# Psychologic impact of chronic orofacial pain: A critical review

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# **Abstract**

**Aims:** This critical review explored the prevalence of clinically significant anxiety and depression in adult patients with chronic orofacial pain (COFP) conditions. **Methods:** A systematic online search of Medline (PubMed) and Ovid databases was performed from 2006-2019. Observational studies, including cross sectional, case control and case series and longitudinal prospective studies were included. One hundred and eighteen articles were selected. Prevalence rates of clinically significant anxiety and depression were summarised. **Results:** Most studies focussed on temporomandibular disorder (TMD) pain and less often on neuropathic COFP conditions. Prevalence rates varied widely across studies according to OFP condition and assessment measure; most questionnaire-based assessments yielded respective rates of clinically significant depression and anxiety in 40%-60% and 40%-65% of individuals with TMD and in 20%-50% and 25%-55% of patients with neuropathic, mixed or idiopathic/atypical orofacial pain conditions. Rates of anxiety and depression were lower in studies using diagnostic instruments and in TMD studies with non-patient samples. Most controlled studies showed higher prevalence of anxiety and depression in individuals with COFP than those without. Higher COFP pain levels, and presence of comorbid conditions such as migraines or widespread pain increased the likelihood of anxiety and/or depressive symptoms in individuals. **Conclusion:** Clinically significant anxiety and depression were commonly observed in patients with COFP, was at higher rates than pain-free participants in controlled studies, and was closely linked to pain severity. More research is needed to evaluate the psychologic impact of multiple orofacial pain conditions in an individual and the prevalence of pre-condition psychologic morbidity.

**Key words:** Orofacial pain, Neuropathic/ Non-neuropathic pain, TMD, Anxiety, Depression

**Statement of Clinical Relevance**

Chronic orofacial pain causes distress and disability. It affects life negatively and often leads to anxiety and/or depression and extensive use of the healthcare system. Holistic management for orofacial pain requires a biopsychosocial approach.

# Introduction

Orofacial pain is a noxious, painful experience in the region of the face and /or oral cavity.1 According to International Association for the Study of Pain (IASP), pain is defined as “*an unpleasant sensory and emotional experience associated with actual and potential tissue damage”.*2 Chronic pain continues after the expected time of recovery.3 There is evidence that pre-existing psychologic factors can predict onset of chronic post-surgical pain.4

Patients with chronic pain frequently undergo a change in their beliefs and cognitions; as a result, these affective and cognitive pathways contribute to the sensory perception of pain.5 Over a period, individuals with chronic pain may lose the capability to function optimally and some may retire from work early.6 Non-orofacial chronic pain conditions can cause a significant degree of disability.7 In the United States, it is responsible for 21% of visits to accident and emergency departments and 25% of absenteeism from work annually, significantly increasing the economic burden.8 Orofacial pain (OFP) is specifically linked with increased workday loss and excessive use of the healthcare systems.9, 10

OFP prevalence ranges from 17%-26% with up to 11% considered chronic orofacial pain (COFP).11 COFP is often associated with psychologic disorders and there is a strong link between long standing OFP and depression and anxiety symptoms, with subsequently impaired psychologic function.6 Without acknowledgement of psychologic factors, pain management is limited and the recovery process often compromised, because differences in individual’s psychologic predisposition result in differential responses to pain.12

The aim of this review was to investigate studies of psychologic functioning (anxiety and depression) in patients with COFP, with consideration of both neuropathic and non-neuropathic COFP conditions.

# Materials and Methods

The review protocol, including the search strategy, was registered with Prospero, an international prospective register of systematic reviews ‘PROSPERO’(Registration number: CRD42016043703).13 Meta-analyses were not possible due to the heterogeneity of included studies. The cumulative evidence from the included studies was assessed, summarised and narrated.

## Search strategy and selection criteria

The review included observational studies published between 2006 and 2019. These were cross sectional, case series, and prospective and retrospective cohort studies. The information source was from Medline (PubMed) and Ovid databases. Grey literature was searched from Google Scholar. Studies in English language, which investigated at least one type of OFP condition in adults (aged 18 and older) and explored psychologic factors such as depression, somatisation, post-traumatic stress disorder and catastrophizing were selected. Studies recruiting individuals under the age of 18 years and studies exploring dental and periodontal inflammatory conditions and their psychosocial impacts or influences were excluded.

**Definitions**

Chronic pain is defined as a pain that exceeds a du­ration of 3 months,3 and this definition was applied to COFP for the present study.

Psychology was defined as a scientific study of individual’s behaviours and their mental processes.14 According to the World Health Organisation (WHO), depression is a mental disorder that presents with depressed mood, loss of interest or pleasure, decreased level of interest and concentration, disturbed sleep, lack of appetite with hopelessness and worthlessness.15 Depression can often be associated with anxiety symptoms.15 Generalised anxiety disorder was defined as six months of excessive worry on daily issues which may be associated with autonomic symptoms.15  State (St) anxiety is a temporary emotional arousal to a perceived threat and trait (Tr) anxiety is a personality characteristic and pattern of response (with anxiety) to a threat.16 Phobias, obsessive-compulsive disorder and panic disorders were included in anxiety disorders. Phobia is a constant pronounced fear of a situation that can result in either avoidance or panic attacks.15

## Search terms

The key words used were psychosocial, psychologic, depression, psychiatric comorbidity, post-traumatic stress disorder (PTSD) and anxiety. These with “OR” and “AND” were used with the following conditions; orofacial pain, temporomandibular joint pain/disorder, trigeminal neuralgia, trigeminal nerve injury, burning mouth syndrome, persistent dento-alveolar pain, atypical facial pain and atypical odontalgia.

## Outcome measures

The objective of this review was to investigate studies of anxiety and depression in patients with COFP, and more specifically, to identify the reported prevalence of anxiety and depression caseness in affected individuals and their relationship with pain chronicity, pain severity and demographic factors such as gender and age.

## Data extraction

The initial search yielded 5024 articles. Suitable articles were identified (n=252) for the title and abstract screening through the process of selection and filtration. Duplicates were removed. Full text screening of 134 articles was carried out. Based on inclusion and exclusion criteria, a total of 118 articles were selected.

[Insert Figure 1 about here]

Initially, to establish their relevance for the review, one reviewer (AK) read the title and abstract of each article. After reading the abstract and ensuring that the article provided the necessary information for the review, the entire article was retrieved and read to further establish if it fulfilled the eligibility criteria. Any study that was unclear about inclusion criteria was read by the second (JS), third (LM) and fourth (TR) reviewers. After discussion, consensus was reached for all articles included. Bibliographies of the selected articles were also manually searched.

The studies on COFP were categorised according to the classification (diagnostic) system of International Classification of Headache Disorders-3 (ICHD-3),17 Research Diagnostic Criteria Temporomandibular Disorders (RDC/TMD),18 and the IASP and American Academy of Orofacial Pain (AAOP).19, 20 All studies were assessed on the following parameters; type of study, type of pain under investigation, sample size, psychologic scale used, psychologic comorbidities under investigation, reported prevalence of psychologic comorbidities in each study and the year of the study.

Meta-analyses was not considered appropriate as there were insufficient number of studies with required level of homogeneity in study design, COFP population under study and depression/anxiety scale or method of assessment used.21

## Risk of bias (RoB) assessment

This study used a method previously employed in systematic reviews of oral conditions to assess the risk of bias (RoB).22-24 Studies were evaluated on the following criteria: 1. Study group characteristics (whether consecutive or random patient selection) was performed; 2. Presence of an appropriate control group (sex and age matched); 3. Prospective study or data collected on purpose for the specific study; 4. Whether participants or the investigators were blinded if appropriate according to the study design.

Criteria were assessed as met, unmet, or unclear for each. Three factors were used to assess the study's overall validity: 1.There is a low risk of bias because all of the criteria were met according to the study design; 2. There is a high risk of bias if at least one criterion unmet or three criteria unclear; 3. There is a moderate risk of bias if one or two criteria are unclear or one or two criteria were not applicable according to study design. Four reviewers independently evaluated the RoB. All studies were distributed equally among the reviewers.

# Results

The defining characteristics and key findings are summarised in Table 1.

[Insert Table 1 about here]

## Participant characteristics

**Diagnosis**

The majority of included studies (63) focussed exclusively on TMD pain 25-87 and its impact on psychologic wellbeing (i.e. anxiety/depression). Twenty-four studies recruited patients with a single neuropathic pain condition (16 burning mouth syndrome (BMS), 88-103 2 post traumatic neuropathic pain (PPTN) 104, 105 and 6 trigeminal neuralgia (TN) 106-111). Fifteen studies compared patients with various types of OFP conditions; 16, 112-125 these included studies comparing BMS with trigeminal neuralgia (TN), PPTN/TN with TMDs, idiopathic continuous orofacial neuropathic pain with TMDs, TN with TMDs, TMDs with migraine and headaches (neurovascular pain), TN with atypical facial pain and BMS with atypical odontalgia (AO). Six studies focused on OFP in general (where pain types were not specified) 126-131 and one recruited patients with atypical odontalgia.132 Sample sizes across all studies ranged from 08 – 3904 participants.

## Gender

With the exception of the clinical trial of PPTN patients, where gender was evenly distributed,104 mixed gender studies involving clinical OFP populations employed samples that predominantly comprised females (range 60-97%), with the exception of two studies where females were in the minority (36%/38%).61, 106 Eight studies included females (TMD & BMS) only. 36, 44, 51, 52, 71, 74, 93, 97 Aside from the community survey of elderly people (77% female), 128 studies recruiting patients from the (general) healthcare population tended to have a small majority of females (range 51%-64%).31, 48, 58, 131 The age range of study population across most studies was 18–80 years except for one where the upper limit was 100 years.118

## Study design

Eighty-six studies were cross sectional in design 25, 27-32, 34, 36-42, 44, 47, 49, 50, 53, 55-57, 59, 60, 62-65, 67-71, 73-77, 79-81, 83-91, 94, 95, 97-100, 102, 103, 105, 107, 108, 110-114, 116-124, 126-128, 133, 134 and 11 were longitudinal prospective studies.33, 43, 45, 46, 48, 54, 109, 111, 129-131 Ten were designed as case control,16, 35, 51, 52, 58, 61, 78, 82, 96, 132 8 were retrospective 26, 66, 92, 101, 106, 110, 115, 133 , one was a case series 93 and two were clinical trials.72, 104 An exception was made to include two clinical trials, as the studies measured the association post-intervention between the level of pain experienced and the degree of observed anxiety and depression.

**Studies characteristics**

Sixty-seven studies 16, 28, 31, 35, 44, 45, 47, 48, 51, 52, 54, 55, 57, 58, 60, 64-67, 70, 71, 73, 74, 77, 79-100, 102, 104-112, 114-116, 118, 119, 122, 125, 126, 129, 131, 133 investigated the association of OFP with anxiety and depression, 9 studies 25, 39, 42, 46, 59, 61, 75, 76, 103 with anxiety only, 31 studies 26, 27, 29, 30, 32, 33, 36-38, 40, 41, 43, 49, 50, 53, 56, 62, 63, 68, 69, 72, 101, 113, 117, 120, 121, 123, 124, 127, 130, 132 with depression only, one with psychologic distress 128 and one also investigated hypochodriacal beliefs.34 Seventy-seven 27-33, 36-38, 40-49, 55, 57-62, 64-73, 76, 78-80, 82-84, 87, 89, 92, 93, 96, 99-101, 105-109, 111, 112, 117-119, 122, 123, 125-130, 132, 133, 135-139 provided prevalence data for anxiety and/or depression, although three studies did not reported prevalence rates separately for OFP and non-OFP groups.42, 60, 129 Most of the research was carried out in Europe (56), followed by Asia (38), Latin America (15), USA (6), Australia (1) and 2 spanned across continents. There were 33 (28.0%) low RoB studies and 27 (22.9%) high RoB studies; almost half of the studies (58 or 49.2%) had a moderate risk of bias (Table 2).

[Insert Table 2 about here]

## Orofacial pain assessment criteria

Ninety-seven percent of the studies followed an established diagnostic criteria/classification system for the OFP conditions. These included Research Diagnostic Criteria/ TMD (RDC/TMD),25-30, 32, 34-42, 47, 49, 52-54, 56, 58, 61-64, 66, 68, 70, 73, 75, 76, 78, 80, 81, 83, 84, 86, 87, 114, 115, 121, 123 Helkimo Anamnestic Dysfunction Index for TMD,31, 33, 57, 59, 60, 65, 77, 79 International Headache Society (IHS) International Classification of Headache Disorder (ICHD) criteria,78, 89, 91, 93, 94, 96, 97, 99, 100, 102, 108, 109, 112, 115, 122-125, 129, 133 American Academy of Orofacial Pain (AAOP) criteria,46, 48, 50, 51, 112, 114 International Association for the Study of Pain (IASP),90, 107, 114, 115, 117, 120 Cranio-mandibular Index (CMI)43, 116 and European Academy of Cranio-mandibular Disorder (EACD).45 The Liverpool criteria for trigeminal nerve pain was used by one study16 while another used Xu-chen Ma + Zen-Kang Zhang classification for TMD pain.44

## Psychologic screening tools used

Sixty-nine studies used a single psychologic tool while 49 studies used a combination of psychologic assessment tools. The Research Diagnostic Criteria/Temporomandibular Disorders (RDC/TMD) (Axis II) questionnaire 25-27, 29, 32, 36-41, 47, 49, 53, 56, 58, 62, 63, 66, 70, 72, 83, 121, 123, 132 was used exclusively for TMD pain, the Symptom Check List -90-Revised (SCL-90-R) 26, 28, 37, 38, 40, 41, 44, 47, 52, 53, 63, 66, 69, 70, 94, 97, 113, 116, 120, 121, 127 to assess psychologic symptoms/distress and the Hospital Anxiety and Depression Scale (HADS) 31, 35, 45, 54, 57, 60, 61, 65, 67, 71, 73-75, 78, 79, 91, 92, 104, 105, 107, 111, 114, 115, 122, 126 was most commonly used to screen for anxiety and/or depression. Five studies used the Structured Clinical Interview for Diagnosis-Diagnostic and Statistical Manual of Mental Disorders (SCID-DSM-4/5) guide. 28, 112, 119, 131, 133

## Prevalence of anxiety and depression in patients with orofacial pain

The prevalence of depression and/or anxiety disorder in OFP, according to OFP group and assessment instrument, are summarised in Figures 2a/2b and 3a/3b. With respect to standardised questionnaire assessments, rates were included only for those patients evidencing moderate or severe symptoms (where questionnaires included an umbrella classification of ‘mild-to-moderate’, patients scoring in this range were also considered) or, in the case of HADS, those showing borderline-clinical or clinically significant levels. Where studies included assessments at two time points, only the first was included.

For TMD conditions, the prevalence of observed depression ranged from 7.0%-77.4% (Figure 2a). In general, studies using RDC/TMD or SCL-90-R assessments reported the most consistent prevalence rates, with 14 of 20 (70%) studies observing depression in 41.4%-56.0% of participants. Studies adopting other standardised questionnaires (e.g., HADS/BDI) reported lower rates of depression - although this varied considerably across studies - while diagnostic assessments of depression were consistently around 20% (15.7%-22.3%). Rates of (clinically significant) anxiety in TMD also varied widely across studies (7.4%-78.0%; Figure 2b), although observed prevalence in studies using RDC/TMD or SCL-90-R and HADS assessments were more comparable, with 11 of 14 studies adopting either measure yielding anxiety caseness rates between 43.9% and 63.0%. The single study that estimated anxiety prevalence using CID-S 48 reported high rates of anxiety in both TMD MP (78.0%) and TMD JP (64.8%). In contrast, GAD-7 assessments of TMD anxiety 80, 84, 87 resulted in lower prevalence rates, ranging from 11.4%-20.0%. Notably, irrespective of assessment method, studies with low prevalence of depression and/or anxiety tended to recruit non-clinical samples 31, 46, 62, 79 or TMD samples with low pain disability levels 44 while higher rates were observed in clinical studies of patients with TMD and headache.73, 123

[Insert Figures 2a/2b about here]

The prevalence of depression and anxiety for neuropathic, mixed and idiopathic/atypical orofacial pain conditions ranged from 2.2-100% and 0%-80.7%, respectively (Figures 3a/3b). Rates of depression and anxiety varied widely in TN samples, with low prevalence rates reported in studies using diagnostic assessments 106, 112 and higher rates in TN with associated comorbidities such as chronic facial pain 118 and MS.111 Prevalence rates of depression and anxiety in BMS were more consistent. Aside from one small clinical study of 8 patients with treatment-resistant BMS which observed depression in all patients, 93 questionnaire-based assessments yielded moderate-to-severe symptoms in between a quarter and a half of BMS patients across studies. Clinically signifcant levels of anxiety in BMS were highest in studies using HARS and HADS (39.3%-80.7%) 92, 93, 136, 139 and lowest in those employing the BAI (21.0%-33.3%).96, 138 Three of the four BMS studies with diagnostic assessments reported anxiety disorders in between a third and a half of participating patients. 89, 117, 119 In one study of PPTN pain, clinically significant anxiety was found in 51.2% of individuals and depression in 30.0% of cases.105 Depression in AO was reported at 74.0% in one study which used the SCL-90-R 132 but only 15.4% in a diagnostic assessment study. 133 Similarly, rates of diagnosed anxiety disorders in AO samples were uncommon in two studies (10.1%-10.8%); 117, 133

[Insert Figures 3a/3b about here]

## Prevalence of anxiety and depression in orofacial pain conditions versus control participants

A number of studies comparing prevalence rates in TMD and control participants reported significantly higher rates of anxiety 31, 45, 58, 59, 61, 71, 73, 79, 82, depression 36, 58, 68, 71, 73 or anxiety and/or depression 57, 65 in individuals with TMD. One TMD study of dental students failed to find significant differences in state and trait anxiety between those with and without TMD 76, while another three studies of pre-university/university students reported significantly higher anxiety prevalence in TMD cases versus controls but non-significant elevations in depression.31, 45, 79 Significantly higher rates of depression were also observed in studies comparing mixed OFP patients to individuals without OFP.33, 127, 130

Although studies comparing mean scores of standardised questionnaires assessing anxiety and depression in neuropathic OFP conditions such as TN or BMS against control participants have reported elevated scores in the former (indicative of greater levels of symptoms of anxiety/depression,91, 102, 110 fewer controlled studies have compared prevalence rates of clinically relevant anxiety or depression. However, two controlled studies observed significantly elevated rates of both anxiety and depressive disorders in patients with TN 106 and BMS 89 while another study comparing BMS and secondary oral burning patients reported elevated rates of moderate-to-severe depression (BDI) in BMS but comparable rates of anxiety (BAI).138 Finally, one study comparing AO and control participants found significantly more of the AO patients showed moderate-to-severe depression levels. 132

**Single study comparisons of different OFP conditions**

Thirteen studies compared two or more types of OFP conditions.16, 112-115, 117-122, 124, 125 In one study, neuropathic pain (TN and trigeminal neuropathy) and TMD pain patients were significantly (but comparably) impaired in domains of anxiety (state and trait anxiety) and depression when compared with controls.16 Another study reported that TN patients showed numerically higher scores on measures of psychologic impairment than TMD patients, although there were no statistically significant differences between the two groups.114 When TN and atypical facial pain (ATFP) were investigated, it was observed that TN patients evidenced significantly higher levels of pain perception than ATFP patients and were significantly more likely to exhibit moderate to severe depression levels (76% versus 0%). 118 Another study reported that BMS and ATFP demonstrated comparable levels of depression symptoms.119 Komiyama and colleagues compared patients with BMS and TN and reported that pain levels were higher in TN than BMS. However, regression analysis indicated the associated risk of depression in BMS patient was significantly higher than that in TN patients.120 Takenoshita and colleagues investigated mood in COFP patients (BMS and atypical odontalgia (AO)) using Zung’s Self-Rating Depression Scale and observed depressive tendencies in 32.1% of BMS patients and 33.3% of individuals with AO.117 Gerrits and colleagues’ large-scale study of chronic pain suggested, onset of anxiety and/or depression with pain and observed that pain specifically in orofacial region was associated with depression symptoms. 131 A study on BMS and ATFP, used Structured Clinical Interviews (SCID) reported high rates of psychiatric disorders, most commonly major depression (30.2%), social phobia (15.9%), specific phobia (11.1%), and panic disorder (7.9%); and in these cases illness run a chronic course and difficult to treat.119 Another study on TMD pain using the same interview technique exhibited frequent presence of psychiatric history in myofascial pain patients. 28 Melek and colleagues compared TN with PPTTN, depression was reported in 54% of TN and 36% of PPTTN, while anxiety was comparable in both groups (34%-39% respectively).125

## Association between orofacial pain severity and chronicity with anxiety and depression

The majority of selected studies (with both neuropathic and non-neuropathic pain samples) demonstrated that an increase in pain intensity and/or pain chronicity (more than 3 months duration) 3 elevated patients’ anxiety and depression symptom levels.

**Neuropathic orofacial pain**

For patients with neuropathic pain, consistent associations of anxiety and depression with pain intensity were identified. For example, patients with severe trigeminal nerve injury pain showed elevated levels of depression on the HADS, compared with patients with moderate and mild pain levels in one study.105 In another study, change in post-traumatic peripheral neuropathic pain levels was significantly associated with change in anxiety and depression levels; 104 every two point decrease in level of pain (0-10 numeric rating scale) was associated with 1.5 points reduction in anxiety and 1.2 points reduction in depression on the HADS.104 BMS patients have also demonstrated a positive association between levels of depression and (BMS) symptom severity.88 Additionally, one study found an association between presence of anxiety symptoms and pain severity among elderly individuals with neuropathic pain (BMS).103

**TMD pain**

For TMD pain, cases were divided into acute and chronic by some investigators and were compared. Depression was more prevalent in patients with chronic TMD pain,36, 40, 43, 66, 69 and severity of depression and anxiety increased with higher graded chronic pain scores.44, 47, 49, 63, 66, 68, 116 Su et al compared TMD patients with high- and low-intensity pain and reported marked differences in prevalence of both moderate-to severe anxiety (27.9% vs. 11.4%) and moderate-to-severe depression (33.5% vs. 10.2%).84 Multiple pain sites were also associated with higher levels of depression in another study.40 A number of investigators also reported significant associations between anxiety levels and chronic TMD pain,31, 39, 42, 58, 61, 70 most obviously for myofascial subtype of TMD.25, 45, 48, 64 Patients with TMD pain, especially muscle pain, presented with more psychologic problems compared to patients with TMD joint pain in one study.28 Moderate-to-severe anxiety and depression in chronic TMD was reported as high as 58.3% and 61.2%, respectively, in another study.66

Some studies with TMD patients reported significant associations between the level of physical/psychologic disability and pain intensity using hierarchical pain grading approach (Graded Chronic Pain Scale) which classifies pain/disability into 4 broad categories; grade I (lower pain intensity / low disability), grade II (high intensity / low disability), grade III (moderately limiting pain / high disability) and grade IV (severely limiting pain / high disability).140 For example, in one study psychologic impact tended to be greater in patients with grade III/IV pain; anxiety was identified in 53.8% of individuals and depression in 76.9% of individuals,44 while in another study severe depression was prevalent in 40.7% of patients with grade III/IV pain.38

# **Orofacial pain, gender/age and anxiety and depression**

Most but not all studies considering gender suggested women with OFP may report higher levels of anxiety or depressive symptoms than men. For example, in one study, younger (under the age of 24) and middle aged (between 35-55 years) women with OFP scored higher on a depression scale compared to men of similar ages.56 Licini and colleagues 32 reported that moderate to severe depression was evident in 56.1% of women with TMD pain compared to only 10% of men. Women with chronic TMD myofascial pain also scored marginally higher on a depression scale than men in another study, 35 although men with other chronic facial painful conditions (post-surgery pain, post-traumatic or neuropathic pain) and not specifically TMD pain were more depressed compared to females.35 In contrast, Giannakopoulos and colleagues did not find any differences in anxiety between men and women with TMD, suggesting poorer psychologic well-being in women is not uniformly observed in studies of OFP.35

## Impact of comorbid conditions on anxiety and depression in individuals with orofacial pain

Both neuropathic and non-neuropathic (TMD) OFP can co-exist with other medical conditions such as degenerative disease, migraine and widespread pain, and reviewed studies suggested their presence can increase the likelihood of significant psychologic disability in affected individuals.30, 71, 78, 111, 113, 119, 121, 123, 127, 129 For example, a study of acute TMD subtypes showed that individuals with muscles and joint pain, along with a history of degenerative joint disorder, have significantly higher levels of depression compared to those with a single condition.30 Cioffi and colleagues’ study of TMD pain and migraine found that individuals with a combination of chronic TMD myofascial pain and migraine were experiencing significantly higher levels of depression compared to isolated TMD groups.121 Ballegaard and colleagues’ studied depressive symptoms in patients with headache and compared them with patients having headache and comorbid TMD; the authors reported that 34.1% of headache patients had depressive symptoms compared to more than 70% (70.9%) of those with headache and comorbid TMD pain. 123

A similar pattern of results emerged from studies of neuropathic OFP. For instance, Lopez-Jornet and colleagues observed a positive association between BMS, poor sleep quality and comorbid anxiety/depression (as measured using HADS). Regression analyses indicated that for every 1-point increase in HADs depression score, the odds of sleep quality deterioration increased 1.26 times.91 McMillan and colleagues found that while patients with OFP were 3.5 times more likely to exhibit moderate to severe depression than control participants, psychologic distress was observed most often in individuals with OFP pain who had widespread pain symptoms, these patients constituted 13.5% of their OFP sample.127

# Discussion

The purpose of this study was to review research describing anxiety and depression in patients with (neuropathic and/or non-neuropathic pain) OFP. The results showed that experience of OFP is associated with both anxiety and depression that can be disabling in nature and markedly influences individuals’ emotional wellbeing. This review of 118 studies identified positive associations between pain intensity, chronicity and symptom severity and the presence of anxiety and/or depression. The prevalence of clinically significant or moderate-to-severe anxiety in neuropathic, mixed and idiopathic/atypical orofacial pain conditions ranged from 0%-80.7%, of cases while prevalence of clinically significant or moderate-to-severe depression ranged from 2.2%-100% of cases. In non-neuropathic (TMD) pain conditions, the observed ranges were also wide; anxiety ranged from 7.4%-78.0% of cases and depression from 7.0%-77.4% of cases. The large variance in observed rates across studies likely reflects the differential method of assessment and/or nature of the recruited samples in included studies. For TMD conditions, the majority of RDC/TMD or SCL-90-R assessments yielded depression rates of around 40%-60%, most RDC/TMD, SCL-90-R or HADS assessments resulted in anxiety prevalence of 40%-65%, while diagnostic assessments of depression and anxiety suggested disorder rates of 15%-20% and 15%-35%, respectively. Irrespective of assessment method, the lowest observed prevalence rates were in TMD studies employing student samples rather than clinical populations. The majority of questionnaire-based assessment in patients with TN yielded rates of depression and anxiety of around 20%-35% and 40%-55%, respectively, with lower rates in studies reporting diagnostic assessments, while questionnaire-based assessments of depression and anxiety in BMS studies showed moderate-severe symptoms in between a quarter and a half of patients, with similar rates reported in most diagnostic studies of BMS patients.

The association between pain and depression is complicated due to their common neurobiology, complex environmental influences and negative cognitions.141 Neurotransmitters such as serotonin, nor epinephrine, glutamate and GABA are intimately linked with pain processing as well as mood.141 For instance, serotonin and norepinephrine reduction are associated with impeded gate control mechanism and mood disorder progression.142  The review identified a close association between COFP and psychologic comorbidities. This is in line with available literature where psychologic factors are now recognised as important comorbid features in presentation of OFP.143, 144 All types of pain are influenced by psychologic components; however, negative affect appears particularly important in the emergence and maintenance of chronic pain syndromes.145, 146 COFP has a profound influence on psychologic health of individuals; this includes anxiety, stress, phobias, depressive symptoms, catastrophizing and emotional disturbances, 12 as well as oral health-related quality of life.9 Increased pain intensity negatively impacts quality of life also.10 The American Psychiatric Association (APA) have recognised that mental illnesses such as anxiety disorders, somatoform disorders and mood disorders are closely related to medical conditions including hypersensitive pain perception.145 TMD myofascial pain patients are more likely to have higher levels of psychologic symptoms.147 This concurs with the findings of a recent systematic review reporting the frequent co-occurrence of psychiatric disorders and masticatory muscle pain.148

Pain perception and experience differs considerably across individuals and varies according to gender. The overrepresentation of females in OFP pain samples, especially in studies of TMD pain, was illustrated in this review. Further, gender differences in the few studies directly addressing the role of gender in psychologic correlates of OFP suggested that both anxiety and depression are more often observed in females rather than males in TMD pain. There are reports that oestrogen (female hormone) may have a role in pain regulatory mechanism of TMD pain subgroups.149 However, this needs further investigation. The impact of gender on comorbid anxiety and/or depression in individuals with neuropathic OFP is less clear and needs addressing in future studies.

The present review also suggests that individuals presenting with multiple pain conditions are more likely to have pronounced psychologic problems.121, 123, 131 More specifically, across reviewed studies, individuals with multiple OFP conditions were more likely to have severe negative psychologic impairment, most obviously high levels of depression, compared to those with single conditions. Similar findings have been reported in OFP literature150 and is broadly consistent with studies of body pain where patients with widespread chronic pain (e.g., fibromyalgia) often present with marked negative affective and cognitive states.151

There was a substantial degree of variability in the design and associated risk of bias of studies included in this review, which contributed to the difficulty in arriving at a consensus. Eleven studies used a longitudinal prospective design, 10 were designed as case control and 8 were retrospective. The absence of (pain free) control groups was a frequent shortcoming of studies included in this review.Nevertheless, the overwhelming majority of studies (46) where a control sample was employed evidenced higher rates of anxiety and/or depression in OFP patients (neuropathic, mixed OFP and TMD) compared to pain free controls.16, 132 The only exception to this was a small number of TMD studies which recruited student (non-patient) populations in which the individuals diagnosed with TMD were not currently receiving or seeking treatment. 31, 45, 76, 79

Most studies, particularly those with neuropathic orofacial pain samples, were conducted at tertiary care units through opportunity sampling. Of course, patient recruitment from a tertiary care unit may not be representative of general population, reducing generalizability and external validity of the included studies. More specifically, this may have resulted in over presentation of anxiety and/or depression in individuals with OFP. Most studies (86) were cross sectional, where the data was collected at a single point in time, rendering it difficult to differentiate between cause and effect through simple association.152 As such from this review, a clear association on the aetiological pathway could not be established, specifically, if pain resulted in psychologic morbidity or vice versa. It is important to consider that a number of studies have suggested that a range of premorbid psychologic variables can predict the development of OFP, particularly TMD.153, 154 However, the available evidence suggest a bidirectional relationship between anxiety/depression and pain, 155 supported in part by functional neuroimaging studies suggesting shared underlying neuro mechanisms.156

Significant variation in the use of psychologic tools for data collection was found. Various self-reported questionnaires were utilised and the majority of studies did not make distinction between acute and chronic pain, although most of the patients included in studies had OFP for more than 3 months. This may have affected the validity of the data due to variation in personal characteristics, levels of patients’ education, their ethnicity, culture and social beliefs.157 The majority of studies in the current review employed only a single psychologic scale and most adopted the questionnaire-specific cut-off points for caseness of anxiety or depression which remain difficult to interpret across measures. For example, comparability between STAI State 158 can be made with HADS but a compelling comparison data set is as yet not available35 and STAI Trait also includes a number of depression items related to depressive symptomatology.159 Few studies have used SCIDs based on Diagnostic and Statistical Manual of Mental Disorders-IV (DSM IV) criteria, 28, 112, 119, 131  which is a formal diagnostic tool as opposed to questionnaires such as HADS, which better serve as screening instruments (i.e. do not allow for definite diagnoses) and provide dimensional rather than categorical representations of mood.160 More research is needed through employment of a standardised set of questionnaires and screening tools which also address wider psychologic and social aspects of psychologic function in patients with OFP.

Notable differences emerged in the diagnostic procedures of COFP conditions across studies, in so much as there were several classification systems used that do not entirely concur with one another; therefore results across different studies with OFP samples are not completely comparable. Literature on orofacial pain classification have discussed this issue in detail,143, 161 emphasising the need for a standardized biopsychosocial classification of OFP which is highlighted again in this review.

For this review, limited data sets were considered and only English language articles were searched reducing the scope of reviewed studies. Nevertheless, the review demonstrated substantive evidence for an association of anxiety and depression with both neuropathic and non-neuropathic pain OFP conditions. Both within and across studies, no meaningful differences in anxiety or depression levels between patients with neuropathic conditions and those with TMD pain were found,16, 121 consistent with broader evidence that psychologic impact of chronic pain is universal, irrespective of neuropathic or nociceptive characteristics of experienced symptoms.162 Differences instudy designs and psychologic assessment tools employed may have limited the ability to detect differential rates of psychologic comorbidities according to presenting OFP symptoms. Due to heterogeneity of studies, meta-analyses were not possible, however, reducing the strength of the findings. Nevertheless, the results are consistent with the hypothesis that orofacial pain conditions have an impact on psychologic wellbeing of individuals and are meaningful in the context of formulating treatment strategies.

# Conclusion

Orofacial pain has a significant impact on patients’ psychologic wellbeing. This critical review, within its limitations, highlighted an association between OFP and psychologic comorbidity. Due to heterogeneity across studies, it was not possible to conduct meta-analyses in order to substantiate evidence in a robust manner. Most work to date involves patients with TMD pain (non-neuropathic); much less concerns other types of pain such as neurovascular, neuropathic and idiopathic OFP. OFP requires a biopsychosocial approach for holistic management.163 Future research should focus on comparing psychologic morbidity in different types of COFP with a view to developed more tailored treatment strategies for individuals according to presenting symptomatology. There is also a need for studies exploring pre-condition psychologic morbidity that may have a significant role in predisposing individuals to develop chronic pain.4, 142

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**Figure Captions**

Figure 1. Flow diagram of study selection

Figure 2. Rates of depression (2a) and anxiety (2b) across studies of TMD conditions. Studies are ordered according to TMD condition, depression measure and percentage of depression reported. Value labels represent percentages. Abbreviations are detailed in footnote of Table 1.

Figure 3. Rates of depression (3a) and anxiety (3b) across studies of neuropathic, mixed and idiopathic/atypical orofacial pain conditions. Studies are ordered according to OFP condition, depression measure and percentage of depression reported. Value labels represent percentages. Abbreviations are detailed in footnote of Table 1.