Anxiety, Depression and Somatization in Patients with Oral Lichen Planus

Rashmi Malhotra

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Committee:

Lisa J. Heaton, Chair

Michael D. Martin

Lloyd A. Mancl

Karen Manookin

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Abstract

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Rashmi Malhotra

Chair of the Supervisory Committee:
Assistant Professor, Lisa J. Heaton
Department of Oral Health Sciences

Psychosocial factors have been mentioned frequently to be associated with oral lichen planus (OLP). However, these comorbidities have not been explored as frequently in patients with oral lichenoid lesions (OLL). Most of the cited OLP/OLL studies appear to be anecdotal or lack appropriate control groups. The primary aim of this study was to assess anxiety, depression, and somatization (with and without pain) in patients suffering from OLP/OLL using the Symptom Checklist (SCL-90R), compared to patients with myofascial pain and healthy controls. Another objective of this study was to determine and compare the levels of pain aversiveness and pain intensity of OLP and OLL patients. This cross-sectional study identified 152 OLP/OLL eligible subjects who attended the Oral Medicine Clinical Services (OMCS) at University of Washington between January 2011 and March 2017. The SCL-90R subscales, Visual Analog Scale (VAS) for pain intensity and pain aversiveness, and sociodemographic variables of the study groups were assessed. For the SCL-90R subscales of anxiety, depression and somatization, the myofascial pain

group had the highest median scores followed by the OLP group, OLL group and finally the control group as hypothesized. For somatization without pain, the OLP group had the highest median score followed by myofascial pain subjects, OLL patients and finally controls. There was a significant difference between patients with OLP and controls with regard to somatization without pain. However, no statistical significant differences were seen between patients with OLP, patients with OLL and controls with regard to anxiety, depression and somatization subscales when adjusted for age and gender, though a trend approaching significance was seen in OLP patients with higher risk to have moderate/severe anxiety than controls. This study found that the patients with OLP are likely to experience psychosocial comorbidities, which indicate that psychological assessment should be routinely done for these patients.

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DEDICATION

This work is dedicated to my husband Nitin, my son Aditya and my parents for their unconditional support and inspiration.

Chapter 1. INTRODUCTION

1.1 ORAL LICHEN PLANUS (OLP)

Lichen planus is considered to be a common chronic inflammatory autoimmune disease affecting the skin and mucous membranes. The estimated prevalence of lichen planus (LP) is in the range of 0.22% to 5% worldwide [1] and oral lichen planus (OLP) exists in 0.5% to 2.5% of the world population [2]. OLP may occur clinically in various forms including reticular plaques, hyperkeratotic plaques, mucosal erythema, erosions, or ulcerations. It typically presents bilaterally with a characteristic presentation in the buccal mucosa, tongue, lower lip, labial mucosa, gingiva, and less commonly on the palate, upper lip and floor of the mouth [3-5].

Lichen planus has been associated with factors such as genetics, chronic liver disease, human papilloma virus (HPV), as well as with psychosocial factors [6]. Some studies reported high levels of cortisol in OLP patients, suggesting stress and anxiety may be correlated with this disease [7, 8]. Ivanovski et al considered "psycho-somatization" as a possible etiopathologic factor of OLP and found cortisol, CD4 and CD8 levels were significantly greater in patients with erosive OLP than in control group [9]. The precise etiopathogenesis of lichen planus is unknown, but recent studies suggest it may be mediated by activation of $CD4^+$ (helper), $CD8^+$ (cytotoxic) T lymphocytes and Th1 cytokine (e.g. IL-2, tumor necrosis factor alpha, interferon gamma). Once activated, these cells attack the oral epithelial cells resulting in apoptosis of keratinocytes [10-12]. Th1 and Th2 cells are the subsets of T helper cells which begin to proliferate and activate when they are presented with antigen and appropriate cytokines. Th1 cells help in cell mediated immunity, antibody mediated immunity and are also essential for controlling intracellular pathogens. Th2 cells help B cells and are essential for production of antibodies against extracellular pathogens [13]. Differentiation of Th1 and Th2 cells is mediated by interferon gamma

and IL-4 respectively and whose altered ratio might induce the pathologic state in OLP patients [13].

1.2 Oral Lichenoid Lesions (OLL)

Oral lichenoid lesions (OLL) and OLP have similar clinical presentations. OLL is usually triggered by extrinsic agents like drugs, allergens, altered self-antigens, or super-antigens [3]. Oral lichenoid drug reactions (OLDR) can result from systemic drug exposures including nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, diuretics, beta blockers, and HIV antiretroviral medications. OLL can also develop secondary to local allergic contact hypersensitivity, termed oral lichenoid contact reaction (OLCR), after exposure to restorative materials (amalgam, gold), dental adhesives (eugenol, acrylate), or flavorings (cinnamon) etc. [3]. The classic Wickham's striae of lichen patients are seen in close association with the etiologic restorative material. Wickham's striae are defined as "fine white lines with lichenoid, polygonal papular skin lesions" [14]. Erosive, erythematous or bullous patterns also can be possible with OLL. The regression of OLL is usually seen with the removal of etiologic factors, such as a suspected medication or restorative material [3].

1.3 Treatment

The common management strategies for OLP is palliative and use of topical corticosteroids, topical retinoid, cyclosporine or other topical medications. For treatment of OLL, removal of the etiologic factor is recommended along with topical corticosteroids therapy if required [3]. Frequent recurrences of oral lesions have been seen in OLP patients despite getting appropriate therapeutic treatment [3]. Similarly, removal of a known allergen may not lead to resolution of lesions in patients with OLL [11]. Various factors could be attributed to poor treatment response in OLL and

OLP patients. One of them might be due to mucosal antigen retention and continuous exposure of the allergen in the oral cavity. Variable immune responses and diverse etiopathology could also lead to poor treatment response. Another consideration is the possibility of diagnostic errors. As an example, OLP is commonly mistaken for pre-neoplastic leukoplakias [3].

1.4 STRESS AND OLP

An immune response modified by stress and/or depression can also play a role in sustaining the disease states of OLP and OLL. Some studies have reported stress to be the most frequent cause of acute flare ups in OLP patients, in comparison with other precipitants like heavy alcohol consumption, tobacco use, dental procedures, systemic illness, citrus and spicy foods [3, 5, 15]. Stressful life events could induce and/or aggravate OLP by modifying and promoting dysregulation of immune functions with increase of TH2 and alterations in ratio and balance of TH1 with TH2 [6, 10].

1.4.1 *Quality of Life*

Stress could lead to greater sensitivity to noxious stimuli which is a possible explanation of psychologically distressed and depressed patients having reduced pain threshold to stimuli [16, 17]. Therefore, depressed patients with chronic pain and a sustained OLP/OLL disease state may be more pain sensitive than patients suffering from chronic pain alone, but without psychosocial distress. Consequently, this can produce a negative effect on quality of life of these patients.

Patients with chronic disease conditions like OLP and OLL often have high levels of emotional distress, social withdrawal and poor coping which might trigger anxiety or depression, and compromise the resilience of the immune system [18].

1.4.2 *Psychotherapeutic Management*

Chronic stress in OLP patients as explained by Ivanovski et al is often considerably associated with somatization [9] and patients could experience psychological distress in the form of unexplained physical symptoms. Persistent somatization leads some patients to seek unnecessary medical evaluations and treatments. Therefore, the patients suffering from OLP/OLL should be assessed for psychological disorders, especially anxiety, depression and somatization, and based on this evaluation the treatment approach should be aimed to improve the functional status of patients.

1.5 DSM-V DEFINITIONS

Depression can be described as 'anhedonia', that is, the inability to enjoy activities or experience pleasure [19]. Depressive disorders, as described by the Diagnostic and Statistical Manual of Mental Disorders – 5th Edition (DSM-V), are characterized by "the presence of sad, empty, or irritable mood, accompanied by somatic and cognitive changes that significantly affect the individual's capacity to function". Anxiety, according to the (DSM-V) is described as "the apprehensive anticipation of future danger or misfortune accompanied by a feeling of worry, distress, and/or somatic symptoms of tension. The focus of anticipated danger may be internal or external". Few studies have suggested that patients with anxiety disorders exhibit higher somatic symptoms [20, 21]. Somatization refers to the experience of the psychological distress in the form of physical symptoms. The somatic symptoms and related disorders according to DSM-V are "related to significant distress and impairment". Individuals with this disorder express discomfort and somatic symptoms which are difficult to explain and generally without evident medical findings.

With the reduction of depression and psychosocial distress, many aspects of rehabilitation and therapeutic treatment may be more easily accomplished. As mentioned in 'Bonica's Management of Pain', pain severity and amount of pain could decrease with the improvement in the depressive symptoms. "Patients typically report that their pain is still present, but it doesn't bother them anymore. This statement is very telling – the affective component of pain has significantly improved" [19p.401]. Therefore, therapeutic treatment for pain along with psychosocial support can provide significant improvement in the quality of life.

OLP and OLL can have a significant impact on a patient's quality of life. Some patients with these conditions may change their diet to prevent pain; they may avoid social situations because talking is painful; and they may experience significant worry over the nature of their condition. Furthermore, this condition can be sometimes difficult to manage, filling practitioners with uncertainty about how to best help their patients. Successful treatment for these patients, therefore, requires management of patient's psychosocial well-being along with the condition itself.

Chapter 2. RESEARCH POTENTIAL

A study by Kalkur et al [22] revealed higher incidence of psychiatric comorbidities like depression, anxiety and stress in OLP cases compared to control group using DASS-42 (Depression, Anxiety and Stress Scale). Depression, anxiety and stress levels in OLP patients tended to be higher (13.8%, 18.3%, 25.4%, respectively) compared to control group's levels of 12.2%, 13.9% and 16.4%, respectively. However, there was no statistically significant difference between scores of OLP and control groups in all three variables ($P = 0.1435$ for depression, $P = 0.3158$ for anxiety, $P = 0.0994$ for stress). This could be due to a smaller sample size (25 people) in the study [22]. In the study done by Alves et al [2], no significant difference was found in trait anxiety ($P = 0.087$) between erosive OLP patients versus control group. However, a significant difference was seen in state anxiety ($P = 0.033$) using the State-Trait Anxiety Inventory (STAI) scale. A significant difference was also seen in the prevalence of depressive symptoms between the two groups.

Additional studies [8, 9, 23-31] have reported significantly higher levels of anxiety and depression in patients with OLP patients using different anxiety scales such as the Spielberger State-Trait Anxiety Inventory as a general aspect of personality (STAI-T) [8, 27, 28] and state anxiety as a response to specific situation (STAI-S) [8, 23, 27, 28], Minnesota Multiphasic Personality Inventory (MMPI)-202 [9], Becks Depression Inventory (BDI) [23, 27, 28], General Health Questionnaire–version 28 [24], Hospital Anxiety and Depression Scale (HADS) [24, 31], Hamilton Anxiety Scale [26], Montgomery-Asberg Depression Rating Scale [26], Cartel Personality Questionnaire 16PF [27], Hassanyeh Rating of Anxiety-Depression-Vulnerability [27], Raskin Depression Screen [27], and Covi Anxiety Screen [27], General Perceived Stress Questionnaire (PSQ) [23], Self-rating Anxiety scale (SAS) [29], Self-rating Depression

Scale(SDS) [29], Hamilton Depression Scale for Depression (HAMD) [29][30] and Anxiety (HAM-A) [30] and Life Event Scale (LES) [29].

Despite the remarkable difference in the levels of stress and anxiety in OLP cases versus control group, Soto Araya et al [25] has reported the levels of depression within the normal range in OLP patients using the HADS. For the stress levels, the average value for group of cases was 'high' (374.53) and for control group the average value was 'normal' (239.75) showing significant differences ($p<0.05$). In relation to anxiety, the average for group of cases was 'morbid' (11.59) as compared to control group which scored in the 'normal' range (7.25) obtaining significant difference ($p<0.05$) whereas for depression, the group of cases and controls scored 'normal' values 7.03 and 3.95, respectively ($p<0.05$). Gupta et al [32] used DASS-21 (Depression Anxiety Stress Scale-21) and reported a significant difference between in depression ($p=0.010$) and stress scores ($P=0.009$) amongst OLP patients and controls but not anxiety scores ($P=0.693$). Gavic et al [33] assessed the psychological profile of the OLP patients by using BDI, STAI and Ways of Coping questionnaire (WCQ). 50.08% OLP patients had positive depression test, 50% had positive stress test and 39.79% had positive anxiety tests. This study could not determine positive association between anxiety level and OLP.

Several studies [15, 34, 35] found no significant differences in anxiety or depression between OLP patients and control groups. McCartan et al [15] found anxiety levels slightly elevated in erosive OLP cases using the HADS ($p=0.46$) and the Cattell 16 PF Questionnaire ($p=0.13$) while depression scores measured on the HADS were low ($p=0.57$). Hirota et al [34] used the STAI-T and Center for Epidemiologic Studies Depression Scale (CES-D) to assess anxiety and depression in OLP versus control group. No statistically significant differences were seen in anxiety or depression between OLP and control group ($p>0.05$). The analysis by gender revealed that female

and male patients presented a significantly higher score for one item in the STAI-T scale respectively (questions 4 and 20 which are: 4. “I would like to be as happy as the other people seem to be” and 20. “I feel very disturbed when I think on my own problems”- translated paper from Italian), but none on the CES-D scale compared to the control group. Logistic regression analyses found statiscially significant differences for several groups and questions in the STAI-T. For both genders in OLP patients versus controls, $p=0.01$ for question 4 and $p=0.007$ for question 20. After breakdown by gender, on STAI-T (female) OLP versus control subjects, $p=0.03$ for question 4 and on STAI-T (male) OLP versus control group, $p=0.01$ for question 20. Allen et al [35] used the STAI-T to measure anxiety in OLP patients and found no difference amongst OLP patients and a control group of people ($p>0.05$) in which biopsy was performed for irritation fibroma, and a control group of healthy patients (for mean age $p=0.750$ and for gender distribution $p=0.870$).

Only one study, by Bergdahl et al [36] has reported the psychosocial aspects of OLL patients using the Karolinska Scales of Personality (KSP), the Personality Scale (PS), the Psychological Functioning Scale (PFS) and the Quality of Life Scale (QLS). OLL patients in this study were found to have significantly higher sad thoughts ($p<0.001$) and anxiety ($p<0.05$) than control group.

To sum up, the relation of depression and anxiety to the development of OLP/OLL has been a subject of debate [10]. Most of the cited cases appear to be anecdotal or lack appropriate controls. There is no consensus seen with the present literature for association of anxiety and depression in OLP/OLL patients and only one of the studies [9] has reported the association of somatization with the lichen planus patients. No study to date has used Symptom Checklist-90 (SCL-90) or SCL-90R (revised version) instrument to measure anxiety, depression and somatization subscales in OLP patients.

None of the studies described above compared psychosocial measures between oral lichen planus and oral lichenoid lesion patients. Although OLP and OLL may exhibit similarity and some clinicians diagnose these two as the same disease, several studies have suggested a variable etiology and diagnostic criteria to distinguish between two conditions [3, 10, 62]. Based on their etiologies, these two conditions should be treated in different manner and therefore, we opted to report the SCL-90R measures (anxiety, depression, somatization with or without pain) separately for OLP and OLL patients.

The SCL-90 (Symptom Checklist-90) is one of the most popular instruments used to assess psychosocial measures with well-established reliability and validity. The internal consistency coefficient of the SCL-90 has been reported to be in a range of 0.77 - 0.90 [37] and the test-retest reliability had a range of 0.68 - 0.80 (Derogatis, 2000). The validity of the SCL-90 has also been proven in strong convergence with the Minnesota Multiphasic Personality Inventory (MMPI) [37]. Therefore, it is considered an established measure of general symptom severity and changes in symptom severity. We use the SCL-90R scale in the Oral Medicine Clinical Services (OMCS) clinic at the University of Washington to assess the psychosocial factors in mucosal and chronic pain patients. This is the shortened version of original SCL-90 with 46 questions and is available in different languages. It takes less time for completion of this questionnaire compared to other scales like the MMPI-2 (576 questions) or SCL-90 (90 questions) but still includes specific questions assessing depression, anxiety, and somatization. Therefore, this appears to be the optimal instrument that helps us to measure the psychological distress and somatization among the patients in a non-psychiatric setting.

No studies to our knowledge have reported pain aversiveness and pain intensity (using the Visual Analog Scale (VAS)) affecting the quality of life of OLL and OLP patients. Therefore,

there is a definite need to investigate the psychosocial aspects of OLL and OLP patients with objective methods for reliable evaluation, as it may improve the care of these patients.

The psychosocial profiles have been well-studied in patients suffering from temporomandibular disorders (TMD), and studies have reported the comorbidity of psychosocial factors in TMD patients. But only one of the studies [24], to our knowledge has compared myofascial pain patients with OLP/OLL patients. The studies by Nifosi et al and Manfredini et al suggested that myofascial pain patients alone, or combined with temporomandibular joint (TMJ) pain had high scores for SCL-90R instrument subscales [38, 39]. Comparing SCL-90R scores between OLP and OLL patients with myofascial pain patients will help us to supplement the diagnosis of involvement of psychosocial factors amongst the OLP and OLL patients. In addition to comparing with the established norms of SCL-90R, we will be able to assess the anxiety, depression and somatization in OLP and OLL patients in comparison with the orofacial pain patients group suffering from myofascial pain in which the involvement of psychiatric comorbidities has been established.

2.1 RESEARCH OBJECTIVES

- To assess the anxiety, depression and somatization levels in patients suffering from OLP/OLL using the SCL-90R instrument.
- To compare anxiety, depression and somatization levels between:
    - OLP patients vs. OLL patients
    - OLP patients vs. healthy controls
    - OLL patients vs. healthy controls
    - OLP patients vs. myofascial pain patients

    - OLL patients vs. myofascial pain patients
- To determine and compare the levels of pain aversiveness and pain intensity of OLP and OLL patients.

2.2 HYPOTHESES

We hypothesized that SCL-90R scores for depression, anxiety, and somatization would be higher in OLP and OLL patients than healthy controls; OLP patients would have higher SCL-90R scores than OLL patients; and SCL-90R scores for OLP and OLL patients would be lower than for myofascial pain patients.

We also hypothesized that OLP patients would have higher pain aversiveness and pain intensity scores than OLL patients.

Chapter 3. METHODS AND MATERIALS

3.1 OVERVIEW

A combined retrospective chart review and prospective cross-sectional study was conducted to assess levels of anxiety, depression and somatization with/without pain in OLP patients and OLL patients compared to controls and patients with myofascial pain.

3.2 STUDY POPULATION AND ELIGIBILITY CRITERIA

3.2.1 *Patients with OLP/OLL*

The study setting was the Oral Medicine Clinical Services (OMCS) clinic at University of Washington. The subjects were examined by Oral Medicine specialists in OMCS clinic to confirm the diagnosis of OLP or OLL The diagnosis of OLL and OLP was done clinically, with or without biopsy.

This study included patients attending the OMCS from January 2011 until March 2017. The SCL-90R and VAS instruments for pain aversiveness and pain intensity were reviewed for patients who attended the OMCS beginning in January 2011 in order to identify patients eligible to be included in the study. We identified 127 OLP patients, 46 OLL patients and 11 patients having both OLP & OLL during this period. One patient was diagnosed with OLP initially which transformed into squamous cell carcinoma. The SCL-90R scores of OLP and OLL patients were recorded. Out of 185 patients, 176 patients completed the SCL- 90R and VAS instruments at the initial visit and 9 patients completed the SCL-90R questionnaire at later visits. The number of days between the initial visit and the visit when these 9 patients filled SCL-90R ranged from 25 days to 2002 days.

Subjects who could read and understand English and were 18 years old or older were eligible. Patients exhibiting dysplasia histopathologically were excluded. Patients diagnosed (clinically, with or without biopsy) with paraneoplastic lesions, candida or any other mucosal lesions were not included in the study. There were 19 patients with possible or confirmed candidiasis, and 5 patients with other lesions (leukoplakia, squamous cell carcinoma, moderate epithelial dysplasia, cold sores in the oral cavity) other than OLP were excluded. After excluding these patients, we had total of 161 patients in our study group. There were 112 patients diagnosed with OLP, 40 diagnosed with OLL, and 9 had diagnoses of both OLP and OLL.

3.2.2 *Patients with Myofascial Pain*

Data from 185 participants who were diagnosed with myofascial pain in the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) Validation study, recruited from the University of Washington, [40] were also included for analysis and comparison with our OLP/OLL sample. Participants were 18 to 70 years old. For the myofascial palpation test the pressure of 2 to 4 pounds of pressure was used as the examination protocol for palpation of masseter and temporalis muscles. This study evaluated the validity and reliability of Axis I (physical) and Axis II (psychological) factors of the RDC/TMD. Participants were recruited from August 2003 until September 2006.

The participants completed the Axis II instruments of the SCL-90R and the Graded Chronic Pain Scale [38]. The SCL-90R scale in this study included 90 items (See Appendix C for the questions). The symptom dimensions assessed with this scale were: Depression, Vegetative, Somatization-pain, Somatization-no pain, Somatization full, Anxiety, Obsessive Compulsive, Interpersonal sensitivity, Hostility, Phobia, Paranoid, Psychotic, Global Severity Index. It included 13 Depression scale items along with 7 additional items to evaluate vegetative symptoms of

Depression and the Nonspecific Physical Symptoms (Somatization) instrument consisting of 12 items. These are identical to the corresponding items in SCL-90R scale by Derogatis et al [41].

Total of 90 healthy participants from the RDC/TMD study [40] were used as a control group. This is a multisite study and patients were recruited from University at Buffalo (UB), University of Minnesota (UM) and University of Washington (UW). The control patients were healthy individuals with negative history of pain, depression or nonspecific physical symptoms.

The inclusion criteria for healthy controls were [40]: no lifetime history of TMD symptoms ("supercontrols") or if they had no history of TMD symptoms in last 6 months ("controls") and prior to 6 months ago there were no more than 5 isolated episodes of TMJ noise, with each episode lasting less than 1 day and not associated with jaw pain or limited mouth opening, and no more than 1-2 isolated episodes of locking or catching of the jaw in wide open mouth position, and no headaches in temporal area affected by jaw movement, function, or parafunction. On clinical examination, the control and supercontrol patients had no symptoms of TMD (like any pain in the joint, clicking or crepitus). The magnetic resonance imaging (MRI) and computed tomography (CT) of TMJ were negative for anterior disc displacement and osteoarthrosis.

The participants diagnosed with myofascial pain and control subjects were excluded if they had history of [40]:

a. Systemic rheumatic, neurologic/neuropathic, endocrine, or immune/autoimmune diseases or wide spread pain. (Exception: participants with medical documentation of rheumatoid arthritis or fibromyalgia).
b. Pathologic processes found on imaging including neoplasm (Exception: Disc displacements and osteoarthritis/osteoarthrosis)
c. Radiation treatment to head and neck.

d. TMJ surgery.
e. Trauma to jaw in the last 2 months (exclusion regardless of time: jaw trauma from auto accident).
f. Presence of non-TMD orofacial pain disorders.
g. Pregnancy.
h. Unable to participate due to language barrier or mental/intellectual incompetence.
i. Use of narcotic pain medication, muscle relaxants or steroid therapy unless discontinued for 1 week prior to examination.
j. Use of antidepressant drugs unless the participant has been on a stable dose for 60 days.
k. Use of prescription or over-the-counter nonsteroidal anti-inflammatory medications unless the medication(s) were discontinued for 3 days prior to the examination (use of acetaminophen was allowed as a rescue drug).
l. Drug abuse.
m. Ongoing dental treatments.
n. Wearing dentures.
o. Contraindications for imaging.
p. Ongoing TMD treatments unless on a stable regimen for at least 2 months.
q. Unable or unwilling to give informed consent.

The patients diagnosed clinically with non-TMD orofacial pain disorders or if they were diagnosed with any TMJ related or non-TMJ related pathologies on imaging were also excluded.

3.3 DATA COLLECTION METHODS

3.3.1 *SCL-90R*

The SCL-90 was initially developed by Derogatis in 1973 and was originally oriented towards symptomatic behavior of psychiatric patients. It has since been used as an instrument to measure the psychosocial distress and assess the symptom severity along with the psycho-somatization in variable population [42].

In the OMCS at the University of Washington School of Dentistry, a shortened (46-item) and revised SCL-90R version is used to assess psychosocial distress for a time frame of the previous one month. Each item of the questionnaire is rated by the patient on a five-point scale of distress from 0 ("not at all"), 1 ("A little bit"), 2 ("Moderate"), 3 ("Quite a bit"), 4 ("extreme").

The SCL-90R consists of the following principle symptom dimensions labeled as: Depression, Anxiety, and Somatization.

- **Depression**: This dimension is composed of symptoms that manifest dysphoric mood and affect, signs of withdrawal of life interest, and lack of motivation. Feelings of worthlessness, thoughts of suicide, and cognitive and somatic correlates of depression are included. Twenty questions are included under this measure.
    - The questions included under this subscale are: "Loss of sexual interest or pleasure", "Feeling low in energy or slowed down", "Sleep that is restless or disturbed", "Poor appetite", "Crying easily", "Feeling of being caught or trapped", "Blaming yourself for things", "Feeling lonely", "Feeling blue", "Worrying too much about things", "Feeling no interest in things", "Trouble falling asleep", "Feeling hopeless about future", "Thoughts of death or dying", "Overeating", "Awakening in the early

morning", "Thoughts of ending your life", "Feeling everything is an effort", "Feelings of worthlessness", "Feelings of guilt".

- **Anxiety**: Symptoms associated with anxiety like nervousness, tension, trembling, feelings of horror and panic are reflected here. Ten questions are included on this measure.
    - The questions included under this subscale are: "Nervousness or shakiness inside", "Trembling", "Suddenly being scared for no reason", "Feeling fearful", "Heart pounding or racing", "Feeling tense or keyed up", "Spells of terror or panic", "Feeling so restless you couldn't sit still", "The feeling that something bad is going to happen", "Thoughts and images of a frightening nature".
- **Somatization**: This dimension focuses on distress arising from perceptions of bodily dysfunctions (Derogatis, 1975). Twelve questions are included under the 'somatization' subscale.
    - The questions included in the 'Somatization' subscale are: "Headaches", "Faintness or dizziness", "Pain in the heart or chest", "Pain in the lower back", "Nausea or upset stomach", "Soreness of your muscles", "Trouble getting your breath", "Hot or cold spells", "Numbness or tingling in parts of your body", "A lump in your throat", "Feeling weak in parts of your body", "Heavy feelings in your arms or legs".
    - **Somatization without pain:** Seven items were used from the Somatization subscale above to create a subset of items that represent 'somatization without pain'.

      The items included in this subscale were: "Faintness or dizziness", "Trouble getting your breath", "Hot or cold spells", "Numbness or tingling in parts of your body", "A lump in your throat", "Feeling weak in parts of your body", "Heavy feelings in your arms or legs".

- The four additional questions included in the SCL-90R scale were clinically relevant for the providers but donot load onto any of the scales mentioned above. The questions are: “Feeling easily annoyed or irritated”, “Difficulty making decisions”, “The idea that something is wrong with your body”, “The idea that something is wrong with your mind”.

3.3.2 *SCL-90R Measures*

Preliminary normative values have been assessed based on the population of over 1000 psychiatric outpatients for the SCL-90 scale [37]. An individual is said to have normal levels of anxiety if the score is less than 0.445, moderate if it lies between 0.445 to less than 1.105 and severe anxiety if it is more than 1.105 . For the clinical subscale of depression, the normal range involves scores less than 0.535, moderate if the score lies between 0.535 to less than 1.100, and severe if it is more than 1.100. For the subscale of somatization with pain, the score is normal if it is less than 0.500, moderate if it lies between 0.500 to less than 1.000 and severe if it is greater than 1.000. For the subscale of somatization without pain, the score is considered normal if it is less than 0.428, moderate if it lies between 0.428 to less than 0.857 and severe if it is greater than 0.857.

Table 3.1: SCL-90R Score Comparison

	Normal	Moderate	Severe
Anxiety	<.445	.445 to <1.105	>1.105
Depression	<.535	.535 to 1.100	>1.100
Somatization	<.500	.500 to <1.000	>1.000
Somatization w/o Pain	<.428	.428 to .857	>.857

3.3.3 *SCL-90R Questionnaire*

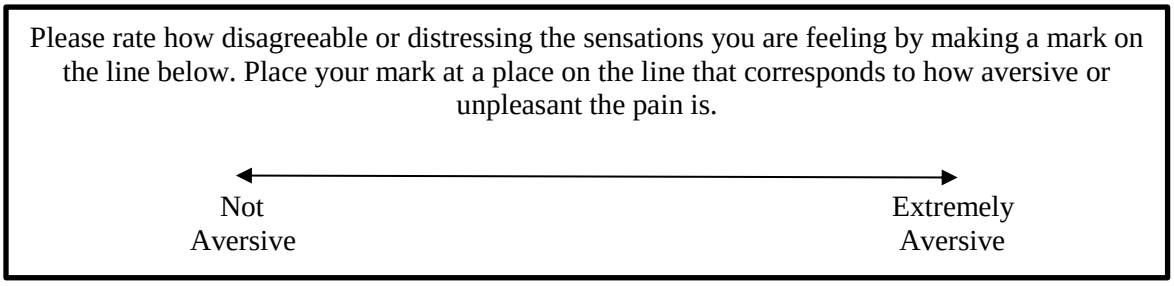
The SCL-90R form completed by the OLP and OLL study group is shown in Appendix A. The SCL- 90R questionnaire that was given to myofascial pain and control subjects is shown in Appendix B.

3.3.4 *Visual Analog Scale (VAS)*

Pain aversiveness and intensity ratings of the Chronic Graded Pain Scale are calculated by using a standard 100 mm VAS. This is a quick and extensively used questionnaire that can be used to measure changes in pain levels across various medical complications like rheumatic disorder, chronic pain problems, etc.[43]. These are simple and easy to use especially with people who have difficulty with complicated questionnaires [44]. This VAS scale has been reported to be used in diverse populations and many studies have reported its good reliability [45-48] and validity [49, 50].

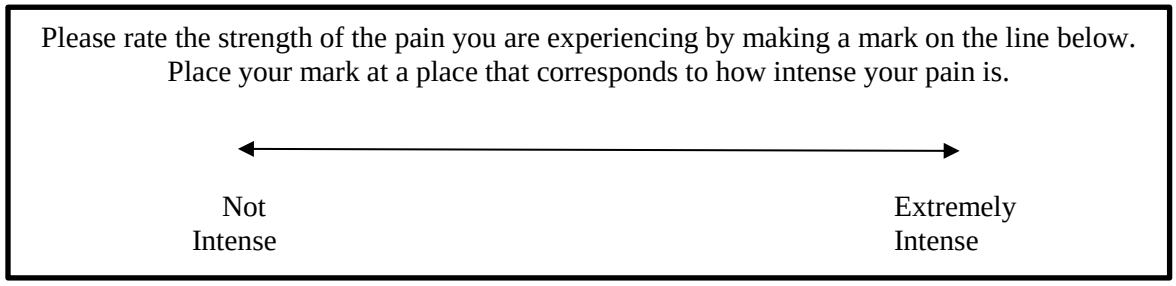
Pain Aversiveness: Patients were asked to place a mark anywhere on the line that corresponded to how aversive or unpleasant their pain is.

Figure 3.1: Pain Aversiveness Scale



Pain Intensity Rating: Similar to pain aversiveness, pain intensity is calculated by measuring the placement of a mark (from 0-100 mm), placed by the patient on the scale that corresponds to the strength/intensity of the patient's pain.

Figure 3.2: Pain Intensity Scale



The VAS used for the description of pain aversiveness and pain intensity should have standard length of 100mm. The photocopying of the forms resulted in the variability in to the standard 100 mm VAS. Therefore, the adjustments were made for the measurement by using the formula mentioned below:

B= Length of the VAS in mm

A= Measure of score on B mm VAS

X= converted equivalent if 100 mm VAS

X= A x 100/B

Chapter 4. STATISTICAL ANALYSIS

Data for OLL and OLP patients were extracted from OMCS patient records and entered into a REDCap form (Research Electronic Data Capture, hosted at the University of Washington), described in the appendices. The information from the REDCap form was exported into an Excel spreadsheet and then into SAS 9.3 (SAS Institute, Cary, NC) and R3.3 for analysis [51].

To describe the sociodemographics of the study groups, the following variables were considered: age, gender, race, insurance (public insurance (Medicaid or Medicare) versus private insurance versus self-pay) and education level as proxy for socioeconomic status, and duration of chief complaint/ pain.

Descriptive statistics were computed separately for the four study groups (OLP, OLL, myofascial pain and control subjects), including mean and standard deviation for symmetrically distributed continuous measures (e.g., pain measures), median and interquartile range for skewed continuous measures (e.g., SCL-90R measures), and frequency and percent for categorical measures (e.g., SCL-90R categories). Average pain aversiveness and pain intensity was compared between OLL and OLP patients using a two-sample test and analysis of covariance, which adjusted for age, sex, symptoms (symptomatic versus asymptomatic), and biopsy diagnosis. Given the distributions of SCL-90R subscales were skewed, the four study groups were compared using the nonparametric Kruskal-Wallis test and post-hoc pairwise comparisons using Dunn's method [52].

Categories of SCL-90R subscales (normal, moderate or severe) were first compared among the four study groups using the chi-square test and post-hoc pairwise comparisons using Holm's method to account for the multiple testing [51]. Given the small number of subjects with severe SCL-90R scores, moderate and severe categories were combined for analyses that compared the four study groups, which adjusted for age and gender. Log-binomial regression was used for these

analyses, producing adjusted relative risks, and Holm's method was used for the post-hoc pairwise comparisons [53]. A 0.05 significance level was used to determine statistical significance.

We identified 112 OLP patients, 40 OLL patients and 9 patients diagnosed with both OLP and OLL from OMCS records between January 2011 and March 2017 who met the inclusion and exclusion criterias. The 9 patients with both OLP and OLL were not used for linear regression bivariate comparisons and chi square tests, thus we considered 152 patients in our study group for analysis. The two comparison groups consisted of 90 healthy controls and 185 subjects with a myofascial pain diagnosis from the RDC/TMD Validation study. The sample sizes were predicted to provide estimate with sufficient precision to describe the average symptom and pain levels OLL and OLP patients, and to compare the healthy controls and myofascial pain group. The expected sample sizes for OLL and OLP patients were calculated to provide precision of ¼ standard deviation or smaller for estimates of the average symptom and pain levels and precision of at least 12% or smaller for estimates of the rate of moderate to severe symptoms. A power of 80% or greater was calculated to demonstrate a difference of 0.5 standard deviation or larger in average symptom levels among the four study groups.

Chapter 5. RESULTS

5.1 DEMOGRAPHICS

We identified 161 eligible OLP and OLL patients who completed SCL-90R questionnaire. They were identified through the chart review between January 2011 and March 2017. The majority of patients were female (73.3%) and Caucasian (71.4%). The age of OLP and OLL patients ranged from 28 to 86 years old with a mean (SD) of 62.7 (12.5) years. Out of 161 patients sample, 69.6% of patients were diagnosed with OLP, 24.8% of patients were diagnosed with OLL, and 5.6% of patients had both OLL and OLP. Majority of the sample (65.6%) had private insurance, 6.9% had both private and state insurances and 26.9% had state insurance and 0.6% were self-pay. Out of 161 total patients, approximately 8.7% of the patients were unemployed, 49.1% were employed, 40.3% were retired and almost 1.9% did not report their occupation. Of 161 patients, 27 patients (16.8%) reported using antidepressants, 12 patients (7.5%) were using anxiolytics and 2 patients (1.2%) were using antipsychotics. Other prescription medications (81.4%) and over the counter medications (83.2%) were most used by the majority of the patients.

We did not consider patients diagnosed with both OLP and OLL for further statistical analyses because of this group's small size (n=9). Thus, a total of 152 patients was used for the remaining analyses. Detailed demographic description of OLP and OLL study groups is shown in **Table 5.1**. The diagnosis for more than half of the total patients (57.9%) in the study group was confirmed by biopsy. Most of the OLL patients (82.5%) and almost half of the OLP diagnoses (49.1%) were biopsy confirmed. Detailed demographics with biopsy and non-biopsy diagnosed OLP and OLL can be seen in **Table 5.2**. Most patients (60.5%) had a chief complaint of redness/inflammation, followed by a complaint of pain in 50.0% of the sample. The details of other complaints and their frequencies are shown in **Table 5.4**. The duration of the chief complaint for patients who reported

this, ranged from approximately 0.8 month to 420 months with a mean (SD) of 47.4 (75.0) months. Eight patients didn't complete the information about duration of their chief complaint.

The two comparison groups consisted of 90 controls and 185 myofascial pain subjects from the RDC/TMD validation study. There were 65.6% females in the control group and the majority of patients were Caucasian (84.4%). The age of the controls ranged between 18 and 66 years old with a mean (SD) of 35.8 (12.8) years. The myofascial pain group also consisted primarily of females (85.4%) and Caucasians (88.6%) (**Table 5.3**). The age of the participants in myofascial group ranged between 18 and 67 years old with a mean (SD) of 37.6 (13.4) years.

5.2 PSYCHOSOCIAL DESCRIPTORS

5.2.1 *Anxiety*

For the anxiety subscale, the myofascial pain group showed the highest score with a median (IQR) of 0.2 (0.0-0.4), followed by the OLP group with a median (IQR) score of 0.1 (0.0-0.3), the OLL group with a median (IQR) score of 0.0 (0.0-0.1), and finally the control group with a median (IQR) score of 0.0 (0.0-0.1). We do not describe the means and standard deviations here as the results were highly skewed. **Table 5.5** shows the comparison of anxiety scores among OLP vs OLL vs myofascial pain vs control subjects.

In the OLP study group, 13.5% of patients had moderate and 4.5% of patients had severe anxiety. In the OLL group, 5.0% of patients had moderate and 5.0% had severe anxiety. Interestingly, the percentage of patients in the myofascial pain group with moderate anxiety was 12.4%, which was slightly lesser than in OLP group, while 10.3% had severe anxiety. In the control group, 6.7% patients had moderate anxiety and none had severe anxiety **(Table 5.6).**

Figure 5.1 shows the bivariate analysis/comparision of anxiety for OLP vs OLL vs controls vs myofascial pain subjects. There was a statistically significant difference between myofascial pain and control group. The unadjusted results are reported in **Table 5.7** and adjusted results are reported in **Table 5.8**. The subjects in myofascial pain group were more likely to have moderate/severe anxiety than control patients after adjusting for age and gender (adjusted RR = 3.3, 95% CI: 1.5 to 7.4, $p<0.05$). The difference between OLP and OLL patients, OLL and controls was not statistically significant after adjusting for age and gender. The difference between OLP and controls was not statistically significant after adjusting for multiple comparisons. However, the trend towards significance was seen in the OLP patients (adjusted RR = 3.3, 95% CI: 1.2 to 9.2, $p=0.02$) with relatively higher risk to develop moderate/severe anxiety than controls.

5.2.2 *Depression*

For the depression subscale, the myofascial pain group had the highest median score of 0.4 and IQR of (0.2-0.9), followed by OLP group with a median (IQR) of 0.3 (0.2-0.7), then the OLL group with a median (IQR) of 0.3 (0.2-0.5), and finally the control group with a median (IQR) score of 0.2 (0.1-0.5) (**Table 5.5**).

In the OLP group, 22.3% of patients were found to have moderate and 11.6% had severe depression. In the OLL group, 15.0% had moderate and 7.5% had severe depression. The prevalence of depression in the OLP group was comparable to the myofascial pain group, in which 25.4% of patients had moderate and 16.8% had severe depression. In the control group, 14.4% of patients had moderate depression scores and 4.4% had severe depression scores (**Table 5.6)**.

Figure 5.2 shows the comparison of depression scores of OLP vs OLL vs controls vs myofascial pain subjects. The unadjusted results are reported in **Table 5.7** and adjusted results in **Table 5.8**. Myofascial pain subjects were more likely to have moderate/severe depression than

control patients after adjusting for age and gender (adjusted RR = 2.1, 95% CI: 1.3 to 3.3, $p<0.05$). There was no significant difference between the OLP and myofascial pain groups with regards to depression. The difference between OLP and OLL patients, OLL and controls was not statistically significant after adjusting for age and gender. OLP patients had significantly ($p=0.02$) higher depression scores than did control patients without adjusting for age and gender. However, the difference was no longer significant after adjusting for age and gender between OLP and controls (adjusted RR = 1.4, 95% CI: 0.8 to 2.5, $p>0.05$).

5.2.3 *Somatization*

For the somatization scale, the myofascial pain group showed the highest median (IQR) score of 1.2 (0.6-1.8), followed by the OLP group with a median (IQR) score of 0.3 (0.1-0.7), the OLL group with a median (IQR) score of 0.2 (0.1-0.6), and finally the control group with a median (IQR) score of 0.2 (0.0-0.4) (**Table 5.5**).

In the OLP study group, 18.8% of patients had moderate and 17.0% patients had severe somatization. In the OLL group, 17.5% of patients had moderate and 10.0% had severe somatization. Interestingly, the percentage of patients having moderate somatization in the myofascial pain group was 23.8%, and 56.8% had severe somatization, which is remarkably high percentage of the sample. In the control group, 16.7% of patients had moderate somatization and 6.7% had severe somatization (**Table 5.6)**.

Figure 5.3 shows the bivariate analysis /comparison of somatization for OLP vs OLL vs controls vs myofascial pain subjects. Myofascial pain subjects had significantly higher ($p<0.0001$) somatization scores than other three groups, whereas the results were not significant difference for OLP, OLL and control groups. The unadjusted results for somatization are reported in **Table 5.7** and adjusted results are reported in **Table 5.8**. After adjusting for age and gender, myofascial pain

subjects were most likely to have moderate/severe somatization than control patients (adjusted RR = 3.2, 95% CI: 2.2 to 4.6, p <0.05). There was significant difference seen in the OLP vs myofascial groups (adjusted RR = 0.5, 95% CI: 0.3 to 0.6, p<0.05) and the OLL vs myofascial groups (adjusted RR= 0.4, 95% CI: 0.2 to 0.6, p<0.0.5). There was no statistically significant difference in somatization between OLP group and control group after adjusting for age and gender (adjusted RR=1.5, 95% CI: 0.9 to 2.3, p=0.11). Females were more likely than males to have moderate/severe somatization (RR = 1.48; 95% CI: 1.1 to 1.9; p = 0.004). There was a significant interaction between study groups and sex (p=0.039). The association (myofascialvs the other 3 groups) was stronger in males than females, but the differences were small.

5.2.4 *Somatization without pain*

For the somatization without pain scale, the OLP group showed the highest median (IQR) score of 0.3 (0.0-0.6), followed by the myofascial pain group with a median (IQR) score of 0.1 (0.0-0.6), the OLL group with a median (IQR) score of 0.1 (0.0- 0.4), and finally the control group with a median (IQR) score of 0.0 (0.0) (**Table 5.5**).

For somatization without pain, 19.6% of patients had moderate and 18.8% of patients had severe scores in the OLP group, while in the OLL group, 15.0% patients had moderate and 12.5% had severe somatization without pain. The percentage of patients having moderate somatization without pain in the myofascial pain group was 20.5% and 14.1% had severe somatization with pain, which is almost equal in prevalence as the OLP group. Interestingly, in the control group, 2.2% patients had moderate and 3.3% had severe somatization without pain; this is significantly lower percentage than in the other groups (**Table 5.6**).

Figure 5.4 shows the bivariate analysis /comparison of somatization without pain scores of OLP vs OLL vs controls vs myofascial pain subjects. Control patients had lower somatization

without pain item scores than the other three groups. There was a significant difference seen between control groups versus the TMD, OLP and OLL groups ($p<0.05$). The unadjusted results are shown in **Table 5.7**. After adjusting for age and gender, it was identified that OLP patients were more likely to have moderate/severe somatization without pain than controls (adjusted RR = 4.1, 95% CI: 1.6 to 10.4, $p<0.05$) (**Table 5.8**). Also, the myofascial pain subjects were more likely to have moderate/ severe somatization without pain than control patients (adjusted RR = 5.4, 95% CI: 2.3 to 12.8, $p<0.05$). The myofascial pain subjects were seen to be more likely to have moderate/severe somatization without pain than OLP group (adjusted RR = 4.1, 95% CI: 1.6 to 10.4, $p<0.05$). It has been noted that the difference between the OLL and control group patients was significant (adjusted RR =3.3, 95% CI: 1.2 to 9.2, $p=0.02$) but the increased risk was not significant after adjusting for multiple comparisons.. Older subjects were more likely to have moderate severe somatization without pain (RR = 1.0; 95% CI: 1.0 to 1.03; $p = 0.005$). Also, females were more likely than males to have moderate/severe somatization (RR = 2.1; 95% CI: 1.2 to 3.5; $p = 0.006$).

5.3 Pain Aversiveness and Pain Intensity

The pain aversiveness and pain intensity scores were higher on average qualitatively, for the OLP group as compared to the OLL group. Pain aversiveness for 83 OLP patients ranged between 1.4 and 100 with the mean (SD) of 51.0 (28.3). Pain aversiveness for 35 OLL patients ranged between 1.8 and 100 with the mean (SD) of 39.0 (29.1). Pain intensity for 82 OLP patients ranged between 0.5 and 100.0 with the mean (SD) 45.9 (29.4). Pain intensity for OLL patients ranged between 2 and 88.7 with the mean (SD) 32.2 (27.0) (**Table 5.9**).

Average pain aversiveness was significantly higher for OLP than for OLL patients without adjusting for the variables (difference=12.0, 95% CI: 0.4 to 23.6; $p = 0.043$). However, the

difference was no longer significant after adjusting for age and sex (difference = 10.1; p=0.089). Results were similar after adjusting for symptoms (symptomatic or asymptomatic) and biopsy. Similarly, the average pain intensity was significantly higher for OLP than OLL patients without adjusting for the variables (difference = 13.7, 95%CI: 2.0 to 25.4; p=0.02). As seen with pain aversiveness, the difference was attenuated and no longer significant after adjusting for age and gender (difference = 11.7; p=0.063). The results were similar (no longer significant) when adjusted for symptoms and biopsy.

Figure 5.1: Comparison of Anxiety Scores

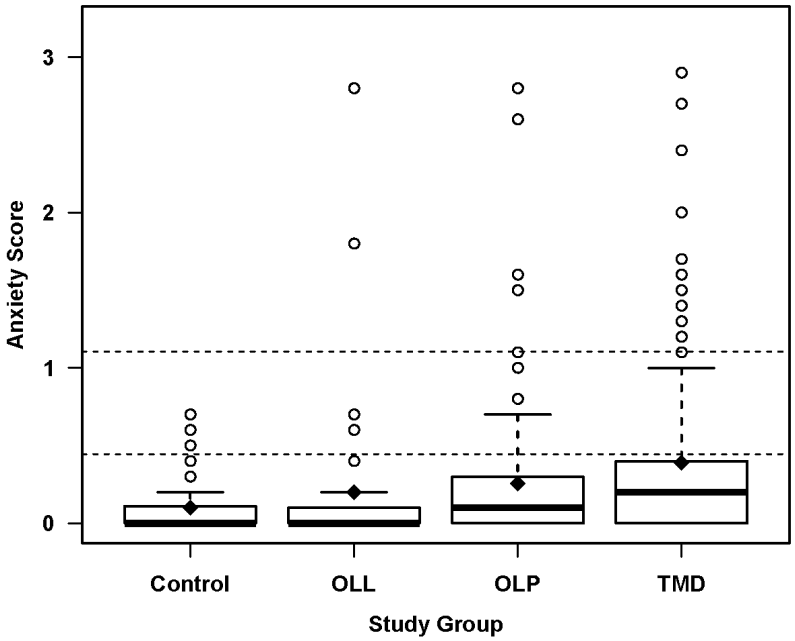
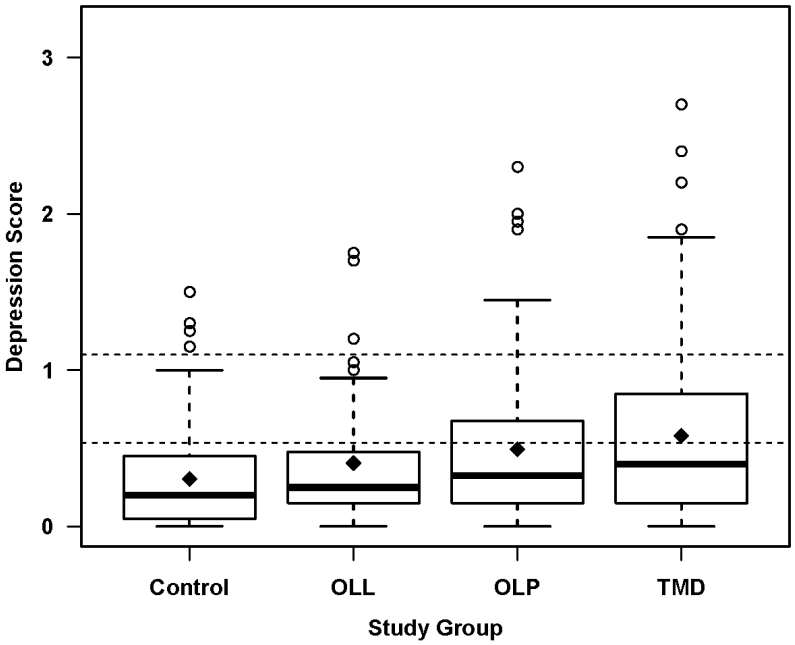


Figure 5.2: Comparison of Depression Scores



(Horizontal lines at cut points depicts moderate and severe levels)
(TMD = Myofascial pain subjects)

Figure 5.3: Comparison of Somatization Scores

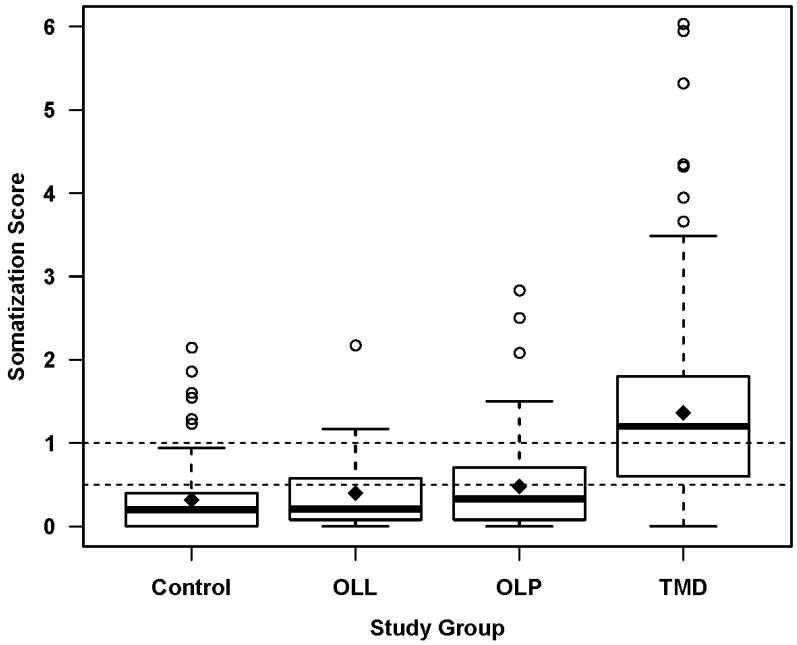
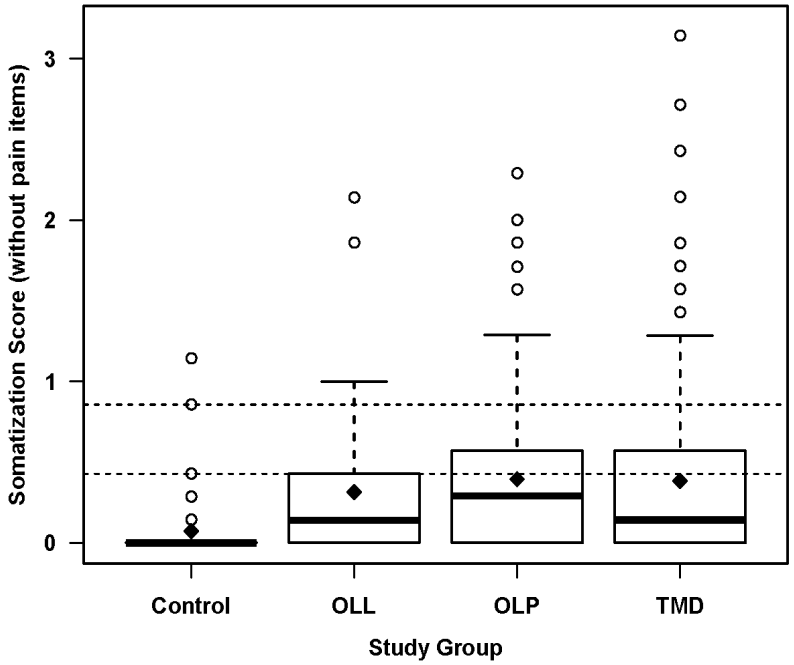


Figure 5.4: Comparison of Somatization without Pain Scores



(Horizontal lines at cut points depicts moderate and severe levels)
(TMD = Myofascial pain subjects)

Table 5.1: Patient Demographics: OLP and OLL

		OLP		OLL	
		N	***%***	***N***	***%***
Age					
	28-37	6	5.4%	4	10.0%
	38-47	8	7.1%	3	7.5%
	48-57	17	15.2%	5	12.5%
	58-67	34	30.4%	16	40.0%
	68-77	37	33.0%	9	22.5%
	78+	10	8.9%	3	7.5%
Gender					
	Female	87	77.7%	27	67.5%
	Male	25	22.3%	13	32.5%
Race					
	Asian	10	8.9%	2	5.0%
	African-American	1	0.9%	2	5.0%
	Caucasian	84	75.0%	24	60.0%
	East Indian	6	5.4%	2	5.0%
	*Other**	1	0.9%	2	5.0%
	Unknown/Not Reported	10	8.9%	8	20.0%
Insurance					
	Private	70	63.1%	29	72.5%
	Public	32	28.8%	8	20.0%
	Both	8	7.2%	3	7.5%
	Self pay	1	0.9%	0	0.0%
Occupation					
	Employed	48	42.9%	26	65.0%
	Unemployed	12	10.7%	2	5.0%
	Retired	49	43.8%	12	30.0%
	Not reported	3	2.7%	0	0.0%
Medications					
	Antidepressants	16	14.3%	9	22.5%
	Anxiolytics	10	8.9%	0	0.0%
	Antipsychotics	2	1.8%	0	0.0%
	Other prescription	92	82.1%	31	77.5%
	OTC	94	83.9%	33	82.5%
Symptoms					
	Symptomatic	91	81.3%	35	87.5%
	Asymptomatic	21	18.8%	5	12.5%
Diagnosis					
	Biopsy	55	49.1%	33	82.5%
	Non-biopsy	57	50.9%	7	17.5%

**Other - includes Hispanic*

Table 5.2: Patient Demographics: OLP and OLL (Biopsy & Non-biopsy)

		OLP *Biopsy*		**OLP** *Non-biopsy*		**OLL** *Biopsy*		**OLL** *Non-biopsy*	
Age									
	Mean (SD)	62.69 (10.83)		64.28 (13.69)		61.64 (12.44)		55.43 (15.39)	
		N	*%*	*N*	*%*	*N*	*%*	*N*	*%*
Gender									
	Female	41	74.5%	46	80.7%	20	60.6%	7	100%
	Male	14	25.5%	11	19.3%	13	39.4%	0	0.0%
Race									
	Asian	5	9.1%	5	8.8%	2	6.1%	0	0.0%
	African-American	0	0.0%	1	1.8%	1	3.0%	1	14.3%
	Caucasian	42	76.4%	42	73.7%	20	60.6%	4	57.1%
	East Indian	3	5.5%	3	5.3%	2	6.1%	0	0.0%
	*Other**	1	1.8%	0	0.0%	2	6.1%	0	0.0%
	Unknown/Not Reported	4	7.3%	6	10.5%	6	18.2%	2	28.6%
Insurance									
	Private	36	66.7%	34	59.6%	23	69.7%	6	85.7%
	Public	15	27.8%	17	29.8%	8	6.1%	0	0.0%
	Both	2	3.7%	6	10.5%	2	3.7%	1	14.3%
	Self pay	1	1.9%	0	0.0%	0	0.0%	0	0.0%
Occupation									
	Employed	24	44.4%	24	41.4%	20	60.6%	6	85.7%
	Unemployed	7	13.0%	5	8.6%	2	6.1%	0	0.0%
	Retired	22	40.7%	27	46.6%	11	33.3%	1	14.3%
	Not reported	1	1.9%	2	3.4%	0	0.0%	0	0.0%
Medications									
	Antidepressants	7	12.7%	9	15.8%	6	18.2%	3	42.9%
	Anxiolytics	5	9.1%	5	8.8%	0	0.0%	0	0.0%
	Antipsychotics	0	0.0%	2	3.5%	0	0.0%	0	0.0%
	Other prescriptions	47	85.5%	45	78.9%	25	75.8%	6	85.7%
	OTC	44	80.0%	50	87.7%	28	84.8%	5	71.4%

**Other - includes Hispanic*

Table 5.3: Patient Demographics: OLP, OLL, Myofascial, Control Subjects

		OLP		OLL		Myofascial		Control	
		N	***%***	***N***	***%***	***N***	***%***	***N***	***%***
Age									
	18-27	0	0.0%	0	0.0%	60	32.4%	28	31.1%
	28-37	6	5.4%	4	10.0%	39	21.1%	26	28.9%
	38-47	8	7.1%	3	7.5%	32	17.3%	17	18.9%
	48-57	17	15.2%	5	12.5%	39	21.1%	14	15.6%
	58-67	34	30.4%	16	40.0%	15	8.1%	5	5.6%
	68-77‡	37	33.0%	9	22.5%	-	-	-	-
	78+‡	10	8.9%	3	7.5%	-	-	-	-
Gender									
	Female	87	77.7%	27	67.5%	158	85.4%	59	65.6%
	Male	25	22.3%	13	32.5%	27	14.6%	31	34.4%
Race									
	*AI/AN**	0	0.0%	0	0.0%	2	1.1%	1	1.1%
	Asian	10	8.9%	2	5.0%	9	4.9%	6	6.7%
	African-American	1	0.9%	2	5.0%	4	2.2%	5	5.6%
	Caucasian	84	75.0%	24	60.0%	163	88.6%	76	84.4%
	East Indian‡	6	5.4%	2	5.0%	-	-	-	-
	*NH/PI***	0	0.0%	0	0.0%	1	0.5%	0	0.0%
	*Other****	1	0.9%	2	5.0%	5	2.7%	2	2.2%
	Unknown/Not Reported‡	10	8.9%	8	20.0%	-	-	-	-

**AI/AN - American Indian/Alaskan Native*

***NH/PI - Native Hawaian / Other Pacific Islander*

****Other - Includes Hispanic*

‡ *Not categorized in Myofascial & Control groups*

Table 5.4: Chief Complaint

Chief Complaints	No. of Patients	Percentage
Redness / Inflamation	92	60.5%
Pain	76	50.0%
White lesions	65	42.8%
Ulceration	49	32.2%
Burning tongue or mouth	42	27.6%
Gum swelling, growth or swelling	26	17.1%
Loss of taste/abnormal taste/metallic taste	24	15.8%
Blisters	22	14.5%
Too little saliva / Dry mouth	18	11.8%
OLP/ lichenoid lesions	17	11.2%
Breath / Odors	13	8.6%
Infection	12	7.9%
Strange / Reduced smell	12	7.9%
Drooling sometimes/ too much saliva	11	7.2%
Increased plaque	9	5.9%
Altered consistency of saliva	7	4.6%
Palpable mass	6	3.9%
Numbness	3	2.0%
Metal allergies	2	1.3%
Others including: sore mouth, red lesion inside lip, leukoplakia, persistent sore spot on gum, mucosal changes	5	3.3%

Table 5.5: Median Scores of Anxiety, Depression, Somatization with and without Pain

		OLP	OLL	Myofascial Pain	Control
Anxiety					
	Median	0.10	0.00	0.20	0.00
	(25th - 75th percentile)	(0.0 - 0.3)	(0.0 - 0.1)	(0.0 - 0.4)	(0.0 - 0.1)
Depression					
	Median	0.33	0.25	0.40	0.20
	(25th - 75th percentile)	(0.2 - 0.7)	(0.2 - 0.5)	(0.2 - 0.9)	(0.1 - 0.5)
Somatization					
	Median	0.33	0.21	1.20	0.20
	(25th - 75th percentile)	(0.1 - 0.7)	(0.1 - 0.6)	(0.6 - 1.8)	(0.0 - 0.4)
Somatization w/o Pain					
	Median	0.29	0.14	0.14	0.00
	(25th - 75th percentile)	(0.0 - 0.6)	(0.0 - 0.4)	(0.0 - 0.6)	(0.0 - 0.0)

Table 5.6: Anxiety, Depression, Somatization with and without Pain in Study Groups

		OLP	OLL	Myofascial Pain	Control
		N (%)	*N (%)*	*N (%)*	*N (%)*
Anxiety					
	Normal	91 (82.0%)	36 (90.0%)	143 (77.3%)	84 (93.3%)
	Moderate	15 (13.5%)	2 (5.0%)	23 (12.4%)	6 (6.7%)
	Severe	5 (4.5%)	2 (5.0%)	19 (10.3%)	0 (0%)
Depression					
	Normal	74 (66.1%)	31 (77.5%)	107 (57.8%)	73 (81.1%)
	Moderate	25 (22.3%)	6 (15.0%)	47 (25.4%)	13 (14.4%)
	Severe	13 (11.6%)	3 (7.5%)	31 (16.8%)	4 (4.4%)
Somatization					
	Normal	72 (64.3%)	29 (72.5%)	36 (19.5%)	69 (76.7%)
	Moderate	21 (18.8%)	7 (17.5%)	44 (23.8%)	15 (16.7%)
	Severe	19 (17.0%)	4 (10.0%)	105 (56.8%)	6 (6.7%)
Somatization w/o Pain					
	Normal	69 (61.6%)	29 (72.5%)	121 (65.4%)	85 (94.4%)
	Moderate	22 (19.6%)	6 (15.0%)	38 (20.5%)	2 (2.2%)
	Severe	21 (18.8%)	5 (12.5%)	26 (14.1%)	3 (3.3%)

Table 5.7: Log-binomial Regression Results for Moderate/Severe vs Normal Symptoms (Unadjusted)

		OLL vs Control	OLP vs Control	Myofascial vs Control	OLL vs Myofascial	OLP vs Myofascial	OLP vs OLL
Anxiety							
	Risk Ratio (RR)	1.5	2.7	3.4*	0.4	0.8	1.8
	Confidence Limits(CL)	0.4 - 5.0	1.1 - 6.4	1.5 - 7.7	0.2 - 1.2	0.5 - 1.3	0.7 - 5.0
Depression							
	Risk Ratio (RR)	1.2	1.8	2.2*	0.5	0.8	1.5
	Confidence Limits(CL)	0.6 - 2.4	1.1 - 3.0	1.4 - 3.5	0.3-1.0	0.6 - 1.1	0.8 - 2.8
Somatization							
	Risk Ratio (RR)	1.2	1.5	3.5*	0.3*	0.4*	1.3
	Confidence Limits(CL)	0.6 - 2.2	1.0 - 2.4	2.4 - 5.1	0.2 - 0.6	0.3 - 0.6	0.7 - 2.8
Somatization w/o Pain							
	Risk Ratio (RR)	5.0*	6.9*	6.2*	0.8	1.1	1.4
	Confidence Limits(CL)	1.8 - 13.3	2.9 - 16.7	2.6 - 14.9	0.5 - 1.4	0.8 - 1.5	0.8 -2.4

** = Significant (P <0.05), Holm's post-hoc method for pairwise comparisions*

Table 5.8: Log-bionomial Regression Results for Moderate/Severe vs Normal Symptoms (Adjusted for Age & Gender)

		OLL vs Control	OLP vs Control	Myofascial vs Control	OLL vs Myofascial	OLP vs Myofascial	OLP vs OLL
Anxiety							
	Risk Ratio (RR)	1.9	3.3	3.3*	0.6	1.0	1.8
	Confidence Limits(CL)	0.5 - 6.8	1.2 - 9.2	1.5 - 7.4	0.2 - 1.6	0.5 - 2.0	0.6 - 4.9
Depression							
	Risk Ratio (RR)	1.0	1.4	2.1*	0.5	0.7	1.4
	Confidence Limits(CL)	0.5 - 2.1	0.8 - 2.5	1.3 - 3.3	0.2-0.9	0.5 - 1.0	0.8 - 2.6
Somatization							
	Risk Ratio (RR)	1.2	1.5	3.2*	0.4*	0.5*	1.2
	Confidence Limits(CL)	0.6 - 2.2	0.9 - 2.3	2.2 - 4.6	0.2 - 0.6	0.3 - 0.6	0.7 - 2.1
Somatization w/o Pain							
	Risk Ratio (RR)	3.3	4.1*	5.4*	0.6	0.8	1.2
	Confidence Limits(CL)	1.2 - 9.2	1.6 - 10.4	2.3 - 12.8	0.3 - 1.1	0.5 - 1.1	0.7 -2.1

** = Significant (P <0.05), Holm's post-hoc method for pairwise comparisions*

Table 5.9: Pain Aversiveness and Intensity

		OLP	OLL	p-value
Pain Aversiveness				0.089
	Mean	51.0	39.0	
	Std	28.3	29.1	
	95% CI	44.8 - 57.2	29.0 - 49.0	
Pain Intensity				0.063
	Mean	45.9	32.2	
	Std	29.4	27.0	
	95% CI	39.5 - 52.4	22.3 - 42.1	

Chapter 6. DISCUSSION

The main objective of this cross-sectional study was to evaluate psychosocial comorbidities in a sample of patients in Washington state and nearby areas diagnosed with OLP and OLL. The study was designed to assess the symptom dimensions of SCL-90R scale in these patients and compare them with the control population and myofascial pain subjects from RDC/TMD study.

In our study, the sample consisted of almost 78% females in the OLP group. Other OLP studies reported that females comprised 70% or higher in their study groups [7, 15, 27, 30, 35]. The mean age of the OLP/OLL patients in this study is similar to some studies [30][28] but it seems to be slightly higher than other studies [15, 27]. It is interesting to note that the mean age of myofascial pain subjects (38 years) and controls (36 years) is much lower than the patients with OLP (64 years) and OLL (61 years) in this study. The percentage of women in the myofascial pain group (85%) is higher than the average percentage of women in the control (66%), OLP (78%) and OLL (68%) groups in our study.

Only one previous study [36] has reported the psychologic aspects of OLL patients. The mean age of the sample in our study in OLL group (61 years) is higher than the mean age reported in their study (52 years) and they have more women (80%) as compared to our study which comprises of 68% females in OLL group.

We hypothesized that OLP patients would have higher psychosocial comorbidities than OLL and control patients. As expected, OLP patients had higher anxiety scores on average than OLL and control patients. However, after adjusting for multiple comparisons, the analysis indicates that there was no significant difference in SCL-90R values for anxiety in OLP and control patients. This finding is in line with a few previous reports that found no significant association between anxiety and the presence of OLP in patients [35][31][32][54]. In contrast, many studies have also

reported significantly high levels of anxiety [8 ,9, 15, 23-31]. This difference could be due to the different anxiety measures used in these studies [23-31]. The smaller sample size [55] or different kind of study groups could be another reason for different result. For instance, study done by Lundqvist et al had patients with oral and genital erosive lichen planus which is a chronic painful condition, in whom it is obvious to have high anxiety scores [23]. In our study, a trend towards significance was seen in the OLP patients with relatively higher risk to develop moderate/severe anxiety than controls.

OLP patients had higher depression scores on average as compared to controls. The difference, however, was not significant when adjusted for age and gender which could be due to a large difference (28 years) in the mean age of these groups. Some researchers have found the level of depression to be in the normal range in OLP patients [15, 25, 34] which is consistent with our study findings. Few studies have found a significant difference in depression scores between OLP patients and controls [23, 27, 30, 32]. This could be due to the small samples of OLP patients in some studies. For instance, one study [30] reported their OLP group consisted of 30 people. Alternatively, the difference could be due to a different scale like BDI used in this study to identify depression [33].

The levels of somatization in OLP and OLL patients were found to be non-significantly different as compared to controls. In contrast, a previous study found that OLP patients have higher somatization [9]. Our study found that 36% of OLP patients and 28% of OLL patients had moderate to severe somatization with pain as compared to 23% in controls.

The OLP patients in our study were more likely to have moderate/severe somatization without pain as compared to control and OLL patients. The scores for OLP patients were significantly higher than controls after adjusting for age and sex ($p<0.05$). No other study in past has decribed

the symptom dimension somatization without pain in OLP/OLL patients. However, it has been well studied that the presence of somatization and other psychological comorbidities might affect disease outcomes [56]. Also, somatization could mask the real symptomatology which could further lead to the worsening of the prognosis [57]. One study has stated that 'psychosomatic constitution' and the intensity of psychosocial stressors might play a significant role in the reactivation or even onset of OLP disease [58]. Therefore, it is highly important to diagnose these symptoms so that appropriate treatment can be sought.

The SCL-90R scores for the myofascial pain patients were higher than in OLP and OLL groups except for the somatization without pain subscale. The only study we found in the literature that compared stress, anxiety and depression between OLP and myofascial pain patients is Chaudhary et al, which found no significant difference between patients with OLP and the positive controls [24]. They identified equal levels of stress, anxiety and depression in OLP and control patients. One of the reasons could be that the positive control group in that study consisted of patients with burning mouth syndrome, and atypical pain patients in addition to myofascial pain patients. It is noted in our study that myofascial pain subjects had fairly higher values of somatization with pain as compared to patients with OLP, OLL and control subjects. It has been reported in previous studies that patients suffering from myofascial pain are seen to have more depression, and somatization as compared to patients with temporomandibular joint pain alone [38, 39, 59, 60]. This could be due to the multifactorial etiology and the chronic nature of their pain.

Another important outcome of the study was to compare the pain intensity and aversiveness between OLP and OLL patients. OLP patients in our study had more pain intensity and aversiveness than OLL patients on average. Therefore, it is not surprising to find that OLP patients

are noticed to have higher SCL-90R scores as compared to OLL and control subjects in this study. However, after adjusting for age, sex, symptoms and biopsy, there was no significant difference seen between OLP and OLL patients in pain aversiveness or intensity.

A significant limitation of this study is that it is a cross sectional observational study and therefore a causal relation cannot be implied by the results of this study. There is also a possibility of response bias in the self-reported questionnaires as the psychosocial measures have been assessed by the subjective measures. Also, there could be a possibility of misdiagnosis in differentiating between OLP and OLL. There has been a controversy seen in the literature regarding the appropriate distinction between OLP and OLL [61][62], but recent studies have suggested diagnostic criteria to differentiate between OLP and OLL [62]. We used clinical notes to record the diagnoses and almost half of the OLP patients (49%) and majority of the OLL patients (83%) were diagnosed through biopsy. Another drawback is that we came up with a small group in our study which was diagnosed with both OLP and OLL. This group had SCL-90R scores almost equal to the myofascial pain group, but analyses were not done for this group because of the small sample size as compared to the other groups. We also recognize that there is a considerable difference in the mean ages between OLP/OLL, myofascial pain and control subjects which could have caused some biases in the results.

The sample size of this study is larger than previous studies examining this issue. Also, including an OLL patient group in our study has helped us determine their characteristics and psychosocial comorbidities as studies so far have focused mostly on studying OLP. Another strength of the study is that we have included four groups in our study to help us better understand the psychosocial stressors in patients with OLP and OLL, as the levels of these comorbidities have been well established in myofascial pain patients. This study has evaluated the comparable level

of SCL-90R symptom dimensions among the myofascial pain subjects and OLP patients in our study. It has been well studied that remarkable improvement in TMD (myofascial) patients can be seen with psychological therapies [63] in conjunction with other treatments. Therefore, it seems reasonable that patients with OLP and OLL should be evaluated and treated accordingly for any psychosocial comorbidities which can help improve their prognosis and quality of life.

Future studies should examine the psychosocial comorbidities in other mucosal lesions besides OLP or OLL like pemphigus, benign mucous membrane pemphigoid, recurrent aphthous ulcers, burning mouth syndrome, etc.. A multicenter design might be beneficial to assess the psychosocial comorbidities and to establish the generalizability of the findings. The study in collaboration with other centers could compare the psychosocial measures to better understand the association of anxiety, depression and somatization with the OLP and OLL patients. Longitudinal studies would be helpful to evaluate the causal relationship between pain, psychosocial comorbidities, OLP and OLL.

Chapter 7. CONCLUSION

Our study found comparable levels of anxiety and somatization without pain in the OLP and myofascial study groups. These psychosocial measures may affect the treatment choices and/or outcomes in the myofascial patients and likewise in patients with OLP, which suggest that psychosocial distress should be evaluated in patients with OLP, not just myofascial pain patients. Psychological status should be routinely assessed for the OLP patients, specifically for those who have high SCL-90R scores and have not responded to treatment or when their oral symptoms cannot be correlated with the morphology of the lesions. However, the presence of psychosocial comorbidities like anxiety, depression and somatization does not exclude the presence of an organic medical condition. The psychosocial stressors should be considered along with organic etiology. Psychotherapy in addition to pharmacological treatment of OLP might be reassuring to the patients and could help alleviate their suffering.

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APPENDIX A

SCL-90 FORM					
In the LAST MONTH, how much have you been distressed by	NOT AT ALL	A LITTLE BIT	MODERATELY	QUITE A BIT	EXTREMELY
a. Headaches	O	O	O	O	O
b. Nervousness or shakiness inside	O	O	O	O	O
c. Faintness or dizziness	O	O	O	O	O
d. Loss of sexual interest or pleasure	O	O	O	O	O
e. Feeling easily annoyed or irritated	O	O	O	O	O
f. Pain in the heart or chest	O	O	O	O	O
g. Feeling low in energy or slowed down	O	O	O	O	O
h. Sleep that is restless or disturbed	O	O	O	O	O
i. Trembling	O	O	O	O	O
j. Poor appetite	O	O	O	O	O
k. Crying easily	O	O	O	O	O
l. Feeling of being caught or trapped	O	O	O	O	O
m. Suddenly being scared for no reason	O	O	O	O	O
n. Blaming yourself for things	O	O	O	O	O
o. Pains in the lower back	O	O	O	O	O
p. Feeling lonely	O	O	O	O	O
q. Feeling blue	O	O	O	O	O
r. Worrying too much about things	O	O	O	O	O
s. Feeling no interest in things	O	O	O	O	O
t. Feeling fearful	O	O	O	O	O
u. Heart pounding or racing	O	O	O	O	O
v. Nausea or upset stomach	O	O	O	O	O
w. Soreness of your muscles	O	O	O	O	O
x. Trouble falling asleep	O	O	O	O	O
y. Difficulty making decisions	O	O	O	O	O
z. Trouble getting your breath	O	O	O	O	O

In the LAST MONTH, how much have you been distressed by	NOT AT ALL	A LITTLE BIT	MODERATELY	QUITE A BIT	EXTREMELY
aa. Hot or cold spells	O	O	O	O	O
bb. Numbness or tingling in parts of your body	O	O	O	O	O
cc. A lump in your throat	O	O	O	O	O
dd. Feeling hopeless about the future	O	O	O	O	O
ee. Feeling weak in parts of your body	O	O	O	O	O
ff. Feeling tense or keyed up	O	O	O	O	O
gg. Heavy feelings in your arms or legs	O	O	O	O	O
hh. Thoughts or death or dying	O	O	O	O	O
ii. Overeating	O	O	O	O	O
jj. Awakening in the early morning	O	O	O	O	O
kk. Thoughts of ending your life	O	O	O	O	O
ll. Feeling everything is an effort	O	O	O	O	O
mm. Spells of terror or panic	O	O	O	O	O
nn. Feeling so restless you couldn't sit still	O	O	O	O	O
oo. Feeling of worthlessness	O	O	O	O	O
pp. The feeling that something bad is going to happen to you	O	O	O	O	O
qq. Thoughts and images of a frightening nature	O	O	O	O	O
rr. Feelings of guilt	O	O	O	O	O
ss. The idea that something serious is wrong with your body	O	O	O	O	O
tt. The idea that something is wrong with your mind	O	O	O	O	O

APPENDIX B

Record Date (M-D-Y) * must provide value	Today M-D-Y
Age (years)	View equation
Gender (M/F)	
Race	
Insurance	
Occupation	
Chief Complaint	Expand
Duration of Chief Complaint / Pain	Years Months Weeks Days Other
Diagnosis Info	
Diagnosis	
Other Oral Diseases Associated With OLP	
Mental Disorders (Schizophrenia etc.)	
Medications	
Medication	Anti-Depressants Anxiolytics Antipsychotics Other Prescription Medications OTC

SCL-90R Data	
Date of SCL-90 (M-D-Y)	Today M-D-Y
Anxiety Score	
Depression Score	
Somatization with Pain Score	
Somatization without Pain Score	
Pain Aversiveness Calculation	
VAS Aversiveness Length	Measured with ruler manually
Patient Pain Aversiveness Score	Measured with ruler manually
Pain Aversiveness	View equation Converted equation of 100mm VAS
Pain Intensity Calculation	
VAS Intensity Length	Measured with ruler manually
Patient Pain Intensity Score	Measured with ruler manually
Pain Intensity	View equation Converted equation of 100mm VAS
Form Status	
Complete?	Incomplete

Save & Exit Form Save & Stay

-- Cancel --

APPENDIX C

SCL-90-R

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Subject_ID

Birthdate

TodaysDate

Examiner

Visit

0 - not at all
1 - a little bit
2 - moderately
3 - quite a bit
4 - extremely

Gender

scl1		headache	scl46		trouble deciding
scl2		nervousness	scl47		fear public transport
scl3		unpleasant thoughts	scl48		shortness of breath
scl4		faintness	scl49		hot cold spells
scl5		low sex drive	scl50		avoidance of stuff
scl6		critical of others	scl51		mind blank
scl7		others control you	scl52		numbness
scl8		blame others	scl53		lump in throat
scl9		bad memory	scl54		hopelessness
scl10		worried carelessness	scl55		poor concentration
scl11		easily annoyed	scl56		weakness
scl12		chest pain	scl57		tense
scl13		afraid open spaces	scl58		heaviness
scl14		low energy	scl59		death thoughts
scl15		suicidal thoughts	scl60		overeatting
scl16		hearing voices	scl61		uneasy with others
scl17		trembling	scl62		foreign thoughts
scl18		cannot trust others	scl63		urge to hurt others
scl19		poor appetite	scl64		early awakening
scl20		cry easily	scl65		repeating actions
scl21		shy with opp sex	scl66		restless sleep
scl22		feeling caught	scl67		urges to damage things
scl23		suddenly scared	scl68		unique ideas
scl24		temper outbursts	scl69		self-conscious
scl25		afraid to leave house	scl70		uneasy in public
scl26		blame self	scl71		all is effortful
scl27		low back pain	scl72		terror or panic
scl28		activities blocked	scl73		cannot eat in public
scl29		lonely	scl74		frequent arguments
scl30		blue	scl75		nervousness when alone

SCL-90-R

scl31 ____ excess worry
scl32 ____ lack of interest
scl33 ____ fearful
scl34 ____ feelings hurt
scl35 ____ others read mind
scl36 ____ others not understand
scl37 ____ people unfriendly
scl38 ____ excess correctness
scl39 ____ heart pounding
scl40 ____ nausea
scl41 ____ inferior to others
scl42 ____ muscles soreness
scl43 ____ others watch you
scl44 ____ onset insomnia
scl45 ____ checking

scl76 ____ not recognized by others
scl77 ____ lonely with others
scl78 ____ restlessness
scl79 ____ worthlessness
scl80 ____ bad things happen
scl81 ____ shout or throw
scl82 ____ fear of fainting
scl83 ____ others take advantage
scl84 ____ sex thoughts
scl85 ____ need to be punished
scl86 ____ fearful thoughts
scl87 ____ wrong with body
scl88 ____ not close to others
scl89 ____ guilt
scl90 ____ wrong with mind