.2. The result of minimum expected sample size was 69 for every regression analysis. The sample size for Chi-square test provides the minimum expected sample size was 64. In conclusion, the sample needed would be at least 69 chronic TMD pain patients.

2. Collecting data process

In this study, the information we need to collect includes: demographic data (age, gender, familial historical), pain parameters (pain duration, pain intensity, and pain frequency), widespread pain index (WPI), and the presence of comorbidities (HD, PB, PV, CFS, IBS, FB, IC). Because the information needs to be collected is different among patients (demographic data for all of outpatients, WPI for both chronic and acute TMD pain patients, comorbidities in chronic pain patients only), we classified participants into three groups before collecting data: 1-No TMD pain; 2-Acute TMD pain; 3-Chronic TMD pain.

Flowchart of collecting data process:



4. Diagnostic questionnaire of seven comorbidities

3. Demographic data and categorizing patients to No TMD pain/ Acute TMD

pain/ or Chronic TMD pain groups

Age, gender and familial history with chronic pain were collected in all of outpatients. The familial history with general chronic pain will be evaluated by one Yes/No question: “Among your parents, grandparents, siblings, and your children, is there anybody facing long-term pain or fatigue? (pain more than 3 continuous months in head, thorax, abdomen, pelvis, lower back, and limbs).

Categorizing patients was based on an interview and clinical examination following Diagnostic criteria for TMD, and the definition of chronic pain of IASP (1), patients were divided to three groups: 1- Chronic TMD pain, 2- Acute TMD pain, and 3- No TMD pain. The patients would be diagnosed with TMD if they reported pain in masticatory muscle and TMJ within 30 days, clinical confirmation was tenderness to palpation in the muscle and TMJ (56). Chronic TMD pain was defined as pain which lasted 3 months or longer, without any interruption of one month or longer. Acute TMD pain was defined as pain less than 3 months, with at least one pain-free month prior to the pain. Patients who did not have history with TMD pain during the past 30 days, and patients who reported tenderness only to palpation, were categorized as “No TMD pain”.

4. Pain parameters measurement

Pain duration was the number of years, months and days with pain. Pain

intensity was evaluated by three first questions of the Thai version of Graded Chronic Pain Scale (57):

1. How would you rate your facial pain on a 0 to 10 scale at present

2. In the past six months, how intense was your worst pain, rated from 0 to 10

3. In the past six months, on average, how intense was your pain rated on a 0-10 scale? (That is your usual pain at times you were experiencing pain).

Pain frequency in this study was assessed as the number of pain days that patients have over a 2-week period.

5. Widespread pain index (WPI)

The WPI was assessed using the pain map of the American College of Rheumatology fibromyalgia questionnaire (58). The map comprises 19 pain sites; they are two facial sides, neck, two shoulder sides, two upper arm sides, two lower arm sides, chest or breast, abdomen, upper back, lower back, two hips or buttock sides, two upper leg sides, and two lower leg sides. The number of comorbid pain site was described as the WPI. To evaluate the level of spreading pain in TMD pain patients, two facial sides were excluded from the WPI, so the WPI ranged from 0 to 17. According to the introduction to the questionnaire, sites which have identified causes

of pain are not included in the WPI. Therefore, participants were asked: “Have you asked your doctor about the cause of the pain? Is there any local disease or injury which can explain your pain?”

6. Diagnostic questionnaires of seven comorbidities

Comorbidities diagnosis – In this study, seven pain comorbidities, namely fibromyalgia (FB), chronic fatigue syndrome (CFS), irritable bowel syndrome (IBS), interstitial cystitis (IC), frequent headache (HD), chronic low-back pain (LB), and chronic pelvic pain (PV), were diagnosed using self-reported questionnaires which are the American College of Rheumatology fibromyalgia questionnaire 2016 (for FB) (58), the Schedule of Fatigue and Anergy/General Physician (for CFS) (59), the ROME III questionnaire (for IBS) (60), and the Pelvic pain and urgency/frequency symptom scale (for IC) (61, 62). HD was diagnosed if it occurred every week for at least 3 months, or every month for at least 10 months (35). PV and LB was diagnosed if the pain was present every month for at least 12 months in the relevant area (35). Particularly, the Thai version of the ROME III questionnaire was employed from The ROME Foundation. Other questionnaires were translated into Thai by a Thai expert who can speak English fluently, then back translated into English by an English native speaker who can speak Thai fluently. To validate the details in the Thai version, every back-translated version was revised by the authors of the questionnaires. The final Thai version was tested with a small group of patients to check their

understanding and cultural acceptance.

Headache questionnaire (Part 3 – Appendix 1): HD was defined as the headache occurred every week for at least 3 months, or every month for at least 10 months. Therefore, patients were asked three questions.

Fibromyalgia questionnaire – American College of Rheumatology fibromyalgia questionnaire (2016): The American College of Rheumatology fibromyalgia questionnaire (ACRFQ) is a diagnostic instrument for fibromyalgia by asking the patients to point out the areas of the body they experienced pain during one week before the questioning time. The original ACRFQ includes two parts. The first part is the pain map which was described in "WPI" (Part 4 – Appendix 1). The second part is "Symptom severity score (SS score)" including part 5 and 6 (Appendix 1). Part 5 has four options for each question, the score for options ranges from 0 to 3, the highest score is 9. Part 6 has 2 choices for each question: "No" equal to 0, "Yes" equal to 1. The highest score is 3. According to the introduction of American College of Rheumatology fibromyalgia questionnaire, subjects will be defined as Fibromyalgia if they have four following criteria:

- WPI ≥ 7 and SS score ≥ 5 OR WPI of 4–6 and SS score ≥ 9.
- Generalized pain which is defined as the pain presents in at least 4 of 5 regions (jaw, chest, and abdominal pain are not included in generalized pain

definition).

- Symptoms have generally been present for at least 3months.
- There are no exclusion criteria for the presence of other illness. Scoring in questionnaire: The possible score ranges from 0 to 31 points. A score equal to 13 or more is consistent with a diagnosis of fibromyalgia.

Chronic fatigue syndrom – Schedule of Fatigue Anergia questionnaire for general practitioners (SOFA/GP)) (Part 7 – Appendix 1): Following the definition of the Centers for Disease Control and Prevention, chronic fatigue syndrome is the condition characterized by severe disabling fatigue, combined with impairment in concentration, short-term memory and sleep disturbances, and musculoskeletal pain for at least 1 month. The SOFA is a proven diagnosis instrument for chronic fatigue syndrome. The questionnaire is divided into two forms, SOFA/CFS for specialist clinics, and SOFA/GP for general health care providers. In this study, SOFA/GP will be used to identify patients with chronic fatigue syndrome. SOFA/GP consists of 10 questions asking about subjective symptoms. The answers include four choices for each question, which are "1: None or a little 2: Some of the time 3: Good part of the time 4: Most of the time". If the patients select the 3rd or 4th choice for a question, examiners will grade that question with a score of 1, while the 1st or 2nd choice will be graded as 0. The total score can be cut off at 2 or 3. Cutting off at 3 was recommended to have the highest specificity (100% at 81% sensitivity) in

excluding non-CFS subjects. Therefore, patients who have a total score ≥ 3 will be classified as chronic fatigue syndrome.

Irritable bowel syndrome – ROME III questionnaire (Part 8 – Appendix 1): The irritable bowel syndrome is diagnosed follow the validated symptom based criteria of ROME Foundation. The criteria include "recurrent abdominal pain or discomfort for at least 3 days/months in the last 3 months with symptom onset for at least 6 months prior to diagnosis, associated with two or more of the following: improvement with defecation; onset associated with a change in frequency of stool; onset associated with a change in form (appearance) of stool.

The symptom criteria are fulfilled for at least 3 months since symptoms onset, or 6 months before diagnosis. According to the criteria of ROME III questionnaire, 8 items are assessed:

- Recurrent abdominal pain or discomfort for at least 3 days/month: Question 1 > 2 or question 2 = 0 or 2 for women.
- Symptom onset for at least 6 months prior to diagnosis: Question 3 = 1.
- Improvement with defecation: Pain or discomfort gets better after defecation at least sometimes: Question 4 > 0.
- Onset associated with a change in frequency of stool: Onset of pain or discomfort associated with more/fewer stools at least sometimes: Question 5, 6> 0.
- Onset associated with a change in form (appearance) of stool: Onset of pain

or discomfort associated with looser/harder stools at least sometimes: Question 7, 8 > 0.

Question 3 is the condition; other questions will be considered if question 3 = 1. Patients will be considered as IBS comorbidity if they have: Question 1 > 2 or question 2 = 0 or 2, accompany with 2 or 3 following criteria: question 4 > 0; question 5 or 6 > 0; question 7 or 8 > 0.

Interstitial cystitis – Pelvic pain and urgency/frequency patient symptom scale (PUF)) (Part 9 – Appendix 1): In clinical examination, the gold standard to diagnose interstitial cystitis (IC) is the potassium sensitivity test (PST). In general screening, PUF designed by Parson et al is considered as an indication diagnosis for IC. In testing the accuracy of PUF in comparison with PST, the sensitivity of PUF varies with levels of 74%, 76%, 91% corresponding to scoring 10 to 14, 15 to 19, and 20 or more, respectively. In this study, a total score of 20 is chosen as the cut-off point; those have a total score of 20 or more will be noted as IC.

Chronic pelvic and lower-back pain (Part 10 – Appendix 1): Chronic back pain is the pain in the low-back area which occurs at least 11 episodes of LBP in the past 12 months. Chronic pelvic pain, in the definition of the IASP, is referred to as the pain related to the pelvis, persisting for 6 months or more. Therefore, chronic pelvic and lower-back pain were evaluated by 2 questions:

- Do you have frequent pain (average 1 time/month) in the pelvic area? If yes, how long have you had it? (include menstruation pain without specific diagnosis)
- Do you have frequent pain (average 1 time/month) in the lower-back area? If yes, how long have you had it?

7. Translation and validation

The Thai version of the ROME III questionnaire was employed from The ROME Foundation. Three other questionnaires (American College of Rheumatology fibromyalgia questionnaire; Schedule of Fatigue Anergia questionnaire for general practitioners; and Pelvic pain and urgency/frequency patient symptom scale) were translated into Thai by a Thai expert who can speak English fluently, then back translated into English by an English native speaker who can speak Thai fluently. To validate the details in the Thai version, every back-translated version was revised by the authors of the questionnaires. The final Thai version was tested with a small group of patients to check their understanding and cultural acceptance.

8. Statistical analysis

Dependent variables were the number of comorbidity and WPI; independent variables comprised the three pain parameters. Pain duration was converted from “year, month, day” to “month” to be consistent for all patients. According to definition of chronic pain, the "pain duration" variable in the chronic pain group was at least 3 months. Pain frequency was calculated by the percentage of pain days in

two weeks. Because pain duration can be < or ≥ 2 weeks, we calculated the pain frequency differently between those that had pain of ≥ 2 weeks, and those that has pain of < 2 weeks:

When pain duration is ≥ 2 weeks:

Pain frequency = (Number of day with pain in 2 weeks) / (14 days) x 100

When pain duration is < 2 weeks

Pain frequency = (Number of day with pain in 2 weeks) / (Pain duration) x 100

Pain intensity was calculated as the mean of three pain scores:

Pain Intensity = (Pain Right Now + Worst Pain + Average Pain) / 3

Because the distribution of the data of three pain parameters and age were not normally distribution, non-parametric analyses were selected. The bivariate association between WPI, the number of comorbidities and each pain parameter, age, gender was analyzed by Spearman rank correlation coefficient. Age and gender were the potential confounders, so the level of significant for them was set < 0.25. The pain parameters and confounders which had significant association with WPI score / the number of comorbidities were included in Multiple linear regression model to analyze the association between pain and WPI score or the number of comorbidities.

The probability of spreading pain or comorbidities was predicted using Binary logistic regression, in which dependent variables were the pain parameters and

confounders being associatied with the number of comorbidities and WPI in Multiple linear regression model.

The relationship between the presence of chronic TMD pain and familial history with chronic pain diseases and was assessed by Chi-square test.

The significance level was set at ≤ 0.05 (except the analysis of confounders)

All statistical analyses were conducted with SPSS for Mac software version 22 (IBM, Armonk, NY).

CHAPTER IV: RESULTS

Demography of participants

From January to August 2017, there were 496 outpatients came to the Occlusion Clinic. We missed 29 patients. There were 98 patients met exclusion criteria (80 were either younger than 16 or older than 65 years old, 1 had HIV, 1 had cancer, 3 had burning mouth syndrome, 2 had rheumatoid arthritis, 1 with Sjogren's syndrome, 1 had IBS, 1 was dumb, 2 had mental problem and could not communicate, 6 were not Thai). 369 patients were eligible for our study; however, 11 of them denied joining our study. We interviewed and provided questionnaires to 358 patients who signed consent form to participate our project. Among 358 received questionnaires, 07 questionnaires were excluded due to missing necessary information (Figure 1). Finally, we got 351 questionnaires from 88 chronic TMD pain patients, 110 acute TMD pain patients, and 153 patients who came for other reasons, e.g. trauma from occlusion, parafunctional habits, and etc.

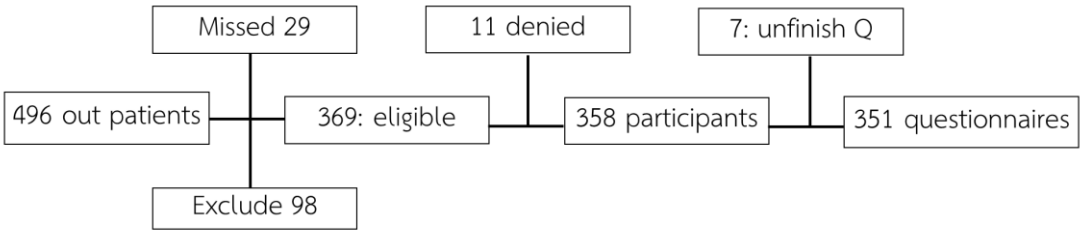


Figure 8: The flow chart of participants

351 patients are aged 16 to 65 years old (mean = 36.6, SD = 14.1), 72.6% were female. All of three groups, chronic TMD pain, acute TMD pain and no TMD pain had insignificant difference of age or percentage of gender compare to the data of total patients. Majority of TMD patients was diagnosed with myalgia, while arthralgia only was the least diagnosis (Table 1).

The reported pain parameters of TMD pain patients are shown in Table 2. The average pain duration of TMD pain patients was 14.4 ± 5.6 months, in which chronic pain group was 31.4 ± 49.2 months, acute pain group was 0.75 ± 0.74 months. The mean pain intensity was 5.6 ± 0.7, and not significantly different between chronic and acute pain groups. The pain frequency (percentage of pain day out of pain duration) was 70.3% ± 36.1, and not significantly different between chronic and acute pain groups.

Table 1: Demographic data and pain type distribution of the study participants.

Group	*n*	*Age*	*Gender: n (%)*		*Myalgia*	*Arthralgia*	*Combined*
			Female	Male			
Chronic TMD pain (≥ 3 months)	88	34.6 ± 12.6	72 (81.8%)	16 (18.2%)	52 (59.1%)	8 (9.1%)	28 (31.8%)
Acute TMD pain (<3 months)	110	33 ± 11.9	79 (71.8%)	31 (28.2%)	67 (60.9%)	19 (17.3%)	24 (21.8%)

No TMD pain	153	40.3 ± 15.5	104 (68%)	49 (32%)
Total	351	36.6 ± 14.1	255 (72.6%)	96 (27.4%)

Table 2: Pain parameters of TMD pain patients.

Group	Pain duration (month)	Pain intensity (0 – 10)	Pain frequency (*"% pain day out of pain duration)*
Chronic TMD pain (≥ 3 months)	31.4 ± 49.2	5.9 ± 1.9	68.5 ± 34.8
Acute TMD pain (<3 months)	0.75 ± 0.74	5.4 ± 1.9	77.6 ± 36.8
Total TMD pain patients	14.4 ± 5.6	5.6 ± 0.7	70.3 ± 36.1

Pain parameters and widespread pain index (WPI)

The number of pain sites were illustrated as a WPI (excluding the two facial sides). Among 198 TMD pain patients, 108 (54.5%) reported spreading pain (Table 3).

Table 3: Prevalence of the presence of comorbidities in chronic and acute TMD pain group and prevalence of spreading pain and the whole TMD pain patients

	Acute TMD pain	*Chronic TMD pain*	*Total*
Widespread pain			
Yes	44 (40%)	64 (72.7%)	108 (54%)
No	66 (60%)	24 (27.3%)	90 (46%)
Comorbidity			
Yes	-	66 (82.5%)	66 (33.3%)
No		22 (17.5%)	132 (67.7%)

Table 4 shows the result of bivariate correlation as well as multiple linear regression analysis between WPI score and three pain parameters. A positive correlation was found between WPI score and pain duration ($p < 0.001$), and pain intensity ($p = 0.005$). Age and gender were determined to be confounders ($p = 0.001$ and 0.16 respectively). The Multiple linear regression model revealed that gender was no longer associated with the WPI ($p= 0.5$). Finally, three variables had sinignificant correlation with WPI were pain duration, pain intensity, and age. The logistic regression analyzing the relation between the presence of spreading pain and pain duration, pain intensity, and age in the total of TMD pain patients provided the function of odd of having spreading pain as:

$$\text{Odd} = e^{0.044*m+0.2*i+0.03*a - 2.3}$$

m: pain duration counted in month

i: pain intensity

a: age of patients

Table 4: Correlation between three pain parameters, two potential confounders and WPI in all TMD pain patients.

		Pain duration	*Pain intensity*	*Pain frequency*	*Age*	*Gender*
Bivariate correlation analysis	R	0.48	0.2	-0.09	0.25	-0.1
	p value	0.00*	0.00*	0.22	0.00*	0.16*
Multiple linear regression model	R	0.05	0.25	-	0.04	0.28
	p-value	0.00*	0.01*	-	0.02*	0.5

The prevalence of comorbidities in chronic TMD pain patients

Among 88 chronic TMD pain patients, the presence of comorbidities was reported by 66 patients (82.5%); 50 females, and 11 males (Table 3). Prevalence of the seven comorbidities is shown in Figure 2. The HD and CFS were two most common comorbidities with prevalence > 40%. PV and LB were the second common comorbidities, with prevalence higher than 30%. IBS and FB were rare comorbidities with the prevalence around 10%. The IC was the rarest with prevalence of only 2.3%.

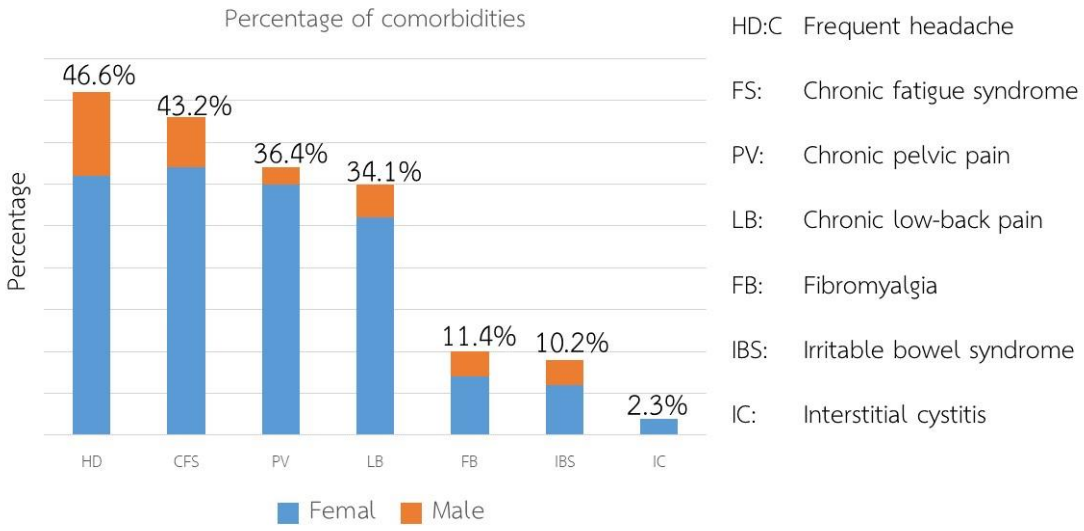


Figure 9: Prevalence of seven comorbidities in chronic TMD pain group.

Pain parameters and the number of comorbidities

The results of Spearman rank bivariate correlation between the number of comorbidities and three pain parameters, as well as two potential confounders (age and gender) was shown in Table 5. Among three pain parameters, only pain duration had a significant correlation with the number of comorbidities ($p = 0.04$). Age was

identified as the confounder (p = 0.02). The Multiple linear regression which analyzed the association between the number of comorbidities and duration with age revealed that age was no longer associated with the number of comorbidities. The logistic regression analyzing the relation between pain duration and comorbidity presence in chronic TMD pain patients provided the function of odd of having comorbidities:

$$Odd = e^{0.028*m+0.524}$$ m: pain duration counted in month

Table 5: Correlation between three pain parameters, two potential confounders and the number of comorbidities in the chronic TMD pain group

		Pain duration	*Pain intensity*	*Pain frequency*	*Age*	*Gender*
Bivariate correlation analysis	R	0.22	0.00	0.08	0.25	0.06
	p-value	0.04*	0.99	0.46	0.02*	0.61
Multiple linear regression model	R	0.01			0.02	
	p-value	0.05*	-	-	0.18	-

The presence of chronic TMD pain and familial history with chronic pain disease

The result of Chi-square test showed that there was no significant difference in familial history with chronic pain diseases between chronic TMD pain patients and acute TMD pain patients (p = 0.38). Odd ratio of having positive familial history with chronic pain disease between patients with chronic TMD pain and those with acute pain was 1.31 (95% confidence interval was 0.78 – 2.21).

CHAPTER V: DISCUSSION

Validation of questionnaire

In our study, the main research tool was a questionnaire for TMD pain parameters, WPI and comorbidities. These measurements of the three pain parameters have acceptable validity and reliability (63). The WPI question was the pain map in the American College of Rheumatology fibromyalgia questionnaire 2016, with good reliability and validity (58). The seven comorbidities in our study were frequent headache (HD), chronic pelvic pain (PV), chronic low-back pain (LB), chronic fatigue syndrome (CFS), irritable bowel syndrome (IBS), fibromyalgia (FB), and interstitial cystitis (IC). Among these comorbidities, HD, PV, LB were the sole symptoms. Each of them was explored by one question, following criteria of previous studies (32, 35). Four other comorbidities including CFS, IBS, FB, and IC were explored by using four standard questionnaires (58-60). The validity and reliability of the original version of the questionnaire were high.

Prevalence of comorbidities in chronic TMD pain patients

Comorbidities were prevalent in Thai chronic TMD pain patients. In the present study, 82.5% of chronic TMD pain patients reported at least one comorbidity, similar to the studies Western population, in which > 60% to 83.1% of TMD pain patients reported comorbidties (35, 36, 39). The group of symptoms including HD, PV, LB, and CFS was much more common than the group of comorbid diseases (FB, IBS,

IC). Except IBS, and PV, the prevalence of other comorbidities was quite similar to previous studies (32, 39, 44). The studies in the United States reported the prevalence of IBS and PV was 23 – 28% and 7% (32, 35, 39) while the prevalence in our study was 10% and 36% respectively. The difference in these prevalence is not caused by different research methods, because the previous studies used the same questionnaire and diagnostic criteria with ours. The differences may be due to the different prevalence of IBS and PV in the general population between the United States and Thailand. The prevalence of IBS in the USA is > 20% and while the prevalence in Thailand is < 10% (64). Likewise, the prevalence of PV in the United States is 10 – 20% while in Thai, it is > 30% (65).

Pain duration

In our study, pain duration was positively associated with both WPI and number of comorbidities. These findings consist of the mechanism in central sensitization of spreading pain and comorbidities developing.

The association between pain duration and the degree of spreading of pain:

The spreading of pain was shown to be related to the long-term potentiation of NMDA receptors (15) which need an adequate time to be induced. The degree of spreading of pain is associated with the structural remodeling of connection between neurons (25). The amount of neurons affected by long-term potentiation is positively associated with the time that stimulus exists (25). As a result, the longer the pain

occurs, the more synapses are affected, the wider spreading of pain. A longitudinal cohort study revealed that the number of comorbid pain sites was significantly higher in patients with pain lasting for 5 years, regardless pain sensitivity (66). Another study reported that the prevalence of spreading pain is significantly higher in chronic pain patients (67).

The association between pain duration and the number of comorbidities:

Not only long-term potentiation, but the developing of comorbidities in chronic pain patients is also related to the response of the brain to pain. The neuroplastic changes in the brain in chronic pain patients are related to time (30, 31). In our study, the number of comorbidities present was in positive association with pain duration. This finding coincides with the concept of long-term potentiation as well as the maladaptation of the brain (25). A previous study reported that the number of comorbidities presented in chronic TMD pain patients was positively associated with the pain duration, even when the interested comorbidities in that study were different with ours (39).

Pain intensity

In our study, pain intensity was only associated with WPI, but was not associated with number of comorbidities. This finding is partly consistent with the concept of central sensitization. Biologically, the mechanism of long-term potentiation was shown to be enhanced by the frequency of stimulation (16). The

higher the pain intensity is, the more sensory neurons are recruited, the more frequent action potential occurs, the more synapses are modulated in neuroplasticity (15, 25). Possibly, the pain intensity should be positively related to the number of pain sites and comorbidities. However, the role of pain intensity in inducing spreading pain and comorbidities is controversial. Several previous studies reported that pain intensity was linearly associated with the number of comorbidities (39); the higher degree of spreading of pain was more common in higher intensity pain patients (67); the presence of bilateral hyperalgesia was significantly related to the hypersensitivity of local hyperalgesia (68). On the other hand, other studies showed that pain intensity was an important factor to implicate patients' seeking to treatment, but was not associated with the degree of spreading pain (69, 70). The review of long-term potentiation mechanism shown that the high frequency stimuli still cannot induce the long-term potentiation (25) if the stimuli occur for a short period of time. Reversely, the low or moderate frequency stimulation can induce long-term potentiation if it lasts long enough (25). The review of central sensitization showed that most of previous studies produced spreading pain through persistent low-frequency stimulation (22).

Also, pain intensity is strongly affected by recall bias. The recalled pain is also positively related to pain duration (71). The recall of pain intensity is acceptably accurate at the fifth day after commencing, but just modest after 3 months (71). The

repeated experience of pain might bias the memory of pain (72). The way that patients respond to pain also affects their reported pain intensity (73). Specifically, the pain intensity in chronic pain patients with endurance-response pattern (ER) and fear-avoidance-response pattern (FAR) was different. Patients with FAR tended to report higher pain intensity than those with ER (74) even when the severity of their disease was not significant. It is possible that long lasting pain and various response to pain in patients may lead to a significant bias of reported pain intensity. Interestingly, in overall, although our results showed that pain intensity was associated with WPI, when we dichotomized patients to chronic and acute pain groups, and tried to rerun the Multiple linear regression model, the association between WPI and pain intensity disappeared in chronic pain group and remained in only acute pain group. This change maybe because of the controversial role of pain intensity in inducing long-term potentiation, and possibly, because of the recall bias in chronic pain patients. In addition to recall bias, the self-reported pain intensity is also influenced by culture, ethnicity, and religion (51, 75). For example, Africans reported higher pain intensity, pain-related disability than Europeans. Indians and Asians reported higher pain tolerance than Africans and Caucasians. People with religious faith usually accept pain as an important part of life and reported better coping with pain. Individuals who find out the meaning of their pain reported less suffering than those think that their pain is meaningless (75). Previous study which showed that pain intensity was related to WPI and the number of comorbidities did

not select Asians as participants (67, 76). Therefore, the influence of culture and race may contribute to the difference in results between our study and theirs.

Pain frequency

In our study, pain frequency was the parameter which did not show any significant relation to WPI or to the number of comorbidities. We assume that, this result is caused by two reasons. The first reason is the controversial role of the frequency of stimulus in generating long-term potentiation. Similar to pain intensity, pain frequency is represented as the frequency of stimuli. The high frequency stimuli cannot implicate the risk of long-term potentiation as aforementioned (22, 25). The second reason may be due to the quantitative pain frequency measurement in our study. The reason of using a quantitative pain frequency scale (77) which reflects the percentage of pain days out of pain duration is to reduce the survey bias of patients. However, this measurement is unable to differentiate patients with pain duration of 1 day and patients with pain duration of 1 year, when they all reported they have pain every day. To overcome this shortcoming, we tried to select patients with pain duration for 1 months (the most common pain duration) and rerun the bivariate correlation between pain frequency and WPI, the result was positive correlation with $p = 0.01$. This finding shows that, pain duration is a confounder in the relationship between pain frequency and WPI or the number of comorbidities. Therefore, to analyze the correlation between pain frequency and WPI and the number of

comorbidities, the effect of pain duration should be eliminated first. Otherwise, a qualitative scale of pain frequency such as Likert scale (which divides pain frequency to very frequently/ frequently/ occasionally/ rarely/ never) can be used.

Prediction probability of having spreading pain and comorbidities based on reported pain parameters and demographic data

The result of Logistic regression analysis led us to formulate the odds ratio (OR) of having comorbidities as: $OR= e^{0.028*\Delta m}$ with Δm is the number of months increase. As the result of this formula, if the pain duration increases 12 months, the odds of having comorbidities will increase 1.4 times (95% IC: 1.17 – 1.66). Likewise, the OR of having spreading pain was formulated as: $OR= e^{0.044*\Delta m+0.2*\Delta i+0.03*\Delta a}$. Thus, if the pain duration increases 1 months, the odds of having spreading pain will increase 1.04 times (95% IC: 1.03 – 1.06), if the pain intensity increase 1 score, the odd of having spreading pain will increase 1.22 times (95% IC: 1.12 – 1.33), and if the age of patients increases 5 years, the odd of having spreading pain will increase 1.03 times (95% IC: 1.02 – 1.05). We also can estimate approximately the probability of having spreading pain and comorbidity in a patient ($P = \frac{Odd}{Odd + 1}$). For example, a patient with 40 years of age has pain duration of 2 years, and reports pain intensity of 5, the probability of having comorbidities is 80%, and spreading pain is 72.3%. However, because these formulas can provide only odd, the risk of having spreading pain or comorbidity in patients cannot be evaluated precisely. Another drawback of

these formulas is that they were formulated from a small sample size, and the lack of pain frequency, as well as being suitable with Thai sample only. Future studies with an adequate sample size can be conducted in the same way with our design to develop a suitable prediction for different populations.

Confounders

In our study, the chronic female pain group did not show a higher prevalence of comorbidity (p = 0.61). This result differs from previous findings (35, 36, 39), which mostly shown that females are more likely to develop comorbidity. This heterogeneity might due to different effect of gender on each comorbidity. Specifically, females have a higher prevalence of IBS (64), CFS (78) and PV (79), and FB (80) but not a significantly higher prevalence of LB (81). Although females are more susceptible to pain, and tended to report higher levels of pain intensity, males and females have insignificant risk of developing central sensitization (22). Specifically, the study of Jensen and Petersen showed that spreading pain induced by heat and capsaicin injection was not significantly different between genders (82). Interestingly, gender showed a weak effect on WPI (p = 0.16), assessed by bivariate correlation analysis. However, in the multiple linear regression model, the correlation between gender and WPI became not significant (p = 0.5). This alteration may be explained by females usually reporting higher pain intensity than males (49). Therefore, if gender is a dependent variable, females would be more likely to have a

higher risk of spreading pain developing than males. Inversely, if we evaluate gender and pain intensity in the same set, those who report a higher pain intensity are assumed to have a higher level of spreading pain, regardless of gender.

Age had a significant association with both WPI and the number of comorbidities. This finding is consistent with previous studies which consider the relationship between pain and elders (49). Elderly people have higher prevalence of chronic pain conditions (e.g. leg pain and back pain), as well as chronic diseases (e.g. IBS). As a result, the higher number of pain sites and comorbidities in the elderly does not mean that the elder people are more susceptible to neuroplastic changes than the younger, but means that the pain sites and comorbidities may present before the appearance of TMD pain.

The relation between familial history with chronic pain and the presence of chronic TMD pain

The result of Chi-square test was an insignificant relation between familial history with chronic pain and the presence of chronic TMD pain. Although the role of familial etiology in chronic pain was considered, it is still doubted.

Some studies suggested that the familial role in chronic pain is related to psychology and disability rather than the sensation only. The familial model for chronic pain is exposed in the 1960s suggested that the pain of patients was enhanced by psychological problems of siblings. Specifically, the illness of pain

sufferers was higher in patients whose parents also have persistent pain, and the illness was similar to the illness that their mothers were suffering. The emotion-based pain was more frequent in the patients whose mothers were psychological patients. The pain was more recurrent in the patients whose families were suffering from recurrent illness, pseudo-illness, and psychological issues (83).

In contrary, several studies also reported the direct effect of familial factor on pain. In 1978, Mohamed el at exposed the "marital maladaptation" model of pain in which the pain experienced by spouses was related to the pain of patients. The prevalence of chronic pain in the families of chronic pain patients was higher than in the families of control (83). In addition, recent years, the other considered aspect of familial factors was genetic factor. Several genes were demonstrated relating to the appearance of chronic pain diseases (84).

Our study concerned chronic TMD pain only. Our finding agreed with previous studies in which TMD pain was analyzed in the relation with familial environment and genetic factor. Michalowicz et al compared the prevalence of related-TMD sign and symptom between dizygotic twins and monozygotic twin in reared-together and reared-apart environment (85). They reported that the prevalence of related-TMD signs and symptoms was not different in dizygotic or monozygotic twins. The prevalence of the signs and symptoms was also not different between reared-apart or reared-together environment. Focusing on TMD myalgia only, a study of Raphael et al showed that TMD myalgia among family members of TMD myalgia patients was

not higher than family members of control (86). A review of etiologies of TMD suggested that neither familial environment nor genetic factor was related to the presence of TMD signs and symptoms (87).

Limitations and implications

Our study was a cross-sectional design, which cannot explore the causal effect between the three pain characteristics and the comorbidities, as well as the spreading pain. The cohort studies in 2013 (45, 46, 88) have demonstrated that patients with chronic pelvic pain, low back pain and frequent headache have a significantly higher incidence of TMD pain. These findings mean that TMD pain can be developed before or after comorbidities. The patients with short pain duration can still have a higher number of comorbidities present because such patients have suffered from other chronic pain diseases before developing TMD pain. Our findings may be underpowered due to the small number of patients (88 chronic pain patients; 198 in total), as well as the large difference between the number of female and male patients. Another drawback of our study was that using only a quantitative frequency scale could not reflect how much the TMD pain influenced the daily life of patients.

Demonstrating the causal effect of central sensitization from TMD pain to spreading pain and comorbidities is difficult. To explore the etiology, cohort studies are required to follow up TMD pain patients who do not have any other pain disease

and are not provided with any treatment for TMD. Calculating accurately the risk of co-occurrence pain and comorbidities presence also needs a cohort study design. However, this design conflicts with medical research ethics. Preclinical studies with animals may be possible, but may also have ethical constraints. Recall bias of pain intensity can be eliminated by pressure pain threshold measurement in two states; at rest and the state which makes the pain worst (e.g. when chewing or mouth opening). Pain frequency should also be evaluated by a combination of qualitative and qualitative measurement, accompany with elimination of pain duration's effect.

In spite of the aforementioned limitations, our study provided several benefits. It was the first which reports the distribution of comorbidities in chronic TMD patients in an Asian sample. Our results also confirm the hypothesis of the dependence of the presence of spreading pain and comorbidities on TMD pain parameters. To our knowledge, this study is the first estimating the probability of spreading pain and comorbidity in TMD pain patients. Hence, dentists can predict the chance of additional pain problems in the TMD pain patients, and recommend consultation with other specialists.

APPENDIX

แบบสอบถามอาการปวดและ/หรือความเจ็บป่วยที่อาจเกิดร่วมกับอาการปวดกล้ามเนื้อ/ข้อต่อขากรรไกรเรื้อรัง

ส่วนที่ 1: ข้อมูลผู้ป่วย

HN:..... อายุ:.....ปี.....เดือน เพศ:.....การวินิจฉัย: .....

มีประวัติอาการปวดจาก TMD: ❑ใช่ ❑ ไม่ใช่ ปัญหาหลักเกี่ยวข้องกับ: ☐ Muscles ☐ TMJ ☐ Combined

สำหรับผู้วิจัยถาม

		ไม่มี	มี
1.	ในครอบครัวของผู้ป่วย (พ่อ แม่ ปู่ ย่า ตา ยาย พี่ น้อง และลูก) มีผู้ที่มีอาการปวดเรื้อรัง หรือมีอาการอ่อนเปลี้ยเพลียแรง หรือรู้สึกไม่สบายบริเวณศีรษะ หน้าอก ท้อง เอว ท้องน้อย หรือแขนขา นานเกิน 3 เดือน หรือไม่	☐	☐
		ไม่เคย	**เคย**
2.	ในช่วง 30 วันที่ผ่านมา คุณเคยปวดตรงขากรรไกร, ขมับ, ในหู, หรือหน้าหูข้างใดข้างหนึ่งของคุณ หรือไม่	☐	☐
		ไม่	**ใช่**
3.	ในช่วง 30 วันที่ผ่านมา, กิจกรรมต่อไปนี้ทำให้อาการปวดตรงขากรรไกร, ขมับ, ในหรือหน้าหูข้างใดข้างหนึ่งของคุณเปลี่ยนแปลงหรือไม่ (นั่นคือ ทำให้ดีขึ้นหรือทำให้แย่ลง)	☐	☐
	A. เคี้ยวอาหารแข็งหรือเหนียว	☐	☐
	B. อ้าปาก หรือเคลื่อนขากรรไกรไปด้านหน้าหรือด้านข้าง	☐	☐
	C. นิสัยเกี่ยวกับขากรรไกร เช่น แตะฟันบนล่าง/ไว้ด้วยกัน, กัดเน้น/บดถูฟัน หรือเคี้ยวหมากฝรั่ง	☐	☐
	D. ใช้ขากรรไกรทำกิจกรรมอื่นๆ เช่น พูด, จูบ หรือหาว	☐	☐
4.	คุณเริ่มปวดตรงขากรรไกร, ขมับ, ในหู, หรือหน้าหูมานานเท่าไหร่แล้ว .....ปี..... เดือน.....วัน		

ส่วนที่ 2 คำถามเกี่ยวกับอาการปวดบริเวณใบหน้า/ขากรรไกร/ข้อต่อขากรรไกร

ขอให้คุณสนใจเฉพาะอาการปวดบริเวณใบหน้า/ขากรรไกร แล้วตอบคำถามต่อไปนี้

1. ระดับความปวด: *ถ้าเลขศูนย์หมายถึง ไม่ปวดเลย เลขสิบ หมายถึง ปวดมากที่สุดเท่าที่จะเป็นได้ ขอให้คุณประเมินความปวดดังนี้*

1.1 ระดับความปวดที่ใบหน้า/ขากรรไกรของคุณ<u>ในขณะนี้</u> เป็นเท่าไหร่ (ใช้สเกล 0-10)

1 2 3 4 5 6 7 8 9 10

1.2 ใน 6 เดือนที่ผ่านมา ระดับความปวดที่ใบหน้า/ขากรรไกรของคุณ <u>ที่รุนแรงที่สุด</u> เป็นเท่าไหร่ (ใช้สเกล 0-10)

1 2 3 4 5 6 7 8 9 10

1.3 ใน 6 เดือนที่ผ่านมา ระดับความปวดที่ใบหน้า/ขากรรไกรของคุณ <u>โดยเฉลี่ย</u>เป็นเท่าไหร่ (ใช้สเกล 0-10)

1 2 3 4 5 6 7 8 9 10

2. ในช่วง 2 สัปดาห์ที่ผ่านมา คุณมีอาการปวดกี่วัน (วงกลมล้อมรอบคำตอบ)

1 2 3 4 5 6 7 8 9 10 11 12 13 14 วัน

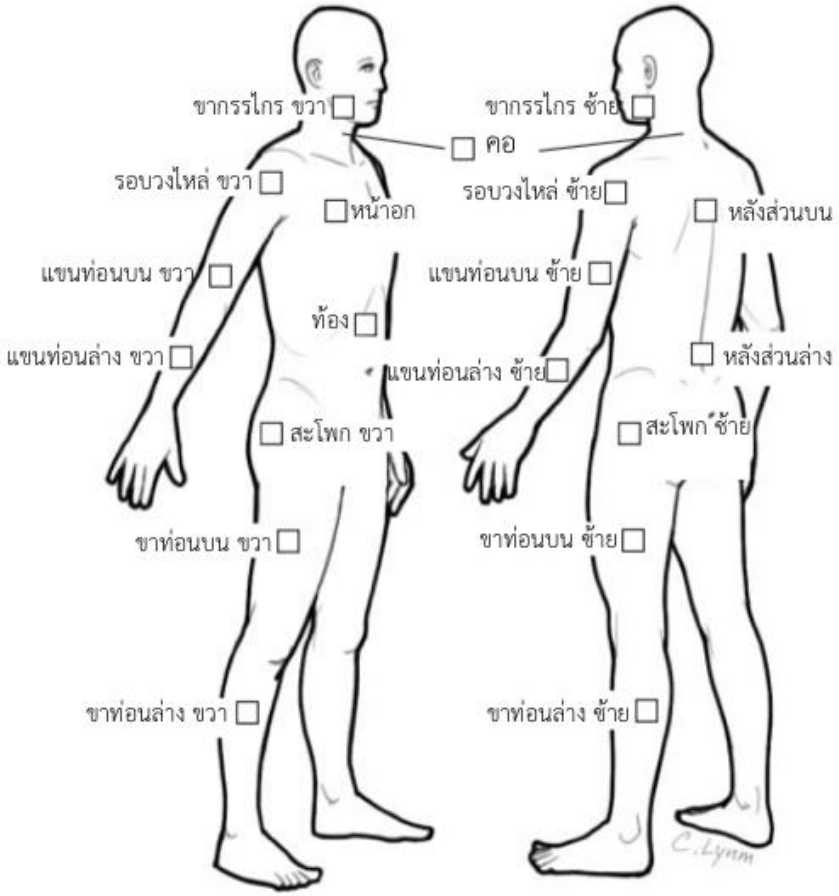
ส่วนที่ 3 คำถามเกี่ยวกับอาการปวดศีรษะ

ขอให้คุณตอบคำถามที่เกี่ยวกับอาการปวดศีรษะต่อไปนี้ โดยทำเครื่องหมาย 🖷 ในช่องสี่เหลี่ยมที่ตรงกับคำตอบของคุณ

1. ในช่วงปีที่ผ่านมา คุณมีอาการปวดศีรษะบ้างไหม ❑มี ❑ ไม่มี
2. อาการปวดศีรษะนั้นเป็นมานานแค่ไหน .....ปี.....เดือน
3. คุณมีอาการปวดศีรษะบ่อยแค่ไหน ❑< 1 ครั้ง/เดือน ❑≥ 1 ครั้ง/ เดือน ❑ทุกสัปดาห์
4. คุณเพิ่งมีอาการไข้หวัดรุนแรง หรือได้รับบาดเจ็บที่ศีรษะ หรือเพิ่งผ่าตัดบริเวณศีรษะหรือไม่ ❑มี ❑ ไม่มี
5. คุณมีประวัติความดันโลหิตสูงหรือไม่ ❑มี ❑ ไม่มี
6. คุณมีประวัติเป็นไซนัสอักเสบเรื้อรัง หรือมีอาการติดเชื้อเรื้อรังที่หู คอ จมูก หรือไม่ ❑มี ❑ ไม่มี

ส่วนที่ 4 คำถามเกี่ยวกับบริเวณที่มีอาการปวด

ให้ทำเครื่องหมาย 🖷 ในช่อง ☐ ตรงตำแหน่งที่คุณปวดในหนึ่งสัปดาห์ที่ผ่านมา



สำหรับผู้วิจัย

WPI score:

..... (0 – 17)

ส่วนที่ 5 คำถามเกี่ยวกับความรุนแรงของอาการที่อาจเกี่ยวข้อง

ให้ทำเครื่องหมาย 🖷 ตรงช่อง ☐ เพื่อบอกว่าคุณรู้สึกมีอาการต่อไปนี้มากน้อยเพียงใดในหนึ่งสัปดาห์ที่ผ่านมา

	ไม่มีปัญหา	มีปัญหาเล็กน้อย	มีปัญหาปานกลาง	ปัญหารุนแรง
อ่อนเปลี้ยเพลียแรง	☐	☐	☐	☐
ตื่นขึ้นอย่างไม่สดชื่น	☐	☐	☐	☐
ความทรงจำและสมาธิบกพร่อง	☐	☐	☐	☐

ส่วนที่ 6 **คำถามที่เกี่ยวกับอาการผิดปกติต่าง ๆ**: ในช่วง 6 เดือนที่ผ่านมา คุณถูกรบกวนด้วยสิ่งต่อไปนี้หรือไม่ กรุณาตอบโดยให้ทำเครื่องหมาย 🖷 ในช่อง ☐

ปวดหรือเป็นตะคริวในช่องท้องส่วนล่าง	☐ ไม่มี	☐ มี
ซึมเศร้า	☐ ไม่มี	☐ มี
ปวดศีรษะ	☐ ไม่มี	☐ มี

ส่วนที่ 7 คำถามเกี่ยวกับความเจ็บป่วยทั่วไปและอาการอ่อนล้า: ให้ทำเครื่องหมาย 🖷 ในช่องที่ตรงกับอาการของคุณมากที่สุด

	ไม่มี หรือมีน้อยมาก	บางครั้ง	ส่วนใหญ่	เกือบตลอดเวลา
1. ฉันรู้สึกเหนื่อยอยู่นานหลังทำกิจกรรมที่มีการเคลื่อนไหวร่างกาย	☐	☐	☐	☐
2. สมาธิฉันไม่ดีเลย	☐	☐	☐	☐
3. กล้ามเนื้อฉันอ่อนแรงมากหลังทำกิจกรรมที่มีการเคลื่อนไหวร่างกาย	☐	☐	☐	☐
4. ฉันปวดศีรษะ	☐	☐	☐	☐
5. ฉันต้องการนอนหลับยาวๆ	☐	☐	☐	☐
6. ฉันปวดกล้ามเนื้อ หลังทำกิจกรรมที่มีการเคลื่อนไหวร่างกาย	☐	☐	☐	☐
7. ฉันนอนหลับไม่ดีเลย	☐	☐	☐	☐
8. ฉันมีปัญหาในการพูด เช่น ลืมว่าจะพูดอะไรออกมา	☐	☐	☐	☐
9. ความจำฉันไม่ดีเลย	☐	☐	☐	☐
10. ฉันปวดกล้ามเนื้อแม้อยู่เฉยๆ ก็ตาม	☐	☐	☐	☐

ส่วนที่ 8 อาการที่เกี่ยวกับลำไส้: กรุณาทำเครื่องหมาย 🖷 ทับช่อง ☐ ที่ตรงกับอาการของคุณมากที่สุด

1.	ในช่วง 3 เดือนที่ผ่านมา, คุณรู้สึกปวดท้องหรือไม่สบายในท้องบ่อยแค่ไหน	☐ ไม่เคย ☐ น้อยกว่า 1 วันต่อเดือน ☐ วันต่อเดือน ☐ หรือ 3 วันต่อเดือน ☐ วันต่อสัปดาห์ ☐ ทุกวัน
2.	สำหรับผู้หญิง: คุณรู้สึกปวดท้องหรือไม่สบายในท้องเฉพาะช่วงที่มีประจำเดือนเท่านั้นไม่ได้เกิดในเวลาอื่น	☐ ไม่ใช่ ☐ ใช่ ☐ ตอบไม่ได้ เพราะมีการเปลี่ยนแปลงเกิดขึ้นในชีวิต เช่น หมดประจำเดือนแล้ว
3.	คุณรู้สึกปวดท้องหรือไม่สบายในท้องเป็นเวลานานอย่างน้อย 6 เดือน	☐ ไม่ใช่ ☐ ใช่
4.	อาการปวดท้องหรือไม่สบายในท้องดีขึ้นหลังถ่ายอุจจาระ	☐ ไม่มีเลยหรือแทบไม่มีอาการนี้เลย ☐ เป็นบางครั้ง ☐ เป็นบ่อย ☐ มักจะเป็น ☐ เป็นเสมอ
5.	อาการปวดท้องหรือไม่สบายในท้องเกิดร่วมกับอาการท้องเสีย	☐ ไม่มีเลยหรือแทบไม่มีอาการนี้เลย ☐ เป็นบางครั้ง ☐ เป็นบ่อย ☐ มักจะเป็น ☐ เป็นเสมอ
6.	อาการปวดท้องหรือไม่สบายในท้องเกิดร่วมกับอาการท้องผูก	☐ ไม่มีเลยหรือแทบไม่มีอาการนี้เลย ☐ เป็นบางครั้ง ☐ เป็นบ่อย ☐ มักจะเป็น ☐ เป็นเสมอ
7.	อาการปวดท้องหรือไม่สบายในท้องเกิดร่วมกับการถ่ายอุจจาระแข็ง	☐ ไม่มีเลยหรือแทบไม่มีอาการนี้เลย ☐ เป็นบางครั้ง ☐ เป็นบ่อย ☐ มักจะเป็น ☐ เป็นเสมอ

8.	อาการปวดท้องหรือไม่สบายในท้องเกิดร่วมกับการถ่ายอุจจาระเหลว	☐ ไม่มีเลยหรือแทบไม่มีอาการนี้เลย ☐ เป็นบางครั้ง ☐ เป็นบ่อย ☐ มักจะเป็น ☐ เป็นเสมอ

ส่วนที่ 9 คำถามเกี่ยวกับความเจ็บป่วยและความรู้สึกไม่สบายเมื่อคุณเข้าห้องน้ำ

ในช่วง 2 สัปดาห์ที่ผ่านมา คุณมีอาการผิดปกติในสิ่งต่อไปนี้หรือไม่ กรุณาทำเครื่องหมาย 🖷 ทับช่อง ☐ ที่ตรงกับอาการของคุณมากที่สุด

1	ปกติคุณปสสาวะกี่ครั้งในหนึ่งวัน ตั้งแตหลังตื่นนอนในตอนเชาถึงกอนนอนตอนกลางคืน	☐ 3-6 ครั้ง	☐7-10 ครั้ง	☐ 11-14 ครั้ง	☐15-19 ครั้ง	☐ 20 ครั้ง หรือมากกว่า
2	ปกติคุณตองตื่นมาปสสาวะตอนกลางคืนกี่ครั้งนับตั้งแตนอนหลับแลวถึงตื่นนอนในตอนเชา	☐ 0 ครั้ง	☐ 1 ครั้ง	☐ 2 ครั้ง	☐ 3 ครั้ง	☐ 4 ครั้ง หรือ มากกว่า
	การตื่นไปปัสสาวะตอนกลางคืน มันรบกวนคุณไหม	☐ ไม่มีเลย	☐ นานๆครั้ง	☐ บ่อยครั้ง	☐ เสมอๆ	
3	บ่อยแค่ไหนที่คุณมีอาการปวดหรือมีอาการผิดปกติขณะหรือหลังจากมีเพศสัมพันธ์	☐ ไม่มีเลย	☐ นานๆครั้ง	☐ บ่อยครั้ง	☐ เสมอๆ	
	บ่อยแค่ไหนที่อาการปวดหรืออาการอยากถ่ายปัสสาวะอย่างทันทีทันใดทำให้คุณถึงกับต้องหลีกเลี่ยงการมีเพศสัมพันธ์	☐ ไม่มีเลย	☐ นานๆครั้ง	☐ บ่อยครั้ง	☐ เสมอๆ	
4	คุณมีอาการปวดแถวกระเพาะปัสสาวะหรือท้องน้อยหรือไม่	☐ ไม่มีเลย	☐ นานๆครั้ง	☐ บ่อยครั้ง	☐ เสมอๆ	
5	ถ้าคุณมีอาการปวดแถวกระเพาะปัสสาวะหรือท้องน้อย อาการปวดนี้รุนแรงแค่ไหน		☐ เล็กน้อย	☐ ปานกลาง	☐ รุนแรง	

	อาการปวดนี้รบกวนคุณบ่อยแค่ไหน	☐ ไม่มีเลย	☐ นานๆครั้ง	☐ บ่อยครั้ง	☐ เสมอๆ
6	บ่อยแค่ไหนที่คุณมีอาการอยากถ่ายปัสสาวะอย่างทันทีทันใด หลังจากเพิ่งเข้าห้องน้ำมา	☐ ไม่มีเลย	☐ นานๆครั้ง	☐ บ่อยครั้ง	☐ เสมอๆ
7	ถ้าคุณมีอาการอยากถ่ายปัสสาวะทันทีทันใด อาการนี้รุนแรงแค่ไหน		☐ นานๆครั้ง	☐ บ่อยครั้ง	☐ เสมอๆ
	อาการอยากถ่ายปัสสาวะอย่างทันทีทันใดนี้รบกวนคุณบ่อยแค่ไหน	☐ ไม่มีเลย	☐ นานๆครั้ง	☐ บ่อยครั้ง	☐ เสมอๆ

ส่วนที่ 10 อาการปวดบริเวณท้องน้อยและหลังช่วงล่าง

คุณมีอาการปวดแถวท้องน้อยบ่อย (อย่างน้อย 1 ครั้ง/เดือน) หรือไม่

☐ ไม่มี ☐ มี ถ้ามี อาการปวดนี้เป็นมานานเท่าไหร่แล้ว (รวมถึงอาการปวดประจำเดือนที่ไม่ได้เกิดจากการเป็นโรคใดๆด้วย)

.....ปี.....เดือน.....สัปดาห์

คุณมีอาการปวดหลังส่วนล่างบ่อย (อย่างน้อย 1 ครั้ง/เดือน) หรือไม่

☐ ไม่มี ☐ มี ถ้ามี อาการปวดนี้เป็นมานานเท่าไหร่แล้ว

.....ปี.....เดือน.....สัปดาห์

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APPENDIX

VITA

Ms. Tra Thu Nguyen was born in Hanoi, the capital city of Vietnam. She graduated from High School for Gifted Students, Hanoi University of Science, and DDS from the Hanoi Medical University. At the moment, she is participating in Master of science program in Occlusion and Orofacial Pain at Chulalongkorn University, Thailand.