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Review Article

# Efficacy of Psychotropic Drugs in the Treatment of Temporomandibular Disorders: A Systematic Review

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## Abstract

**Introduction:** Temporomandibular disorders (TMD) are a group of clinical problems related to the temporomandibular joint (TMJ), masticatory muscles, and associated structures. They affect function and are a major cause of orofacial pain. They have a multifactorial etiology with biomechanical, biological, and psychosocial components. Psychotropic drugs have been used in the treatment of TMD, but their effectiveness is controversial.

**Objective:** To assess the effectiveness of psychotropic drugs in the treatment of TMD.

**Materials and Methods:** A systematic literature review was conducted using electronic information sources, such as PubMed, Cochrane Central, Scopus, LILACS, Google Scholar, OpenGrey, and Trip database since 2020, following the PRISMA protocol, and using the Cochrane RoB-2 bias assessment tool and MINORS methodological index. The protocol was registered in PROSPERO CRD420251248245.

**Results:** Eight controlled trials with a total of 444 patients were included. The use of amitriptyline, nortriptyline, duloxetine, diazepam, citalopram, and gabapentin significantly reduced pain. Furthermore, it improves and increases mouth opening, significantly reduces interleukin-6, and patients' oral health-related quality of life.

**Conclusion:** Psychotropic drugs appear to be effective for the treatment of TMD. Both their use alone and in combination with other therapies can offer favorable results. Findings highlight the need for well-designed, long-term randomized controlled trials before endorsing routine use in dental practice.

***Keywords:*** *Temporomandibular Joint Dysfunction Syndrome; Temporomandibular Disorders; TMD; Psychotropic Drugs*

## Introduction

Temporomandibular joint disorders (TMD) are a group of clinical problems related to the temporomandibular joint (TMJ), the masticatory muscles, and other associated structures, with a direct impact on their function [1]. They manifest clinically through objective signs such as joint noises (crepitus, grinding, or clicking) during mandibular movements, stiffness and deviation when opening or closing the mouth, as well as restricted range of motion. On palpation, tenderness is evident in the orofacial region and in the masticatory muscles [2,3].

Among the symptoms, patients primarily report pain, which may be arthrogenic-originating in the TMJ and linked to inflammatory or degenerative processes-or myogenic-arising from the masticatory muscles and described as diffuse, dull, and persistent [2]. In addition, it is accompanied by headache, pain in the neck, ear, and facial region, muscle fatigue and stiffness, and in more severe cases is associated with vertigo and sleep disturbances [2-4]. Furthermore, patients may present symptoms that overlap with other conditions, such as fibromyalgia and certain neurological disorders [3]. It has been observed that the pain associated with TMD, in terms of intensity, frequency, and impact on daily activities, is similar to that of other painful conditions, such as low back pain and chronic pain, among others [5].

According to global data presented in a recent systematic review [6], TMDs affect approximately 29.5% of the general population worldwide. Geographically, they are most common in Europe (33.8%), followed by Asia (27.9%) and South America (27.3%); the lowest prevalence was recorded in North America (19.4%). There are gender differences: women tend to suffer more than men (36.7% versus 26.7%). By age, they occur in 38.5% of those under 18 and 34.1% of adults. They represent one of the main causes of orofacial pain [6,7].

From an etiological standpoint, the origin of TMD is complex and multifactorial, as it includes both physiological and psychological factors [8]. Among the physiological factors are occlusal abnormalities, orthodontic treatments, parafunctional habits, orthopedic instability, macro/microtrauma, joint laxity, and the influence of exogenous estrogens [2]. On the psychological front, stress, mental tension, poor sleep quality, anxiety, and depression stand out, which may or may not occur in combination [9,10].

Regarding the pathophysiology of TMD, it is characterized by a disruption of the balance between the functional load of the stomatognathic system and the adaptive capacity of its tissues, which triggers a molecular cascade of oxidative stress and hypoxia. This cascade can be initiated by various etiological factors, such as mechanical trauma or parafunctional habits, as well as by genetic and hormonal predisposition [11]. This process induces the release of neuropeptides, substance P, and calcitonin gene-related peptide (CGRP), as well as pro-inflammatory cytokines (such as IL-1β, IL-6, and TNF-α) [11,12]. These mediators activate matrix metalloproteinases (MMPs), which degrade fibrocartilage and the articular disc, and vascular endothelial growth factor (VEGF) promotes abnormal neovascularization and subsequently synovitis [12]. Simultaneously, at the muscular level, peripheral sensitization of muscle nociceptors occurs due to algogenic substances, such as glutamate and serotonin, which are elevated in the masseter muscle of patients with myogenic TMD [13]. This process has implications for the central nervous system, manifesting as hyperexcitability of neurons in the caudal subnucleus of the trigeminal nerve and an alteration of descending pain modulation mechanisms [13,14]. This neurobiological dysfunction facilitates chronicity and explains the comorbidity with psychosocial disorders, such as stress, anxiety, and depression, and perpetuates the clinical picture through dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system [14,15].

The diagnostic criteria for TMD (CD/TMD) encompass two complementary axes: Axis I focuses on muscular and joint disorders and structural dysfunctions. This is based on a detailed medical history and clinical examination of the patient [3,8,16]. Axis II includes validated tools (for example, the Graded Chronic Pain Scale, PHQ-9, GAD-7, MPI-B, OHQ-14) to address the oral health-related quality of life (OHRQoL), anxiety, stress, and depression [16,17]. Psychosocial assessment informs not only diagnosis but also treatment planning and pharmacological decisions. Imaging methods, such as magnetic resonance imaging and cone-beam computed tomography, allow for the evaluation of the TMJ [18]. Recently, biochemical tests have been proposed to identify cortisol levels in patients with TMD [19], which is considered an indicator for assessing accumulated stress in the body [20,21].

Cortisol is a glucocorticoid that exerts essential systemic effects, such as energy mobilization and the suppression of inflammation

through the inhibition of pro-inflammatory cytokines [22]. This entire process is closely linked to the activation of the HPA axis, the primary neuroendocrine stress response system. This axis functions via a negative feedback loop that begins with the release of corticotropin-releasing hormone (CRH) in the hypothalamus, followed by the secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland, which stimulates the adrenal cortex to produce and secrete cortisol [22,23]. However, chronic activation or dysfunction of the HPA axis (common in patients with persistent psychological stress) can disrupt the feedback mechanism, generating a pro-inflammatory state that leads to central sensitization with the potential to exacerbate and perpetuate TMD [16,23,24].

Given its multifactorial nature, a multidisciplinary therapeutic approach is recommended, including nonpharmacological [25] and pharmacological [26] therapies. Non-pharmacological therapies include: occlusal splints [27], physical therapy and jaw exercises [28], behavioral medicine [28], psychological therapy [29], TMJ surgery [30], intra-articular pharmacological therapies [31] and muscle therapies targeting the masticatory muscles [32].

Pharmacological treatment, for its part, includes various therapeutic classes [33], such as analgesics [34], muscle relaxants [33], anticonvulsants [35], sedatives [34], hypnotics [34], anxiolytics, and antidepressants [36,37]. The use of psychotropic drugs (e.g. antidepressants, anxiolytics, benzodiazepines, gabapentinoids, muscle relaxants with central activity) in patients with TMD does not aim to affect mood per se, but rather to modulate neuronal plasticity and neuromodulate nociceptive pathways in the central nervous system [37]. Benzodiazepines [34,38] act as positive allosteric modulators of the GABAA receptor, potentiating inhibition mediated by gamma-aminobutyric acid; this reduces anxiety and tension in the masticatory muscles [39]. Tricyclic antidepressants (TCAs) [38,40] and serotonin and norepinephrine reuptake inhibitors (SNRIs) increase the bioavailability of these monoamines in the synaptic cleft, which strengthens the descending inhibitory pain system and improves sleep architecture [41]. On the other hand, gabapentinoids stabilize neuronal membranes by inhibiting voltage-gated calcium channels, thereby reducing the release of excitatory neurotransmitters such as glutamate and substance P, a mechanism essential for reversing central sensitization [35]. Finally, centrally acting muscle relaxants, such as cyclobenzaprine, decrease the tonic hyperactivity of the muscles of the stomatognathic system by reducing the excitability of alpha and gamma motor neurons in the brainstem [42].

Recent studies have evaluated the effectiveness of various psychotropic drugs in the treatment of TMD [43]. Anxiolytics, antidepressants, and benzodiazepines have been associated with improvements in OHRQoL in patients with chronic and neuropathic pain related to TMD [36,37,42,44]. Within this group, tricyclic antidepressants (TCAs), such as amitriptyline and nortriptyline, have shown effectiveness in the treatment of chronic neuropathic pain [45]. Low-dose amitriptyline produces a significant reduction in spontaneous pain in patients with chronic TMD [46]. Regarding their impact on OHRQoL, significant improvements in OHIP-14 scores have also been reported [47].

On the other hand, the effectiveness of SNRIs for certain TMDs has been investigated. The combination of duloxetine with cognitive-behavioral therapies improved severe pain, pain-related disability, and painful comorbidities (such as headache or fibromyalgia) [48]. It has also been found that, as an adjunct to arthrocentesis, it reduces pain and increases mouth opening [45]. Finally, when comparing gabapentin alone and in combination with nortriptyline [47], it was found that combination therapy reduced pain more rapidly, increased mouth opening, and reduced the number of muscle tender points [47]. However, it is evident that there is controversy regarding the effectiveness of psychotropic drugs in the treatment of TMD [49]. Some dopaminergic agents improve motor control, while others, such as psychostimulants, cause hypersensitization that affects motor pathways and exacerbates muscle pain [11,12,50,51].

Given the growing interest in the efficacy of psychotropic drugs for TMD and the controversy surrounding their use, several systematic reviews have been conducted to synthesize the available evidence [36,37,42,52,53]. The efficacy of psychotropic drugs combined with cognitive-behavioral therapy for the treatment of TMD has been reported. Anxiolytics and antidepressants significantly reduce pain and improve OHRQoL [37], amitriptyline, and duloxetine significantly reduce pain in patients with chronic TMD [36] and duloxetine combined with arthrocentesis produces a significant reduction in pain [42]. In contrast, another study [54] found insufficient evidence to support the safe and effective use of

psychotropic drugs as a treatment for TMD. Conversely, several reviews [43,49-51,55] found that the use of psychotropic drugs is associated with the development of TMD.

A detailed examination of the available evidence has revealed that most previous reviews are traditional narrative reviews [43,49-51,55], while others do not systematize the process of searching for, selecting, evaluating, and synthesizing evidence [25,34,38,56]. Some include outdated studies [37,52,53], heterogeneous studies [42], and diverse groups of drugs [52,53]. Studies with low-quality evidence and a high risk of bias are included [37]. Boujoual., *et al.* [37] did not assess the risk of bias, which compromises the quality of their results. Furthermore, the exclusion of studies in languages other than English may have omitted relevant evidence.

Given the existing controversies, an updated, protocol-driven systematic review is needed to critically synthesize the available evidence, applying strict inclusion criteria, and using standardized tools to assess methodological quality and risk of bias, in order to provide valuable, up-to-date evidence supporting the clinical use of psychotropic drugs for the treatment of TMD. Therefore, to close this gap, the current systematic review aims to critically synthesize evidence on the efficacy, safety, and methodological limitations of studies evaluating the effectiveness of psychotropic drugs in the management of TMD.

## Materials and Methods

### Protocol and registration

This systematic review was conducted following the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statements [57]. A preliminary literature scoping search was conducted to identify existing evidence, knowledge gaps, and to refine the research question and methodological design. The study protocol was registered in the PROSPERO international prospective register of systematic reviews under number CRD420251248245, with the aim of ensuring transparency, reproducibility, and traceability of the methodological process.

### PICO research question

A research question was formulated using the PICO strategy (Patients, Intervention, Comparison, Outcome, detailed in table 1) [58]: What is the effectiveness of using psychotropic drugs to treat TMD based on a review of clinical trials published since 2020?

| Criteria | Description |
|---|---|
| Population | Patients with a clinical diagnosis of TMD of muscular, joint, or combined origin, according to validated diagnostic criteria (DC/TMD or equivalents). |
| Intervention | Use of psychotropic drugs as treatment for TMD. |
| Comparison | Placebo, no treatment, conventional treatment (NSAIDs, splints, physical therapy), or comparison with other psychotropic drugs. |
| Outcome | Effectiveness of psychotropic drugs considering the following parameters: pain, mandibular function, maximum mouth opening, muscle sensitivity, patient self-assessment, OHRQoL, or reduction in associated signs and symptoms. |
| Study design | Controlled clinical trials. |

***Table 1:*** *Analysis of the PICO question.*

### Search strategies

A systematic search was conducted in electronic databases from 2020 to 2026. The search combined relevant MeSH in PubMed and Cochrane Central, and free-text terms, such as for TMD, psychotropic drugs, and related outcomes, for the rest of the data sources, as described in table 2. A manual search of the reference lists of included studies was also performed to identify additional relevant articles.

| Database | Descriptors | No. |
|---|---|---|
| PubMed | "Psychotropic Drugs"[Mesh]) OR "Antidepressant Agents"[Mesh]) OR "Tranquilizing Agents"[Mesh]) OR "Central Nervous System Depressants"[Mesh]) OR "Narcotics"[Mesh]) OR "Opioid Analgesics"[Mesh]) AND "Temporomandibular Joint Disorders"[Mesh]) OR "Temporomandibular Joint Dysfunction Syndrome"[Mesh] | 249 |
| Cochrane Central | | 0 |
| Scopus | Temporomandibular disorders; pharmacology; complementary therapy; integrative medicine; pain management; chronic pain; nociceptive pain; Drugs; Pharmacological treatment; antidepressants; orofacial pain | 48 |
| LILACS | | 0 |
| Google Scholar | | 272 |
| OpenGrey | | 0 |
| Trip database | | 0 |

***Table 2:*** *Search queries applied in each database.*

### Eligibility criteria

Studies with the following characteristics were included:

- Published between 2020 and 2026.
- Written in English or Spanish.
- Included adults diagnosed with TMD according to DC/TMD or other recognized diagnostic criteria.
- Included adults diagnosed with TMD according to DC/TMD or other recognized diagnostic criteria.
- Were controlled clinical trials (randomized or non-randomized).
- Were available in full text.
- Evaluated the use of psychotropic drugs as a specific treatment for TMD.
- Reported therapeutic efficacy outcomes for TMD.

Studies were excluded if they:

- Focused on orofacial pain not clearly attributable to TMD.
- Did not specify the dental or clinical context of psychotropic drug use.
- Were case reports, case series, observational studies, or narrative/systematic reviews.

### Selection and data extraction

Study selection was performed in three stages with all authors participating Independently. In the first stage, titles and abstracts were screened according to the predefined inclusion and exclusion criteria. Duplicate records were removed using the automated duplicate detection feature in Mendeley Reference Manager® and through manual verification. In the second stage, full-text versions of potentially eligible studies were retrieved and assessed for final inclusion.

Data extraction was performed manually using a structured Microsoft Excel® template. The following variables were recorded for each study: authorship, year of publication, country, study design, sample size, participant characteristics, type of psychotropic drug administered, dosage and route, comparison group, follow-up period, primary and secondary outcomes, and main conclusions.

### Data analysis

All authors independently screened titles and abstracts. Discrepancies in the selection phase were resolved by discussion and consensus. For full-text reviews, any further disagreements were resolved by a reviewer not involved in the current paper, whose decision was binding. A structured qualitative synthesis was performed, grouping studies according to the class of psychotropic drug (e.g. tricyclic antidepressants, SSRIs, SNRIs, benzodiazepines, anticonvulsants, anxiolytics, opioids, antipsychotics) and reported outcomes (e.g. pain reduction, mandibular function, mouth opening, muscle sensitivity, subjective patient response, OHRQoL).

### Assessment of methodological quality and risk of bias

The assessment of methodological quality and risk of bias was conducted using specific tools tailored to the design of each included study, with the aim of determining their internal validity, external validity, and clinical applicability. Non-randomized studies and comparative clinical trials were evaluated using the Methodological Index for Non-Randomized Studies (MINORS) [59] (Table 5). Each item is scored from 0 to 2. The final assessment classifies studies as low quality (0-8 points), moderate quality (9-16 points), or high quality (17-24 points). Randomized clinical trials, meanwhile, were evaluated using the RoB-2 tool [60], which examines four domains (Table 5). Each domain is classified as low, high, or uncertain risk.

## Results

### Description of the search and selection process

As shown in figure 1, the initial search identified a total of 2,273 documents. Following an initial screening phase based on the review of titles, abstracts, and keywords, 22 articles were selected. Subsequently, 16 articles were selected for a comprehensive evaluation through full-text reading. Finally, after rigorously applying the eligibility criteria, 8 articles were included for qualitative analysis in this review.

### Bias assessment of the included studies

Five of the eight studies were classified as having a high risk of bias [45,47,61-63], as they partially met or did not meet any of the domains of the tool used. Meanwhile, three studies [46,64,65] were classified as having a risk of bias with some concerns, as they partially met the domains of the tool (Table 3).

### Assessment of the methodological quality of the included studies

The total scores range from 16 to 21, indicating good methodological quality in the included studies. Specifically, a score of 21 for two studies [46,65], a score of 19 for a single study [61], a score of 18 for a single study [64], a score of 17 for two studies [47,62] and a score of 16 for two trials [45,63] (Table 4).

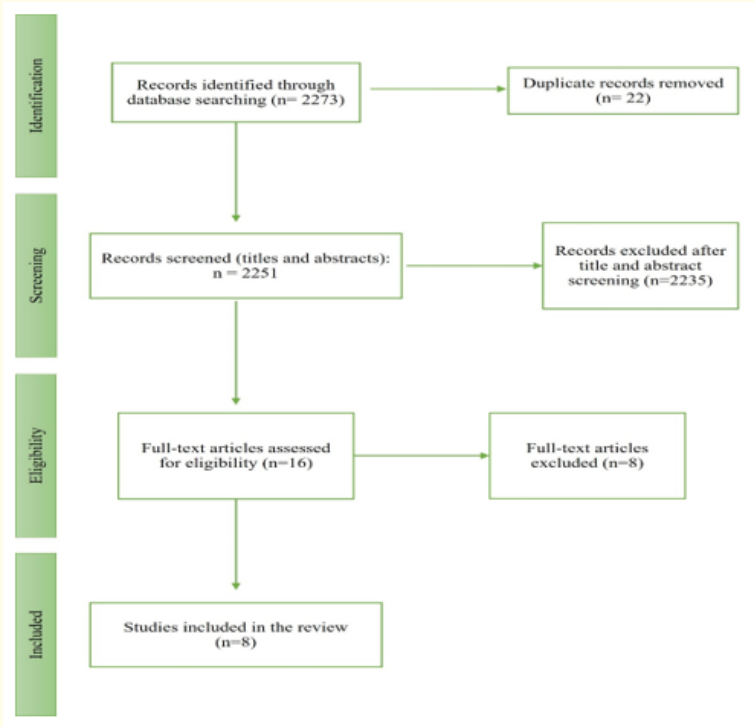


***Figure 1:*** *Flowchart of the selection and search process..*

| Author Year | Bias due to | | | | | |
|---|---|---|---|---|---|---|
| | Randomization process | Non-adherence to protocol | Incomplete data reporting | Outcome measurement | Selection of reported outcomes | Classification |
| Brakus., *et al.* 2025 [46] | + | + | ? | + | ? | ? |
| Kumar., *et al.* 2025 [45] | ? | - | ? | ? | ? | - |
| Raja., *et al.* 2025 [33] | ? | ? | ? | ? | ? | ? |
| Macedo de Sousa., *et al.* 2024 [65] | + | ? | ? | + | ? | ? |
| Ferreira., *et al.* 2024 [48] | ? | + | - | + | - | - |
| Rehman., *et al.* 2021 [62] | + | - | ? | ? | ? | - |

| | | | | | | |
|---|---|---|---|---|---|---|
| Tak., *et al*. 2021 [47] | ? | - | ? | - | ? | - |
| Goyal., *et al*. 2020 [63] | - | - | ? | ? | ? | - |

***Table 3:*** *Assessment of risk of bias in the included articles (RoB-2).*

*(+) = Low risk; (?) = Some concerns; (-) = High risk.*

| Authors | Clearly stated objective | Inclusion of consecutive patients | Prospective data collection | Appropriate outcome | Unbiased assessment | Adequate follow-up | Loss to follow-up ≤5% |
|---|---|---|---|---|---|---|---|
| Brakus., *et al*. 2025 [46] | 2 | 1 | 2 | 2 | 2 | 2 | 1 |
| Kumar., *et al*. 2025 [45] | 2 | 1 | 1 | 2 | 1 | 1 | 1 |
| Raja., *et al*. 2025 [33] | 2 | 1 | 1 | 2 | 2 | 1 | 1 |
| Macedo., *et al*. 2024 [65] | 2 | 1 | 2 | 2 | 2 | 2 | 1 |
| Ferreira., *et al*. 2024 [48] | 2 | 1 | 2 | 2 | 2 | 1 | 0 |
| Rehman., *et al*. 2021 [62] | 2 | 1 | 1 | 2 | 1 | 1 | 1 |
| Tak., *et al*. 2021 [47] | 2 | 1 | 1 | 2 | 1 | 1 | 1 |
| Goyal., *et al*. 2020 [63] | 2 | 1 | 1 | 2 | 1 | 1 | 1 |

**Continuation of table 4**

| Authors | Prospective sample size calculation | Appropriate control group | Contemporary groups | Baseline equivalence of groups | Appropriate statistical analysis | Rating |
|---|---|---|---|---|---|---|
| Brakus., *et al*. 2025 [46] | 1 | 2 | 2 | 2 | 2 | 21 |
| Kumar., *et al*. 2025 [45] | 0 | 2 | 2 | 1 | 2 | 16 |
| Raja., *et al*. 2025 [33] | 0 | 2 | 2 | 2 | 2 | 18 |
| Macedo., *et al*. 2024 [65] | 1 | 2 | 2 | 2 | 2 | 21 |
| Ferreira., *et al*. 2024 [48] | 1 | 2 | 2 | 2 | 2 | 19 |
| Rehman., *et al*. 2021 [62] | 0 | 2 | 2 | 2 | 2 | 17 |
| Tak., *et al*. 2021 [47] | 0 | 2 | 2 | 2 | 2 | 17 |
| Goyal., *et al*. 2020 [63] | 0 | 2 | 2 | 1 | 2 | 16 |

***Table 4:*** *Assessment of the methodological quality of the included articles (MINORS).*

| Author and year | Study objective | Sample and subgroups | Pharmacological intervention | Comparison group | Pain | Mouth opening | Joint noises | Inflammation | OHRQoL | Muscle relaxant | Conclusions |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Brakus., *et al*. 2025 [46] | To evaluate the efficacy of amitriptyline in chronic TMD | N=40; 2 groups (amitriptyline vs. placebo) | Amitriptyline 25 mg/day for 2 months | Placebo | Significant reduction in VAS pain | N.R. | N.E. | N.E. | Improvement in OHIP-14 | N.R. | Amitriptyline superior to placebo for pain and OHRQoL |
| Kumar., *et al*. 2025 [45] | Comparison of duloxetine vs. amitriptyline as adjuncts to arthrocentesis | N=10; 2 groups of 5 | Arthrocentesis + duloxetine 20 mg twice daily for 15 days | Arthrocentesis + amitriptyline 25 mg twice daily | Pain reduction in both groups | Increase in the duloxetine group | No significant differences between the drugs when combined with arthrocentesis | N.E. | N.E. | N.R. | Duloxetine showed greater functional improvement, evidence limited by sample size |
| Raja., *et al*. 2025 [33] | Comparing diazepam vs. ibuprofen in TMD | N=60; 2 groups (Diazepam vs. Ibuprofen) | Diazepam 5 mg | Ibuprofen 400 mg | Greater reduction with diazepam | Increase with diazepam | N.E. | N/A | N/A | Yes (diazepam) | Diazepam more effective for pain and dilation |
| Macedo., *et al*. 2024 [65] | Comparing antidepressants vs. splint for chronic orofacial pain | N=64; 3 groups | Citalopram 10 mg/day; Amitriptyline 25 mg/day | Nocturnal splint | Pain reduction in all; greater with amitriptyline | N.R. | N.E. | N.E. | N.E. | N.R. | Amitriptyline showed a greater sustained reduction in pain |
| Ferreira., *et al*. 2024 [48] | To analyze the analgesic response to duloxetine in the management of myalgia and arthralgia. | N=80; duloxetine vs. placebo + self-care | Duloxetine up to 60 mg/day for 12 weeks | Placebo + self-management | Favorable ≥30% in subgroup with high psychological burden | N.R. | N.E. | N.E. | N.R. | N.R. | Greater benefit in phenotypes with central sensitization |
| Tak., *et al*. 2021 [47] | Evaluate gabapentin + nortriptyline combination vs. monotherapy | N=40; 2 groups of 20 | Gabapentin + nortriptyline twice daily | Gabapentin alone twice daily | Greater pain reduction with combination | Increased mouth opening with combination | N.E. | N.E. | N.E. | N.R. | Best combination for muscle pain and sensitivity |
| Rehman., *et al*. 2021 [62] | Comparison of ibuprofen vs. diazepam for TMD pain | N=120; 60 per group | Ibuprofen 400 mg twice daily | Diazepam 5 mg/day | Greater reduction with ibuprofen | N.R. | N.E. | N.E. | N.E. | No (Diazepam) | Ibuprofen more effective than diazepam in this trial |
| Goyal., *et al*. 2020 [63] | Evaluate duloxetine vs. arthrocentesis vs. combination | N=30; 3 groups of 10 | Duloxetine 30 mg twice daily for 3 months | Arthrocentesis alone or in combination | Greater reduction with combination | Increased range of motion with combination | No significant differences between groups | Decrease in IL-6 in groups with arthrocentesis | N.E. | N.R. | The combination of arthrocentesis and duloxetine was the most effective overall |

***Table 5:*** *Summary of the results of the included studies.*

*Note: N.R.: Not reported; N.E.: Not evaluated; VAS: Visual Analog Scale.*

## Description of the included studies

Table 5 details the methodological characteristics and main findings of the included studies. Eight studies published between 2020 and 2025 were included. No studies published in 2026 were found: Seven randomized clinical trials [45-48,62,64,65] and one non-randomized trial [63]. The clinical trials were conducted in: Brazil [48], India [45,47,63], Pakistan [33,62], Portugal/Spain [65], and Croatia [46]. A total of 444 adult patients with a clinical diagnosis of TMD were included. The psychopharmacological interventions evaluated TCAs (amitriptyline [45,46,65] and nortriptyline [47]), SSRIs (duloxetine [45,48,63]), anxiolytics (diazepam [33], citalopram [65]), and anticonvulsants (gabapentin and pregabalin [47]). The effectiveness of these drugs was compared with placebo groups, NSAIDs [33,62], conventional therapies (splints [65], physical therapy [48], arthrocentesis [45,63]), or with each other. Follow-up periods ranged from two to twelve weeks.

## Summary of results

Overall, the results of this systematic review demonstrate that the use of the evaluated psychotropic drugs was effective for the treatment of TMD (Table 5). In all studies, the psychotropic drugs significantly reduced pain [45-47,61-65]. Regarding mouth opening, four studies found an increase in mouth opening [45,47,63,64]. For joint crepitus, only two studies reported no significant difference [45,63]. In the study by Goyal., *et al*. [63], the combination of arthrocentesis with duloxetine was associated with a statistically significant reduction in interleukin-6 (IL-6) levels, suggesting anti-inflammatory effects. In the study by Brakus., *et al*. [46], amitriptyline was found to improve OHRQoL. in the study by Raja., *et al.* [64], anticonvulsants (gabapentinoids) were generally associated with improvement in reducing muscle hyperactivity.

The results of the included studies are presented below according to the outcomes evaluated:

- **Pain:** In all studies [45-47,61-65], psychotropic drugs significantly reduced pain, which was assessed using the VAS. Brakus., *et al*. [46] demonstrated a significant reduction with amitriptyline compared to placebo. Macedo., *et al*. [65] observed a greater reduction with amitriptyline compared to citalopram and a splint. Tak., *et al*. [47] reported a greater reduction with the gabapentin- bination. Ferreira., *et al*. [48] identified a clinical response to duloxetine in subgroups with a high psychosocial burden. Goyal., *et al*. [63] found a greater reduction with the duloxetine-arthrocentesis combination. In contrast, Rehman., *et al*. [62] observed a greater reduction with ibuprofen compared to diazepam, while Raja., *et al*. [33] reported the opposite result.
- **Mouth opening:** Four studies showed an increase in mouth opening [45,47,63,64]. Tak., *et al*. [47] demonstrated a greater increase with combination therapy. Kumar., *et al*. [45] reported an increase in mouth opening in the duloxetine group. Raja., *et al*. [33] and Goyal., *et al*. [63] reported a significant increase in opening, especially when combined with arthrocentesis.
- **Joint crepitus:** Joint crepitus was evaluated in only two studies. Kumar., *et al*. [45] and Goyal., *et al*. [63] found no significant differences in the reduction of joint crepitus with the use of psychotropic drugs. In the study by Kumar., *et al*. [45] arthrocentesis combined with amitriptyline did not significantly reduce crepitus or duloxetine. In the study by Goyal., *et al*. [63], arthrocentesis combined with duloxetine also did not significantly reduce crepitus, suggesting that these drugs may have limited effect on joint sounds.
- **Inflammation:** Goyal., *et al*. [63] evaluated the effect of psychotropic drugs on inflammation using inflammatory markers, specifically IL-6. They observed a statistically significant reduction in IL-6 levels in the group treated with arthrocentesis and duloxetine, suggesting that this combination may have anti-inflammatory properties.
- **OHRQoL:** In the study by Brakus., *et al*. [46] amitriptyline improved OHRQoL as measured by the OHIP-14 instrument. This suggests that psychotropic drugs may enhance not only pain management but also overall quality of life in patients with TMD.
- **Muscle tone:** The results of the studies by Raja., *et al*. [33] and Rehman., *et al*. [62] are controversial. One study reported no significant improvement in muscle tone with the use of diazepam [62], while the other study by Raja., *et al*. [33] observed improved muscle relaxation with the use of diazepam. This discrepancy highlights the need for further research to clarify the role of diazepam in muscle relaxation for TMD.

## Discussion

The aim of this systematic review was to synthesize the available and up-to-date scientific evidence on the effectiveness of psychotropic drugs in the treatment of temporomandibular disorders (TMD) in the last seven years. Overall, the findings indicate that the psychotropic medications evaluated, both as monotherapy and in combination with conservative interventions, were generally associated with clinical improvement in TMD. Reported benefits included pain reduction [45-47,61-65], increased mouth opening [45,47,63,64], muscle relaxation [33,62], decreased inflammatory markers [63] and improved in OHRQoL [46].

Across all included studies, psychotropic produced statistically significant reductions in pain intensity, typically assessed using the Visual Analogue Scale (VAS) [45-47,61-65]. Trials involving antidepressants (amitriptyline, nortriptyline, duloxetine) [46,48,63,65], anticonvulsants (gabapentin, pregabalin) [33,62] and combination therapies [45,63] demonstrated clinically relevant decreases in pain scores. In particular, treatment with amitriptyline [45,46,65] resulted in a reduction of approximately 63.3% in pain after two months of therapy compared to a much smaller decrease in the placebo group; comparable results were observed with gabapentin combined with nortriptyline [47], which showed greater pain reduction than gabapentin monotherapy [47], as well as in studies comparing NSAIDs and muscle relaxants, where significant decreases in pain scores were recorded following treatment [33,62].

Importantly, none of the included studies primarily targeted patients with diagnosed psychiatric disorders; thus, the observed efficacy of psychotropic drugs appears to be due to their neuromodulatory effects on nociceptive pathways and central sensitization rather than to mood regulation per se [34,35,37]. The analgesic effects of tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors may be explained by inhibition of serotonin and norepinephrine reuptake, leading to increased monoamine availability in the synaptic cleft and enhanced descending inhibitory control of nociceptive input at trigeminal and spinal levels [13,48,66]. TCAs and SNRIs such as amitriptyline and duloxetine inhibit the reuptake of serotonin and norepinephrine [38,40,45,66], which increases the bioavailability of these neurotransmitters in the synaptic cleft. Consequently, they block nociceptive transmission in the central nervous system, specifically pain signals in the caudal subnucleus of the trigeminal nerve, thereby reducing the chronic myofascial pain typical of TMD [13,67]. Gabapentinoids, by inhibiting voltage-gated calcium channels, reduce the release of excitatory neurotransmitters such as glutamate and substance P, thereby attenuating central sensitization and chronic pain maintenance [34,35].

These results are consistent with previous systematic reviews that have reported that various psychotropic medications, including antidepressants, muscle relaxants, and anti-inflammatory drugs, can reduce pain intensity in patients with TMD, although the magnitude of the effect varies across studies [52]. Likewise, it has been observed that amitriptyline or duloxetine can reduce pain when used alone or in combination with other therapeutic interventions [36].

Four studies showed consistent improvement in maximum mouth opening in patients with TMD following pharmacological or combined interventions [45,47,63,64]. Combination regimens (e.g. gabapentin plus nortriptyline or duloxetine plus arthrocentesis) tended to produce larger gains in interincisal opening than monotherapies or procedural interventions alone [47]. The combination of duloxetine with arthrocentesis produced a greater increase in mouth opening compared to the therapies used alone [45,63], while another clinical trial comparing duloxetine and amitriptyline as adjuncts to arthrocentesis also showed a significant increase in mouth opening [45].

Previous studies have observed that the improvement in mouth opening and recovery of mandibular range of motion is due to the interruption of the pain-spasm-pain cycle [13,68]. When the muscle groups comprising the TMJ are affected by some form of TMD, a protective co-contraction may occur, manifesting as a reflex response of the stomatognathic system mediated by the central nervous system, which increases the tonic activity of the antagonist muscles to limit the movement of an injured or threatened structure, functioning as a physiological splint [14,68]. The presence of pain associated with TMD, whether of articular or muscular origin, activates this mechanism to prevent further damage, which clinically manifests as restricted mouth opening and muscle fatigue [68].

Likewise, the use of certain psychotropic drugs can reverse this functional limitation by acting through two mechanisms. On the one hand, the central analgesic action of antidepressants and anticonvulsants reduces the nociceptive input that triggers the co-contraction reflex [13,35] and eliminates the stimulus that the nervous system interprets as a threat. On the other hand, certain agents such as benzodiazepines directly reduce the excitability of gamma motor neurons, which decreases muscle spindle sensitivity and promotes muscle relaxation in a state of tonic hyperactivity [34,38].

Similarly, other systematic reviews have found that psychotropic drugs can produce functional changes such as increased mouth opening, although the magnitude of the effect varies across studies and does not always reach statistical significance [52]. Comparably, Dei., *et al*. [36] report functional improvements, including increased mouth opening, when antidepressants are used in combination with other conservative therapies.

On the other hand, Goyal., *et al*. [63] demonstrated a significant reduction in joint inflammatory markers; biochemical analysis of the synovial fluid revealed a significant decrease in IL-6 levels in the groups treated with arthrocentesis alone and with arthrocentesis combined with duloxetine.

The reduction in inflammation in the TMD is due to a combined effect of local neurochemistry and the systemic stress response [11,12,69,70]. Pain initiates a molecular cascade in which mediators such as substance P and CGRP activate immune system cells, leading to the release of proinflammatory cytokines such as IL-6 and TNF-α [11,12]. This process, known as neurogenic inflammation, contributes to peripheral sensitization, in which joint nociceptors become hyperexcitable even in response to normal mechanical stimuli [13,14]. The use of psychotropic drugs such as duloxetine intervenes in this cycle by reducing the release of excitatory neurotransmitters and modulating descending pain pathways, which indirectly decreases pro-inflammatory neurogenic signaling [63,66,71]. Furthermore, these drugs help normalize chronic activation of the HPA axis [66,71]. Prolonged dysfunction of this axis, common in patients with chronic stress, leads to resistance to natural glucocorticoids (such as cortisol), which generates a systemic pro-inflammatory state that perpetuates synovitis and the deterioration of articular fibrocartilage [12]. By stabilizing this neuroendocrine response with the help of psychotropic drugs, a measurable reduction in inflammatory markers in the synovial fluid is observed, which facilitates tissue repair and an improvement in the symptoms of TMD [16,23,24,63].

One study evaluated the effect of psychotropic drugs as muscle relaxants. Brakus., *et al*. [46] compared the effect of gabapentin alone versus gabapentin combined with nortriptyline; the number of muscle tenderness sites decreased significantly after three weeks of treatment, with final values of 1.15 in the monotherapy group and 0.40 in the combination therapy group, indicating greater muscle relaxation with the combination regimen.

The effect on the relaxation of TMJ-related muscles is explained by the central action of the drugs used. Some psychotropic drugs modulate the excitability of motor neurons at the brainstem level [34,38,66]. In the case of anxiolytics, such as benzodiazepines, these act as positive allosteric modulators of the GABA-A receptor. If inhibition mediated by this neurotransmitter in the central nervous system increases, anxiolytics produce a muscle-relaxing effect by reducing the tension resulting from sustained contraction [38,66,71]. Additionally, medications such as gabapentin help stabilize neuronal membranes and reduce the hyperexcitability that perpetuates muscle tension [66]. Nortriptyline, for its part, acts on the serotonergic and noradrenergic systems involved in the descending modulation of pain [35]. Consistent with these findings, previous studies have observed that centrally acting drugs, including antidepressants and muscle relaxants [35,42], can reduce muscle hyperactivity and improve myofascial symptoms associated with TMD.

Finally, Brakus., *et al*. [46] demonstrated a significant improvement in OHRQoL in patients with TMD after two months of treatment with amitriptyline. The improvement in quality of life is not an isolated event; it is the consequence of comprehensive neuromodulation of the pain experience [45,46]. TMDs have a negative impact on OHRQoL as they cause muscle fatigue, restricted jaw movements, and sleep disturbances, creating a vicious cycle of stress, anxiety, and pain exacerbation [45,47]. The administration of antidepressants such as amitriptyline improves sleep quality by increasing restorative sleep phases, which optimizes the recovery of masticatory tissues and reduces daytime fatigue [46].

By reducing pain intensity and sensitivity to muscle palpation, psychotropic drugs decrease the disorder's interference with basic biopsychosocial functions such as efficient mastication and social interaction [14,45,63]. Additionally, it improves the patient's perception of general well-being [35,37]. This indicates that psychopharmacological treatment alleviates physical symptoms such as chewing and speech and promotes patient´s general well-being, which are the primary indicators of OHRQoL [47]. Similar findings were reported in previous reviews [37,52,53].

On the other hand, the results of the present review differ from those of some previous reviews [43,49-51,55], which have observed that the use of psychotropic drugs is associated with the development of TMD. Another review [54] found that there was insufficient evidence to assert that psychotropic drugs are effective as treatments for TMD. In any case, in line with the findings of previous reviews, there remains a need for further clinical research on this relationship [43,49,50,51,55].

This review also faced methodological limitations that must be considered when interpreting its conclusions. First, one non-randomized controlled trial was included, and overall study quality ranged from low to moderate, as reflected by MINORS and RoB-2 assessments. Second, we restricted inclusion to studies published in English or Spanish between 2020 and 2026, which may have resulted in language and time-lag bias. Third, heterogeneity in diagnostic criteria, outcome measures, and comparison treatments precluded a robust quantitative meta-analysis and required reliance on qualitative synthesis. Finally, the short follow-up durations limit our understanding of the long-term efficacy and safety of psychotropic drugs in TMD management.

Despite these limitations, the present review provides updated, protocol-driven evidence suggesting that psychotropic medications may offer clinically meaningful benefits for selected patients with TMD when used as part of a multimodal, biopsychosocial approach. Future research should prioritize well-designed, adequately powered randomized controlled trials with standardized diagnostic criteria, clearly defined outcomes (including adverse events), and longer follow-up. In parallel, evidence-based clinical guidelines are needed to define precise indications, contraindications, monitoring parameters, and interdisciplinary collaboration for the use of psychotropic drugs in TMD.

## Conclusion

Within the limitations of this review, psychotropic drugs appear to be potentially effective in the management of TMD, although the underlying evidence is characterized by marked methodological heterogeneity and small, short-term trials. Current data are sufficient to suggest benefit for some agents, particularly when combined with conservative physical therapies; however, they are not robust enough to establish definitive conclusions, reinforce long-term safety, or define optimal regimens. Findings highlight the need for high-quality randomized clinical trials and a personalized approach tailored to each patient's clinical presentation.

Future research should consist of large-scale, well-designed studies with longer follow-up periods, standardized diagnostic criteria, and harmonized outcome measures, including systematic reporting of adverse effects and comparisons among different psychotropic classes according to TMD subtype. Clinically, pharmacological management with psychotropic medications should be embedded in a multimodal, interdisciplinary care model, prescribed only by professionals with solid training in psychopharmacology, and accompanied by efforts to strengthen pharmacology education on the rational, evidence-based use of these agents in TMD patients.

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