11-12-2018 5:30 PM

Effect of Clear Aligner Therapy on Masticatory Muscle Tenderness and Orthodontic Pain

Johnny Tran
The University of Western Ontario

Supervisor
Tassi, Ali
The University of Western Ontario

Graduate Program in Orthodontics
A thesis submitted in partial fulfillment of the requirements for the degree in Master of Clinical Dentistry

Abstract

Introduction: Patients undergoing orthodontic clear aligner therapy (CAT) may experience discomfort in their teeth and jaws, and often present with visible wear on their aligners. This multi-site prospective clinical study aimed to analyze tooth pain and masticatory muscle tenderness in patients subjected to CAT with Invisalign©.

Methods: Twenty-seven healthy adults undergoing treatment with Invisalign© were recruited from three university-based orthodontic clinics. Tooth pain and muscle tenderness were reported on visual analog scales in pain diaries prior to, and after starting CAT. Pressure pain thresholds (PPT) measured using pressure algometers were used to assess somatosensory changes in trigeminal and extra-trigeminal locations.

Results: The aligners resulted in tooth pain, which was greater with the initial passive aligner than the subsequent active aligners (all $p<0.001$). Mild jaw muscle tenderness was triggered by both the active and passive aligners (all $p<0.001$). No significant differences were found with PPT measurements before and after CAT ($p>0.05$).

Conclusion: In the short-term, CAT results in mild tooth pain and jaw muscle tenderness of likely limited clinical significance, and does not result in significant somatosensory changes.

Keywords: clear aligner therapy, aligners, removable appliances, Invisalign, orthodontic pain, tooth pain, muscle tenderness, masticatory muscles, clenching, temporomandibular disorder, trigeminal

Co-Authorship Statement

The completion of this research project was only possible due to the contribution of said individuals. Thank you for your dedication and support.

Johnny Tran	DMD Candidate, Master of Clinical Dentistry (Orthodontics) Division of Graduate Orthodontics & Dentofacial Orthopaedics Schulich School of Medicine & Dentistry University of Western Ontario
Contribution:	Study design, patient recruitment, data collection and analysis and author of thesis
Ali Tassi	BSc, DDS, MClD Assistant Professor & Clinic Director Division of Graduate Orthodontics & Dentofacial Orthopaedics Schulich School of Medicine & Dentistry University of Western Ontario
Contribution:	Assisted with study design, data analysis and review of thesis
Iacopo Cioffi	DDS, PhD Assistant Professor, Orthodontics, Faculty of Dentistry Research Scientist, Centre for the Study of Pain University of Toronto
Contribution:	Assisted with study design, data analysis and review of thesis

Acknowledgements

First and foremost, I would like to express my sincere and heartfelt gratitude to my supervisors, Drs. Ali Tassi and Iacopo Cioffi, for their perpetual support of my research project. With their unmatched dedication, motivation and knowledge, I am tremendously fortunate to call them my mentors. You truly are an inspiration for us all mere mortals. And to my other mentor, department chair, and clinical professor, thank you Dr. Antonios Mamandras for giving me a chance at this once in a lifetime opportunity. I will be forever grateful being introduced to the Western Graduate Orthodontics family and the orthodontic profession. My sincerest thanks and appreciation to my research committee members, Drs. Bruce Hill, Sonia Palleck, and Jeffrey Dixon, for their soaring wisdom and support for the project. It has been a privilege and joy learning from all of you throughout my education at Western.

To all the clinical instructors and support staff of the Western Graduate Orthodontics who have dedicated their time and efforts in creating such a positive learning and working environment. You are all not only my teachers and mentors during my years at Western, but also my friends. I could not have asked for a better experience and a place I call my second home to complete my orthodontic residency. Thank you to my fellow co-residents in the Class of 2019, Drs. Woody Neilson and Diego Diaz. You cannot go unmentioned for your camaraderie and genuine friendship over the past three years. I could not have assembled a more inspiring, selfless, and handsome trio. To all my other classmates and now colleagues; Christos Papadopoulous, Michelle Wartroba, Erin Eyer, Michael Greene, Pia Canales, Jennifer Curran, Fraser Young, Bill Taylor, Leah Van Sant, Dustin Wilson, Harman Jassar and Oscar Renison. Thank you for the memories and sense of humour, it will always be a pleasure meeting again.

Last but not least, I would like to wholeheartedly thank my fiancé and future wife, Nicole Cordon, for supporting me every step of the way. Your patience and unconditional love cannot simply be expressed in words. And to my mother, Theresa Tran, and late father, Thanh Tran, thank you for teaching me perseverance, kindness, compassion and integrity. I love you both dearly.

Table of Contents

List of Tables

List of Figures

List of Appendices

List of Abbreviations

ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BDI	Beck depression inventory
CAD/CAM	Computer-aided design and computer-aided manufacturing
CAT	Clear aligner therapy
CPM	Conditioned pain modulation
CT	Computed tomography
EMG	Electromyography
IL-1β	Interleukin-1β
MVC	Maximum voluntary contraction
OBC	Oral behaviour checklist
PCS	Pain catastrophizing scale
PgE	Prostaglandin E
PPT	Pressure pain threshold
RDC/TMD	Research diagnostic criteria for temporomandibular disorders
SEM	Standard error of the mean
sEMG	Surface electromyography
SPSS	Statistical package for the social sciences
SSAS	Somatosensory amplification scale
STAI	State-trait anxiety inventory
TMD	Temporomandibular joint disorder
TMJ	Temporomandibular joint
VAS	Visual analogue scale

Chapter 1: Review of Literature

1.1 The Concept of Clear Aligner Therapy

Fig. 1 — Orthodontic Clear Aligner Appliance

The development of an orthodontic system capable of tooth movement without the use of orthodontic bands, brackets, or wires was described first in 1945 by Dr. H. D. Kesling,[1] who used a flexible rubber-based tooth positioning appliance. Kesling proposed the concept of using them in successive series for incremental tooth movements. Later, other types of overlay appliances such as invisible retainers were introduced. It was not until the 1960s that Nahoum[2] introduced the first clear thermoplastic appliance capable of orthodontic tooth movement. Ponitz[3] developed the first "invisible retainer" in the 1970s, which was later refined by McNamara in the 1980s. A similar appliance known as the Essix retainer was then developed by Sheridan[4] in 1993 and manufactured by Raintree Essix (New Orleans, USA). This technique is based on clear aligners formed on plaster models of the dental arches. The aligners are then modified physically with "divots,", which create a pushing force on individual teeth, and "windows," which create the space for the teeth to move into.[5]

With the continuing rise of the digital age of the 21st century, the integration of modern technology into these earlier fundamental principles gave rise to contemporary clear aligner systems that allow for a more comprehensive approach to orthodontic treatment. Clear aligner therapy (CAT) is an orthodontic treatment modality initially introduced to the mass market by Align Technology (Santa Clara, California, USA) in 1997.[6] This CAT, well-known as the Invisalign© system, further advances the principles of Kesling and Raintree Essix. Utilizing CAD/CAM stereolithographic technology, tooth movement is simulated and multiple custom-made aligners are subsequently fabricated from a single digital or analog impression.[7] Presently, other companies exist that also manufacture clear aligners for orthodontic therapy with CAD/CAM technology.[8] The core functionality of clear aligner therapy draws concepts from both traditional and clear removable orthodontic appliances[9]. Recent technological advancements have allowed CAT to emerge as a popular treatment option for orthodontic patients.[5]

For each patient undergoing CAT, the orthodontist obtains a set of polyvinyl siloxane impressions or digitally scanned impressions, a bite registration in centric occlusion, a panoramic radiograph, a lateral cephalometric radiograph, and diagnostic intraoral and extraoral photographs, which are sent to the desired clear aligner manufacturing company. For converting analog impressions, one method is to pour them in dental plaster and then place them in a tray encased with epoxy and urethane. A scanner then uses its rotating blades to make numerous passes over the epoxy-encased models, removing a thin layer on each pass. A computer linked with the scanner then re-assembles the scanned information to create a 3-D digital rendering of the models. Another

method to convert the analog impression is to apply a computed-tomography (CT) scan of the impression. This scanning step is omitted if digital impressions were acquired.

After the bite has been established (to relate the upper and lower dental arches) an orthodontic technician uses software to "cut" the virtual models and separate the teeth into individual units. Using the orthodontist's treatment prescription, proper alignment of the teeth and occlusion is established virtually, with the company's software. Once the final setup has been established, tooth movements are staged so that there are no occlusal and interproximal interferences, and the velocities of movements are within the range of limits set by the computer software. The number of stages equates to the number of aligners manufactured for a particular orthodontic case. And this number depends on the amount and complexity of three-dimensional tooth movement. The orthodontist has the opportunity to modify the treatment plan including the staging of tooth movements and final tooth positions.

Once it is approved, the individual stages are converted into physical models by a process of stereolithography. Stereolithography utilizes laser technology to polymerize resin for the fabrication of multiple resin models. These models are then used to fabricate the thermoplastic clear aligners. Aligners are then trimmed, labelled, disinfected, packaged and shipped to the doctor's office.[5]

The main advantages of CAT include removability for ease of eating and maintaining oral hygiene, improved esthetics and reduced short-term periodontal risk.[7, 10, 11] Additionally, its smaller size compared to conventional fixed orthodontic appliances has also led to improved

patient acceptance of orthodontic treatment.[12, 13] CAT is often described as less painful compared to conventional fixed orthodontic appliances, but recent research has shown that it may produce greater levels of initial pain.[14] Although CAT is widely accepted by patients, it is still not known how the masticatory muscles react to this treatment modality.

1.2 Pain and Discomfort in Orthodontic Treatment

Pain is defined by the International Association for the Study of Pain as "an unpleasant and emotional experience associated with actual or potential tissue damage or described in terms of such damage".[15] It is well-understood that pain and discomfort can be a highly complex and subjective experience[16] and is often a concern among patients undergoing orthodontic treatment.[17–19] The anticipation and fear of pain is a major reason why patients decline orthodontic treatment.[20–22] In one particular survey conducted by O'Connor,[23] patients rated pain as the greatest dislike in regard to their experience with orthodontic treatment, and ranked fourth among major fears and apprehensions. Orthodontic pain can also negatively impact patients' compliance, oral hygiene, lead to increased frequency of missed appointments, as well as compromising the overall treatment results and patient satisfaction.[12, 16, 24, 25] Additionally, in some instances, the impact of pain on patients' daily lives could be a significant factor for discontinuation of orthodontic treatment.[20, 26, 27] On the other hand, it is not surprising patients who experience low levels of orthodontic pain tend to have an improved level of compliance, cooperation and satisfaction with orthodontic treatment.[16, 28]

The majority of patients will experience varying amounts and frequencies of pain during their course of orthodontic treatment.[17] The initial pattern of pain experienced by patients with

traditional fixed orthodontic appliance therapy has been well documented,[12, 17, 29–32] with the pain and discomfort that may be experienced further into treatment not as thoroughly studied. In the initial stages, patients experience peak levels of pain within approximately the first 24 hours of archwire placement, followed by a gradual decrease towards baseline levels within 7 days.[14, 17, 33–36] Other studies have found that the first 4 to 7 days were the most critical for the patient in terms of general discomfort.[32] These results are in agreement with studies that found patients are generally able to tolerate and adapt to new appliances within a week after placement.[12]

The initial peak in pain and discomfort following the first 24 hours of orthodontic appliance activation has been correlated with an acute inflammatory response.[37] The cause of pain and discomfort has been thought to be caused by the compression of the periodontal ligament due to the applied initial orthodontic force. During the initial period of 24 to 48 hours, ischemia, edema and release of pro-inflammatory mediators is experienced by the local periodontium.[38, 39] An analogous pattern is observed with PgE and IL-1β levels found in the gingival crevicular fluid, which reach peak levels within the first 24 hours of initial orthodontic appliance activation and gradually decrease to baseline levels after a week.[40] Hence, the clinically observed pattern of pain progression during the first week of orthodontic treatment may be attributed to changes at the molecular level involving inflammatory mediators within the local periodontium.[35]

1.3 Comparison of Pain Between Clear Aligners and Fixed Appliances

Multiple studies have demonstrated that the patients' perception of pain, discomfort and quality of life varies between fixed appliances and removable appliances including clear aligners.[33] In general, fixed appliances tend to produce higher levels of discomfort, tension, pressure, tightness,

pain and sensitivity compared to removable or functional appliances.[16, 32, 41, 42] However, patients undergoing functional or removable appliances experience problems related to speech and swallowing more frequently than fixed appliance patients.[12, 32, 42, 43] Removable appliances deliver intermittent levels of force application, which has been speculated to allow the dentoalveolar tissues time to repair and re-organize before the compressive forces are re-applied.[44]

Miller et al.[33] conducted the first study in 2007 comparing the differences in pain and quality of life experienced by participants undergoing orthodontic treatment with CAT and fixed appliance therapy. The study was a prospective longitudinal cohort study with 33 in the CAT group and 27 in the fixed appliance group. The participants were instructed to use a daily diary for 7 days, measuring functional, psychosocial and pain-related impacts[45]. The diary consisted of questions modified from the Geriatric Oral Health Assessment Index,[46] a 5-point Likert scale for demographic data and a visual analog scale for pain. The results illustrated that the progression of pain in aligner treatment followed a similar pattern to that of fixed appliances, where pain peaked after 24 hours and then gradually returned to baseline (Fig. 2). The initial levels of pain were higher for the fixed appliance group along with higher levels of analgesic consumption. Both groups recovered to baseline levels within 7 days.

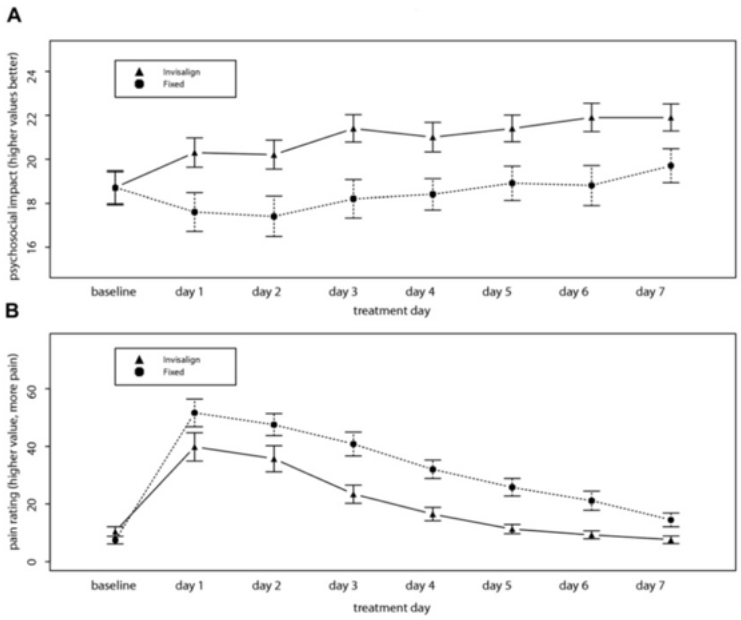


Fig. 2 — Miller et al. (2007) Mean Psychosocial Scores and Mean Pain Scores
A: Mean psychosocial scores for CAT group and fixed appliance group over a 7-day period. Higher scores mean more positive psychosocial measure; B: Mean pain ratings for CAT group and fixed appliance group over a 7-day period. Higher scores mean more pain.[33]

In a subsequent study by Shalish et al.,[14] 68 participants being treated either by buccal fixed appliances, lingual fixed appliances or CAT were recruited to complete a previously validated patient-reported outcome questionnaire[47–55] and visual analogue scales for pain during the first week and the 14th day (Fig. 3). The results illustrated that the average initial pain levels were consistently higher in the lingual fixed appliance and CAT groups, with analgesic consumption paralleling and coinciding with the pain levels, without reaching statistical significance. In all three groups, the pain levels subsided to baseline within one week (Fig. 3).

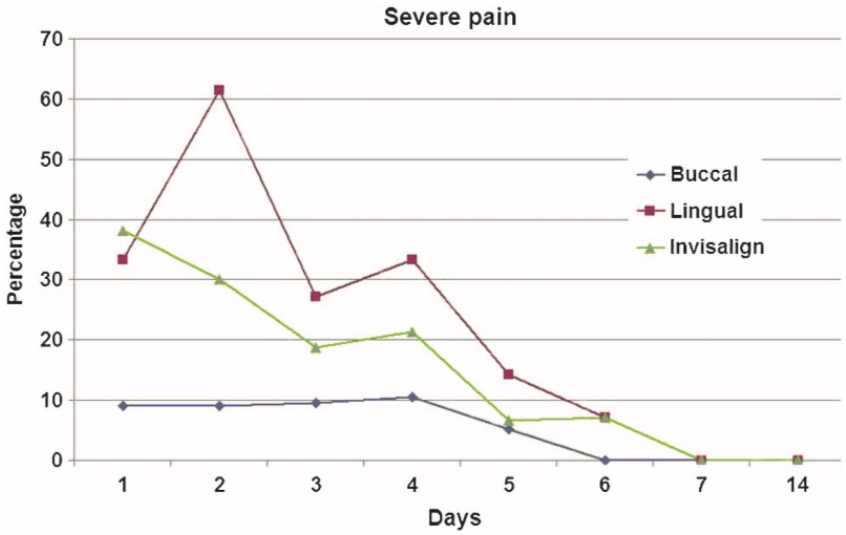


Fig. 3 — Shalish et al. (2012) Level of Reported Pain
Patients' level of reported pain when undergoing treatment with either buccal fixed appliances, lingual fixed appliances or CAT.[14]

To further explain and compare the pain levels between these orthodontic treatment modalities, Fujiyama et al.[34] performed a prospective clinical trial with 145 participants undergoing either CAT, fixed appliances, or a hybrid treatment of both. Using a visual analogue scale, the participants were requested to record their pain levels at time points of 60 s, 6 h, 12 h, 1 to 7 days post-appliance insertion. This was then repeated at the 3rd and the 5th week post-appliance insertion. Their results showed a similar pattern of pain progression during the first week of appliance delivery for all groups studied (Fig. 4).[29, 30, 37] They point out however, that the overall pain levels were significantly more intense and longer lasting for the fixed appliance group than either aligner or the hybrid group.

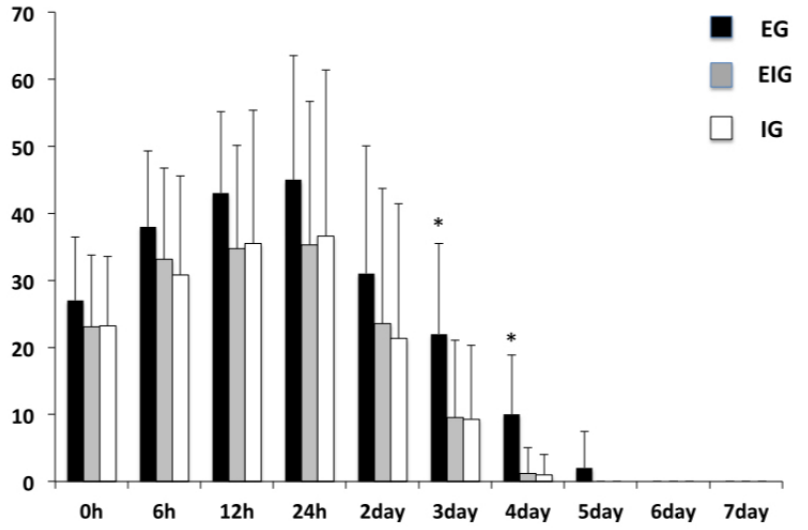


Fig. 4 — Fujiyama et al. (2014) Intensity of Pain
Intensity of Pain measured by VAS scores during the first week of appliance insertion. EG: Edgewise group; EIG: Edgewise and Invisalign group; IG: Invisalign group; asterisk (*): indicating statistical significance between EG and IG groups.[34]

In a more recent study by White et al.[35] in 2017, 41 participants were randomly allocated to either a CAT or fixed appliance treatment group to examine the differences in their pain levels. Daily diary entries with pain measured on a visual analogue scale were recorded by the participants. The diary was completed at initial appliance delivery, daily for the first week, as well as the first 4 days after their next two follow-up appointments. They found the pattern of pain progression during the first week following initial appliance activation was in good agreement with past studies.[14, 17, 29, 30, 33, 34] The CAT group experienced consistently lower levels of pain than the fixed appliance group, and their rate of analgesic consumption closely paralleled the pattern of pain progression during the first week (Fig. 5). Similarly, over the longer term of 2 months, the pain level was less in the CAT group than the fixed appliance group. This was thought to be related to the role of proinflammatory mediators, such as IL-1β. After initial appliance insertion, pain sensitization is increased through activation of receptor-associated kinases and ion channels. And in the subsequent months, these mediators induce transcriptional

up regulation of receptors, leading to hyperalgesia as described by Opree et al.[39] The participants in the fixed appliance group may have experienced an increased initial inflammatory response, which led to an increased sensitization of the nociceptors, and higher pain sensation in subsequent follow-up appointments.[35]

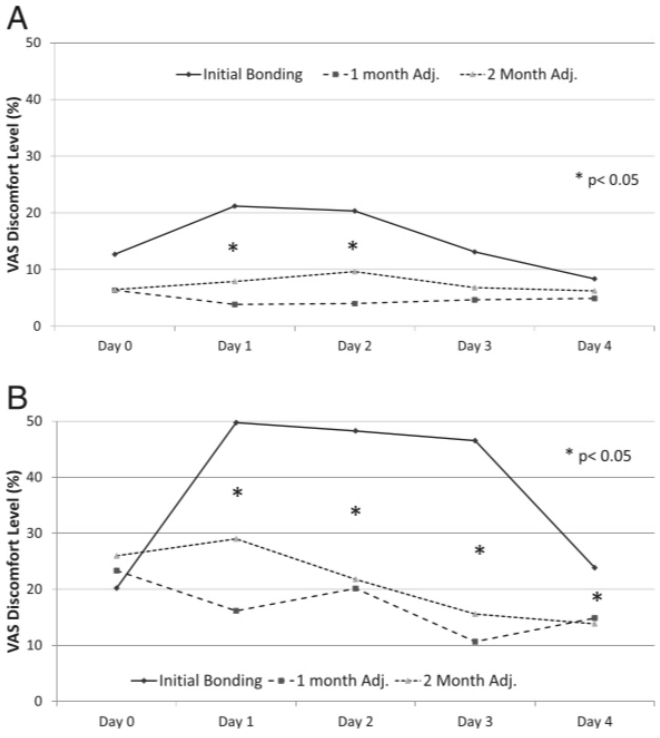


Fig. 5 — White et al. (2017) Median Levels of Discomfort
Median levels of discomfort of patients treated using CAT (A) and fixed appliances (B) at initial appliance insertion, 1 month and 2 month follow-up appointments.[35]

The results of pain and discomfort comparison studies between CAT and fixed appliances by White et al.,[35] Fujiyama et al.,[34] and Miller et al.[33] are in general agreement with each other, as well as past studies that showed fixed appliances cause more pain than removable appliances. These results are however in contrast to the findings from Shalish et al.,[14] which reported pain

was greater in participants treated with CAT than buccal fixed appliances. A possible reason for this inconsistency could be the variation in the aligner material composition. White's[35] study was the only study to utilize SmartTrack, a newer thermoplastic aligner material by Align Technology introduced in 2013, whereas the previous studies used the older EX30 aligner material. Limited evidence suggest that SmartTrack may be more comfortable than the older materials,[56] but further studies are needed to validate this. Additionally, Shalish's[14] research does speculate that the differences in pain levels observed may possibly have been due to a higher mechanical force level being applied early in treatment for the CAT group compared to the fixed appliance group.

1.4 Adaptation of Jaw Muscles to Orthodontic Therapy

The two main factors that may influence the adaptation of jaw muscles to orthodontic therapy are pain and occlusal changes that occur during treatment. Tooth pain is a major negative sequelae that is experienced by patients undergoing orthodontic treatment[27] and it has been shown to adversely impact the patients' quality of life.[50, 51] Sergl et al.[12] illustrated that the acceptance of and compliance with an orthodontic appliance and treatment in general may be predicted by the amount of initial pain and discomfort experienced. When patients are faced with traditional fixed appliances, they may adapt by avoiding tooth contact in an effort to reduce tooth pain related to orthodontic treatment. This phenomenon follows the principles of the pain-adaptation model proposed by Lund et al.,[57] which may provide an explanation for why orthodontic pain may lead to a decrease in electromyographic activity.[58]

The pain-adaptation model has been used to explain the observation that pain associated with initial orthodontic tooth movement causes patients to have a suppression of jaw muscle activity

and thus avoidance of chewing.[58] This avoidance could be the result of conditioned, and/or nociceptive reflexes in response to the pain associated with the initial tooth movement after orthodontic appliance activation. Pain is believed to be a result of the effects of compression or tension of the pain receptor endings in the periodontal ligament.[59] In a study by Stohler[60] and quoted by Lund et al.,[57] pain is associated with a decrease in electromyographic (EMG) activity of a muscle acting as an agonist and an increase when the muscle acts as an antagonist. In this proposed theoretical model, Lund and others suggest motor programs control the premotor nociceptive interneuron to agonist and antagonist motor neurons in a reciprocal way. The feedback of pain to the motor command lowers the agonist muscle output via excitation of the inhibitory motor neuron supplying them and inhibits the excitatory motor neurons supplying the agonist muscle group.

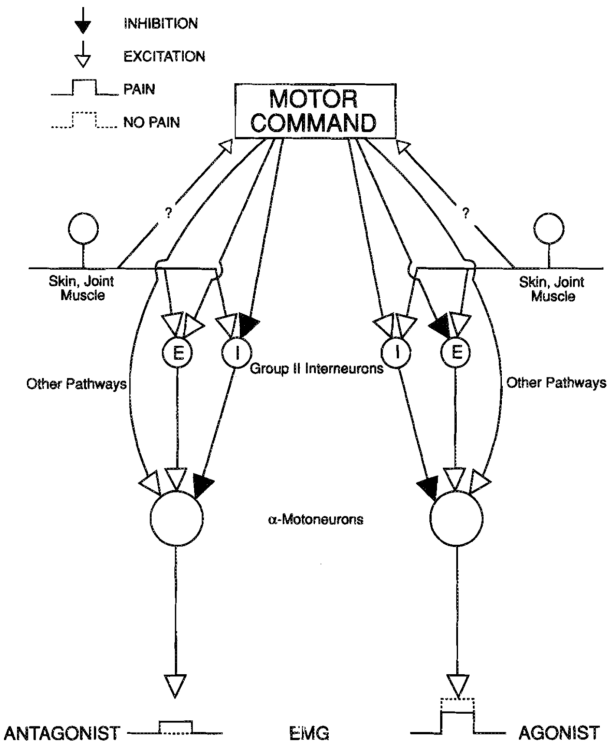


Fig. 6 — Lund et al. (1991) Theoretical Mechanism for the Pain-Adaptation Model
Hypothetical model to explain the changes in muscle activity caused by chronic pain.[57]

Clinical findings reveal some patients undergoing CAT with Invisalign© report jaw muscle tenderness[10] and present wear facets on their clear aligner trays, thus suggesting that the aligners may have acted as occlusal splints.[61] Therefore, it is possible that a different adaptation mechanism involving repetitive tooth clenching may have occurred in these patients. This has been suggested and supported in a study in which it was found that the frequency of daytime tooth clenching increases while undergoing CAT.[62] Perhaps it is possible that patients are triggered to clench on the aligner trays to alleviate orthodontic pain. Farzanegan et al.[63] has described this as being similar to clenching on plastic wafers. Proffit proposed, as long as light orthodontic forces were used, the amount of pain experienced by patients could be reduced by having them engage in repetitive chewing of gum or plastic wafers during the first 8 hours after

the appliance is activated. This would cause repetitive temporary displacement of the teeth which may promote blood flow through the compressed areas of periodontal ligament, thus preventing the accumulation of pro-algesic mediators in the periodontal ligament space, and promoting pain relief.[64, 65]

In addition, repetitive clenching on the aligner trays can act as a conditioning stimulus to reduce the perception of the orthodontic noxious stimuli in a conditioned pain modulation paradigm, as proposed by Yarnitsky.[66] This coincides with clinical reports of wear facets evident on the aligner trays and muscle tenderness in some CAT patients.[10] Therefore, it is a possibility that patients undergoing CAT may have transient symptoms of myofacial pain and temporomandibular joint disorder (TMD) as a result of repetitive clenching in order to relieve orthodontic pain. Conditioned pain modulation (CPM) is a term used to describe a psychophysical paradigm in which one noxious stimulus can be used as a conditioning stimulus to reduce the perception of pain by another stimulus.[66] CPM may be observed using a variety of tests involving the "pain inhibits pain" model (Fig. 7).[67]

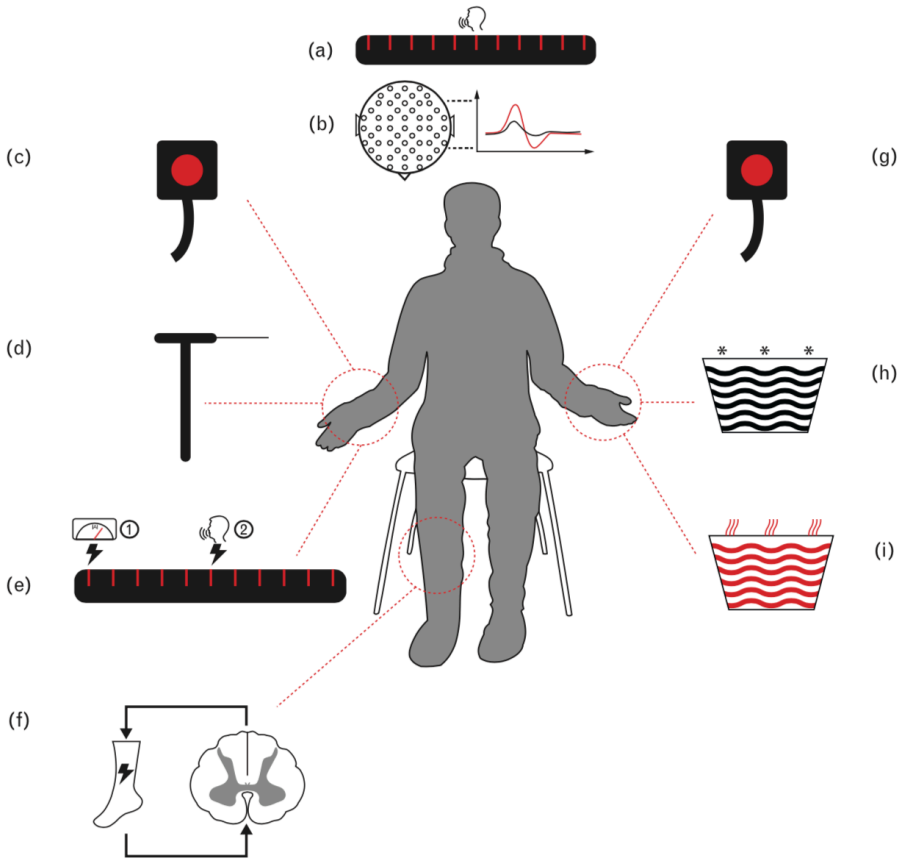


Fig. 7 — Nir et al. (2015) Schematic Illustration of Conditioned Pain Modulation
CPM is expressed by the reduced pain sensation of the test stimulus induced by the application of the conditioning stimulus. This may be depicted by either subjective numerical pain scores (a) or objective features of pain-evoked potentials recorded using an electroencephalogram detecting magnitude and latency (b). Representative test stimuli include thermal contact-heat administered using a thermode (c), mechanical pressure (d), electrical pain detection threshold (e1), and suprathreshold pain ratings (e2), and nociceptive withdrawal reflex responses (f). Typical conditioning stimuli primarily consist of thermal contact-heat (g), cold pressor test (h), and hot water bath test (i). CPM, conditioned pain modulation.[67]

1.5 Relationship Between Oral Parafunction and TMD

Oral parafunction behaviours are daytime activities such as gum chewing, clenching, nail/lip/cheek biting, and other object biting, which go beyond physiological oral functioning such as chewing, swallowing and talking.[68] These are typically harmless; however when the forces produced exceed an individual's physiologic structural tolerance, they could result in harmful effects on muscles and joints,[69 70–72] and could be considered as adverse behaviours.

Daytime clenching (ie. awake bruxism) continues to be a subject of interest and discussion within the dental community for its possible relationship with temporomandibular disorder (TMD) pain.[73, 74] Experimental sustained low-level tooth clenching has been shown to cause soreness in elevator jaw muscles in healthy subjects.[75] [76] A significant association between daytime clenching and myofacial pain of the masticatory muscles was demonstrated by self-reports[68–70] and by objective recordings.[77–79] The contributing role of oral parafunction to the onset of TMD has been further supported recently by a large-scale prospective cohort study[74] and by the significant reduction of pain symptoms after reversal treatment of the habit.[80]

On the other hand, a number of studies have shown a limited contribution,[81] and the absence of clinically relevant relationships between different types of self-reported parafunctions (including daytime clenching) with TMD-pain complaints,[82] as well as a lack of a correlation with facial pain intensity.[83] Also, other studies, using tooth wear (attrition) as an indicator for long-term parafunctional behaviours, have failed to find a clinically relevant dose-response relationship between clenching and TMD pain.[84, 85]

These contradictory findings between studies have been primarily related to the technical difficulty in identifying the presence of waking-state oral parafunctions in the natural environment because people are often unaware of their oral habits.[68] Therefore, objective and more reliable measurement techniques based on electromyographic assessments should be performed to confirm or deny the possibly relationship between daytime clenching and TMD pain. With recent novel technical advancements, surface electromyography (sEMG) has become an objective, reliable and non-invasive technique for evaluating the extent and duration of muscle

activity.[86] In controlled experimental conditions, EMG has been shown to be a powerful tool for the clinical evaluation of elevator jaw muscles, to detect muscle hyper- and hypo- function, rest position and fatigue.[87] EMG evaluation also allows the ability to distinguish between functional and non-functional oral behaviours.[88]

The possible relation between clenching and masticatory muscle pain has been tested in several EMG studies, which have shown that experimental low-level clenching tasks are associated with muscle soreness and fatigue, leading to TMD-like pain symptoms[76, 89] and that experimental high-level clenching was found not to be related to long-lasting pain of the masticatory muscles. [76, 90] Additionally, a delayed-onset of masticatory muscle soreness and a temporary diagnosis of myofacial pain occur in subjects performing episodes of eccentric and concentric jaw muscle contractions with different intensities.[72] In a recent study by Cioffi et al.,[91] with the utilization of sEMG, it was found that individuals diagnosed with myofacial pain of the masticatory muscles have an increased frequency in both high and low intensity daytime clenching episodes compared to pain-free individuals. The results were in agreement with previous reports showing that the frequency of non-functional tooth clenching is higher in TMD than in TMD-free individuals[77, 92, 93] and that daytime clenching and oral parafunctions are more frequent in subjects with a myofacial pain diagnosis.[69, 70, 74, 75]

1.6 Relationship Between TMD and Orthodontic Treatment

Temporomandibular disorder (TMD) is a collective term that encompasses a number of clinical problems that involve the masticatory muscles, temporomandibular joints (TMJ) and associated structures, and forms the most prevalent clinical entity affecting the masticatory system.[94]

Therefore, it is recognized as a musculo-skeletal disorder. In addition, TMD is the main cause of pain of non-dental origin in the oro-facial region including the head, face and related structures.[95] The etiology and pathophysiology of TMD is poorly understood and it is generally accepted that the etiology of TMD is multifactorial, involving a large number of direct and indirect causal factors. A thorough review of the literature shows that there are at least five major etiologic factors that have a possible association with TMD: occlusion, physical trauma, emotional stress, deep pain input and parafunction.[96] In addition to these variables is each patient's adaptability, which is another factor that has yet to be well-investigated. Of these known etiologies of TMD, orthodontic therapy routinely affects only one factor: occlusion. However, even occlusal factors are not always related to TMD.[97] The role of occlusion in TMD has been extensively debated, leading to many opinions and much controversy. It continues to be a resounding issue in orthodontics and interest in it is appropriate because orthodontists routinely and often completely change a patient's occlusal relationship during orthodontic treatment.[96]

Prior to the late 1980s, a very limited number of well-designed clinical studies focussing on occlusion and TMD were available. The attention of the orthodontic community regarding TMD exploded in the late 1980s after litigation involving orthodontic treatment as the cause of TMD in some patients.[98] However, evidence to suggest that orthodontic treatment had not caused TMD was lacking. In a review by Reynders[99] published in 1990, it was found that of the 91 articles published between 1966 and 1988, only six were sample studies involving large groups of individuals. The remaining articles were case reports (n=30) and viewpoint articles (n=55), mostly giving an expert's opinion with almost no data to support the claims. By the mid-1990s, a series of studies became available with the goal of finding the possible relationship between

occlusion and TMD. In summary, the data obtained did not suggest that orthodontic therapy was a significant risk factor for the development of symptoms of TMD.[100] Most of these studies were well-designed, leading readers to conclude that orthodontic therapy is not a risk factor for TMD. Therefore, one might say that orthodontic treatment is simply unrelated to TMD. Although most orthodontists would be comfortable accepting this concept, such a broad statement is more than likely too simple.

The majority of long-term studies on the relationship between orthodontic therapy and TMD have been accomplished with well-controlled orthodontic therapies. Almost all the studies were performed in university graduate orthodontic programs, where treatments were well-supervised and controlled. Perhaps poorly completed orthodontic treatment may reveal risk factors for TMD. Another consideration in interpreting the results is that many patients who received orthodontic treatment were young, healthy and adaptive. A developing masticatory system may help young patients adapt to occlusal changes and joint positions, rendering them less likely to have functional issues in the future. This variable has not been well-studied and is certainly a consideration when it comes to the development of TMD.

A more recent systematic review was conducted by Manfredini et al.,[101] with an inclusion criterion of studies of adults, assessed the association between TMD and dental occlusion. Twenty-five studies were included, and of these, 17 had a case-control design. Variation existed in the definition of TMD between studies which led to a marked degree of heterogeneity. They concluded there was an absence of evidence that supports the hypothesis that dental occlusion has a role in the pathophysiology of TMD. However, we must keep in mind that the absence of

evidence does not necessarily mean that there is a lack of an effect. Because TMD is a multifactorial pathology, it may be difficult to demonstrate a direct correlation between one of the causes, such as occlusion. It has been suggested that variables are so many and so mixed that we do not have adequate diagnostic instrumentation to establish a clear correlation.[94]

Several therapeutic protocols have been suggested for TMD management. As a consequence of the multifactorial etiology, multidisciplinary non-invasive therapies, which are also reversible, are generally suggested. Treatments should address not only the physical diagnosis, but also the psychological distress and the psychosocial dysfunction found in patients affected with chronic pain conditions.[102] A stable masticatory system includes a stable occlusal position in harmony with a stable joint position. From an orthodontic stand-point, the criteria for optimum orthopedic stability in the masticatory system, as explained by Okeson,[96] would be to have even and simultaneous occlusion of all possible teeth when the mandibular condyles are in their most superoanterior position, resting against the posterior slopes of the articular eminences, with the discs properly interposed. In other words, the musculo-skeletally stable position of the condyles should coincide with the maximum intercuspal positions of the teeth. Establishing an orthopedically stable relationship between the occlusal position of the teeth and the joint position is important for proper masticatory function throughout the patient's lifetime. Although in most situations orthodontic treatment neither causes nor prevents TMD, the orthodontist is in an excellent position to provide and support orthopedic stability in the masticatory structures. Orthodontic treatment goals should be routinely directed toward establishing orthopedic stability in the masticatory structures and achieving these goals will most likely reduce the patient's risk factors for developing TMD.[96]

1.7 Pressure Pain Thresholds of the Masticatory Muscles

Among TMDs, myofacial pain of the jaw muscles forms the most prevalent clinical entity affecting the masticatory apparatus. Muscle tenderness to palpation is an important clinical sign and is found in nearly 90% of patients with TMD.[103] With muscle tenderness to palpation a key component in the diagnostic process, the need for reliable clinical measurement is advocated. Tenderness upon palpation is either assessed by the examiner or by the patient and questions have been raised regarding the validity and reliability of either method.[104]

The diverse methods of manual palpation are difficult to quantify and standardize, and as such, better methods are required clinically. Reliability of muscle tenderness can be improved if, instead of using the finger, the examiner uses an instrument that applies pressure over a specific area at a constant uniform rate. Pressure algometers have been utilized to measure the pressure pain threshold (PPT), which is defined as the amount of applied pressure necessary for a subject to report the onset of pain or when the pressure has become unpleasant[105]. PPT is an investigative tool for measurement of muscle tenderness,[106, 107] and is usually determined by palpation procedures, either digitally or with the aid of a pressure device like an algometer. Pressure algometry has produced reliable and valid measures of PPT in patients with a variety of musculoskeletal pain syndromes[107, 108] and in asymptomatic subjects[106, 109, 110] and is more objective than manual palpation. Algometers can improve reliability because of their constant area of skin contact and their ability to control the rate and direction of pressure application.[111]

According to McMillan and Blasberg,[112] reliable PPT data can be obtained from an algometer if some factors (size of tip, rate of pressure, and degree of muscle contraction) are standardized.

The consistent observation of lower PPT in myofacial pain subjects than in pain-free controls is evident in several studies[91, 107, 110, 113, 114] and supports the validity of pressure algometry for the assessment of muscle tenderness. Ohrbach et al.[108] have shown that between-session PPT with pressure algometry across multiple sessions is reliable and without significant differences. The lack of inter-session differences is also consistent with other reports in the literature.[105, 109] Having been proven successful in evaluating jaw muscle tenderness in myofacial pain patients, algometry has also been found to be practical for use in population studies,[115, 116] for diagnostic purposes,[110] for evaluating the efficacy of management strategies,[109, 112, 117] and for investigation of tension-type headaches.[118, 119]

1.8 Psychological Effects on Orthodontic Treatment, Parafunction & Pain

Considerable interest in clinical and pain assessment literature continues to be focussed on identifying and managing specific cognitive factors that are related to pain and the individual's response to persistent pain.[120] In clinical practice, pain is a common consequence and expected with treatment. It is easy to assume that all such pain is a direct consequence of, and directly proportionate to, the nociception activated by the clinical procedure (eg. placement of a new orthodontic archwire or placement of new elastomeric chains). However, it is apparent clinically that the perception of pain varies considerably across individuals when the same stimulus, such as an initial light archwire, is activated. The expected procedural pain of a new archwire activation is generally believed to be relatively minor and self-limiting; however, some patients will report a much different experience.[121] It is generally accepted that particular affective and cognitive behavioural factors contribute to these differences in individual pain perception.[122, 123]

Specifically relevant to the medical and dental settings, pain perception is influenced by factors such as somatosensory amplification and anxiety.[124, 125]

It has been previously established that experimentally induced orthodontic pain is greater in individuals who exhibit higher levels of trait anxiety,[121] and oral parafunctional behaviours are more frequent in patients with higher trait anxiety.[121, 126] The State-Trait Anxiety Inventory (STAI) is a self-report questionnaire to measure the presence and severity of current symptoms of anxiety and a generalized propensity to be anxious. It is composed of two components, the first being the State Anxiety Scale (S-Anxiety) which evaluates the current state of anxiety using items that measure subjective feelings of apprehension, tension, nervousness, worry, and activation/arousal of the autonomic nervous system. The Trait Anxiety Scale (T-Anxiety) measures relatively stable aspects of "anxiety proneness," including general states of calmness, confidence and security. It refers to a general pattern of physical dysregulation and concern that is characteristic of an individual.[127] The STAI is composed of 40 items with 20 allocated to each of the S-Anxiety and T-Anxiety subscales. The test-retest reliability coefficients on initial development ranged from 0.31 to 0.86 (ranging from 1 hour to 104 days). Not surprising, since the S-Anxiety scale tends to detect transitory states, test-retest coefficients were lower for this scale as compared to the T-Anxiety scale. Internal consistency (Cronbach's α) were quite high ranging from 0.86 to 0.95.[127]

The Somatosensory Amplification Scale (SSAS) is a self-evaluation questionnaire for measuring amplification while somatizing. Somatosensory amplification refers to the tendency to perceive a given somatic sensation as intense, noxious and disturbing.[128] What may be a minor "soreness", is

a severe, consuming pain to the amplified, psychologically distressed individual. The 10-item questionnaire has established a test-retest reliability of 0.7-0.8 (over an average of 74 days) and internal consistency of 0.8 (Cronbach's α) in multiple studies.[129–131] It also has been shown that elevated levels of somatosensory amplification are evident in patients with myofascial pain.[132] It has been previously observed that trait anxiety may contribute to somatosensory amplification.[128] In addition, a number of studies have demonstrated that somatosensory amplification is correlated with several indices of general distress, including anxious and depressive symptoms[133–135]. The observed correlations ranged between 0.28 and 0.54 indicating a potential relationship between the two constructs that is clinically important.

In addition to general psychological distress, catastrophizing may be another important cognitive factor that affects perception of and response to persistent pain. Catastrophizing is defined as "an exaggerated negative mental set brought to bear during actual or anticipated painful experience".[136] Previous investigations have shown catastrophizing to be an important predictor of psychological distress, disability, analgesic use, and dysfunctional adjustment to pain in clinical and non-clinical samples.[137–141] In a review of cognitive mediators of pain, Turk and Rudy noted that "the most important factor in poor coping both in laboratory and clinical pain appears to be presence of catastrophizing rather than differences in adaptive coping strategies".[142] The Pain Catastrophizing Scale (PCS) is a 13-item scale for use in assessing catastrophizing in clinical and nonclinical populations. The internal consistency for the PCS has shown to be 0.87-0.95 (Cronbach's α) in literature with a test-retest reliability of 0.75 for 6 weeks and 0.70 at 10 weeks.[120, 143]

Another important psychological condition to consider is depression. Patients who present with depression along with medical illness tend to have more severe symptoms, more difficulty adjusting to their health condition, and more medical costs than patients who do not have a co-existing depression.[144] Prompt and early recognition of treatable depression can result in faster recovery and improved outcome of the co-occuring physical illness. Several patient-related assessment scales for detecting depression were proposed throughout the second half of the 20th century, along with the discovery of effective antidepressant drugs and development of cognitive-behavioural therapy. A popular instrument includes the Beck Depression Inventory (BDI).[145] Among the investigations on using self-assessment measures to evaluate depression, the BDI outnumbers other instruments in the amount of published research — more than 7,000 studies are using this scale.[146] The BDI has been translated and validated in 17 languages thus far and recently, the BDI has been ever-increasingly used in the medically ill to evaluate depressive states that occur at high prevalence in healthcare settings. The reliability of the BDI among medical samples has proven to be satisfactory with an internal reliability of approximately 0.9 (Cronbach's α). No studies on the test re-test reliability is available for medical samples. However, the stability of the BDI, as expressed by re-test coefficients of Pearson's r of 0.9 was reported by Beck and colleagues for psychiatric and student samples.[147] Evaluating depression may be an important factor for orthodontic patients as those who have high levels of depression may experience relatively more pain than those with lower to no levels of depression.

Oral parafunctional behaviours include activities such as clenching, grinding, object biting, gum chewing, and tongue and jaw movements that go beyond physiologic functioning. These adverse behaviours can potentially have detrimental effects on the dentition, temporomandibular joints

and muscles of mastication.[70, 71] Therefore, the detection of patients' oral behaviours can be useful for clinicians in the management and prevention of TMD. Wake-time oral behaviours were identified by the Oral Behaviour Checklist (OBC).[148] The OBC is an instrument widely used in research and clinical settings and is a self-reporting questionnaire, quantifying the frequency of observable and non-observable parafunctional oral behaviours. It has proven to be a reliable questionnaire with its excellent test-retest correlation of 0.86-0.88.[83, 149, 150] Self-reported waking-state oral parafunctional behaviours are found to be more prevalent in TMD-symptomatic patients who have mood disorders, such as anxiety.[79, 126] However, it has been found that trait anxiety is weakly correlated to the frequency of oral behaviours in pain-free individuals.[149]

1.9 Summary of Problem

Routine orthodontic procedures are a common source of acute and self-limiting pain.[16, 124, 151] The extent of pain associated with these procedures, however, vary considerably across patients, just as any pain varies. It has been found that anxiety appears to influence the perception of orthodontic pain[16] and patients with prolonged pain during orthodontic treatment exhibit higher levels of anxiety scores than do individuals with pain of short duration.[152] It also has been shown that orthodontic pain perception is significantly greater in patients who exhibit high levels of both trait anxiety and somatosensory amplification compared to patients with low levels of both.[121] Associations between oral parafunctional behaviours and orofacial pain, and between oral parafunctional behaviours and anxiety have also been observed.[70, 79] But whether oral parafunction as a trait behaviour contributes to the pain, whether oral parafunction is a mediating variable, or whether oral parafunction is a consequence of pain are presently

unknown.[153] Stress and anxiety can be considered as variables functioning to modulate oral parafunction and pain. Further evaluation of the above psychological constructs discussed could be of interest to possibly identify individuals who may be more sensitive to pain and discomfort during orthodontic therapy. This could lead to important orthodontic treatment implications, such as whether initial consultations for treatment should include consideration of behavioural constructs and, as indicated, include behavioural treatment such as anxiety and stress management and symptom perception management as an adjunct for susceptible patients.

Chapter 2: Objectives & Hypothesis

2.1 Research Question

In adult patients with orthodontic malocclusions, what is the effect of clear aligner therapy (CAT) on orthodontic tooth pain and jaw muscle tenderness within the first few weeks of treatment compared to baseline and what are the modulating effects?

2.2 Objectives of Study

The primary aim of this study was to evaluate orthodontic tooth pain and jaw muscle tenderness in patients undergoing CAT with Invisalign© within the first few weeks of treatment.

The secondary aims of the study were to:

a. Determine whether CAT could favour the onset of somatosensory changes in trigeminal and extra-trigeminal locations;
b. Assess if levels of stress, trait anxiety, somatosensory amplification, depression and catastrophizing might affect orthodontic pain perception and jaw muscle tenderness in patients undergoing CAT

2.3 Hypothesis

Patients undergoing their first few weeks of CAT will experience an increase in orthodontic tooth pain with a coincident increase in jaw muscle tenderness.

Chapter 3: Materials and Methods

3.1 Research Ethics

Ethics approval was obtained from the Health Sciences Research Ethics Board (HSREB) at the University of Western Ontario (approval #109148, Appendix 11).

3.2 Patient Recruitment

Eligible patients for the study were 18 years or older, and candidates for CAT with Invisalign© (Align Technology, Santa Clara, California, USA) with no prior history of clear aligner use. Patients were recruited from the graduate orthodontic clinics at the University of Western Ontario, University of Toronto and University of Turin. Exclusion criteria consisted of: current symptoms of TMD or orofacial pain, current use of muscle relaxants or other medications affecting jaw muscle activity, presence of any systemic disorders, and daily use of any analgesics.

Prior to entering the study, each patient underwent a preliminary examination by a single-examiner at each clinic according to the Research Diagnostic Criteria for temporomandibular disorders (RDC/TMD)[154] (Appendix 3). A preliminary screening questionnaire based off of a modified version of the TMD-Pain screener questionnaire[155] was also completed by each potential patient (Appendix 4)(question #1 — "in the last 30 days, how long did any pain last in your jaw or temple area on either side? No pain, pain comes and goes, pain is always present). The TMD-Pain screener questionnaire was used to detect facial TMD pain in individuals and has a high specificity and sensitivity, 99.1% and 96.9% respectively.[155] This questionnaire has proven to be a valid tool to identify patients with symptoms of TMD.

Each eligible patient was further asked to complete another set of questionnaires at the beginning of the study: the State Trait Anxiety Inventory[127] (STAI — Appendix 5), the Oral Behaviour Checklist[148] (OBC — Appendix 6), the Somatosensory Amplification Scale[156] (SSAS — Appendix 7), the Pain Catastrophizing Scale[143] (PCS — Appendix 8), and the Beck Depression Inventory[145] (BDI — Appendix 9). The use of these questionnaires allowed for determining the association with certain psychological traits, as well as pre-existing parafunctional oral behaviours, on differences in individual pain perception. Each patient was given an information and consent package regarding the current study (Appendix 10) and was provided thorough verbal explanation. All questions were answered and patients provided written and verbal consent acknowledging the receipt of the information package and willingness to participate in the study.

The initial participant pool consisted of 34 eligible patients from all three graduate clinics (Fig. 8). Seven eligible patients refused to participate in the study for various reasons. The final sample size was 27 patients, consisting of 5 males and 22 females (mean age ± SD = 35.3±17.6 years). There were no dropouts during the experimental period and all patients fully completed the longitudinal monitoring of pain and jaw muscle tenderness aspect of the study (primary outcome measures).

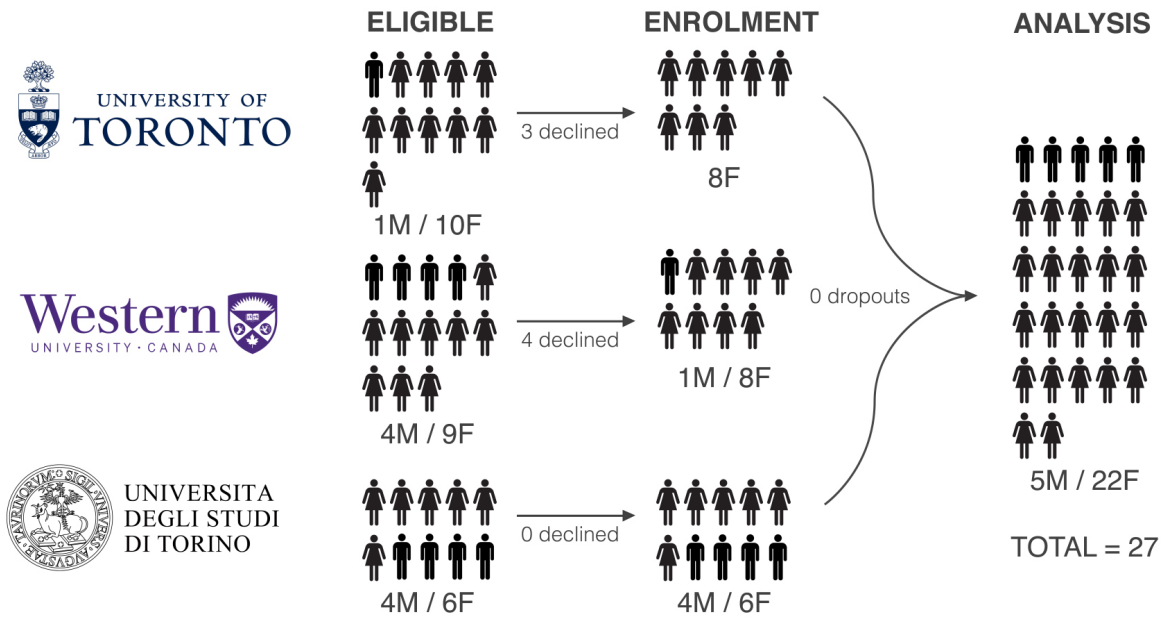


Fig. 8 — Schematic Diagram Illustrating Flow of Patient Recruitment

3.3 Experimental Procedure

All patients were treated with Invisalign© clear aligners, made of the latest generation of clear plastic, SmartTrack, which is a multi-layer thermoplastic polyurethane-based material with an elastomeric component.[157, 158] Using the ClinCheck Pro software, the first stage of aligners for all patients consisted of upper and lower aligners programmed with no active tooth movements (passive trays). Active tooth movements from the aligners were only incorporated at the subsequent stages. To negate any potential effect on the results from the auxiliary bonded attachments on the teeth, all attachments were placed either at the beginning of baseline measurements or after the experimental period.

The decision was made to solely use one brand of CAT for all patients in the experiment to eliminate any potential confounding factors associated with using a variety of clear aligner

manufacturers. These confounding factors would include differences in plastic aligner material composition, thickness, flexibility, force activation, stress-relaxation differences, etc. It has been shown that the quality of orthodontic force exerted by a thermoplastic clear aligner appliance is highly dependent on the mechanical properties of its fabrication material.[162]

3.4 EMG Recordings

The coincident study to this project focused on surface electromyography (sEMG) to evaluate the daytime activity of the masticatory muscles in the same patients undergoing CAT in the present study. This will allow for the assessment of how the masticatory muscles adapt to CAT and to potentially better understand how orthodontic pain affects the muscle response to this removable orthodontic appliance. Therefore, all of the individuals of the final patient sample of this experiment were also subjected to sEMG evaluation for this purpose. sEMG has been proven in literature to be an objective, reliable and non-invasive tool for evaluation of the masticatory muscles. sEMG permits the detection of hyper- and hypo- function, rest, and fatigue, and is capable of distinguishing between function and non-functional oral behaviours.[86, 87, 159–161]

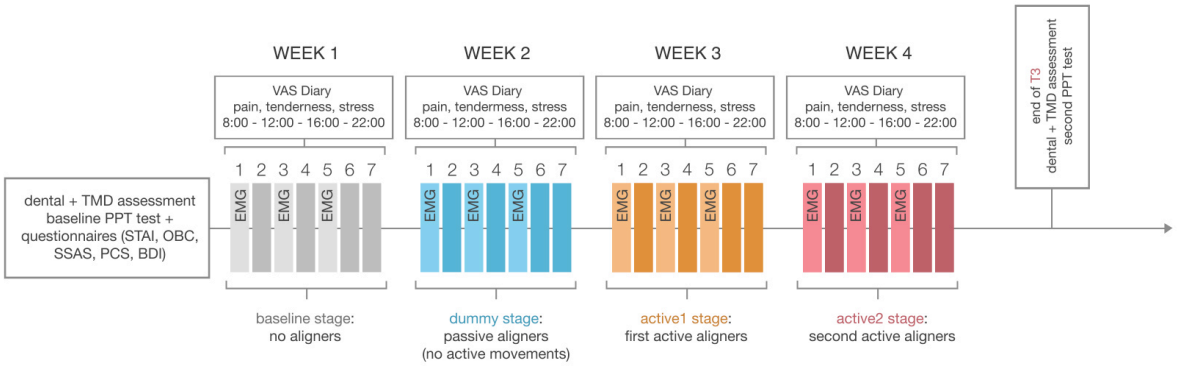


Fig. 9 — Schematic Illustration of Experimental Design

Patients were each provided with a portable sEMG device (MicroEMG, OT Bioelettronica, Turin, Italy) to self-record EMG signals at home for 4 hours per session starting anytime after 12:00 noon. Disposable bipolar self-adhesive concentric electrodes were used for recording surface EMG signals. Prior to electrode placement, patients were instructed to clean the skin with a disposable alcohol swab to diminish impedance.[91] Electrodes were placed by the patient at their right masseter muscle, along a line projecting from the mandibular angle to the lateral canthus of the eye, approximately 20 mm above the mandibular angle.[159] The centre of the electrode was located on a landmark on the skin of the cheek that closely approximates the largest muscle "bulge" when the patient clenched their teeth together. Patients were instructed to avoid exercising, chewing and eating during recording sessions.

Each patient was instructed to turn on the device on the day scheduled for recording, and record his/her maximum voluntary jaw muscle contraction (MVC) in maximum intercuspal position (without aligner trays) by clenching as hard as possible and to maintain the same level of contraction for 3 seconds. This test was repeated three consecutive times, separated by 5 second intervals, as done previously.[91] Patients were asked to turn off the device after 4 hours of recording. The assessment of MVC at the beginning of each recording acted as a baseline millivolt measurement which will be used to detect and distinguish parafunctional tooth clenching episodes.

Data were collected for 4 full-week intervals (Fig. 9), with each week consisting of three separate 4 hour records on day 1, day 3 and day 5. The first week, "baseline" stage, was done prior to the patient wearing their first clear aligner tray and acted as a baseline measurement week. From this time forward, patients were instructed to record their orthodontic tooth pain and muscle tenderness subjectively with VAS 4-times per day. The second week, "dummy" stage, consisted of the patient wearing a passive or "dummy" clear aligner tray that elicited no active orthodontic forces. The non-active (passive) clear aligner tray was worn by the patient to favour habituation, with the intention of reducing compliance issues during the active phases of treatment. The passive aligner tray also allowed the determination whether or not the presence of clear aligners by itself (without active tooth movement forces) could elicit a pain response or muscle tenderness. The third week, "active1" stage, took place during the week of the patient wearing their first active clear aligner tray. The fourth week, "active2" stage took place during the week of the patient wearing their second active clear aligner tray.

3.5 Daily Diary Recordings

Patients were provided a custom-made diary (Appendix 1 and Appendix 2) to evaluate and record their tooth pain, occlusal discomfort and jaw muscle soreness at 4 time points during each day (08:00, 12:00, 16:00, and 22:00-before going to sleep) with visual analog scales (VAS — 0-100 mm, left endpoint: no pain/discomfort, right endpoint: worst pain/discomfort one could imagine). Patients also recorded their overall stress at the end of the day using a separate single VAS. Patients were instructed to take note of any intake of analgesics. The return of the self-report pain diary occurred after the end of the fourth week. At this point, they each underwent another TMD examination (Appendix 3)(refer to Fig. 9).

3.6 Pressure Pain Thresholds

Pressure pain thresholds (PPTs) were assessed with an electronic algometer (Wagner Inc., Greenwich, CT, USA) equipped with a rubber tip of 1 cm^2 surface area. This device was used to assess patients' sensitivity to pain before and after three weeks of CAT. The data acquired served as an indirect objective measurement of patients' jaw muscle tenderness and to determine if CAT resulted in trigeminal and extra-trigeminal somatosensory changes. The PPT tests were performed in a silent and comfortable room in each of the graduate orthodontic clinics. Each patient was asked to sit on a stable chair, head upright and with a table in front of them to rest their hands.

The algometer was positioned perpendicular to the skin surface at the selected sites and pressure applied at an increasing rate of approximately 20 kPa/sec. A single examiner at each research centre, trained and calibrated, performed all PPT measurements, as previously described.[91] The PPT was determined as the point at which the pressure stimulus changed from a sensation of pressure into a sensation of pain. The patient indicated this by raising one hand to signal the examiner to release the pressure and the peak pressure value prior to release was recorded. Patients were asked to keep the muscles relaxed during the evaluation. Inter-examiner error and calibration was accounted for by computing the intra-class correlation to estimate the inter-rater reliability between all research sites. The results confirmed a high inter-rater reliability (ICC 0.966 [0.938-0.981]; $p<0.001$).

All measurements were taken at three locations on both right and left sides. For the masseter muscle, the site was located midway between the origin and insertion, 1 cm posterior to its anterior boundary. For the anterior temporalis muscle, the site was located on the line from the top edge of the eyebrow to the highest point of the pinna of the ear, 2 cm posterior to the anterior margin of the muscle as determined by palpating the muscle during voluntary contraction. For the thenar muscle, measurements were made on the skin of the palmar side of the hand, on the thenar prominence. The selection of these sites allowed for testing whether CAT caused somatosensory changes at both trigeminal and extra-trigeminal locations. It has been shown previously by Silva et al.[114] that the masseter and temporalis muscles require different pressures (lower for the masseter) for distinguishing pain from only pressure and that the anterior temporalis has the highest sensitivity for testing and has the most suitable discriminative capacity.

Clear templates were fabricated for each patient during the first PPT trial at the beginning of baseline week. Templates consisted of an outline tracing of the patient's lips, eyebrows, ears, and location for PPT evaluation of the masseter and anterior temporalis muscles. These custom templates were used for each patient again at their subsequent PPT tests to ensure consistent algometer placement between trials.

PPT measurements were taken at two timepoints for each patient, at baseline prior to any aligner wear and at the end of the fourth experimental week after wearing the second active aligner (Fig. 9). The measurements were repeated for a total of 4 trials at each muscle, with 1 minute intervals between trials. The order of muscle site measurements were randomized across patients.

Randomization was accomplished utilizing the PairRandomizer application (San Francisco, CA, USA) for iOS Apple mobile devices. While assessing the PPT at masticatory muscle locations, the patients head was supported by counter-pressure from the opposite hand of the operator. PPTs at the thenar muscles were measured with hands supinated flat on the table.

3.7 Statistical Analyses

The sample size calculation was determined on the basis of our collective primary outcome measures of: sEMG analysis and self-report pain and muscle tenderness. Based on previous studies by Michelotti,[163] a minimum of 17 participants would be required to detect a 10% change in EMG amplitude after CAT, with an effect size of 0.86, α-error set at 0.05 and β-error set at 0.1.

The normality of distributions of all variables were verified first with the Kolmogorov-Smirnov test. Data were not normally distributed. The variation of VAS ratings for tooth pain and muscle tenderness were assessed over time by utilizing generalized linear mixed effect models with Bonferonni correction. Two models were used, one for each of the primary outcome variables, tooth pain and muscle tenderness. In each model, day, gender and aligner condition (baseline, dummy tray, first active tray, second active tray) were used as fixed factors. Gender was incorporated into the model because pain is affected by gender.[164, 165] Daily VAS stress measures were incorporated in the mixed models as a covariate. A sensitivity analysis with Pearson correlations were performed for both longitudinal tooth pain (Appendix 12) and muscle tenderness (Appendix 13) to various psychological traits: STAI, SSAS, PCS, and BDI.

Pearson correlations were also used to determine which psychological variables best fitted the model including daily VAS stress trajectories. All covariates were found to be correlated to each other (Appendix 14). Self-reported VAS stress was included in the model since it was the most significant predictor out of all the covariates. Interactions between the model's variables were tested and retained in the model when statistically significant (Appendix 15 and 16). To account for biologic and physiologic differences between individuals and since these differences are random, we included in the model unique patient IDs as a random factor. Mixed effect models were used in favour of ANOVA of repeated measures because mixed models properly account for intercorrelations between repeated measurements and multicollinearity. In other words, mixed effect models account for the variation between multiple repeated measures, whereas ANOVA only accounts for the differences between means and not multicollinearity.

The secondary outcome measure of pressure pain thresholds (PPT) were calculated by discarding the first measurement and then computing the mean of the subsequent 3 trials obtained at each PPT location. Differences between right and left sides in PPTs at the masseter, temporalis and thenar eminence were tested using a T-test. Since there were no differences between sides ($p<0.001$), the data was pooled for each muscle location. ANCOVA was used to test whether PPTs at different muscle locations changed after 4 weeks. Gender was included in the model as a fixed factor.

The statistical significance was set at $p<0.05$. SPSS software ver. 24.0 (IBM, Armonk, NY, USA) was used for the statistical analysis.

Chapter 4: Results

The clear aligners resulted in an increase in mean orthodontic tooth pain according to self-report VAS (0-100 mm). The first stage passive aligner ("dummy") and both subsequent active aligners ("active1" and "active2") produced higher levels of tooth pain compared to baseline ($p<0.001$). Overall, the first stage passive aligner elicited more mean tooth pain than the active aligners ($p<0.001$) (Fig. 10). There was a significant decrease in mean pain from the passive aligner to the first active aligner ($p<0.001$) and from first active aligner to second active aligner ($p<0.001$). There was a significant difference in mean tooth pain (±SEM) between males (3.2±0.8 mm) and females (11.2±1.6 mm) ($p<0.001$).

Daily tooth pain score trajectories within each week of baseline, passive aligner, first and second aligner stages are shown on Figure 11. For the majority of days, the passive aligner and active aligners produced more tooth pain than at baseline ($p<0.05$), and during the first 4 days, the passive aligner produced more pain than the active aligners ($p<0.05$). Tooth pain was reported highest (VAS=16 mm) on day 2 of the passive aligner stage and decreased significantly from day 2 to day 7 ($p<0.05$). The first active aligner produced mild tooth pain as well, but less than that of the passive tray. There were no significant differences across days with the first active aligner ($p>0.05$). The second active aligner produced milder tooth pain compared to the first active aligner. Pain was significantly less at day 7 than day 1 with the second active aligner ($p<0.05$). When the covariate of daily stress was incorporated into the statistical mixed effect model, it was found that the variations in pain response were less attributed to the days. This indicated that the variation of stress across the days has an association with the perception of pain compared to the days within each appliance condition (passive, first and second active aligners). In addition, trait

anxiety and reported tooth pain was found to be moderately correlated (r=0.473; p=0.008) (Appendix 12).

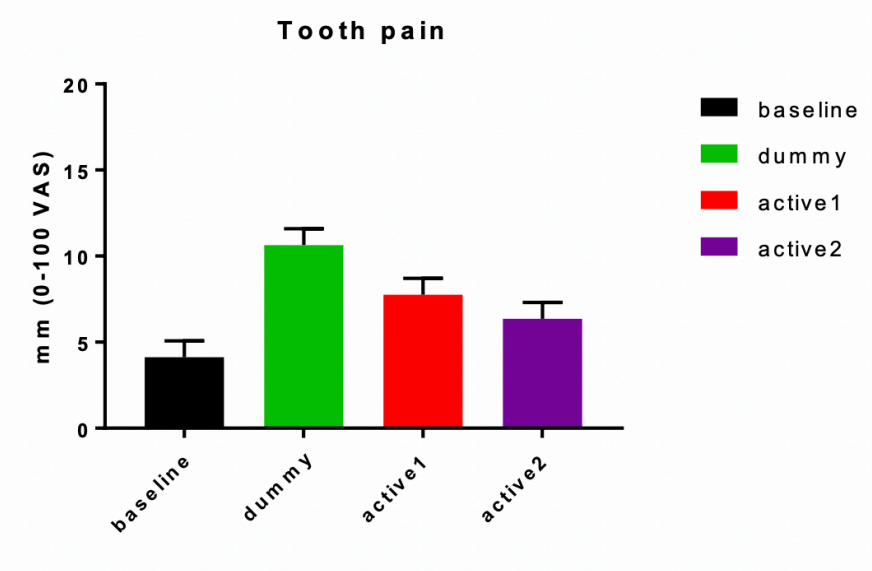


Fig. 10 — Mean Tooth Pain Self-Report VAS
Mean orthodontic tooth pain (±SEM) from self-report VAS at baseline and for each aligner condition (passive aligner, first and second active aligners). Estimated values from the mixed effect model after taking into consideration the effect of covariates. All pairwise comparisons are statistically significant at p<0.001.

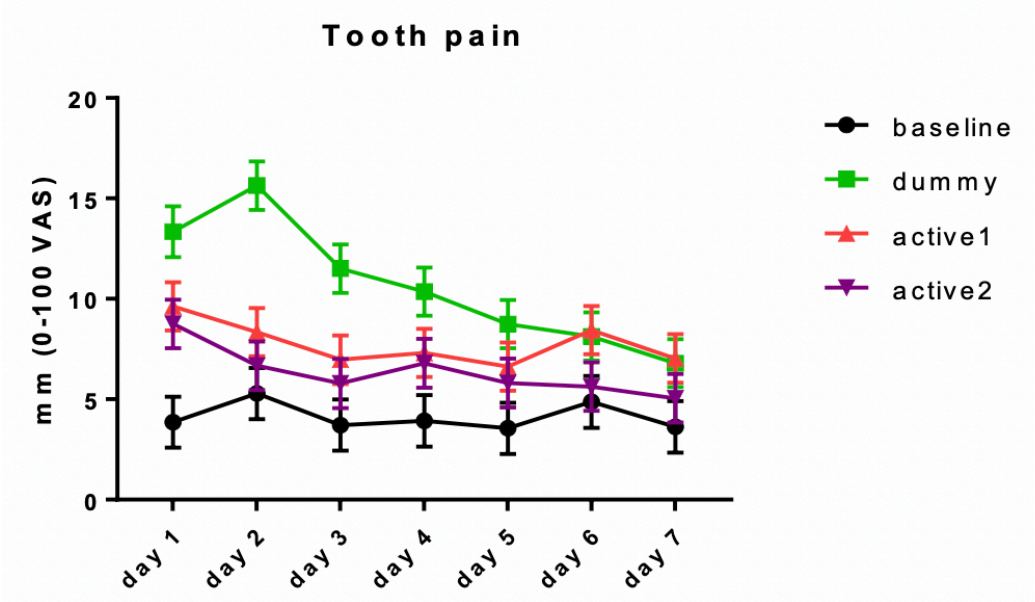


Fig. 11 — Tooth Pain Trajectories Over 7 Days at Baseline and for Each Aligner Condition
At day 1 all pairwise (between conditions) comparisons were statistically significant (all p<0.05) except for active1 vs. active2 (p=0.441). At day 2 all pairwise comparisons were statistically significant (all p<0.05) except for active1 vs. active2 (p=0.286) and active 2 vs. baseline (p=0.286). At day 3 all pairwise comparisons were statistically significant (all p<0.05) except for active1 vs. active2 (p=0.303) and active2 vs. baseline (p=0.189). At day 4 all pairwise comparisons were statistically significant (all p<0.05) except for active1 vs. active2 (p=0.652). At day 5 all pairwise comparisons were statistically significant (all p<0.05) except for active1 vs. active2 (p=0.466), active1 vs. dummy (p=0.182), and active2 vs. baseline (p=0.182). At day 6 pairwise comparisons were statistically significant only for active1 vs. baseline (p=0.020), and dummy vs. baseline (p=0.040). At day 7 pairwise comparisons were statistically significant only for active1 vs. baseline (p=0.032), and dummy vs. baseline (p=0.044).
At baseline, there were no significant differences in tooth pain between days (all p=1.000). With the dummy tray, pain decreased significantly from day 2 to day 7 (p<0.05). No significant differences were found across days during active1 (all p>0.05). In active 2, pain was significantly less at day 7 than day 1 (p=0.028).

Mild jaw tenderness was triggered according to self-report VAS (0-100 mm) by both the passive aligners ($p<0.001$) and the second active aligner ($p<0.001$) compared to baseline (Fig. 12). The first active aligner resulted in less mean muscle tenderness than the passive aligner ($p<0.001$). The second week of active treatment resulted in more mean muscle tenderness than the first week of active treatment ($p<0.001$). Estimated mean jaw muscle tenderness had no differences in regards to gender ($p>0.05$).

Daily muscle tenderness score trajectories within each week of baseline, passive aligner, first and second active aligner stages are shown on Figure 13. All pairwise comparisons between conditions within each day were not statistically significant (all $p>0.05$). At baseline and with the first and second active aligners, there were no significant differences across the days ($p>0.05$). During the passive aligner, muscle tenderness decreased significantly from day 1 to day 6 ($p<0.05$). The covariate of daily stress was also incorporated into the mixed effect model for muscle tenderness and it was found to have the same effect on the outcome measure as it did to the mixed effect model for orthodontic pain. The variation of stress across the days had an interaction effect with the perception of muscle tenderness compared to the days within each appliance condition. It was found that muscle tenderness was moderately correlated with both reported wake-time oral parafunctions (OBC) ($r=0.515$; $p=0.004$) and anxiety ($r=0.343$; $p=0.047$) (Appendix 13). Additionally, daily reported stress was moderately correlated with OBC ($r=0.393$; $p=0.026$)(Appendix 14)

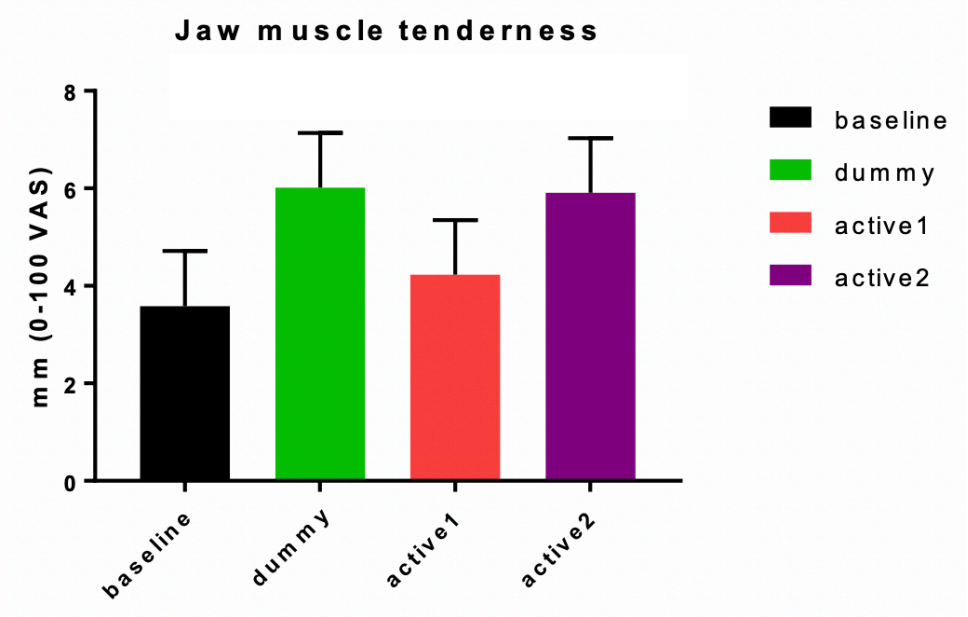


Fig. 12 — Mean Muscle Tenderness Self-Report VAS

Mean jaw muscle tenderness (±SEM) from self-report VAS at baseline and for each aligner condition (passive aligner, first and second active aligners). All pairwise comparisons are statistically significant at $p<0.001$ except between passive and second active aligners and between baseline and first active aligners ($p>0.05$).

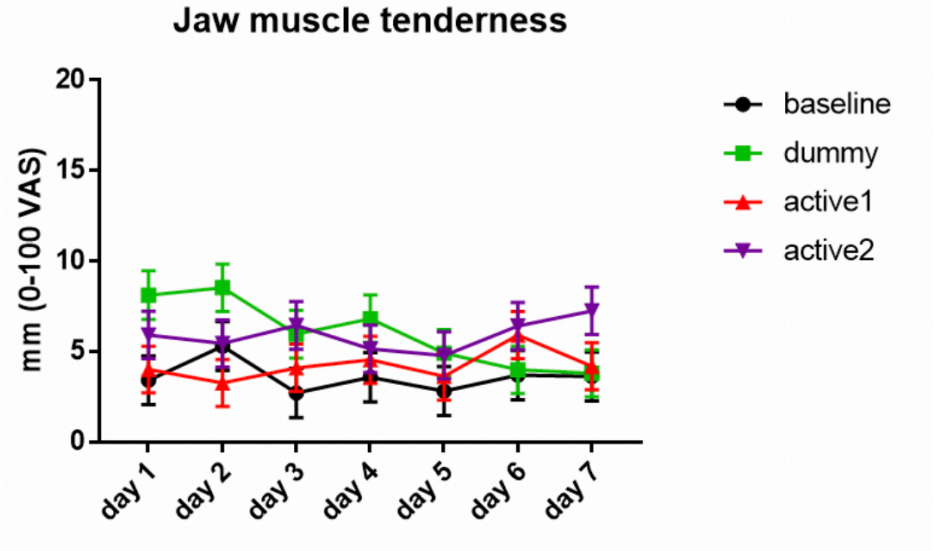


Fig. 13 — Muscle Tenderness Trajectories Over 7 Days at Baseline and for Each Aligner Condition

All pairwise (between conditions) comparisons within each day were not statistically significant (all $p>0.05$). At baseline, and with the trays active1 and active2, there were no significant differences in jaw muscle tenderness between days (all $p>0.05$). With the dummy tray, pain decreased significantly from day 1 to day 6 ($p<0.05$).

Although patients reported an onset of jaw muscle tenderness during treatment, no patients developed a diagnosis of TMD according to their RDC/TMD examinations (Appendix 3) before and during the initial weeks of treatment.

According to the psychophysical measurements from pressure algometer tests, there were no statistically significant variations of PPTs from baseline to after 3 weeks of CAT at both trigeminal and extra-trigeminal locations (all with $p>0.05$). However, a significant effect of gender was found on PPTs regardless of the intervention ($p<0.001$)(Fig. 14). Results from ANCOVA for the PPT measurements at baseline and at 4 weeks for the masseter, temporalis and thenar muscles are shown in Appendices 17, 18 and 19 respectively. Descriptive statistics for the PPT measurements at baseline and at 4 weeks for the masseter, temporalis and thenar muscles are shown in Table 1.

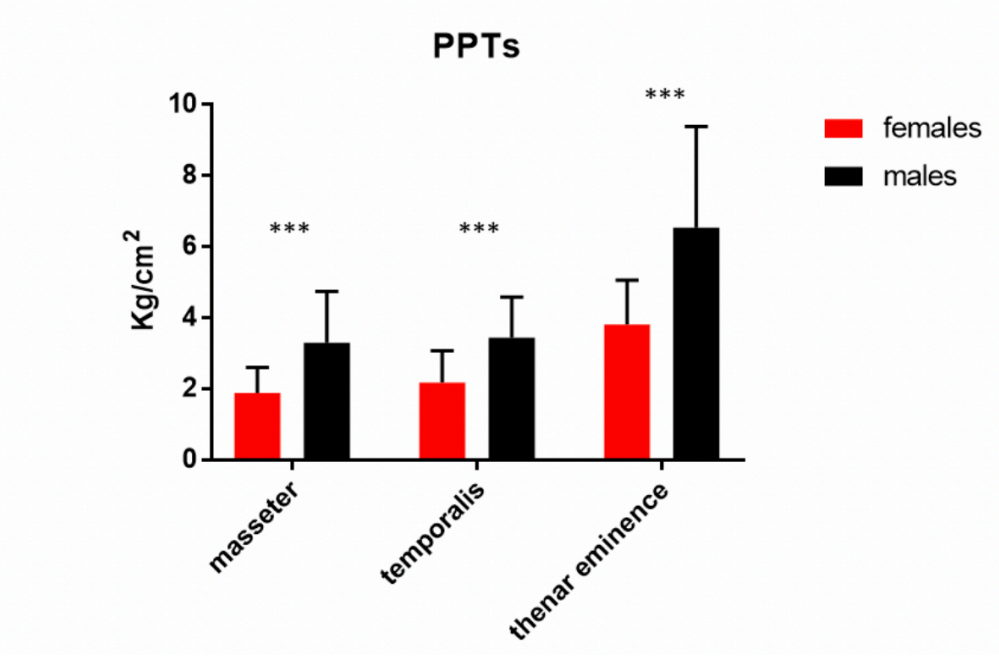


Fig. 14 — Effect of Gender on Mean PPT Results for All Muscle Sites
Mean±SD pressure pain thresholds at both trigeminal and extra trigeminal locations in males and females patients. Significant differences between genders at all muscle locations, at $p<0.001$.

Descriptive Statistics for Masseter, Temporalis and Thenar Muscles PPT			
Muscle Location	Timepoint	Mean	Std. Deviation
Masseter	Baseline	2.11	1.05
	At 4 Weeks	2.21	1.06
Temporalis	Baseline	2.33	1.02
	At 4 Weeks	2.50	1.10
Thenar	Baseline	4.43	2.14
	At 4 Weeks	4.24	1.78

Table 1 — Descriptive Statistics for Masseter, Temporalis and Thenar Muscles PPT
PPT descriptive statistics for masseter, temporalis and thenar muscles (in Kg x cm^2) at baseline and at 4 weeks. No Statistical significance between baseline and at 4 weeks at all muscle locations, at $p>0.05$.

Chapter 5: Discussion

Pain is an unpleasant and emotional experience associated with actual or potential tissue damage.[15] It can be a highly complex and subjective experience[16] and is often a concern among patients undergoing orthodontic treatment.[17–19] The source of orthodontic pain is mainly from the application of tooth movement forces, which results in the release of pro-algesic mediators from free nerve endings.[16, 166] Orthodontic tooth pain is concerning as it can decrease patient compliance and compromise the effectiveness and overall satisfaction of orthodontic treatment.[24] The adaptation to clear aligner therapy (CAT) may differ from that to fixed orthodontic appliances where an increase in parafunctional jaw muscle activity may act as a conditioning stimulus to alleviate the perception of tooth pain, as described by the conditioned pain modulation paradigm.[10, 61, 66] As a consequence, the increase in parafunctional jaw muscle activity could result in jaw muscle tenderness. It is well-known that orthodontic pain can be affected by multiple factors including psychological traits, such as somatosensory amplification, trait anxiety and stress.[121, 124, 125] This study attempted to determine the effect of CAT on orthodontic tooth pain and jaw muscle tenderness during the first few weeks of treatment and whether certain psychological traits and oral parafunctional behaviours have modulating influences.

Orthodontic pain associated with CAT has been investigated in previous studies.[14, 33–35] And in general, when compared to traditional fixed appliances, it has been shown CAT results in less reported tooth pain. Only Shalish's study in 2012,[14] reported higher pain in the CAT compared to the fixed appliances group. However, Shalish did report that the differences in pain levels observed may have been due to a higher mechanical force level being applied early in treatment

for the CAT group. In the present study, the levels of patient reported orthodontic pain are, in general, less than observed in these previous studies but follow the same pattern in terms of trending towards baseline levels after 7 days. Tooth pain only reached a maximum of approximately 16 mm on VAS, which occurred during the first week of treatment with the passive aligners. Interestingly, this maximum reported tooth pain is similar to that reported by White's study[35] in 2017, which is also the only other previous study that utilized Invisalign©'s newest generation multi-layer thermoplastic material, SmartTrack, as was done in the present study. In the previous literature, the older generation EX30 thermoplastic material was used in the Invisalign© groups, and coincidently, these studies reported significantly higher pain scores in the first week of treatment (up to 40 mm on VAS). Limited evidence suggests SmartTrack may be more comfortable than the older generation materials,[56] but further studies are needed to validate this. Studies of buccal fixed appliances and lingual fixed appliances have shown pain VAS scores reach up to 50 mm[33–35] and 60 mm,[14] respectively, substantially higher than those reported with CAT in the present study.

Significant increases in pain from baseline (mean VAS=4 mm) to the first stage passive aligner (mean VAS=11 mm) was evident. When active tooth movements were programmed into the first active aligners, there was a significant decrease in pain (mean VAS=8 mm). This demonstrates that pain was elicited most by the passive aligner and less so by the active aligner. There was also a decrease in pain from the first to second active aligners (mean VAS=6 mm), further demonstrating that active tooth movements did not elicit pain but rather an adaptation to pain occurring within the first few weeks of CAT. Orthodontic pain was reported to be mild and of limited clinical significance according to VAS scores,[121, 167, 168] however, the passive aligner

produced the most pain and discomfort. This could be the result of the fit[12, 32] of the passive aligner, the introduction of iatrogenic posterior occlusal interferences,[79, 174] and the apprehension and stress involved with starting orthodontic treatment with a new appliance.[16, 121, 169] Clear aligners are appliances that cover the occlusal surfaces and crowns of the dentition, and due to the uniform thickness of the plastic they are clinically assumed to have the propensity of introducing iatrogenic posterior occlusal interferences which can lead to tooth pain.[174] It was found in this study that the variation of stress had a significant interaction effect (Appendix 15) with the perception of pain compared to the days within each appliance condition (passive, first active and second active aligners). In other words, pain perception in the passive aligner stage was significantly related to stress and it is very possible that stress contributes to and promotes an adaptation to the first week of CAT. With the findings of the present study, active tooth movements with CAT do not cause substantial tooth pain, and if one modulates the stress of the patient during the first stages, there may even be further reduced pain perception. It has been previously established that experimentally induced orthodontic tooth pain is greater in patients with higher trait anxiety.[121]

Jaw muscle tenderness resulting from clear aligner therapy has been minimally investigated. It has been demonstrated by Brien,[62] that CAT with Invisalign© produces transient symptoms of TMD in the form of muscle tenderness within the first two weeks of treatment and subsides to baseline levels over time. This was not a consistent finding in the present study according to our self-report VAS scores as mild muscle tenderness was reported but did not subside to baseline levels. Rather, it increased during the second week of the experiment with the passive aligners and also the fourth week with the second active aligners. However, the muscle tenderness

reported by patients were mild and likely of limited clinical significance (reaching a maximum of approximately 8 mm on VAS) as no patients developed a diagnosis of TMD during CAT according to their RDC/TMD clinical examinations before and during active treatment. However, because CAT does produce some muscle tenderness, it may not be advisable to be used as a splint in patients who have active TMD. If muscle tenderness is increased, it is possible that clear aligners are promoting parafunctional activities. The largest change in muscle tenderness is evident between baseline and the passive aligner stage (approximately +3 mm on VAS), so there is likely an increase in muscular activities in the first week of CAT. Theoretically, the increase in muscle tenderness in the passive aligner stage may be explained by the conditioned pain modulation paradigm.[66] In this case, CAT elicited transient symptoms of mild myofacial pain and muscle tenderness as a result of repetitive clenching in order to relieve the perception of pain and discomfort from the fit of the passive aligner. This hypothesis requires confirmation by sEMG which will be evaluated with the coincident study whose primary objective is to evaluate the daytime activity of the masticatory muscles by means of sEMG in the same patients.

Advancing to the second active aligner from the first active aligner, also produced a statistically significant increase (approximately +2 mm on VAS) in muscle tenderness. An explanation for this could be the masticatory muscles become fatigued due to an increase in parafunctional behaviours with further active tooth movements or there is an effect of tooth pain on muscle activation. Otherwise, there would not be a difference between the first and second active aligner stages. In the present study, the first few weeks of CAT seem to mostly follow the principles of the conditioned pain modulation paradigm where one noxious stimulus (parafunctional activity) acts

as a conditioning stimulus to relieve the perception of pain from another stimulus (CAT) resulting in an increase in jaw muscle tenderness.

However, an opposing theory of fear avoidance behaviour[170, 171] could be occurring between the passive aligner stage and the first active aligner. The greatest pain perceived by the patients are during this transition, and teeth become sore as a result. It is possible that the increase in clenching initially to reduce the initial perception of pain may be followed by subsequent reduced clenching, otherwise an increase in tooth pain would result. The fear avoidance behaviour in this case would be pain and discomfort caused by the passive aligners producing a peripheral inflammatory condition that stimulates the activity of nociceptive specific neurons in the trigeminal nerve nuclei leading to a feedback avoidance behaviour of the muscle.[172] Perhaps this is the compensatory mechanism of the muscle in the following week with the first active aligner. This is evident by the lower muscle tenderness reported at the first active aligner stage. The decrease in activity of the masticatory muscles in the first active aligner stage will again be confirmed in the sister study that examines the muscle activity via sEMG.

It is possible that the increase in jaw muscle tenderness is the result of an increase in muscle hyperactivity more related to the introduction of occlusal interferences[79, 173] than to orthodontic tooth pain and the conditioned pain modulation paradigm. A number of studies have investigated the potential influence of experimentally induced occlusal interferences on signs and symptoms of TMD and the overall findings indicate that it can increase the risk of developing TMD, but also that the symptoms are transient.[174] Therefore it is possible that CAT creates occlusal interferences leading to hyperactivity of the muscles, which in turn leads to muscle

fatigue and pain. This is not explicitly proven in literature; however, it has been shown that the application of an occlusal interference has different effects in individuals reporting a low or high frequency of oral parafunctions — a minor impact in individuals reporting a low frequency of parafunctions and an aggravation in jaw muscle pain in those who report a high frequency of parafunctions.[79] Further studies are required to determine the effects of occlusal interferences from clear aligners on parafunction and muscle tenderness.

In the present study, as expected, longitudinal muscle tenderness measures had a moderate correlation ($r=0.515$; $p=0.004$) with OBC scores (waking-state oral parafunctional behaviours) (Appendix 13), supporting the hypothesis that muscle tenderness may be modulated by motor activity of the masticatory muscles (OBC) as previously described.[83, 148] Consistent with literature,[82, 121, 126] our correlation studies of the psychological parameters revealed stress and OBC to be correlated (Appendix 14) which justifies the use of stress as the covariate in the statistical mixed effect model. Additionally, stress played a substantial role in the perception of muscle tenderness compared to the days within each appliance condition (Appendix 16). It is very possible that stress contributed to and promotes an adaptation to the first week of CAT.

In regards to the psychophysical measurements of PPT from pressure algometer tests, CAT did not result in a somatosensory change in trigeminal locations in the short-term. This is contrary to what was found in previous studies[175, 176] where inducing a stimulus in the trigeminal area via orthodontic intervention resulted in significant somatosensory changes in trigeminal locations. However, this may just demonstrate jaw muscle tenderness produced by CAT in this study is only mild and of limited clinical significance. Both trigeminal and extra-trigeminal muscle locations

had no differences in PPT from baseline to 4 weeks of CAT. The PPT measurements found in the present study for the masseter, temporalis and thenar muscles were within ranges previously found in TMD-free individuals.[91, 107, 110, 113, 114] A significant effect of gender was found at both trigeminal and extra-trigeminal sites, with females having lower mean PPT scores than males. Gender differences in clinical and experimental pain conditions have been previously described[177] with females generally demonstrate higher pain sensitivity than males via lower tolerance to pressure pain.[178]

Chapter 6: Limitations

The present study does have some limitations. Firstly, the passive aligners may not have been truly passive which can result in the first stage of aligners actually having active tooth movements. Theoretically, passive aligners should not produce any active tooth movements, but this is difficult to prove clinically. It is also possible that iatrogenic occlusal interferences were introduced leading to intrusive forces causing tooth pain. The accuracy of the passive aligner to the actual dental arch is not only dependent on the impression technique and material used, but also the accuracy of the ClinCheck Pro© software and whether it is truly able to program the first set of aligners to be absolutely passive. Additionally, Invisalign©'s CAD/CAM manufacturing (production of stereolithographic models and vacuum-formed thermoplastic aligners) affects the accuracy of the aligner trays as well.

Another limitation was that the passive aligner stage was not allocated in random order with respect to the other aligner stages. To test a more true effect on the outcome measures with the passive aligners, they should have been staged in various timepoints (ie. before first active, between first and second active, and after second active aligners). Nonetheless, this most likely would have been an issue with research ethics because it would cause a delay in active treatment; whereas using the passive trays as the first stage, only delays initiating treatment — which the research ethics board did not consider as problematic.

The next limitation is that patients did not have identical tooth movements in the active aligner stages — it is highly probable some patients had more tooth movements and a greater number of teeth subjected to forces than others. This is because there is heterogeneity in the patient sample

in terms of their malocclusion. Additionally, in clinical practice, malocclusions tend to be less severe for those treated with CAT compared to those treated with fixed appliances. [179, 180] Therefore, it should follow that patients treated with CAT often require a lower magnitude of tooth movements, and as such, are subjected to potentially less tooth pain. It was found in the present study that tooth pain during the first few weeks of CAT was not elicited by active tooth movement, but this may be due to the speculation that the active tooth movements were only minor and simply did not reach the threshold to cause tooth pain.

Another limitation was that compliance with the CAT trays could not be completely verified. All patients were assumed to have worn their aligners full-time (at least 22 hours per day) during the experimental period. All patients were asked to return their passive and first two active aligners along with the rest of the research material after 4 weeks. Although Invisalign© Compliance Markers were incorporated in the trays, it was found that determining compliance with the appliance involved a significant degree of subjectivity. The compliance markers were also prone to separating from the aligners during wear.

A further limitation is that the methodology for PPT determination could be improved, even though the inter-rater reliability between study sites were high. Truer measures could have been obtained if participants were provided with a physical button to signal and freeze the digital pressure reading once the threshold was met. A time lag exists from when the patient signals their physical hand to when the operator of the algometer releases the pressure to obtain a digital reading.

Lastly, the patient sample was limited in number with a strong female predilection. The final limitations are recall bias due to the use of paper-based diaries,[181, 182] and having a small sample size.

Chapter 7: Clinical Significance

Clear aligner therapy (CAT) is associated with mild tooth pain and jaw muscle tenderness as per patient self-reports. However, according to this study, they are low in magnitude and likely only limited in clinical significance. This is in contrast to fixed buccal and lingual orthodontic appliances, which have been shown to produce significantly higher levels of pain.[14, 33-35] Tooth pain and muscle tenderness, if any, during the initial weeks of CAT may mostly be due to the fitting of the aligner and individual psychological stress rather than orthodontic tooth movement. CAT does not result in any significant somatosensory changes in trigeminal and extra-trigeminal locations. From a clinical standpoint, excessive pain during treatment can compromise patient satisfaction and overall treatment compliance and results. The first week of CAT may elicit the highest levels of tooth pain that returns to near baseline levels after 7 days. Jaw muscle tenderness mildly increases and remains at stable levels over the first few weeks of treatment. CAT in patients with active TMD may not be advised as CAT could result in an increase in muscle tenderness likely from an increase in parafunctional activities. Keeping orthodontic forces light aids in making tooth movements predictable and it also favours habituation. Programming and producing an initial passive aligner (instead of an initial active aligner) would likely result in discomfort anyway due to the fit, introduction of occlusal interferences and potential stress involved with starting a new orthodontic appliance.

Stress appears to play a significant role in the perception of pain and contributes to appliance adaptation during the first week of CAT. Another clinical implication is whether initial consultations for orthodontic treatment should include behavioural and psychological assessment questionnaires to identify individuals who may be more susceptible to pain. And perhaps anxiety

management and symptom perception management can be recommended for these individuals. Furthermore, patients should be prepared for encountering pain during orthodontic treatment and have their psychological adaptation strengthened by reinforcing and educating them that pain may be neutralized by diverting their attention from it. OBC (oral parafunctional behaviours) and STAI (state-trait anxiety) questionnaires can be completed chair-side prior to commencing orthodontic treatment, providing a baseline to estimate and predict the magnitude of tooth pain secondary to orthodontic intervention.

Chapter 8: Future Study

The coincident study will evaluate the daytime activity of the masticatory muscles by means of sEMG in patients undergoing CAT with Invisalign©. The same patient sample will be used as sEMG data was collected concurrently with tooth pain and jaw muscle tenderness data. With the addition of sEMG data, it will be possible to test whether the response of masticatory muscles to CAT is dependent and related to perceived orthodontic pain. This will be the first study to investigate the masticatory muscle response to clear aligner therapy.

Chapter 9: Conclusions

1. Clear aligner therapy produces mild tooth pain of limited clinical significance which reaches the highest level with the first stage of passive aligners and decreases with the subsequent active aligners.
2. Jaw muscle tenderness mildly increases with the first stage of passive aligner and varies with the subsequent active aligner stages.
3. Individual psychological stress has a substantial modulating effect in the perception of pain and jaw muscle tenderness, and appears to play a role in the adaptation to the first week of clear aligner therapy.
4. Clear aligner therapy does not produce somatosensory changes in trigeminal and extra-trigeminal muscle locations after the first few weeks of treatment.

References

1. Kesling HD. The philosophy of the tooth positioning appliance. American Journal of Orthodontics and Dentofacial Orthopedics. 1945;31:297-304.
2. Nahoum HI. The vacuum formed dental contour appliance. NY State Dent J. 1964;9:385-390.
3. Ponitz RJ. Invisible retainers. American journal of orthodontics. 1971;59:266-272.
4. Sheridan JJ. Essix retainers: fabrication and supervision for permanent retention. J Clin Orthod. 1993;27:37-45.
5. Wong BH. Invisalign A to Z. American Journal of Orthodontics and Dentofacial Orthopedics. 2002;121:540-541.
6. Tuncay O. The Invisalign system. Digital Planning and Custom Orthodontic Treatment. 200669-79.
7. Kravitz ND, Kusnoto B, BeGole E, Obrez A, Agran B. How well does Invisalign work? A prospective clinical study evaluating the efficacy of tooth movement with Invisalign. Am J Orthod Dentofacial Orthop. 2009;135:27-35.
8. Weir T. Clear aligners in orthodontic treatment. Australian dental journal. 2017;62:58-62.
9. McNamara JA, Kramer KL, Juenker JP. Invisible retainers. Journal of clinical orthodontics: JCO. 1985;19:570.
10. Boyd RL. Esthetic orthodontic treatment using the Invisalign appliance for moderate to complex malocclusions. Journal of dental education. 2008;72:948-967.
11. Miethke R-R, Brauner K. A Comparison of the periodontal health of patients during treatment with the Invisalign system and with fixed lingual appliances. J Orofac Orthop. 2007;68:223-231.
12. Sergl HG, Klages U, Zentner A. Pain and discomfort during orthodontic treatment: causative factors and effects on compliance. American Journal of Orthodontics and Dentofacial Orthopedics. 1998;114:684-691.
13. Miller KB, McGorray SP, Womack R et al. A comparison of treatment impacts between Invisalign aligner and fixed appliance therapy during the first week of treatment. Am J Orthod Dentofacial Orthop. 2007;131:302.e1-9.
14. Shalish M, Cooper-Kazaz R, Ivgi I et al. Adult patients' adjustability to orthodontic appliances. Part I: a comparison between Labial, Lingual, and Invisalign™. Eur J Orthod. 2012;34:724-730.
15. Jeffery MM, Butler M, Stark A, Kane RL. Multidisciplinary pain programs for chronic non-cancer pain. 2011
16. Krishnan V. Orthodontic pain: from causes to management—a review. The European Journal of Orthodontics. 2007;29:170-179.
17. Scheurer PA, Firestone AR, Bürgin WB. Perception of pain as a result of orthodontic treatment with fixed appliances. The European Journal of Orthodontics. 1996;18:349-357.
18. Kvam E, Gjerdet NR, Bondevik O. Traumatic ulcers and pain during orthodontic treatment. Community Dentistry and Oral Epidemiology. 1987;15:104-107.
19. Lew KK. Attitudes and perceptions of adults towards orthodontic treatment in an Asian community. Community dentistry and oral epidemiology. 1993;21:31-35.
20. Oliver RG, Knapman YM. Attitudes to orthodontic treatment. British Journal of Orthodontics. 1985;12:179-188.

21. Asham AA. Readers' forum: orthodontic pain. American journal of orthodontics and dentofacial orthopedics: official publication of the American Association of Orthodontists, its constituent societies, and the American Board of Orthodontics. 2004;125:18A.
22. Keim RG. Managing orthodontic pain. Journal of clinical orthodontics: JCO. 2004;38:641-642.
23. O'Connor PJ. Patients' perceptions before, during, and after orthodontic treatment. Journal of clinical orthodontics: JCO. 2000;34:591.
24. Ukra A, Bennani F, Farella M. Psychological aspects of orthodontics in clinical practice. Part one: treatment-specific variables. Progress in orthodontics. 2011;12:143-148.
25. Cozzani M, Ragazzini G, Delucchi A et al. Self-reported pain after orthodontic treatments: a randomized controlled study on the effects of two follow-up procedures. European journal of orthodontics. 2015;38:266-271.
26. Haynes S. Discontinuation of orthodontic treatment relative to patient age. Journal of dentistry. 1974;2:138-142.
27. Brown DF, Moerenhout RG. The pain experience and psychological adjustment to orthodontic treatment of preadolescents, adolescents, and adults. Am J Orthod Dentofacial Orthop. 1991;100:349-356.
28. Albino JEN, Lawrence SD, Lopes CE, Nash LB, Tedesco LA. Cooperation of adolescents in orthodontic treatment. Journal of behavioral medicine. 1991;14:53-70.
29. Jones M, Chan C. The pain and discomfort experienced during orthodontic treatment: A randomized controlled clinical trial of two initial aligning arch wires. American Journal of Orthodontics and Dentofacial Orthopedics. 1992;102:373-381.
30. Ngan P, Kess B, Wilson S. Perception of discomfort by patients undergoing orthodontic treatment. American Journal of Orthodontics and Dentofacial Orthopedics. 1989;96:47-53.
31. Wilson S, Ngan P, Kess B. Time course of the discomfort in young patients undergoing orthodontic treatment. Pediatr Dent. 1989;11:107-110.
32. Stewart FN, Kerr WJS, Taylor PJS. Appliance wear: the patient's point of view. European Journal of Orthodontics. 1997;19:377-382.
33. Miller KB, McGorray SP, Womack R et al. A comparison of treatment impacts between Invisalign aligner and fixed appliance therapy during the first week of treatment. American Journal of Orthodontics and Dentofacial Orthopedics. 2007;131:302. e1-302. e9.
34. Fujiyama K, Honjo T, Suzuki M, Matsuoka S, Deguchi T. Analysis of pain level in cases treated with Invisalign aligner: comparison with fixed edgewise appliance therapy. Prog Orthod. 2014;15:64.
35. White DW, Julien KC, Jacob H, Campbell PM, Buschang PH. Discomfort associated with Invisalign and traditional brackets: A randomized, prospective trial. The Angle Orthodontist. 2017;87:801-808.
36. Bergius M, Kiliaridis S, Berggren U. Pain in orthodontics. Journal of Orofacial Orthopedics/Fortschritte der Kieferorthopädie. 2000;61:125-137.
37. Krishnan V, Davidovitch Z. Cellular, molecular, and tissue-level reactions to orthodontic force. American Journal of Orthodontics and Dentofacial Orthopedics. 2006;129:469. e1-469. e32.
38. Dray A. Inflammatory mediators of pain. British journal of anaesthesia. 1995;75:125-131.
39. Opree A, Kress M. Involvement of the proinflammatory cytokines tumor necrosis factor-α, IL-1β, and IL-6 but not IL-8 in the development of heat hyperalgesia: effects on heat-

evoked calcitonin gene-related peptide release from rat skin. Journal of Neuroscience. 2000;20:6289-6293.
40. Grieve WG, Johnson GK, Moore RN, Reinhardt RA, DuBois LM. Prostaglandin E (PGE) and interleukin-1β (IL-1β) levels in gingival crevicular fluid during human orthodontic tooth movement. American Journal of Orthodontics and Dentofacial Orthopedics. 1994;105:369-374.
41. Sergl HG, Klages U, Zentner A. Functional and social discomfort during orthodontic treatment-effects on compliance and prediction of patients' adaptation by personality variables. The European Journal of Orthodontics. 2000;22:307-315.
42. Sergl HG, Zentner A. A comparative assessment of acceptance of different types of functional appliances. The European Journal of Orthodontics. 1998;20:517-524.
43. Noll D, Mahon B, Shroff B, Carrico C, Lindauer SJ. Twitter analysis of the orthodontic patient experience with braces vs Invisalign. The Angle Orthodontist. 2016;87:377-383.
44. Graber LW, Vanarsdall RL, Vig KWL, Huang GJ. Orthodontics-E-Book: Current Principles and Techniques. Elsevier Health Sciences; 2016
45. Carp FM, Carp A. The validity, reliability and generalizability of diary data. Experimental Aging Research. 1981;7:281-296.
46. Atchison KA, Dolan TA. Development of the geriatric oral health assessment index. Journal of dental education. 1990;54:680-687.
47. Jokovic A, Locker D, Stephens M, Kenny D, Tompson B, Guyatt G. Validity and reliability of a questionnaire for measuring child oral-health-related quality of life. Journal of dental research. 2002;81:459-463.
48. Locker D. Application of self-reported assessments of oral health outcomes. J dent educ. 1996;60:494-500.
49. Locker D, Jokovic A. Using subjective oral health status indicators to screen for dental care needs in older adults. Community dentistry and oral epidemiology. 1996;24:398-402.
50. O'Brien K, Kay L, Fox D, Mandall N. Assessing oral health outcomes for orthodontics--measuring health status and quality of life. Community dental health. 1998;15:22-26.
51. Cunningham SJ, Hunt NP. Quality of life and its importance in orthodontics. Journal of Orthodontics. 2001
52. Chaushu G, Becker A, Zeltser R, Branski S, Chaushu S. Patients' perceptions of recovery after exposure of impacted teeth with a closed-eruption technique. American journal of orthodontics and dentofacial orthopedics. 2004;125:690-696.
53. Chaushu G, Becker A, Zeltser R, Vasker N, Branski S, Chaushu S. Patients' perceptions of recovery after routine extraction of healthy premolars. American Journal of Orthodontics and Dentofacial Orthopedics. 2007;131:170-175.
54. Chaushu S, Becker A, Zeltser R, Vasker N, Chaushu G. Patients' perceptions of recovery after surgical exposure of impacted maxillary teeth treated with an open-eruption surgical-orthodontic technique. The European Journal of Orthodontics. 2004;26:591-596.
55. Chaushu S, Becker A, Zeltser R, Branski S, Vasker N, Chaushu G. Patients' perception of recovery after exposure of impacted teeth: a comparison of closed-versus open-eruption techniques. Journal of oral and maxillofacial surgery. 2005;63:323-329.
56. Bräscher AK, Zuran D, Feldmann RE, Benrath J. Patient survey on Invisalign®treatment compare the SmartTrack®material to the previous aligner material. J Orofac Orthop. 2016;77:432-438.

57. Lund JP, Donga R, Widmer CG, Stohler CS. The pain-adaptation model: a discussion of the relationship between chronic musculoskeletal pain and motor activity. Canadian journal of physiology and pharmacology. 1991;69:683-694.
58. Goldreich H, et al. The effect of pain from orthodontic arch wire adjustment on masseter muscle electromyographic activity. Am J Orthod Dentofacial Orthop. 1994;106:365-370.
59. Gianelly AA, Goldman HM. Biologic basis of orthodontics. Lea & Febiger; 1971
60. Stohler CS, Ashton-Miller JA, Carlson DS. The effects of pain from the mandibular joint and muscles on masticatory motor behaviour in man. Archives of oral biology. 1988;33:175-182.
61. Schupp W, Haubrich J, Neumann I. Invisalign® treatment of patients with craniomandibular disorders. International orthodontics. 2010;8:253-267.
62. Brien J. Effets du port continu de coquilles correctrices Invisalign® sur l'articulation temporo-mandibulaire et les muscles du complexe facial. 2015
63. Farzanegan F, Zebarjad SM, Alizadeh S, Ahrari F. Pain reduction after initial archwire placement in orthodontic patients: a randomized clinical trial. Am J Orthod Dentofacial Orthop. 2012;141:169-173.
64. Proffit WR, Fields HW, Sarver DM. Contemporary Orthodontics 5th Edition. Elsevier Health Sciences; 2014
65. Otasevic M, Naini FB, Gill DS, Lee RT. Prospective randomized clinical trial comparing the effects of a masticatory bite wafer and avoidance of hard food on pain associated with initial orthodontic tooth movement. Am J Orthod Dentofacial Orthop. 2006;130:6.e9-15.
66. Yarnitsky D. Conditioned pain modulation (the diffuse noxious inhibitory control-like effect): its relevance for acute and chronic pain states. Curr Opin Anaesthesiol. 2010;23:611-615.
67. Nir R-R, Yarnitsky D. Conditioned pain modulation. Curr Opin Support Palliat Care. 2015;9:131-137.
68. Ohrbach R, Markiewicz MR, McCall Jr WD. Waking-state oral parafunctional behaviors: specificity and validity as assessed by electromyography. European journal of oral sciences. 2008;116:438-444.
69. Huang GJ, LeResche L, Critchlow CW, Martin MD, Drangsholt MT. Risk factors for diagnostic subgroups of painful temporomandibular disorders (TMD). Journal of dental research. 2002;81:284-288.
70. Michelotti A, Cioffi I, Festa P, Scala G, Farella M. Oral parafunctions as risk factors for diagnostic TMD subgroups. J Oral Rehabil. 2010;37:157-162.
71. Winocur E, Littner D, Adams I, Gavish A. Oral habits and their association with signs and symptoms of temporomandibular disorders in adolescents: a gender comparison. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics. 2006;102:482-487.
72. Koutris M, Lobbezoo F, Sümer NC, Atis ES, Türker KS, Naeije M. Is myofascial pain in temporomandibular disorder patients a manifestation of delayed-onset muscle soreness. The clinical journal of pain. 2013;29:712-716.
73. Christensen LV. Jaw muscle fatigue and pains induced by experimental tooth clenching: a review. Journal of Oral Rehabilitation. 1981;8:27-36.
74. Ohrbach R, Bair E, Fillingim RB et al. Clinical orofacial characteristics associated with risk of first-onset TMD: the OPPERA prospective cohort study. The Journal of Pain. 2013;14:T33-T50.

75. Glaros AG, Williams K. Tooth contact versus clenching: oral parafunctions and facial pain. Journal of orofacial pain. 2012;26
76. Farella M, Soneda K, Vilmann A, Thomsen CE, Bakke M. Jaw muscle soreness after tooth-clenching depends on force level. Journal of dental research. 2010;89:717-721.
77. Chen C-Y, Palla S, Erni S, Sieber M, Gallo LM. Nonfunctional tooth contact in healthy controls and patients with myogenous facial pain. Journal of orofacial pain. 2007;21
78. Cioffi I, Farella M, Festa P, Martina R, Palla S, Michelotti A. Short-term sensorimotor effects of experimental occlusal interferences on the wake-time masseter muscle activity of females with masticatory muscle pain. J Oral Facial Pain Headache. 2015;29:331-339.
79. Michelotti A, Cioffi I, Landino D, Galeone C, Farella M. Effects of experimental occlusal interferences in individuals reporting different levels of wake-time parafunctions. Journal of orofacial pain. 2012;26:168.
80. Glaros AG, Kim-Weroha N, Lausten L, Franklin KL. Comparison of habit reversal and a behaviorally-modified dental treatment for temporomandibular disorders: a pilot investigation. Applied psychophysiology and biofeedback. 2007;32:149-154.
81. Velly AM, Gornitsky M, Philippe P. Contributing factors to chronic myofascial pain: a case–control study. Pain. 2003;104:491-499.
82. van der Meulen MJ, Lobbezoo F, Aartman IHA, Naeije M. Self-reported oral parafunctions and pain intensity in temporomandibular disorder patients. Journal of orofacial pain. 2006;20
83. Meulen MJ, Lobbezoo F, Aartman IHA, Naeije M. Validity of the Oral Behaviours Checklist: correlations between OBC scores and intensity of facial pain. Journal of oral rehabilitation. 2014;41:115-121.
84. Hirsch C, John MT, Lobbezoo F, Setz JM, Schaller H-G. Incisal tooth wear and self-reported TMD pain in children and adolescents. International Journal of Prosthodontics. 2004;17
85. Schierz O, John MT, Schroeder E, Lobbezoo F. Association between anterior tooth wear and temporomandibular disorder pain in a German population. Journal of Prosthetic Dentistry. 2007;97:305-309.
86. Castroflorio T, Bracco P, Farina D. Surface electromyography in the assessment of jaw elevator muscles. J Oral Rehabil. 2008;35:638-645.
87. Hugger S, Schindler HJ, Kordass B, Hugger A. Clinical relevance of surface EMG of the masticatory muscles.(Part 1): Resting activity, maximal and submaximal voluntary contraction, symmetry of EMG activity. International journal of computerized dentistry. 2011;15:297-314.
88. Gallo LM, Guerra PO, Palla S. Automatic on-line one-channel recognition of masseter activity. Journal of dental research. 1998;77:1539-1546.
89. Takeuchi T, Arima T, Ernberg M, Yamaguchi T, Ohata N, Svensson P. Symptoms and Physiological Responses to Prolonged, Repeated, Low-Level Tooth Clenching in Humans. Headache: The Journal of Head and Face Pain. 2015;55:381-394.
90. Svensson P, Arendt-Nielsen L. Effects of 5 days of repeated submaximal clenching on masticatory muscle pain and tenderness: an experimental study. Journal of orofacial pain. 1996;10
91. Cioffi I, Landino D, Donnarumma V, Castroflorio T, Lobbezoo F, Michelotti A. Frequency of daytime tooth clenching episodes in individuals affected by masticatory muscle pain and pain-free controls during standardized ability tasks. Clin Oral Investig. 2016

92. Fujisawa M, Kanemura K, Tanabe N et al. Determination of daytime clenching events in subjects with and without self-reported clenching. Journal of oral rehabilitation. 2013;40:731-736.
93. Funato M, Ono Y, Baba K, Kudo Y. Evaluation of the non-functional tooth contact in patients with temporomandibular disorders by using newly developed electronic system. Journal of oral rehabilitation. 2014;41:170-176.
94. Michelotti A, Iodice G. The role of orthodontics in temporomandibular disorders. Journal of oral rehabilitation. 2010;37:411-429.
95. De Leeuw R, Klasser GD. Orofacial pain: guidelines for assessment, diagnosis, and management. Am J Orthod Dentofacial Orthop. 2008;134:171.
96. Okeson JP. Evolution of occlusion and temporomandibular disorder in orthodontics: Past, present, and future. American Journal of Orthodontics and Dentofacial Orthopedics. 2015;147:S216-S223.
97. Okeson JP. Management of Temporomandibular Disorders and Occlusion-E-Book. Elsevier Health Sciences; 2014
98. Pollack B. Michigan jury awards+ 850,000 in ortho case: a tempest in a teapot. American journal of orthodontics and dentofacial orthopedics: official publication of the American Association of Orthodontists, its constituent societies, and the American Board of Orthodontics. 1988;94:358-360.
99. Reynders RM. Orthodontics and temporomandibular disorders: a review of the literature (1966–1988). American Journal of Orthodontics and Dentofacial Orthopedics. 1990;97:463-471.
100. McNamara Jr JA, Seligman DA, Okeson JP. Occlusion, orthodontic treatment, and temporomandibular disorders: a review. Journal of orofacial pain. 1995;9:73-91.
101. Manfredini D, Lombardo L, Siciliani G. Temporomandibular disorders and dental occlusion. A systematic review of association studies: end of an era. Journal of oral rehabilitation. 2017
102. Ohrbach R. Disability assessment in temporomandibular disorders and masticatory system rehabilitation. Journal of oral rehabilitation. 2010;37:452-480.
103. Truelove EL, Sommers EE, LeResche L, Dworkin SF, Von Korff M. Clinical Diagnostic Criteria for TMD New Classification Permits Multiple Diagnoses. The Journal of the American Dental Association. 1992;123:47-54.
104. Le Resche L, Burgess J, Dworkin SF. Reliability of visual analog and verbal descriptor scales for" objective" measurement of temporomandibular disorder pain. Journal of dental research. 1988;67:33-36.
105. Davenport JC. Pressure-pain thresholds in the oral cavity in man. Archives of oral biology. 1969;14:1267-IN2.
106. Fischer AA. Pressure algometry over normal muscles. Standard values, validity and reproducibility of pressure threshold. Pain. 1987;30:115-126.
107. Reeves JL, Jaeger B, Graff-Radford SB. Reliability of the pressure algometer as a measure of myofascial trigger point sensitivity. Pain. 1986;24:313-321.
108. Ohrbach R, Gale EN. Pressure pain thresholds in normal muscles: reliability, measurement effects, and topographic differences. Pain. 1989;37:257-263.
109. Jensen K, Andersen HØ, Olesen J, Lindblom U. Pressure-pain threshold in human temporal region. Evaluation of a new pressure algometer. Pain. 1986;25:313-323.

110. Ohrbach R, Gale EN. Pressure pain thresholds, clinical assessment, and differential diagnosis: reliability and validity in patients with myogenic pain. Pain. 1989;39:157-169.
111. List T, Helkimo M, Karlsson R. Influence of pressure rates on the reliability of a pressure threshold meter. Journal of Craniomandibular Disorders. 1991;5
112. McMillan AS, Blasberg B. Pain-pressure threshold in painful jaw muscles following trigger point injection. Journal of orofacial pain. 1994;8
113. Farella M, Michelotti A, Steenks MH, Romeo R, Cimino R, Bosman F. The diagnostic value of pressure algometry in myofascial pain of the jaw muscles. Journal of oral rehabilitation. 2000;27:9-14.
114. Silva RDS, Conti PCR, Lauris JRP, da Silva ROF, Pegoraro LF. Pressure pain threshold in the detection of masticatory myofascial pain: an algometer-based study. Journal of Orofacial Pain. 2005;19
115. Jensen R, Rasmussen BK, Pedersen B, Lous I, Olesen J. Cephalic muscle tenderness and pressure pain threshold in a general population. Pain. 1992;48:197-203.
116. Isselée H, Laat A, Lesaffre E, Lysens R. Short-term reproducibility of pressure pain thresholds in masseter and temporalis muscles of symptom-free subjects. European journal of oral sciences. 1997;105:583-587.
117. Fredriksson L, Alstergren P, Kopp S. Absolute and relative facial pressure-pain thresholds in healthy individuals. Journal of orofacial pain. 2000;14
118. Kim H-S, Chung S-C, Kim Y-K, Lee S-W. Pain-pressure threshold in the head and neck region of episodic tension-type headache patients. Journal of orofacial pain. 1995;9
119. Langemark M, Jensen K, Jensen TS, Olesen J. Pressure pain thresholds and thermal nociceptive thresholds in chronic tension-type headache. Pain. 1989;38:203-210.
120. Osman A, Barrios FX, Gutierrez PM, Kopper BA, Merrifield T, Grittmann L. The Pain Catastrophizing Scale: further psychometric evaluation with adult samples. Journal of behavioral medicine. 2000;23:351-365.
121. Cioffi I, Michelotti A, Perrotta S, Chiodini P, Ohrbach R. Effect of somatosensory amplification and trait anxiety on experimentally induced orthodontic pain. Eur J Oral Sci. 2016;124:127-134.
122. Meana M, Lykins A. Negative affect and somatically focused anxiety in young women reporting pain with intercourse. Journal of Sex Research. 2009;46:80-88.
123. Sturgeon JA, Zautra AJ. Psychological resilience, pain catastrophizing, and positive emotions: perspectives on comprehensive modeling of individual pain adaptation. Current Pain and Headache Reports. 2013;17:317.
124. Beck VJ, Farella M, Chandler NP, Kieser JA, Thomson WM. Factors associated with pain induced by orthodontic separators. Journal of oral rehabilitation. 2014;41:282-288.
125. Baeza-Velasco C, Gély-Nargeot MC, Vilarrasa AB, Bravo JF. Joint hypermobility syndrome: problems that require psychological intervention. Rheumatology international. 2011;31:1131-1136.
126. Khawaja SN, Nickel JC, Iwasaki LR, Crow HC, Gonzalez Y. Association between waking-state oral parafunctional behaviours and bio-psychosocial characteristics. Journal of oral rehabilitation. 2015;42:651-656.
127. Spielberger CD, Gorsuch RL, Lushene RE. Manual for the state-trait anxiety inventory. 1970
128. Barsky AJ, Goodson JD, Lane RS, Cleary PD. The amplification of somatic symptoms. Psychosomatic Medicine. 1988;50:510-519.

129. Barsky AJ, Wyshak G, Klerman GL. The somatosensory amplification scale and its relationship to hypochondriasis. Journal of psychiatric research. 1990;24:323-334.
130. Güleç H, Sayar K. Reliability and validity of the Turkish form of the Somatosensory Amplification Scale. Psychiatry Clin Neurosci. 2007;61:25-30.
131. Köteles F, Simor P. Modern health worries, somatosensory amplification and subjective symptoms: a longitudinal study. International journal of behavioral medicine. 2013;20:38-41.
132. Raphael KG, Marbach JJ, Gallagher RM. Somatosensory amplification and affective inhibition are elevated in myofascial face pain. Pain Medicine. 2000;1:247-253.
133. Aronson KR, Barrett LF, Quigley KS. Feeling your body or feeling badly: evidence for the limited validity of the Somatosensory Amplification Scale as an index of somatic sensitivity. Journal of psychosomatic research. 2001;51:387-394.
134. Duddu V, Isaac MK, Chaturvedi SK. Somatization, somatosensory amplification, attribution styles and illness behaviour: a review. International Review of Psychiatry. 2006;18:25-33.
135. Mantar A, Yemez B, Alkin T. The validity and reliability of the Turkish version of the anxiety sensitivity index-3. Turk Psikiyatri Dergisi. 2010;21:1.
136. Sullivan MJL, Thorn B, Haythornthwaite JA et al. Theoretical perspectives on the relation between catastrophizing and pain. The Clinical journal of pain. 2001;17:52-64.
137. Chaves JF, Brown JM. Spontaneous cognitive strategies for the control of clinical pain and stress. Journal of behavioral medicine. 1987;10:263-276.
138. Flor H, Turk DC. Chronic back pain and rheumatoid arthritis: predicting pain and disability from cognitive variables. Journal of behavioral medicine. 1988;11:251-265.
139. Heyneman NE, Fremouw WJ, Gano D, Kirkland F, Heiden L. Individual differences and the effectiveness of different coping strategies for pain. Cognitive Therapy and Research. 1990;14:63-77.
140. Jacobsen PB, Butler RW. Relation of cognitive coping and catastrophizing to acute pain and analgesic use following breast cancer surgery. Journal of behavioral medicine. 1996;19:17-29.
141. Turk DC, Rudy TE. Assessment of cognitive factors in chronic pain: a worthwhile enterprise. Journal of consulting and Clinical Psychology. 1986;54:760.
142. Turk DC, Rudy TE. Cognitive factors and persistent pain: A glimpse into Pandora's box. Cognitive Therapy and Research. 1992;16:99-122.
143. Sullivan MJL, Bishop SR, Pivik J. The pain catastrophizing scale: development and validation. Psychological assessment. 1995;7:524.
144. Katon WJ. Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. Biological psychiatry. 2003;54:216-226.
145. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry. 1961;4:561-571.
146. Wang Y-P, Gorenstein C. Assessment of depression in medical patients: a systematic review of the utility of the Beck Depression Inventory-II. Clinics. 2013;68:1274-1287.
147. Beck AT, Steer RA, Brown GK. Beck depression inventory-II. San Antonio. 1996;78:490-498.
148. Markiewicz MR, Ohrbach R, McCall Jr WD. Oral behaviors checklist: reliability of performance in targeted waking-state behaviors. Journal of orofacial pain. 2006;20

149. Donnarumma V, Cioffi I, Michelotti A, Cimino R, Vollaro S, Amato M. Analysis of the reliability of the Italian version of the Oral Behaviours Checklist and the relationship between oral behaviours and trait anxiety in healthy individuals. Journal of oral rehabilitation. 2018;45:317-322.
150. Kaplan SEF, Ohrbach R. Self-Report of Waking-State Oral Parafunctional Behaviors in the Natural Environment. Journal of Oral & Facial Pain & Headache. 2016;30
151. Cioffi I, Piccolo A, Tagliaferri R, Paduano S, Galeotti A, Martina R. Pain perception following first orthodontic archwire placement-Thermoelastic vs superelastic alloys: A randomized controlled trial. Quintessence international. 2012;43
152. Bergius M, Broberg AG, Hakeberg M, Berggren U. Prediction of prolonged pain experiences during orthodontic treatment. American Journal of Orthodontics and Dentofacial Orthopedics. 2008;133:339. e1-339. e8.
153. Glaros AG. Temporomandibular disorders and facial pain: a psychophysiological perspective. Applied psychophysiology and biofeedback. 2008;33:161.
154. Schiffman E, Ohrbach R, Truelove E et al. Diagnostic criteria for temporomandibular disorders (DC/TMD) for clinical and research applications: recommendations of the International RDC/TMD Consortium Network and Orofacial Pain Special Interest Group. Journal of oral & facial pain and headache. 2014;28:6.
155. Gonzalez YM, Schiffman E, Gordon SM et al. Development of a brief and effective temporomandibular disorder pain screening questionnaire: reliability and validity. The Journal of the American Dental Association. 2011;142:1183-1191.
156. Barsky AJ, Goodson JOHND, Lane RICHARDS, Cleary PD. The amplification of somatic symptoms. Psychosomatic medicine. 1988;50:510-519.
157. Technology A. Align Technology Receives U.S. Patents for SmartTrack(R) Invisalign(R) Aligner Material. 2017
158. Technology A. Align Technology Announces January 21st Availability of SmartTrack(R) Invisalign(R) Aligner Material. 2013
159. Castroflorio T, Farina D, Bottin A, Piancino MG, Bracco P, Merletti R. Surface EMG of jaw elevator muscles: effect of electrode location and inter-electrode distance. Journal of Oral Rehabilitation. 2005;32:411-417.
160. Castroflorio T, Icardi K, Becchino B et al. Reproducibility of surface EMG variables in isometric sub-maximal contractions of jaw elevator muscles. Journal of Electromyography and Kinesiology. 2006;16:498-505.
161. Castroflorio T, Icardi K, Torsello F, Deregibus A, Debernardi C, Bracco P. Reproducibility of surface EMG in the human masseter and anterior temporalis muscle areas. CRANIO®. 2005;23:130-137.
162. Zhang N, Bai Y, Ding X, Zhang Y. Preparation and characterization of thermoplastic materials for invisible orthodontics. Dental materials journal. 2011;30:954-959.
163. Michelotti A, Farella M, Gallo LM, Veltri A, Palla S, Martina R. Effect of occlusal interference on habitual activity of human masseter. Journal of dental research. 2005;84:644-648.
164. Ruau D, Liu LY, Clark JD, Angst MS, Butte AJ. Sex differences in reported pain across 11,000 patients captured in electronic medical records. The Journal of Pain. 2012;13:228-234.
165. Tighe PJ, Riley III JL, Fillingim RB. Sex differences in the incidence of severe pain events following surgery: a review of 333,000 pain scores. Pain Medicine. 2014;15:1390-1404.

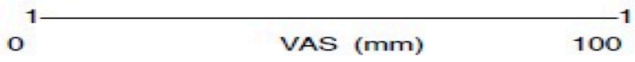
166. Giannopoulou C, Dudic A, Kiliaridis S. Pain discomfort and crevicular fluid changes induced by orthodontic elastic separators in children. The Journal of Pain. 2006;7:367-376.
167. Kelly AM. The minimum clinically significant difference in visual analogue scale pain score does not differ with severity of pain. Emergency Medicine Journal. 2001;18:205-207.
168. Mark MSM, Au TTS, Choi YF, Wong TW. The minimum clinically significant difference in visual analogue scale pain score in a local emergency setting. Hong Kong Journal of Emergency Medicine. 2009;16:233-236.
169. Aljabaa A, McDonald F, Newton JT. A systematic review of randomized controlled trials of interventions to improve adherence among orthodontic patients aged 12 to 18. The Angle Orthodontist. 2014;85:305-313.
170. Asmundson GJG, Taylor S. Role of anxiety sensitivity in pain-related fear and avoidance. Journal of behavioral medicine. 1996;19:577-586.
171. Waddell G, Newton M, Henderson I, Somerville D, Main CJ. A Fear-Avoidance Beliefs Questionnaire (FABQ) and the role of fear-avoidance beliefs in chronic low back pain and disability. Pain. 1993;52:157-168.
172. Sessle BJ, Greenwood LF. Inputs to trigeminal brain stem neurones from facial, oral, tooth pulp and pharyngolaryngeal tissues: I. Responses to innocuous and noxious stimuli. Brain research. 1976;117:211-226.
173. Kirveskari P, Jämsä T. Health risk from occlusal interferences in females. The European Journal of Orthodontics. 2009;31:490-495.
174. Clark GT, Tsukiyama Y, Baba K, Watanabe T. Sixty-eight years of experimental occlusal interference studies: what have we learned. The Journal of prosthetic dentistry. 1999;82:704-713.
175. editors. Somatosensory changes in orthodontics—findings from quantitative sensory testing (QST) studies. Seminars in Orthodontics; 2018; Elsevier; 2018.
176. Shen H, Shao S, Zhang J et al. Fixed orthodontic appliances cause pain and disturbance in somatosensory function. European journal of oral sciences. 2016;124:26-32.
177. Jang K, Kim Y. Comparison of oral sensory function in complete denture and implant-supported prosthesis wearers. Journal of oral rehabilitation. 2001;28:220-225.
178. Racine M, Tousignant-Laflamme Y, Kloda LA, Dion D, Dupuis G, Choinière M. A systematic literature review of 10 years of research on sex/gender and experimental pain perception–Part 1: Are there really differences between women and men. Pain. 2012;153:602-618.
179. AH Ali SA, Miethke HR. Invisalign®, an innovative invisible orthodontic appliance to correct malocclusions: advantages and limitations. Dental update. 2012;39:254-260.
180. Phan X, Ling PH. Clinical limitations of Invisalign. Journal of the Canadian Dental Association. 2007;73
181. Karimi Z, Pilenko A, Held SM, Hasenbring MI. Recall bias in patients with chronic low back pain: Individual pain response patterns are more important than pain itself. International journal of behavioral medicine. 2016;23:12-20.
182. Stone AA, Shiffman S, Schwartz JE, Broderick JE, Hufford MR. Patient non-compliance with paper diaries. Bmj. 2002;324:1193-1194.

Appendices

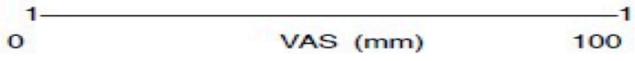
Appendix 1 — Patient Custom-Made Diary (Single Day Example)

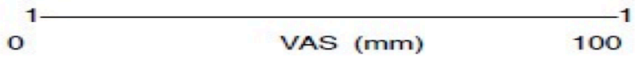
DAY 8 of 28 (May 31th, 2018) ALIGNERS #1
EMG RECORDING DAY #4

TOOTH PAIN (How severe is your tooth pain today? Place a vertical mark on the line below to indicate how bad you feel your tooth pain is today)

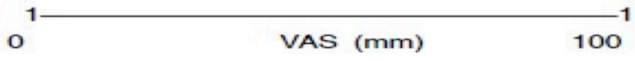
08.00


12.00

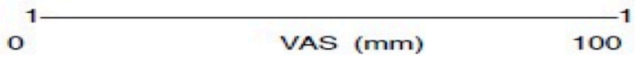

16.00


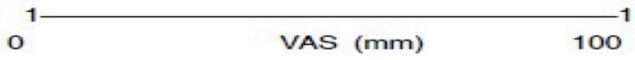
22.00


OCCLUSAL DISCOMFORT (How severe is your occlusal discomfort today? Place a vertical mark on the line below to indicate how bad you feel your occlusal discomfort is today)

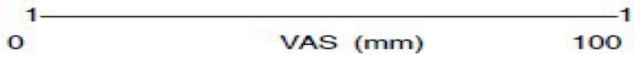
08.00


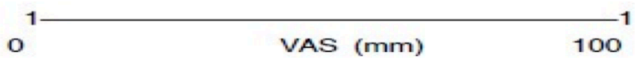
12.00

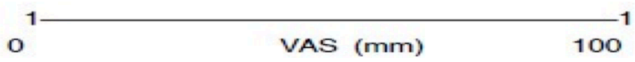

16.00


22.00


JAW MUSCLE TENDERNESS (Do you feel that your jaw muscles are tense today? Place a vertical mark on the line below to indicate how bad you feel your jaw muscle tenderness is today)

08.00


12.00


16.00


22.00


PERCEIVED STRESS (How severe was your perceived stress today? Place a vertical mark on the line below to indicate how bad you feel your perceived stress is today)

NOTES (Please note events, such as time of day when analgesic was consumed, touching of electrode, chewing, exercising, etc.)

Appendix 2 — Patient Summary Calendar for 4-Week Experimental Period

MAY/JUNE 2018 — Outline of Recording for ID# 9792

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
				MAY 24 *(First day of Recording; no aligners)* EMG DAY #1 no aligners PAIN DIARY	**25** *(no aligners)* PAIN DIARY	**26** *(no aligners)* EMG DAY #2 PAIN DIARY
27 *(no aligners)* PAIN DIARY	**28** *(no aligners)* EMG DAY #3 PAIN DIARY	**29** *(no aligners)* PAIN DIARY	**30** *(no aligners)* PAIN DIARY	**31** *(aligners #1)* EMG DAY #4 PAIN DIARY	**JUNE 1** *(aligners #1)* PAIN DIARY	**2** *(aligners #1)* EMG DAY #5 PAIN DIARY
3 *(aligners #1)* PAIN DIARY	**4** *(aligners #1)* EMG DAY #6 PAIN DIARY	**5** *(aligners #1)* PAIN DIARY	**6** *(aligners #1)* PAIN DIARY	**7** *(aligners #2)* EMG DAY #7 PAIN DIARY	**8** *(aligners #2)* PAIN DIARY	**9** *(aligners #2)* EMG DAY #8 PAIN DIARY
10 *(aligners #2)* PAIN DIARY	**11** *(aligners #2)* *EMG DAY #9* PAIN DIARY	**12** *(aligners #2)* PAIN DIARY	**13** *(aligners #2)* PAIN DIARY	**14** *(aligners #3)* EMG DAY #10 PAIN DIARY	**15** *(aligners #3)* PAIN DIARY	**16** *(aligners #3)* EMG DAY #11 PAIN DIARY
17 *(aligners #3)* PAIN DIARY	**18** *(aligners #3)* EMG DAY #12 PAIN DIARY	**19** *(aligners #3)* PAIN DIARY	**20** *(aligners #3)* PAIN DIARY Last day of recording			

Appendix 3 — Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) Examination Form

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 **FDI #11** O **FDI #21** 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				LEFT SIDE			
		Pain	Familiar Pain	Familiar Headache		Pain	Familiar Pain	Familiar Headache
B. Maximum Unassisted Opening	Temporalis	(N) (Y)	(N) (Y)	(N) (Y)	Temporalis	(N) (Y)	(N) (Y)	(N) (Y)
	Masseter	(N) (Y)	(N) (Y)		Masseter	(N) (Y)	(N) (Y)	
	TMJ	(N) (Y)	(N) (Y)		TMJ	(N) (Y)	(N) (Y)	
	Other M Musc	(N) (Y)	(N) (Y)		Other M Musc	(N) (Y)	(N) (Y)	
	Non-mast	(N) (Y)	(N) (Y)		Non-mast	(N) (Y)	(N) (Y)	
C. Maximum Assisted Opening	Temporalis	(N) (Y)	(N) (Y)	(N) (Y)	Temporalis	(N) (Y)	(N) (Y)	(N) (Y)
	Masseter	(N) (Y)	(N) (Y)		Masseter	(N) (Y)	(N) (Y)	
	TMJ	(N) (Y)	(N) (Y)		TMJ	(N) (Y)	(N) (Y)	
	Other M Musc	(N) (Y)	(N) (Y)		Other M Musc	(N) (Y)	(N) (Y)	
	Non-mast	(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				LEFT SIDE			
		Pain	Familiar Pain	Familiar Headache		Pain	Familiar Pain	Familiar Headache
A. Right Lateral	Temporalis	(N) (Y)	(N) (Y)	(N) (Y)	Temporalis	(N) (Y)	(N) (Y)	(N) (Y)
	Masseter	(N) (Y)	(N) (Y)		Masseter	(N) (Y)	(N) (Y)	
	TMJ	(N) (Y)	(N) (Y)		TMJ	(N) (Y)	(N) (Y)	
	Other M Musc	(N) (Y)	(N) (Y)		Other M Musc	(N) (Y)	(N) (Y)	
	Non-mast	(N) (Y)	(N) (Y)		Non-mast	(N) (Y)	(N) (Y)	
B. Left Lateral	Temporalis	(N) (Y)	(N) (Y)	(N) (Y)	Temporalis	(N) (Y)	(N) (Y)	(N) (Y)
	Masseter	(N) (Y)	(N) (Y)		Masseter	(N) (Y)	(N) (Y)	
	TMJ	(N) (Y)	(N) (Y)		TMJ	(N) (Y)	(N) (Y)	
	Other M Musc	(N) (Y)	(N) (Y)		Other M Musc	(N) (Y)	(N) (Y)	
	Non-mast	(N) (Y)	(N) (Y)		Non-mast	(N) (Y)	(N) (Y)	
C. Protrusion	Temporalis	(N) (Y)	(N) (Y)	(N) (Y)	Temporalis	(N) (Y)	(N) (Y)	(N) (Y)
	Masseter	(N) (Y)	(N) (Y)		Masseter	(N) (Y)	(N) (Y)	
	TMJ	(N) (Y)	(N) (Y)		TMJ	(N) (Y)	(N) (Y)	
	Other M Musc	(N) (Y)	(N) (Y)		Other M Musc	(N) (Y)	(N) (Y)	
	Non-mast	(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

Appendix 4 — Questionnaire: Diagnostic Criteria for Temporomandibular Disorders: Demographics and TMD-Pain Screener

1. What is your current marital status?
   - ☐ Married
   - ☐ Living as married
   - ☐ Divorced
   - ☐ Separated
   - ☐ Widowed
   - ☐ Never married

2. What is your ethnicity*?
   - ☐ Canadian
   - ☐ French
   - ☐ English
   - ☐ German
   - ☐ Scottish
   - ☐ Irish
   - ☐ Italian
   - ☐ Ukrainian
   - ☐ Dutch (Netherlands)
   - ☐ Chinese
   - ☐ Jewish
   - ☐ Polish
   - ☐ Portuguese
   - ☐ South Asian (e.g., East Indian, Pakistani, Sri Lankan, etc.)
   - ☐ Norwegian
   - ☐ Welsh
   - ☐ Swedish
   - ☐ First Nations (North American Indian)
   - ☐ Métis
   - ☐ Inuit
   - ☐ Other - Specify

3. What is your race? Mark all that apply*.
   - ☐ Aboriginal/First Nations
   - ☐ White
   - ☐ South Asian (e.g., East Indian, Pakistani, Sri Lankan, etc.)
   - ☐ Chinese
   - ☐ Black
   - ☐ Filipino
   - ☐ Latin American
   - ☐ Arab
   - ☐ Southeast Asian (e.g., Vietnamese, Cambodian, Malaysian, Laotian, etc.)
   - ☐ West Asian (e.g., Iranian, Afghan, etc.)

☐ Korean
☐ Japanese
☐ Other

4. What is the highest grade or level of schooling that you have completed?*
   ☐ Less than high school diploma or its equivalent
   ☐ High school diploma or a high school equivalency certificate
   ☐ College, CEGEP or other non-university certificate or diploma
   ☐ University certificate or diploma below the bachelor's level
   ☐ Bachelor's degree (e.g., B.A., B.Sc.)
   ☐ University certificate, diploma, degree above the bachelor's level

5. What is your family's current annual household income? Please include all sources of income for all family members such as wages, salaries, investments, etc*.
   ☐ No income
   ☐ $15,000-$29,999
   ☐ $30,000-$49,999
   ☐ $50,000-$79,999
   ☐ $80,000 -$99,999
   ☐ $100,000 -$119,999
   ☐ $120,000 or more

6. Do you have any neurologic or metabolic disorders?
   ☐ Yes
   ☐ No
   ☐ Maybe/Unsure

7. Do you habitually use any of the following analgesics*?
   ☐ NSAIDs (i.e., Advil, Motrin, Nuprin, Aleve, Naprosyn, Celebrex)
   ☐ Acetaminophen (i.e., Tylenol, Paracetamol)
   ☐ Opioids (i.e., codeine, fentanyl, hydrocodone, methadone)
   ☐ Anti-epileptics (i.e., Clonazepam, Gabapentin, Lamotrigine, Phenytoin)

8. Do you have fibromyalgia or recurrent headaches?
   ☐ Yes
   ☐ No
   ☐ Maybe/Unsure

9. Do you have any of the following pre-existing orofacial pain?
   ☐ Dental
   ☐ Periodontal
   ☐ Joint/TMJ
   ☐ Muscle/Myofascial
   ☐ None

10. Do you have any of the following pre-existing pain elsewhere in the body?
    ☐ Head
    ☐ Neck
    ☐ Shoulder
    ☐ Back
    ☐ Chest

- ☐ Thorax
- ☐ Abdomen
- ☐ Umbilicus
- ☐ Upper Limb
  - ☐ Arm
  - ☐ Elbow
  - ☐ Forearm
  - ☐ Wrist
  - ☐ Hand
  - ☐ Fingers
- ☐ Pelvic
- ☐ Lower Limb
  - ☐ Thigh
  - ☐ Knee
  - ☐ Leg
  - ☐ Calf
  - ☐ Ankle
  - ☐ Foot
  - ☐ Toes
- ☐ Elsewhere
- ☐ None

---

11. Did you have braces?*
    - ☐ No
    - ☐ Yes
    - ☐ I have braces now
    - ☐ I will have them soon

---

12. Do you have a removable or fixed dental prosthesis (bridge with at least three teeth)?*
    - ☐ No
    - ☐ Yes

TMD-PAIN SCREENER

1. In the last 30 days, how long did any pain last in your jaw or temple area on either side?
   a. No pain
   b. Pain comes and goes
   c. Pain is always present

2. In the last 30 days, have you had pain or stiffness in your jaw on awakening?
   a. No
   b. Yes

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

   A. Chewing hard or tough food
      a. No
      b. Yes

   B. Opening your mouth or moving your jaw forward or to the side
      a. No
      b. Yes

   C. Jaw habits such as holding teeth together, clenching, grinding, or chewing gum
      a. No
      b. Yes

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

Appendix 5 — Questionnaire: State-Trait Anxiety Inventory (STAI)

DIRECTIONS:

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you feel *right* now, that is, *at this moment*. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	NOT AT ALL	SOMEWHAT	MODERATELY SO	VERY MUCH SO
1. I feel calm	1	2	3	4
2. I feel secure	1	2	3	4
3. I am tense	1	2	3	4
4. I feel strained	1	2	3	4
5. I feel at ease	1	2	3	4
6. I feel upset	1	2	3	4
7. I am presently worrying over possible misfortunes	1	2	3	4
8. I feel satisfied	1	2	3	4
9. I feel frightened	1	2	3	4
10. I feel comfortable	1	2	3	4
11. I feel self-confident	1	2	3	4
12. I feel nervous	1	2	3	4
13. I am jittery	1	2	3	4
14. I feel indecisive	1	2	3	4
15. I am relaxed	1	2	3	4
16. I feel content	1	2	3	4
17. I am worried	1	2	3	4
18. I feel confused	1	2	3	4
19. I feel steady	1	2	3	4
20. I feel pleasant	1	2	3	4

DIRECTIONS

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you *generally* feel. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe how you generally feel.

	ALMOST NEVER	SOMETIMES	OFTEN	ALMOST ALWAYS
21. I feel pleasant	1	2	3	4
22. I feel nervous and restless	1	2	3	4
23. I feel satisfied with myself	1	2	3	4
24. I wish I could be as happy as others seem to be	1	2	3	4
25. I feel like a failure	1	2	3	4
26. I feel rested	1	2	3	4
27. I am "calm, cool, and collected"	1	2	3	4
28. I feel that difficulties are piling up so that I cannot overcome them	1	2	3	4
29. I worry too much over something that really doesn't matter	1	2	3	4
30. I am happy	1	2	3	4
31. I have disturbing thoughts	1	2	3	4
32. I lack self-confidence	1	2	3	4
33. I feel secure	1	2	3	4
34. I make decisions easily	1	2	3	4
35. I feel inadequate	1	2	3	4
36. I am content	1	2	3	4
37. Some unimportant thought runs through my mind and bothers me	1	2	3	4
38. I take disappointments so keenly that I can't put them out of my mind	1	2	3	4
39. I am a steady person	1	2	3	4
40. I get in a state of tension or turmoil as I think over my recent concerns and interests	1	2	3	4

STAIP-AD Test Form Y
www.mindgarden.com

Appendix 6 — Questionnaire: Oral Behaviour Checklist (OBC)

How often do you do each of the following activities, based on **the last month**? If the frequency of the activity varies, choose the higher option. Please place a (√) response for each item and do not skip any items.

	Activities During Sleep	None of the time	< 1 Night /Month	1-3 Nights /Month	1-3 Nights /Week	4-7 Nights/ Week
1	Clench or grind teeth **when asleep**, based on any information you may have	☐	☐	☐	☐	☐
2	Sleep in a position that puts pressure on the jaw (for example, on stomach, on the side)	☐	☐	☐	☐	☐
	Activities During Waking Hours	**None of the time**	**A little of the time**	**Some of the time**	**Most of the time**	**All of the time**
3	Grind teeth together **during waking hours**	☐	☐	☐	☐	☐
4	Clench teeth together **during waking hours**	☐	☐	☐	☐	☐
5	Press, touch, or hold teeth together other than while eating (that is, contact between upper and lower teeth)	☐	☐	☐	☐	☐
6	Hold, tighten, or tense muscles without clenching or bringing teeth together	☐	☐	☐	☐	☐
7	Hold or jut jaw forward or to the side	☐	☐	☐	☐	☐
8	Press tongue forcibly against teeth	☐	☐	☐	☐	☐
9	Place tongue between teeth	☐	☐	☐	☐	☐
10	Bite, chew, or play with your tongue, cheeks or lips	☐	☐	☐	☐	☐
11	Hold jaw in rigid or tense position, such as to brace or protect the jaw	☐	☐	☐	☐	☐
12	Hold between the teeth or bite objects such as hair, pipe, pencil, pens, fingers, fingernails, etc	☐	☐	☐	☐	☐
13	Use chewing gum	☐	☐	☐	☐	☐
14	Play musical instrument that involves use of mouth or jaw (for example, woodwind, brass, string instruments)	☐	☐	☐	☐	☐
15	Lean with your hand on the jaw, such as cupping or resting the chin in the hand	☐	☐	☐	☐	☐
16	Chew food on one side only	☐	☐	☐	☐	☐
17	Eating between meals (that is, food that requires chewing)	☐	☐	☐	☐	☐
18	Sustained talking (for example, teaching, sales, customer service)	☐	☐	☐	☐	☐
19	Singing	☐	☐	☐	☐	☐
20	Yawning	☐	☐	☐	☐	☐
21	Hold telephone between your head and shoulders	☐	☐	☐	☐	☐

Appendix 7 — Somatosensory Amplification Scale (SSAS)

Somatosensory Amplification Scale.(SSAS)					
	Not at all	A little	Moderately	Quite a bit	Extremely
Sudden loud noises really bother me	0	1	2	3	4
I hate to be too hot or too cold	0	1	2	3	4
I have a low tolerance for pain	0	1	2	3	4
I am often aware of various things happening within my body	0	1	2	3	4
Sudden loud noises really bother me	0	1	2	3	4
I am a quick to sense the hunger contractions in my stomach	0	1	2	3	4
When someone else coughs,it makes me cough too	0	1	2	3	4
I can't stand smoke,smog,or pollutants in the air	0	1	2	3	4
I can sometimes hear my pulse or my heartbeat throbbing in my ear	0	1	2	3	4
Even something minor,like an insect bite or a splinter,really bothers me	0	1	2	3	4
When I bruise myself,it stays noticeable for a long time	0	1	2	3	4

Appendix 8 — Pain Catastrophizing Scale (PCS)

	Not at all	To a slight degree	To a moderate degree	To a great degree	All the time
I worry all the time about whether the pain will end	0	1	2	3	4
I feel I can't go on	0	1	2	3	4
It's terrible and I think it's never going to get any better	0	1	2	3	4
It's awful and I feel that it overwhelms me	0	1	2	3	4
I feel I can't stand it anymore	0	1	2	3	4
I become afraid that the pain will get worse	0	1	2	3	4
I keep thinking of other painful events	0	1	2	3	4
I anxiously want the pain to go away	0	1	2	3	4
I can't seem to keep it out of my mind	0	1	2	3	4
I keep thinking about how much it hurts	0	1	2	3	4
I keep thinking about how badly I want the pain to stop	0	1	2	3	4
There's nothing I can do to reduce the intensity of the pain	0	1	2	3	4
I wonder whether something serious may happen	0	1	2	3	4

Appendix 9 — Becks Depression Inventory (BDI)

1.
- 0 I do not feel sad.
- 1 I feel sad
- 2 I am sad all the time and I can't snap out of it.
- 3 I am so sad and unhappy that I can't stand it.

2.
- 0 I am not particularly discouraged about the future.
- 1 I feel discouraged about the future.
- 2 I feel I have nothing to look forward to.
- 3 I feel the future is hopeless and that things cannot improve.

3.
- 0 I do not feel like a failure.
- 1 I feel I have failed more than the average person.
- 2 As I look back on my life, all I can see is a lot of failures.
- 3 I feel I am a complete failure as a person.

4.
- 0 I get as much satisfaction out of things as I used to.
- 1 I don't enjoy things the way I used to.
- 2 I don't get real satisfaction out of anything anymore.
- 3 I am dissatisfied or bored with everything.

5.
- 0 I don't feel particularly guilty
- 1 I feel guilty a good part of the time.
- 2 I feel quite guilty most of the time.
- 3 I feel guilty all of the time.

6.
- 0 I don't feel I am being punished.
- 1 I feel I may be punished.
- 2 I expect to be punished.
- 3 I feel I am being punished.

7.
- 0 I don't feel disappointed in myself.
- 1 I am disappointed in myself.
- 2 I am disgusted with myself.
- 3 I hate myself.

8.
- 0 I don't feel I am any worse than anybody else.
- 1 I am critical of myself for my weaknesses or mistakes.
- 2 I blame myself all the time for my faults.
- 3 I blame myself for everything bad that happens.

9.
- 0 I don't have any thoughts of killing myself.
- 1 I have thoughts of killing myself, but I would not carry them out.
- 2 I would like to kill myself.
- 3 I would kill myself if I had the chance.

10.
- 0 I don't cry any more than usual.
- 1 I cry more now than I used to.
- 2 I cry all the time now.
- 3 I used to be able to cry, but now I can't cry even though I want to.

11.

0 I am no more irritated by things than I ever was.
1 I am slightly more irritated now than usual.
2 I am quite annoyed or irritated a good deal of the time.
3 I feel irritated all the time.

12.

0 I have not lost interest in other people.
1 I am less interested in other people than I used to be.
2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.

13.

0 I make decisions about as well as I ever could.
1 I put off making decisions more than I used to.
2 I have greater difficulty in making decisions more than I used to.
3 I can't make decisions at all anymore.

14.

0 I don't feel that I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel there are permanent changes in my appearance that make me look unattractive
3 I believe that I look ugly.

15.

0 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

16.

0 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.

17.

0 I don't get more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

18.

0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.

19.

0 I haven't lost much weight, if any, lately.
1 I have lost more than five pounds.
2 I have lost more than ten pounds.
3 I have lost more than fifteen pounds.

20.

0 I am no more worried about my health than usual.
1 I am worried about physical problems like aches, pains, upset stomach, or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think of anything else.

21.

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I have almost no interest in sex.
3 I have lost interest in sex completely.

Appendix 10 — Letter of Information and Consent for Research Study

Effect of Invisalign on the habitual and parafunctional activities of the masticatory muscles

Letter of Information & Consent

Principle Investigator

Dr. Ali Tassi
Assistant Professor, Division of Graduate Orthodontics
Schulich School of Medicine and Dentistry
University of Western Ontario
University Hospital — Department of Dentistry

Co-Investigator

Dr. Johnny Tran
Masters Student, Division of Graduate Orthodontics
Schulich School of Medicine and Dentistry
University of Western Ontario

Version Date: 27/05/2017

Introduction

You are being invited to consider participating in a study directed by Dr. Ali Tassi along with his resident, Dr. Johnny Tran. More than 80% of patients report dental and/or muscular pain during orthodontic treatment. Recent research suggests that patients subjected to orthodontic treatment with Invisalign® also experience mild to moderate discomfort. But recent reports suggest that low-level clenching may inhibit pain sensitivity and that clenching may contribute to alleviate tooth pain during orthodontic treatment. The aim of the study is to assess how the jaw muscles adapt to Invisalign® orthodontic treatment and whether or not it is related to any symptoms of pain and discomfort.

Why is this study being done?

The purpose of the study is to evaluate the activity of masticatory muscles (chewing muscles) and dental and muscular discomfort symptoms while subjected to orthodontic treatment with Invisalign®. The possible relationship between individual orthodontic pain symptoms and the activity of the jaw muscles will also be investigated.

What will happen during this study?

You have been asked to participate because you are an adult orthodontic patient undergoing Invisalign® without previous orofacial pain nor the usage of any related medications. This research will be involving only those who choose to take part. This patient information and consent form describes the study so you can make an informed decision on participating. Please take time to decide and if necessary, discuss this proposal with your family members and friends, as you feel inclined. Please feel free to ask questions if anything is unclear or there are words or phrases you do not understand.

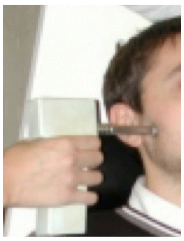
This study will take place over approximately 4 weeks. If you agree to participate, you will be asked to:

- Undergo a dental visit and answer some questionnaires
- Perform a pain-sensitivity testing before and after study (pressure pain thresholds)
- Record your perceived orthodontic pain in a provided diary for 3 weeks during the orthodontic treatment
- Wear an electronic muscle activity monitor on your right cheek for 4 hours per day, for a total of 12 days over a 4-week time interval

Dental Visit and Questionnaires

We will assess the function of your masticatory (chewing) muscles by palpation, and evaluate your oral hygiene status and your occlusion (bite). This will require approximately 5 minutes of your time. If we find a condition (for examples caries) that needs treatment, we will refer you to your dentist or to the local dental clinic. You will be asked to answer some questionnaires about your state of calm/anxiety/stress/fear and the habitual activity of your masticatory muscles. We need to investigate on these factors because they may affect our measurements.

Measurement of Pressure Pain Thresholds



This test will measure your pressure pain threshold. We will press your cheeks and temples with a special instrument called an algometer, which is similar to the rubber tip of an eraser-end of a pencil. Pressure will be placed with said instrument onto the surface of your cheek and temple. This will continue until the point in time where you indicate and decide that the pressure sensation has changed into a discomforting sensation. The instrument will be withdrawn immediately. We will do three tests for each cheek (masseter), temple (temporalis) and hand. This test will require approximately 20 minutes.

The pain-sensitivity testing will be done by Dr. Tran/Dr. Tassi at the graduate orthodontic clinic at three time points for your muscles of mastication:

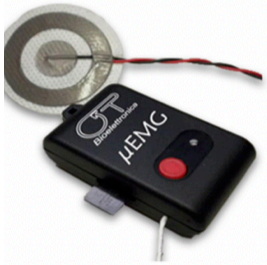
- Before your orthodontic treatment
- Right after the end of the study
- 4 months after the end of the study

Pain diary

We will give you a pain diary. You will be asked to score your perceived pain/discomfort and stress 4 times per day over 4 weeks. The orthodontic pain-diary completed by yourself at your own home or any location. It will require 4 daily entries at the following time intervals:

- 08.00
- 12.00
- 16.00
- 22.00 (before going to sleep)

Monitoring the activity of your muscles



We will ask you to wear a portable battery-powered surface electromyography (EMG) device to assess the behaviour of your masticatory (chewing) muscles while you wear your orthodontic appliance. A plastic electrode will be placed onto your cheek with a connected wire to the EMG recording device that can be tucked underneath your shirt on your collarbone. A second one may be placed on your collarbone, if necessary. You will attach these electrode(s) by yourself and the one for your cheek will be placed on a mark the size of a pin head that will be made by the student researcher with a washable marker. This mark will closely approximate where on the cheek has the largest muscle bulge when you are clenching your teeth together. To reproduce this position when the mark has washed off, you will attach the electrode to your cheek where the bulge of muscle is largest when you are clenching. You will not experience any electrical shocks and/or discomfort during this test. You will be asked to record the activity of our muscles over 12 days, 4 hours each day in the afternoon or evening while awake. It is possible that after the procedure your cheek will present the impression of the electrode. This will disappear few minutes after the procedures. Allergies are rare from the electrode. If you have facial hair in the area of the electrode placement, we will ask you to shave prior to placing the electrodes. The size of the electrode is approximately the size of a loonie. We will also advise that you do not eat, sleep or exercise while wearing the EMG device. We would prefer you to stay home while recording the activity of your muscles. You could use the device while you are studying or working, but only if your job does not require physical exercise. You will be asked to perform twelve 4-hour recording sessions over a 4-week period as follows:

- Week 1: Prior to receiving any Invisalign® aligners (3 recordings, day 1-3 -5)
- Week 2: First week of passive fitting Invisalign® aligners (3 recordings, day 1-3 -5)
- Week 3: Second week of active fitting Invisalign® aligners (3 recordings, day 1-3 -5)
- Week 4: Third week of active fitting Invisalign® aligners (3 recordings, day 1-3 -5)

The first week of passive fitting Invisalign® aligners will be the first set of clear aligner trays. Although they do not have any active forces to move your teeth, their purpose is to get you accustomed to wearing the appliance. If there are any issues or concerns during this week, it is important to inform your treating resident to address these problems prior to advancing to the active tooth movement aligner trays. This is a normal standard of care for patients undergoing clear aligner orthodontic therapy.

How many people will take part in this study?

A sample of adult (> 18 years of age) individuals submitted to orthodontic therapy with Invisalign® will be invited to participate in the research study. Eligible patients will be selected from 3 different teaching facilities: University of Western Ontario, University of Toronto and University of Turin, Italy. There will be potentially a maximum of 18 individuals participating in this study in London, Ontario. In total, there are potentially 30-40 individuals who may participate in this research study from all three study locations.

What are the risks and burdens for participants of the study?

Your participation in this study will require a significant taking of your time. The muscle activity monitoring method is done via a surface electromyography device. This device is totally harmless. You will not experience any electrical shocks and/or discomfort during this test. It is possible that after the procedure your cheek will present the impression of the electrode. This will disappear few minutes after the procedures. You will be asked to wear the device 12 hours per week for 4 weeks. You will also be asked to record your perceived orthodontic pain in a provided diary for 3 weeks during the orthodontic treatment. Your pain sensitivity will also be evaluated during your initial visit and two additional visits using a pain pressure measuring device (pressure algometer). During these pressure tests, you will experience a short intermittent feeling of discomfort. During the initial visit, you will also be asked fill out questionnaires. Information about all aspect of this study will be provided to you, including the functionalities of all your aligner trays, devices used and questionnaires. You will not be deceived in any aspect of this study.
If you would like to contact one of the research team members or have any questions please feel free to contact the principle researcher at University of Western Ontario site, Dr. Ali Tassi or the co-investigator Dr. Johnny Tran.

Are there benefits to taking part in the study?

Participants of this study will not benefit from study participation. However, the information we collect will help us better understand how Invisalign® treatment affects the activity of the masticatory muscles and potentially how pain symptoms are related to the activity of the muscles. We would like to kindly invite you to take part in this study. You may refuse to participate or withdraw at any moment without any repercussions.

What are the costs to participants?

If you agree to participate in this study, upon successful completion (at the end of the data collection), we will compensate by offering a $50 mall gift card per week and up to a maximum of $250.00 in total for your participation in the study. This compensation to participants are for expenses related to parking for appointments and time given to the study. The Invisalign® aligner trays are at the cost of the participant

(included in the fixed fee for comprehensive orthodontic treatment at the Graduate Orthodontic Clinic of at Western Ontario).

Your compensation for this research will be managed as follows:

1) week 1 – 50 dollar mall gift card
2) week 1 + week 2 – 100 dollar mall gift card
3) week a + week 2+ week 3 — 150 dollar mall gift card
4) week 1+ week 2 + week 3 + week 4 — 200 dollar mall gift card
5) week 1+ week 2 + week 3 + week 4 + assessment of pressure pain thresholds after 4 months — 250 dollar mall gift card

How will your information be kept confidential?

We are committed to protecting your personal information and your privacy will be respected and kept confidential. If results of this study are published, your name will not be used and no other information that discloses your identity will be released. To allow for delivery of monitoring devices, follow-up appointments and follow-up phone calls, we will have your name and phone number indicated on a participant master list. This master list will be stored and kept safe in a locked filing cabinet. To monitor the conduct of research, the research team, authorized study personnel, and the Western University Health Science Research Ethics Board may require access to your study-related records. Additionally, representatives of the Research Ethics Board may follow up with you directly for the same purpose. By signing the consent form you allow us to review the diary you complete during the study. This consent form will be stored in a locked filing cabinet and any data will be stored on a security encrypted password protected USB data drive. Data will be shared and transferred with The University of Toronto to be combined with other study sites. Data transferred will contain only a unique study ID (not your name or any other identifying information). Study data will be kept for 5 years, and at the end of this time your data will be disposed.

Can you choose to leave the study?

Eligible participants will have full autonomy whether or not they wish to participate in the proposed study. If you decide to withdraw from the study, you have the right to request withdrawal of information and data collected.

What are my rights as a research participant?

If you are harmed as a direct result of taking part in this study, all necessary medical treatment will be made available to you at no cost. You do not waive any legal right by signing this consent form. If you have any questions about your rights as a research participant or the conduct of this study, you may contact The Office of Research Ethics

Who can I call if I have questions about the study?

We hope you will be interested in helping with this study. If you would like more information or have any questions during the study, or wish to withdraw from the study at any time, you may contact Dr. Ali Tassi at or Dr. Johnny Tran

Thank you for your time!

This study has been explained to me and any questions I had have been answered to my satisfaction. I know that I may leave the study at any time. I agree to take part in this study.

I have read and understand the consent form for this study. I am voluntarily agreeing to participate in this study. I will be provided with a copy of this consent form for my own information, if I wish.

By signing below, I am agreeing to participate in this study.

Name: _____

Date: _____

Signature: _____

Consent obtained by:

Name: _____

Date: _____

Signature: _____

Appendix 11 — Western University Health Science Research Ethics Board Approval

Western Research

Research Ethics

Western University Health Science Research Ethics Board
HSREB Delegated Initial Approval Notice

Principal Investigator: Dr. Ali Tassi
Department & Institution: Schulich School of Medicine and Dentistry\Schulich School of Medicine & Dentistry,Western University

Review Type: Delegated
HSREB File Number: 109148
Study Title: Effect of Invisalign on the habitual and parafunctional activities of the masticatory muscles

HSREB Initial Approval Date: June 01, 2017
HSREB Expiry Date: June 01, 2018

Documents Approved and/or Received for Information:

Document Name	Comments	Version Date
Instruments	Questionnaires - Received 4/18/2017	
Letter of Information & Consent	V3	2017/05/30
Western University Protocol	V2	2017/05/25
Other	Reference List	2017/05/25

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above named study, as of the HSREB Initial Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Appendix 12 — Correlations of Tooth Pain Measures to Psychological Traits

Summary of Pearson correlations for longitudinal tooth pain measures to various psychological covariates (STAI, OBC, PCS, SSAS and BDI). Significance was found with state-anxiety, trait-anxiety (both $p<0.01$) and with somatosensory amplification ($p<0.05$)

Correlations of: Tooth Pain and State-Anxiety

		Tooth Pain	State-Anxiety
Tooth Pain	Pearson Correlation	1	**0.466****
	Significance (1-tailed)		0.009
	N	26	25
State-Anxiety	Pearson Correlation	**0.466****	1
	Significance (1-tailed)	0.009	
	N	25	25

** Correlation is significant at the 0.01 level (1-tailed)

Correlations of: Tooth Pain and Oral Behaviour Checklist

		Tooth Pain	OBC
Tooth Pain	Pearson Correlation	1	0.006
	Significance (1-tailed)		0.489
	N	26	25
OBC	Pearson Correlation	0.006	1
	Significance (1-tailed)	0.489	
	N	25	25

Correlations of: Tooth Pain and Trait-Anxiety

		Tooth Pain	Trait-Anxiety
Tooth Pain	Pearson Correlation	1	**0.473****
	Significance (1-tailed)		0.008
	N	26	25
Trait-Anxiety	Pearson Correlation	**0.473****	1
	Significance (1-tailed)	0.008	
	N	25	25

** Correlation is significant at the 0.01 level (1-tailed)

Correlations of: Tooth Pain and Pain Catastrophizing

		Tooth Pain	PCS
Tooth Pain	Pearson Correlation	1	0.047
	Significance (1-tailed)		0.412
	N	26	25
PCS	Pearson Correlation	0.047	1
	Significance (1-tailed)	0.412	
	N	25	25

Correlations of: Tooth Pain and Somatosensory Amplification

		Tooth Pain	SSAS
Tooth Pain	Pearson Correlation	1	**-0.348****
	Significance (1-tailed)		0.044
	N	26	25
SSAS	Pearson Correlation	**-0.348****	1
	Significance (1-tailed)	0.044	
	N	25	25

* Correlation is significant at the 0.05 level (1-tailed)

Correlations of: Tooth Pain and Becks Depression

		Tooth Pain	BDI
Tooth Pain	Pearson Correlation	1	-0.247
	Significance (1-tailed)		0.098
	N	26	24
BDI	Pearson Correlation	-0.247	1
	Significance (1-tailed)	0.098	
	N	24	24

Appendix 13 — Correlations of Muscle Tenderness Measures to Psychological Traits

Summary of Pearson correlations for longitudinal jaw muscle tenderness measures to various psychological covariates (STAI, OBC, PCS, SSAS and BDI). Significance was found with state-anxiety ($p<0.05$) and with oral behaviour checklist ($p<0.01$)

Correlations of: Muscle Tenderness and State-Anxiety

		Muscle Tenderness	State-Anxiety
Muscle Tenderness	Pearson Correlation	1	**0.343***
	Significance (1-tailed)		0.047
	N	26	25
State-Anxiety	Pearson Correlation	**0.343***	1
	Significance (1-tailed)	0.047	
	N	25	25

* Correlation is significant at the 0.05 level (1-tailed)

Correlations of: Muscle Tenderness and Oral Behaviour Checklist

		Muscle Tenderness	OBC
Muscle Tenderness	Pearson Correlation	1	**0.515****
	Significance (1-tailed)		0.004
	N	26	25
OBC	Pearson Correlation	**0.515****	1
	Significance (1-tailed)	0.004	
	N	25	25

** Correlation is significant at the 0.01 level (1-tailed)

Correlations of: Muscle Tenderness and Trait-Anxiety

		Muscle Tenderness	Trait-Anxiety
Muscle Tenderness	Pearson Correlation	1	0.268
	Significance (1-tailed)		0.098
	N	26	25
Trait-Anxiety	Pearson Correlation	0.268	1
	Significance (1-tailed)	0.098	
	N	25	25

Correlations of: Muscle Tenderness and Pain Catastrophizing

		Muscle Tenderness	PCS
Muscle Tenderness	Pearson Correlation	1	-0.056
	Significance (1-tailed)		0.395
	N	26	25
PCS	Pearson Correlation	-0.056	1
	Significance (1-tailed)	0.395	
	N	25	25

Correlations of: Muscle Tenderness and Somatosensory Amplification

		Muscle Tenderness	SSAS
Muscle Tenderness	Pearson Correlation	1	0.023
	Significance (1-tailed)		0.456
	N	26	25
SSAS	Pearson Correlation	0.023	1
	Significance (1-tailed)	0.456	
	N	25	25

Correlations of: Muscle Tenderness and Becks Depression

		Muscle Tenderness	BDI
Muscle Tenderness	Pearson Correlation	1	-0.175
	Significance (1-tailed)		0.207
	N	26	24
BDI	Pearson Correlation	-0.175	1
	Significance (1-tailed)	0.207	
	N	24	24

Appendix 14 — Correlations of Daily Stress Measures to Psychological Traits

Summary of Pearson correlations for daily stress measures to various psychological covariates (STAI, OBC, PCS and SSAS). Significance was found with OBC ($p<0.05$).

Correlations of: Daily Stress and State-Anxiety

		Daily Stress	State-Anxiety
Daily Stress	Pearson Correlation	1	0.213
	Significance (1-tailed)		0.153
	N	26	25
State-Anxiety	Pearson Correlation	0.213	1
	Significance (1-tailed)	0.153	
	N	25	25

Correlations of: Daily Stress and Oral Behaviour Checklist

		Daily Stress	OBC
Daily Stress	Pearson Correlation	1	**0.393***
	Significance (1-tailed)		0.026
	N	26	25
OBC	Pearson Correlation	**0.393**	1
	Significance (1-tailed)	0.026	
	N	25	25

* Correlation is significant at the 0.05 level (1-tailed)

Correlations of: Daily Stress and Trait-Anxiety

		Daily Stress	Trait-Anxiety
Daily Stress	Pearson Correlation	1	0.201
	Significance (1-tailed)		0.167
	N	26	25
Trait-Anxiety	Pearson Correlation	0.201	1
	Significance (1-tailed)	0.167	
	N	25	25

Correlations of: Daily Stress and Pain Catastrophizing

		Daily Stress	PCS
Daily Stress	Pearson Correlation	1	0.230
	Significance (1-tailed)		0.134
	N	26	25
PCS	Pearson Correlation	0.230	1
	Significance (1-tailed)	0.134	
	N	25	25

Correlations of: Daily Stress and Somatosensory Amplification

		Daily Stress	SSAS
Tooth Pain	Pearson Correlation	1	0.238
	Significance (1-tailed)		0.125
	N	26	25
State-Anxiety	Pearson Correlation	0.238	1
	Significance (1-tailed)	0.125	
	N	25	25

Appendix 15 — Mixed Effect Model: Tooth Pain

Summary of mixed effect model for orthodontic tooth pain outcome measure. All fixed effects , covariate of stress, and interactions significant at p<0.001.

Mixed Effect Model: Tooth Pain		
	F-value	P-value
Sex	19.176	**<0.001**
Day	4.872	**<0.001**
Condition	68.293	**<0.001**
Stress	210.945	**<0.001**
Day*Stress	10.576	**<0.001**
Day*Condition	2.982	**<0.001**

Appendix 16 — Mixed Effect Model: Muscle Tenderness

Summary of mixed effect model for jaw muscle tenderness outcome measure. Significance found for variation across the days (p<0.05), condition of aligners, stress and interactions (p<0.001)

Mixed Effect Model: Muscle Tenderness		
	F-value	P-value
Sex	0.833	0.361
Day	2.403	**0.026**
Condition	16.772	**<0.001**
Stress	380.471	**<0.001**
Day*Stress	23.877	**<0.001**
Day*Condition	2.914	**<0.001**

Appendix 17 — PPT Results from ANCOVA for Masseter Muscle

PPT results from the general linear model (ANCOVA) for the masseter muscle. The intervention of CAT did not affect PPT at the master after 4 weeks. Significant effect of gender on PPTs of masseter muscle($p<0.001$).

PPT Results from ANCOVA for Masseter Muscle		
	F-value	P-value
Sex	19.178	**<0.001**
Timepoint	0.222	0.639
Sex*Timepoint	0.120	0.731

Appendix 18 — PPT Results from ANCOVA for Temporalis Muscle

PPT results from the general linear model (ANCOVA) for the temporalis muscle. The intervention of CAT did not affect PPT at the master after 4 weeks. Significant effect of gender on PPTs of temporalis muscle ($p<0.001$).

PPT Results from ANCOVA for Temporalis Muscle		
	F-value	P-value
Sex	14.068	**<0.001**
Timepoint	0.725	0.399
Sex*Timepoint	0.300	0.586

Appendix 19 — PPT Results from ANCOVA for Thenar Muscle

PPT results from the general linear model (ANCOVA) for the thenar muscle. The intervention of CAT did not affect PPT at the master after 4 weeks. Significant effect of gender on PPTs of thenar muscle ($p<0.001$).

PPT Results from ANCOVA for Thenar Muscle		
	F-value	P-value
Sex	14.068	**<0.001**
Timepoint	0.725	0.399
Sex*Timepoint	0.3	0.586

Appendix 20 — Copyright Clearance for use of Figures/Illustrations

LICENSE #: 4506150801818 **Order Date:** 01/11/2019 View printable order	Current Opinion in Supportive and Palliative Care **Title:** Conditioned pain modulation **Type of use:** Dissertation/Thesis	**Fee:** 0.00 USD
LICENSE #: 4506150362630 **Order Date:** 01/11/2019 View printable order	Publication1 **Title:** Canadian journal of physiology and pharmacology **Type of use:** Thesis/Dissertation	**Fee:** 0.00 USD
LICENSE #: 4506140457342 **Order Date:** 01/11/2019 View printable order	The European Journal of Orthodontics **Title:** Adult patients' adjustability to orthodontic appliances. Part I: a comparison between Labial, Lingual, and Invisalign™ **Type of use:** Thesis/Dissertation	**Fee:** 0.00 USD
LICENSE #: 4506140309459 **Order Date:** 01/11/2019 View printable order	American Journal of Orthodontics and Dentofacial Orthopedics **Title:** A comparison of treatment impacts between Invisalign aligner and fixed appliance therapy during the first week of treatment **Type of use:** reuse in a thesis/dissertation	**Fee:** 0.00 CAD

License Number	4506150362630
License date	Jan 11, 2019
Licensed content publisher	Canadian Science Publishing
Licensed content title	Canadian journal of physiology and pharmacology
Licensed content date	Jan 1, 1964
Type of Use	Thesis/Dissertation
Requestor type	Academic institution
Format	Print, Electronic
Portion	chart/graph/table/figure
Number of charts/graphs/tables/figures	1
The requesting person/organization is:	Dr. Johnny Tran (Thesis author)
Title or numeric reference of the portion(s)	Fig. 4
Title of the article or chapter the portion is from	The pain-adaptation model: a discussion of the relationship between chronic musculoskeletal pain and motor activity.
Editor of portion(s)	N/A
Author of portion(s)	Donga, R ; Lund, J P
Volume of serial or monograph.	69
Issue, if republishing an article from a serial	5
Page range of the portion	690
Publication date of portion	May 1, 1991
Rights for	Main product
Duration of use	Life of current edition
Creation of copies for the disabled	no
With minor editing privileges	no
For distribution to	Canada
In the following language(s)	Original language of publication
With incidental promotional use	no
The lifetime unit quantity of new product	Up to 499
Title	Effect of Clear Aligner Therapy on Orthodontic Pain and Masticatory Muscle Tenderness
Institution name	n/a
Expected presentation date	Jan 2019
Billing Type	Invoice
Billing Address	

Total (may include CCC user fee)	0.00 USD

License Number	4506140457342
License date	Jan 11, 2019
Licensed content publisher	Oxford University Press
Licensed content publication	The European Journal of Orthodontics
Licensed content title	Adult patients' adjustability to orthodontic appliances. Part I: a comparison between Labial, Lingual, and Invisalign™
Licensed content author	Shalish, Miri; Cooper-Kazaz, Rena
Licensed content date	Jul 12, 2011
Type of Use	Thesis/Dissertation
Institution name	
Title of your work	Effect of Clear Aligner Therapy on Orthodontic Pain and Masticatory Muscle Tenderness
Publisher of your work	n/a
Expected publication date	Jan 2019
Permissions cost	0.00 USD
Value added tax	0.00 USD
Total	0.00 USD
Title	Effect of Clear Aligner Therapy on Orthodontic Pain and Masticatory Muscle Tenderness
Institution name	n/a
Expected presentation date	Jan 2019
Portions	Fig. 2
Requestor Location	

Publisher Tax ID	GB125506730
Billing Type	Invoice
Billing Address	

Total	0.00 USD

License Number	4506140309459
License date	Jan 11, 2019
Licensed Content Publisher	Elsevier
Licensed Content Publication	American Journal of Orthodontics and Dentofacial Orthopedics
Licensed Content Title	A comparison of treatment impacts between Invisalign aligner and fixed appliance therapy during the first week of treatment
Licensed Content Author	Kevin B. Miller,Susan P. McGorray,Randy Womack,Juan Carlos Quintero,Mark Perelmuter,Jerome Gibson,Teresa A. Dolan,Timothy T. Wheeler
Licensed Content Date	Mar 1, 2007
Licensed Content Volume	131
Licensed Content Issue	3
Licensed Content Pages	9
Start Page	302.e1
End Page	302.e9
Type of Use	reuse in a thesis/dissertation
Portion	figures/tables/illustrations
Number of figures/tables/illustrations	1
Format	both print and electronic
Are you the author of this Elsevier article?	No
Will you be translating?	No
Original figure numbers	Fig. 2B and Fig. 2C
Title of your thesis/dissertation	Effect of Clear Aligner Therapy on Orthodontic Pain and Masticatory Muscle Tenderness
Expected completion date	Jan 2019
Estimated size (number of pages)	100
Requestor Location	

Publisher Tax ID	GB 494 6272 12
Total	0.00 CAD

License Number	4506150801818
License date	Jan 11, 2019
Licensed Content Publisher	Wolters Kluwer Health, Inc.
Licensed Content Publication	Current Opinion in Supportive and Palliative Care
Licensed Content Title	Conditioned pain modulation
Licensed Content Author	Rony-Reuven Nir and David Yarnitsky
Licensed Content Date	Jun 1, 2015
Licensed Content Volume	9
Licensed Content Issue	2
Type of Use	Dissertation/Thesis
Requestor type	Individual
STM publisher name	
Portion	Figures/table/illustration
Number of figures/tables/illustrations	1
Figures/tables/illustrations used	Fig. 1
Author of this Wolters Kluwer article	No
Title of your thesis / dissertation	Effect of Clear Aligner Therapy on Orthodontic Pain and Masticatory Muscle Tenderness
Expected completion date	Jan 2019
Estimated size(pages)	100
Requestor Location	

Billing Type	Invoice
Billing Address	

Total	0.00 USD

Compliance With Ethical Standards

Conflict of Interest

Dr. Johnny Tran declares he has no conflict of interest in regards this research study. Both Drs. Ali Tassi and Iacopo Cioffi declare as well having no conflict of interest.

Funding

This research study was supported by Align Technology through an orthodontic research funding grant award.

Ethical Approval

All procedures of this research study performed on human participants were approved and in accordance with the ethical standards of Western University Health Science Research Ethics Board (HSREB Delegated Board) (see Appendix 11).

Informed Consent

Patient informed consent to participate in the research study was obtained verbally and written via the "Letter of Information and Consent" package (Appendix 10). Each patient was asked to sign the consent acknowledging the receipt of the information package and willingness to participate in the study.

Curriculum Vita

Name	Johnny Tran	
Place of Birth	Regina, Saskatchewan, Canada	
Post-secondary Education	University of Regina Regina, Saskatchewan, Canada Bachelor of Science	2007-2010
	University of Saskatchewan Saskatoon, Saskatchewan, Canada Doctor of Dental Medicine	2010-2014
	University of Western Ontario London, Ontario, Canada Master of Clinical Dentistry	2016-2019
Related Work Experience	General Practice Residency Mount Sinai Hospital, University of Toronto Toronto, Ontario, Canada	2014-2015
	General Dentist Private Practice Vernon, British Columbia, Canada	2015-2016