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Influence of a diagnosis of depression and/or anxiety on temporomandibular joint treatment, a retrospective study

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RESUMO

Introdução: As Disfunções Temporomandibulares (DTM) incluem patologias multifatoriais do sistema estomatognático. A saúde mental tem influência na sua patogénese. Diferentes subtipos de DTM têm protocolos de tratamento específicos. Coloca-se a hipótese de que a depressão e/ ou ansiedade contribuam para piores resultados clínicos no tratamento e para a necessidade de reintervenção.

Métodos: Realizou-se um estudo retrospetivo no Instituto Português da Face, Portugal, de Fevereiro de 2018 a Fevereiro de 2022, incluindo doentes submetidos a tratamento da DTM. Analisaram-se as seguintes variáveis: 1) dor articular temporomandibular (VAS); 2) impacto da DTM na qualidade de vida (VASLife); 3) abertura máxima oral (MMO); 4) grau de mialgia. O rastreio para depressão e/ ou ansiedade realizou-se pelos questionários validados *PHQ-2* e *GAD-2*. Para a análise dos dados recorreu-se ao SPSS e GraphPad Prism.

Resultados: Foram incluídos 247 doentes (202 sexo feminino), idade média 40,51 ± 17,04. 222 doentes (89,9%) apresentaram diagnóstico de mialgia; 155 doentes (37,2%) de artralgia e 144 doentes (38,2%) deslocamento do disco com dor. Os rastreios de ansiedade e depressão foram positivos em 133 (53,8%, GAD-2 ≥3) e em 91 pacientes (38,4%, *PHQ-2* ≥ 2), respetivamente. Um maior *burden* psicológico correlacionou-se significativamente com o VASLife pré-tratamento (p=0.040, PHQ-2 ≥ 2; p=0.025, GAD-2 ≥3) e com os níveis de mialgia (p=0.013, PHQ-2 ≥ 2; p=0.038, GAD-2 ≥3). Em pacientes com ansiedade, a mialgia persistiu significativamente pós-tratamento (p=0.038, GAD-2 ≥3). As restantes variáveis clínicas não foram significativas. O VASLife pré-tratamento (OR=1,67; p=0,008) e, em pacientes ansiosos, o grau de mialgia pós-tratamento (OR=1,89; p<0,001) foram fatores determinantes para reintervenção.

Conclusão: Depressão e/ ou ansiedade correlacionaram-se com piores resultados clínicos após tratamento das DTM, particularmente de origem muscular. Doentes com maior impacto de doença e sintomas refratários requerem abordagens multidisciplinares individualizadas. Estudos mais representativos, com estratégias sequenciais de rastreio deverão incentivar-se para confirmar estes resultados.

Palavras-chave: disfunção temporomandibular; depressão; ansiedade; GAD-2; PHQ-2

ABSTRACT

Background: Temporomandibular disorders (TMD) comprise multifactorial conditions of the stomatognathic system. Mental health plays an important role in TMD pathogenesis. TMD subtypes have specific treatment protocols. The authors hypothesize that depression and/ or anxiety are associated with poorer clinical outcomes and may contribute to the need for reintervention.

Methods: A retrospective study was conducted at Instituto Português da Face, Portugal, including patients treated for TMD from February 2018 to February 2022. The following variables were assessed: 1) Temporomandibular joint pain (VAS); 2) Health-related quality of life (VASLife); 3) Maximal Mouth Opening (MMO); 4) Myalgia degree. Screening for depression and/ or anxiety was assessed through *PHQ-2* and *GAD-2* validated questionnaires. Data analyses were obtained using SPSS and GraphPad Prism.

Results: 247 patients (202 female), mean age 40.51 ± 17.04, were enrolled. Myalgia was present in 222 patients (89.9%), arthralgia in 155 patients (37.2%), and painful disc displacement disorder in 144 patients (38.2%). 133 patients (53.8%, GAD-2 ≥3) screened positive for anxiety, and 91 patients (38.4%, PHQ-2 ≥ 2) for depression. A higher psychological distress burden was significantly correlated with pre-treatment VASLife (p=0.040, PHQ-2 ≥ 2; p=0.025, GAD-2 ≥3) and myalgia levels (p=0.013, PHQ-2 ≥ 2; p=0.038, GAD-2 ≥3). Myalgia significantly subsisted after treatment in patients with anxiety (p=0.038, GAD-2 ≥3). No significance was found for other variables. The pre-treatment VAS Life (OR=1.67; p=0.008) and, in patients screening positive for anxiety, post-treatment myalgia degree (OR=1.89; p<0.001) were determinant factors for reintervention.

Conclusion: Preexistent depression and/ or anxiety correlated to lower clinical outcomes, particularly in myogenous TMD. Patients reporting a higher disease burden and refractory symptoms require multidisciplinary and personalized treatment programs. Future broader studies with sequential screening methodologies are strongly recommended to confirm our results.

Keywords: temporomandibular disorders; depression; anxiety; GAD-2; PHQ-2

SUMMARY

LIST OF ABBREVIATIONS

Abbreviation	Meaning
ATrP	Active Trigger Point
BTX	Botulinum Toxin
BTX-A	Botulinum Toxin type A
CAML	Centro Académico de Medicina de Lisboa
CT	Computed Tomography
DC/TMD	Diagnostic Criteria for Temporomandibular Disorders
DDwoR	Disc Displacement without Reduction
DDwR	Disc Displacement with Reduction
GAD	Generalized Anxiety Disorder
GAD-2/ GAD-7	Generalized Anxiety Disorder-2/-7 questionnaires
GCPS	Graded Chronic Pain Scale
ICOP-I	International Classification of Orofacial Pain, first edition
JFLS	Jaw Functional Limitation Scale
LS	Limbic System
LTrP	Latent Trigger Point
MMO	Maximal Mouth Opening
MRI	Magnetic Resonance Imaging
OBC	Oral Behaviors Checklist
PHQ-2/PHQ-4/PHQ-9	Patient Health Questionnaire-2/-4/-9 questionnaires
PRP	Platelet-Rich Plasma
PTJR	Prosthetic Total Joint Replacement
RDC/TMD	Research diagnostic criteria for Temporomandibular Disorders
RCT	Randomized Clinical Trial
SD	Standard Deviation
TMD	Temporomandibular Disorders
TMJ	Temporomandibular Joint
TrP	Trigger Point
VAS	Visual Analog Scale
VASLife	Temporomandibular Disorder Health-related quality of life scale

LIST OF TABLES AND FIGURES

INTRODUCTION

Temporomandibular Disorders

Temporomandibular disorders (TMD) comprise a class of heterogeneous and multifactorial conditions related to functional and morphological deformities in the temporomandibular joint (TMJ) and associated structures (Benoliel et al., 2020; De Leeuw & Klasser, 2018; Dion Tik Shun Li & Leung, 2021; Valesan et al., 2021). In TMD, masticatory muscles are far more frequently affected than the TMJ (Dimitroulis, 2018; Kalladka et al., 2021; Liu & Steinkeler, 2013).

Demographics

TMD is the second most common musculoskeletal disorder and the most common cause of chronic pain of non-dental origin in the orofacial region (Kalladka et al., 2021; Pihut et al., 2014; Schiffman et al., 2014). Most studies accept prevalence values beyond 30% (Calixtre et al., 2014; de Leeuw & Klasser, 2018; Manfredini et al., 2010; Pedroni et al., 2003; Valesan et al., 2021). With an annual incidence rate of 2%, more than 50% of the population report symptoms related to TMD (De Leeuw & Klasser, 2018; Li & Leung, 2021; Vedolin et al., 2009). All studies have shown higher TMD prevalence for women. TMD affects about 31% of adults/elderly and 11% of children/adolescents (de Leeuw & Klasser, 2018; Gonçalves et al., 2010; Kalladka et al., 2021; Valesan et al., 2021).

Clinical Presentation & Evaluation

TMD negatively affect jaw function, and patients present with a set of three major complaints - (1) orofacial pain (TMJ pain or referred pain, such as toothache of non-dental origin, otalgia, tinnitus, headache, cervicalgia, shoulder pain); (2) joint noise (clicking sounds); and (3) mandibular functional limitation (jaw deviation, masticatory muscle tension, limited maximal mouth opening, MMO) (Dimitroulis, 2018). Other complaints are frequently associated. The most frequent symptom is pain, mainly in the masticatory muscles or the preauricular area (de Leeuw & Klasser, 2018). In addition, clenching, bruxism, and other parafunctional habits have an important role in pain

pathophysiology (Dimitroulis, 2018; Liu & Steinkeler, 2013). Only 3.6% to 7% of the affected individuals require or seek TMD treatment (de Leeuw & Klasser, 2018).

Comprehensive patient history acquisition is essential to the diagnosis of TMD. The symptoms that most commonly occur are often subjective and not specifically diagnostic (Dimitroulis, 2018; Kalladka et al., 2021; Dion Tik Shun Li & Leung, 2021; Liu & Steinkeler, 2013). Therefore, the clinical consultation should focus on the main complaints, any history of trauma, previous episodes, risk factors, associated symptoms, parafunctional activities, previous investigations or treatments attempted, and past medical history, including a complete medication list. Pain assessment should also include pain onset, nature, intensity, location, duration, and its relation to other symptoms (pain modification by jaw function, movement, or parafunction). A visual analog scale helps measure patients' complaints (Dimitroulis, 2018; Li & Leung, 2021; Liu & Steinkeler, 2013). The clinician should also investigate psychosocial functioning or concurring significant life events (Schiffman et al., 2014). Physical examination, the most critical step in diagnosing TMD, requires general inspection of the head and neck, palpation of the masticatory muscles and assessment of triggered pain, occlusal evaluation, examination of the jaw opening and closing, and palpation of the TMJ (Dimitroulis, 2018; Li & Leung, 2021; Liu & Steinkeler, 2013).

Complementary imaging diagnosis, such as magnetic resonance imaging (MRI) and/or cone-beam computed tomography (CT) scans, is routinely used in patients with suspected or known TMD to assess the TMJ integrity and its functionality (Dimitroulis, 2018; Dion Tik Shun Li & Leung, 2021).

Etiopathogenesis

Multiple factors are implied in TMD etiopathogenesis and may interact synergistically, including biological (anatomical, genetic, biochemical), environmental (smoking, trauma), emotional (stress, depression, anxiety, somatization), social (culture, family behavior, and socioeconomic status) and cognitive factors. The interaction of initiating, predisposing, and perpetuating factors, may be responsible for TMJ bone and soft tissue remodeling. Although structural changes in the TMJ promote TMD symptoms, biopsychosocial factors seem to play a dominant role in the pathogenesis of TMD. It is consensual that TMD are linked to a higher prevalence of depression and somatization

(Calixtre et al., 2014; de Leeuw & Klasser, 2018; Kalladka et al., 2021; Kmeid et al., 2020; Li & Leung, 2021; Valesan et al., 2021; Vedolin et al., 2009; Wieckiewicz et al., 2015).

TMD Classification

TMD are classified into two main subgroups according to the structures primarily involved: TMJ disorders with changes in the disc-condyle relationship (including joint pain, joint disorders, joint diseases, fractures, and congenital disorders), further classified into inflammatory and noninflammatory arthropathies (arthrogenous TMD), and masticatory muscle disorders or myogenous TMD (muscle pain, contracture, hypertrophy, neoplasms, movement disorders, muscle pain attributed to systemic/ central pain disorders, headache attributed to TMD) (Li et al., 2021; Li & Leung, 2021; Liu & Steinkeler, 2013; Schiffman et al., 2014; Valesan et al., 2021).

The most common diagnoses of TMD include six myogenous conditions: myalgia, local myalgia, myofascial pain, myofascial pain with referral, headache attributed to TMD; and six arthrogenous conditions: arthralgia, disc displacement with reduction (DDwR), DDwR with intermittent locking, disc displacement without reduction (DDwoR) with a limited opening, DDwoR without limited opening, degenerative joint disease, subluxation. Multiple diagnoses may be present at any time in a single patient and may change with the natural history of the disease (Dion Tik Shun Li & Leung, 2021). Hence, it is also crucial to consider other common differential diagnoses, such as neuropathic pain, odontogenic pain, intracranial pain, pain from other adjacent structures, headaches not attributed to TMD, referred pain, and psychogenic pain (Dimitroulis, 2018; Li & Leung, 2021).

Diagnostic criteria intend to standardize and reproduce results across different studies (ICOP, 2020; Li & Leung, 2021; Schiffman et al., 2014; Valesan et al., 2021). Research diagnostic criteria for TMD (RDC/TMD) and the diagnostic criteria for TMD (DC/TMD) are validated standardized diagnostic protocols based on the biopsychosocial model of pain, widely used to classify these conditions. RDC/TMD, initially published in 1992, includes an Axis I physical evaluation and an Axis II psychosocial status and pain-related disability assessment. DC/TMD was then developed to meet the need for refinement and convergence on orofacial pain taxonomy. Moreover, these new evidence-based guidelines bring further attention to patients' cognitive, emotional, and

behavioral responses to pain. DC/TMD includes: (1) an Axis I TMD Pain Screener - a simple, reliable, and valid self-report instrument designed to identify any pain-related TMD, with sensitivity and specificity ≥0.95; (2) an Axis II assessment protocol with screeners for pain intensity (Graded Chronic Pain Scale, GCPS), pain locations (pain drawing), physical function (GCPS), limitation (Jaw Functional Limitation Scale, JFLS), distress (Patient Health Questionnaire-4, PHQ-4), depression (PHQ-9), anxiety (Generalized Anxiety Disorder-7, GAD-7), physical symptoms (PHQ-15) and parafunction (Oral Behaviors Checklist, OBC). These tools proportionate a holistic patient-centered evaluation (Schiffman et al., 2014). The International Classification of Orofacial Pain, first edition (ICOP-I) was created in 2020, further promoting multidisciplinary, international convergence on orofacial pain taxonomy (ICOP, 2020).

Depression/ anxiety in temporomandibular disorders

Depression, anxiety, and somatization are the most common mental health disorders in primary and secondary care medical populations (Kroenke et al., 2010; Sapra et al., 2020). The current lifestyle and pandemic contingencies have contributed to an increased incidence of depressive and anxiety symptoms (de Medeiros et al., 2020; Saccomanno et al., 2020).

In 2019, around 1 out of 5 people in Portugal lived with a mental health disorder (Caldas et al., 2019; Dattani et al., 2021; Vos et al., 2020), thereby becoming the European country with the highest prevalence of mental health disorders (Dattani et al., 2021; Vos et al., 2020). Implementing the World Mental Health Survey Initiative methodology in the national setting also revealed that anxiety disorders (16.5%) and affective disorders (7.9%) are the most prevalent psychiatric disorders (Caldas et al., 2019; Caldas de Almeida et al., 2013). Dattani et al. reported prevalence values of 8,8% and 4.8% for anxiety and depression, respectively, in the Portuguese population (Dattani et al., 2021; Vos et al., 2020). Only 33.1% of those diagnosed with any mental health disorder received appropriate medical treatment, and a median gap of 3 to 4 years was reported between diagnosis and treatment. The 2014 National Health Survey reports a 10% prevalence of depressive symptoms, with frequencies increasing to 38.7% in the elderly (Caldas et al., 2019; Caldas de Almeida et al., 2013). In the primary care setting,

depending on the country's region, anxiety and depression prevalence range between 5.4-8.8% and 7.3-13.4%, respectively (Caldas et al., 2019).

As the standardized diagnostic protocols for TMD recognize, there is a continuous association between TMD symptoms and depressive and/ or anxiety disorders (Schiffman et al., 2014). The “Orofacial Pain: Prospective Evaluation and Risk Assessment” (OPPERA) study confirmed this relationship and showed that previous life events, perceived stress, and negative affect strongly influenced TMD incidence. Global psychological and somatic symptoms were the most robust risk factors for incident TMD (Fillingim et al., 2013). Psychological maladjustment also predicts the long-term persistence of TMD pain (Epker & Gatchel, 2000; Garofalo et al., 1998; Ohrbach & Dworkin, 1998). Stressful events may also exacerbate TMD symptoms and contribute to the development of TMD (Auerbach et al., 2001; Calixtre et al., 2014; de Medeiros et al., 2020; Gameiro et al., 2006; Kmeid et al., 2020; Saccomanno et al., 2020; Tsai et al., 2002; Vedolin et al., 2009; Yap et al., 2003).

Psychological factors may also promote oral parafunctional habits, associated with lower pressure pain threshold and masticatory muscle tenderness (Auerbach et al., 2001; Gameiro et al., 2006; Kmeid et al., 2020; Vedolin et al., 2009). In response to stress and anxiety, neuroendocrine modulation allows physical and psychosocial adjustment. Epinephrine is released, promoting acetylcholine activity at the motor endplate, and triggering a sequence of events, which culminates in a decreased threshold at muscle nociceptors and pain. Other stress-system-related variables, such as personality, maladaptive coping, or illness behavior, may modify or exacerbate the effects of stressors on TMD outcomes (Gameiro et al., 2006; Vedolin et al., 2009). Masticatory muscles are susceptible to physiological changes in stressful conditions sustained over time (Vedolin et al., 2009).

General distress is reported as the most salient single factor across most individuals with chronic TMD pain (de Leeuw & Klasser, 2018; Gameiro et al., 2006; Kalladka et al., 2021). In addition, inappropriate adaptational responses may act as stressors, perpetuating a sustained vicious cycle (Gameiro et al., 2006).

Depressive/ Anxiety Symptoms Assessment

After validating the Primary Care Evaluation of Mental Disorders instrument (PRIME-MD) for diagnosing common mental health disorders in different medical settings, the development of the PHQ allowed mental health conditions screening optimization (Kroenke et al., 2010; Levis et al., 2020). Subsequently, it was also validated a seven-item scale to use in the diagnosis of anxiety, GAD-7. These different modules can be used independently or collectively in clinical practice. Moreover, they do not consider the influence of age, sex, or race/ ethnicity (Kroenke et al., 2003, 2010).

PHQ-9 is a questionnaire to assess the probability of a major depressive disorder (MDD) diagnosis (Kroenke et al., 2010). It can also be used as a continuous measure to evaluate the severity of depressive symptoms. PHQ-9 score varies from 0 to 27, and cutoff values of 5, 10, 15, and 20 represent mild, moderate, moderately severe, and severe depressive symptoms. MDD is considered probable in patients who meet at least five out of the nine symptoms as present "more than half the days" when one of the first two symptoms (depressed mood or anhedonia) is also present (PHQ-9 ≥10) (Kroenke et al., 2010; Schiffman et al., 2014).

The PHQ-2 is a brief screening tool based on the first two items of PHQ-9, representing the core elements of MDD. This version requires at least one of the criteria to make a probable diagnosis of MDD or other depressive disorder. For a PHQ-2 cutoff score of ≥3, the original validation study established: sensitivity, specificity of 83% and 90% as a screener for MDD (Kroenke et al., 2003). According to the populational setting, both ≥2 and ≥3 cutoff values may be used as suggestive of clinically significant depression and should prompt completion of the full PHQ-9 and/or a clinical interview to evaluate the probability of MDD (Bisby et al., 2022; Kroenke et al., 2003, 2010; Levis et al., 2020; Manea et al., 2016). In more time-constrained clinical settings, PHQ-2 is a reliable symptom assessment method and clinically validated questionnaire for the screening of MDD (Bisby et al., 2022; Kroenke et al., 2010; Levis et al., 2020; Mitchell et al., 2009).

GAD-7 (GAD-7 ≥10) evaluates the severity of anxiety symptoms on a scale ranging from 0 to 27, with 5, 10, and 15 corresponding to mild, moderate, and severe levels of anxiety (Kroenke et al., 2010; Sapra et al., 2020). Besides generalized anxiety disorder (GAD), it has also demonstrated acceptable performance in detecting three other

common anxiety disorders (panic disorder, social anxiety, and post-traumatic stress disorder) (Sapra et al., 2020). Furthermore, there is a strong association between GAD-7 severity scores and worsening function on health-related quality of life scales (Spitzer et al., 2006).

GAD-2, the short form of the previous instrument, consists of the first two diagnostic criteria for GAD. Hence, it highlights core elements present regardless of the underlying specific diagnosis (Kroenke et al., 2010; Sapra et al., 2020). The UK and US national clinical guidelines recommended using the GAD-7 and GAD-2 questionnaires for case-finding (Plummer et al., 2016). A score of ≥ 3 has the highest sensitivity/ specificity (86% sensitivity, 83% specificity for GAD) balance for GAD screening. It should prompt the completion of the full GAD-7 and a clinical interview to determine the type of anxiety disorder and assess the need to treat/ refer to specialized help (Plummer et al., 2016). With outstanding clinical performance, GAD-2 has an excellent discriminant capability for being used as the first screening tool for GAD (Kroenke et al., 2010; Plummer et al., 2016).

A previous retrospective study including 120 patients treated for TMD, also conducted at Instituto Português da Face, reported a prevalence of 38,3% (46 patients) and 25.0% (30 patients) for a previous anxiety or depression diagnosis, respectively. The authors have emphasized the importance of early addressing patients expectations and highlighted the positive association between comorbid depression and the need for further TMD treatment (Rodrigues et al., 2023).

A study on the Lebanese population, strongly affected by humanitarian crises, screened TMD association with common mental health disorders – depression, anxiety, and general distress. GAD-7, PHQ-9, and Beirut Distress Scale were used. The authors found a prevalence of undiagnosed TMD of 19.7% (55.9% female patients), with mean depression, anxiety, and stress scores of 6.51 ± 4.51, 5.78 ± 4.04, and 11.43 ± 9.40 respectively. The study also found that depressed patients were more likely to suffer from bruxism. Likewise, higher TMD severity correlated with higher depression, anxiety, and stress burden. On the contrary, an older age seemed to be a protective factor (Kmeid et al., 2020).

Simoen et al. also reported statistically significantly higher PHQ-9 and GAD-7 scores in patients with orofacial pain. 19,4% of the patients screened positive for

depression (PHQ-9 ≥10) and 29% for anxiety (GAD-9 ≥10). In the general population without TMD, the referred values were 7% and 6%, respectively (Simoen et al., 2020).

Aiming for holistic TMD treatment protocols, Yeung et al. established 17% MDD and 20% GAD prevalence, using PHQ-9 and GAD-7, as part of a new integrated mental health screening system to manage TMD patients (Yeung et al., 2017).

Treatment Options for TMD

The adequate treatment protocol varies according to the individual diagnosis and severity of TMD. However, the main treatment goals are to reduce pain, restore function, prevent further damage, improve the overall quality of life and limit disease-related morbidities (Dimitroulis, 2013; Dion Tik Shun Li & Leung, 2021; Liu & Steinkeler, 2013).

TMD should be addressed promptly to avoid chronic pain, psychological deterioration, and somatization (Dion Tik Shun Li & Leung, 2021). Therefore, it is essential to ensure a step-up and multidisciplinary, coordinated approach (including TMJ surgery, neurology, general dentistry, oral medicine, orofacial pain, orthodontics, oral surgery, physical and/or speech therapy, and psychiatry) (Liu & Steinkeler, 2013).

The conventional treatment protocol for TMD can start with conservative options, progressing to other modalities only if required (Dimitroulis, 2013; Dion Tik Shun Li & Leung, 2021; Liu & Steinkeler, 2013). However, a change in paradigm advocates minimally invasive options as an early treatment in the management of arthrogenous TMD (Al-Moraissi et al., 2020; Li & Leung, 2021).

Noninvasive Treatment

Noninvasive treatment options are still the most effective way of managing 75 to 90% of patients (Ahmad & Schiffman, 2016; Dimitroulis, 2018). After explaining and reassuring the patient about TMD, the treatment plan should focus on patient education, promoting cognitive awareness training, and relaxation therapy (Dimitroulis, 2018; Wieckiewicz et al., 2015). Patient literacy on the factors promoting TMD, such as emotional stress and parafunctional activities, allows their modification (Dimitroulis, 2018; Kalladka et al., 2021; Dion Tik Shun Li & Leung, 2021; Wieckiewicz et al., 2015). Patients should be advised to maintain a soft diet, avoid foods requiring considerable

chewing, extreme mandible movements, and apply cold or heat (Dimitroulis, 2018; Dion Tik Shun Li & Leung, 2021; Wieckiewicz et al., 2015). Restrictive muscle training, the simplest form of conservative treatment, is effective in 70% of cases (Wieckiewicz et al., 2015).

Behavioral therapy and psychotherapy are helpful as co-adjuvant treatments to reduce TMD-associated complaints. Psychogenic disorders are more frequent in the myofascial pain and dysfunction group of TMD and require integrated psychotherapeutic approaches. It is vital to assess how peripheral and central mechanisms contribute to the instigation and persistence of pain (Dimitroulis, 2018; Kalladka et al., 2021; Li & Leung, 2021; Wieckiewicz et al., 2015).

Different lines of evidence support the use of conservative treatments, including counseling, physiotherapy, occlusal splint therapy, massage, manual therapy, and others as first-choice therapy with a shallow risk of side effects (Liu & Steinkeler, 2013; Sipahi Calis et al., 2019; Wieckiewicz et al., 2015).

Physiotherapy

Frequently used as an adjuvant in the outpatient setting, this therapy targets musculoskeletal pain and inflammation, restoring motor function. It is imperative in managing myofascial pain, TMJ closed lock and is crucial following TMJ surgery (Dimitroulis, 2018; Kalladka et al., 2021; Liu & Steinkeler, 2013; Wieckiewicz et al., 2015).

Pharmacotherapy

Pharmacological therapy for TMD intends to treat the underlying disease process and alleviate disease-associated symptoms. It is preferably used in other somatic symptoms such as sleep disorders, chronic pain, arthralgias, inflammatory disease, myalgias, or neuropathies associated with TMD (Liu & Steinkeler, 2013; Wieckiewicz et al., 2015).

It should be used rationally as a valuable adjunctive aid therapy rather than a primary treatment. The combination of different classes of medications is often required. Avoiding prolonged exposure to certain pharmacological classes, such as analgesics, is recommended to prevent drug tolerance and dependency. Several studies

reported limited effectiveness supporting the use of pharmacological therapy (Dimitroulis, 2018; Kalladka et al., 2021; Liu & Steinkeler, 2013).

Pain, inflammation, and stress associated with TMD should be actively addressed, and their treatment is recommended (Sipahi Calis et al., 2019).

Examples of pharmacological classes are as follows: NSAIDs, opioids, corticosteroids, myorelaxants, antidepressants, and anxiolytics (Dimitroulis, 2018; Kalladka et al., 2021; Dion Tik Shun Li & Leung, 2021; Liu & Steinkeler, 2013; Wieckiewicz et al., 2015).

Botulinum toxin type A (BTX-A) Injections

Introduced as a therapeutic agent in 1977, botulin toxin (BTX) is produced by *Clostridium botulinum*. It is an exotoxin associated with food-borne botulism, characterized by autonomic dysfunction and flaccid paralysis. A BTX intramuscular injection produces local muscle paresis through temporary chemodenervation, blocking the presynaptic release of acetylcholine in the neuromuscular plate. BTX is particularly helpful for hyperfunctional muscle disorders. The administered dose determines the degree of paresis (Blitzer & Sulica, 2001). Usually well tolerated by the patient, it may be associated with the following side effects: flu-like symptoms due to a systemic reaction to the injection and nasal regurgitation related to local seepage of BTX into pharyngeal/ palatal muscles. Widespread weakness, fatigue, shortness of breath, dysphagia, and difficult accommodation may occur for very high doses (Bakke et al., 2005; Emara et al., 2013; Sipahi Calis et al., 2019).

BTX has been proven effective in different TMD, particularly in myogenous TMD (bruxism, oromandibular dystonia, myofascial pain, trismus, masseter, or temporalis hypermobility, hypertrophy, headaches, migraine, neck pain) (Ataran et al., 2017; Bakke et al., 2005; Emara et al., 2013; Sipahi Calis et al., 2019). It is essential to exclude arthrogenous causes prior to BTX treatment (Sipahi Calis et al., 2019). Several studies support excellent efficacy for pain reduction following BTX treatment (Aquilina et al., 2004; Arinci et al., 2009; Ataran et al., 2017; Bentsianov et al., 2004; Chaurand et al., 2017; Freund et al., 1999, 2000; Karacalar et al., 2005; Sipahi Calis et al., 2019; von Lindern, 2001). BTX type A (BTX-A) injection promotes an efficient harmonious motion of the TMJ, which is explained by reducing muscle tone, inflammation, and, subsequently, pain. (Ataran et al., 2017; Chaurand et al., 2017; Sipahi Calis et al., 2019).

TMJ sounds and TMD are often associated with an anterior disc displacement (ADD). ADD is thought to result from abnormal and unstabilized disc movements due to an unsynchronized action of the two heads of the lateral pterygoid muscle (Bakke et al., 2005; Emara et al., 2013). It is possible to treat disc displacements with BTX-A injections in the lateral pterygoid muscles resulting in a reduction in myofascial pain, muscle tension, and neuromuscular tonus (Bakke et al., 2005; Emara et al., 2013; Dion Tik Shun Li & Leung, 2021; Wieckiewicz et al., 2015).

Occlusal or Stabilization Splints

Splints are one of the most common initial treatments for TMD-associated pain. Although some studies suggest that splints have an unloading effect on the condyle and are thought to protect the condyle-disc complex from degeneration and excessive articular strain, restoring central relaxation, with multiple designs available, the evidence supporting their use is controversial (Alkhutari et al., 2020; Christidis et al., 2019; Dimitroulis, 2018; Kalladka et al., 2021; Dion Tik Shun Li & Leung, 2021; Liu & Steinkeler, 2013; Wieckiewicz et al., 2015).

A meta-analysis of randomized clinical trials (RCT) revealed good evidence (reduced reported pain; higher frequency of responders - lower number needed to treat) for hard stabilization appliances in painful TMD compared to non-occluding devices (active placebo) and no treatment (passive placebo) (Alkhutari et al., 2020). Moreover, a 2018 systematic review supports clinical efficacy with improved patient-related outcomes, such as significant pain reduction and patient-reported treatment satisfaction (J et al., 2018).

Nonetheless, a Cochrane Database review unveiled insufficient evidence for or against their use (Al-Ani et al., 2004; Liu & Steinkeler, 2013). Better operationalized study designs may clarify their clinical potential(Liu & Steinkeler, 2013).

Surgical Treatment

Evidence shows that about 5 to 10% of all patients undergoing treatment for TMD require surgical intervention (Dimitroulis, 2018; D. T.S. Li et al., 2021). More localized symptoms usually predict a greater probability of benefit from surgery. Therefore, pain triggered by direct TMJ palpation, loading of the TMJ, and functional

movement alteration are signs of surgical disease. Chronic severe limited mouth opening and significant mechanical interference constitute specific indications for TMJ surgery. Ankylosis, neoplasia, dislocation (recurrent or chronic), and congenital disorders are absolute indications for TMJ surgery (Dimitroulis, 2018).

The Wilkes' Staging Classification (1989) for Internal Derangement of the TMJ categorizes intracapsular disorders in stages I to V, according to clinical, radiologic, and anatomic findings (Dion Tik Shun Li & Leung, 2021; Liu & Steinkeler, 2013). Based on the latter, but encompassing a broader scope of TMJ surgical disorders, the Dimitroulis Classification guides the adequate surgical procedure (Dimitroulis, 2013). The Dimitroulis Classification divides TMJ disorders into five categories, with category one being normal and category five referring to end-stage derangement of the joint requiring total TMJ replacement (Dimitroulis, 2013, 2018).

Minimally Invasive Treatment

Timely management of pain conditions, such as TMD, prevents further progression into chronicity (D. T.S. Li et al., 2021; Dion Tik Shun Li & Leung, 2021). It is now consensual that minimally invasive options should be used as initial or early treatments in TMD management whenever conservative approaches fail (Al-Moraissi et al., 2020; Li & Leung, 2021; Liu & Steinkeler, 2013; Renapurkar, 2018; Wieckiewicz et al., 2015).

TMJ arthrocentesis & Intra-articular injections

TMJ arthrocentesis is a quick, cost-effective standard procedure for TMJ closed lock and arthralgia of non-locking etiology with a success rate of over 80% (Liu & Steinkeler, 2013; Monje-Gil et al., 2012). Conventional TMJ arthrocentesis evolved to improve clinical outcomes. Both single and double-portal procedures are possible, with some side effects more associated with each treatment protocol (Ângelo et al., 2021; Dimitroulis, 2018; Dion Tik Shun Li & Leung, 2021). A highly differentiated surgeon can perform TMJ superior joint space lavage through joint needles with irrigation fluid, such as ringer lactate, and eventually with other pharmacological agents. This procedure lubricates the joint, reduces inflammation and pain, and improves function (Dimitroulis, 2018; D. T.S. Li et al., 2021; Dion Tik Shun Li & Leung, 2021; Wieckiewicz et al., 2015). A

recent integrated review and meta-analysis revealed that TMJ arthrocentesis is beneficial independently of the timing of the procedure in the natural history of the disease (D. T.S. Li et al., 2021).

Another option is to directly inject therapeutical agents into the TMJ space, such as hyaluronic acid, corticosteroids, or platelet-rich plasma (PRP) (Al-Moraissi et al., 2020; Li & Leung, 2021; Liu & Steinkeler, 2013; Pihut et al., 2015; Wieckiewicz et al., 2015). However, this approach is not globally accepted due to the safety associated with these procedures.

PRP intra-articular injection enhances the healing environment and is effective in patients with persistent pain attributed to severe TMJ dysfunction (Pihut et al., 2015; Wieckiewicz et al., 2015). Although less commonly used, inferior articular space or simultaneous upper and lower spaces injections are more effective than superior space injection alone in increasing mouth opening and decreasing TMJ-associated pain (Liu & Steinkeler, 2013). In a network meta-analysis, Al-Moraissi et al. established intra-articular injection of hyaluronic acid as the most effective treatment in terms of short-term pain relief among the minimally invasive options (Al-Moraissi et al., 2020). Corticosteroids also had good results in pain relief. However, due to numerous side effects, their use should be cautious (Al-Moraissi et al., 2020).

TMJ arthrocentesis and arthroscopy allow the co-administration of the same drugs into the articular TMJ space, which proved to be significantly superior over conservative TMD management in MMO and pain reduction (Al-Moraissi et al., 2020; Li & Leung, 2021). In fact, for patients with arthrogenous TMD, Arthroscopy-PRP resulted in the greatest MMO (Al-Moraissi et al., 2020).

TMJ arthroscopy

TMJ arthroscopy adds the possibility to visualize the internal anatomy of the TMJ and perform surgical procedures (disc repositioning, arthroplasty, removal of debris, adhesiolysis) through the insertion of an arthroscope (Dimitroulis, 2018; D. T.S. Li et al., 2021; Dion Tik Shun Li & Leung, 2021; Liu & Steinkeler, 2013; Wieckiewicz et al., 2015). Arthroscopy significantly improves joint mobility, pain, and function with a more than 90% success rate (Al-Moraissi et al., 2020; McCain et al., 1992). Its therapeutical effect

is mainly due to lysis and lavage of the joint and is not directly related to disc position (Dion Tik Shun Li & Leung, 2021).

The clinical effect of TMJ arthroscopy or arthrocentesis is debatable (Li & Leung, 2021; Liu & Steinkeler, 2013; Rigon et al., 2015). Nevertheless, arthrocentesis is often suggested as a first option due to its simplicity, low morbidity, and high success rate (Dion Tik Shun Li & Leung, 2021; Monje-Gil et al., 2012). In arthrogenous TMD, however, Al-Moraissi et al. demonstrated superiority for arthroscopic procedures compared to arthrocentesis for post-treatment MMO (Al-Moraissi et al., 2020).

Although rare, complications are possible and include bleeding, wound infection, soft tissue edema (preauricular area, pharyngeal), instrument fracture, laceration of the external auditory canal, facial or trigeminal nerve lesion, permanent occlusal modification, relapsing joint pain, alteration of visual accuracy. Frequently, in the postoperative period is helpful to associate TMJ arthrocentesis and arthroscopy with intra-articular injections, occlusal splints, pharmacotherapy, and physical therapy (Ângelo et al., 2021; Liu & Steinkeler, 2013).

Invasive Treatment

Arthroplasty

The most severe cases, with significant articular derangement (osteophytes, erosions, and irregularities) refractory to other treatment forms, require reshaping the articular surface (Liu & Steinkeler, 2013; Renapurkar, 2018; Wieckiewicz et al., 2015). Surgical procedures can include disc repositioning, discopexy, discoplasty, discectomy alone, or discectomy with graft replacement (Dimitroulis, 2018; Li & Leung, 2021; Liu & Steinkeler, 2013).

For structurally intact healthy mobile discs, discopexy or discoplasty involves an arthrotomy followed by reshaping and/ or repositioning the intra-articular disc. The procedure has a high success rate (80-94%) (Renapurkar, 2018). Deformed, dysfunctional discs that cannot be salvaged are eligible for discectomy. Evidence supports its efficacy for pain relief and functional improvement (Eriksson & Westesson, 1985; Holmlund et al., 1993; Renapurkar, 2018; Tolvanen et al., 1988). A controversial association with degenerative joint disease following discectomy has been suggested (Renapurkar, 2018; Widmark et al., 1997). These bony changes and the persistence of

symptoms in some patients led to the idea that disc replacement would be required, leading to the implementation of autogenous and alloplastic disc prostheses (Renapurkar, 2018). Nonetheless, TMJ discectomy alone or combined with autogenous interpositional grafts produced similar results (Kramer et al., 2005; Renapurkar, 2018).

The need for a rehabilitation physiotherapy program should be ensured to promote long-term functional improvement (Dimitroulis, 2018; Liu & Steinkeler, 2013).

TMJ open Joint Surgery & Total Joint Replacement

Open joint surgery – arthrotomy - is rarely indicated, but it is a viable option for end-stage TMD and some pathologic etiologies, such as ankylosis and neoplasms (Li & Leung, 2021). Arthrotomy allows a wide range of surgical procedures (discopexy, discoplasty, discectomy, or condylectomy) through direct surgical exposure of the TMJ with a preauricular incision. When a condylectomy is performed, an asymmetrical lower face and severe malocclusion will result. Therefore, a prosthetic total joint replacement (PTJR) is required (Dimitroulis, 2014, 2018; Dolwick, 2001; Montgomery et al., 1992).

PTJR's primary goals are to restore TMJ form and function. Autogenous costochondral bone grafts, biocompatible metals (mainly titanium), and plastic materials are used for TMJ prostheses. Biocompatible prostheses are fixed to the remaining jaw and skull bones with miniature bone screws (Dimitroulis, 2018). The potential risk of harvest-site morbidity and failure during transplantation makes biocompatible materials more attractive (Liu & Steinkeler, 2013). The PTJR implant must withstand the joint's stresses and maintain full motion. (Mamidi et al., 2019).

A 3 to 4 weeks jaw physiotherapy and recovery period should be anticipated and is an essential part of rehabilitation (Dimitroulis, 2018).

STUDY OBJECTIVES

This study aims to answer the following hypotheses: (1) Are PHQ-2 and GAD-2 scores associated with lower TMD clinical outcomes? (2) Can some TMD subtypes possibly have a stronger association with depression and/ or anxiety? (3) Does a higher psychological burden contribute to the need for reintervention?

MATERIALS AND METHODS

Study Design

A cross-sectional retrospective study was conducted at Instituto Português da Face (IPF) in Lisbon, Portugal, including patients treated for TMD from February 2018 to February 2022. The ethics committee of *Instituto Português da Face* and the ethics committee of Centro Académico de Medicina de Lisboa (CAML) both approved the study (appendix). All the enrolled patients were aware of its implications and gave their free term of consent in writing, accordingly to current legislation and with the Declaration of Helsinki.

The inclusion criteria were: 1) Age > 14 years old; 2) arthrogenous and/or myogenous TMD; 3) conservative treatment without any improvement at least for three months; 4) Dimitroulis Classification between 1-4; 5) indication for one of the following TMD treatments: injection of botulinum toxin; TMJ arthrocentesis; TMJ arthroscopy; TMJ open surgery without alloplastic material. Exclusion criteria: 1) previous TMJ surgical intervention; 2) impaired cognitive capacity; 3) age < 14 years old; 4) pregnant or breastfeeding women.

All participants were comprehensively clinically examined by the same TMJ surgeon (David Ângelo, Ph.D., MD.).

The variables measured throughout the study were obtained pre and post-treatment: 1) TMJ pain, with a Visual Analog Scale (VAS, 0-10, with 0 corresponding to the absence of pain and 10 maximum insupportable pain); 2) Health-related quality of life (VASLife) through the question: "If you could give a life impact score to your TMJ problem in a 0 to 10 scale, where 0 means no impact and 10 means the maximum impact possible, what would be your score?"; 3) Maximal Mouth Opening (MMO, mm) employing a certified ruler between the incisor's teeth; 4) Myalgia degree (0-3). Myalgia was graded accordingly with pain intensity in each muscle: 0 = No Pain/Pressure Only; 1

= Mild Pain; 2 = Moderate Pain; 3 = Severe Pain (Goiato et al., 2017). Myogenous disease, including myalgia, was diagnosed according to a clinical history positive for 1) in the past 30 days, pain in the jaw, temple, in front of the ear, or in the ear with examiner confirmation of pain location in the temporalis or masseter muscle and 2) pain modified with jaw movement, function or parafunction and a positive clinical evaluation for palpation pressure (5 seconds/1kg pressure) in masseter and temporalis muscles as defined in DC/TMD (Schiffman et al., 2014). Arthralgia was diagnosed through positive history for both of the following criteria: 1) pain in TMJ, in the ear, or front of ear; 2) pain modified with jaw movement, function, or parafunction. Positive examination for arthralgia was reported if it was observed: pain location in the TMJ area and pain on palpation of the lateral pole or around the lateral pole or pain on maximum unassisted or assisted opening, right or left lateral movements, or protrusive movements. The final arthrogenous diagnosis was confirmed with MRI.

Each patient was further categorized, and the decision of which treatment to apply was based on Dimitroulis' TMJ Surgical Classification (Dimitroulis, 2013).

Category 1: patients without arthrogenous disease, with TMJ pain associated with myofascial pain. These patients were treated with botulinum toxin injections.

Category 2: diagnosis of DDwR with joint clicking and intermittent pain or indication of inflammation with normal condyles. These patients were treated with arthrocentesis.

Category 3: patients with long-standing closed lock (> 2 months), diagnosis of DDwoR, absence of clicks, arthrogenous TMD, or synovial chondromatosis. These cases were treated with TMJ arthroscopy.

Category 4: radiological signs of changes in condylar morphology such as osteophytes, small subchondral cysts, loss or thinning of cartilage layer, severe displaced and deformed articular discs, including disc perforation. When the disc was salvageable, the patients were treated with discopexy, and a discectomy was performed when unsalvageable.

Independently of the Dimitroulis category, all patients with myalgia grades 2 and 3 received a 155U and 195U botulinum toxin injection in the masticatory muscles (masseter and temporal), respectively. This treatment was performed 10-15 days before the surgery.

All patients were instructed to follow a soft diet for 3 days after surgery. In addition, 5 physiotherapy sessions and 3 speech therapy exercise sessions started 3-5 days after the intervention.

PHQ-2 & GAD-2 questionnaires

For each patient, screening for depressive and/ or anxiety disorder was assessed in the first consultation through validated PHQ-2 and GAD-2 questionnaires (Kroenke et al., 2003, 2007).

A PHQ-2 cutoff of ≥ 2 was considered likely of clinically significant depressive disorder, according to Levis et al. The authors established sensitivity and specificity of 0.91 and 0.67 for a PHQ-2 score ≥2 and 0.72 and 0.85 for a PHQ-2 score ≥3 (Levis et al., 2020). Accordingly, a diagnostic meta-analysis on PHQ-2 accuracy in the screening of MDD by Manea et al. found similar operating characteristics for this lower cutpoint (sensitivity of 0.91, specificity of 0.70) (Manea et al., 2016). Bisby et al. also suggested the lower PHQ-2 cutpoint of ≥2 since it demonstrated optimal sensitivity and specificity (Bisby et al., 2022). The higher sensitivity results in better case-finding ability, which comes at the expense of lower specificity. To account for the risk of a high rate of false positives and reduced clinical utility, a PHQ-2 score ≥2 should be implemented in settings with a high prevalence of the condition (Bisby et al., 2022; Manea et al., 2016). Considering the high prevalence of depressive symptoms and disorders among the Portuguese population, a cutoff of ≥2 was adopted (Caldas et al., 2019).

A GAD-2 cutoff of ≥ 3 suggested clinically significant anxiety disorder (Kroenke et al., 2007). For a cutoff ≥3, GAD-2 has the following operating characteristics: sensitivity and specificity of 86,0% and 83,0% in GAD screening; sensitivity and specificity of 65,0% and 88,0% in any anxiety disorder screening (Kroenke et al., 2007).

Patients with a positive screening result for a depressive and/ or anxiety disorder received advice on the currently available resources for appropriate treatment and follow-up in the Portuguese setting.

Table 1. PHQ-2

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all	Several days	More than half the days	Nearly every day
A. Little interest or pleasure in doing things.	0	+1	+2	+3
B. Feeling down, depressed, or hopeless.	0	+1	+2	+3
PHQ-2 Score	A + B			

Adapted from (Kroenke et al., 2003).

Table 2. GAD-2

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all	Several days	More than half the days	Nearly every day
A. Feeling nervous, anxious or on edge.	0	+1	+2	+3
B. Not being able to stop or control worrying	0	+1	+2	+3
GAD-2 Score	A + B			

Adapted from (Kroenke et al., 2010).

Statistical Analysis

Descriptive analysis of the study was performed through measures, absolute frequencies, and mean. The mean was used as a location measure accompanied by its standard deviation (SD) in the form of mean ± SD. The normality analysis was performed for all tests using the Kolmogorov-Smirnov test. Bivariate contingency tables containing the absolute frequency in each possible combination of categorical variables were created. The non-parametric Chi-square test (χ^2) and Fisher's exact test were used to assess the existence of associations between these variables.

The Student T-test or non-parametric Mann-Whitney U Test was used for continuous variables. Multivariable logistic regression analysis was used to assess the impact of depression and anxiety on reintervention treatment. Multivariable analysis was adjusted for: Pre-treatment VASLife; GAD-2; PHQ-2; Post-treatment Myalgia * GAD-2; Post-treatment Myalgia * PHQ-2. P-value <0.05 was considered statistically significant for all analyses. Data analysis was obtained using SPSS (v26) and graphical representation through GraphPad Prism (v9) software.

RESULTS

A total of 247 patients (202 female and 45 male) were enrolled. The mean age of the participants was 40.51 ± 17.04 years, ranging from 14-88 years (Table 3).

The clinical pre-treatment variables evaluated in the study are reported in Table 4. The mean pre-treatment VAS (0-10) was 4.25 ± 2.62, VASLife (0-10) was 6.60 ± 2.36, and MMO was 37.15 ± 9.50 (mm). The more frequent pre-treatment intra-articular diagnoses were: (1) disc dislocation with reduction (DDwR) (101 patients, 40.9%); (2) disc dislocation without reduction (DDwoR) (93 patients, 37.7%); (3) Osteoarthrosis (OA) (83 patients, 33.6%). Pre-treatment myalgia was identified in 222 patients (89.9%): I – 24 (9.7%); II – 70 (28.3%); III – 128 (51.8%). 155 patients (37.2%) had arthralgia, and 144 (38.2%) had a disc displacement disorder with pain associated. TMD severity, evaluated using the Dimitroulis Classification, was heterogeneous. It was observed: 18 patients (19.4%) in Dimitroulis 1; 110 patients (44.5%) in Dimitroulis 2; 53 patients (21.5%) in Dimitroulis 3, and 36 patients (14.6%) in Dimitroulis 4. The decision of which treatment to perform was according to the Dimitroulis classification. The mean follow-up period was 252.9 ± 278.8 days, ranging from 31 to 1224 days.

The absolute and relative frequencies for GAD-2 and PHQ-2 scores (0-6) are summarized in figure 1 and figure 2, respectively. The mean GAD-2 and PHQ-2 scores were 2.94 ± 1.78 and 1.33 ± 1.67. 133 patients (53.8%, GAD-2 ≥3) screened positive for an anxiety disorder, and 91 patients (38.4%, PHQ-2 ≥ 2) for depression.

The bivariate analysis of the sociodemographic variables associated with GAD-2 and PHQ-2 status are summarized in table 5. The mean age was significantly associated with PHQ-2 status (P=0.049). However, no significant association was found concerning patients' sex.

The correlation of clinical variables (pre- and post-treatment) with GAD-2 and PHQ-2 status was analyzed (Table 6). There was a statistically positive association between PHQ-2 screening with the following clinical outcomes: pre-treatment VASLife (6.95±2.49; p=0.040), myalgia (reported by 95,6% of the patients with a PHQ-2 score ≥2; p=0.011), and myalgia degree (2.43±0.83; p=0.013). For a positive GAD-2, there was a statistically significant association for pre-treatment VASLife (6.92±2.37; p=0.025), myalgia degree (2.35 ± 0.91; p=0.038), and post-treatment myalgia degree (0.67 ± 1.08; p=0.036). For other clinical variables (pre-treatment VAS, MMO and intra-articular diagnosis, post-treatment VAS and MMO, Dimitroullis Classification, arthralgia diagnosis, and disc displacement disorder with pain), no statistically significant differences were found.

Forty patients (16.2%) required reintervention. A multivariable logistic regression predicting patients requiring reintervention was adjusted for the screening measures status (GAD-2 and PHQ-2), pre-treatment VASLife, and post-treatment myalgia degree (Table 7). Although GAD-2 and PHQ-2 alone were not explanatory of the profile of reintervened patients, significance was found for pre-treatment VASLife (odd ratio (OR)=1.67; p=0.008). The composed variable of post-treatment myalgia degree and GAD-2 status was also significant (OR=1.89; p<0.001).

Table 3. Demographic data.

Number of patients	247	
Sex		Number of patients (%)
	Female	202 (81.8%)
	Male	45 (18.2%)
Age Mean (mean ±SD)	40.51 ± 17.04	

Table 4. Clinical evaluation.

Pre-treatment VAS (0-10) (mean ± SD)	4.25 ± 2.62	
VASLife (0-10) (mean ± SD)	6.60 ± 2.36	
Pre-treatment MMO (mean ± SD)	37.15 ± 9.50	
Pre-treatment Myalgia Degree (mean ± SD)	2.22 ± 0.99	
Pre-treatment Intra-articular Diagnosis		Number of patients (%)
	DDwR	101 (40.9%)
	DDwoR	93 (37.7%)
	OA	83 (33.6%)
Pre-treatment Myalgia Diagnosis		Number of patients (%)
	Myalgia	222 (89.9%)
	I	24 (9.7%)
	II	70 (28.3%)
	III	128 (51.8%)
Dimitroulis Classification		Number of patients (%)
	I	48 (19.4%)
	II	110 (44.5%)
	III	53 (21.5%)
	IV	36 (14.6%)
Arthralgia diagnosis	155 (37.2%)	
Disc displacement disorder with pain	144 (58.3%)	
Follow-up period (days)	252.9 ± 278.2 (31-1224)	

Figure 1. GAD-2 distribution among patients. (A) GAD-2 mean and distribution by the different classifications. (B) Distribution of positive and negative GAD-2.

A

GAD-2 (mean ± SD)		2.94 ± 1.78
		Number of patients (%)
GAD-2	0	31 (12.6%)
	1	14 (5.7%)
	2	69 (27.9%)
	3	33 (13.4%)
	4	50 (20.2%)
	5	24 (9.7%)
	6	26 (10.5%)

B

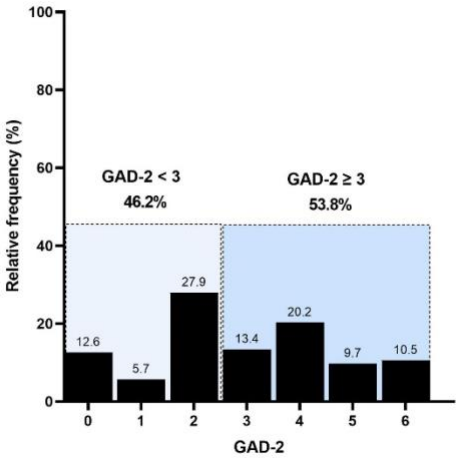

Figure 2. PHQ-2 distribution among patients. (A) PHQ-2 mean and distribution by the different classifications. (B) Distribution of positive and negative PHQ-2.

A

PHQ-2 (mean ± SD)		1.33 ± 1.67
		Number of patients (%)
PHQ-2	0	115 (46.6%)
	1	31 (12.6%)
	2	42 (17.0%)
	3	19 (7.7%)
	4	13 (5.3%)
	5	10 (4.0%)
	6	7 (2.8%)

B

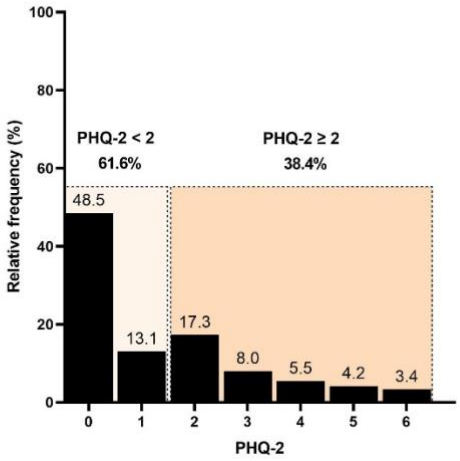

Table 5. Demographic characteristics according to GAD-2 and PHQ-2 status.

Variable		GAD-2			PHQ-2		
		GAD-2 (0-2)	GAD-2 ≥3	p-value or χ^2; df; p-value	PHQ-2 (0-1)	PHQ-2 ≥2	p-value or χ^2; df; p-value
Sex	F	92 (80.7%)	110 (82.7%)	0.166; 1; 0.684	120 (82.2%	72 (79.1%)	0.344; 1; 0.558
	M	22 (19.3%	23 (17.3%)		26 (17.8%)	19 (20.9%)	
Age Mean (mean ±SD)		38.19 ± 24.02	40.71±18.91	0.731	39.11±17.48	43.32±16.74	**P=0.049**

Table 6. Diagnosis and treatment outcomes according to GAD-2 and PHQ-2 status.

Variable		GAD-2			PHQ-2		
		GAD-2 (0-2)	GAD-2 ≥3	p-value or χ^2; df; p-value	PHQ-2 (0-1)	PHQ-2 ≥2	p-value or χ^2; df; p-value
Pre-treatment VAS (0-10) (mean ± SD)		4.12 ± 2.38	4.37 ± 2.81	0.335	4.06 ± 2.57	4.42 ± 2.68	0.233
Pre-treatment VASLife (0-10) (mean ± SD)		6.25 ±2.31	6.92±2.37	**0.025**	6.34 ± 2.26	6.95 ± 2.49	**0.040**
Pre-treatment MMO (mean ± SD)		37.40 ± 9.87	36.93 ± 9.21	0.704	37.16 ± 9.90	37.86 ±8.93	0.589
Intra-articular diagnosis	DDwR	50 (43.9%)	51 (38.3%)	0.772; 1; 0.380	59 (40.4%)	35 (38.5%)	0.089; 1; 0.765
	DDwoR	44 (38.6%)	49 (36.8%)	0.080; 1; 0.777	51 (54.2%)	37 (40.7%)	0.788; 1; 0.375
	OA	40 (35.1%)	43 (32.3%)	0.209; 1; 0.647	47 (32.2%)	34 (37.4%)	0.666; 1; 0.414
Myalgia		98 (86.7%)	123 (93.2%)	2.872; 1; 0.090	124 (84.9%)	87 (95.6%)	**6.538; 1; 0.011**
Myalgia degree (mean ± SD)		2.07 ± 1.06	2.35 ± 0.91	**0.038**	2.07 ± 1.07	2.43 ± 0.83	**0.013**
Post-treatment VAS (0-10) (mean ± SD)		0.67 ± 1.59	1.07 ± 2.43	0.614	0.75 ± 1.93	0.73 ± 1.90	0.679
Post-treatment myalgia degree (0-10) (mean ± SD)		0.46 ± 0.78	0.67 ± 1.08	**0.038**	0.53 ± 0.89	0.57 ± 0.97	0.957
Post-treatment MMO (mean ± SD)		41.00 ± 7.08	40.32 ± 4.67	0.447	40.90 ±6.24	40.71 ± 5.32	0.836
Dimitroullis Classification	1	18 (15.8%)	30 (25.8%)	3.36; 3; 0.340	26 (17.8%)	22 (24.2%)	3.436; 3; 0.329
	2	55 (48.2%)	55 (41.4%)		72 (49.3%)	34 (37.4%)	
	3	27 (23.7%)	26 (19.5%)		28 (19.2%)	21 (18.8%)	
	4	14 (12.3%)	22 (16.5%)		20 (13.7%)	14 (15.4%)	
Arthralgia diagnosis		71 (62.3%)	84 (63.2%)	0.020; 1; 0.887	91 (62.3%)	58 (63.7%)	0.048; 1; 0.827
Disc displacement disorder with pain		30 (26.3%)	42 (31.6%)	0.823; 1; 0.364	39 (26.7%)	32 (35.2%)	1.909; 1; 0.167

Table 7. Multivariable logistic regression predicting reintervention treatment adjusted for VASLife, GAD-2, PHQ-2, myofascial pain diagnosis, and post-treatment MT degree.

Variable	OR	95% CI	p-value
Pre-treatment VASLife	1.67	1.14-2.44	**0.008**
GAD-2	0.93	0.60-1.46	0.759
PHQ-2	0.76	0.42-1-39	0.379
Post-treatment myalgia degree * GAD-2	1.89	1.35-2.64	**<0.001**
Post-treatment myalgia degree * PHQ-2	0.747	0.49-1.15	0.181

DISCUSSION

The association between psychological disorders, namely anxiety and depression with TMD has been reported in several studies (Auerbach et al., 2001; Calixtre et al., 2014; Gameiro et al., 2006; Kmeid et al., 2020; Saccomanno et al., 2020; Schiffman et al., 2014; Simoen et al., 2020; Yap et al., 2003; Yeung et al., 2017). However, few studies seem to have evaluated the preliminary diagnosis of anxiety and depression on the clinical outcomes of TMD patients and the need for surgical reintervention.

Mental health disorders are a significant public health challenge. It has been estimated that almost 14% of Europeans were affected by mental health disorders in 2019. In Portugal, the estimates reach almost 19%, thereby being the country with the highest psychopathological burden (Dattani et al., 2021; Vos et al., 2020). Anxiety disorders were the most prevalent (4,69%), followed by depressive disorders (3,79%) (Dattani et al., 2021; Vos et al., 2020). According to the Epidemiological National Mental Health Study (2008-2009), part of the World Mental Health Survey Initiative, in Portugal, anxiety and affective disorders are the most prevalent psychiatric diagnoses, with a prevalence of 16,5% and 7,9%, respectively (Caldas et al., 2019; Caldas de Almeida et al., 2013). Self-reported depressive symptoms reach a 10% prevalence (Caldas et al., 2019; Caldas de Almeida et al., 2013). Dattani et al. reported prevalence values of 8,8% and 4.8% for anxiety and depression, respectively, in the Portuguese population (Dattani et al., 2021; Vos et al., 2020). In our study, 38,4% and 53,8% of the patients screened positive for depression and anxiety, respectively. In line with a previous study in the Portuguese setting (Rodrigues et al., 2023), the higher prevalence found potentially reflects the consensual association between TMD and psychological distress. A future comparative study using GAD-2 and PHQ-2 in a population not diagnosed with TMD will

be required to confirm these data. Moreover, GAD-2 and PHQ-2 are easy and reliable clinically validated screening tools. Nonetheless, as brief screening measures, a positive result should be complemented with other discriminatory methods or a directed clinical interview (Bisby et al., 2022; Kroenke et al., 2003, 2007, 2010; Levis et al., 2020; Manea et al., 2016). In our study, the values obtained could be overdiagnosis, and confirmation through other tools is necessary. If a sequential diagnosis based on PHQ-2 > PHQ-9 and GAD-2 > GAD-7 is implemented, a lower prevalence but a more accurate diagnosis will be obtained. Previous studies including PHQ-9 and GAD-7 screening tools, in patients with TMD or chronic orofacial pain established depression and anxiety prevalence values of 17-21% (PHQ-9 ≥10) and 15-29% (GAD-7 ≥10)(Bhalang et al., 2020; Simoen et al., 2020; Yeung et al., 2017). The biomolecular mechanisms in depression and/or anxiety disorders that trigger the biomechanical alterations in the TMJ are unsure. However, it is thought that depression and anxiety interact with pain-modulating networks and change the perception of pain, resulting in greater awareness of somatic and interoceptive cues (de Medeiros et al., 2020; Fillingim et al., 2013). Besides, it has been demonstrated that comorbid psychological distress promotes the long-term persistence of TMD-related pain and TMD chronicity (Auerbach et al., 2001; De Leeuw & Klasser, 2018; Epker & Gatchel, 2000; Gameiro et al., 2006; Garofalo et al., 1998; Kalladka et al., 2021; Ohrbach & Dworkin, 1998).

Psychological factors may be prominently relevant in myogenous disease and pain of muscle origin (Auerbach et al., 2001; Dimitroulis, 2018; Kalladka et al., 2021; Kmeid et al., 2020; Liu & Steinkeler, 2013; Manfredini et al., 2011). Psychosocial factors (stressful life events, psychological distress, and pathology) arouse the Central Nervous System, promoting excessive muscle activity (Golanska et al., 2021; Katon et al., 2001; Ohrbach & Michelotti, 2018; Sherin & Nemeroff, 2011). While multiple systems might be affected and influence myofascial pain, the limbic system (LS) and the neurologically related periaqueductal gray are primarily involved in the adjustment of emotions, defensive conduct, and pain modulation (Golanska et al., 2021; Macphail, 2014; Rajagopalan et al., 2017). The emotional motor systems orchestrate the LS response to the perceived environment. Hence, each specific emotion generates certain changes in the body – stress contributes to pain related to muscle tension and trigger point (TrP) formation and perpetuates the body response, causing more stress and pain

(hyperalgesia) (Golanska et al., 2021; Holstege et al., 1996; Pedroni et al., 2003). Muscular TrP is the critical element of myofascial pain syndrome and is classified as active (ATrP) or latent (LTrP). The latter is defined as the focus of hyperirritability in a taut muscle band and is clinically associated with a local twitch response, tenderness, and/ or referred pain upon manual examination (Barbero et al., 2019; Çelik & Mutlu, 2012; Simons, 2004). It has been shown that a higher number of LTrP is associated with a higher frequency of depressive symptoms reported by healthy individuals (Çelik & Mutlu, 2012). Likewise, anxiety seems to increase the likelihood of muscle tenderness (Mongini et al., 2007). In patients with tension-type headache, the number of ATrPs was associated with the physical burden of headache and trait anxiety levels (Palacios-Ceña et al., 2017). Furthermore, the LS outputs also impact autonomic, endocrine, somatic, nociceptive, and immune systems (Golanska et al., 2021; Macphail, 2014). The autonomic sympathetic nervous system is of primary relevance. A chronically activated fight or flight response leads to neuroendocrine disequilibrium, contributing to muscle hyperactivity and exacerbating perceived pain (Golanska et al., 2021; Macphail, 2014).

In our study, a high number of patients (89,9%) have been diagnosed with myogenous TMD. Depression was significantly associated with myalgia and myalgia degree. The tie was even more consistent for anxiety, where a significant association was shown for myalgia degree and post-treatment myalgia degree. Vedolin et al. have also shown that individuals with myofascial pain TMD reported higher anxiety levels than healthy people (Vedolin et al., 2009). The positive correlation between TMD and psychological factors would anticipate that higher levels of anxiety and depression would lead to a greater number of tender points, lower MMO, and reduced functionality (Auerbach et al., 2001; Calixtre et al., 2014; de Medeiros et al., 2020; Gameiro et al., 2006; Kmeid et al., 2020; Saccomanno et al., 2020; Tsai et al., 2002; Vedolin et al., 2009). However, no significant differences were found for the more objective clinical variables. Changes in the most subjective physical examination variables (e.g., muscle and joint palpation pain) seem to have the most robust relationship to changes in pain (Ohrbach & Dworkin, 1998). Stress and anxiety contribute to parafunctional oral habits and influence muscle pressure pain threshold (PPT) and pain. It has been shown that the masticatory muscles PPT of subjects with myofascial pain are markedly lower during stressful events, demonstrating an interaction with stress and anxiety levels (Ohrbach

et al., 2013; Vedolin et al., 2009). Masticatory muscles may be exceptionally responsive to stressful conditions of personal value (Flor et al., 1991; Vedolin et al., 2009).

Chronic TMD patients are more frequently diagnosed with muscular TMD and suffer from greater baseline psychological distress (Garofalo et al., 1998; Ohrbach & Dworkin, 1998). In our subset of patients requiring reintervention, higher pre-treatment perceived impact on health-related quality of life attributed to TMD (VASLife) and the composed variable of post-treatment myalgia degree and GAD-2 status were predictors of the need for reintervention. Hence, awareness should be raised to identify patients reporting a higher disease burden and whose symptoms subsist after treatment.

Physicians should educate patients on good oral habits and screen and treat underlying associated anxiety and depression. Cognitive behavioral therapy has been proven effective in TMD, particularly of muscular origin, and offers an integrated approach to psychological symptoms (Dimitroulis, 2018; Kalladka et al., 2021; Kmeid et al., 2020; Dion Tik Shun Li & Leung, 2021). The ultimate objective is to further assess how specific areas of psychological dysfunction influence specific subtypes of TMD patients to tailor more efficient early intervention and pain management programs (Auerbach et al., 2001; Kalladka et al., 2021).

Study Limitations

(1) The multivariable prediction model for reintervened patients was limited by the small subset of reintervened patients.

(2) The authors did not implement a sequential depression and/or anxiety screening methodology. Despite the great case-finding ability of PHQ-2 and GAD-2 as initial screening measures, specificity could be improved by applying GAD-7 and PHQ-9.

(3) The follow-up period was different between patients.

(4) All patients were treated in one single institution by the same surgeon.

More studies are required to characterize these and other patient-related variables that may influence treatment outcomes and further enhance the profiling of reintervened patients.

CONCLUSIONS

In this retrospective study, preexistent depression and/ or anxiety were highly prevalent, with 38.4% of the patients screening positive for depression and 53.8% for anxiety. Psychological distress was far more frequent in our TMD patients than in the Portuguese population, probably reflecting the relation between TMD and mental health disorders.

In this study, a higher psychopathological burden was significantly associated with pre-treatment VASLife ($p=0.040$, PHQ-2 ≥ 2; $p=0.025$, GAD-2 ≥3) and myalgia levels ($p=0.013$, PHQ-2 ≥ 2; $p=0.038$, GAD-2 ≥3). Myalgia significantly subsisted after treatment in anxious patients ($p=0.038$, GAD-2 ≥3). For the other clinical variables, including the more objective ones, no significant differences were found. In line with previous studies, myogenous TMD was highly prevalent, affecting 89.9% of our patients. The clinical variables displaying significance specifically correlate with this TMD subtype - myalgia.

Furthermore, in anxious patients, our study suggested that a higher pre-treatment VASLife and the subsistence of post-treatment myalgia levels might predict reintervention. Nonetheless, a more accurate model is necessary to predict which patients will likely need reintervention due to the limited sample size.

Our study established that pre-treatment depression and/ or anxiety significantly impact TMD clinical outcomes, particularly in myogenous TMD, and contribute to the need for reintervention. The presence of comorbid mental health disorders should warn the physician/surgeon to efficiently invest and manage resources and treatment strategies in a multidisciplinary treatment program, ideally including psychotherapeutic strategies and maximizing potential health gains.

Future studies should aim to implement accurate sequential mental health disorders screening methodologies and personalized early intervention programs promoting effective holistic TMD approaches.

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APPENDIX – APPROVAL BY THE ETHICS COMMITTEE OF CAML

CENTRO ACADÉMICO DE MEDICINA DE LISBOA | CENTRO HOSPITALAR LISBOA NORTE, EPE | HOSPITAL DE SANTA MARIA | Hospital Pulido Valente | LISBOA | FACULDADE DE MEDICINA LISBOA | MM Instituto de Medicina Molecular | João Lobo Antunes

Exma. Senhora

Dra. Rita Alexandra Nunes Rodrigues

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Lisboa, 26 de Dezembro de 2022

Nossa Refª. Nº 311/22

Assunto: Estudo "Influência de um diagnóstico de depressão e/ou ansiedade nos tratamentos da articulação temporomandibular, um estudo retrospetivo"

Pela presente se informa que o projeto citado em epígrafe a realizar no âmbito do Mestrado integrado em Medicina da Faculdade de Medicina da Universidade de Lisboa, obteve, na reunião realizada em 2 de Dezembro de 2022, parecer favorável da Comissão de Ética, considerando-se observados os imperativos que fundeiam as Boas práticas clínicas, os preceitos internacionalmente reconhecidos de qualidade ética e científica que devem ser respeitados na conceção e na realização dos estudos clínicos que envolvam a participação de seres humanos.

No uso das competências próprias constantes do disposto no Decreto-Lei. N.º 97/95 de 10 de Maio, e no exercício das suas funções em observância ao deliberado na Lei n.º 21/2014 de 16 de Abril, que aprova a lei da investigação clínica, na sua atual redação alterada pela Lei n.º 73/2015 de 27/07/15, complementada pelo Decreto-Lei n.º 80/2018 (DR n.º 198-2018, Série I de 2018/10/15) que reforça o papel das comissões de ética no contexto da instituição em que se integram, na sua missão de contribuir para o cumprimento de princípios da ética e da bioética, na prestação de cuidados de saúde e na realização de investigação clínica, e ainda em harmonia com os regulamentos internos do CHULN, os códigos deontológicos, as convenções, e as recomendações constantes das declarações e diretrizes internacionais, designadamente as Declarações de Helsínquia a de Tóquio, da Organização Mundial de Saúde e da União Europeia, a Comissão de Ética avaliou o projeto, que considera obedecer aos requisitos éticos fundamentais que devem ser respeitados, refletindo o primado da dignidade e da integridade humanas.

Encontra-se assegurado o direito à integridade moral e física do participante, cumpre as precauções essenciais, cujo desígnio visa minimizar eventuais danos para os seus direitos de personalidade, bem como o direito à privacidade e à proteção dos dados pessoais que lhe dizem respeito, respeitando os imperativos refletidos no Regulamento Geral sobre a Proteção de Dados (RGPD) entrado em vigor em 25 de Maio de 2016 e plenamente aplicável a partir de 25 de Maio de 2018, (Regulamento (UE) 2016/679 do Parlamento Europeu e do Conselho de 27/04/16), de 27 de abril, publicado no Jornal Oficial da União Europeia, no dia 4 de Maio de 2016, e na Lei n.º 58/2019, de 8 de Agosto

Com os melhores cumprimentos

O Presidente da Comissão de Ética do CAML

Prof. Doutor João Forjaz de Lacerda

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1