The contribution of insomnia, obstructive sleep apnea and fatigue on the transition from acute to chronic painful temporomandibular disorders, and its persistence: a prospective 3-month cohort study

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DEDICATION

I would like to dedicate this work to my deceased mother Magda Atia, born in 1955 in Egypt who passed away on September 13, 2013, of a sudden diagnosis of stage IV pancreatic cancer, and to my beloved father Mohammed Elsaraj. They both worked very hard and dedicated their life to their three children (Sherif, Bassam, and Mahmoud) to provide them with the best possible education and future. A special dedication to my wife Ryma, and my beautiful children Amir and Amal Elsaraj for their love, support, prayers, and patience.

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LIST OF ABBREVIATIONS

TMD: Temporomandibular Disorders

ACTION: Acute to Chronic Transition

OSA: Obstructive Sleep Apnea

GCPS: Graded Chronic Pain Scale

FSS: Fatigue Severity Scale

ESS: Epworth Sleepiness Scale

ISI: Insomnia Severity Index

PHQ-4: Patient Health Questionnaire-4

CFS: Chronic Fatigue Syndrome

RDC/TMD: Research Diagnostic Criteria for Temporomandibular Disorder

DC/TMD: Diagnostic Criteria for Temporomandibular Disorder

OR: Odds Ratio

CI: Confidence Interval

CS: Central sensitization

JGH: Jewish General Hospital

MGH: Montreal General Hospital

IASP: International Association of Study of Pain

NIH: National Institute of Health

CPI: Characteristic pain intensity

ABSTRACT

Background: Previous studies have demonstrated that insomnia, obstructive sleep apnea (OSA), and fatigue are associated with chronic temporomandibular disorders (TMD)-related pain. TMD pain is a group of a musculoskeletal condition affecting the muscles of mastication, the temporomandibular joints, or both. The International Association for the Study of Pain (IASP) defines chronic pain as "persistent or recurrent pain lasting longer than 3-months" and is associated with significant dysfunction.

Objective: This prospective 3-month cohort study aimed to determine whether insomnia, OSA, and fatigue are associated with the transition from acute to chronic TMD-related pain as well as its' persistence, when chronic pain is defined by: (i) pain duration (> 3 months), and (ii) dysfunction (Graded Chronic Pain Scale (GCPS II-IV).

Methods: Acute (≤ 3 months) and Chronic (> 3 months) TMD-related pain subjects were recruited between 2015 to 2021, through four different sites in Montreal and Ottawa. Subjects received a clinical examination and completed questionnaires at baseline and 3-month follow-up. A diagnosis was obtained using the Research Diagnostic Criteria or the Diagnostic Criteria for Temporomandibular Disorders. At baseline, insomnia, OSA, and fatigue were assessed using the Insomnia Severity Scale (ISI), the Epworth Sleepiness Scale (ESS), and the Fatigue Severity Scale (FSS), respectively. Subjects completed GCPS form at baseline and 3-month follow-up.

Results: From 454 subjects recruited 376 completed the follow-up. Borderline associations were found between OSA and the transition or persistent risk when chronic pain was defined by pain duration ($RR_{adjusted\_duration}$ = 1.11, P = 0.07) and dysfunction ($RR_{adjusted\_dysfunction}$ =1.40, P = 0.052), contrary to insomnia ($RR_{adjusted\_duration}$ = 0.94, P = 0.27, $RR_{adjusted\_dysfunction}$ =1.00, P = 0.99). The

secondary analyses found that OSA was specifically associated with the persistence of TMD-related pain (RR = 1.13, $P = 0.04$). Fatigue was not associated with increased risk of transition or persistence risk at 3-month follow-up when chronic pain was defined by duration ($RR_{adjusted} = 1.01$, $P = 0.99$). However, when chronic pain was defined as dysfunction, fatigue was associated with an increased transition or persistence risk ($RR_{adjusted} = 1.72$, $P = 0.002$). Results indicate that fatigue and OSA are contributing factors to the transition or persistence of TMD-related pain. These results suggest that OSA and fatigue assessment may be considered as part of the comprehensive clinical exam for TMD patients, and that their management should be tested to prevent the transition and persistence of TMD-related pain.

RÉSUMÉ

Contexte: Des études antérieures ont démontré que l'insomnie, l'apnée obstructive du sommeil (AOS) et la fatigue sont associées à des douleurs chroniques liées aux troubles temporo-mandibulaires (DTM). TMD est un groupe d'affections musculo-squelettiques affectant les muscles de la mastication, les articulations temporo-mandibulaires, ou les deux. L'Association internationale pour l'étude de la douleur (IASP) définit la douleur chronique comme « une douleur persistante ou récurrente d'une durée supérieure à 3 mois » et est associée à un dysfonctionnement important.

Objectif: Cette étude de cohorte prospective de 3 mois visait à déterminer si l'insomnie, l'AOS et la fatigue sont associés à la transition d'une douleur aiguë à une douleur chronique liée à l'ATM ainsi que sa persistance, lorsque la douleur chronique est définie par : (i) la douleur durée (> 3 mois) et (ii) dysfonctionnement (échelle de douleur chronique graduée (GCPS II-IV).

Méthodes: Des sujets souffrant de douleurs aiguës (≤ 3 mois) et chroniques (> 3 mois) liées aux ATM ont été recrutés entre 2015 et 2021, dans quatre sites différents à Montréal et à Ottawa. Les sujets ont reçu un examen clinique et ont rempli des questionnaires au départ et à 3 mois de suivi. Un diagnostic a été obtenu en utilisant les critères de diagnostic de recherche ou les critères de diagnostic des troubles temporo-mandibulaires. Au départ, l'insomnie, l'AOS et la fatigue ont été évalués à l'aide de l'échelle de gravité de l'insomnie (ISI), de l'échelle de gravité d'Epworth (ESS) et de l'échelle de gravité de la fatigue (FSS), respectivement. Les sujets ont rempli le formulaire GCPS au départ et au suivi des 3 mois.

Résultats: Sur 454 sujets recrutés, 376 ont complété le suivi. Des associations limites ont été trouvées entre l'AOS et le risque de transition ou persistante lorsque la douleur chronique était définie par la durée de la douleur ($RR_{adjusted\_duration}$ = 1.11, P = 0.07) et le dysfonctionnement

(RRadjusted_dysfunction = 1.40, P = 0.052), contrairement à l'insomnie ($RR_{adjusted\_duration}$ = 0.94, P = 0.27, $RR_{adjusted\_dysfunction}$ = 1.00, P = 0.99). L'analyse secondaire a révélé que l'AOS était spécifiquement associée à la persistence (RR = 1.13, P = 0.04). La fatigue n'était pas associée à un risque accru de transition ou de persistance au suivi de 3 mois lorsque la douleur chronique était définie par la durée ($RR_{ajusté}$ = 1.01, P = 0.99). Cependant, lorsque la douleur chronique était définie comme un dysfonctionnement, la fatigue était associée à un risque accru de transition ou de persistance ($RR_{ajusté}$ = 1.72, P = 0.002). Les résultats indiquent que la fatigue et l'AOS contribuent à la transition ou à la persistance de la douleur liée aux ATM. Ces résultats suggèrent que l'évaluation de l'AOS et de la fatigue peut être envisagée dans le cadre de l'examen clinique complet des patients atteints de DTM, et que leur prise en charge doit être testée pour prévenir la transition et la persistance de la douleur liée aux DTM.

PREFACE

In this thesis work, I have attempted to address essential questions related to the contribution of insomnia, obstructive sleep apnea, and fatigue on the transition from acute to chronic TMD-related pain, and its persistence. Additionally, I have also demonstrated the application of multiple analytical techniques in a prospective control study. This dissertation follows a manuscript-based format as outlined by Graduate and Postdoctoral Studies, McGill University. I have organized this dissertation into eleven chapters, including introduction, literature review, study aims and hypotheses, study originality, methods, two manuscripts focusing on each aim and corresponding results, followed by an overall discussion, conclusions and appendix files. All chapters of this dissertation are written by me (Sherif Elsaraj, PhD candidate) under the supervision of Dr. Ana Velly and Dr. Richard Hovey. The following section outlines the contribution of authors.

CONTRIBUTION OF AUTHORS

Manuscript I: The contribution of insomnia and obstructive sleep apnea on the transition from acute to chronic painful temporomandibular disorders, and its persistence: a prospective 3-month cohort study.

Manuscript II: The contribution of fatigue on the transition from acute to chronic painful temporomandibular disorders, and its persistence: a prospective 3-month cohort study.

Sherif Elsaraj, D.M.D, M.Sc., Ph.D. Candidate: contributed to the original concept of the research protocol, participated in the recruitment and follow-up of patients, data collection, interpretation of the results, and in the preparation of the text; writing thesis and manuscripts.

Mervyn Gornitsky, Professor Emeritus, McGill University, provided clinical and research expertise in the field of orofacial pain.

Richard Hovey, BEd, MA, Ph.D., Associate Professor in the Division of Oral Health and Society, Faculty of Dentistry, McGill University brings his expertise as a qualitative researcher investigating patient experiences living with chronic pain.

Ana Miriam Velly, Associate Professor, Faculty of Dentistry McGill University, Montreal, Quebec, Canada: She has a DDS degree, an MS in Neurological Sciences, a Ph.D. degree in Epidemiology, as well as post-doctoral training from the Randomized Clinical Trial Unit in the Dept. of Epidemiology at McGill University. She conceived this investigation, designed, provided funding, supervised this study, carried out the statistical analysis, and contributed to manuscript writing.

1 INTRODUCTION

Temporomandibular disorders (TMD) is a collective term used to describe musculoskeletal conditions characterized by pain in the muscles of mastication and temporomandibular joint or both, and/or associated structures.[1] The common signs and symptoms include tenderness in the muscles upon palpation, pain within the range of motion, or limitation of the jaw upon opening. This is followed by interference with vital functions such as eating, swallowing, and speaking.[2]

The prevalence of TMD-related pain ranges between 5% to 12% [3, 4] and the annual incidence is 3.9%.[5] TMD-related pain is more common among females than males.[4] Nevertheless, approximately 33% of TMD-related pain patients continue to suffer from moderate to severe levels of pain and disability, independent of treatment received.[6, 7]

Many risks were identified to be associated with TMD. Prospective studies put in evidence the risk factors of TMD. Oral habits,[8-11] psychological factors,[8, 12, 13] and trauma[8, 14-16] are associated with TMDs risk. Previous studies also showed that females have a greater risk of TMD than males.[17, 18]

In addition, it has been suggested that pain (e.g., neck pain, back pain, headache, and fibromyalgia),[19-21] and sleep comorbidities such as obstructive sleep apnea,[22, 23 24] fatigue,[25-27] and insomnia[22, 28, 29] are also associated with chronic TMD-related pain.

A large number of studies were conducted to investigate factors associated with the persistence of chronic TMD-related pain. This is very important since persistent chronic pain is common.[7, 30-32] In addition to the common TMD symptoms, patients complain about headaches, neck pain, back pain, and fibromyalgia. These other pain conditions are referred to as comorbidities. Comorbidities are defined as the co-occurrence of two or more medically diagnosed

conditions or diseases in the same patient.[33] Psychological disorders[8, 34-36] and comorbidities[8, 9, 20, 34-37] contribute to the persistence of chronic TMD-related pain as well.

Why does TMD-related pain persist if patients are receiving recommended treatment? We hypothesize is that it is difficult to manage TMD-related pain when it is present for a long time. Thus, by identifying factors associated with acute to chronic painful transition we could identify preventive intervention protocols that may prevent this transition. The risk factors implicated in the transition are to be determined. The National Institute of Health (NIH) reported "we do not fully understand how acute progresses to chronic pain at any level, from molecular to behavioral".[38] This is the reason why, in 2015, the Acute to Chronic TMD Transition (ACTION) program was initiated by Dr. Ana Velly and her team. The overall aims of this program are to determine the risk factors that contribute to the transition from acute to chronic TMD-related pain and its persistence. The first ACTION study, a critical review, found that psychological factors were more common in chronic than acute TMD pain patients. However, these factors did not increase the transition risk in the multivariable model. Myofascial and baseline pain intensity were associated with the transition at a 6-month follow-up.[39] The results of this review are summarized in section 1.1.8. To our knowledge, none of the previous studies investigated the contributions of insomnia, obstructive sleep apnea (OSA), and fatigue to the transition. Therefore, the overall objective of this specific ACTION prospective cohort study is to determine if insomnia, OSA, and fatigue are associated with the transition as well as its persistence.

The following section provides an overview of the definition of acute and chronic TMD-related pain, epidemiology of TMD, its prevalence and incidence, and potential risk factors under investigation.

2 LITERATURE REVIEW

2.1 Acute and Chronic Temporomandibular Disorders-related pain Definition

We used two criteria to define acute and chronic TMD pain: (i) pain duration of chronic TMD-related pain is in accordance with the International Association for the Study of Pain (IASP) which defines chronic pain as pain lasting for more than 3 months,[40, 41] and (ii) dysfunction defined as grades II, III and IV with any disability points on the Graded Chronic Pain Scale (GCPS).[42]

2.2 Graded Chronic Pain Scale

The Graded Chronic Pain Scale (GCPS) is an instrument used to assess overall chronic pain severity based on the level of pain intensity and pain-related disability. The GCPS grades are low-intensity pain, no disability (Grade I); high-intensity pain, without pain-related disability (Grade IIa); (iii) high-intensity pain, with low pain-related disability (Grade IIb), moderately limiting (Grade III), and severely limiting (Grade IV).

Table 1. Graded Chronic Pain Scale[42, 43]

Graded Chronic Pain	**Grade**	**Pain Intensity (0-100) ***	**Disability Level (Points)$**
Normal	Grade 0	None	None
Low intensity pain	Grade I	Low (<50)	0 points
No disability and High pain intensity	Grade IIa	High (≥50)	0 points
Low disability and High pain intensity	Grade IIb	High (≥50)	Low (<3 points)
Moderate disability	Grade III	Low or high	Moderate limiting (3-4 points)
High disability	Grade IV	Low or high	Severely limiting (5-6 points)

* Pain intensity (0-10) = mean (pain now, worst pain, average pain) x 10

$ Disability level (0-6 points) = disability days (0-3 points) + disability score (0-3 points)

The scoring is based on the subject's responses to several items: 1) current; 2) worst; and 3) average pain intensity (0–10 numeric scales); 4) pain-related disability days, and pain-related interference with daily activities; work; and social or family activities (0–10 numeric). Characteristic pain intensity (CPI) measured by the GCPS is the average of 0–10 ratings of current, worst and average pain in the prior 3 months multiplied by 10. The disability score is the average of 3, 0–10 interference ratings: daily activities, work, and social or family activities multiplied by 10 prior 3 months. The following table describes the disability points score.

Table 2. Description of Disability Points Score[30, 42]

Disability Days (0-180)	**Points**	**Disability Score (0-100)**	**Points**
0-6 days	0 points	0-29	0 points
7-14 days	1 point	30-49	1 point
15-30 days	2 points	50-69	2 points
31+ days	3 points	70+	3 points
Note: Disability score (0-100) = Mean (daily activities, social activities, work activities) x 10.			

2.3 Epidemiology of Temporomandibular Disorders

2.3.1 Prevalence of Chronic Temporomandibular Disorders-related Pain

Table 3 shows the point and period prevalence estimates of TMD-related pain. Prevalence is defined as the frequency of an existing condition in a given population at a certain time or period.[44] Point prevalence, period prevalence, and lifetime prevalence are three different types of prevalence. Point prevalence is the proportion of the study population that has the event or condition at a specific point in time.[44] Period prevalence indicates the proportion of individuals

that has a disease during a defined period of time.[44, 45] Lifetime prevalence is the proportion of people that has experienced the disease during an individual's past up to the present time.[44, 45]

A survey conducted among 1,016 participants recruited from the Health Maintenance Organization in Seattle, US, with an 80.3% participation rate estimated that the 6-month period prevalence of facial pain was 12%, and the lifetime prevalence was 34% within the age group of 70 years and more.[4]

In Toronto, using digit dialing, the point prevalence estimated of temporomandibular joint pain (TMJ) during jaw function or while at rest among 1,002 adults 18 years and older was 12.9%. The participation rate was (67.7%, n = 677).[46]

A telephone survey of a representative sample of the French-speaking population of Quebec done by Goulet et al. revealed that one-third of the 897 participants aged 18 years and over reported pain either in the jaw joints and/or muscles of mastication.[47] Results revealed that more than two-thirds (69%) of the participants reported moderate to severe and 7% of the respondents reported frequent episodes of pain, and the point prevalence was 5%.

Another survey in the US estimated a 3-month period prevalence of 5% among 30,978 contributors (17,498 females and 13,480 males), aged 18 years or older.[3]

Another survey in the US, among 19,586 women participants estimated a 6-month period prevalence of myofascial TMD pain was 10.5%. TMD was assessed by asking the participants questions: "Other than a toothache or sinus pain, did you have pain in your face, in the front of your ear or jaw, more than one time, in the last 6 months?" If "yes", then: "Was that pain caused only by a headache?", "Did you ever have these pains over a period of at least 2 weeks, even if you were not in pain constantly?". The participation rate was 60%. Interestingly, this prevalence was similar to that assessed among 782 women (10.5%) who were examined using RDC/TMD.[48]

Table 3. Prevalence of Temporomandibular Disorders-related pain								
Authors, Year	**Study Design**	**Gender**	**Age**	**Sample Size**	**Participation rate**	**Prevalence (%)**	**Condition**	**Assessment**
Von Korff et al., 1988	Survey 6-months	M & F	≥ 18	1,016	80%	12	Facial Pain	Mailed questionnaire (SCL-R90) followed by a telephone interview
Locker et al., 1988	Survey 4-months	M & F	≥ 18	677	68%	12.9	Painful TMD (rest and movement)	Telephone Survey, questionnaire
Goulet et al., 1995	Survey 5 days	M & F	≥ 18	897	64%	5	Painful TMD	Telephone Survey, questionnaire
Schmitter et al., *2007*	Survey	F	18 – 65	171	95%	9.93	Painful TMD	Questionnaire / RDC/TMD Clinical Examination
Isong et al., 2008	Survey 3-months	M & F	≥ 18	30,987	Not provided	4.6	Painful TMD	TMJMD-Type pain questionnaire
Janal et al., 2008	Survey 6-months	F	18 – 75	782	60%	10.5	Painful TMD	Telephone Survey/ RDC/TMD Clinical Examination
Gillborg et al., 2017	Survey 6-months	M & F	20 – 89	6,300	63%	11.0	Painful TMD	Mailed 58 questions Questionnaire

Another cross-sectional study surveyed 6,123 individuals (3480 women (57%) and 2643 men (43%) (response rate 63%) aged 20 to 89 years. Out of the 58 questions used, two questions were intended to identify TMD pain: "Do you have pain in your face, jaw, temple, in front of the ear, or in your ear once a week or more often?", and "Do you have pain when you open your mouth or when you chew once a week or more often?". This study used RDC/TMD to assess for signs and symptoms of TMD and found that the prevalence of self-reported TMD pain was 11.0%.[49]

It is a common belief that the age distribution of TMD patients is characterized with a Gaussian curve with a peak prevalence between 35 and 45 years and a decrease in younger and older people. Manfredini et al., however, identified two distinct age peaks for the prevalence of TMD-related pain patients, one at 30-35 years and another at about 50-55 years[50] among 243 participants between the age range of 18-80, seeking TMD treatment at the TMD clinic. All participants underwent an RDC/TMD assessment where a TMD diagnosis was obtained. The 30-50 years peak represented participants showing disc displacement in the absence of degenerative disorders (muscle disorders and/or arthralgia) and the 50-55 years peak was presented by people with signs and symptoms of inflammatory-degenerative joint disorders (osteoarthritis and/or osteoarthrosis). The former comprised 107 participants (20 males, 18.7%; 87 females, 81.3%) with a mean age of 32.7±14.5 years. The latter comprised 46 participants (4 males, 87%; 42 females, 91.3%) with a mean age of 54.2±15.1 years. The mean age of all patients was 39.7±17.1 years (range 18-80). Therefore, the prevalence of TMD may change depending on the age and gender distribution of the population.

These studies provide evidence that TMD-related pain is common with the prevalence ranging from 5 to 12.9%. Furthermore, it is more common among females than males.

2.3.2 Incidence of Temporomandibular Disorders-related pain

Incidence is defined as the proportion or rate of new disease or condition which occurs in a population during a specific period.[51] Table 4 shows studies assessing the incidence of TMD-related pain in different populations. Incidence is measured in two ways: cumulative incidence and incidence rate or density. The cumulative or annual incidence is the proportion of new cases in a population that is initially free of disease who developed the disease in a given time interval.[52] The incidence rate is the number of new cases per total number of person-years at risk.[51]

A cohort study of 1,016 individuals aged between 18 and 65 years (participation rate 80.3%) from the Maintenance Organization found that an incidence of TMD-related pain was about 6.5% three years cumulative incidence. The participants were asked whether the pain has been present in the past 6 months. In this study, the incidence of TMD was higher in females than in males (7.7% vs. 4.8).[53] In this study, the dropout rate was only 15%.

In Okayama, Japan, a cohort study among 672 participants (304 males and 368 females) with a mean age of 49.7 years, the cumulative incidence of TMD-related pain was 6.1% during a 4-year follow-up. 367 (40% dropout rate) completed the subsequent questionnaire.[54]

Swedish adolescents from public dental services clinics were included in a cohort study by Nilsson et al. with the aim to estimate the incidence of TMD-related pain by age and gender and to describe the temporal patterns of TMD-related pain. These two questions were asked to the study participants at annual follow-up: “Do you have pain in your temples, face, temporomandibular joint, or jaws once a week or more?” and “Do you have pain when you open your mouth wide or chew once a week or more?” The eligible patients (n = 2255) who completed regular annual check-ups for four years and with 12–19 years age range were included in the study.

The results showed an annual incidence rate of 2.9% among the participants. However, the girls (4.5%) had a higher annual incidence of TMD-related pain than boys (1.3%).[55]

Another cohort study in the US among 2,737 US residents aged 18 to 44 years (16% dropout rate) found that the annual incidence of TMD-related pain was approximately 4%. The incidence among younger participants aged 18 to 24 was 2.5%, and among middle-aged participants, 35 to 44 years was 4.5%. Interestingly, females had only slightly higher incidence than males (3.6 vs. 2.8).[5]

Table 4. Incidence of Temporomandibular Disorders-related pain

Authors, Year	Study Design	Gender	Age	Sample Size	Dropout rate	Condition	Incidence (%)	Assessment
Von Korff et al.,1993	Cohort	M & F	18+	1,016	15%	Painful TMD	6.5	Questionnaire
Kamisaka et al.,2000	Cohort	M & F	20+	171	40%	Painful TMD	6.1	Questionnaire
Nilsson et al., 2007	Cohort	M & F	12-19	2,255	10%	Painful TMD	2.9	Clinical Examination/ Questionnaire
Slade et al., 2013	Cohort	M & F	18-44	2,737	16%	Painful TMD	3.9	Clinical Examination (RDC/TMD)

2.4 Classification and Diagnosis of Temporomandibular Disorders

Several classification systems of Temporomandibular Disorders (TMD), such as Helkimo's Index, Craniomandibular Index (CMI), Research Diagnostic Criteria (RDC/TMD), and Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) have been established for the diagnosis of

TMD. The RDC/TMD is the most recent validated diagnostic protocol used for TMD research.[56] This system consists of two axes: (i) Axis I, physical assessment to provide a physical diagnosis[57] and (ii) Axis II, psychological assessment and pain-related disability to identify characteristics that could affect pain management (e.g., depression, pain intensity).[58]

Axis I includes three subgroups: Groups I, II, and III representing muscle disorders, disc displacements and joint diseases, respectively.[56, 57] Group I, muscle disorders, is divided into two groups: 1) myofascial pain refers to pain in the muscles of mastication or on palpation in minimally three places, one of which aligns with the reported pain; and 2) myofascial pain with limited mouth opening refers to pain in the jaw area and/or muscles of mastication that limits jaw function, such as the pain-free unassisted opening of less than 40 mm. Group II represents disc displacements and is classified into three groups: 1) disc displacement with reduction, the temporomandibular joint is pain-free, emitting a clicking noise on vertical activity (opening or closing), but not on thrusting or forward motion; 2) disc displacement without reduction with a limited opening is also pain-free up to a degree of $\leq$ 35mm during unassisted opening and the articular disc produces no detectable sound during function, and 3) disc displacement without reduction without limited opening, pain only occurring once the mouth, has reached a width of 35mm or more during unassisted opening. Group III represents joint disorders categorized into three groups: 1) arthralgia (pain in the joints without crepitus); 2) osteoarthritis which constitutes pain and crepitus in the joint; and 3) osteoarthrosis characterized by pain-free with crepitus. More details about the RDC/TMD protocol are described elsewhere.[56-58]

For the DC/TMD, Axis I includes: 1) muscle pain diagnosis which is categorized into four major subclasses: myalgia (local myalgia, myofascial pain and myofascial pain with referral); 2) TMJ disorders; 3) headache attributed to TMD; and 4) intra-articular TMD.[59] I) Muscle disorders are divided into four subtypes: myalgia, tendonitis, myositis, and spasm. Myalgia includes three

subcategories: local myalgia, myofascial pain, and myofascial pain with referral. II) TMJ disorders include arthralgia, disc displacement with reduction, disc displacement with reduction with intermediate locking, disc displacement without reduction with a limited opening, disc displacement without reduction without limited opening, osteoarthritis, osteoarthrosis, luxation, and subluxation. III) Headache includes headache attributed to TMD. Physical diagnosis (Axis I) is divided into pain diagnosis (muscle pain diagnosis, arthralgia, headache attributed to TMD) and joint diagnosis (disc displacement, degenerative joint disease, and subluxation). Whereas psychological status (Axis II) is divided into distress and pain disability aimed to evaluating pain behavior, psychological status, and psychosocial functioning.[59]

In a validation RDC study, which included 705 participants (614 TMD cases and 91 controls)[60], the target sensitivity and specificity (≥ 0.70 and ≥ 0.95, respectively) were not observed in any of the eight RDC/TMD diagnoses. Myofascial pain and myofascial pain with limited opening had high validity.[60] Since the sensitivity and specificity targets of the original RDC/TMD were not obtained, an attempt was made modifying the original RDC/TMD. Compared to the revised RDC/TMD, the sensitivity and specificity improved overall, especially for myofascial pain and myofascial pain with limited opening, sensitivity and specificity (0.75 and 0.97, respectively), and without limitations, sensitivity and specificity (0.83 and 0.99, respectively).[61]

2.5 Risk factors of chronic Temporomandibular Disorders-related pain

Prospective studies put in evidence the risk factors of TMD. Oral habits,[8-10] psychological factors,[8, 12, 13] and trauma[8, 14-16] are associated with TMDs risk. In addition, it has been suggested that pain (e.g., neck pain, back pain, headache, and fibromyalgia),[19-21] and sleep comorbidities

such as obstructive sleep apnea,[22, 23 24] fatigue,[25-27] and insomnia[22, 28, 29] are also associated with chronic TMD-related pain.

2.6 Difference between acute and chronic Temporomandibular Disorders-related pain

Gatchel[62] et al. conducted a case-control study enrolling 51 acute and 50 chronic TMD pain patients referred by dentists and oral surgeons in the Dallas-Fort Worth area to the Division of Psychology at the University of Texas Medical Center. Diagnosis was based on Laskin's criteria, and chronic TMD pain was defined as pain that persists for equal or more than 6 months. In two cross-sectional studies,[63, 64] chronic TMD pain was defined as pain that persists for 3 months or more. In Cao et al. [65] cross-sectional study, chronic TMD pain was defined as pain that persists for more than 3 months. TMD diagnosis was TMD diagnosis was based on RDC/TMD or Diagnostic Criteria. The samples in Reiter et al.[63] Nguyen et al.[64] and Cao et al.[65] studies consisted of 188 TMD patients from Tel Aviv University, 198 patients from the Dental Hospital of Chulalongkorn University, and 112 TMD pain patients from the Center for TMDs and Orofacial Pain, Peking University School and Hospital of Stomatology, respectively.

2.6.1 Demographics

No statistically significant differences were found on the mean age [62-65], race[62], education[62], and social class[62,63] distributions between the acute and the chronic TMD-related pain groups. Gatchel et al.[62] and Nguyen et al.[64] did not provide the *P-values* or 95% confidence intervals (95%CI), and Reiter et al.[63] did not show numerical values (count, percentage, or mean), only the *P-values*: P_{sex} = 0.28, P_{age} = .28, $P_{\text{employment status}}$ = .28, $P_{\text{marital status}}$ = .66, P_{income} = .28, $P_{\text{education}}$ = .97, and $P_{\text{missing work days}}$ = .73. While Cao et al.[65] demonstrated that relative to males, females had

higher odds of chronic than acute TMD-related pain (Odds ratio [OR] = 3.39, 95% Confidence Interval [CI] = 1.15-9.90), most studies did not find a significant sex difference between groups.[62-64]

2.6.2 Psychological factors

Three studies found higher levels of depression and somatoform disorders among chronic TMD pain groups when compared to the acute group. Significant differences in depression were found in all three studies.[62, 63, 65] Gatchel et al.[62], and Reiter et al.[63] found that somatoform disorders were significantly different between groups. Cao et al.[65] found stress significantly more common among the chronic than the acute group.

There were conflicting results assessing the distribution of anxiety found in three studies. Gatchel et al.[62] study found that chronic TMD-related pain patients presented significantly lower rates of lifetime and current anxiety disorders than acute. Most of the Diagnostic and Statistical Manual of Mental Disorders Revised Third Edition (DSM-III-R) Axis II personality disorders prevalence estimates were lower among acute TMD-related pain patients when compared to chronic, but no statistically significant differences were found between groups.[62] The evidence of nondifference between groups is limited to a single study with small sample size, making the conclusions weak. It is peculiar that paranoia was found in 16% and 18% of acute and chronic TMD-related pain patients, respectively. It is possible that this finding was caused by selection bias since the patients were referred to the Division of Psychology at the University of Texas Medical Center.[62] Reiter et al.[63] and Cao et al.[65] found no statistically significant difference between groups.

2.6.3 Temporomandibular Disorders diagnosis, pain intensity, Graded Chronic Pain Scale, and comorbidities

Reiter et al.[63] found statistically significant differences in the frequency of myofascial pain without limited opening ($P = 0.008$), myofascial pain with limited opening ($P = 0.02$) and arthralgia ($P = 0.02$) between acute and chronic TMD-related pain groups, a borderline difference on the disability score ($P = 0.07$), and a statistically non-significant difference on Graded Chronic Pain Scale (GCPS $P = 0.88$), and disability days ($P = 0.83$). Reiter et al. did not provide the results (number and percentage) of each group.[63] Nguyen et al.[64] demonstrated that myalgia was the most common diagnosis for both groups, and arthralgia was more common in the acute group, even though this difference was not statistically significant.

Cao et al. [65] found that chronic TMD-related pain patients had higher levels of sleep impairment mostly due to the use of sleep medication. Nguyen et al.[64] found that coexisting pain beyond orofacial areas (e.g. facial pain, neck, abdomen) was more common among patients with chronic TMD-related pain participants presented comorbidities (e.g. fibromyalgia, chronic fatigue syndrome).

2.7 Risk factors associated with the transition from acute to chronic Temporomandibular Disorders-related pain

Three 6-month cohort studies were conducted by Garofalo et al.[67], and Epker et al.[68,69] to identify predictors for the transition from acute to chronic TMD-related pain. The methodologies of these studies[67-69] were similar. TMD-related pain patients were referred by general dentists or oral and maxillofacial surgeons to the TMD Clinical Treatment Program at the University of Texas Southwestern Medical Center in Dallas. Newspaper or university campus flyers also advertised

the study to recruit potential patients. Acute TMD-related pain patients were eligible if they had never looked for treatment or they had sought treatment for TMD within six months of the first visit evaluation. The authors justified that their criteria for defining acute TMD-related pain were aimed at decreasing the chance of recall bias since recalling when pain begins is very difficult, and patients tend to look for treatment when the pain reaches a clinically significant level. Patients were diagnosed as per the RDC/TMD protocol.[56] A telephone interview was conducted at 3- and 6-month follow-ups using the Graded Chronic Pain Scale (GCPS) questionnaire[42] to assess the transition from acute to chronic TMD-related pain, defined by a CPI score greater or equal to 15 at 6 months of follow-up.

In the Garofalo et al. study,[67] out of 164 acute TMD pain cohorts recruited at baseline, 153 (93.3%) completed the 6-month follow-up, and 87 (56.9%) developed chronic TMD pain. In the first Epker et al. study,[68] from 204 acute cohorts, 175 (85.8%) completed the follow-up, and 144 (82.3%) developed chronic TMD. It is possible that the Epker cohort included patients from the Garofalo cohort.

The Garofalo et al.[67] and Epker et al.[68] prospective 6-months cohort studies revealed that only CPI and myofascial pain (Axis I Group I disorder) at baseline were associated with the transition risk. Epker et al.[68] found a negative association between CPI and transition (β = - 0.06, $P < .001$) on the logistic regression analyses, in contrast to Garofalo et al. (β = 0.03, $P = .003$).[67] Both authors concluded that the CPI score at baseline was positively associated with acute to chronic TMD pain transition risk. In addition, a borderline association was found with GCPS III or IV by Garofalo et al. (1998).[67] The association between myofascial pain and the transition risk appears to be modified by sex ($\beta_{\text{interaction factor between Group I and sex}} = 1.22$, $P = .09$). Psychological factors and age were not associated with this transition.[67, 68]

Epker and Gatchel's studies[69] performed a secondary analysis among 115 acute TMD patients to investigate coping profiles as predictors in the transition from acute to chronic TMD. Using the Multidimensional Pain Inventory (MPI) instrument, patients were classified as: dysfunctional (greater severity of pain, higher levels of affective distress, lower levels of activity, and greater pain interferences), interpersonally distressed (lacking support from significant others), and adaptive copers (less severe pain, lower levels of pain-related interference and interpersonal distress). Of the acute TMD patients, 83% with dysfunctional and interpersonally distressed profiles and 48.4% with adaptive coper profiles developed chronic TMD ($P < 0.001$).

In conclusion, to date, prospective cohort studies have found that pain intensity and myofascial pain contribute to the transition from acute to chronic TMD pain. Moreover, the association between myofascial pain and transition risk appears to be modified by sex. Lastly, individuals with dysfunctional and interpersonally distressed and adaptive coping profiles developed chronic TMD.

2.7.1 Introducing potential risk factors under investigation

To our knowledge, no study assessed if insomnia, OSA, and fatigue are associated with the transition from acute to chronic TMD risk. This section will introduce insomnia, OSA and fatigue and discuss their association with pain.

2.7.2 Insomnia

Insomnia is another sleep disorder and is defined as a complaint of prolonged sleep latency, difficulties in maintaining sleep, or the experience of non-refreshing or poor sleep, which have to be associated with impairments in daytime functioning such as lack of concentration, dysphoria, and other symptoms.[70-72] Its prevalence in the general population ranges from 9% for persistent

sleep disturbances to 27% for occasional insomnia.[73, 74] Insomnia is a patient reported problem characterized by difficulty falling asleep or difficulty maintaining sleep (i.e. frequent awakening too early with inability to return to sleep).[72] Individuals with insomnia are reliably distinguished from good sleepers by self-reported sleep symptoms such as sleep latency or time to fall asleep or wakefulness after sleep onset of longer than 30 minutes.[75] Objective sleep measures derived from polysomnography show more overlap between individuals with insomnia and good sleepers, making these methods less sensitive and specific than self-reports for identifying insomnia.[76] Although polysomnography is the "gold standard" for assessing sleep disorders such as sleep apnea, it is not recommended for routine use in the clinical assessment of insomnia.[77] The Insomnia Severity Index (ISI) is a reliable validated instrument, with 94% sensitivity and 94% specificity, used as a screening tool to quantify perceived insomnia severity in young and older patients.[78]

Smith et al. estimated the prevalence of insomnia in the TMD population is 36%.[29] Ohayon M. et al. assessed how age and daytime activities are related to insomnia in the general population. Their representative samples of three general populations (n=13057) consisted of the United Kingdom (n=4972), Germany (n=4115), and Italy n=(3970).[79] A clinical questionnaire on insomnia was administered. Results found that insomnia symptoms were reported by more than one-third of the population aged 65 and older. Multivariate models showed that age was not a predictive factor of insomnia symptoms when controlling for activity status and social life satisfaction. The authors concluded that the aging process is not responsible for the increase in insomnia often reported in older groups. Instead, inactivity, dissatisfaction with social life, and the presence of organic disease and mental disorders were the best predictors of insomnia. Ohayon M. et al. investigated the prevalence of insomnia using the International Classification of Sleep Disorders (ICSD) and the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) classification systems. [80] This cross-sectional study involved 25,579 individuals aged 15 years and

over representative of the general population of France, the United Kingdom, Germany, Italy, Portugal, Spain, and Finland. The participants were interviewed on sleep habits and disorders managed by the Sleep-EVAL expert system using DSM-IV and ICSD classifications.[80] The prevalence of insomnia was 8.6% (95% CI: 8.1-9.1) in women and 4.6% (95% CI: 4.2-5.0) in men; total insomnia prevalence in this group was 6.6% (95% CI: 6.3-6.9). The prevalence of insomnia is 34.5% (95% CI: 33.7-34.8), and it is higher among individuals who are 65 years of age or older (47.7%, 95% CI: 46.3-49.1).[80]

2.7.3 Obstructive sleep apnea

Obstructive sleep apnea (OSA) is associated with chronic TMD-related pain. A recent prospective cohort study found an increased risk of chronic TMD among individuals who had symptoms of OSA.[23] The prevalence of OSA is between 3-14% in the adult population. [81,82] Smith et al. estimated that the prevalence of OSA in the TMD population is 28.4%.[29] Sleep apnea affects 2-14% in the community-screened normal population but has a much higher prevalence in certain patient subgroups. The prevalence increases with age, especially in people over 60 years old and with obesity. A recent study by Tentindo G. et al. found a prevalence of 58.2% in a hospital-based population (mean age 59.2±13.6) based on a self-reported sleep apnea (STOP-BANG) screening questionnaire.[83] The prevalence estimates of moderate to severe sleep-disordered breathing (apnea-hypopnea index, measured as events/hr, ≥15) are 10% (95% Confidence Interval (CI): 7, 12) among 30-49 year-old men; 17% (95% CI: 15, 21) among 50-70 year-old men; 3% (95% CI: 2, 4) among 30-49 year-old women; and 9% (95% CI: 7, 11) among 50-70 year-old women. Lavigne and Montplaisir demonstrated the influence age on OSA prevalence estimates. [84] This is further supported by Bixler et al. who also found that the prevalence of sleep apnea increases with

age (65-100 years of age, n=75 30.5%; 95% CI: 21.2,41.7). Sleep apnea increases with age for men (40-49 years of age) and for women (50-60 years of age).[85, 86] Heinzer R. et al., using sleep study tests (polysomnography), found that the prevalence of moderate-to-severe sleep-disordered breathing (≥15 events per h) was 23.4% (95% CI 20.9–26.0) in women and 49.7% (46.6–52.8) in men; higher than those obtained by Peppard P. et al. 2013.[87]

Cunali PA et al. found that 52% of OSA patients presented with TMD pain.[24] This study population consisted of OSA patients referred for an oral appliance therapy and TMD diagnosis was obtained using the RDC/TMD. The latest prevalence estimates by Alessandri-Bonetti A et al. among 41 patients with OSA found 21 (51%) presented signs and/or symptoms of TMD compared to 13 (32%) from the untreated OSA control group. These patients were prospectively recruited from the Department of Otorhinolaryngology at the A. Gemelli Hospital in Italy, and the TMD diagnosis was obtained using the DC/TMD protocol.[88]

An apnea is defined as the complete cessation of airflow for at least 10 seconds. There are three types of apneas: obstructive, central and mixed. In obstructive sleep apnea, respiratory effort is maintained but ventilation decreases or disappears because of partial or total occlusion in the upper airway. Central sleep apnea is defined as reduced respiratory effort resulting in reduced or absent ventilation. Mixed apnea is often characterized by starting with central apnea and ending with obstructive events. Obstructive sleep apnea is a condition characterized by repetitive obstruction of the upper airway often resulting in oxygen desaturation and arousals from sleep. The classic daytime manifestation is excessive sleepiness but other symptoms such as unrefreshing sleep, poor concentration and fatigue are commonly reported.[89, 90] It is crucial to screen patients for OSA since it has been linked to numerous diseases including hypertension, coronary artery disease, stroke, atrial fibrillation, increased motor vehicle accidents, congestive heart failure, daytime sleepiness, decreased quality of life, and increased mortality.[23, 91, 92]

Comprehensive sleep evaluation for the likelihood of having OSA can be accomplished using the validated Epworth Sleepiness Scale (ESS) (93.5% sensitivity and 100% specificity).[93] ESS has been used to screen daytime sleepiness for those at high risk for OSA. This instrument is widely used in sleep clinics to screen for suspected OSA patients prior to authorizing a polysomnography study.

2.7.4 Fatigue

Fatigue is a subjective experience with symptoms including a persisting lack of energy, exhaustion, physical and mental tiredness, and apathy.[25] The prevalence of fatigue varies from 0.2% to 6.41%.[94] Fatigue prevalence is considerably higher among subjects with TMD-related pain (14-43%).[25, 27, 95] Dahan et al. [95] found that fatigue was positively associated with chronic TMD-related pain intensity and duration.

Chen et al. diagnosed 159 TMD pain patients using a modified version of the RDC/TMD criteria from an orofacial pain clinic and found that 10% reported chronic fatigue syndrome.[26] Hoffmann et al. surveyed 1,511 TMD pain patients and found that 42-43% reported having chronic fatigue syndrome after onset of TMD pain.[27] Dahan et al. in a cross-sectional study assessing fatigue found 14.4% of chronic fatigue syndrome patients present in their chronic TMD pain population.[96] Fatigue was assessed using the validated Fatigue Severity Scale (FSS) which has 90% sensitivity and 93% specificity.[97]

3 AIMS AND HYPOTHESES

The current prospective cohort study is part of the Acute to Chronic TMD Transition (ACTION) program, with an overall goal to identify the risk factors implicated in the transition from acute to chronic TMD-related pain and its persistence. The aim of the current study was to assess whether insomnia, OSA, and fatigue are associated with the transition from acute to chronic TMD-related pain risk as well as with its persistence at a 3-month follow-up. Thus, the specific aims are as followed:

Aim 3.3.1. To determine if insomnia, OSA, and fatigue are associated with the transition or persistence risk when chronic TMD-related pain is defined as recurrent or persistent pain for more than 3 months.

Aim 3.3.2. To determine the contribution of insomnia, OSA and fatigue on the transition or persistence risk when chronic TMD-related pain is defined by dysfunction as classified by GCPS (Graded Chronic Pain Scale Grades II-IV).[42]

The rationale to define chronic pain based on pain duration and dysfunction is described below. First, the International Association for the Study of Pain (IASP) defines chronic pain as recurrent or persistent pain lasting for more than 3 months.[40, 41] Second, IASP states that chronic pain is associated with significant disability.[41] Therefore, chronic TMD-related pain was defined as a dysfunction state consisting of clinically significant pain and disability.[42]

The study hypotheses are that insomnia, OSA, and fatigue increase the risk of a transition from acute to chronic TMD-related pain as well as its persistence when chronic TMD-related pain is defined by duration of pain or by dysfunction. To date, we are not aware of any study investigating the contribution of insomnia, OSA, and fatigue on transition from acute to chronic TMD-related pain as well as its persistence.

4 STUDY ORIGINALITY

When an acute TMD-related pain becomes chronic, it often results in disability, absenteeism, and significantly higher care cost. Approximately half to two-thirds of TMD patients seek professional care from dentists or physicians, and at least one-third of these patients continue to suffer from moderate to severe levels of pain, disability, and psychological distress independent of the treatment received. There are few longitudinal studies directed towards elucidating the risk factors and corresponding mechanisms that lead to the transition from acute to chronic TMD-related pain. Because of this lack of understanding, the National Institute of Health has assigned the highest research priority to examine the transition from acute to chronic pain. This study determined the effect of insomnia, OSA, and fatigue on the transition from acute to chronic TMD pain and its persistence. Consequently, critical information for predicting the transition from acute to chronic TMD pain and its persistency will be provided. This new knowledge will allow us to develop evidence-based treatment strategies for the prevention of chronic TMD pain and to further improve TMD management. The development of the scientific foundation for personalized care by recognizing contributing factors to transition or persistent chronic pain will decrease treatment failure and prolonged chronic pain that harms the quality of life of patients.

The following session Chapter 5 describes in detail the methodology used in Manuscripts I and II. This section includes study design and study population, data collection, study outcomes, assessment of potential risk factors (OSA, insomnia, fatigue), potential confounders and effect modifiers, study feasibility, statistical analyses and discuss ethical and privacy considerations. We combined them for easy and simple flow to the reader in order to avoid redundancy.

5 METHODS

5.1 Study Design and Study Population

In order to address the study aims, we conducted a prospective cohort study that followed acute and chronic TMD pain participants enrolled in the ACTION program, for 3 months. This program was approved by the McGill Institutional Review Board in Montreal, Canada (approval number: A12-M113-14A) and by the DOCS dental Group in Ottawa, Ontario (approval number: 240-400).

Eligible subjects with acute or chronic TMD-related pain were recruited between August 2015 and March 2021 from four different sites: the Jewish General Hospital (JGH) general dental clinic, the Faculty of Dentistry of McGill University oral diagnosis (OD) clinic, the Montreal General Hospital dental department (MGH) and the Ottawa DOCS dental Group TMD-specialized clinic.

5.1.1 Inclusion and exclusion criteria

The inclusion criteria for the participation in this study required subjects to be of 18 to 85 years of age with a positive diagnosis of TMD-related pain (muscle and/or joint) in accordance with Research Diagnostic DC[56] or the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD).[59] The excluded subjects were those who had other orofacial pain (e.g. dental pain), cancer, no access to a telephone, those who were unable to provide informed consent or incapable of understanding French or English.

5.1.2 Subject recruitment

Patients who fulfilled the inclusion criteria at the four centers: the Jewish General Hospital (JGH) general dental clinic, the Faculty of Dentistry of McGill University oral diagnosis (OD)

clinic, Montreal General Hospital (MGH) and the Ottawa DOCS dental Group, were approached during routine clinic visits by a clinician participating in the study and invited to participate. Information regarding the study was given to potential subjects initially verbally, and then if they expressed interest, a consent form which included detailed information about the study we are conducting was also provided (see appendices B & C). At each study center, a chart-review was completed on each patient who attended the clinic. Eligible patients who fulfilled the inclusion criteria were invited to join the study by signing the consent form. The 3-month follow-up visits were scheduled. Those who were not able to attend the follow-ups were called and the 3-month follow-up forms were completed (see appendices O & P).

5.2 Data Collection

Information was gathered from subjects who agreed to participate in the study at their convenience (see appendices E & J). All patients at the four locations were approached during their scheduled visit by one of our researchers and invited to participate. If they consented (see appendices B & C), the researcher would complete the baseline questionnaire of the study and then the patients would be given a follow-up appointment at 3 months. Most patients completed the questionnaire on site. A few numbers of patients were allowed to take the questionnaire home and return the completed questionnaire at their next scheduled appointment or mail it back to us. We provided the patient with a stamped envelope with our return address. The clinical examination and TMD diagnosis were obtained at the first visit.

5.3 Study outcomes

The primary outcomes were the transition from acute to chronic TMD-related pain or the persistence of chronic pain at the 3-month follow-up when chronic pain was defined by pain

duration and dysfunction. Secondary outcomes were the transition and the persistence state, both also defined by pain duration and dysfunction.

5.4 Assessment of the potential risk factors

5.4.1 Insomnia

The Insomnia Severity Index (ISI), a seven-item validated questionnaire used to evaluate sleep disturbances in subjects. This instrument has excellent sensitivity (94%) and specificity (94%). This instrument evaluates: (1) the severity of sleep-onset, (2) sleep maintenance, (3) early morning awakening problems, (4) satisfaction with current sleep pattern, (5) sleep-related interference with daily function, (6) noticeability of impairment attributed to sleep problems, and (7) level of distress caused by sleep problems. Participants rate each of these factors on a 5-point (0–4) scale, with possible scores ranging from 0 (No Clinically Significant Insomnia) to 28 (Severe Clinical Insomnia).[78] A total score is calculated, and sums between 0–7 indicate "no clinically significant insomnia", 8–14 "Subthreshold insomnia", and a score of 15 or more represents clinically significant insomnia. The scoring cutoffs are: < 15: no insomnia; and ≥ 15: clinically significant insomnia.

5.4.2 Obstructive sleep apnea

Comprehensive sleep evaluation for the likelihood of having OSA was assessed using the validated Epworth Sleepiness Scale (ESS) questionnaire.[93] Excellent sensitivity (93.5%) and specificity (100%) are found with ESS.[98] This 8-item validated questionnaire is being used to assess daytime sleepiness in patients who are at high risk for OSA. The score for ESS is the sum of the score of all questions. A score between 0–9 is considered normal, whereas scores in the 10–24 indicate that expert medical advice is required. For instance, scores of 11–15 are shown to

indicate the possibility of mild to moderate OSA, where a score of 16 and above indicates the possibility of severe OSA. ESS instrument is widely used in sleep clinics to screen for suspected OSA patients before authorizing a polysomnography study.[98] The scoring cutoffs are: < 10: no OSA; and ≥ 10: OSA.

5.4.3 Fatigue

Fatigue severity and functionality were assessed using the Fatigue Severity Scale (FSS), a validated and reliable instrument.[97] The FSS has 90% sensitivity and 86% specificity, with high reliability (Cronbach $\alpha = 0.93$). The scoring cutoffs are: < 36: no fatigue; and ≥ 36: fatigue.

5.5 Potential Confounders and Effect Modifiers

In our study, the possible confounders all assessed at baseline were acute and chronic pain status, dysfunction, psychological factors (anxiety, depression), CPI, sex, and age. The Patient Health Questionnaire-4 (PHQ-4) is a validated and reliable instrument used for screening for psychological factors: anxiety and depression.[99] PHQ-4 scoring cutoffs are: < 3: no anxiety and depression; and ≥ 3: anxiety and depression.

5.6 Sample size calculation

Table 5. Sample size effective by odds ratio and occurrence of outcomes

Occurrence of outcome for aims # 3.3.1 and 3.3.2 (%)	**Odds ratios**			
	1.5	1.7	2	2.5
	Sample size			
30	162	85	42	18
40	97	49	22	8
50	58	27	11	-

We have demonstrated that the effective sample sizes described in Table 5 provides 80% of power to detect conservative odds ratios ranging from 1.7 to 2.5 or more. In these estimations, we considered the frequency occurrence of outcomes ranging from 30% to 50%[67, 100-102] and alpha equal to 5%. The results of this prospective cohort study will provide data for a precise estimation of the sample size due to the absence of appropriate data in the TMD-related pain literature.

5.7 Study Feasibility

Our target recruitment was 125 subjects with chronic and 125 acute TMD-related pain to achieve a final sample size of 100 acute and 100 chronic TMD-related pain subjects, who completed the 3-follow-ups. This completion rate estimate is conservative compared to our previous study (80%)[30] and other prospective studies (89%).[67] This target recruitment is possible because patients were recruited from JGH, OD, MGH and DSO dental clinics, which are important centers providing TMD treatment. The qualifications of our world-class research team with extensive experience in epidemiology and chronic pain should further validate the feasibility of this study.

5.8 Statistical Analyses

Chi-squared, Fisher's exact test, analysis of variance, and Student t-test were used to test statistical differences between categories of TMD-related pain groups relative to insomnia, OSA, and fatigue, acute and chronic pain status, GCPS grades (GCPS I-IV), CPI, age, sex, and psychological factors.

5.8.1 Primary Analyses

For aim 3.3.1, we conducted binary logistic regression. The dependent variable was the presence or absence (yes or no) of chronic TMD-related pain at 3-month of follow-up. The risk factors under investigation in our study were insomnia, OSA, and fatigue (yes or no), the putative confounders were acute-chronic pain status at baseline, age, sex, CPI and psychological factors.

For aim 3.3.2, a binary logistic regression analysis was also performed to assess the relative risk of insomnia, OSA, and fatigue. The dependent variable was GCPS at 3-month of follow-up: 0-I (no dysfunction) vs and II-IV (dysfunction). The risk factors were insomnia, OSA, and fatigue (yes or no), and the putative baseline confounders dysfunction were acute-chronic pain status at baseline, age, sex, and psychological factors.

In both analyses (Aims 3.3.1 and 3.3.2), the relative risk (RR) and their 95% confidence intervals (CI) were estimated. In the final multivariable models, we kept in the model fatigue, the covariates associated with the dependent variable, and the effect modifiers (interaction). The likelihood ratio test was used to assess the significance of the RR and the interactions in the model. All analyses were performed using the statistical software package SAS (SAS 9.4; SAS Institute, Cary, NC, US), with the significance level for type I error set at the 0.05 level.

5.8.2 Secondary Analyses

Interaction terms were created between fatigue and acute-chronic pain status and dysfunction status both at baseline, to determine whether fatigue's risk depended on these covariates. The interaction term was retained in the model only if the significance level of the regression coefficient was equal to or lower than 0.10. Further, the analyses were stratified by pain duration (acute [≤ 3 months], chronic [> 3 months]) and dysfunction (no [GCPS I] and yes [II-IV]).

5.9 Ethical and Privacy Consideration

The study was conducted according to ethical principles stated in the declaration of Helsinki.[103] Ethical approval of this study was obtained from the research ethics committees of the McGill University Institutional Review Board in Montreal, Canada (approval number: A12-M113-14A) and by the DOCS dental Group in Ottawa, Ontario (approval number: 240-400). Consent forms, which took into consideration the well-being, free will, and respect of the participants, including respect of privacy, were collected from each patient that participated in the study. The questionnaires did not contain any identifying information and were instead coded. Once a patient had completed the questionnaires, the document was stored in the private office of the principal investigator. Then, the information from the documents was tabulated into an Excel sheet to be used for analysis and stored in an encrypted computer.

6 *Supplemental material* - Sleep disorders - Manuscript I

The contribution of insomnia and obstructive sleep apnea on the transition from acute to chronic painful temporomandibular disorders, and its persistence: a prospective 3-month cohort study

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Abstract

Insomnia and obstructive sleep apnea (OSA) are common among TMD-related pain subjects, and OSA was found to increase the risk of chronic TMD-related pain. This prospective cohort study aims to determine the contribution of insomnia and OSA on acute to chronic transition as well as its persistence when chronic pain is defined by: (i) duration (> 3 months), and (ii) dysfunction (Graded Chronic Pain Scale [GCPS II-IV]). The International Association for the Study of Pain (IASP) defines chronic pain as "persistent or recurrent pain lasting longer than 3 months" and is associated with significant dysfunction. From 456 subjects recruited between 2015 to 2021, through four locations in Canada, 378 completed the follow-up. A diagnosis was obtained using the Research Diagnostic Criteria or the Diagnostic Criteria for Temporomandibular Disorders. Insomnia and OSA were assessed at baseline with Insomnia Severity and Epworth Severity Scales. Subjects completed the GCPS form at baseline and 3-month follow-up. Borderline associations were found between OSA and the transition or persistent risk when chronic pain was defined by pain duration ($RR_{adjusted\_duration}$ = 1.11, P = 0.07) and dysfunction ($RR_{adjusted\_dysfunction}$ =1.40, P = 0.05). Insomnia was not related to the study outcomes ($RR_{adjusted\_duration}$ = 0.94, P = 0.27, $RR_{adjusted\_dysfunction}$ =1.00, P = 0.99). Results indicate that OSA (RR = 1.13, P = 0.04) contrary to insomnia contributed to the transition or the persistence of chronic TMD-related pain risk at a 3-month follow-up. Failure to recognize and manage contributing factors to the transition and persistent pain may lead to treatment failure and prolonged chronic pain which can affect the quality of life of patients. This result suggests that OSA assessment may be considered as part of the comprehensive clinical exam for TMD patients, and that its management should be tested to prevent the transition and persistence of TMD-related pain.

1. Introduction

Temporomandibular disorders (TMD) are a group of musculoskeletal conditions characterized by pain and dysfunction in the muscles of mastication, the temporomandibular joints, or both [1-3]. TMD is the second most commonly occurring musculoskeletal disorder after chronic lower back pain [2] and is an important public health concern due to it affects a significant portion of the general population, with prevalence estimates ranging from 5% to 12% [4, 5]. Many factors have been identified to increase the risk of TMD [6-13].

Insomnia is common among individuals with TMD (36%)[14]. Insomnia is a sleep disorder that is defined as the subjective experience of difficulty initiating sleep, maintaining sleep, and/or early morning awakening for at least three nights a week for three consecutive months, while there is adequate opportunity for undisturbed sleep and the complaints are also not adequately explained by other mental or physical problems.

The OPPERA case-control study found that TMD subjects were almost four times more likely to present with OSA compared to controls [15]. The OPPERA prospective cohort study found that OSA increased the risk of TMD onset. This study used some questions from the Pittsburgh Sleep Quality Index and the STOP-BANG questionnaire [15]. OSA is another breathing disorder that is a serious and potentially life-threatening condition characterized by brief interruptions of breathing during sleep [14].

To date, however, there is no evidence demonstrating insomnia or OSA as risk factors contributing to the transition from acute to chronic TMD-related pain. In the present prospective cohort study, we examined their association with the transition from acute to chronic TMD-related pain and contributions to persistent chronic pain.

This study is part of a global project called ACTION (Acute to Chronic Pain Transition), aimed at identifying risk factors contributing to the transition from acute to chronic TMD-related pain and its

persistence. The aim of the current study was to assess whether insomnia and OSA are associated with the transition from acute to chronic TMD-related pain risk as well as with its persistence at a 3-month follow-up.

Aim # 1. To determine if insomnia and OSA are associated with the transition or persistence risk when chronic TMD-related pain is defined as recurrent or persistent pain for more than 3 months.

Aim # 2. To determine the contribution of insomnia and OSA on the transition or persistence risk when chronic TMD-related pain is defined by dysfunction as classified by GCPS (Graded Chronic Pain Scale Grades II-IV) [16].

The rationale to define chronic pain with pain duration or dysfunction is due to following the recommendations of the International Association for the Study of Pain (IASP) that defines chronic pain as recurrent or persistent pain lasting for more than 3 months [17, 18], and states that it is associated with significant disability [18]. A dysfunction state consists of clinically significant pain and disability [16]. The study hypotheses are that insomnia and OSA increase the risk of a transition from acute to chronic TMD-related pain as well as its persistence when chronic TMD-related pain is defined by duration of pain or dysfunction. To date, we are not aware of any study investigating insomnia and OSA contributions on the transition from acute to chronic TMD-related pain and on persistent risk of chronic pain.

2. Methods

2.1 *Study design and study population*

The ACTION program received approvals from the McGill Institutional Review Board in Montreal, Canada (approval number: A12-M113-14A) and the Dental Specialists Group in Ottawa, Ontario (approval number: 240-400).

Eligible subjects with acute or chronic TMD-related pain were recruited from four different sites between August 2015 and March 2021. These locations were the Jewish General Hospital (JGH) general dental clinic, the Faculty of Dentistry of McGill University oral diagnosis (OD) clinic, the Montreal General Hospital dental department (MGH), and the Dental Specialists Group TMD-specialized clinic. To be included in this study, study required subjects to be of 18 to 85 years of age with a positive diagnosis of TMD-related pain (muscle and/or joint) in accordance with Research Diagnostic DC [19] or the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) [20]. The exclusion criteria were subjects who had other orofacial pain (e.g. dental pain), cancer, no access to a telephone, those who were unable to provide informed consent or incapable of understanding French or English.

2.2 ***Acute and chronic pain classification***

Two criteria were used to define acute and chronic TMD pain: (i) pain duration of chronic TMD-related pain is in accordance with the IASP that defines chronic pain as pain lasting for more than 3 months [17, 18], and (ii) dysfunction defined as grades II, III and IV with any disability points on the GCPS [16].

To assess overall chronic pain severity based on the level of pain intensity and pain-related disability, we used the GCPS instrument. The GCPS grades are low-intensity pain, no disability (Grade I); high-intensity pain, without pain-related disability (Grade IIa); (iii) high-intensity pain, with low pain-related disability (Grade IIb), moderately limiting (Grade III), and severely limiting (Grade IV). The GCPS scoring is based on the subject's responses to several items: 1) current; 2) worst; and 3) average pain intensity (0–10 numeric scales); 4) pain-related disability days, and pain-related interference with daily activities; work; and social or family activities (0–10 numeric). Characteristic pain intensity (CPI) measured by the GCPS is the average of 0–10 ratings of current, worst and average pain in the prior 3 months multiplied by 10. The disability score is the average of 3, 0–10 interference ratings: daily activities, work, and social or family activities multiplied by 10 prior 3 months.

2.3 *Outcome variables*

The transition from acute to chronic TMD-related pain or the persistence of chronic pain at the 3-month follow-up when chronic pain was defined by pain duration and dysfunction were the primary outcomes of our prospective cohort study. The secondary outcomes were also the transition and persistence states, both stratified by duration or dysfunction.

2.4 *Assessment of the potential risk factors*

2.4.1 *Insomnia screening instrument*

A seven-item validated questionnaire called the Insomnia Severity Index (ISI), with an excellent sensitivity (94%) and specificity (94%) was used to evaluate sleep disturbances in subjects. This instrument evaluates: (1) the severity of sleep-onset, (2) sleep maintenance, (3) early morning awakening problems, (4) satisfaction with current sleep pattern, (5) sleep-related interference with daily function, (6) noticeability of impairment attributed to sleep problems, and (7) level of distress caused by sleep problems. Participants rate each of these factors on a 5-point (0–4) scale, with possible scores ranging from 0 (No Clinically Significant Insomnia) to 28 (Severe Clinical Insomnia) [21]. A total score is calculated, and sums between 0–7 indicate “no clinically significant insomnia”, 8–14 “Subthreshold insomnia”, and a score of 15 or more represents clinically significant insomnia. The scoring cutoffs are less than 15: no or subthreshold insomnia; and greater than or equal to 15: clinically significant insomnia.

2.4.2 *OSA screening instrument*

Comprehensive sleep evaluation for the likelihood of having OSA was assessed using the validated Epworth Sleepiness Scale (ESS) questionnaire [22]. Excellent sensitivity (93.5%) and specificity (100%) are found with ESS [23]. This 8-item validated questionnaire is being used to assess daytime sleepiness in

patients who are at high risk for OSA. The score for ESS is the sum of the score of all questions. A score between 0–9 is considered normal, whereas scores in the 10–24 indicate that expert medical advice is required. For instance, scores of 11–15 are shown to indicate the possibility of mild to moderate OSA, where a score of 16 and above indicates the possibility of severe OSA. ESS instrument is widely used in sleep clinics to screen for suspected OSA patients before authorizing a polysomnography study [23]. The scoring cutoffs are less than 10: no OSA; and greater than or equal to 10: OSA.

2.5 *Assessment of putative confounders and effect modifiers*

The possible confounders and effect modifiers in our study were the acute and chronic pain status, dysfunction, psychological factors (anxiety, depression), sex, and age. Screening for psychological factors: anxiety and depression was accomplished with the Patient Health Questionnaire 4 (PHQ 4) [24]. This scoring cutoffs for the PHQ4 are less than 3: no anxiety and depression; and greater than or equal to 3: anxiety and depression.

2.6 *Statistical analysis*

Chi-squared, Fisher's exact test, analysis of variance, and Student t-test were used to test statistical differences between categories of TMD-related pain groups relative to insomnia and OSA, acute and chronic pain status, GCPS grades (GCPS I-IV), CPI, age, sex, and psychological factors.

2.6.1 *Primary analysis*

For aim 1, we conducted binary logistic regression. The dependent variable was the presence or absence (yes or no) of chronic TMD-related pain at 3-month of follow-up. The risk factors under study were insomnia and OSA (yes or no) and the putative confounders were acute-chronic pain status at baseline, age, sex, CPI, and psychological factors.

For aim 2, a binary logistic regression analysis was also performed to assess the relative risk of insomnia and OSA. The dependent variable was GCPS at 3-month of follow-up: 0-I (no dysfunction) vs. and II-IV (dysfunction). The risk factors were insomnia/score (yes or no) and OSA/score (yes or no) and the putative baseline confounders dysfunction were acute-chronic pain status at baseline, age, sex, and psychological factors. CPI was not included in the multivariable model because it is part of the GCPS instrument.

The relative risk (RR) and their 95% confidence intervals (CI) were estimated in both analyses for Aims 1 and 2. We kept OSA, and the covariates in the final multivariable model. The likelihood ratio test was used to assess the significance of the RR and interactions in the model. All analyses were performed using the statistical software package SAS (SAS 9.4; SAS Institute, Cary, NC, US), with the significance level for type I error set at the 0.05 level.

2.6.2 *Secondary analysis*

Interaction terms between each sleep disorder and acute-chronic pain status and GCPS status both at baseline were introduced. This was done to determine whether the sleep disorders risks were modified by these covariates. The interaction terms were retained in the model only if the significance level of the regression coefficient was equal to or lower than 0.10. The analyses were stratified by pain duration (acute [≤ 3 months], chronic [> 3 months]) and dysfunction (no [GCPS I] and yes [II-IV]).

3. Results

3.1 *Baseline profile of the acute and chronic TMD-related pain cohort defined by pain duration*

From a total of 516 subjects informed of the study, 10 refused to participate and 50 were not eligible due to lack of time and distress. Baseline characteristics of acute and chronic TMD-related pain cohorts is

demonstrated in Table1. The total number of TMD related pain subjects enrolled was 456, from which a 123 (26.96%) subjects were included in the acute cohort (≤ 3 months) and 333 (73.03%) in the chronic (> 3 months). Insomnia and OSA were slightly more common in the chronic TMD-related pain cohort compared to the acute (insomnia: 28.23% vs. 22.76%, *P* = 0.24; OSA: 49.70% vs. 44.72%, *P* = 0.34). No statistically significant differences were found between groups. Females were more present in the chronic TMD-related pain cohort compared to acute than the acute cohort (78.68% vs. 69.92%, *P* = 0.05).

Table 2 shows the baseline profile of the acute and chronic TMD-related pain cohorts that completed the 3-month follow-up. The number of participants who completed the follow-up was 378 subjects (82.89%) from a total enrolled of 456. Insomnia and OSA remained slightly higher in the chronic pain cohort compared to the acute (insomnia: 30.80% vs. 23.53%, *P* = 0.17; OSA: 49.08% vs. 45.10%, *P* = 0.49). No statistically significant differences were found between groups.

From the acute TMD-related pain cohort including 102 subjects who completed the 3-month follow-up, half of the subjects (n = 52) presented a transition to chronic TMD-related pain, and approximately the other half (n = 50) had no pain. From the chronic TMD-related pain cohort 75.72% (n = 209/276) had persistent chronic pain, whereas almost a quarter (n = 67) of subjects had no pain at 3-month follow-up.

Table 3 shows the baseline profile of subjects with and without chronic TMD-related pain at 3-months follow-up (261 vs. 117). Almost one-third of those with (29.50%) and without (27.35%) chronic TMD-related pain presented insomnia (*P* = 0.67). OSA was more common among the subjects with chronic TMD-related pain (50.58%) than those without pain (42.24%). However, this difference was not statistically significant (*P* = 0.13).

3.1.1 *The contribution of sleep disorders on the transition and persistence of chronic TMD-related pain*

Table 4 highlights OSA and insomnia crude and multivariable logistic regression analyses. Relative risk (RR) estimates showed no significant associations between insomnia and the transition and persistence risk at 3-month follow-up (RR_{crude} = 1.03, $RR_{model\ II}$ = 0.94, *P* = 0.27). A borderline association was found between the transition or persistent risk and OSA ($RR_{ModelIII}$ = 1.11, *P* = 0.07), when the model included the acute and chronic pain status, CPI, sex, age, and psychological factors. To improve the precision of the model, insomnia was not included in model III.

3.1.2 *Secondary analyses*

No interactions were found between each sleep disorders and the acute and chronic status at baseline (*P* > 0.28). The stratified analysis found that insomnia (RR = 1.20, 95%CI: 0.68-2.12, *P* = 0.52) and OSA (RR = 0.85, 95%CI: 0.55-1.31, *P* = 0.45) were not related to the transition risk. However, a significant persistent risk was found with OSA (RR = 1.13, 95%CI: 1.00-1.26, P = 0.04), but not with insomnia (RR = 0.92, 95%CI: 0.81-1.05, P = 0.22). These models included sex, age, psychological factors and CPI.

Regarding the score analysis, apnea score was not related to the transition or persistent risk (RR = 1.01, 95%CI: 0.99-1.02, *P* = 0.32). The stratified analyses, however, found that OSA score contributed to the persistence of TMD-related pain (RR = 1.01, 1.00-1.03, *P* = 0.047), but it was not related to the transition (RR = 0.98, 0.94-1.02, *P* = 0.30). These analyses were adjusted for all covariates. Furthermore, insomnia score was not related to the transition or persistence (RR = 1.00, 95%CI: 0.99-1.01, *P* = 0.61). The stratified analysis also showed that insomnia score was not related to the transition (RR = 1.02, 95%CI: 0.99-1.01, *P* = 0.16) and with the persistence outcome (RR = 1.00, 95%CI: 0.99-1.01, *P* = 0.88).

3.2 *Acute and chronic cohort defined by dysfunction*

At baseline, insomnia (32.50% vs. 12.88%, $P < .0001$), and OSA (51.57% vs. 41.98%, $P = 0.06$) were all more common among subjects with dysfunction compared to those without (Table 5).

Table 6 shows baseline characteristics of the no dysfunction and dysfunction cohorts who completed the 3-month follow-up. Insomnia (34.33% vs. 14.95%, $P = 0.0002$) and OSA (51.50% vs. 40.57% $P = 0.06$) were more prevalent in the dysfunction than in the no dysfunction cohort.

The number of subjects who completed the 3-month follow-up presented with or without dysfunction was 268 and 107, respectively. The dysfunction cohort showed 90 (33.58%) subjects with the persistence of chronic TMD-related pain compared to 178 (66.42%) without dysfunction. From the no dysfunction baseline cohort, eight (7.48%) presented a transition to chronic TMD-related pain and 92.52% (n = 99) of subjects remained without dysfunction

Table 7 shows the baseline cohort characteristics of subjects with or without dysfunction at 3-month follow-up. Insomnia (36.73%, $P = 0.04$) and OSA (59.38%, $P = 0.01$) remained to be more frequent among subjects with dysfunction compared to those without dysfunction.

3.2.1 *The contribution of sleep disorders on the transition and persistence of chronic TMD-related pain defined by dysfunction*

Table 8 shows the findings of the crude and multivariable logistic regression analyses for insomnia and OSA including 375 subjects. Insomnia at baseline was associated with the transition or persistence risk based on dysfunction in the crude (RR = 1.43, $P = 0.04$). In the multivariable analysis the RR was weaker and non-significant ($RR_{ModelII} = 1.00$, $P = 0.99$). To improve the precision of the model, insomnia was not included in model III. In the crude analysis, OSA was associated with the increased risk at a 3-

month follow-up (RR = 1.56, *P* = 0.01). However, a borderline association was found in the multivariable analyses (RR = 1.40, *P* = 0.051). In model III, we kept in the sex and acute and chronic TMD-related pain in the model even if they were not statistically significant, contrary to psychological factors and age since these covariates improved the precision.

3.2.3 *Secondary analysis*

At baseline, interaction analysis found no interaction between insomnia and OSA and the dysfunction status (*P* > 0.42). Furthermore, stratified analysis showed no association between OSA and the transition from acute to chronic pain defined by dysfunction (RR = 2.18, 95%CI: 0.56-8.47, *P* = 0.26). A borderline association, however, was found with persistence of chronic TMD-related pain (RR = 1.35, 95%CI: 0.95-1.91, *P* = 0.09).

Insomnia was not associated with persistence risk (RR = 1.12, 95%CI = 0.778-1.60, *P* = 0.53). It was not possible to assess the impact of insomnia on the transition risk since in this acute cohort including only the 107 subjects none of the subjects with insomnia (n = 16) presented a transition.

There were no statistically significant differences between subjects who dropout (n = 85) and who did not (n = 441): OSA (*P* = 0.72), acute to chronic (*P* = 0.93), dysfunction (*P* = 0.45), psychological factors (*P* = 0.14), age (*P* = 0.36), sex (*P* = 0.35), and CPI (*P* = 0.81). However, subject who dropout less frequently reported insomnia (n = 13, 16.67%) than those who did not dropout (n = 109, 28.34%, *P* = 0.03).

4. Discussion

This prospective cohort study demonstrated that OSA contributed to the transition from acute to chronic TMD-related pain as well as the persistence at a 3-month follow-up when chronic pain was

defined by duration and dysfunction. This increased risk appeared to be specific to the persistence of chronic TMD-related pain status. We found that this increase remained when the model was adjusted by the covariates associated with the study outcome.

The frequency of OSA in our chronic TMD-related pain cohort was slightly higher than that found in other studies (Table 1). In the OPPERA study, almost 6% of TMD subjects presented OSA. This study showed that TMD subjects were more likely to present OSA when compared to controls. In this study, OSA was assessed using 3 questions from Pittsburgh Sleep Quality Index (PSQI) and four questions from the STOP-BANG (SB) [15]. Polysomnography OSA prevalence among individuals with chronic TMD pain was 28.4% [14]. Furthermore, the prevalence of TMD is higher among patients with OSA referred for oral appliance therapy [25].

Insomnia assessed by polysomnography among TMD subjects was 36% (n = 52) in a chronic painful TMD [22]. Barjandi *et al*. [26] found that insomnia was prevalent among individuals with myalgia (31.3%) and myofascial pain with a referral (69.1%). Our estimated frequency of insomnia was lower than that study (Tables 1-2).

The prospective cohort study is the best design to achieve our study objectives because it ensures that the risk and potential contributing factors preceded the onset of chronic pain [27]. To decrease the chance of finding a positive association specific to a given hospital because of a referral pattern, subjects were recruited from four different dental clinics. To decrease misclassification bias, patients were diagnosed by four different investigators following the same study protocol. To decrease information bias, all questionnaires used were validated and have adequate specificity and sensitivity [16, 22, 23].

A limitation of this study relates to different classifications of acute and chronic TMD-related pain used among researchers. We followed the IASP to classify chronic pain (> 3 months) and used the GCPS [16] to classify those subjects with or without dysfunction, to overcome this limitation by avoiding

misclassification. Another limitation is the sample size of the acute cases was not large enough due to the difficulty of recruiting acute TMD patients. This was the case before and even after COVID19 closure restrictions that were introduced on March 2019. It is possible that larger sample size in the acute cohort could have strengthened the 80% power of analysis we conservatively estimated. In our study, our dropout rate is 10.2%. No significant differences were found between subjects who dropout and did not. Additionally, the stratified analysis for insomnia had a lower sample size which contributed to the sample size limitation in our study.

Our study is the first to demonstrate the contribution of OSA on the increased risk of transition from acute to chronic pain as well as its persistence at a 3-month follow-up when chronic pain is defined by duration or dysfunction. Insomnia, however, was not related to the study outcomes. This result suggests that OSA assessment may be considered as part of the comprehensive clinical exam for TMD patients and that OSA management should be tested to prevent the transition and persistence of TMD-related pain.

5. Conflict of interest statement

The authors do not have any conflicts of interest associated with this manuscript.

6. Acknowledgements

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Table 1. Baseline characteristics of acute and chronic TMD-related pain cohorts defined by duration

Risk factors and covariates	**Category**	**Acute cohort (≤ 3 months) n (%)** 123 (26.96)	**Chronic cohort (> 3 months) n (%)** 333 (73.03)	***P*-value**
Insomnia, n (%)	≥ 15	28 (22.76)	94 (28.23)	0.24
	< 15	95 (77.24)	239 (71.77)	
OSA, n (%)	≥ 10	55 (44.72)	164 (49.70)	0.34
	< 10	68 (55.28)	166 (50.30)	
Sex, n (%)	Female	86 (69.92)	262 (78.68)	0.05
	Male	37 (30.08)	71 (21.32)	
Psychological factors, n (%)	≥ 3	69 (56.10)	207 (62.16)	0.24
	< 3	54 (43.90)	126 (37.84)	
Age (years)	Mean, median, (SD)	42.64, 39.00, (16.11)	41.74, 39.00 (16.29)	0.60
CPI (0-100 NRS)	Mean, median, (SD)	57.43, 56.66, (21.42)	57.41, 60.00, (21.65)	0.98

CPI = characteristic pain intensity, SD = standard deviation, NRS = numeric pain rating scale
n = number of subjects, % = percentage
Insomnia < 15 = No, ≥ 15 = Yes
OSA < 10 = No, ≥ 10 = yes
Psychological factors ≥ 3 = Yes, < 3 = No

Table 2. Baseline profile of the acute and chronic TMD-related pain cohorts who completed the 3-month follow-up

Risk factors and covariates	Category	Acute cohort (≤ 3 months) n (%)	Chronic cohort (> 3 months) n (%)	Total n (%)	*P*-value
		102 (26.98)	276 (73.02)	378	
Insomnia, n (%)	≥ 15	24 (23.53)	85 (30.80)	109 (28.84)	0.17
	< 15	78 (76.47)	191 (69.20)	269 (71.16)	
OSA, n (%)	≥ 10	46 (45.10)	134 (49.08)	180 (48.00)	0.49
	< 10	56 (54.90)	139 (50.92)	195 (52.00)	
Sex, n (%)	Female	72 (70.59)	214 (77.54)	286 (75.66)	0.16
	Male	30 (29.41)	62 (22.46)	92 (24.34)	
Psychological factors, n (%)	≥ 3	58 (56.86)	176 (63.77)	234 (61.90)	0.22
	< 3	44 (43.14)	100 (36.23)	144 (38.10)	
Age (years)	Mean, median, (SD)	42.34, 39.00, (16.70)	41.52, 39.00, (16.15)	41.59, 39.00, (16.14)	0.74
CPI (0-100 NRS)	Mean, median, (SD)	57.94, 60.00, (20.26)	57.29, 60.0, (21.73)	57.46, 60.0, (21.33)	0.71

CPI = characteristic pain intensity, SD = standard deviation, NRS = numeric pain rating scale
n = number of subjects, % = percentage
Insomnia < 15 = No, ≥ 15 = Yes
OSA < 10 = No, ≥ 10 = yes
Psychological factors ≥ 3 = Yes, < 3 = No

Table 3. Baseline profile of subjects with chronic TMD-related pain and those without pain at 3-month follow-up

Risk factors and covariates	**Category**	**No TMD-related pain n (%)**	**Chronic TMD-related pain n (%)**	***P*-value**
		117 (30.95)	261 (69.05)	
Insomnia, n (%)	≥ 15	32 (27.35)	77 (29.50)	0.67
	< 15	85 (72.65)	184 (70.50)	
OSA, n (%)	≥ 10	49 (42.24)	131 (50.58)	0.13
	< 10	67 (57.76)	128 (49.42)	
Sex, n (%)	Female	76 (64.96)	210 (80.46)	0.001
	Male	41 (35.04)	51 (19.54)	
Psychological factors, n (%)	≥ 3	69 (58.97)	165 (63.22)	0.43
	< 3	48 (41.03)	96 (36.78)	
Mean age, (95% CI)	Years	40.11 (37.17-43.06)	42.39 (40.42-44.36)	0.21
Mean CPI (95%CI)	0-100 NRS	51.06 (47.24-54.88)	60.41 (57.85-62.96)	<.0001

CPI = characteristic pain intensity, CI = confidence interval, NRS = numeric pain rating scale
n = number of subjects, % = percentage, Chronic > 3 months
Insomnia < 15 = No, ≥ 15 = Yes
OSA < 10 = No, ≥ 10 = yes
Psychological factors ≥ 3 = Yes, < 3 = No

Table 4. Crude and multivariable logistic regression analyses assessing the contribution of insomnia and OSA on transition and persistent TMD-related pain at 3-month follow-up

Risk factors and covariates at baseline	**Category**	**Model I RR (95% CI)**	***P*-Value**	**Model II RR (95% CI)**	***P*-Value**	**Model III RR (95% CI)**	***P*-Value**
Insomnia	< 15	1.0 (reference)	0.66	1.0 (reference)	0.27	*Not in the model*	
	≥ 15	1.03 (0.89-1.19)		0.94 (0.84-1.05)			
OSA	< 10	1.0 (reference)	0.13	1.0 (reference)	0.19	1.0 (reference)	0.07
	≥ 10	1.11 (0.97-1.27)		1.07 (0.97-1.18)		1.11 (0.99-1.25)	
Acute and chronic TMD-related pain	≤ 3 m	1.0 (reference)	0.0001	1.0 (reference)	0.002	1.0 (reference)	<.0001
	> 3 m	1.48 (1.21-1.81)		1.23 (1.08-1.40)		1.47 (1.20-1.79)	
Mean CPI	0-100 NRS	1.01 (1.00-1.01)	0.0001	1.00 (1.00-1.01)	0.008	1.00 (1.00-1.01)	0.0001
Sex	Male	1.0 (reference)	0.005	1.0 (reference)	0.07	1.00 (reference)	0.02
	Female	1.32 (1.09-1.61)		1.13 (0.99-1.29)		1.25 (1.04-1.51)	
Mean age	Years	1.00 (0.99-1.01)	0.21	1.00 (0.99-1.00)	0.70	1.00 (0.99-1.00)	0.54
Psychological factors	< 3	1.0 (reference)	0.44	1.0 (reference)	0.91	1.0 (reference)	0.35
	≥ 3	1.06 (0.92-1.22)		0.99 (0.89-1.11)		0.94 (0.83-1.07)	

RR = relative risk, m = months, Insomnia < 15 = No, ≥ 15 = Yes; OSA < 10 = No, ≥ 10 = yes; Acute ≤ 3 m, Chronic > 3 m
CPI = characteristic pain intensity, NRS = numeric pain rating scale
Model I = crude analysis, Model II = multivariable model including sleep disorders and all covariates
Model III = multivariable model including OSA and all covariates
Psychological factors ≥ 3 = Yes, < 3 = No

Table 5. Baseline profile of the acute and chronic TMD-related pain cohorts defined by dysfunction

Risk factors and covariates	**Category**	**No dysfunction (GCPS I) n (%)**	**Dysfunction (GCPS II-IV) n (%)**	***P*-value**
		132 (29.20)	320 (70.80)	
Insomnia, n (%)	≥ 15	17 (12.88)	104 (32.50)	<.0001
	< 15	115 (87.12)	216 (67.50)	
OSA, n (%)	≥ 10	55 (41.98)	164 (51.57)	0.06
	< 10	76 (58.02)	154 (48.43)	
Sex, n (%)	Female	98 (74.24)	247 (77.19)	0.50
	Male	34 (25.76)	73 (22.81)	
Psychological factors, n (%)	≥ 3	63 (47.73)	212 (66.25)	0.0002
	< 3	69 (52.27)	108 (33.75)	
Mean age, (95% CI)	Years	39.78 (37.02, 42.53)	42.90 (40.12-44.68)	0.06
Acute to chronic TMD pain defined by pain duration	Acute (n = 121)	35 (28.93)	86 (71.07)	0.94
	Chronic (n = 331)	97 (29.31)	234 (70.69)	

CI = confidence interval, n = number of subjects, % = percentage
Insomnia < 15 = No, ≥ 15 = Yes
OSA < 10 = No, ≥ 10 = yes
Acute ≤ 3 m, Chronic > 3 m
Psychological factors ≥ 3 = Yes, <3 = No

Table 6. Baseline profile of the no dysfunction and dysfunction cohorts who completed the 3-month follow-up

Risk factors and covariates	**Category**	**No dysfunction (GCPS I) n (%)**	**Dysfunction (GCPS II-IV) n (%)**	**Total n (%)**	***P*-value**
		107 (28.53)	268 (71.47)	375	
Insomnia, n (%)	≥ 15	16 (14.95)	92 (34.33)	108 (28.80)	0.0002
	< 15	91 (85.05)	176 (65.67)	267 (71.20)	
OSA, n (%)	≥ 10	43 (40.57)	137 (51.50)	180 (48.39)	0.06
	< 10	60 (59.43)	129 (48.50)	192 (51.61)	
Sex, n (%)	Female	80 (74.77)	203 (75.75)	283 (75.47)	0.84
	Male	27 (25.23)	65 (24.25)	92 (24.53)	
Psychological factors, n (%)	≥ 3	55 (51.40)	177 (66.04)	232 (61.87)	0.008
	< 3	52 (48.60)	91 (33.96)	143 (38.13)	
Age (years)	Mean, median, (SD)	39.47, 38.72, (16.10)	42.44, 41.00, (16.05)	42.27, 40.00, (16.35)	0.11
Acute to chronic TMD pain defined by pain duration, n (%)	Acute	27 (27.27)	72 (72.73)	99 (26.40)	0.75
	Chronic	80 (28.99)	196 (71.01)	276 (73.60)	

SD = standard deviation, n = number of subjects, % = percentage
Insomnia < 15 = No, ≥ 15 = Yes
OSA < 10 = No, ≥ 10 = yes
Acute ≤ 3 months, Chronic > 3 months
Psychological factors ≥ 3 = Yes, <3 = No

Table 7. Baseline profile of cohorts without or with dysfunction at 3-month follow-up

Risk factors and covariates	**Category**	**No dysfunction (GCPS I) n (%)** 277 (73.87)	**Dysfunction (GCPS II-IV) n (%)** 98 (26.13)	***P*-value**
Insomnia, n (%)	≥ 15	72 (25.99)	36 (36.73)	0.04
	< 15	205 (74.01)	62 (63.27)	
OSA, n (%)	≥ 10	123 (44.57)	57 (59.38)	0.01
	< 10	153 (55.43)	39 (40.63)	
Sex, n (%)	Female	203 (73.29)	80 (81.63)	0.10
	Male	74 (26.71)	18 (18.37)	
Psychological factors, n (%)	≥ 3	160 (57.76)	72 (73.47)	0.006
	< 3	117 (42.24)	26 (26.53)	
Age (years)	Mean, median, (SD)	41.63, 37.00, (17.00)	41.47, 42.00, (16.06)	0.98
Acute to chronic TMD pain defined by pain duration, n (%)	Acute (99)	79 (79.80)	20 (20.20)	0.12
	Chronic (276)	198 (71.74)	78 (28.26)	

SD = standard deviation, n = number of subjects, % = percentage
Insomnia < 15 = No, ≥ 15 = Yes
OSA < 10 = No, ≥ 10 = yes
Acute ≤ 3 months, Chronic > 3 months
Psychological factors ≥ 3 = Yes, <3 = No

Table 8. Crude and multivariable logistic regression analyses assessing the contribution of insomnia and OSA on the transition to chronic TMD-related pain based on dysfunction at 3-month follow-up using GCPS

Risk factors and covariates at baseline	**Category**	**Model I RR (95% CI)**	***P*-Value**	**Model II RR (95% CI)**	***P*-Value**	**Model III RR (95% CI)**	***P*-Value**
Insomnia	< 15	1.0 (reference)	0.04	1.0 (reference)	0.99	*Not in the model*	
	≥ 15	1.43 (1.02-2.03)		1.00 (0.70-1.43)			
OSA	< 10	1.0 (reference)	0.01	1.0 (reference)	0.16	1.0 (reference)	0.05
	≥ 10	1.56 (1.09-2.22)		1.29 (0.90-1.85)		1.40 (1.00-1.97)	
Acute and chronic TMD-related pain	≤ 3 m	1.0 (reference)	0.13	1.0 (reference)	0.19	1.0 (reference)	0.15
	> 3 m	1.40 (0.91-2.16)		1.32 (0.86-2.02)		1.37 (0.90-2.08)	
Dysfunction	No	1.0 (reference)	<.0001	1.0 (reference)	<.0001	1.0 (reference)	<.0001
	Yes	4.49 (2.25-8.93)		4.09 (2.05-8.19)		4.21 (2.11-8.36)	
Sex	Male	1.0 (reference)	0.11	1.0 (reference)	0.16	1.0 (reference)	0.20
	Female	1.44 (0.92-2.27)		1.37 (0.88-2.16)		1.33 (0.86-2.07)	
Mean age	Years	0.99 (0.98-1.01)	0.93	0.99 (0.98-1.00)	0.37	*Not in the model*	
Psychological factors	< 3	1.0 (reference)	0.008	1.0 (reference)	0.13	*Not in the model*	
	≥ 3	1.70 (1.14-2.53)		1.36 (0.91-2.03)			

RR = relative risk, m = months, Insomnia < 15 = No, ≥ 15 = Yes; OSA < 10 = No, ≥ 10 = yes; Acute ≤ 3 m, Chronic > 3 m
Model I = crude analysis, Model II = multivariable model including insomnia and OSA and all covariates
Model III = multivariable model including OSA and all covariates
Dysfunction is characterized by a combination of an average of 5 or greater over the three pain questions and pain related disability
Psychological factors ≥ 3 = Yes, <3 = No

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7 *Supplemental material* - Fatigue - Manuscript II

The contribution of fatigue on the transition from acute to chronic painful temporomandibular disorders, and its persistence: a prospective 3-month cohort study

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Abstract

Previous studies have demonstrated that fatigue is associated with chronic temporomandibular disorders (TMD) pain. TMD is a group of a musculoskeletal condition affecting the muscles of mastication, the temporomandibular joints, or both. This prospective cohort study determines whether fatigue is associated with the transition from acute to chronic TMD-related pain as well as its' persistence, when chronic pain is defined by: (i) duration (> 3 months), and (ii) dysfunction (Graded Chronic Pain Scale (GCPS II-IV). The International Association for the Study of Pain (IASP) defines chronic pain as "persistent or recurrent pain lasting longer than 3-months" and is associated with significant dysfunction. From 454 subjects recruited between 2015 to 2021, through four locations in Canada, 376 completed the follow-up. A diagnosis was obtained using the Research Diagnostic Criteria or the Diagnostic Criteria for Temporomandibular Disorders. Fatigue was assessed at baseline with the Fatigue Severity Scale. Subjects completed the GCPS form at baseline and 3-month follow-up. When chronic pain was defined as dysfunction, fatigue was associated with an increased transition or persistence risk ($RR_{adjusted}$ = 1.72, P = 0.002), contrary to pain duration ($RR_{adjusted}$ =1.01, P = 0.99). This multivariable analysis was adjusted by baseline acute and chronic pain status, dysfunction, and sex. Results indicate that fatigue contributed to the transition (RR = 5.92, P = 0.02) and persistence (RR = 1.62, P = 0.007) of chronic TMD-related pain risk at a 3-month follow-up when chronic pain was defined by dysfunction contrary to defined by duration. This result suggests that fatigue assessment may be an essential part of a comprehensive clinical examination.

1. Introduction

Temporomandibular disorders (TMD) is a collective term used to describe musculoskeletal conditions characterized by pain in the muscles of mastication and temporomandibular joint or both, and/or associated structures [1]. The common signs and symptoms include tenderness in the muscles upon palpation, pain within the range of motion, or limitation of the jaw upon opening. This is followed by interference with vital functions such as eating, swallowing, and speaking [20].

The prevalence of TMD-related pain ranges between 5% to 12% [10, 23] and the annual incidence is 3.9% [16]. TMD-related pain is more common among females than males [23]. Nevertheless, approximately 33% of TMD-related pain patients continue to suffer from moderate to severe levels of pain and disability, independent of treatment received [13, 14].

Fatigue is a subjective experience with symptoms including a persisting lack of energy, exhaustion, physical and mental tiredness, and apathy [2]. The prevalence of fatigue varies from 0.2% to 6.41%[11] Fatigue prevalence is considerably higher among subjects with TMD-related pain (14-43%) [2, 5, 9]. Dahan *et al.* [5] found that fatigue was positively associated with chronic TMD-related pain intensity and duration.

The current prospective cohort study is part of the Acute to Chronic TMD Transition (ACTION) program, with an overall goal to identify the risk factors implicated in the transition from acute to chronic TMD-related pain and its persistence. The current study aimed to assess whether fatigue was associated with the transition from acute to chronic TMD-related pain risk as well as with its persistence at a 3-month follow-up. Thus, the specific aims are:

Aim # 1. To determine if fatigue is associated with the transition and persistence risk when chronic TMD-related pain is defined as recurrent or persistent pain for more than 3 months.

Aim # 2. To determine the contribution of fatigue on the transition or persistence risk when chronic TMD-related pain is defined by dysfunction as classified by GCPS (Graded Chronic Pain Scale Grades II-IV) [24].

The rationale to define chronic pain based on pain duration and dysfunction is described below. First, the International Association for the Study of Pain (IASP) defines chronic pain as recurrent or persistent pain lasting for more than 3 months [18, 19]. Second, IASP states that chronic pain is associated with significant disability [19]. Therefore, chronic TMD-related pain was also defined as a dysfunction state consisting of clinically significant pain and disability [24]. The study hypotheses are that fatigue increases the risk of a transition from acute to chronic TMD-related pain as well as its persistence when chronic TMD-related pain is defined by pain duration or dysfunction. To date, we are not aware of any study investigating the contribution of fatigue on the transition from acute to chronic TMD-related pain as well as its persistence.

2. Methods

2.1 *Study design and study population*

The Acute to Chronic TMD Transition (ACTION) program received approval from the McGill Institutional Review Board in Montreal, Canada (approval number: A12-M113-14A) and by the Dental Specialists Group in Ottawa, Ontario (approval number: 240-400).

Eligible subjects with acute or chronic TMD-related pain were recruited between August 2015 and March 2021 from four different sites: the Jewish General Hospital (JGH) general dental clinic, the Faculty of Dentistry of McGill University oral diagnosis (OD) clinic, the Montreal General Hospital dental department (MGH), and the Dental Specialists Group TMD-specialized clinic. The inclusion criteria for the participation in this study required subjects to be of 18 to 85

years of age with a positive diagnosis of TMD-related pain (muscle and/or joint) in accordance with Research Diagnostic DC [6] or the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) [15]. The excluded subjects were those who had other orofacial pain (e.g. dental pain), cancer, no access to a telephone, those who were unable to provide informed consent or incapable of understanding French or English.

2.2 *Acute and chronic pain classification*

We used two criteria to define acute and chronic TMD-related pain: (i) pain duration of chronic TMD-related pain is in accordance with the International Association for the Study of Pain (IASP) which defines chronic pain as pain lasting for more than 3 months [18, 19], and (ii) dysfunction defined as grades II, III and IV with any disability points on the Graded Chronic Pain Scale (GCPS) [24].

GCPS is an instrument used to assess overall chronic pain severity based on the level of pain intensity and pain-related disability. The GCPS grades are low-intensity pain, no disability (Grade I); high-intensity pain, without pain-related disability (Grade IIa); (iii) high-intensity pain, with low pain-related disability (Grade IIb), moderately limiting (Grade III), and severely limiting (Grade IV). The scoring is based on the subject's responses to several items: 1) current; 2) worst; and 3) average pain intensity (0–10 numeric scales); 4) pain-related disability days, and pain-related interference with daily activities; work; and social or family activities (0–10 numeric). Characteristic pain intensity (CPI) measured by the GCPS is the average of 0–10 ratings of current, worst and average pain in the prior 3 months multiplied by 10. The disability score is the average of 3, 0–10 interference ratings: daily activities, work, and social or family activities multiplied by 10 prior 3 months.

2.3 *Outcome variables*

The primary outcomes were the transition from acute to chronic TMD-related pain or the persistence of chronic pain at the 3-month follow-up when chronic pain was defined by pain duration and dysfunction. Secondary outcomes were the transition and the persistence state, both also defined by pain duration and dysfunction.

2.4 *Assessment of fatigue*

Fatigue severity and functionality were assessed using the Fatigue Severity Scale (FSS), a validated and reliable instrument [21]. The FSS has 90% sensitivity and 86% specificity, with high reliability (Cronbach $\alpha = 0.93$). The scoring cutoffs are: < 35: no fatigue; and ≥ 36: fatigue.

2.5 *Putative confounders and effect modifiers assessment*

In our study, the possible confounders all assessed at baseline were acute and chronic pain status, dysfunction, psychological factors (anxiety, depression), CPI, sex, and age. The Patient Health Questionnaire-4 (PHQ-4) is a validated and reliable instrument used for screening for psychological factors: anxiety and depression [12]. PHQ-4 scoring cutoffs are: < 3: no anxiety and depression; and ≥ 3: anxiety and depression.

2.6 *Statistical analysis*

Chi-squared, Fisher's exact test, analysis of variance, and Student t-test were used to test statistical differences between categories of TMD-related pain groups relative to fatigue, acute and chronic pain status, GCPS grades (GCPS I-IV), CPI, age, sex, and psychological factors.

2.6.1 *Primary analysis*

For aim 1, we conducted binary logistic regression. The dependent variable was the presence or absence (yes or no) of chronic TMD-related pain at 3-month of follow-up. The risk factor under study was fatigue (yes or no) and the putative confounders were acute-chronic pain status at baseline, age, sex, CPI, and psychological factors.

For aim 2, a binary logistic regression analysis was also performed to assess the relative risk of fatigue. The dependent variable was GCPS at 3-month of follow-up: 0-I (no dysfunction) vs and II-IV (dysfunction). The risk factor was fatigue (yes or no) or fatigue score (yes or no) and the putative baseline confounders dysfunction were acute-chronic pain status at baseline, age, sex, and psychological factors An interaction term was created with GCPS status at baseline and fatigue or fatigue score to determine whether this covariate modify the RR associated with fatigue.

In both analyses (Aims 1 and 2), the relative risk (RR) and their 95% confidence intervals (CI) were estimated. In the final multivariable models, we kept in the model fatigue, the covariates associated with the dependent variable, and the effect modifiers (interaction). The likelihood ratio test was used to assess the significance of the RR and the interactions in the model. All analyses were performed using the statistical software package SAS (SAS 9.4; SAS Institute, Cary, NC, US), with the significance level for type I error set at the 0.05 level.

2.6.2 *Secondary analysis*

Interaction terms were created between fatigue and acute-chronic pain status and dysfunction status both at baseline, to determine whether fatigue's risk depended on these covariates. The interaction term was retained in the model only if the significance level of the regression coefficient was equal to or lower than 0.10. Further, the analyses were stratified by

pain duration (acute [≤ 3 months], chronic [> 3 months]) and dysfunction (no [GCPS I] and yes [II-IV]).

3. Results

3.1 *Description of the baseline acute and chronic cohort defined by pain duration*

A total of 514 subjects were informed about the study. Of these, 10 refused to participate (lack of time and distress), and 50 were not eligible. Table 1 shows the baseline characteristics of acute and chronic TMD-related pain cohorts defined by duration. From a total of 454 TMD-related pain subjects recruited, 123 (27.09%) were included in the acute cohort (≤ 3 months) and 331 (72.91%) in the chronic (> 3 months). The chronic cohort included a larger number of subjects with fatigue (48.34%) and females (78.32%) than the acute cohort (35.77%, $P = 0.02$, 69.40%, $P = 0.04$).

From 454 subjects enrolled, 376 (82.28%) completed the 3-month follow-up. The chronic cohort included a larger number of subjects with fatigue (50.0%) than the acute cohort (34.31%, $P = 0.007$) (Table 2).

From the acute TMD-related pain cohort including 102 subjects who completed the 3-month follow-up, 50.98% (n = 52) of subjects presented a transition to chronic TMD-related pain, and 49.02% (n = 50) of subjects had no pain. From the 274 chronic TMD-related pain cohort, 75.91% (n = 208) subjects had persistent chronic TMD-related pain whereas 24.09% (n = 66) of subjects had no pain, at 3-month follow-up.

Table 3 shows the baseline profile of subjects with (n = 260) and without chronic TMD-related pain (n = 116) at a 3-month follow-up. Fatigue was present in 49.62% of the chronic TMD-related pain subjects, and in 37.07% of the subjects without pain at 3-month follow-up ($P = 0.02$).

3.1.1 *Fatigue contribution to the transition and persistence of chronic TMD-related pain*

Table 4 shows the findings of the binary logistic regression analyses. Fatigue at baseline was associated with the transition or persistence risk at 3-month follow-up (RR = 1.17, 95%CI: 1.02-1.34, *P* = 0.02). When the model was adjusted by the covariates associated with the study outcome, fatigue RR was weaker and not significant (RR =1.01, *P* = 0.99).

3.1.2 *Secondary analyses*

No interaction was found between fatigue and acute and chronic TMD-related pain at baseline (*P* = 0.17). Furthermore, the stratified analyses showed that fatigue was not associated with the transition (RR = 1.22, 95%CI: 0.84-1.75, *P* = 0.28) and persistent (RR = 0.98, 95% CI: 0.86-1.11, *P* = 0.78) risks.

3.2 ***Acute and chronic cohort defined by dysfunction***

Table 5 shows baseline characteristics of cohorts with and without dysfunction. At baseline, fatigue was present in 50.0% of the dysfunction subjects, and in 33.33% of subjects without dysfunction (*P* = 0.001). The chronic cohort included a larger number of subjects with psychological symptoms (66.35%) than the acute cohort (47.73%, *P* = 0.0002).

Table 6 exhibits a baseline profile of the no dysfunction and dysfunction cohorts who completed the 3-month follow-up. Fatigue was more common in the dysfunction cohort (50.38%) when compared to those without dysfunction (33.64%, *P* = 0.003). Psychological symptoms remained different between these cohorts that completed the follow-up (66.17% vs 51.40%, *P* = 0.008).

From the no dysfunction baseline cohort including 107 subjects who completed the 3-month follow-up, only eight (7.48%) presented a transition to chronic TMD-related pain defined by dysfunction, and 92.52% (n = 99) of subjects had no transition and remained with no dysfunction.

The dysfunction cohort (n = 266) displayed 90 (33.83%) subjects with the persistence of chronic TMD-related pain defined by dysfunction at a 3-month follow-up.

Table 7 shows the baseline profile of cohorts of subjects with or without dysfunction at 3-month follow-up. Fatigue remained to be more frequent among subjects with dysfunction (63.27%) compared to those without dysfunction (39.27%, P <.0001).

3.2.1 *Fatigue contributions to the transition and persistence of chronic TMD-related pain defined by dysfunction*

Table 8 displays the findings of the binary logistic regression analysis including 373 subjects. Fatigue at baseline was associated with the transition or persistence risk based on dysfunction (RR_{crude} = 2.05, 95% CI: 1.44-2.94, P < .0001) and remained significant in the multivariable analysis ($RR_{ModelIII}$ = 1.72, 95%CI: 1.21-2.44, P = 0.002) adjusted for dysfunction (RR = 4.07, P < .0001), acute and chronic pain status (RR = 1.27, P = 0.27), and sex (RR = 1.41, P = 0.12). Psychological factors and age were not included in the final multivariable model because they were not associated with chronic TMD-related pain and did not improve the precision of the model.

3.2.2 *Secondary analysis*

No interaction was found between fatigue and dysfunction at baseline (P = 0.12). The stratified analysis demonstrated that fatigue was associated with increased risk of transition from acute to chronic TMD-related pain (RR = 5.92, 95% CI: 1.25-27.85, P = 0.02), and with the persistence of chronic pain (RR = 1.62, 95% CI: 1.14-2.30, P = 0.007).

Crude ($RR_{crude\_analysis}$ = 1.03. 95% CI: 1.02-1.05, $P < .0001$) and the multivariable analysis adjusted for acute and chronic pain status, sex, psychological factors and clinically significant pain and dysfunction at baseline (n = $RR_{multivariable\ model}$ = 1.01. 95% CI: 1.00-1.03, $P < .002$) demonstrated that fatigue score was associated with an increased risk of transition and persistent at a 3-month follow-up. An interaction was found between fatigue score and dysfunction at baseline ($P = 0.06$), suggesting that the RR of fatigue score is modified by dysfunction at baseline. Based on stratification analyses, the fatigue score was also positively association with no dysfunction (RR = 1.02, 95% CI: 1.01-1.04, $P < .0001$) and with dysfunction (RR = 1.03, 95% CI: 1.01-1.03, $P < .0001$), regardless of acute and chronic pain status at baseline and sex.

There were no statistically significant differences between subjects who dropout (n = 78) and who did not (n = 376): fatigue ($P = 0.45$), acute to chronic ($P = 0.97$), dysfunction ($P = 0.45$), psychological factors ($P = 0.18$), age ($P = 0.35$), sex ($P = 0.46$), and CPI ($P = 0.81$).

4. Discussion

The primary finding of this prospective 3-month cohort study is that fatigue was associated with the risk of transition and persistent TMD-related pain, at a 3-month follow-up when chronic pain is defined by dysfunction (GCPS II-IV). Further, this association was not confounded by subjects' age, sex, psychological symptoms, acute and chronic pain status and dysfunction at baseline (Table 8). Additionally, fatigue risk was not modified by the acute or chronic pain status risk. Finally, the risk of transition and persistence of chronic TMD-related pain was positively related to fatigue score. Fatigue, however, was not related to the transition from acute to chronic TMD-related pain risk when chronic pain is defined by pain duration (Table 4).

A search of the literature revealed nil studies examined the contribution of fatigue on the

transition from acute to chronic TMD-related pain as well as its persistence.

Chen *et al.* diagnosed 159 TMD-related pain patients using a modified version of the RDC/TMD criteria from the orofacial pain clinic and found 10% report having fatigue [3]. Dahan *et al.* in a cross-sectional study found a fatigue prevalence of 14.4% in their chronic myofascial TMD-related pain population [4]. In our study, fatigue was reported by 35.77% of the acute TMD-related pain cohort, and 48.34% of the chronic cohort. These percentages of fatigue are close to those observed by Hoffmann *et al.* who surveyed 1511 TMD-related pain patients and found that 42-43% reported having fatigue after the onset of TMD-related pain [9].

We investigated if the risk would be confounded by the potential confounders such as age, sex, psychological factors (anxiety and depression), CPI, acute and chronic pain status, and dysfunction at baseline, on the fatigue's risk. Our baseline findings show dysfunction (GCPS II-IV) present in the chronic (n = 232, 72.96%) compared to acute (n= 86, 27.04%). Similar findings were found of dysfunction distribution among acute (n = 99, 26.54%) and chronic (n = 72, 73.46) at 3-month follow-up. This is consistent with findings from Garofalo *et al.* [8] showing dysfunction prevalence of more than 70% at baseline at 6-month follow-up. In this study, the mean CPI at baseline was also higher in individuals of chronic TMD-related pain at 6-month follow-up in comparison to those with CPI means of less than 15. The mean age and sex distribution of our subjects at baseline were similar to Garofalo *et al.* [8]. Garofalo *et al.* [8] also found that CPI of chronic TMD-related pain increased the risk of transition from acute to chronic pain at 6-month of follow-up. In addition, a borderline association risk was found with disability (GCPS III-IV) [8].

Regardless, although causality cannot be evaluated due to the design of the present study, these findings raise the hypothesis that fatigue may contribute to a dysregulation of pain

modulatory systems involving central and peripheral sensitization that contribute to the transition and persistence of chronic pain defined by dysfunction [22].

The findings of this study are strengthened by the strong methodology utilized and the characteristics of the study population. This is a prospective cohort study that ensures that the risk factors preceded the transition and persistence of chronic TMD-related pain. Prospective cohort studies are considered the gold standard of observational research [17]. Subjects were recruited from four different dental clinics, which decreased the chance of finding a positive association specific to a given hospital because of a referral pattern. Patients were diagnosed by four investigators following the same protocol to decrease misclassification. The questionnaires used are validated and have adequate specificity and sensitivity.

It is important to bear in mind that even though this study has several strengths, it also has a few limitations. First, the classification of acute and chronic TMD-related pain has been used differently among researchers. To avoid misclassification, we followed the IASP to classify chronic pain, which suggested more than 3 months. GCPS is a validated instrument that we used to classify subjects with or without dysfunction [24]. Second, a self-report method was used to collect data. This method might have some disadvantages such as, misunderstanding, exaggeration, and/or not remembering some details. Third, the acute cases sample size was not large enough to adequately study the transition from acute to chronic TMD-related pain. This is due to the difficulty of recruiting acute TMD patients due to COVID19 restrictions that were initiated on March 2019 closures. The known number of patients required to recruit enough eligible subjects for the study is not precise. We have conservatively estimated that 80% of patients who meet the criteria will be interested in the study to enable us to meet the sample size. The sample size for acute patients may have been close to achieving our power of analysis but yet was

smaller than planned (120 subjects versus 150 subjects). Therefore, type 2 error was introduced, where some results did not reach statistical significance although the hypothesized trend was evident. A larger sample size in the acute cohort may have strengthened the power to demonstrate the associations in this study. This study design also takes time and is conducted at high costs which may be a limitation to some researchers. Finally, a major disadvantage of this type of prospective cohort design is a loss of follow-up. A follow-up rate of 50-80% has been suggested as acceptable by different authors [7]. In our study, our dropout rate is 10.2%. No significant differences were found between subjects who dropout and did not.

This study has several clinical implications. We found that fatigue contributed to the risk of transition and persistence risk of chronic TMD-related pain when chronic pain is defined by dysfunction. Assessing the patient's level of fatigue may be introduced into a comprehensive clinical exam protocol to aid in the management of TMD-related pain patients. It is critical to match the level of complexity of the case with the appropriate management program. For example, a patient reporting single comorbidity will be managed differently from a patient presenting with multiple comorbidities. The latter may require an interdisciplinary pain clinic setting that uses a team of clinicians to address different aspects of the problem in a concerted fashion. Failure to identify and to address the entire scope of the problem may lead to no improvement in pain or function, and further perpetuation of the problem.

In conclusion, this prospective cohort study is the first study to reveal the contribution of fatigue on an increased risk of transition from acute to chronic pain and the persistence of chronic TMD-related pain at a 3-month follow-up when chronic pain is defined by dysfunction. Fatigue did not contribute to an increased risk of transition from acute to chronic, and the persistence of chronic TMD-related pain at a 3-month follow-up, when chronic pain was defined by duration.

This result suggests that fatigue assessment should be considered as part of the comprehensive clinical exam for TMD patients and that its management should be tested as potential management to prevent the transition and persistence of TMD-related pain.

5. Conflict of interest statement

The authors do not have any conflicts of interest associated with this manuscript.

6. Acknowledgments

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Table 1. Baseline characteristics of acute and chronic TMD-related pain cohorts defined by duration

Risk factor and covariates	**Category**	**Acute cohort (≤ 3 months) n (%)** 123 (27.09)	**Chronic cohort (> 3 months) n (%)** 331 (72.91)	***P*-value**
Fatigue, n (%)	≥ 36	44 (35.77)	160 (48.34)	0.02
	< 36	79 (64.23)	171 (51.66)	
Sex, n (%)	Female	93 (69.40)	307 (78.32)	0.04
	Male	41 (30.60)	85 (21.65)	
Psychological factors, n (%)	≥ 3	69 (56.10)	206 (62.24)	0.23
	< 3	54 (43.90)	125 (37.76)	
Mean age, (95% CI)	Years	31.70 (23.39-40.01)	32.62 (27.56-37.69)	0.85
Mean CPI (95%CI)	0-100 NRS	57.44 (53.60-61.27)	57.37 (55.03-59.69)	0.97

CPI = characteristic pain intensity, CI = confidence interval, NRS = numeric pain rating scale
n = number of subjects, % = percentage
Fatigue ≥ 36 = Yes, < 36 = No
Psychological factors ≥ 3 = Yes, < 3 = No

Table 2. Baseline profile of the acute and chronic TMD-related pain cohorts who completed the 3-month follow-up

Risk factor and covariates	**Category**	**Acute cohort (≤ 3 months) n (%)**	**Chronic cohort (> 3 months) n (%)**	**Total n (%)**	***P*-value**
		102 (27.13)	274 (72.87)	376	
Fatigue, n (%)	≥ 36	35 (34.31)	137 (50.00)	172 (45.74)	0.007
	< 36	67 (65.69)	137 (50.00)	204 (54.26)	
Sex, n (%)	Female	72 (70.59)	212 (77.37)	92 (24.47)	0.17
	Male	30 (29.41)	62 (22.63)	284 (75.53)	
Psychological factors, n (%)	≥ 3	58 (56.86)	175 (63.87)	233 (61.97)	0.21
	< 3	44 (43.14)	99 (36.13)	143 (38.03)	
Age (years)	Mean, median, SD	42.64, 39.0, (16.11)	41.57, 39.00, (16.18)	41.86, 39.00, (16.15)	0.87
CPI (0-100 NRS)	Mean, median, SD	57.43, 56.67, (20.87)	57.37, 60.0, (21.69)	57.36, 60.0, (21.45)	0.71

CPI = characteristic pain intensity, SD = standard deviation, NRS = numeric pain rating scale
n = number of subjects, % = percentage
Fatigue ≥ 36 = Yes, < 36 = No
Psychological factors ≥ 3 = Yes, < 3 = No

Table 3. Baseline profile of subjects with chronic TMD-related pain and those without pain at 3-month follow-up

Risk factor and covariates	**Category**	**Chronic TMD-related pain n (%)** 260 (69.15)	**No TMD-related pain n (%)** 116 (30.85)	***P*-value**
Fatigue, n (%)	≥ 36	129 (49.62)	43 (37.07)	0.02
	< 36	131 (50.38)	73 (62.93)	
Sex, n (%)	Female	209 (80.38)	75 (64.66)	0.001
	Male	51 (19.62)	41 (35.34)	
Psychological factors, n (%)	≥ 3	165 (63.46)	68 (58.62)	0.37
	< 3	95 (36.54)	48 (41.38)	
Mean age, (95% CI)	Years	34.23 (28.48-39.97)	30.17 (21.57-38.77)	0.44
Mean CPI (95%CI)	0-100NRS	60.45 (57.89-63.00)	50.84 (47.00-54.67)	<.0001

CPI = characteristic pain intensity, CI = confidence interval, NRS = numeric pain rating scale
n = number of subjects, % = percentage, Chronic > 3 months
Fatigue ≥ 36 = Yes, < 36 = No
Psychological factors ≥ 3 = Yes, < 3 = No

Table 4. Crude and multivariable logistic regression analyses assessing the contribution of fatigue on transition and persistent TMD-related pain at 3-month follow-up

Risk factor and covariates at baseline	**Category**	**Model I RR (95% CI)**	***P*-Value**	**Model II RR (95% CI)**	***P*-Value**	**Model III RR (95% CI)**	***P*-Value**
Fatigue	< 36	1.0 (reference)	0.02	1.0 (reference)	0.90	1.0 (reference)	0.99
	≥ 36	1.17 (1.02-1.34)		1.01 (0.89-1.14)		1.01 (0.86-1.10)	
Acute and chronic TMD-related pain	≤ 3 m	1.0 (reference)	0.0001	1.0 (reference)	0.0003	1.0 (reference)	0.0004
	> 3 m	1.49 (1.22-1.82)		1.45 (1.18-1.77)		1.44 (1.18-1.77)	
Mean CPI	0-100 NRS	1.01 (1.00-1.01)	0.0001	1.00 (1.00-1.01)	0.003	1.01 (1.01-1.01)	0.003
Sex	Male	1.0 (reference)	0.005	1.0 (reference)	0.04	1.0 (reference)	0.03
	Female	1.33 (1.09-1.61)		1.23 (1.01-1.50)		1.24 (1.02-1.50)	
Mean Age	Years	1.00 (0.99-1.00)	0.19	1.00 (0.99-1.00)	0.71	*Not in the model*	
Psychological factors	< 3	1.0 (reference)	0.38	1.0 (reference)	0.68	*Not in the model*	
	≥ 3	1.07 (0.92-1.22)		0.97 (0.86-1.10)			

RR= relative risk, m = months, CPI = characteristic pain intensity, NRS = numeric pain rating scale
Acute ≤ 3 m, Chronic > 3 m
Fatigue ≥ 36 = Yes, < 36 = No
Model I = crude analysis, Model II = multivariable model including fatigue and all covariates
Model III = multivariable model including fatigue and all covariates
Psychological factors ≥ 3 = Yes, < 3 = No

Table 5. Baseline profile of the acute and chronic TMD-related pain cohorts defined by dysfunction

Risk factor and covariates	Category	No dysfunction (GCPS I) n (%)	Dysfunction (GCPS II-IV) n (%)	*P*-value
		132 (29.33)	318	
Fatigue, n (%)	≥ 36	44 (33.33)	159 (50.00)	0.001
	< 36	88 (66.67)	159 (50.00)	
Sex, n (%)	Female	98 (74.24)	245 (77.04)	0.52
	Male	34 (25.76)	73 (22.96)	
Psychological factors, n (%)	≥ 3	63 (47.73)	211 (66.35)	0.0002
	< 3	69 (52.27)	107 (33.65)	
Mean age, (95% CI)	Years	39.78 (37.02, 42.53)	42.72 (40.95-44.50)	0.08
Acute to chronic TMD pain defined by pain duration	Acute (n = 121)	35 (26.52)	86 (27.04)	0.93
	Chronic (n = 329)	97 (73.48)	232 (72.96)	

CI = confidence interval, n = number of subjects, % = percentage
Fatigue ≥ 36 = Yes, < 36 = No
Acute ≤ 3 m, Chronic > 3 m
Psychological factors ≥ 3 = Yes, <3 = No

Table 6. Baseline profile of the no dysfunction and dysfunction cohorts who completed the 3-month follow-up

Risk factor and covariates	**Category**	**No dysfunction (GCPS I) n (%)**	**Dysfunction (GCPS II-IV) n (%)**	**Total n (%)**	***P*-value**
		107 (28.69)	266 (71.31)	373	
Fatigue, n (%)	≥ 36	36 (33.64)	134 (50.38)	170 (45.58)	0.003
	< 36	71 (66.36)	132 (49.62)	203 (54.42)	
Sex, n (%)	Female	80 (74.77)	201 (75.56)	281 (75.34)	0.87
	Male	27 (25.23)	65 (24.44)	92 (24.66)	
Psychological factors, n (%)	≥ 3	55 (51.40)	176 (66.17)	231 (61.93)	0.008
	< 3	52 (48.60)	90 (33.83)	142 (38.07)	
Age (years)	Mean, median, (SD)	39.92, 36.00, (16.90)	43.22, 41.00, (16.05)	42.27, 40.00, (16.35)	0.81
Acute to chronic TMD pain defined by pain duration, n (%)	Acute	27 (27.27)	72 (72.73)	99 (26.54)	0.72
	Chronic	80 (21.45)	194 (70.80)	274 (73.46)	

SD = standard deviation, n = number of subjects, % = percentage
Fatigue ≥ 36 = Yes, < 36 = No
Acute ≤ 3 months, Chronic > 3 months

Table 7. Baseline profile of cohorts without or with dysfunction at 3-month follow-up

Risk factor and covariates	**Category**	**No dysfunction (GCPS I) n (%)** 275 (73.73)	**Dysfunction (GCPS II-IV) n (%)** 98 (26.27)	***P*-value**
Fatigue, n (%)	≥ 36	108 (39.27)	62 (63.27)	< .0001
	< 36	167 (60.73)	36 (36.73)	
Sex, n (%)	Female	201 (73.09)	80 (81.63)	0.09
	Male	74 (26.91)	18 (18.37)	
Psychological factors, n (%)	≥ 3	159 (57.82)	72 (73.47)	0.006
	< 3	116 (42.18)	26 (26.53)	
Age (years)	Mean, median, (SD)	40.12, 37.00, (16.94)	43.51, 42.00, (16.06)	0.98
Acute to chronic TMD pain defined by pain duration, n (%)	Acute (99)	79 (21.18)	20 (20.41)	0.11
	Chronic (274)	196 (21.27)	78 (79.59)	

SD = standard deviation, n = number of subjects, % = percentage
Fatigue ≥ 36 = Yes, < 36 = No
Acute ≤ 3 months, Chronic > 3 months

Table 8. Crude and multivariable logistic regression analyses assessing the contribution of fatigue on the transition to chronic TMD-related pain based on dysfunction at 3-month follow-up using GCPS

Risk factors and covariates at baseline	**Category**	**Model I RR (95% CI)**	***P*-Value**	**Model II RR (95% CI)**	***P*-Value**	**Model III RR (95% CI)**	***P*-Value**
Fatigue	< 36	1.0 (reference)	<.0001	1.0 (reference)	0.008	1.0 (reference)	0.002
	≥ 36	2.05 (1.44-2.94)		1.62 (1.13-2.33)		1.72 (1.21-2.44)	
Acute and chronic TMD-related pain	≤ 3 m	1.0 (reference)	<.0001	1.0 (reference)	0.28	1.0 (reference)	0.27
	> 3 m	2.49 (1.59-3.88)		1.25 (0.82-1.91)		1.27 (0.83-1.94)	
Dysfunction	No	1.0 (reference)	<.0001	1.0 (reference)	<.0001	1.0 (reference)	<.0001
	Yes	4.52 (2.27-8.99)		4.03 (2.02-8.02)		4.07 (2.05-8.10)	
Sex	Male	1.0 (reference)	0.10	1.0 (reference)	0.11	1.0 (reference)	0.12
	Female	1.45 (0.92-2.29)		1.43 (0.92-2.21)		1.41 (0.91-2.18)	
Mean age	Years	1.00 (0.99-1.01)	0.98	0.99 (0.98-1.01)	0.42	*Not in the model*	
Psychological factors	< 3	1.0 (reference)	0.008	1.0 (reference)	0.25	*Not in the model*	
	≥ 3	1.70 (1.14-2.53)		1.25 (0.85-1.85)			

RR = relative risk, m = months
Fatigue ≥ 36 = Yes, < 36 = No, Acute ≤ 3 m, Chronic > 3 m
Model I = crude analysis, Model II = multivariable model including fatigue and covariates
Model III = multivariable model including fatigue and covariates
Dysfunction is characterized by a combination of an average of 5 or greater over the three pain questions and pain related disability

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8 DISCUSSION

8.1 Rationale

Sleep disorders show high comorbidity with TMDs.[22, 104] Smith et al. found that the majority of people with a TMD met the criteria for at least one sleep disorder, and insomnia was associated with increased pain sensitivity.[29] TMD-related pain patients often report poorer sleep quality, longer sleep latency, and lower sleep efficiency.[105, 106] Self-reported OSA was also associated with a chronic TMD in the OPPERA study.[107] Sleep and pain are likely reciprocally related, such that sleep disturbance may be not only a consequence but also a risk factor for TMDs. Indeed, the OPPERA findings showed that reduced sleep quality and OSA were pre-existing risk factors for TMD onset.[23] Dahan et al. in a cross-sectional study found a fatigue prevalence of 14.4% among chronic TMD-related pain population.[96] Nevertheless, the relationship between fatigue, sleep disorders and the transition from acute to chronic TMD-related pain and its' persistence is unclear. Therefore, additional research is necessary to understand the contribution of insomnia, OSA and fatigue on the transition and the persistence of chronic TMD-related pain when chronic pain is defined by (i) duration or (ii) dysfunction. The rationale to define chronic pain based on pain duration and dysfunction is described below. First, the International Association for the Study of Pain (IASP) defines chronic pain as recurrent or persistent pain lasting for more than 3 months.[40, 41] Second, IASP states that chronic pain is associated with significant disability.[41] Therefore, chronic TMD-related pain was defined as a dysfunction state consisting of clinically significant pain and disability.[42]

8.2 Summary of research findings

The findings of this prospective 3-month cohort study is the first to reveal the contribution of fatigue on an increased risk of transition from acute to chronic pain and the persistence of chronic TMD-related pain at a 3-month follow-up when chronic pain is defined by dysfunction. Fatigue did not contribute to an increased risk of transition from acute to chronic, and the persistence of chronic TMD-related pain at a 3-month follow-up, when chronic pain was defined by duration. Our findings also showed borderline associations between OSA and the transition or persistent risk when chronic pain was defined by pain duration and dysfunction. OSA was associated with increased risk of persistent chronic TMD-related pain defined by dysfunction. Insomnia was not related to the study outcomes.

The frequency of OSA in our chronic TMD-related pain cohort was slightly higher than that found in other studies (Table 1). In the OPPERA study, almost 6% of TMD subjects presented OSA assessed by three questions from the Pittsburgh Sleep Quality Index, and four questions from the STOP-BANG.[23] Polysomnography OSA prevalence among individuals with chronic TMD-related pain was 28.4%.[29] Furthermore, the prevalence of TMD is higher among patients with OSA referred for oral appliance therapy.[24]

Insomnia frequency assessed by polysomnography was 36% (n = 52) among subjects with chronic TMD-related pain.[29] Barjandi et al.[108] found that insomnia was prevalent among individuals with myalgia (31.3%) and myofascial pain with a referral (69.1%). Our estimated frequency of insomnia was close to myalgia findings (Tables 1-2). Two studies found that the prevalence of fatigue was 10%[26]-14.4%.[96] In our study, fatigue prevalence was close to those obtained by Hoffmann et al. who surveyed 1511 TMD-related pain patients and found that 42-43% reported having fatigue after the onset of TMD-related pain.[27] A possible explanation for the variation in

prevalence percentages is the use of different screening questionnaires in different study populations.

We investigated if the risk would be confounded by the potential confounders such as age, sex, psychological factors (anxiety and depression), CPI, acute and chronic pain status, and dysfunction at baseline. Our baseline findings show dysfunction (GCPS II-IV) present in the chronic (70.7%) compared to acute (71.1%). This is consistent with findings from Garofalo et al.[67] showing dysfunction prevalence of more than 70% at baseline and at 6-month follow-up.

The mean age of chronic in the Garofalo[67] study in years was 36.0 for chronic cohort (n= 87) and 33.7 for nonchronic (n = 66). In our study, 32.62 (n=331) for the chronic and 31.70 acute (n=123) cohort. Females were also more common in the Garofalo study when compared to males in both chronic (74.7% vs. 25.3%) and nonchronic (59.1% vs. 40.9%) groups. Although the findings were not significant, but they were of similar pattern to our findings. In our study, females were common in the chronic (73.32% vs. 21.65%) and in acute (69.40% vs. 30.60%) when compared to males.

In the Garofalo et al. study,[67] out of 164 acute TMD-related pain cohorts recruited at baseline, 153 (93.3%) completed the 6-month follow-up, and 87 (56.9%) developed chronic TMD-related pain. In the first Epker et al. study,[68] from 204 acute cohorts, 175 (85.8%) completed the follow-up, and 144 (82.3%) developed chronic TMD. Our study is similar to Garofalo but less than Epker, in which from the acute TMD-related pain cohort including 102 subjects who completed the 3-month follow-up, 50.98% (n = 52/260) of subjects presented a transition to chronic TMD-related pain, and 49.02% (n = 50/116) of subjects had no pain. The difference in percentages might be due to the difference in pain duration and study population.

8.3 Mechanism of Temporomandibular Disorders-related pain

Regardless, although causality cannot be evaluated due to the design of the present study, these findings raise the hypothesis that OSA and fatigue may contribute to a dysregulation of pain modulatory systems involving central and peripheral sensitization that contribute to the transition and persistence of chronic pain defined by dysfunction.[112]

Often enough we think that pain is proportional to the amount of incoming peripheral nociceptive drive dye to injury or inflammation from the site of injury or inflammation. This is not the case with many chronic case patients who are experiencing pain with no obvious sign of peripheral injury. On the other hand, there are patients who have a peripheral injury or inflammation at a location with little or no pain. This leaves us pondering what makes some patients experience intense pain with minimal peripheral nociceptive stimulation and others experience minimal pain with peripheral injury. It is increasingly well accepted in the scientific community that pain can be generated and/or maintained and/or suppressed and/or exacerbated by changes in the central nervous system through higher level processes involving mismatch between peripheral nociceptive drive and perceived pain. TMD-related pain can occur in individuals peripherally or to those whose pain is generated and/or maintained and/or suppressed and/or exacerbated by central nervous system mechanisms. It has been suggested that variability in TMD-related pain etiology has prevented us from adequately treating many individuals who are diagnosed with this condition. Therefore, understanding each person's pain from its own mechanistic standpoint will enable us to deliver personalized care to TMD patients and hopefully provide some relief to complex chronic cases that are more challenging to treat.

It is imperative to understand that TMD is a family of symptoms characterized mainly by pain in the temporomandibular joint (TMJ) and/or surrounding muscles and structures. In many patients

diagnosed with TMD, their pain involves more than pathology in the TMJ and/or associated structures. Comorbid pain is very common and 53% of TMD patients report severe headache/migraines, 54% had neck pain, 62% joint pain, and 64% low back pain while only 17% report pain specific to face and jaw.[113]

The most common comorbid pain conditions observed among TMD patients are fibromyalgia, migraine headache, and neck and back pain. The definition of comorbidities is a "concurrent existence and occurrence of two or more medically diagnosed diseases in the same individual".[33] Many studies found that TMD-related pain patients frequently report pain at sites other than the masticatory system.[30, 114-118] Patients may report the pain persisting for longer periods of time due to the presence of multiple comorbidities. Even though, the specific mechanism to explain the persistence of TMD-related pain is not clearly understood, and some researchers suggest that it involves the central and peripheral nervous systems.[119, 120]

A growing body of evidence is demonstrating that central sensitization represents a common pathophysiological mechanism for comorbid conditions such as TMD and chronic fatigue syndrome.[121] These conditions share many common features including pain, fatigue, sleep difficulties and psychological disturbances.[122] Younus suggests that central sensitization includes TMD, chronic fatigue, fibromyalgia, chronic headaches, and myofascial pain among others.[122] Central sensitization is characterized by allodynia, hyperalgesia, expansion of the receptive field, and usually prolonged pain after stimulus has been removed.[122] The proposed process is complex and includes dysregulation in both ascending and descending central nervous system pathways as a result of acute physical trauma and sustained pain impulses and dysfunction of the stress system, including the hypothalamic-pituitary-adrenal axis.[122, 123] Stress and psychological disturbances are theorized to lead to intracellular central nervous system changes and progression of central

sensitization.[124] Evidence of this process in myofascial TMD-related pain has been demonstrated by reduced subjective pain thresholds in female patients compared to pain-free controls to various stimuli such as electrical, pressure, cold and heat.[125, 126] Neural abnormalities in the trigeminal and limbic systems have been observed in women with chronic myofascial TMD-related pain.[127]

8.4 Bias

Bias is a systematic error which could occur in any epidemiological study, and lead to incorrect observations regarding the association between exposure and outcome. To ensure that a study has internal validity, careful consideration must be given to selecting participants, measuring potential predictors, confounders, and outcomes as well as performing the statistical analyses. In the following paragraphs, we discuss some types of biases that might occur in studies of this nature.

8.4.1 Selection bias

Selection bias refers to any error that arises in the process of identifying and recruiting the study populations.[109] In this prospective cohort study design, participants were identified from four different locations to minimize the chance of selection bias which may lead to a positive association as a result of a referral pattern. The dropout is one of the most important causes of selection bias in cohort study design. In this study, the dropout was low (10.2%). Further, we found no difference between subjects who dropped out and who did not. These indicated that the chance of selection bias associated with dropout is very low.

8.4.2 Information bias

Information bias is a systematic error that may occur during the measurement of exposures or outcomes or during the classification of participants in a study.[109] In this cohort study, subjects were diagnosed by four investigators following the same protocol to decrease misclassification. Further, the questionnaires used are validated and have adequate specificity and sensitivity to decrease information bias.[42, 93, 98]

8.4.3 Confounding

This situation arises when a measure of association or relationship between exposure and outcome is distorted by the presence of another variable. Confounding is the mixing of effects between an exposure, outcome, and another extraneous variable (confounder) which leads to incorrect observations or results since the relationship.[110] Positive confounding (when the observed association is biased away from the null) and negative confounding (when the observed association is biased toward the null) may both occur. In our study, we adjusted for all potential confounders in the analysis stage of this study using multivariable regression analysis.

8.5 Project strengths and limitations

The findings of this study are strengthened by the strong methodology utilized and the characteristics of the study population. This is a 3-month prospective cohort study which ensures that the risk factors preceded the transition of chronic TMD-related pain. Prospective cohort studies are considered the gold standard of observational research.[111] Subjects were recruited from four different dental clinics, which decreased the chance of finding a positive association specific to a given hospital because of a referral pattern. Patients were diagnosed by four investigators following the same protocol to decrease misclassification. The questionnaires used are validated and have adequate specificity and sensitivity.

The classification of acute and chronic TMD-related pain has been used differently among researchers which poses a limitation. We followed the IASP to classify chronic pain (> 3 months) and used GCPS[42] to classify those subjects with or without dysfunction, to avoid misclassification. The acute cases sample size was not large enough due to the difficulty of recruiting acute TMD patients due to COVID19 restrictions that were initiated on March 2019 closures. We have conservatively estimated that 80% of patients who meet the criteria would be interested in the study to enable us to meet the sample size. It is possible that larger sample size in the acute cohort could have strengthened the power. In our study, our dropout rate is 10.2%. No significant differences were found between subjects who dropped out and those who did not. Additionally, the stratified analysis for insomnia had a lower sample size which was a limitation for this study.

8.6 Future research directions

This study has several clinical implications. We found that OSA and fatigue contributed to the risk of transition and persistence risk of chronic TMD-related pain when chronic pain. Assessing the patient's level of OSA and fatigue may be introduced into a comprehensive clinical exam protocol to aid in the management of TMD-related pain patients. It is possible that fatigue and OSA are characteristics of a certain type of personality which may contribute to less responsiveness of treatment or continuation of pain that has psychological element. Therefore, they could be more consequence of particular personality than causal factors for pain continuation. It is critical to match the level of complexity of the case with the appropriate management program. For example, a patient reporting single comorbidity will be managed differently from a patient presenting with multiple comorbidities. The latter may require an interdisciplinary pain clinic setting that uses a team of clinicians to address different aspects of the problem in a concerted fashion. Failure to

identify and to address the entire scope of the problem may lead to no improvement in pain or function, and further perpetuation of the problem.

9 CONCLUSIONS

In conclusion, this prospective cohort study is the first study to reveal the contribution of insomnia, OSA, and fatigue on the transition from acute to chronic pain and the persistence of chronic TMD-related pain at a 3-month follow-up when chronic pain is defined by duration and dysfunction. Fatigue increased transition and the persistence pain risk at a 3-month follow-up when chronic pain is defined by dysfunction contrary to duration. OSA also contributed to the transition from acute to chronic TMD-related pain as well as the persistence at a 3-month follow-up when chronic pain was defined by duration and dysfunction. This increased risk appeared to be specific to the persistence of chronic TMD-related pain status. We found that this increase remained when the model was adjusted by the covariates associated with the study outcome. These results suggest that screening for OSA and fatigue should be incorporated into the dentists' comprehensive clinical exam, and their management should be tested to prevent the transition and persistence of TMD-related pain.

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11 APPENDICES

11.1 Appendix A- Ethical approval from McGill University

McGill

Faculty of Medicine
3655 Promenade Sir William Osler #633
Montreal, QC H3G 1Y6

Faculté de médecine
3655, Promenade Sir William Osler #633
Montréal, QC H3G 1Y6

Fax/Télécopieur: (514) 398-3870
Tél/Tel: (514) 398-3124

08 May 2015

Dr. Ana Velly
Oral Health and Society Unit
Faculty of Dentistry
Jewish General Hospital
3755 Ch. de la Côte Ste Catherine, Room A-017
Montreal QC H3T 1E2

RE: **IRB Study Number A12-M113-14A**
Transition from acute to chronic painful temporomandibular disorders: a prospective cohort study

Dear Dr. Velly,

Thank you for responding to the IRB's correspondence concerning the 1 December 2014 full Board review of the above-referenced study.

The submitted response and revisions are acceptable. Final ethics approval for this study is provided on 8 May 2015:

- Study Protocol and Instruments, version 05 November 2014 (modified submission following IRB review: April 2015);
- English and French Consent Form, IRB dated April 2015.

The ethics approval for this study is valid until **December 2015.** The Certificate of Ethical Acceptability is enclosed.

All research involving human subjects is required to undergo an annual ethics review as stipulated in Federal and Provincial documents guiding and regulating human subjects research. This annual review is scheduled according to the date of initial approval and it is the responsibility of the investigator to submit a completed application form for Continuing Ethics Review to the IRB prior to the stop date of the study's ethics approval. A copy of the Continuing Review form is available on the IRB website at: http://www.mcgill.ca/medresearch/ethics/.

In addition to the continuing review requirements, it is the Investigator's responsibility for ensuring that all documents approved by this IRB are reported to and meet the standards in effect at the institution where subject recruitment occurs and/or where study data is collected. There is a risk that the study's data may be invalidated and research funds frozen for failing to comply. *This study cannot be initiated until institutional approval is obtained from the appropriate administrative office.*

1

Any modifications or unanticipated developments that may occur to the study prior to the annual review must be reported to the IRB promptly. Study modifications cannot be implemented prior to ethics review and approval of the change.

The IRB has assigned this study the following IRB Study Number: A12-M113-14A. Please reference this number for all correspondence with our office.

Regards,

Anita Gagnon, PhD
Co-Chair
Institutional Review Board

Cc: Mr. S. Levy – MUHC
Ms. L. Martin - JGH
A12-M113-14A

11.2 Appendix B : Patient Consent Form (English)

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Hôpital général juif
Jewish General Hospital

McGill

Consent Form

Transition from acute to chronic painful temporomandibular disorders: A prospective cohort study

You are being invited to participate in a study regarding transition from acute to chronic Temporomandibular Disorder 'called TMD', a type of facial pain. You have been selected as we are interested in understanding what may predict health wellbeing associated with facial pain. You have the right to know about the purposes and procedures that are be used in this study and to be informed about its potential benefits, risks and any discomfort that may occur. There is no compensation for your participation. Before you agree to take part in this study, it is important that you read the information in this consent form. You should ask as many questions as you need to in order to understand what you will be asked to do. Your participation is voluntary.

Purpose of this study:

The purpose of this study is to identify the possibilities of having a TMD-related pain and determine the factors associated with this facial pain.

Procedures:

If you agree to participate in our study, you will be asked to do the following:

- You will be invited to complete a questionnaire on the day of your dental appointment (today), and at 3 and 6 months after this first interview. If you cannot do so, we will ask you to complete it at a later time and mail it back to us in a postage-paid envelope that will be provided to you. If you cannot return this questionnaire, a telephone interview will then be conducted by the research assistant. The completion of the questionnaire may take on average 10 to 20 minutes.
- Allow us to collect saliva (5-10 ml) on the day of the first interview. To collect the saliva, the research assistant will ask you to spit into a sterilized centrifuge tube. No hospitalization is required for this purpose. The duration of saliva collection will take a maximum of 10 minutes. Saliva samples will be used to assess if the composition of the saliva is related to TMD-related pain.
- The research team will ask you about your general health using a brief questionnaire. We will see if you have high blood pressure, diabetes, thyroid problem, allergy, and asthma. We will do that to see if these factors may predict health wellbeing associated with facial pain.
- The questions which are going to be asked in the study will help to identify the individuals with TMD, as well as to measure the level of pain and disability related to this condition. Other questions will evaluate the level of general health and psychological characteristics (e.g., anxiety and depression).

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Jewish General Hospital

McGill

Risks, Disadvantages and Side-Effects:
You will be interviewed by the research assistant. If you feel uncomfortable to answer any of the questions, you are free to stop or skip that question and move on to the next one. This interview will take a maximum of 20 minutes of your time.

Benefits:
There is no direct benefit to participate in this study. However, this study will provide the medical and dental community with more definitive evidence of factors that may increase the chance of this type of facial pain. The results of this study may contribute to the development of personalized programs to improve TMD pain management.

Voluntary participation / withdrawal:
Your participation in this study is voluntary. Whether you accept or decline to participate in this study, your future dental care and your patient-doctor relationship will not be affected in any way. You may choose to participate now and decide to stop your participation at any time. If you decide to withdraw from the study, all information obtained about you up to the point of your withdrawal will be kept to preserve the scientific integrity of the study. Upon your withdrawal, you can request to have your saliva samples destroyed.

Confidentiality:
While you take part in this research study, the researcher in charge and study staff will collect and store personal identifiable information about you in a file for the purpose of the research study. Only information necessary for the research study will be collected.

All information and saliva sample obtained about you during this study will be treated confidentially within the limits of the law. Thus, to protect your identity, your name and identifying information will be replaced with a code (numbers). The link between the code and your identity as well as the study file will be kept under the responsibility of Dr. Velly and will be held in a locked drawer in Dr. Velly's office at the Dental Department of the Jewish General Hospital. No information that discloses your identity will be allowed to leave the institution.

The saliva sample will be stored in the saliva freezer at the Lady Davis Institute of the Jewish General Hospital under the responsibility of Drs. Gornitsky, Schipper and Velly. Your sample will be stored until the saliva is used for study analysis. The remaining saliva sample will be destroyed in the laboratory of Dr. Hyman Schipper at the Lady Davis Institute, 10 years after the completion of the study. The sample will only be used for the purposes described in this consent form. The Lady Davis Institute requires a pass for entry, the door to the lab is locked and the results of the samples will be kept in a locked drawer with information being codified. Computer information is restricted by a password.

The result of the analysis will be kept confidential and will not be placed anywhere in your file. Also, you will not be identified in any published report. A copy of this consent form will not be placed in your medical record file and a copy will be given to you.

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Jewish General Hospital

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For the purpose of monitoring this research, your research study file as well as your medical records identifying you could be checked by a person authorized by the Research Ethics Committee of the Jewish General Hospital or the Institutional Review Board of McGill University. This person is obliged to respect your privacy.

For safety purposes, and in order to communicate information that is required in order to protect your well-being, Dr. Velly, the principal researcher of this study will keep your personal information including your name, contact information, the date when your participation in the study began and when it ended separate from the research documents.

You have the right to look at your study file in order to check the information gathered about you and to correct it, if necessary, as long as the study researcher or the institution keeps this information.

Contact information:
If you have any question about this study, please contact Dr. Ana Velly: 514-340-8222 ext 2932, 3755 Cote St. Catherine Road, room A-017, Montreal, Quebec H3T 1E2. For any question regarding your rights as a research participant, please contact Rosemary Steinberg (Jewish General Hospital), local commissioner of complaints and quality of service, at 514-340-8222 ext. 5833 or Pascale Valois (Montreal General Hospital), local commissioner of complaints and quality of service, at 514-934-1934 ext. 44285

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Statement of Consent:

I have read the previous information and my questions were answered to my satisfaction. A copy of this signed consent form will be given to me. My participation is voluntary and I can withdraw from the study at any time without giving reasons. It will not affect my dental care now or later. I do not give up any of my legal rights by participating in this study. I understand that I will be contacted by the research assistant at the first appointment and after three and six months.

I agree to participate in this study.

_____
Printed name of participant

_____ _____
Signature of Subject Date

_____
Printed name of person obtaining consent

_____ _____
Signature of Person Obtaining Consent Date

11.3 Appendix C : Patient Consent Form (French)

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Hôpital général juif | Jewish General Hospital

McGill

Formulaire de consentement

Transition de la douleur aiguë à la douleur chronique liée aux désordres temporomandibulaires: Une étude de cohorte prospective

Vous êtes invité à participer à une étude concernant la transition de la douleur aigue à la douleur chronique liée aux désordres temporomandibulaires, nommés « DAM », un type de douleur au visage. Vous avez été sélectionné car nous sommes intéressés à comprendre ce qui peut prédire le bien-être en santé lié à la douleur faciale. Vous avez le droit de connaître le but et les procédures de cette étude, et d'être informé sur ses potentiels avantages et risques, ainsi que tout inconfort qui peuvent être encourus. Il n'y a aucune rémunération pour participer à cette étude.

Avant d'accepter de prendre part à cette étude, il est important que vous lisiez l'information dans ce formulaire de consentement. Vous devriez poser autant de questions nécessaires afin de comprendre ce que vous serez invité à faire. Votre participation est volontaire.

But de l'étude:
L'objectif de cette étude est de déterminer les possibilités d'avoir de la douleur liée aux désordres temporomandibulaires et de déterminer les facteurs associés à cette douleur au visage.

Procédures:
Si vous acceptez de participer à notre étude, vous serez demandé de faire ce qui suit:

- Vous serez invité à compléter un questionnaire le jour de votre rendez-vous (aujourd'hui), 3 et 6 mois après ce premier entretien. Si vous ne pouvez pas le compléter, nous vous demanderons de le faire ultérieurement et de nous renvoyer le questionnaire dans une enveloppe prépayée que nous vous fournirons. Si vous ne pouvez pas nous retourner ce questionnaire, une entrevue téléphonique sera alors effectuée par l'assistant de recherche. L'achèvement du questionnaire peut prendre en moyenne de 10 à 20 minutes.
- Permettez-nous de recueillir de la salive (5-10 ml) le jour de la première entrevue. Afin de collecter la salive, l'assistant de recherche vous demandera de cracher dans une éprouvette stérilisée. Aucune hospitalisation ne sera nécessaire à ces fins. La durée de la collecte de salive prendra un maximum de 10 minutes. Les échantillons de salive seront utilisés afin d'évaluer si la composition de la salive est liée à cette douleur.
- L'équipe de recherché vous posera des questions sur vos la santé en général en utilisant un bref questionnaire. Nous vérifierons si vous avez de l'hypertension, le diabète, des problèmes de thyroïde, des allergies ou de l'asthme. Nous ferons cela afin de voir si ces facteurs peuvent prédire le bien-être en santé associé à la douleur au visage.
- Les questions qui seront posées lors de cette étude aideront à l'identification des individus atteints de DAM, ainsi que de mesurer le niveau de douleur et

d'incapacité lié à cette condition. D'autres questions évalueront le niveau de la santé en général et les caractéristiques psychologiques (ex. anxiété et dépression).

Les risques, inconforts et effets secondaires:
Vous aurez des entrevues avec l'assistant de recherche. Si vous n'êtes pas confortable à répondre à certaines questions en particulier, vous êtes libres d'arrêter ou de sauter la question et de passer à la suivante. Cette entrevue prendra un maximum de 20 minutes de votre temps.

Avantages:
Il n'y a aucun avantage direct à participer à cette étude. Cependant, cette étude fournira à la communauté médicale et dentaire des preuves plus définitives sur les facteurs qui peuvent augmenter les chances de cette douleur au visage. Ces résultats peuvent contribuer au développement de programmes personnalisés pour améliorer la gestion de la douleur liée aux désordres temporomandibulaires.

Participation volontaire / retrait:
Votre participation à cette étude est volontaire. Indépendamment de si vous accepter ou refuser de participer à cette étude, vos futurs soins dentaire et votre relation dentiste-patient ne seront affectés en aucune façon. Vous pouvez choisir de participer maintenant et d'arrêter à tout moment. Si vous décidez de vous retirer de cette étude, toutes informations recueillies jusqu'au moment de votre retrait seront gardées afin de protéger l'intégrité scientifique de l'étude. Après votre retrait, vous pouvez demander à ce que vos échantillons de salive soient détruits.

Confidentialité:
Durant votre participation à cette étude, le chercheur responsable et le personnel impliqué dans l'étude collecteront et conserveront des informations personnelles pouvant vous identifier dans un dossier aux fins de l'étude. Seules les informations nécessaires à l'étude de recherche seront recueillies.

Toutes les informations et échantillons de salive obtenus de vous au cours de cette étude seront traités confidentiellement dans les limites de la loi. Ainsi, afin de protéger votre identité, votre nom et informations d'identification seront remplacés par un code (chiffres). Le lien entre le code et votre identité ainsi que le dossier d'étude seront maintenus sous la responsabilité du Dr. Velly, et seront conservés dans un tiroir verrouillé dans le bureau du Dr. Velly au département dentaire de l'Hôpital général juif. Aucune information révélant votre identité ne sera autorisé à quitter l'établissement.

L'échantillon de salive sera conservé dans un congélateur contenant des échantillons de salive à l'Institut Lady Davis de l'Hôpital général juif, sous la responsabilité des Drs. Gornitsky, Schipper et Velly. Votre échantillon sera conservé jusqu'à ce que la salive soit utilisée pour des analyses. Le reste de l'échantillon de salive sera détruit dans le laboratoire du Dr. Hyman Schipper à l'Institut Lady Davis, 10 ans après la fin de l'étude. L'échantillon de salive sera utilisé uniquement aux fins des objectifs décrits dans ce formulaire de consentement. L'Institut Lady Davis nécessite un laissez-passer pour y accéder, la porte du laboratoire est verrouillée, et les

résultats des échantillons seront conservés dans un tiroir fermé à clé avec les informations codifiées. Les informations sur l'ordinateur sont limitées par un mot de passe.

Le résultat de l'analyse sera maintenu confidentiel et ne sera pas placé dans votre dossier. En outre, vous ne serez identifié dans aucun rapport publié. Une copie de ce formulaire de consentement ne sera pas placée dans votre dossier médical, et un exemplaire vous sera remis.

Aux fins de surveillance de cette étude, votre dossier de recherche ainsi que vos dossiers médicaux vous identifiant peuvent être vérifiés par une personne autorisée par le comité d'éthique de l'Hôpital général juif ou le comité d'examen institutionnel de l'Université McGill. Cette personne est tenue de respecter votre vie privée.

Pour des raisons de sécurité, et afin de communiquer des informations qui sont nécessaires pour protéger vos données, Dr. Velly, chercheur principal de cette étude, gardera vos informations personnelles, y compris votre nom, vos coordonnées, les dates auxquelles votre participation à l'étude a commencé et a fini séparées des documents de recherche.

Vous avez le droit de consulter votre dossier d'étude afin de vérifier les informations recueillies sur vous et de les corrigées, si nécessaire, tant que le chercheur ou l'institution conserve ces renseignements.

Contacts :

Si vous avez des questions au sujet de cette étude, s'il vous plaît contacter Dr. Ana Velly: 514-340-8222 poste 2932, 3755 Côte Ste. Catherine Road, room A 017, Montréal, Québec H3T 1E2. Pour toute information concernant vos droits à titre de participant à une étude de recherche, veuillez contacter Rosemary Steinberg (Hôpital général juif), commissaire locale aux plaintes et à la qualité du service, au 514-340-8222 poste 5833 ou Pascale Valois (Hôpital général de Montréal), commissaire locale aux plaintes et à la qualité du service, au 514-934-1934 poste 44285.

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McGill

Déclaration de consentement:

J'ai lu les informations et mes questions ont été répondues à ma satisfaction. Une copie de ce formulaire de consentement signé me sera remise. Ma participation est volontaire et je peux me retirer de l'étude à tout moment sans donner de raisons, sans que cela affecte mes soins médicaux maintenant ou plus tard. Je ne renonce à aucun de mes droits légaux en participant à cette étude. Je comprends que je serai contacté par l'assistante de recherche au premier rendez-vous et après trois et six mois.

Je suis d'accord pour participer à cette étude.

_____

Nom du participant

_____ _____

Signature du participant Date

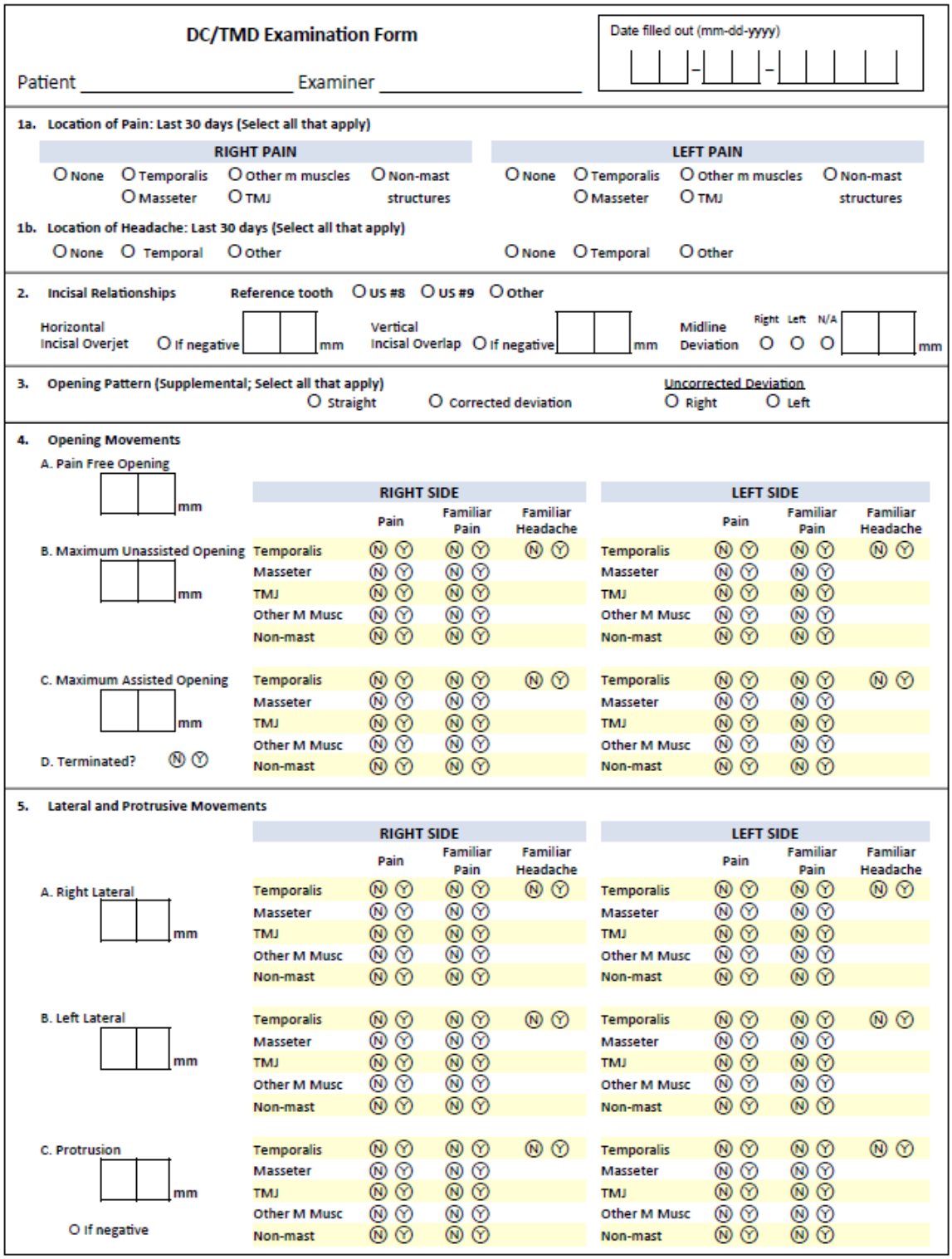
_____

Nom de la personne obtenant le consentement

_____ _____

Signature de la personne obtenant le consentement Date

11.4 Appendix D- Research Diagnostic Criteria (Examination) for Temporomandibular Disorders



DC/TMD Examination Form

Date filled out (mm-dd-yyyy) ___-___-____

Patient _____ Examiner _____

1a. Location of Pain: Last 30 days (Select all that apply)

RIGHT PAIN				LEFT PAIN			
O None	O Temporalis	O Other m muscles	O Non-mast structures	O None	O Temporalis	O Other m muscles	O Non-mast structures
	O Masseter	O TMJ			O Masseter	O TMJ	

1b. Location of Headache: Last 30 days (Select all that apply)

O None	O Temporal	O Other	O None	O Temporal	O Other

2. Incisal Relationships Reference tooth O US #8 O US #9 O Other

Horizontal Incisal Overjet O If negative ___ mm

Vertical Incisal Overlap O If negative ___ mm

Midline Deviation Right O Left O N/A O ___ mm

3. Opening Pattern (Supplemental; Select all that apply)

O Straight O Corrected deviation

Uncorrected Deviation: O Right O Left

4. Opening Movements

A. Pain Free Opening ___ mm

B. Maximum Unassisted Opening ___ mm

C. Maximum Assisted Opening ___ mm

D. Terminated? (N) (Y)

RIGHT SIDE	Pain	Familiar Pain	Familiar Headache
Temporalis	(N) (Y)	(N) (Y)	(N) (Y)
Masseter	(N) (Y)	(N) (Y)	
TMJ	(N) (Y)	(N) (Y)	
Other M Musc	(N) (Y)	(N) (Y)	
Non-mast	(N) (Y)	(N) (Y)	

LEFT SIDE	Pain	Familiar Pain	Familiar Headache
Temporalis	(N) (Y)	(N) (Y)	(N) (Y)
Masseter	(N) (Y)	(N) (Y)	
TMJ	(N) (Y)	(N) (Y)	
Other M Musc	(N) (Y)	(N) (Y)	
Non-mast	(N) (Y)	(N) (Y)	

5. Lateral and Protrusive Movements

A. Right Lateral ___ mm

B. Left Lateral ___ mm

C. Protrusion ___ mm

O If negative

RIGHT SIDE	Pain	Familiar Pain	Familiar Headache
Temporalis	(N) (Y)	(N) (Y)	(N) (Y)
Masseter	(N) (Y)	(N) (Y)	
TMJ	(N) (Y)	(N) (Y)	
Other M Musc	(N) (Y)	(N) (Y)	
Non-mast	(N) (Y)	(N) (Y)	

LEFT SIDE	Pain	Familiar Pain	Familiar Headache
Temporalis	(N) (Y)	(N) (Y)	(N) (Y)
Masseter	(N) (Y)	(N) (Y)	
TMJ	(N) (Y)	(N) (Y)	
Other M Musc	(N) (Y)	(N) (Y)	
Non-mast	(N) (Y)	(N) (Y)	

6. TMJ Noises During Open & Close Movements

RIGHT TMJ

	Examiner: Open	Examiner: Close	Patient	Pain w/ Click	Familiar Pain
Click	N Y	N Y	N **Y** →	N Y	N Y
Crepitus	N Y	N Y	N Y		

LEFT TMJ

	Examiner: Open	Examiner: Close	Patient	Pain w/ Click	Familiar Pain
Click	N Y	N Y	N **Y** →	N Y	N Y
Crepitus	N Y	N Y	N Y		

7. TMJ Noises During Lateral & Protrusive Movements

RIGHT TMJ

	Examiner	Patient	Pain w/ Click	Familiar Pain
Click	N Y	N **Y** →	N Y	N Y
Crepitus	N Y	N Y		

LEFT TMJ

	Examiner	Patient	Pain w/ Click	Familiar Pain
Click	N Y	N **Y** →	N Y	N Y
Crepitus	N Y	N Y		

8. Joint Locking

RIGHT TMJ

	Locking	Reduction: Patient	Reduction: Examiner
While Opening	N Y	N Y	N Y
Wide Open Position	N Y	N Y	N Y

LEFT TMJ

	Locking	Reduction: Patient	Reduction: Examiner
While Opening	N Y	N Y	N Y
Wide Open Position	N Y	N Y	N Y

9. Muscle & TMJ Pain with Palpation

RIGHT SIDE

(1 kg)	Pain	Familiar Pain	Familiar Headache	Referred Pain
Temporalis (posterior)	N Y	N Y	N Y	N Y
Temporalis (middle)	N Y	N Y	N Y	N Y
Temporalis (anterior)	N Y	N Y	N Y	N Y
Masseter (origin)	N Y	N Y		N Y
Masseter (body)	N Y	N Y		N Y
Masseter (insertion)	N Y	N Y		N Y

TMJ	Pain	Familiar Pain	Referred Pain
Lateral pole **(0.5 kg)**	N Y	N Y	N Y
Around lateral pole **(1 kg)**	N Y	N Y	N Y

LEFT SIDE

(1 kg)	Pain	Familiar Pain	Familiar Headache	Referred Pain
Temporalis (posterior)	N Y	N Y	N Y	N Y
Temporalis (middle)	N Y	N Y	N Y	N Y
Temporalis (anterior)	N Y	N Y	N Y	N Y
Masseter (origin)	N Y	N Y		N Y
Masseter (body)	N Y	N Y		N Y
Masseter (insertion)	N Y	N Y		N Y

	Pain	Familiar Pain	Referred Pain
Lateral pole **(0.5 kg)**	N Y	N Y	N Y
Around lateral pole **(1 kg)**	N Y	N Y	N Y

10. Supplemental Muscle Pain with Palpation

RIGHT SIDE

(0.5 kg)	Pain	Familiar Pain	Referred Pain
Posterior mandibular region	N Y	N Y	N Y
Submandibular region	N Y	N Y	N Y
Lateral pterygoid area	N Y	N Y	N Y
Temporalis tendon	N Y	N Y	N Y

LEFT SIDE

(0.5 kg)	Pain	Familiar Pain	Referred Pain
Posterior mandibular region	N Y	N Y	N Y
Submandibular region	N Y	N Y	N Y
Lateral pterygoid area	N Y	N Y	N Y
Temporalis tendon	N Y	N Y	N Y

11. Diagnoses

Pain Disorders	Right TMJ Disorders	Left TMJ Disorders
○ None	○ None	○ None
○ Myalgia	Disc displacement (select one)	Disc displacement (select one)
○ Myofascial pain with referral	○ ...with reduction	○ ...with reduction
	○ ...with reduction, with intermittent locking	○ ...with reduction, with intermittent locking
○ Right Arthralgia	○ ... without reduction, with limited opening	○ ... without reduction, with limited opening
○ Left Arthralgia	○ ... without reduction, without limited opening	○ ... without reduction, without limited opening
	○ Degenerative joint disease	○ Degenerative joint disease
○ Headache attributed to TMD	○ Dislocation	○ Dislocation

12. Comments

11.5 Appendix E : Baseline questionnaire (English)

ACTION PROGRAM BASELINE QUESTIONS FOR TEMPOROMANDIBULAR DISORDERS

Hospital	Patient Number	Initials	

Day	Month	Year

Please answer the following questions:

1. How old are you? _____ *years old*

2. Do you have pain in temple, face, jaw joint, or jaws once a week or more often?

☐ Yes ☐ No

3. Do you have pain when you open your month wide or chew, once a week or more often?

☐ Yes ☐ No

4. In the last 30 days, on average, how long did any pain in your jaw or temple area on either side last?

☐ No pain

☐ From very brief to more than a week, but it does stop

☐ Continuous

5. In the last 30 days, did you have pain or stiffness in your jaw on wakening?

☐ Yes ☐ No

6. In the last 30 days, did the following activities change any pain (that is, make it better or make it worse) in your jaw, temple, in the ear, or in front of the ear on either side?

A. Chewing hard or tough food. ☐ Yes ☐ No

B. Opening your mouth, or moving your jaw forward or to the side. ☐ Yes ☐ No

C. Jaw habits such as holding teeth together or chewing gum. ☐ Yes ☐ No

D. Other jaw activities such as talking, kissing, or yawning. ☐ Yes ☐ No

7. Have you ever had pain in your jaw, temple, in the ear, or in front of the ear on either side?

☐ Yes ☐ No

8. How many years or months ago did your pain in the jaw, temple, in the ear, or in front of the ear first begin?

   ____ Year(s) ____ Month(s)

9. How would you rate your facial pain right now?
   Please rate your pain by circling the number that tells how much pain you have right now.

   No pain — Pain as bad as it could be
   0 1 2 3 4 5 6 7 8 9 10

10. In the last 30 days, how would you rate your worst facial pain?
    Use the same scale, where 0 is "no pain" and 10 is "pain as bad as could be".

    No pain — Pain as bad as it could be
    0 1 2 3 4 5 6 7 8 9 10

11. In the last 30 days, on average, how would you rate your facial pain?
    Use the same scale, where 0 is "no pain" and 10 is "pain as bad as could be".
    (That is, your usual pain at times you were in pain)

    No pain — Pain as bad as it could be
    0 1 2 3 4 5 6 7 8 9 10

12. In the last 30 days, how many days did your facial pain keep you from doing your usual activities like work, school, or housework? *(every day = 30 days)*

    ____ Days

13. In the last 30 days, how much has facial pain interfered with your daily activities? Use a scale where 0 is "no interference" and 10 is "unable to carry on any activities".

    No interference — Unable to carry on any activities
    0 1 2 3 4 5 6 7 8 9 10

14. In the last 30 days, how much has facial pain interfered with your recreational, social and family activities? Use the same scale where 0 is "no interference" and 10 is "unable to carry on any activities".

    No interference — Unable to carry on any activities
    0 1 2 3 4 5 6 7 8 9 10

15. In the last 30 days, how much has facial pain interfered with your ability to work, including housework? Use the same scale where 0 is "no interference" and 10 is "unable to carry on any activities".

No interference										Unable to carry on any activities
0	1	2	3	4	5	6	7	8	9	10

16. How would you describe the duration of this pain in your jaw, temple, ear, or in front of the ear since it first began? *(Select ONE response)*

- ☐ Persistent – continuous pain since initial onset
- ☐ Recurrent – more than one bout of pain, with periods of no pain
- ☐ One time – a prior episode of pain that has ended

17. In the last 30 days, which of the following best describes any pain in your jaw, temple, in the ear, or in front of the ear on either side? (Select ONE response)

- ☐ No pain
- ☐ Pain comes and goes
- ☐ Pain is always present

18. In the last 30 days, how many days per month have you had this pain in your jaw, temple, in the ear, or in front of the ear? *(Select ONE response)*

- ☐ Less than 1 day
- ☐ 1 day or more, but less than 15 days
- ☐ 15 days or more, but not continuous
- ☐ Continuous

19. On average, how long does a single episode of this pain in your jaw, temple, in the ear, or in front of the ear last? *(Select ONE response)*

- ☐ Less than 30 minutes per episode
- ☐ 30 minutes to less than 2 hours per episode
- ☐ 2 hours to less than 4 hours per episode
- ☐ 4 hours to 72 hours (3 days) per episode
- ☐ More than 3 days to 7 days per episode
- ☐ More than 7 days of continuous pain per episode

20. In the last 30 days, have you had any headaches?

☐ Yes ☐ No

If you answered NO to question 20, skip to Question 24.

21. How many years or months ago did your headache first begin?

☐ Year(s) ☐ Month(s)

22. In the last 30 days, rate the intensity, on average, of your headache? *(Select ONE response)*

- ☐ Mild to moderate
- ☐ Moderate to severe

23. Where is the headache located? *(Mark ALL that apply)*

- ☐ Temple
- ☐ Front of head
- ☐ Top of head
- ☐ Back of head
- ☐ Behind the eyes or inside the head

24. In the last 30 days, have you had any jaw joint noise(s) when you moved or used your jaw?

☐ Yes ☐ No

25. Have you ever had your jaw lock or catch, even for a moment, so that it would not open ALL THE WAY?

☐ Yes ☐ No

If you answered NO to question 25, skip to question 29.

26. Was your jaw locked or caught severely enough to limit your jaw opening and interfere with your ability to eat?

☐ Yes ☐ N

27. Is your jaw currently locked or limited so that your jaw will not open ALL THE WAY?

☐ Yes ☐ N

28. At any time in your life, when you opened your mouth wide, did your jaw lock or catch even for a moment such that you could not close it from this wide open position?

☐ Yes ☐ N

29. What treatments did you receive for your pain?

☐ Dental extraction

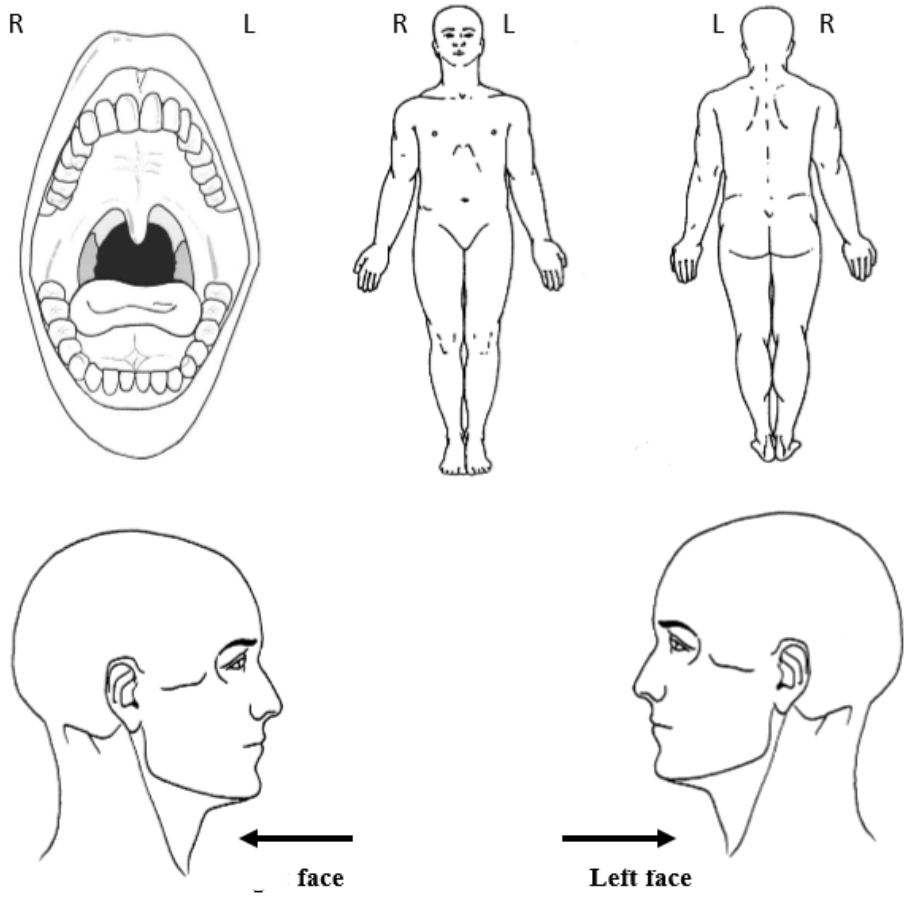
☐ Orthodontics treatment

30. Do you have:

Condition	*Yes*	*No*	*Medication for condition*
a. Diabetes	☐	☐	
b. Allergies (Penicillin/Medication)	☐	☐	
c. Thyroid problem	☐	☐	
d. Rheumatic fever	☐	☐	
e. High blood pressure	☐	☐	
f. Low blood pressure	☐	☐	
g. Smoking (per day)	☐	☐	
h. Asthma	☐	☐	
i. Heart problems	☐	☐	
j. Pain in arms	☐	☐	
k. Pain in legs	☐	☐	
l. Pain in chest	☐	☐	
m. Pain in neck	☐	☐	
n. Pain in back	☐	☐	
o. Pain in abdomen	☐	☐	

31. Pain Diagram

Indicate the location of ALL of your different pains by shading in the area, using the diagrams that are most relevant. If there is an exact spot where the pain is located, indicate the pain with a solid dot (●). If your pain moves from one location to another, use arrows to show the path.



32. On which side of the face is the pain more severe?

☐ Left side ☐ Right side ☐ Both sides equally

33. Using the scale below, please indicate the degree to which you have these feelings.

ACTION PROGRAM BASELINE QUESTIONS FOR TEMPOROMANDIBULAR DISORDERS

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all	Several days	More than half the days	Nearly every day
A. Feeling nervous, anxious or on edge	0	1	2	3
B. Not being able to stop or control worrying	0	1	2	3
C. Worrying too much about different things	0	1	2	3
D. Trouble relaxing	0	1	2	3
E. Being so restless that is hard to sit still	0	1	2	3
F. Becoming easily annoyed or irritable	0	1	2	3
G. Feeling afraid as if something might happen	0	1	2	3

34. Using the scale below, please indicate the degree to which you have these feelings.

Over the last 2 weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
A. Little interest or pleasure in doing things.	0	1	2	3
B. Feeling down, depressed, or hopeless.	0	1	2	3
C. Trouble falling or staying asleep, or sleeping too much.	0	1	2	3
D. Feeling tired or having little energy.	0	1	2	3
E. Poor appetite or overeating.	0	1	2	3
F. Feeling bad about yourself – or that you are a failure or have let yourself or your family down.	0	1	2	3
G. Trouble concentrating on things, such as reading the newspaper or watching television.	0	1	2	3
H. Moving or speaking so slowly that other people could have noticed or the opposite - being so fidgety or restless that you have been moving around a lot more than usual.	0	1	2	3

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all ☐ Somewhat difficult ☐ Very difficult ☐ Extremely difficult ☐

ACTION PROGRAM BASELINE QUESTIONS FOR TEMPOROMANDIBULAR DISORDERS

35. Please answer the following questions about yourself by indicating the extent of your agreement:

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
A. In uncertain times, I usually expect the best.					
B. It's easy for me to relax					
C. If something can go wrong for me, it will.					
D. I'm always optimistic about my future.					
E. I enjoy my friends a lot.					
F. It's important for me to keep busy.					
G. I hardly ever expect things to go my way.					
H. I don't get upset too easily.					
I. I rarely count on good things happening to me.					
J. Overall, I expect more good things to happen to me than bad.					

36. Have you undergone any tooth extraction?

☐ Yes ☐ No

If you answered "Yes", for what reason?

☐ Because of pain ☐ Do not remember ☐ Not because of pain

37. Have you received any orthodontics treatment?

☐ Yes ☐ No

If you answered "Yes", for what reason?

☐ Because of pain ☐ Do not remember ☐ Not because of pain

11.6 Appendix F : Epworth Sleepiness Scale (English)

ACTION PROGRAM BASELINE QUESTIONS FOR TEMPOROMANDIBULAR DISORDERS

38. Write down the number corresponding to your choice in the right-hand column.

Included : ☐ **Yes** ☐ **No**

0 = No chance of dozing
1 = Slight chance of dozing
2 = Moderate chance of dozing
3 = High chance of dozing

Situation	Chance of dozing
Sitting and reading	
Watching TV	
Sitting inactive in a public place (e.g. a theather or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in traffic	

11.7 Appendix H : Fatigue Severity Scale (English)

ACTION PROGRAM BASELINE QUESTIONS FOR TEMPOROMANDIBULAR DISORDERS

40. The Fatigue Severity Scale (FSS) is a method of evaluating the impact of fatigue on you.

This tool allows assessing the impact of fatigue on you. This is a short questionnaire that asks you to rate your level of fatigue. It contains nine statements that rate the severity of your fatigue symptoms.

Read each statement and circle a number from 1 to 7, based on how accurately it reflects your condition during the past week and the extent to which you agree or disagree that the statement applies to you.

A low value (e.g., 1) indicates strong disagreement with the statement, whereas a high value (e.g., 7) indicates strong agreement. It is important to surround a number (1-7) for each question.

During the past week, I have found that:	**Disagree** ⟷ **Agree**						
My motivation is lower when I am fatigued.	1	2	3	4	5	6	7
Exercise brings on my fatigue.	1	2	3	4	5	6	7
I am easily fatigued.	1	2	3	4	5	6	7
Fatigue interferes with my physical functioning	1	2	3	4	5	6	7
Fatigue causes frequent problems for me.	1	2	3	4	5	6	7
My fatigue prevents sustained physical functioning.	1	2	3	4	5	6	7
Fatigue interferes with carrying out certain duties and responsibilities.	1	2	3	4	5	6	7
Fatigue is among my three most disabling symptoms.	1	2	3	4	5	6	7
Fatigue interferes with my work, family, or social life.	1	2	3	4	5	6	7
				Total :			

41. The Insomnia Severity Index has seven questions. For each question:

Please CIRCLE the number that best describes your answer.

11.8 Appendix J : Insomnia Severity Scale (English)

ACTION PROGRAM BASELINE QUESTIONS FOR TEMPOROMANDIBULAR DISORDERS

Please rate the CURRENT (i.e. LAST 2 WEEKS) SEVERITY of your insomnia problem(s).

Insomnia Problem	None	Mild	Moderate	Severe	Very Severe
1) Difficulty falling asleep	0	1	2	3	4
2) Difficulty staying asleep	0	1	2	3	4
3) Problems waking up too early	0	1	2	3	4

4) How SATISFIED/DISSATISFIED are you with your CURRENT sleep pattern?

Very satisfied	Satisfied	Moderately satisfied	Dissatisfied	Very Dissatisfied
0	1	2	3	4

5) How NOTICEABLE to others do you think your sleep problem is in terms of impairing the quality of your life?

Not at all Noticeable	A Little	Somewhat	Much	Very Much Noticeable
0	1	2	3	4

6) How WORRIED/STRESSED are you about your current sleep problem?

Not at all Worried	A Little	Somewhat	Much	Very Much Worried
0	1	2	3	4

7) To what extent do you consider your sleep problem to INTERFERE with your daily functioning (e.g. daytime fatigue, mood, ability to function at work/daily chores, concentration, memory, etc.) CURRENTLY?

Not at all Interfering	A Little	Somewhat	Much	Very Much Interfering
0	1	2	3	4

ACTION PROGRAM BASELINE QUESTIONS FOR TEMPOROMANDIBULAR DISORDERS

To be completed by researcher only

Diagnosis: _____-

__

_____

_____

_____

Treatment received during baseline appointment: _____

_____

_____

_____

Additional notes: _____

_____

_____

_____

_____

_____

_____

_____

11.9 Appendix J : Baseline questionnaire (French)

PROGRAMME ACTION QUESTIONS DE RÉFÉRENCE POUR LES DÉSORDRES TEMPOROMANDIBULAIRES

Hôpital			No. Patient	Initiales	
Jour	**Mois**	**Année**			

S'il-vous-plaît répondez aux questions suivantes:

1. Quel âge avez-vous? _____ *ans*

2. Avez-vous mal à la tempe, au visage, aux mâchoires, ou aux articulations des mâchoires, une fois par semaine ou plus souvent?

   ☐ Oui ☐ Non

3. Avez-vous des douleurs lorsque vous ouvrez votre bouche ou mâcher, une fois par semaine ou plus souvent?

   ☐ Oui ☐ Non

4. Au cours des 30 derniers jours, quelle était la durée de la douleur que vous avez peut-être ressentie dans la/les mâchoire/s ou au niveau de la/des tempe/s?

   ☐ Pas de douleur

   ☐ De très brève durée à plus d'une semaine, mais ça s'arrête

   ☐ Continue

5. Ces 30 derniers jours, avez-vous eu de la douleur ou rigidité dans votre mâchoire au réveil?

   ☐ Oui ☐ No

6. Ces 30 derniers jours, est-ce-que les activités suivantes ont changé la douleur (c'est-à-dire, s'est améliorée, s'est empirée) à la mâchoire, à la tempe, à l'oreille, ou devant l'oreille des deux côtés?

A. Mâcher de la nourriture dure. ☐ Oui ☐ Non

B. Ouvrir la bouche, ou bouger la mâchoire en avant en avant ou sur le côté. ☐ Oui ☐ Non

C. Des habitudes de fonction telles que maintenir les dents serrées, ou mâcher de la gomme. ☐ Oui ☐ Non

D. D'autres activités telles que parler, embrasser ou bailler. ☐ Oui ☐ Non

7. Avez-vous déjà eu de la douleur à la mâchoire, la tempe, dans l'oreille ou en avant de l'oreille d'un côté ou de l'autre?

   ☐ Oui ☐ Non

8. Il y a combien d'années ou de mois qu'a débuté, pour la première fois, votre douleur à la mâchoire, tempe, dans l'oreille, ou en avant de l'oreille?

   ___ Année(s) ___ Mois

9. Veuillez encercler le numéro qui décrit le mieux le niveau de douleur faciale que vous ressentez en ce moment.
   Utilisez une échelle de 0 à 10, où 0 indique «aucune douleur» et 10 indique «la pire douleur possible».

Aucune douleur										La pire douleur possible
0	1	2	3	4	5	6	7	8	9	10

10. Quel est le chiffre qui décrit la plus forte douleur faciale que vous avez ressentie au cours des 30 derniers jours.
    Utilisez la même échelle, où 0 indique « aucune douleur » et 10 indique «la pire douleur possible».

Aucune douleur										La pire douleur possible
0	1	2	3	4	5	6	7	8	9	10

11. Quel est le chiffre qui décrit le niveau de douleur faciale que vous avez ressenti en général au cours des 30 derniers jours.
    Utilisez la même échelle, où 0 indique «aucune douleur» et 10 indique «la pire douleur possible».

Aucune douleur										La pire douleur possible
0	1	2	3	4	5	6	7	8	9	10

12. Ces 30 derniers jours, combien de jours avez-vous été empêché(e) de faire vos activités habituelles tel que emploi, école/cours, ou travaux ménagers par votre douleur faciale? (*tous les jours = 30 jours*)

    ___ Jours

13. Jusqu'à quel point votre douleur faciale a interféré avec vos activités quotidiennes des 30 derniers jours. *Utilisez une échelle de 0 à 10, où 0 indique «aucune interférence» et 10 indique «incapable d'exécuter les activités quotidiennes».*

Aucune interférence — Incapable d'exécuter les activités quotidiennes

0 1 2 3 4 5 6 7 8 9 10

14. Jusqu'à quel point votre douleur faciale vous a empêché de prendre part à des activités sociales, familiales et récréatives au cours des 30 derniers jours. *Utilisez la même échelle, où 0 indique «aucune interférence» et 10 indique «incapable d'exécuter les activités quotidiennes».*

Aucune interférence — Incapable d'exécuter les activités quotidiennes

0 1 2 3 4 5 6 7 8 9 10

15. Jusqu'à quel point votre douleur faciale vous a empêché de faire votre travail au cours des 30 derniers jours (incluant les taches domestique)? *Utilisez la même échelle, où 0 indique «aucune interférence» et 10 indique «incapable d'exécuter les activités quotidiennes».*

Aucune interférence — Incapable d'exécuter les activités quotidiennes

0 1 2 3 4 5 6 7 8 9 10

16. Quel énoncé s'applique à la durée de cette douleur à la mâchoire, tempe, oreille, ou en avant de l'oreille depuis son apparition? (Choisir une seule réponse)

- ☐ Persistante - une douleur continue depuis le début
- ☐ Récurrente - plus d'un épisode de douleur, avec des périodes sans douleur
- ☐ Une fois - un épisode de douleur qui s'est terminé

17. Au cours des 30 derniers jours, laquelle des propositions suivantes décrit le mieux votre douleur à la mâchoire, tempe, dans l'oreille, ou en avant de l'oreille d'un côté ou de l'autre? (Choisir une seule réponse?

- ☐ Aucune douleur
- ☐ La douleur qui vient et disparaît
- ☐ La douleur est toujours présente

18. Au cours des 30 derniers jours, combien de jours avez-vous eu votre douleur à la mâchoire, tempe, dans l'oreille ou en avant de l'oreille? (Choisir une seule réponse)

- ☐ Moins de 1 jour
- ☐ Un jour et plus, mais moins de 15 jours
- ☐ 15 jours et plus, mais pas continuellement
- ☐ Continuellement

19. En moyenne, combien de temps dure un seul épisode de votre douleur à la mâchoire, tempe, dans l'oreille, ou en avant de l'oreille ? (Choisir une seule réponse)

- ☐ Moins de 30 minutes par épisode
- ☐ 30 minutes à moins de 2 heures par épisode
- ☐ 2 heures à moins de 4 heures par épisode
- ☐ 4 heures à 72 heures (3 jours) par épisode
- ☐ Plus de 3 jours à to 7 par épisode
- ☐ Plus de 7 jours à continuellement par épisode

20. Au cours des 30 derniers jours, avez-vous eu des maux de tête?

☐ Oui ☐ Non

Si vous avez répondu NON à la question 20, passez à la question 24.

21. Il y a combien d'années ou de mois que votre mal de tête débuté pour la première fois?

☐ Année(s) ☐ Mois

22. Au cours des 30 derniers jours, évaluez l'intensité en moyenne de votre mal de tête à la tempe. (Choisir une seule réponse)

- ☐ Légère à modérée
- ☐ Modérée à sévère

23. Où est le mal de tête situé? *(Cochez TOUT ce qui s'applique)*

- ☐ Tempe
- ☐ Front
- ☐ Dessus de la tête
- ☐ Arrière de la tête
- ☐ Derrière les yeux ou à l'intérieur de la tête

24. Au cours des 30 derniers jours, avez-vous eu des bruits dans l'articulation de la mâchoire lorsque vous bougez ou utilisez votre mâchoire??

☐ Oui ☐ Non

25. Avez-vous déjà eu la mâchoire bloquée ou coincée au point de ne pouvoir l'ouvrir COMPLÈTEMENT?

☐ Oui ☐ Non

Si vous avez répondu NON à la question 25, passez à la question 29.

26. Est-ce-que le blocage ou coincement de votre mâchoire était suffisamment sévère pour limiter son ouverture et interférer avec votre capacité à manger?

☐ Oui ☐ Non

27. Est-ce que votre mâchoire est actuellement bloquée ou limitée au point de ne pouvoir l'ouvrir COMPLÈTEMENT?

☐ Oui ☐ Non

28. À n'importe quel moment de votre vie lorsque vous avez ouvert la bouche grande, avez-vous déjà eu la mâchoire bloquée ou coincée, même pour un instant, au point de ne pouvoir la fermer de cette position grande ouverte?

☐ Oui ☐ Non

29. Quels traitements avez-vouz reçus contre la douleur?

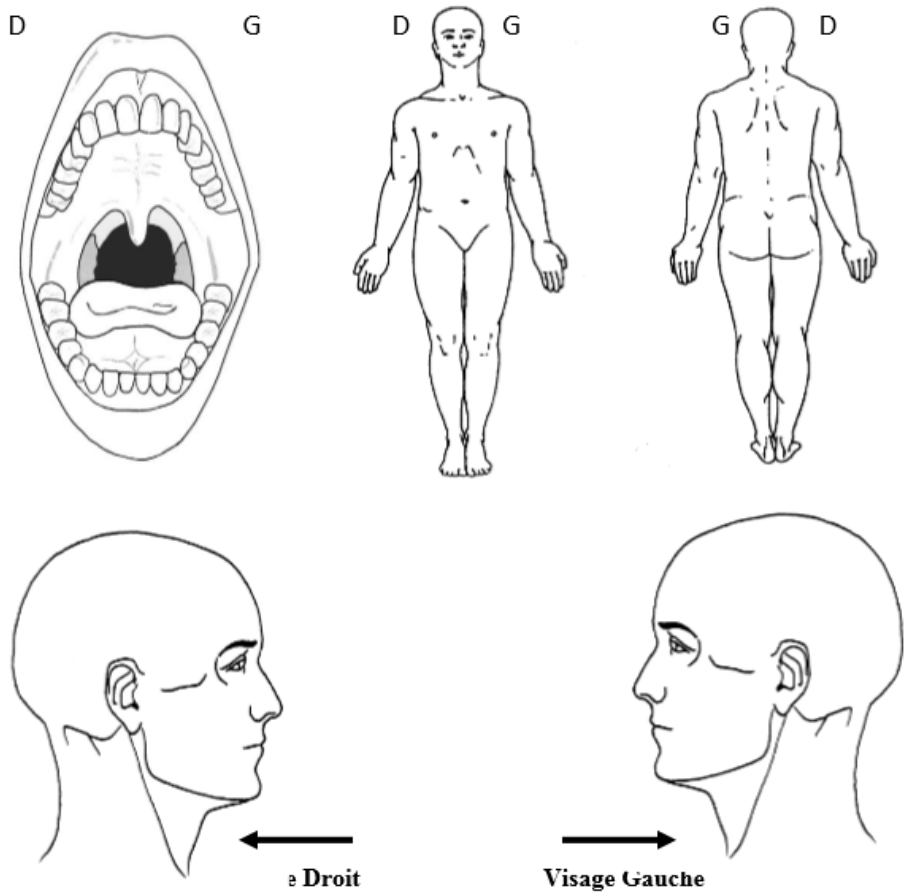
- ☐ Extraction dentaire
- ☐ Traitement orthodontique

30. Avez-vous ces conditions suivantes?

Condition	*Oui*	*Non*	*Médicament(s) pour la condition*
a. Diabète	☐	☐	
b. Allergies (Pénicilline/Médicaments)	☐	☐	
c. Problème de thyroïde	☐	☐	
d. Fièvre rhumatismale	☐	☐	
e. Haute pression sanguine	☐	☐	
f. Basse pression sanguine	☐	☐	
g. Fumez-vous? (nombre par jour)	☐	☐	
h. Asthme	☐	☐	
i. Problème cardiaque	☐	☐	
j. Douleur aux bras	☐	☐	
k. Douleur aux jambes	☐	☐	
l. Douleur à la poitrine	☐	☐	
m. Douleur au cou	☐	☐	
n. Douleur au dos	☐	☐	
o. Douleur à l'abdomène	☐	☐	

31. Diagramme de douleur

Indiquez l'emplacement de TOUTES vos douleurs différentes en colorant la zone, sur les illustrations appropriées. S'il y a un endroit précis où la douleur est localisée, indiquer la douleur avec un point solide (●). Si votre douleur bouge d'un endroit à un autre, utilisez des flèches pour indiquer la trajectoire.



32. De quel côté du visage la douleur est-elle plus sévère?

☐ Côté gauche ☐ Côté droit ☐ Les deux côtés également

33. En utilisant l'échelle ci-dessous, s'il-vous-plaît indiquez la mesure dans laquelle vous avez ces sentiments.

PROGRAMME ACTION QUESTIONS DE RÉFÉRENCE POUR LES DÉSORDRES TEMPOROMANDIBULAIRES

Au cours des 14 derniers jours, à quelle fréquence avez-vous été dérangé(e) par les problèmes suivants?	Jamais	Plusieurs jours	Plus de la moitié des jours	Presque tous les jours
A. Sentiment de nervosité, d'anxiété ou de tension.	0	1	2	3
B. Incapable d'arrêter de vous inquiéter ou de contrôler vos inquiétudes.	0	1	2	3
C. Inquiétudes excessive à propos de tout et de rien.	0	1	2	3
D. Difficulté à se détendre.	0	1	2	3
E. Agitation telle qu'il est difficile de rester tranquille.	0	1	2	3
F. Devenir facilement Contrarie(e) ou irritable.	0	1	2	3
G. Avoir peur que quelque chose d'épouvantable puisse arriver.	0	1	2	3

34. En utilisant l'échelle ci-dessous, s'il-vous-plaît indiquez la mesure dans laquelle vous avez ces sentiments.

Au cours des 14 derniers jours, à quelle fréquence avez-vous été dérangé(e) par les problèmes ou états suivants?	Jamais	Plusieurs jours	Plus de 7 jours	Presque tous les jours
A. Peu d'intérêt ou de plaisir à faire des choses	0	1	2	3
B. Se sentir triste, déprimé(e) ou désespéré(e)	0	1	2	3
C. Difficultés à s'endormir ou à rester endormi(e), ou trop dormir	0	1	2	3
D. Se sentir fatigué(e) ou avoir peu d'énergie	0	1	2	3
E. Peu d'appétit ou trop manger	0	1	2	3
F. Mauvaise perception de vous-même – ou vous pensez que vous êtes un perdant ou que vous n'avez pas satisfaits vos propres attentes ou celles de votre famille	0	1	2	3
G. Difficultés à se concentrer sur des choses tel que lire le journal ou regarder la télévision	0	1	2	3
H. Vous bougez ou parlez si lentement que les autres personnes ont pu le remarquer. Ou au contraire – vous êtes si agité(e) que vous bougez beaucoup plus que d'habitude	0	1	2	3

Si vous avez cochez au moins un des problèmes nommés dans ce questionnaire, répondez a la question suivante : Dans quelle mesure ce(s) problème(s) a-t-il (ont-ils) rendu difficile votre travail, vos taches à la maison ou votre capacité a bien vous entendre avec les autre?

☐ Pas du tout difficile ☐ Plutôt difficile ☐ Très difficile ☐ Extrêmement difficile

35. S'il-vous-plaît répondez aux questions suivantes sur vous-même en indiquant la mesure de votre accord :

	Totalement en désaccord	Plutôt en désaccord	Neutre	Plutôt d'accord	Totalement d'accord
A. Dans les moments d'incertitude, je m'attends habituellement au mieux					
B. J'ai de la facilité à me relaxer					
C. S'il y a des chances que ça aille mal pour moi, ça ira mal					
D. Je suis toujours optimiste face à mon avenir					
E. J'apprécie beaucoup mes amis(e)s					
F. C'est important pour moi de me tenir occupé(e)					
G. Je ne m'attends presque jamais à ce que les choses aillent comme je le souhaite					
H. Je ne me fâche pas très facilement					
I. Je m'attends rarement à ce que de bonnes choses m'arrivent					
J. Dans l'ensemble, je m'attends à ce qu'il m'arrive plus de bonnes choses que de mauvaises					

36. Avez-vous déjà subi une extraction dentaire?

☐ Oui ☐ Non

Si vous avez répondu « Oui », pour quelle raison?

☐ Parce que j'avais mal ☐ Je ne m'en souviens pas ☐ Pas à cause de la douleur

37. Avez-vous déjà eu un traitement orthodontique?

11.10 Appendix K : Epworth Sleepiness Scale (French)

PROGRAMME ACTION QUESTIONS DE RÉFÉRENCE POUR LES DÉSORDRES TEMPOROMANDIBULAIRES

☐ Oui ☐ Non

Si vous avez répondu « Oui », pour quelle raison?

☐ Parce que j'avais mal ☐ Je ne m'en souviens pas ☐ Pas à cause de la douleur

38. Écrivez le numéro correspondant à votre choix dans la colonne de droite.

Inclu: ☐ Oui ☐ Non

0 = Aucun risque de m'assoupir ou de m'endormir
1 = Faible risque de m'assoupir ou de m'endormir
2 = Risque modéré de m'assoupir ou de m'endormir
3 = Risque élevé de m'assoupir ou de m'endormir

Situations	Scores (0, 1, 2 ou 3)
Lire en position assise	
Regarder la télévision	
Être assis(e) inactif(ve) dans un lieu public (par exemple théâtre, réunion etc.)	
Être assis(e) en tant que passager(ère) dans un véhicule pour une période d'une heure sans arrêt	
Être étendu(e) l'après-midi lorsque les circonstances le permettent	
Être assis(e) en parlant avec quelqu'un	
Être assis(e) tranquille après un repas sans boisson alcoolique	
Dans une voiture arrêtée quelques minutes a un feu de circulation ou dans la circulation	

39. Inscrivez votre réponse (*Oui* ou *Non*) dans la colonne de droite.

11.11 Appendix L : Fatigue Severity Scale (French)

PROGRAMME ACTION QUESTIONS DE RÉFÉRENCE POUR LES DÉSORDRES TEMPOROMANDIBULAIRES

40. Fatigue Severity Scale (FSS) des troubles du sommeil.

Cet outil permet d'évaluer l'impact de la fatigue sur vous. Il s'agit d'un court questionnaire qui vous demande de mesurer votre niveau de fatigue. Il contient neuf affirmations qui mesurent la sévérité des symptômes de votre fatigue.

Lisez chaque affirmation et entourez un nombre de 1 à 7 qui semble correspondre à votre état de fatigue durant la semaine dernière.

• Une valeur basse (1) indique que vous n'êtes pas d'accord avec l'affirmation, tandis qu'une valeur haute (7) indique que vous êtes d'accord avec l'affirmation proposée.

• Il est important d'entourer un nombre (1 à 7) pour chaque question.

Durant la semaine passée, j'ai trouvé que :	**Pas d'accord → D'accord**						
Ma motivation est plus basse quand je suis fatigué (e)	1	2	3	4	5	6	7
Les exercices me demandent des efforts	1	2	3	4	5	6	7
Je suis facilement fatigué(e)	1	2	3	4	5	6	7
La fatigue interfère avec mes fonctions physiques	1	2	3	4	5	6	7
La fatigue me cause souvent des problèmes	1	2	3	4	5	6	7
Ma fatigue empêche certaines fonctions physiques	1	2	3	4	5	6	7
La fatigue m'empêche de mener à bien certaines obligations et responsabilités	1	2	3	4	5	6	7
La fatigue est parmi mes 3 symptômes les plus handicapants	1	2	3	4	5	6	7
La fatigue interfère avec mon travail, ma famille ou ma vie sociale	1	2	3	4	5	6	7
				Total :			

41. L'Indice de gravité Insomnia a sept questions. Pour chaque question:

11.12 Appendix N : Insomnia Severity Index (French)

PROGRAMME ACTION QUESTIONS DE RÉFÉRENCE POUR LES DÉSORDRES TEMPOROMANDIBULAIRES

S'il-vous-plaît encerclez le numéro qui décrit le mieux votre réponse. Veuillez noter la SÉVÉRITÉ COURANTE (à savoir, 2 dernières semaines) de votre problème d'insomnie .

Problème d'insomnie	Aucune	Légère	Moyenne	Élevée	Extrême
1) Difficulté à s'endormir	0	1	2	3	4
2) Difficulté à rester endormi(e)	0	1	2	3	4
3) Problème de réveil trop tôt le matin	0	1	2	3	4

4) À quel point êtes-vous SATISFAIT(E) / INSATISFAIT(E) de votre sommeil actuel ?

Très satisfait(e)	Satisfait(e)	Neutre	Insatisfait(e)	Très insatisfait(e)
0	1	2	3	4

5) À quel point considérez-vous que vos difficultés de sommeil sont APPARENTES pour les autres en termes de détérioration de la qualité de vie ?

Aucunement	Légèrement	Moyennement	Extrêmement	Très Extrêmement
0	1	2	3	4

6) À quel point êtes-vous INQUIET(ÈTE) / PRÉOCCUPÉ(E) à propos de vos difficultés de sommeil actuelles ?

Aucunement	Légèrement	Moyennement	Extrêmement	Très Extrêmement
0	1	2	3	4

7) À quel point considérez-vous que vos difficultés de sommeil PERTURBENT votre fonctionnement quotidien (ex. : fatigue, concentration, mémoire, humeur) ACTUELLE?

Aucunement	Légèrement	Moyennement	Extrêmement	Très Extrêmement
0	1	2	3	4

À compléter par le/la chercheur/e

Diagnosis: _____-

__

_____

_____

_____

Treatment received during baseline appointment: _____

_____

_____

_____

Additional notes: _____

_____

_____

_____

_____

_____

_____

_____

11.13 Appendix O : Three-month follow-up questionnaire (English)

ACTION PROGRAM 3 AND 6 MONTHS QUESTIONS FOR TEMPOROMANDIBULAR DISORDERS

Hospital	Patient Number	Initials	

Day	Month	Year

Please answer the following questions:

1. On how many days in the last month have you had facial pain? ____ Days

2. In the last 30 days, which of the following best describes any pain in your jaw, temple, in the ear, or in front of the ear on either side? *(Select ONE response)*

   ☐ No pain

   ☐ Pain comes and goes

   ☐ Pain is always present

3. Do you have pain in temple, face, jaw joint, or jaws once a week or more often?

   ☐ Yes ☐ No

4. Do you have pain when you open your month wide or chew, once a week or more often?

   ☐ Yes ☐ No

5. Do you have pain in the temples once a week or more often?

   ☐ Yes ☐ No

ACTION PROGRAM 3 AND 6 MONTHS QUESTIONS FOR TEMPOROMANDIBULAR DISORDERS

6. In the last 30 days, on average, how long did any pain in your jaw or temple area on either side last? *(Select ONE response)*

- ☐ No pain
- ☐ From very brief to more than a week, but it does stop
- ☐ Continuous

7. In the last 30 days, did you have pain or stiffness in your jaw on awakening?

☐ Yes ☐ No

8. In the last 30 days, did the following activities change any pain (that is, make it better or make it worse) in your jaw, temple, in the ear, or in front of the ear on either side?

A. Chewing hard or tough food.	☐ Yes	☐ No
B. Opening your mouth, or moving your jaw forward or to the side.	☐ Yes	☐ No
C. Jaw habits such as holding teeth together or chewing gum.	☐ Yes	☐ No
D. Other jaw activities such as talking, kissing, or yawning.	☐ Yes	☐ No

9. How would you rate your facial pain right now?
Please rate your pain by circling the number that tells how much pain you have right now.

No pain — Pain as bad as it could be

0 1 2 3 4 5 6 7 8 9 10

10. In the last 30 days, how would you rate your worst facial pain?
Use the same scale, where 0 is "no pain" and 10 is "pain as bad as could be".

No pain — Pain as bad as it could be

0 1 2 3 4 5 6 7 8 9 10

ACTION PROGRAM 3 AND 6 MONTHS QUESTIONS FOR TEMPOROMANDIBULAR DISORDERS

11. In the last 30 days, on average, how would you rate your facial pain?
Use the same scale, where 0 is "no pain" and 10 is "pain as bad as could be".
(That is, your usual pain at times you were in pain)

No pain — Pain as bad as it could be

0 1 2 3 4 5 6 7 8 9 10

12. In the last 30 days, how many days did your facial pain keep you from doing your usual activities like work, school, or housework? *(every day = 30 days)*

___ Days

13. In the last 30 days, how much has facial pain interfered with your daily activities? Use a scale where 0 is "no interference" and 10 is "unable to carry on any activities".

No interference — Unable to carry on any activities

0 1 2 3 4 5 6 7 8 9 10

14. In the last 30 days, how much has facial pain interfered with your recreational, social and family activities? Use the same scale where 0 is "no interference" and 10 is "unable to carry on any activities".

No interference — Unable to carry on any activities

0 1 2 3 4 5 6 7 8 9 10

15. In the last 30 days, how much has facial pain interfered with your ability to work, including housework? Use the same scale where 0 is "no interference" and 10 is "unable to carry on any activities".

No interference — Unable to carry on any activities

0 1 2 3 4 5 6 7 8 9 10

16. What treatments did you receive for your pain?

_____

_____

11.14 Appendix P : Three-month follow-up questionnaire (French)

PROGRAMME ACTION QUESTIONS DE SUIVI DE 3 & 6 MOIS
POUR LES DÉSORDRES TEMPOROMANDIBULAIRES

Hôpital	No. Patient	Initiales	

Jour	Mois	Année

S'il-vous-plaît répondez aux questions suivantes:

1. Pendant combien de jours au cours des 3 derniers mois avez-vous eu des douleurs faciales?

   ____ Jours

2. Au cours des 30 derniers jours, laquelle des propositions suivantes décrit le mieux votre douleur à la mâchoire, tempe, dans l'oreille, ou en avant de l'oreille d'un côté ou de l'autre? (Choisir une seule réponse)

   ☐ Pas de douleur
   ☐ La douleur qui vient et disparaît
   ☐ La douleur est toujours présente

3. Avez-vous mal à la tempe, au visage, aux mâchoires, ou aux articulations des mâchoires, une fois par semaine ou plus souvent?

   ☐ Oui ☐ Non

4. Avez-vous des douleurs lorsque vous ouvrez votre bouche ou mâcher, une fois par semaine ou plus souvent?

   ☐ Oui ☐ Non

5. Avez-vous des douleurs aux tempes une fois par semaine ou plus souvent?

   ☐ Oui ☐ Non

6. Au cours des 30 derniers jours, quelle était la durée de la douleur que vous avez peut-être ressentie dans la/les mâchoire/s ou au niveau de la/des tempe/s?

   ☐ Pas de douleur

   ☐ De très brève durée à plus d'une semaine, mais ça s'arrête

   ☐ Continue

7. Ces 30 derniers jours, avez-vous eu de la douleur ou rigidité dans votre mâchoire au réveil?

   ☐ Oui ☐ Non

8. Ces 30 derniers jours, est-ce-que les activités suivantes ont changé la douleur (c'est-à-dire, s'est améliorée, s'est empirée) à la mâchoire, à la tempe, à l'oreille, ou devant l'oreille des deux côtés?

A. Mâcher de la nourriture dure.	☐ Oui	☐ Non
B. Ouvrir la bouche, ou bouger la mâchoire en avant en avant ou sur le côté.	☐ Oui	☐ Non
C. Des habitudes de fonction telles que maintenir les dents serrées, ou mâcher de la gomme.	☐ Oui	☐ Non
D. D'autres activités telles que parler, embrasser ou bailler.	☐ Oui	☐ Non

9. Veuillez encercler le numéro qui décrit le mieux le niveau de douleur faciale que vous ressentez en ce moment.
   Utilisez une échelle de 0 à 10, où 0 indique «aucune douleur» et 10 indique «la pire douleur possible».

Aucune douleur										La pire douleur possible
0	1	2	3	4	5	6	7	8	9	10

10. Quel est le chiffre qui décrit la plus forte douleur faciale que vous avez ressentie au cours des 30 derniers jours.

Utilisez la même échelle, où 0 indique « aucune douleur » et 10 indique «la pire douleur possible».

Aucune douleur										La pire douleur possible
0	1	2	3	4	5	6	7	8	9	10

11. Quel est le chiffre qui décrit le niveau de douleur faciale que vous avez ressenti en général au cours des 30 derniers jours.
Utilisez la même échelle, où 0 indique «aucune douleur» et 10 indique «la pire douleur possible».

Aucune douleur										La pire douleur possible
0	1	2	3	4	5	6	7	8	9	10

12. Ces 30 derniers jours, combien de jours avez-vous été empêché(e) de faire vos activités habituelles tel que emploi, école/cours, ou travaux ménagers par votre douleur faciale? (*tous les jours = 30 jours*)

___ Jours

13. Jusqu'à quel point votre douleur faciale a interféré avec vos activités quotidiennes des 30 derniers jours.
Utilisez une échelle de 0 à 10, où 0 indique «aucune interférence» et 10 indique «incapable d'exécuter les activités quotidiennes».

Aucune interférence										Incapable d'exécuter les activités quotidiennes
0	1	2	3	4	5	6	7	8	9	10

14. Jusqu'à quel point votre douleur faciale vous a empêché de prendre part à des activités sociales, familiales et récréatives au cours des 30 derniers jours.
Utilisez la même échelle, où 0 indique «aucune interférence» et 10 indique «incapable d'exécuter les activités quotidiennes».

Aucune interférence — Incapable d'exécuter les activités quotidiennes

0 1 2 3 4 5 6 7 8 9 10

15. Jusqu'à quel point votre douleur faciale vous a empêché de faire votre travail au cours des 30 derniers jours (incluant les taches domestique)?
Utilisez la même échelle, où 0 indique «aucune interférence» et 10 indique «incapable d'exécuter les activités quotidiennes».

Aucune interférence — Incapable d'exécuter les activités quotidiennes

0 1 2 3 4 5 6 7 8 9 10

16. Quels médicaments prenez-vous contre la douleur?

_____

_____