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Evaluating amitriptyline's role in chronic TMD management: a placebo-controlled trial

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Abstract

Background To assess the effectiveness of low-dose amitriptyline in reducing pain and improving oral health-related quality of life in individuals with chronic temporomandibular disorders (TMD) over a 2-month period, compared to placebo.

Methods Forty participants were randomly assigned to receive either 25 mg of amitriptyline or a placebo pill for 2 months. The primary outcome was pain intensity, measured using a visual analogue scale (VAS). The secondary outcome was the impact of pain on oral health-related quality of life, assessed by the Oral Health Impact Profile questionnaire (OHIP-14). Evaluations were conducted at baseline and after the 1st and 2nd months of treatment.

Results No statistically significant differences were observed between the treatment groups at baseline ($p > 0.05$). After 2 months of treatment participants in amitriptyline group experienced a significantly greater reduction in spontaneous pain, with a 63.3% decrease in VAS scores. Participants in placebo group showed a much smaller reduction in spontaneous pain, with only a 16.2% decrease in VAS scores. Additionally, the amitriptyline group demonstrated a significant improvement in OHIP-14 scores ($p < 0.001$), whereas the placebo group showed no significant change in oral health-related quality of life ($p = 0.184$).

Conclusion This study highlights low-dose amitriptyline as an effective treatment for chronic TMD, showing significant pain reduction and improved quality of life, underscoring its value in a multimodal approach despite the need for further research to personalize care.

Trial registration This study was registered retrospectively in ISRCTNregistry under the number ISRCTN17622685, on 01/10/2024.

Keywords Temporomandibular disorders, Amitriptyline, Pain reduction

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Introduction

Temporomandibular disorders (TMD) represent a diverse group of conditions characterized by pain and dysfunction in the temporomandibular joints (TMJ), masticatory muscles, and surrounding tissues [26, 33]. As the leading cause of orofacial pain not attributable to dental origins, TMD presents with a range of debilitating symptoms, including pain in the jaw, temple, and ear, often exacerbated by jaw movement, along with restricted jaw mobility, tenderness, and clicking or popping sounds from the TMJ [35, 49]. The persistent and recurrent nature of TMD-related pain severely impacts patients' physical, functional, and psychosocial well-being, resulting in a marked decline in oral health-related quality of life (OHRQoL) [12, 19]. Indeed, the negative impact of TMD on OHRQoL often exceeds that of most other oral conditions.

Additionally, TMD is frequently associated with comorbidities such as psychological stress, anxiety, depression, sleep disturbances, and hormonal imbalances [3, 9, 23]. Despite decades of research, the pathophysiology of TMD remains elusive, with no single causative factor identified. Instead, TMD is widely regarded as a multifactorial condition, with contributions from biomechanical, neuromuscular, psychosocial, and genetic factors [47, 48, 50]. This complex etiology is further compounded by central and peripheral sensitization mechanisms. Tissue damage in TMD releases cytokines, prostaglandin E2, histamine, and serotonin (5-HT), which sensitizes primary sensory neurons and contributes to heightened pain perception [36]. Painful stimuli are transmitted via primary afferent neurons to the dorsal horn of the spinal cord, where they activate neurons projecting to the thalamus and subsequently to the somatosensory cortex, evoking the sensation of pain. Enhanced excitability in these pathways, characterized by greater responsiveness of both primary afferent fibres and dorsal horn neurons, underpins central sensitization—a hallmark feature of chronic pain conditions, including TMD [40]. These mechanisms underscore the importance of addressing both peripheral and central pathways in managing chronic TMD-related pain.

Given the multifaceted nature of TMD, therapeutic goals primarily focus on alleviating pain and restoring TMJ function, thereby improving the patient's overall quality of life. Various treatment modalities have been explored, including occlusal splints, pharmacotherapy, physical exercise, and cognitive behavioral therapy [18, 25, 45]. Among these, pharmacological interventions are of particular interest due to their potential to modulate the complex neurochemical pathways involved in chronic pain [17, 34].

Amitriptyline, a tricyclic antidepressant, has been extensively studied for its off-label use in managing chronic pain conditions, including orofacial pain syndromes such as TMD. Its analgesic effects are thought to stem from its inhibition of serotonin (5-HT) and norepinephrine reuptake, which enhances their concentrations in the synaptic cleft and modulates descending pain pathways [30]. Noradrenaline's role in pain modulation is particularly significant, as it exerts an analgesic effect primarily through α2-adrenergic receptors in the dorsal horn of the spinal cord. Activation of these receptors, mediated by G proteins, inhibits the release of excitatory neurotransmitters from primary afferent fibres and hyperpolarizes post-synaptic dorsal horn cells, reducing their excitability. Although the inhibitory effects of serotonin in neuropathic pain remain less clearly understood, it is thought to exert synergistic effects in combination with noradrenaline [31]. This neurochemical basis aligns with the hypothesized mechanisms underlying chronic TMD-related pain and supports the exploration of amitriptyline as a therapeutic option.

Recent evidence supports the use of low-dose amitriptyline in managing chronic orofacial pain, including TMD. A growing body of clinical research highlights its effectiveness in reducing pain intensity, improving functional outcomes, and enhancing overall patient well-being [13]. A meta-analysis of randomized controlled trials (RCTs) has demonstrated that amitriptyline is significantly more effective than placebo in managing widespread musculoskeletal pain, with benefits observed even at low doses, minimizing the risk of adverse effects [5]. However, the evidence remains moderate to low in quality, with several unanswered questions regarding its efficacy across subpopulations, optimal dosing strategies, and the relative contributions of physiological versus environmental factors [27, 38]. These gaps in the literature highlight the need for rigorous, placebo-controlled trials to elucidate the therapeutic potential of amitriptyline in chronic pain conditions. The moderate to low quality of evidence supporting other common treatments, such as occlusal splints [6], underscores the importance of exploring alternative or adjunctive therapies that may offer more consistent and substantial benefits.

Recognizing the chronic and often debilitating nature of TMD, this randomized, double-blind, controlled trial aims to determine whether low-dose amitriptyline reduces pain and improves oral health-related quality of life in individuals with chronic TMD over two months compared to placebo. By addressing gaps in the existing evidence, this study seeks to contribute valuable insights into the role of amitriptyline in managing chronic orofacial pain and advancing the understanding

of neurobiological mechanisms underlying TMD-related pain. We hypothesize that those taking low dose amitriptyline will have lower pain and improved quality of life compared to those taking active placebo.

Materials and methods

The study was conducted as a part of the Croatian Science Foundation project (IP-2014–09-3070), approved by the Ethics Committee of the University of Zagreb School of Dental Medicine (01-PA-26–6/15). The research adhered fully to the ethical principles outlined in the Declaration of Helsinki.

This study was conducted in accordance with CONSORT reporting guidelines.

This study was retrospectively registered in the ISRCTN registry on October 1, 2024. At the time of trial initiation, the accepted practice involved registering the study with our institutional review board, which met the prevailing ethical and regulatory requirements. International registry registration, as emphasized in more recent CONSORT guidelines, was not standard practice at the time.

Retrospective registration was conducted to comply with current editorial policies and enhance the transparency and accessibility of the study's protocol and findings. Importantly, no deviations occurred between the initial protocol and the study's design, execution, or analysis. All methods, procedures, and outcome measures were implemented exactly as described in the original protocol, ensuring consistency and rigor throughout the study process.

To align with contemporary best practices, we have prospectively registered all ongoing and future trials in internationally recognized registries, reflecting our commitment to transparency and adherence to the highest ethical standards in clinical research.

The study's objectives, treatment process, and potential side effects were thoroughly explained to participants, emphasizing that participation was voluntary and could be withdrawn at any time. Before participating in the study, each participant had to sign an informed consent form.

Participants were selected based on specific inclusion and exclusion criteria, as detailed below.

The study was designed as a controlled, randomized, double-blind trial. Participants were randomly assigned to one of two groups: the amitriptyline (treatment) group or the placebo (control) group. The CONSORT diagram (Fig. 1) illustrates the allocation of participants across the study groups.

Eligibility criteria

Inclusion criteria: age $\geq$ 18 years, reported pain in TMJ and /or masticatory muscles persisting more than three months (according International Association for the Study of Pain), spontaneous pain > 30 mm on the Visual Analogue Scale (VAS) at the moment of first examination [29]. To be included in the study, patients had to be diagnosed with myalgia (pain and dysfunction arise from pathologic and functional processes in the masticatory muscles) and/or arthralgia (spontaneous pain perceived from the region of temporomandibular joint (TMJ) in addition to pain on palpation of the lateral pole or posterior attachment of the TMJ on the same side). Patients were excluded from the study if they had periodontal disease, removable dentures, or complete fixed prosthodontic restorations, were undergoing orthodontic treatment, experienced pain from temporomandibular joint osteoarthritis or other orofacial pain conditions, had mental or neurological disorders, pain related to systemic diseases, were pregnant, had cardiac disease, had a known intolerance to amitriptyline, or were under 18 years of age.

Study setting

This study was conducted at the clinic of a major tertiary academic center in Croatia. The setting provided a comprehensive environment for patient care and ensured access to specialized diagnostic and treatment resources. The baseline evaluation, clinical examination, and final diagnosis of painful TMDs were conducted by two skilled examiners (I.Z.A and R.B.B) using the Croatian version of the RDC/TMD [4]. This tool offers a dual-axis approach, enabling a comprehensive assessment of both the physical (Axis I) and psychosocial (Axis II) dimensions of TMDs. The clinical evaluation included palpation of the masticatory muscles and TMJs and assessment of jaw movements and evaluation of TMJ sounds. The pain elicited during the clinical assessments had to be labelled as "familiar" in order to confirm a diagnosis of pain-related TMD (myalgia, arthralgia, or both).

The intensity of orofacial pain at baseline was measured through the characteristic pain intensity (CPI) and interference scores from the Graded Chronic Pain Scale (GCPS) [46]. The GCPS is a tool that measures pain intensity and pain-related disability to code chronic pain severity as a 4-level categorical variable. CPI is calculated using the mean of questions „current pain ", „worst pain " and „average pain " on a 0 to 10 scale (ranging from 0 = no pain to 10 = worst imaginable pain) multiplied by 10. The disability score is derived from questions „daily activities ", „social activities ", and „work activities ", as the mean interference value on a 0 to 10 scale multiplied by 10 and translated into 0 to 3 disability points using a provided table. Chronic pain grade is then classified into

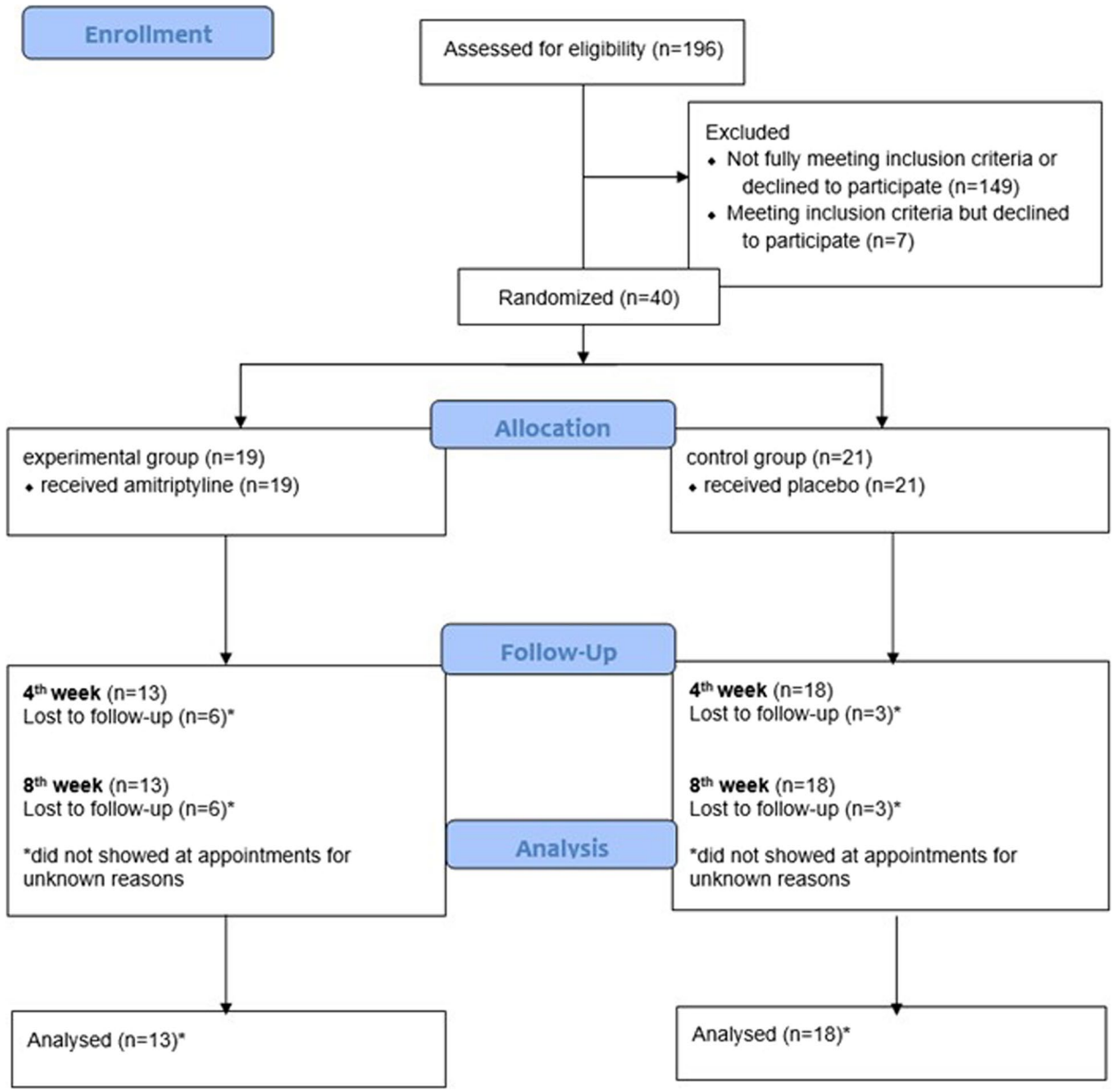

Fig. 1 Patient selection and allocation diagram, according to CONSORT

4 grades (grade 1: low intensity pain, without disability, grade 2: high intensity pain, without disability, grade 3: high pain-related impairment that is moderately limiting, and grade 4: high pain-related impairment that is strongly limiting.)

Observer training

To ensure consistency and reliability in clinical assessments, ten randomly selected subjects underwent repeated evaluations for TMD signs and symptoms by two experienced examiners, following the RDC/TMD protocol. Statistical analysis using paired t-tests revealed no significant differences between the measurements ($p = 0.87–0.89$). Additionally, inter-rater agreement was deemed adequate, with kappa values ranging from 0.86 to 0.88.

Interventions

Amitriptyline was prescribed according to the analgesic dosage range (25 mg) and identical placebo tablets without active ingredients for the control group. To ensure double-blindness, the placebo tablets were

manufactured and packaged in identical dark bottles marked with numbers by MAGDIS d.o.o. pharmaceutical and cosmetic products factory (A. Šenoe 37, Mala Gorica, 10,431 Sveta Nedjelja, Croatia). The patients were not allowed to change the dose or intake times of the medication during the 8-week period. The patients were also monitored at the 8-week follow-up for deviations in their medication.

Adverse events

Participants were closely monitored for any new symptoms or adverse events throughout the study. Notably, none of the participants reported pain unrelated to TMD during the study period. Participants were instructed not to receive any other forms of treatment, and compliance was assessed at each follow-up visit. During these visits, the examiner verified adherence to the therapy instructions. Any deviation from these guidelines would have led to the exclusion of the participant from the study; however, no such violations occurred.

Study protocol

Patients were instructed to cease any ongoing TMD therapies, such as splinting or physical therapy, two weeks prior to the study's initiation. Additionally, due to potential contraindications for amitriptyline (such as glaucoma or cardiac block), participants were advised to consult with their healthcare providers to determine if further evaluation by a cardiologist or ophthalmologist was required.

Upon completing the preparatory period, baseline assessments were conducted. Participants were then randomized, according to a randomization table, to receive either 25 mg of amitriptyline or a placebo pill. The treatment was planned to last three months, with follow-up visits scheduled at the end of the fourth week (1st month), eighth week (2nd month), and twelfth week (3rd month).

Due to insufficient data from the twelfth week, results from this time point are not included in the analysis. Additionally, any side effects and reasons for discontinuing therapy were recorded.

Primary outcome measure

Spontaneous pain

To quantify spontaneous jaw joint pain and/or masticatory muscles at rest or during the function visual analogue scale (VAS) was used. VAS is a line 100 mm long, with a left endpoint indicating a pain-free state and a right endpoint indicating the greatest pain imaginable [16]. Participants marked the line to indicate the level of pain they were experiencing at that moment. The minimum clinically important difference for pain is reported to fall between 1.5 and 3.2 points [11]. Additionally, a 30% reduction in pain is regarded as clinically significant for individuals with chronic pain, based on a distribution-based analysis method [15].

Secondary outcome measure

Impact of the disorder on quality of life

The short-form Oral health impact profile (OHIP-14) questionnaire, translated and validated in Croatian language, was used to evaluate the impact of pain on patients' oral health-related quality of life [19, 41]. The OHIP-14 consists of 14 questions divided into seven categories: functional limitations, physical pain, psychological discomfort, physical disability, psychological disability, social disability, and handicap. Possible results according to this questionnaire ranged from 0 to 56. An OHIP change exceeding 3 points was deemed clinically significant [28].

The intensity of spontaneous pain as well as the impact of pain on patients' oral health-related quality of life were evaluated at the baseline and at all follow-up appointments.

Allocation

To minimize waiting time and reduce the risk of participant withdrawal, we employed a randomization procedure informed by our experience of enrolling 6–8 participants over a 2-month period. Randomization was computer-generated, and participants were randomly assigned to one of two treatment arms: amitriptyline or placebo.

A designated team member (I.B.), who was not involved in the assessment of therapeutic outcomes, managed the allocation of participants according to the randomization list. The investigator (R.B.B.) was provided with a sealed envelope containing the details of the treatment assignments. This envelope remained sealed and was only opened after the completion of the statistical analysis.

Blinding

Participants were informed that they would receive one of two pharmaceutical products but were not provided with details regarding the specific components or differences between the treatments. This approach was designed to prevent any potential influence on participants' expectations or perceptions of the treatment.

To maintain blinding, participants were instructed not to discuss their treatment assignments with anyone during the study. This procedure helped minimize the risk of unblinding that could potentially affect the study outcomes.

The investigator (R.B.B.), who conducted all follow-up evaluations, was blinded to the treatment assignments of the participants. This ensured that the evaluation of outcomes was conducted without bias related to the knowledge of which treatment was administered to each participant.

Sample size determination

We conducted a statistical power analysis for sample size estimation using G*Power, basing the calculation on data from similar studies. The expected difference in pain reduction between the study groups, informed by previous research [37], was approximately 20%, with a standard error of 15%. A sample size calculation for a repeated-measures within-between analysis of variance (ANOVA) with two groups indicated that a total of 30 participants would be needed to achieve 80% power at an alpha level of 0.05. To account for a potential dropout rate of 10%, the final sample size was increased to 40 participants, ensuring adequate statistical power.

Statistical analysis

Data were analyzed using Statistica 13.4.0 software (1984–2018 TIBCO Software Inc.). Normality was checked using the Shapiro–Wilk test. Continuous data were expressed as medians with interquartile ranges or as means with standard deviations, depending on the data distribution. Given the small sample size and the non-normal distribution of the data, non-parametric statistical tests and representations were employed.

Group comparisons were performed using the Mann–Whitney U test, with results illustrated using Box and Whisker plots. Outliers in these plots were defined as values falling more than 1.5 times the interquartile range from the quartiles. Differences in categorical variables were assessed using the χ^2 test. To evaluate changes in dynamic values from the first to the last measurement within each group, the Friedman test was used. The Fisher exact test was employed to analyze differences in the frequency of categorical changes.

A p-value of < 0.05 was considered statistically significant.

Results

During three-year period, 196 patients were referred to the Department of Removable Prosthodontics at the School of Dental Medicine, University of Zagreb, due to orofacial pain and discomfort. Out of 47 patients who met the inclusion criteria, 7 declined to participate in the study due to time constraints, resulting in a final sample size of 40 participants: 35 women (87.5%) and 5 men (12.5%), aged 45.1 ± 16.8 years.

Among 40 patients initially included in the study, 9 withdrew for unspecified reasons, leaving 31 (77.5%) patients (3 M, 28 F) who completed the study. Of these, 13 were in the amitriptyline group and 18 were in the placebo group (Fig. 1).

Dropout analysis

The baseline characteristics of patients who completed versus those who dropped out are summarised in Table 1. No significant difference was observed among those who completed the study when compared to those who dropped out for any of the examined variable ($p > 0.05$). However, the p-value for VAS approached significance, suggesting the possibility of underlying differences.

Table 1 Demographic information, TMD pain status and psychological aspects of all patients at baseline

Variable		Completed	Dropout	p
Age [a]	*Female, mean (SD)*	48.56 (17.6)	37.57 (8.6)	0.111
	Male, mean (SD)	41.00 (33.9)	35.5 (4.9)	0.999
Gender[b]	*Female, n(%)*	28 (90%)	7 (78%)	0.316
	Male, n(%)	3 (10%)	2 (23%)	
Educational level[b]	*Elementary school, n (%)*	4 (12.9%)	1 (11.2%)	0.304
	High school, n (%)	21 (67.7%)	4 (44.4%)	
	Masters Degree, n (%)	6 (19.4%)	4 (44.4%)	
Characteristic pain intensity (0–100)[a] (mean ± SD)		73.11 (16.26)	62.15 (10.73)	0.065
Disability score (0–100)[a] (mean ± SD)[a]		40.21 (31.23)	48.14 (20.41)	0.414
Oral health related QoL-14 score (0–56)[a] (mean ± SD)		26.29 (11.05)	26.00 (13.20)	0.922
Visual Analogue Scale (1–10)[a]		7.8 (1.54)	6.6 (1.32)	0.052

[a] Mann Whitney U test; $p < 0.05$

[b] χ^2-test; df = 2; $p < 0.05$

Table 2 Participants baseline characteristics – comparison between amitryptiline and placebo group

	range	Amitryptiline group *N* = 13	Placebo group *N* = 18	P*
Age (years) [a]		47.92 ± 15.44	48.00 ± 21.42	0.999
Disability score [a]	*0–100*	37.44 ± 26.57	42.22 ± 34.83	0.673
Charateristic pain intesity (CPI) [a]	*0–100*	68.21 ± 15.91	76.67 ± 16.01	0.172
AXIS II: depression[b]**, n (%)**	*< 0.535*	6 (46.2)	9 (50.0)	0.543
	0.535–1.105	5 (38.5)	4 (22.2)	
	> 1.105	2 (15.4)	5 (27.8)	
AXIS II: non specific physical symptoms (questions about pain excluded) [b]**, n (%)**	*< 0.535*	6 (46.2)	11 (61.1)	0.169
	0.535–1.105	4 (30.8)	1 (5.6)	
	> 1.105	3 (23.1)	6 (33.3)	
AXIS II: non specific physical symptoms (questions about pain included[b]**, n (%)**	*< 0.535*	8 (61.5)	12 (66.7)	0.489
	0.535–1.105	1 (7.7)	0 (0)	
	> 1.105	4 (30.8)	6 (33.3)	

[a] Mann Whitney U test; $p < 0.05$

[b] χ^2-test; df = 2; $p < 0.05$

Comparison of participant's data at the beginning of the study

In the group of patients who completed the study, no significant differences between female and male participants were observed for each of the tested variables at baseline:

i) Characteristic pain intensity 71.54 (16.34) vs. 87.77 (1.92), p = 0.052;
ii) Disability score 39.40 (30.74) vs. 47.77 (42.21), $p = 0.728$;
iii) OHIP-14_score 26 (10.68) vs. 29 (16.70), $p = 0.663$;
iv) spontaneous pain according VAS 7.68 (1.56) vs. 9 (1.1), $p = 0.181$.

Therefore, the data for males and females were combined for further analysis.

To ensure comparability between the amitriptyline and placebo groups at baseline, we compared age, functional impairment in daily tasks, and characteristic pain intensity (CPI), as detailed in Table 2. No statistically significant differences were found between the two groups in terms of age, functional impairment, or CPI.

Chronic pain levels were assessed using the RDC/TMD formula, which also indicated the intensity of pain and degree of impairment. Results showed that 45.2% of patients experienced a low level of impairment and low pain intensity (grade 1). A moderate level of impairment with high pain intensity and moderate limitations was observed in 41.9% of patients (grades 2 and 3), while 12.9% of patients had high impairment with extreme limitations (grade 4).

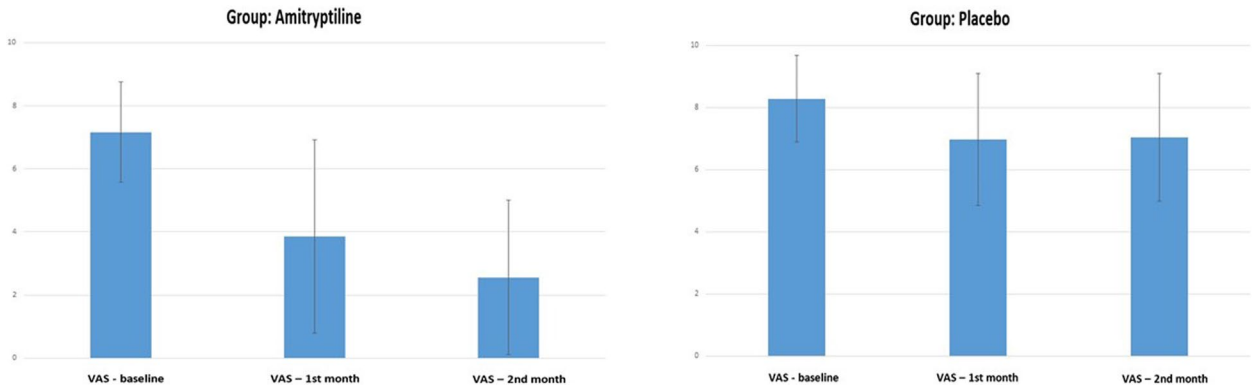

Fig. 2 VAS Score Dynamics **a** placebo group (Friedman Test, $p = 0.009$) and **b**) a group (Friedman Test, $p < 0.001$)

Table 3 Means and SDs of OHIP-14 questionnaire scores for each group at each time point

	Amitriptyline group				Placebo group					
	Baseline	1-month follow-up	2-months follow-up	p [b]	Baseline	1-month follow-up	2-months follow-up	p [b]	Between group comparison 1-month follow-up [a]	Between group comparison 2-month follow-up [a]
OHIP-14 questionnaire										
Physical limitations	1.35 ± 0.99 [c]	1.04 ± 1.09	0.58 ± 0.64	< 0.001	0.56 ± 1.03 [c]	0.56 ± 1.01	0.44 ± 0.73	0.810	0.105	0.301
Physical pain	2.35 ± 1.13	1.46 ± 0.99	0.85 ± 0.92	< 0.001	2.75 ± 1.06	2.28 ± 1.42	2.03 ± 1.27	0.006	0.119	0.010
Psychological discomfort	2.77 ± 0.75	2.04 ± 1.35	1.27 ± 1.27	0.003	2.47 ± 1.12	2.44 ± 1.16	2.17 ± 1.32	0.509	0.294	0.068
Physical inability	2.08 ± 1.32	1.46 ± 1.22	0.81 ± 0.97	< 0.001	2.14 ± 1.35	1.67 ± 1.22	1.61 ± 1.21	0.239	0.556	0.060
Psychological inabilty	2.62 ± 0.94 [c]	1.54 ± 1.09	0.96 ± 1.07	< 0.001	1.47 ± 1.21 [c]	1.22 ± 1.06	1.11 ± 0.96	0.558	0.406	0.589
Social inability	1.62 ± 0.98	1.04 ± 1.07	0.89 ± 0.92	< 0.001	1.50 ± 1.19	1.31 ± 1.18	1.06 ± 0.65	0.176	0.526	0.167
Handicap	1.27 ± 1.07	0.96 ± 1.07	0.69 ± 0.99	0.002	1.61 ± 1.37	1.44 ± 1.19	1.17 ± 1.07	0.529	0.257	0.184

Data are presented as mean ± standard deviation

[a] Mann Whitney *U* test

[b] Friedman test

[c] Statistically significant difference between amitriptyline and placebo groups at baseline

Comparative data from the Axis-II questionnaire are presented in Table 2. The differences between groups were not statistically significant.

Primary outcome measure changes

Differences in VAS scores between the placebo and amitriptyline groups at baseline, and after 1-month and 2-month follow-ups are presented in Fig. 2.

When evaluating the effect of the two different interventions on VAS Score reduction participants in amitriptyline group experienced a significantly greater reduction in spontaneous pain, with a 63.3% decrease in VAS scores. Participants in placebo group showed a much smaller reduction in spontaneous pain, with only a 16.2% decrease in VAS scores. The reduction in VAS scores was statistically significant in both groups, but more pronounced in the amitriptyline group (Kendall's $W = 0.791$, $p < 0.001$) compared to the placebo group (Kendall's $W = 0.279$, $p < 0.009$). Although both groups showed statistically significant reductions in VAS scores, Kendall's W in the amitriptyline group suggests not only a larger effect but also more uniformity in how participants responded to the treatment.

Secondary outcome measure changes

The baseline scores of the OHIP-14 questionnaire for physical limitations and psychological impairment are compared between groups. Participants in the amitriptyline group reported significantly higher scores for physical limitations (1.35 ± 0.99 points) compared to the control (placebo) group (0.56 ± 1.03 points) ($p = 0.010$). Similarly, scores for psychological impairment were higher in the amitriptyline group (2.62 ± 0.94 points) compared to the placebo group (1.47 ± 1.21 points) ($p = 0.012$) (Table 3).

At the 1-month follow-up, there were no statistically significant differences between the placebo and amitriptyline groups. However, at the 2-month follow-up, participants in the placebo group reported significantly higher scores for physical pain (2.03 ± 1.27 points) compared to those in the amitriptyline group (0.85 ± 0.92 points) ($p = 0.010$).

Participants in the amitriptyline group demonstrated 67.85% reduction of the total OHIP-14 score after two months' treatment (Kendall's $W = 0.886$, $p < 0.001$), while in the placebo group total OHIP was not significantly changed with respect to the initial values (Kendall's $W = 0.139$, $p = 0.184$).

When comparing changes in the OHIP-14 scores across categories using the Friedman test, the amitriptyline group demonstrated significantly lower values in each category after two months. In placebo group the reduction after two months was present only for the category physical pain.

Dynamics of changes of the total OHIP-14 scores across different time points, as analyzed using the Friedman test, are presented in Fig. 3.

Discussion

By comparing the therapeutic outcomes between amitriptyline and placebo, this research seeks to provide further insight into the role of tricyclic antidepressants in treating chronic TMD and potentially inform clinical guidelines for its management. While amitriptyline is recognized for its efficacy in managing various chronic pain conditions, its use has declined in some settings due to its side effect profile, which includes drowsiness, dry mouth, weight gain, and potential cardiovascular effects, particularly at higher doses. These side effects have led clinicians to favour newer antidepressants with a more favourable side effect profile, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) [1, 43]. However, amitriptyline's role in chronic pain management, particularly at lower doses, remains significant.

In the context of TMD, the rationale for using amitriptyline is supported by its ability to modulate pain through mechanisms beyond its antidepressant effects. Low-dose amitriptyline, typically prescribed at doses much lower than those used for depression, has been shown to enhance endogenous pain inhibitory mechanisms by increasing levels of serotonin and norepinephrine in the central nervous system. These neurotransmitters play a critical role in descending pain inhibition, a pathway that is often dysregulated in chronic pain conditions, including TMD. The lower doses used in pain management also tend to produce fewer side effects, making the risk–benefit ratio more favourable in this context [21].

Moreover, while newer pharmacological options are available, their efficacy in TMD is not as well-established as that of amitriptyline. The existing body of research, including studies by Alajbeg et al. [2], provides a foundation for considering amitriptyline as a viable option for TMD treatment, in terms that it successfully reduced pain and increased the quality of life. This is especially relevant given the complex and multifactorial nature of TMD, where a multimodal approach to management—including pharmacotherapy targeting central pain mechanisms—may be necessary to achieve optimal outcomes.

Chronic pain syndromes, such as temporomandibular disorders, headaches, fibromyalgia, and irritable bowel syndrome, often co-occur, with one type of pain typically being dominant at any given time [22]. Patients with chronic pain, particularly those with conditions like

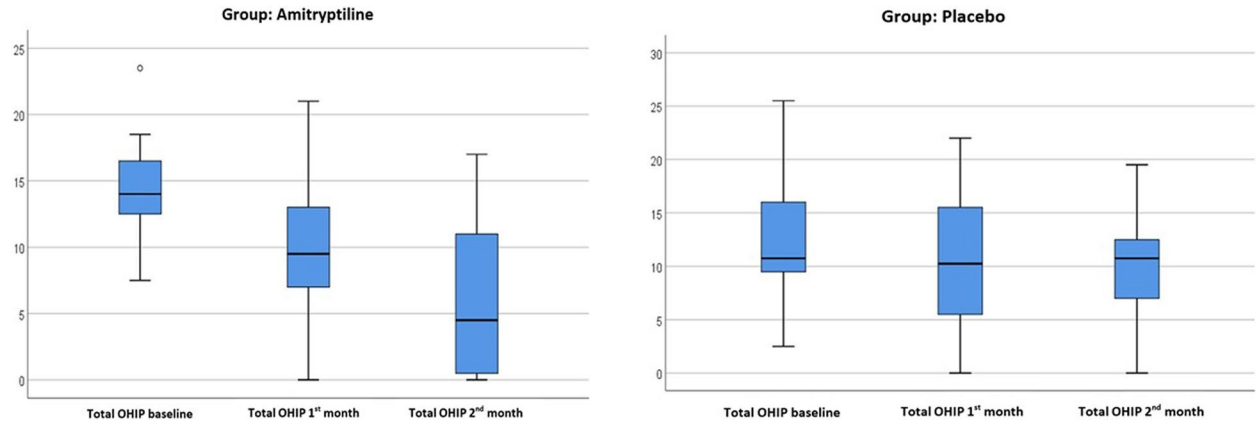

Fig. 3 The dynamics of OHIP-14 Scores: **a** placebo group (Friedman Test, $p = 0.184$) and **b**) amitriptyline group (Friedman Test, $p < 0.001$)

inflammatory or degenerative joint disease, are more susceptible to developing centrally triggered pain, such as fibromyalgia, which occurs at a fourfold higher rate in these patients [20]. Additionally, chronic pain often runs in families, with genetic factors influencing pain sensitivity across generations. Genes like COMT, which are involved in the production of adrenaline, noradrenaline, and dopamine, can create variants with lower enzymatic activity, increasing the risk of chronic pain. Alterations in genes responsible for the serotonin pathway also contribute to the development of depression, anxiety, and other related conditions [14]. All these factors underscore the complexity of chronic pain, including TMD, where the incidence and experience of pain are influenced by a multitude of genetic, psychological, and environmental factors.

This study's findings demonstrated a significant reduction in pain intensity in the amitriptyline group, with VAS scores 63.3% lower, indicating that low-dose amitriptyline can effectively reduce pain, though not eliminate it entirely. The higher Kendall's W for the amitriptyline group suggests that this treatment is both more effective and produces more consistent reductions in pain compared to the placebo group. The weak consistency in the placebo group may reflect variability in how participants perceive pain reduction or the limited efficacy of the placebo. Previous studies have shown similar results, with low doses of amitriptyline providing significant pain relief compared to placebo [24, 39, 42].

Chronic TMD is also associated with a reduced oral health-related quality of life. Various studies using tools like the OHIP-14 and SF-36 have demonstrated that chronic pain negatively impacts patients' perception of their oral health and overall quality of life, further emphasizing the importance of effective pain management [7, 8, 10, 32, 44]. This study's results align with previous findings, showing that OHIP-14 scores in the Amitriptyline group were 67.9% lower than in the Placebo group, confirming the drug's beneficial impact on quality of life in chronic TMD patients.

Our study has several limitations. One notable limitation is the absence of sex matching between the placebo and amitriptyline groups, which could introduce a potential bias. However, no significant differences were observed between male and female participants in our sample. Recruitment of male participants meeting the inclusion criteria proved challenging due to a gender ratio at our clinic that is more skewed than the typical 2:1 observed in TMD studies.

Additionally, while we evaluated baseline differences between participants who completed the study and those who dropped out, which provided useful insights, this analysis alone is insufficient to rule out potential bias from dropouts. Significant differences were not observed in most variables, but moderate differences in the VAS and weak differences in CPI suggest a potential influence of baseline characteristics on the results. Our dropout analysis indicated that some baseline characteristics, such as VAS, might have influenced the likelihood of dropout, suggesting a non-random dropout pattern. Participants with higher symptom severity at baseline were more likely to drop out, which could introduce bias. Under such conditions, standard imputation techniques, which often assume missingness at random, would likely fail to produce unbiased estimates.

Furthermore, performing an intention-to-treat analysis without proper adjustments for baseline differences risks diluting the treatment effects or misrepresenting the results. While adjusting for baseline variables is a potential alternative, these adjustments were not pre-specified in our statistical analysis plan. Retrospective adjustments

could lead to overfitting or introduce unintended biases, further limiting their applicability.

Future studies should incorporate pre-specified strategies for handling missing data, including ITT analyses with baseline adjustments or advanced imputation techniques, to improve the validity and transparency of findings. Additionally, strategies to reduce dropout rates and address non-random missing data mechanisms should be prioritized during the study design phase.

Finally, while our sample size was determined to be adequate based on power analysis, we acknowledge that it is relatively small. However, rather than classifying this as a pilot study, we emphasize that our findings provide meaningful preliminary evidence that warrants further investigation. Larger studies with more diverse populations will be necessary to confirm and expand upon our results. Despite these limitations, the novel findings of this study remain significant and contribute valuable evidence to the understanding and treatment of TMD.

Given the potential side effects, the study design includes careful monitoring and dosage adjustments to minimize adverse effects while still achieving therapeutic benefits. Additionally, the placebo-controlled nature of this trial allows for a rigorous assessment of amitriptyline's true efficacy in TMD management, providing valuable insights that could inform clinical practice and potentially reinstate the drug's relevance in specific patient populations.

Conclusion

This study highlights the potential of low-dose amitriptyline as an effective treatment option for chronic TMD, demonstrating significant pain reduction and improved quality of life compared to placebo. Amitriptyline's established efficacy, particularly in enhancing endogenous pain inhibitory mechanisms, supports its role as a valuable component of a multimodal approach to managing chronic TMD. However, it is important to acknowledge the study's limitations, including potential bias due to non-random dropout patterns, which may impact the generalizability of the findings. Future research should prioritize strategies to address missing data, incorporate baseline adjustments, and adopt robust methodologies to strengthen the evidence base. Given the complex interplay of genetic, psychological, and environmental factors in chronic pain syndromes, continued efforts to optimize treatment strategies and personalize care for individuals suffering from TMD and related conditions remain essential.

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Clinical trial number

The study was registered retrospectively in ISRCTN registry under the number ISRCTN17622685.

Authors' contributions

R.B.B. carried out the research (baseline and made follow-up assessments of the patients) and wrote the manuscript. She also assisted with this study's design and conceptualization. I.B. allocated treatment therapy protocols to participants, interpreted the data and co-wrote the manuscript. A.C. visualisation, helped in co-writing the manuscript. T.G. visualisation, helped in co-writing the manuscript. I.Z.A. conceptualized and designed the study, made the primary assessment of the patients, she analysed and interpreted the data and wrote and critically edited the manuscript. All authors have read and agreed to the published version of the manuscript. R.B.B. and I.Z.A. contributed equally to this work.

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Data availability

Data is contained within the article. Any additional results that may be relevant to this research are accessible upon reasonable request from the corresponding author.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the University of Zagreb School of Dental Medicine and regulated in accordance with the Helsinki Declaration. All subjects were informed and provided written consent before being involved in the research.

Competing interests

The authors declare no competing interests.

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