UNIVERSIDADE DE SÃO PAULO
FACULDADE DE ODONTOLOGIA DE BAURU

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Efficacy of duloxetine in addition to self-management strategies for treatment of chronic paiful temporomandibular disorder: a randomized, placebo-controlled clinical trial

Eficácia da duloxetina em adição as estratégias de autocuidado para tratamento de disfunção temporomandibular dolorosa crônica: um ensaio clínico randomizado, placebo-controlado

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"Numa obra tão sagrada, nenhum lugar deve ser dado a planos e interesses egoístas. Toda ambição, cada motivo, deve estar subordinado ao interesse daquela vida que se mede pela vida de Deus."

Medicina e Salvação

Ellen White

ABSTRACT

Efficacy of duloxetine in addition to self-management strategies for treatment of chronic paiful temporomandibular disorder: a randomized, placebo-controlled clinical trial

Rigorous evidence for combining different therapies for chronic painful temporomandibular disorder (TMD) is limited. Therefore, we conducted a randomized, double-blind, placebo-controlled trial 1) to assess the efficacy of duloxetine in addition to self-management (SM) strategies for treatment of chronic TMD; 2) to investigate whether baseline conditioned pain modulation (CPM) predicts the efficacy of duloxetine in TMD individuals; and 3) to conduct an exploratory analysis of five phenotyping domains – pain, psychological, sleep, quantitative sensory testing and CPM – to examine predictors of response to SM-duloxetine. Participants were randomized 1:1 to duloxetine 60 mg or placebo once daily for 12 weeks. Moreover, all participants were treated with a SM program. The primary outcomes were a) the change in the pain intensity from baseline to week 12 and b) CPM-sequential paradigm at baseline. Supplemental pain measures, physical and emotional functioning outcomes were also evaluated. Modified baseline observation carried forward, ANCOVA, multiple linear regression and relative risk were applied to the data ($p<0.050$). Eighty participants were randomized and 78 were included in the intention-to-treat analysis. Pain intensity decreased significantly over time with participants on SM-duloxetine and SM-placebo, reporting reductions from baseline of 30% and 36%, respectively, but did not differ significantly between groups (0.3, 95% CI: -1.1, 1.7; $p = 0.82$). A more efficient CPM was associated with a greater pain intensity reduction ($p=0.035$) after 12 weeks of treatment, regardless the treatment group. Furthermore, phenotypes, e.g., severe pain intensity, pain disability, painful comorbidity and anxiety symptoms were indicative of the likelihood of response to SM-duloxetine. In conclusion, there is no beneficial effect of adding duloxetine to SM strategies for treatment of chronic TMD, although high attrition and confidence interval interpretation preclude firm conclusions. Moreover, this randomized clinical trial demonstrated the feasibility of applying patient phenotyping assessment to predict short-term treatment response in chronic TMD individuals, which can contribute to the development of mechanism-based treatments of orofacial pain.

Keywords: Temporomandibular joint dysfunction syndrome. Chronic pain. Duloxetine hydrochloride. Self-care. Pain threshold. Randomized controlled trial

RESUMO

Eficácia de duloxetina em adiçao as estretégias de autocuidado para tratamento de disfunção temporomandibular dolorosa crônica: um ensaio clínico randomizado, placebo-controlado

Evidência rigorosa para combinação de diferentes terapias para disfunção temporomandibular dolorosa crônica (DTM) é limitada. Portanto, realizamos um ensaio clínico randomizado, duplo-cego, placebo-controlado para: 1) avaliar a eficácia da duloxetina em adição as estratégias de autocuidado (AC) no tratamento da DTM crônica; 2) investigar se a modulação da dor condicionada (MDC) prediz a eficácia da duloxetina em indivíduos com DTM; e 3) conduzir uma análise exploratória de cinco domínios fenotípicos - dor, psicológico, sono, teste quantitativo sensorial e CPM - para examinar preditores de resposta à combinação AC-duloxetina. Os participantes foram alocados numa taxa 1:1 para duloxetina 60 mg ou placebo, administrados uma vez ao dia, por 12 semanas. Além disso, todos os participantes foram tratados com um programa de AC. Os desfechos primários foram a) mudança na intensidade da dor ocorrida do basal até a semana 12 e b) protocolo sequencial de MDC no basal. Aspectos emocionais e interferência da dor também foram avaliados. Observação de linha de base modificada realizada, ANCOVA, regressão linear múltipla e risco relativo foram aplicados aos dados ($p < 0,050$). Oitenta participantes foram randomizados e 78 foram incluídos na análise por intenção de tratamento. A redução na intensidade de dor foi de 30% e 36%, respectivamente, para os grupos AC-duloxetina e AC-placebo, sem diferença entre os grupos (0,3, 95% CI: -1,1, 1,7; $p = 0,82$) ao final das 12 semanas. Uma MDC eficiente foi associada a uma maior redução da intensidade da dor ($p = 0,035$) ao final do tratamento, independentemente do grupo. Além disso, os fenótipos dor severa, presença de interferência da dor, comorbidade dolorosa e sintomas de ansiedade foram indicativos da probabilidade de resposta à AC-duloxetina. Em conclusão, não há efeito benéfico em adicionar duloxetina às estratégias de AC para o tratamento da DTM crônica, embora a perda de pacientes e a interpretação do intervalo de confiança impeçam conclusões definitivas. Além disso, este ensaio clínico randomizado demonstrou a viabilidade de realizar a fenotipagem do paciente para prever a resposta ao tratamento de curto prazo em indivíduos com DTM crônica, o que pode contribuir para o desenvolvimento de tratamentos baseados em mecanismo de dor orofacial.

Palavras-chave: Síndrome da disfunção da articulação temporomandibular. Dor crônica. Cloridrato de duloxetina. Autocuidado. Limiar de dor. Ensaio clínico controlado aleatório

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1 INTRODUCTION

1 INTRODUCTION

Temporomandibular disorders (TMD) represent a cluster of disorders in masticatory system[1]. TMD affects approximately 10% of the population and has a great impact on the individual quality of life[2, 3]. In addition, TMD has been estimated to generate a substantial impact on the economy through lost productivity and on the health care system through multiple consultations required to TMD diagnose and management[1, 4].

There are many potential treatments for TMD, including self-management (SM), physical therapy, psychological/behavior therapy, medications, intraoral appliances, and surgery[1, 5]. Although evidence-based clinical practice guidelines for treatment of TMD do not currently exist, SM strategies has been considered a core part in TMD management and should be applied to all types of TMD[6].

In the clinical practice, chronic painful TMD individuals concurrently receive combination of non-pharmacological and pharmacological therapy to address many potential mechanisms involved in TMD pathophysiology. However, rigorous evidence for combining different treatments is limited, and more high-quality studies are needed to identify specific treatment combinations that provide added benefit vs other combinations that are either harmful or cost-ineffective[1].

Duloxetine is a serotonin and norepinephrine reuptake inhibitor (SNRI) effective and safety in the treatment of fibromyalgia, chronic low back pain, osteoarthritis pain and diabetic peripheral neuropathic pain[7, 8]. The analgesic effects of duloxetine are believed to result from increased activity of serotonin and norepinephrine within the central nervous system (CNS), presumably either by enhancing the descending pain inhibitory systems in the brain and spinal cord or via other unknown CNS actions[9, 10]. Dysfunction of serotonin and norepinephrine - mediated descending pain inhibitory system is a potential mechanism for the pain experienced by individuals with chronic TMD[11, 12], however, there are no randomized controlled trials testing the efficacy of duloxetine in TMD.

Descending pain inhibitory system can be assessed using psychophysical methods including conditioned pain modulation (CPM), where pain perception evoked by a noxious stimulus can be reduced when presented concurrently or subsequently to another noxious stimulus delivered in a distant body site[13, 14]. Clinical relevance of CPM has been identified, since it provides useful information for drug selection in chronic pain patients. For instance, painful diabetic neuropathy patients with less efficient CPM are more likely to benefit from

treatment with duloxetine[15]. Moreover, knee osteoarthritis patients with more efficacious CPM at baseline reported more pain reduction after 3-week treatment with diclofenac[16]. This is an important area of ongoing work, but at present the value of CPM to predict treatment response has not been properly investigated in chronic TMD.

The overall aim of this thesis was to assess the effect of adding duloxetine to SM strategies (SM-duloxetine) for treatment of chronic TMD and investigate whether baseline CPM predicts the efficacy of duloxetine in TMD individuals (article 1). Moreover, we conducted an exploratory post hoc analysis of five phenotyping domains – pain, psychological, sleep, quantitative sensory testing and CPM – to examine predictors of response to SM-duloxetine for chronic TMD (article 2). We hypothesized that: (1) duloxetine would present additional effect to SM in reducing pain intensity on chronic TMD; (2) a less efficient CPM at baseline would be associated with greater reduction in pain intensity in participants treated with SM-duloxetine and (3) phenotyping characteristics would predict which TMD individuals would respond to SM-duloxetine but not to SM-placebo.

2 ARTICLES

2 ARTICLES

2.1 ARTICLE 1

This article was submitted to *Pain* and was in accordance with this journal (Annex A).

Conditioned pain modulation predicts treatment response in chronic temporomandibular disorder

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Abstract

Conditioned pain modulation (CPM) has been considered a valuable predictor of response to treatment in chronic pain, however, it has not been studied in temporomandibular disorder (TMD). We conducted a randomized, double-blind, placebo-controlled trial of duloxetine in addition to self-management (SM) strategies for treatment of chronic TMD and investigate whether a lower CPM at baseline would predict the duloxetine responsiveness. Participants were randomized to duloxetine 60 mg or placebo once daily for 12 weeks. Moreover, all participants were treated with a SM program. The primary outcomes were a) the change in the pain intensity from baseline to week 12 and b) CPM-sequential paradigm at baseline. Safety, physical and emotional functioning outcomes were also evaluated. Eighty participants were randomized and 78 were included in the intention-to-treat analysis. Pain intensity decreased significantly over time with participants on SM-duloxetine and SM-placebo, reporting reductions from baseline of 30% and 36%, respectively, but did not differ significantly between groups (0.3, 95% CI: -1.1, 1.7; p = 0.82). Multiple linear regression showed that a more efficient CPM was associated with a greater pain intensity reduction (p=0.035) after 12 weeks, regardless the treatment group. Overall, physical, and emotional functioning did not differ significantly between groups, but adverse events (p=0.014), sleep disorders (p=0.003) and catastrophizing symptoms (p=0.001) were more prevalent in SM-duloxetine group. There is no beneficial of adding duloxetine to SM strategies for treatment of chronic TMD, although high attrition and CI interpretation preclude firm conclusions. A greater CPM magnitude can predict analgesic response to SM strategies.

Keywords: Temporomandibular joint dysfunction syndrome. Chronic pain. Duloxetine hydrochloride. Self-care. Pain threshold. Randomized controlled trial

1. Introduction

Conditioned pain modulation (CPM) is a phenomenon in which exposure to a noxious conditioning stimulus reduces the experience of pain from a second test stimulus applied concurrently or subsequently to a distant body site [42]. There is evidence that descending pain inhibitory mechanisms account for the CPM response [38; 41].

It is suggested that CPM assessment is clinically relevant since it provides useful information for drug selection in chronic pain patients. For instance, painful diabetic neuropathy patients with less efficient CPM are more likely to benefit from treatment with duloxetine [44]. Moreover, knee osteoarthritis patients with more efficacious CPM at baseline reported more pain reduction after 3-week treatment with diclofenac [14]. This is an important area of ongoing work, but at present the value of CPM to predict treatment response has not been properly investigated in chronic painful temporomandibular disorders (TMD) patients.

There is substantial evidence in support of efficacy and safety of duloxetine in the treatment of fibromyalgia, chronic low back pain, osteoarthritis pain and diabetic peripheral neuropathic pain [24; 33; 40]. The analgesic effects of duloxetine are the result of increased activity of serotonin (5-HT) and norepinephrine (NE) within the central nervous system (CNS), presumably either by enhancing the descending pain inhibitory systems in the brain and spinal cord or via other CNS actions [9; 22]. Moreover, dysfunction of 5-HT– and NE-mediated descending pain-inhibitory pathways is a potential mechanism for the pain experienced by patients with chronic TMD [20; 31]. Nonetheless, there are no available randomized controlled trials testing the efficacy of duloxetine in chronic TMD patients.

In the clinical practice, chronic TMD patients receive combination of non-pharmacological (self-management [SM] strategies, intraoral appliances, physical therapy, psychotherapy) and pharmacological (nonsteroidal anti-inflammatory drugs [NSAID], muscle relaxants, tricyclic antidepressants, anticonvulsants) therapies to address many potential mechanisms involved in TMD pathophysiology [29; 32]. Although evidence-based clinical practice guidelines for the treatment of TMDs do not currently exist, SM strategies have been considered a core part in TMD management and are generally a first-choice option [12]. Furthermore, rigorous evidence for combining different treatments is limited, and more high-quality studies are needed to identify either treatment combinations that provide additional benefit or combinations that are harmful and/or unsuccessful [29].

To address these knowledge gaps and clinical need, we conducted a 12-week, 2-arms, randomized clinical trial that examined the efficacy of duloxetine in addition to SM strategies in participants with chronic TMD. We also investigated whether CPM capacity at baseline predicted the efficacy of duloxetine in TMD participants. We hypothesized that: (1) duloxetine would present additional effect to SM in reducing pain intensity on chronic TMD; (2) a less efficient CPM at baseline would be associated with greater reduction in pain intensity in participants treated with duloxetine. We also added pragmatic characteristic to our study [34], thus we included TMD individuals with comorbid conditions commonly associated with TMD and with medication use.

2. Methods

2.1 Ethics and recruitment

The study was conducted in accordance with the Declaration of Helsinki and further amendments and approved by the Human Research Ethics Committee of the Bauru School of Dentistry, University of São Paulo, Brazil. All participants gave informed consent after a full explanation of the study. Participants were recruited by posting of flyers at Bauru School of Dentistry, public health centers and hospitals of the municipality and by announcements in newspapers and radio stations. The reporting of the study follows the Consolidated Standards of Reporting Trials (CONSORT) guideline [36]. The trial has been pre-registered in the Brazilian Registry of Clinical Trials (# RBR-6pqx4n).

2.2 Participants

Women and men $\geq$ 18 years of age who were diagnosed with painful TMD according to the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) [35], i.e., arthralgia, myalgia and headache attributed to TMD, and had pain $\geq$ 3 months were eligible. Exclusion criteria included presence of uncontrolled systemic disorders, e.g., diabetes, hypertension or endocrine conditions; presence of epilepsy, kidney, liver and cardiac disorders; presence of neuropathies; history of psychosis or bipolar disorder, substance abuse within the past year, and suicidal ideations; treatment with monoamine oxidase inhibitor within 14 days of study entry; history of known allergy to duloxetine, treatment with SNRIs within 12 months of study entry; pregnancy or breast-feeding; intolerance to duloxetine or any component of the formulation; treatment for TMD in the last 3 months. To maximize generalizability and clinical relevance,

we did not exclude individuals with continuous use of centrally acting medications with constant doses for ≥ 3 months before the study entry and with comorbid conditions commonly associated with TMD, e.g., primary headaches, neck pain, fibromyalgia and anxiety and depression disorders.

The evaluation of the participants to determine their eligibility was made by the first author (DMFC), a dentist and orofacial pain specialist. A detailed medical and dental history interview was applied to investigate the exclusion criteria while a comprehensive clinical examination was performed to determine the inclusion criteria.

2.3 Design and interventions

This 2-arm, randomized, double-blind, placebo-controlled trial consisted of a screening phase followed by a 12-week treatment phase and a 1-week taper phase (Fig. 1). The participants completed 5 scheduled visits: screening, baseline, week 4, week 8 and week 12. In the screening session the participants were assessed for eligibility. The participants were randomized in a 1:1 ratio by a computer-generated random sequence (www.randomizer.org) to duloxetine 60 milligrams per day (mg/d) or placebo for the treatment phase.

We used titration to achieve the target daily dose of 60 mg. At week 1, participants received 30 mg/d (1 capsule) and at week 2 or 3, duloxetine was escalated to 60 mg/d (2 capsules). The researcher DMFC contacted participants in the end of week 1 and 2 to evaluate adverse events (AE) and applied the titration. If only mild or no AE were reported, participants were asked to take 2 capsules once a day. If AE was reported, participants were asked if they could tolerate the current dose (1 capsule) for another week. If AE was still reported, then 1 capsule was kept for the remining weeks.

Extended-release duloxetine and placebo capsules were prepared by an independent pharmacy (Bauru Formulas, Bauru, Brazil). The capsules were identical in appearance. Participants were instructed to take the capsules once a day in the morning, preferably after the breakfast. As per pragmatic, add-on design, the participants were allowed to use acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs) as rescue therapy. Any procedural therapy (e.g., trigger point blocks) were not allowed throughout the trial. Occlusal splint was allowed for participants who had already used it before entering in this study.

At taper phase, participants that completed the 12-week treatment period entered in a 1-week taper period to minimize discontinuation-emergent AE. During this period, individuals who received 2 capsules of duloxetine or placebo during the treatment period received 1 capsule

of duloxetine or placebo per day. Unblinding of the participants were made only after the taper phase by another researcher that was not involved in the assessment or treatment.

In addition to the drug therapy, all participants received a SM program at baseline, which was reinforced in all visits. The SM program involved verbal and written information about a) TMD etiology and prognostic, b) encouragement to adopt of pain-free diet and reduce caffeine consumption, c) use of reminders to avoid oral parafunction, d) relaxation techniques for the jaw, e) sleep hygiene and f) encouragement to practice physical activities. The SM intervention for this study was adapted from a protocol used in our TMD and orofacial pain clinic and follow the international expert consensus for SM in TMD [12].

The randomization was performed by one investigator (YMC), the treatment was provided by another investigator (DMFC) and the outcome assessments were performed by a third investigator (FFSC). Thus, treatment and assessment investigators and participants were blinded to the group allocation.

2.4 Outcomes

We followed the recommendations of the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials in chronic pain (IMMPACT) [13]. The outcome measurements were pain, physical functioning, emotional factors, AE and rescue medication. As further recommended by another IMMPACT publication [15], we assessed the CPM at baseline as possible predictor.

2.4.1 Primary outcomes

2.4.1.1 Pain intensity

The primary efficacy measurement was the change in “average pain intensity over the past week” from baseline to week 12. Participants were asked to rate their average pain intensity over the past week (0 to 10 numeric rating scale - NRS), where 0 means “No pain” and 10 “Pain as bad as you can imagine”. We used a structured form to collect information about pain intensity, AE and rescue medication. The participants were asked to entry with theirs answer once a week.

We also employed the Characteristic of Pain Intensity (CPI) as a measurement of treatment efficacy. CPI is derived from Graded Chronic Pain Scale (GCPS) [39] and is

computed as the mean, multiple by 10, of the average pain, pain right now and worst pain over the past month. CPI was assessed at baseline and weeks 4, 8 and 12.

2.4.1.2 Conditioned pain modulation

A CPM-sequential paradigm was performed using pressure pain threshold (PPT) on the most painful masseter muscle as the test stimulus (TS) and cold-water immersion of the contralateral hand as a conditioning stimulus (CS). PPT testing with cold conditioning is reproducible, sensitive to change and has a good test–retest reliability [23]. The PPT was the mean of three repetitions of ascending stimuli applied over the most painful masseter site according to the self-report and/or physical examination. The contralateral hand was immersed up to the wrist with the palm down and fingers apart into an 8-12°C circulating water bath. The participants were instructed to leave their hand in the water for 120 s or for as much as they could tolerate. Participants rated the cold pain intensity after 30, 60, 90 and 120 s (0 to 100 NRS). The CS pain intensity was maintained $\geq$ 30 NRS for all participants. Immediately after the participants removed their hand from the water, then PPT was re-assessed. The CPM effect was calculated as the difference between the TS_{before} and TS_{after} the CS. Pain inhibition along the protocol was represented by a negative value [43].

2.4.2 Secondary outcomes

2.4.2.1 Physical functioning

Physical functioning was collected at baseline and week 12. The GCPS [39] was used to assess TMD-related disability in functioning. TMD disability was computed as the average of points for interference score and points for disability days from the GCPS. Sleep was assessed with Pittsburg Sleep Quality Index (PSQI) [8]. This 19-item instrument assess sleep quality over the past month across seven components: quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use sleep medication and daytime dysfunction. All seven components are then summed up to create a scale from 0–21 points and a total score > 5 denoted “poor” sleep quality. The number of body painful sites was assessed using the pain drawing from DC/TMD assessment tools [35]. We asked the participants to mark their painful sites for the previous month on the body manikin and then we divided into 45 sections on the front and on the back. The index ranges from 0 to 45 and higher values indicate higher spreading of pain [26].

2.4.2.2 Emotional functioning

Emotional functioning was collected at baseline and week 12. The Hospital Anxiety and Depression Scale (HADS) [30] was used to assess anxiety and depression symptoms. HADS consists of a 14-point self-report questionnaire with anxiety and depression subscales. Every point is marked on a 4-point scale (0-3), with each subscale ranging from 0 to 21. A subscale score $\geq$ 9 is indicative of disorder. Pain catastrophizing was assessed using the total score on the Pain Catastrophizing Scale (PCS) [27]. The PCS consists of 13 items, with scores for each question ranging from 0 to 4. The total PCS score is calculated by summing the values of the 13 items and ranges from 0 to 52. Higher scores correspond to higher levels of pain catastrophizing.

2.4.2.3 Global improvement

Participants perceived improvement with treatment was measured at week 12 with the Patient Global Impression of Change (PGIC) scale [18]. The PGIC is a 7-point scale: -3 = much worse, -2 = somewhat worse, -1= little worse, 0 = no change, 1 = a little better, 2 = somewhat better, 3 = much better. For analysis, this outcome was dichotomized by combining scores from -3 to 0 in one category of “no change or worse” and from 1 to 3 in another category of “better improvement”.

2.4.2.4 Safety

Safety was assessed based on the incidence of AEs during the treatment phase. Because adverse effects are often not mentioned if left to spontaneous self-report, we used a structured form to record AE. The AEs were further categorized in mild to moderate and severe. The proportion of individuals within each category of AE was calculated, and p-values for treatment group differences were computed using Fisher’s exact test.

2.4.2.5 Expectation

At baseline, Stanford Expectations of Treatment Scale (SETS) [45] was used to assess the participant’s expectation. Positive expectation was measured as the average of the 3 positive expectation questions from SETS and negative expectation was measured as the average of the 3 negative questions. Greater positive expectation would be associated with greater response to treatment.

2.5 Statistics

It was expected that a medium effect size f of 0.4 for the mean changes in pain intensity from baseline to week-12 would be worth detecting considering the interactions from ANCOVA with one between-subject factor, baseline CPM as the continuous covariate, a power of 80% and a significance level of 5%. We also anticipated a 20% drop-out rate. Therefore, the sample size estimation was 40 subjects per group.

The outcome variables were reported as means and standard deviation (SD), unless otherwise noticed. Normal distribution of the continuous variables was assessed with the aid of Kolmogorov-Smirnov test and Q-Q plots, and they were all considered normally distributed. The principle of intention-to-treat (ITT) analysis was applied for the primary and secondary outcomes. Mixed analysis of covariance (ANCOVA) was computed to assess mean changes in pain intensity and CPI from baseline to week 12 considering one between-subject factor, group – 2 levels (SM-duloxetine and SM-placebo) and one continuous covariate, i.e., baseline CPM. Pairwise post-hoc comparison analyses were performed using Tukey Honestly Statistical Difference (HSD). Moreover, a multiple linear regression model was applied to predict treatment response. The dependent variable was the mean changes in pain intensity and CPI from baseline to week 12 and the independent variables were the following baseline measurements: a) pain intensity or CPI, CPM, body painful sites, depression symptoms and sleep quality. The significance level was set at 5% ($p = 0.050$).

The imputation for missing data method that was applied was the modified baseline-observation-carried-forward (modified BOCF) endpoint [25]. Thus, for participants who discontinued because of an AE the baseline value was used as the endpoint, and for all other participants, the last no missing post- baseline observation before dropout was used as the endpoint.

T-test for independent samples was applied to evaluate mean changes from baseline to week 12 considering differences for the physical and emotional functioning secondary outcomes. Moreover, $\chi 2$ or the Fisher's exact test were computed to evaluate the proportions of AEs and discontinuation, treatment responders considering pain intensity reduction ≥30 % and ≥50 % and the report of "better improvement". No adjustment was made for the secondary outcomes, so the significance level was set at 5% ($p = 0.050$).

2.5.1 Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

3. Results

3.1 Flow of participants

The flow of participants throughout the study is shown in Figure 2. During the period of data collection (September/2018 to March/2020) 174 participants potentially eligible were evaluated in person. Of these, 94 (54%) were excluded for not meeting inclusion criteria or declined participation. A total of 80 participants were randomized in a 1:1 ratio to treatment with SM-duloxetine or SM-placebo. Twenty-four (60%) and 30 (75%) of those assigned, respectively, to SM-duloxetine and SM-placebo group completed all 12 weeks on study. There was no significant difference in the overall discontinuation rates between groups (p= 0.232). However, more individuals discontinued because of AE in the SM-duloxetine group (n=9) compared with SM-placebo group (n=2) (p=0.047, Table 4).

Thirteen participants received minimal dose therapy (30 mg/day): 8 individuals already took monoamine reuptake inhibitor (6 in SM-duloxetine, 2 in SM-placebo group) and 5 individuals could not keep 60 mg/day dose because AE (4 in SM-duloxetine, 1 in SM-placebo group). One participant was diagnosed with trigeminal neuralgia and another one had intake serotonin and norepinephrine reuptake inhibitor (SNRI) over the past year. Thus, these participants were excluded from the ITT analysis. The safety population comprised all the 80 randomized participants who received at least one dose of the study drug.

3.2 Participants characteristics

Demographic and clinical characteristics of the ITT sample are presented in Table 1. The characteristics were similar among the treatment groups. In general, the sample consisted of women in the mid-30s. Most of participants (85%) had at least two painful TMD diagnoses (see Table S1 in the Supplemental Materials). Painful TMD was generally of longstanding duration, with a frequency $\geq$ 15 days per month in the last 3 months and of moderate to severe intensity over the past week.

Regarding the physical and psychological functioning, the participants had low disability but a poor sleep quality and high levels of anxiety symptoms. Most of participants

(70%) had at least one painful comorbidity, and the most commons were primary headache, neck pain and fibromyalgia (see Table S1, Supplemental Materials).

For concomitant centrally acting medication use, 10% of participants were taking monoamine reuptake inhibitor (antidepressant or appetite suppressant) and 3.8% were taking anticonvulsant. Moreover, muscle relaxant, benzodiazepines and opioids were taking by 8.9%; 3.8% and 2.5% of participants, respectively (Table 1). Finally, both groups presented similar scores for positive and negative expectation of treatment.

3.3 Treatment efficacy and participant ratings of improvement

The ITT analysis revealed that mean pain intensity decreased over 12 weeks for all participants. SM-duloxetine and SM-placebo group reported a pain reduction of, respectively, 30% and 36%, with a mean difference (SM-duloxetine vs SM-placebo) of 0.3 (95%CI = -1.1,1.7). The difference on mean pain intensity from baseline to week 12 was similar between the groups (ANCOVA: $F_{1,75} = 0.05$, $p = 0.820$ and partial $\eta 2 = 0.00$, Table 2 and Fig. 3). Likewise, the effect of SM-duloxetine on the CPI change from baseline to week 12 was not different from SM-placebo (ANCOVA: $F_{1,75} = 2.53$, $p = 0.115$ and partial $\eta 2 = 0.03$). The mean difference (SM-duloxetine vs SM-placebo) was 9.7 (95% CI= 20.3, -0.9). See Table 2 and Fig. S1, Supplemental Materials.

Analyses of the proportion of responders with pain intensity reduction ≥30% and ≥50% also indicated no difference between groups (≥30 %, $p = 0.645$ and ≥50 %, $p = 0.476$). SM-duloxetine presented a number needed to treat (NNT) of 14.3 and 11 considering, respectively, ≥ 30% and ≥ 50% pain reduction (Table 2). Because the responder rate and NNT can vary considerably depending on the response cut-off point used [17], we presented a continuous plot of the percentages of participants in each group across the entire range of possible responses (Fig. 5).

At week 12, 59 participants (28 in SM-duloxetine, 31 in SM-placebo group) provided information about perceived improvement with treatment. There was no significant difference in the proportion of participants that reported “better improvement” between SM-duloxetine (89%) and SM-placebo (84%) groups ($p= 0.709$, Table 2).

However, there was a significant covariation between baseline CPM and the difference on average pain intensity from baseline to week 12, ANCOVA: $F_{1,75} = 4.27$, $p = 0.042$ and partial $\eta 2 = 0.05$ (Fig. 4). Similarly, baseline CPM was significantly associated with the CPI change from baseline to week 12, ANCOVA: $F_{1,75} = 10.81$, $p = 0.001$ and partial $\eta 2 = 0.12$.

3.4 Pain modulation as a predictor of treatment response

There was a significant interaction between baseline CPM and mean change in pain intensity (ANCOVA: $F_{1,75} = 4.27$, $p = 0.042$ and partial $\eta 2 = 0.05$). The multiple regression model significantly predicted the mean changes in pain intensity from baseline to week 12, ($F_{5,72} = 3.12$, $p = 0.013$, adj. $R2 = 0.12$, Table 3). A greater baseline pain intensity was associated with a smaller pain intensity reduction ($p=0.003$) and a more efficient CPM was associated with a greater pain intensity reduction ($p=0.035$) (Table 3 and Fig. 4).

Likewise, the multiple regression model significantly predicted the CPI change from baseline to week 12 ($F_{5,72} = 6.25$, $p < 0.001$, adj. $R2 = 0.25$, Table S1 in the Supplemental Materials). A greater CPI and a higher number of painful sites at baseline were associated with a smaller CPI reduction after 12 weeks of treatment (Table S1, Supplemental Materials). Moreover, a more efficient CPM at baseline was associated with a greater CPI reduction after 12 weeks of treatment (Fig. S2, Supplemental Materials).

3.5 Physical and emotional functioning

Physical and emotional functioning outcomes are shown in Table 2. The groups presented similar responses regarding the reduction in pain disability, number of body painful sites and anxiety and depression symptoms. Interestingly, the sleep quality and pain catastrophizing improvement were greater for SM-placebo than SM-duloxetine group.

3.6 AEs, rescue medication and blinding

The SM-duloxetine group experienced more AEs when compared with the SM-placebo (90% vs. 65%; $p=0.014$). Likewise, a greater proportion of participants treated with SM-duloxetine reported AEs as the reason for discontinuation when compared with participants in the SM-placebo group (22.5% vs. 5%; $p=0.047$). No death occurred and two participants in the SM-duloxetine group reported constipation as serious AE.

Table 4 shows AEs reported by $\geq$ 5% of participants in both treatment groups. In general, the more prevalent AEs were nauseas, drowsiness, headache, dry mouth, dizziness and dyspepsia. Nausea, dry mouth and constipation were more frequent in the SM-duloxetine group when compared with the SM-placebo group (Table 4). Most of AEs were mild to moderate in severity and were reported mostly in the first month.

Rescue medications (NSAIDs and analgesics) were taken by 77% and 76% of participants receiving, respectively, SM-duloxetine and SM-placebo treatment. On average,

participants in the SM-duloxetine group used 10.5 tablets, whereas participants in SM-placebo used 8.4 tablets during the 12 weeks of treatment.

The examiner responsible for the assessment and 56 participants provided information about the perceived treatment allocation after the taper phase. The examiner correctly identified 66% of participants in SM-duloxetine group and 55% in SM-placebo group. Moreover, 44% of participants in the SM-duloxetine and 82% of the SM-placebo group correctly identified their treatment.

4. Discussion

This is the first randomized controlled trial investigating the efficacy of duloxetine in addition to SM strategies on treatment of chronic TMD. The main findings were: 1) there was no beneficial effect of duloxetine in addition to SM strategies for the primary outcome of pain intensity and most of the secondary outcomes and 2) a more efficient CPM at baseline was associated with a greater pain intensity reduction after 12 weeks of treatment regardless the treatment group.

4.1 Treatment efficacy

In this randomized clinical trial, after 12 weeks of treatment, both treatment groups presented a clinically relevant improvement. However, there was no beneficial effect of duloxetine in addition to SM strategies. This result is consistent with previous studies that evaluated the addition of different therapies to SM strategies in TMD patients [1; 10]. For instance, the use of tizanidine or cyclobenzaprine in addition to SM was not more effective than placebo for the management of patients with myofascial jaw pain [1]. Moreover, the simultaneous use of occlusal splint device and SM in myofascial TMD patients did not present additional effect after 3 months of treatment, although it was associated with an earlier improvement of pain intensity [10].

Central sensitization and impaired descending pain inhibition have been implicated as important underlying mechanisms of TMD pain [19]. Given the previously described evidence of the efficacy of duloxetine for the treatment of chronic low back pain and osteoarthritis [40], musculoskeletal conditions also associated with deregulation of descending pain inhibitory systems [2; 3], we might have expected an additional analgesic effect of duloxetine to SM strategies in this clinical trial. Reasons for this lack of effect are not fully clear but may be related to the efficacy of the SM strategies, which involve psychoeducation that can influence

individual's cognitive, behavioral and emotional responses that modulate peripheral and central pain processing [12]. Indeed, a recent meta-analysis showed a medium to very large effect sizes for SM strategies [37]. Therefore, the use of that therapy might have masked the treatment effects of duloxetine. Moreover, SM-duloxetine participants reported more AEs and lower improvement in sleep quality and pain catastrophizing compared with SM-placebo after 12 weeks of treatment. One study has shown that duloxetine 60 mg increased sleep fragmentation and substantially reduced REM sleep, even with morning dosing [5]. Sleep disturbance may worsen pain catastrophizing which in turn may worsen pain [7]. Thus, it is also plausible that the analgesic efficacy of duloxetine was limited due to the negative effect on sleep architecture, but this statement deserves future investigations.

Methodological aspects can also explain the negative findings. The sample size calculation considered a moderate difference in the pain intensity between SM-duloxetine and SM-placebo and assuming a dropout rate of 20%. Attrition was high (32%), although similar to that reported for other recent clinical trials in chronic pain [4]. Finally, considering the 95% CI of the mean difference in pain intensity between the groups and the pain intensity reduction associated with duloxetine for musculoskeletal pain disorders from a meta-analysis of RCTs [40], our investigation is perhaps better interpreted as inconclusive rather than a negative trial.

4.2 Pain modulation as a predictor of treatment response

CPM has been considered a potential valuable predictor of response to analgesic treatment [15]. This study demonstrated that TMD participants with greater CPM magnitude at baseline reported the most pain intensity reduction after 12 weeks, regardless the treatment group. Thus, it can be suggested that CPM can identify a clinically relevant subgroup of TMD individuals who can obtain better analgesia with SM strategies. Obviously, the placebo effect, natural history of the disease and regression towards the mean may also have an important role in the effectiveness of treatment. However, they are unspecific treatment effects that are present in any therapeutical strategy.

Our outcome is contrary to that of Yarnitsky and colleagues [44], who found a better analgesic response to duloxetine in neuropathic pain patients with a less efficient CPM at baseline. Such differences may be related to the observed lack of additional effect of duloxetine to SM strategies, pathophysiological differences between both diseases or the absence of placebo group in Yarnitsky and colleagues [44] study. On the other hand, our findings agree with previous studies investigating the association between baseline CPM and analgesic

response, with a higher magnitude of pre-treatment CPM predicting more pain relief in knee osteoarthritis patients treated with NSAID [14] and in chronic low back pain patients treated with opioids [6]. Therefore, it is possible that ability of an impaired CPM to predict treatment analgesic response may be dependent on the overlap between CPM mechanisms and the therapy mechanisms, like SNRIs [44].

The current findings in a TMD population suggest that further exploring the value of CPM as a potential predictor of clinical analgesic responses may be worthwhile. However, a possible limitation is that the magnitude of the observed associations between CPM and SM-analgesic responses was not strong. Furthermore, the evidence of CPM magnitude in TMD case-control studies is contradictory, with several studies describing impaired CPM while others failed to find such dysfunction, which is evidence of heterogeneity in TMD population [28]. Future research might explore treatment efficacy in TMD patients stratified into a group with normal CPM and another with impairment CPM.

4.3 Adverse Events

The SM strategies have been not associated with adverse effects [37]. Thus, we assumed that the reported AEs were associated with the drug therapy. The safety and tolerability profile of duloxetine was similar with those reported previously [24; 33; 40]. Nauseas, drowsiness, headache, dry mouth, dizziness, and dyspepsia were the most common AEs. However, most of them were mild to moderate in severity, tending to decrease and disappear with continuing duloxetine therapy. Interesting, headache was the third frequent AE reported. Since TMD patients can experience headache attributed to their disease [11], it is difficult for the participant to distinguish between disease-related headache or AE-related headache. The slightly higher rates of AEs compared with previous trials [24; 40], can be attributed to the active surveillance of harms, which yields more AEs than passive surveillance [21] and because participants were aware that we used a generic drug. One study showed that switching from trademark to generic drugs with identical compounds is frequently associated with an increase in adverse events and often leads to treatment discontinuation [16].

4.4 Strengths and limitations

The strengths of the study are: (1) use of validated diagnostic criteria to select participants with TMD; (2) inclusion of participants with possible psychiatric disorders, painful comorbidities and taking commonly used medications. Therefore, the study sample is

representative of the TMD population that seek care for TMD pain. On the other hand, although our sample size was adequate to detect a clinically meaningful effect, attrition was higher than anticipated. Thus, it is possible that the current study was not adequately powered to detect a minimal clinically meaningful difference between SM-duloxetine when compared with SM-placebo. Future investigations should examine these effects in larger samples. This study also lacks a placebo and duloxetine as comparator arms, which may have allowed for comparison of duloxetine efficacy as monotherapy for chronic TMD. Finally, the relatively short duration is also another limitation.

5. Conclusion

This study provides no evidence of a beneficial of adding duloxetine to SM strategies for treatment of chronic TMD, although high attrition and CI interpretation preclude firm conclusions. Nonetheless, efficient CPM was associated with a better treatment response to SM strategies. Thus, this pragmatic RCT was able to demonstrate the feasibility of applying pain modulation assessment to predict short-term treatment response in chronic TMD patients, which can contribute to the development of mechanism-based treatments of orofacial pain.

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Figures

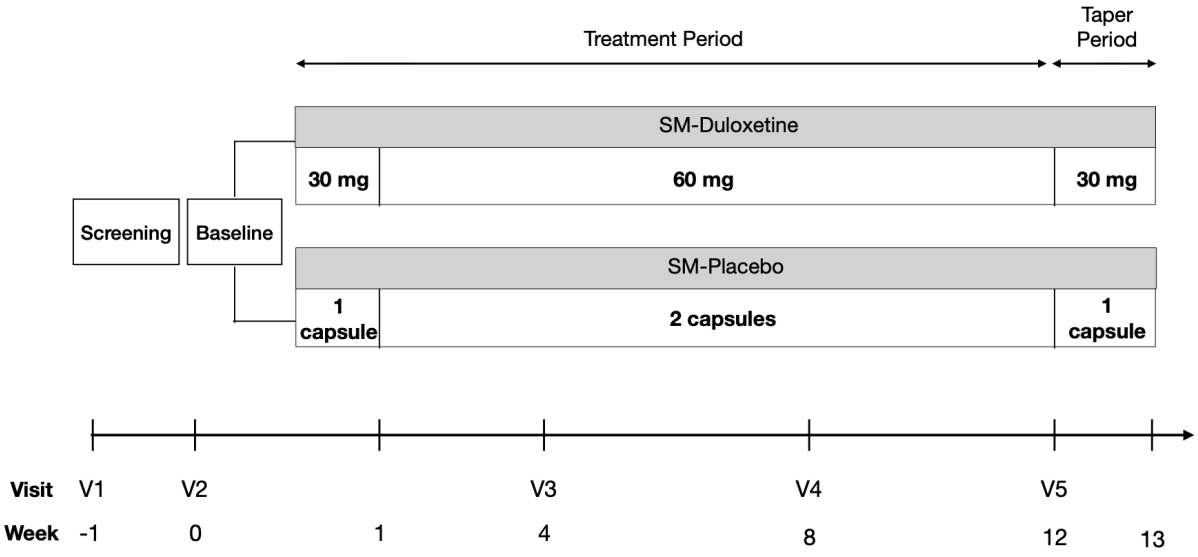


Figure 1. Study design of duloxetine in addition to self-management (SM) strategies for chronic temporomandibular disorders.

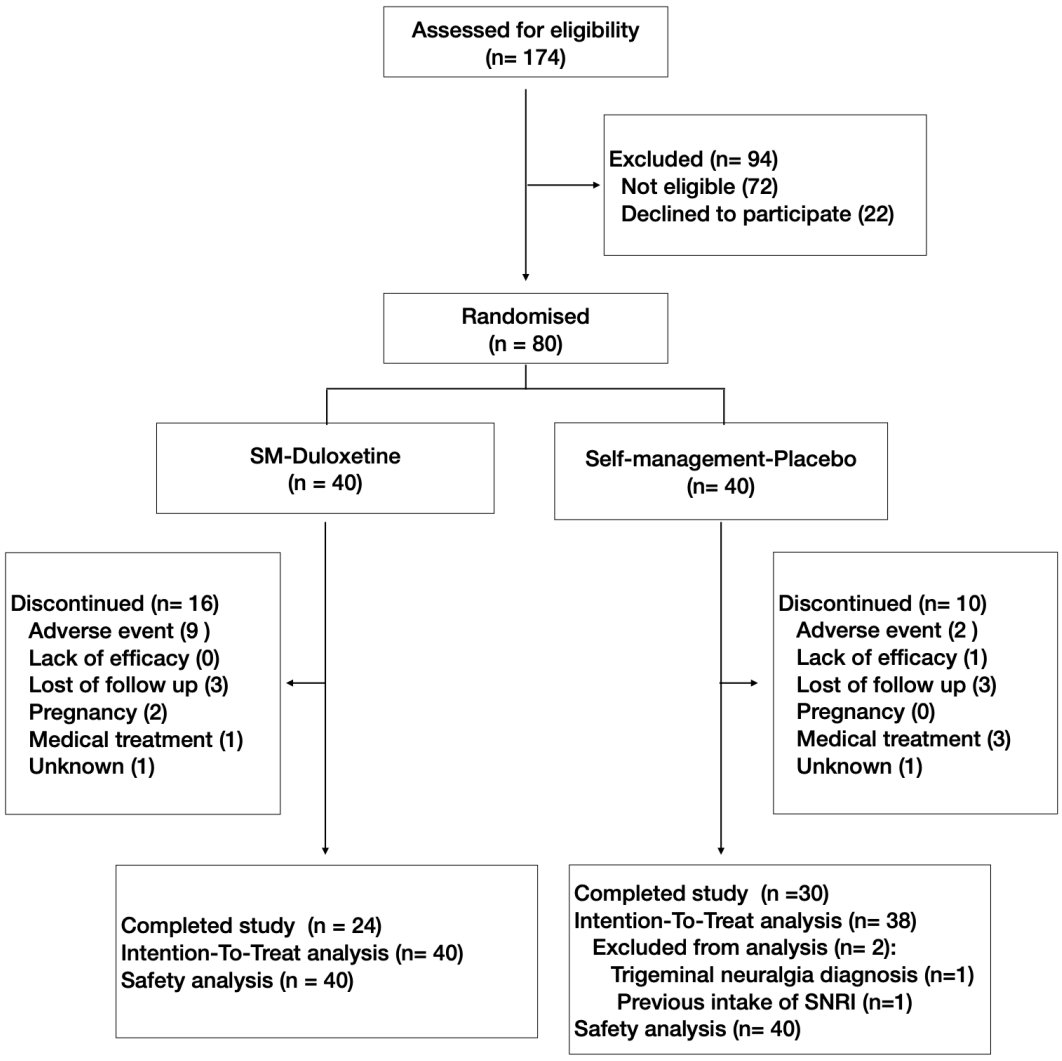


Figure 2. Flow diagram of self-management (SM)-duloxetine compared with SM-placebo for participants with chronic temporomandibular disorders. SNRI= serotonin and norepinephrine reuptake inhibitor.

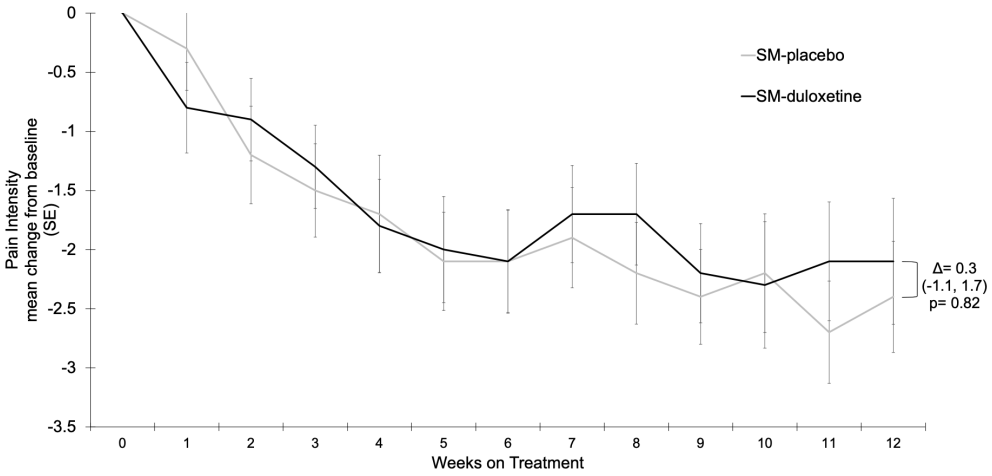
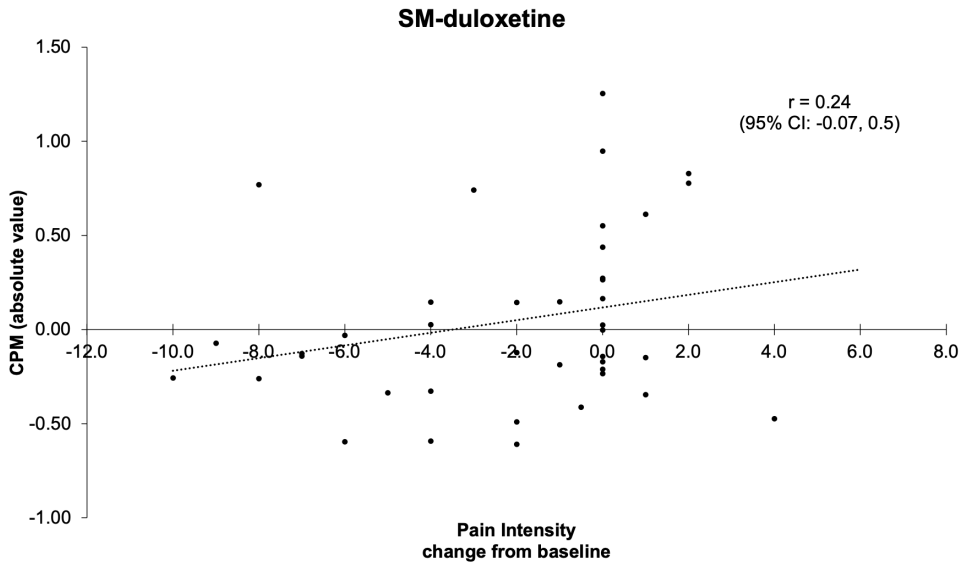


Figure 3. Change in the pain intensity from baseline to week 12 for self-management (SM)-duloxetine and SM-placebo groups. Mean and standard error (SE) shown.

(a)



(b)

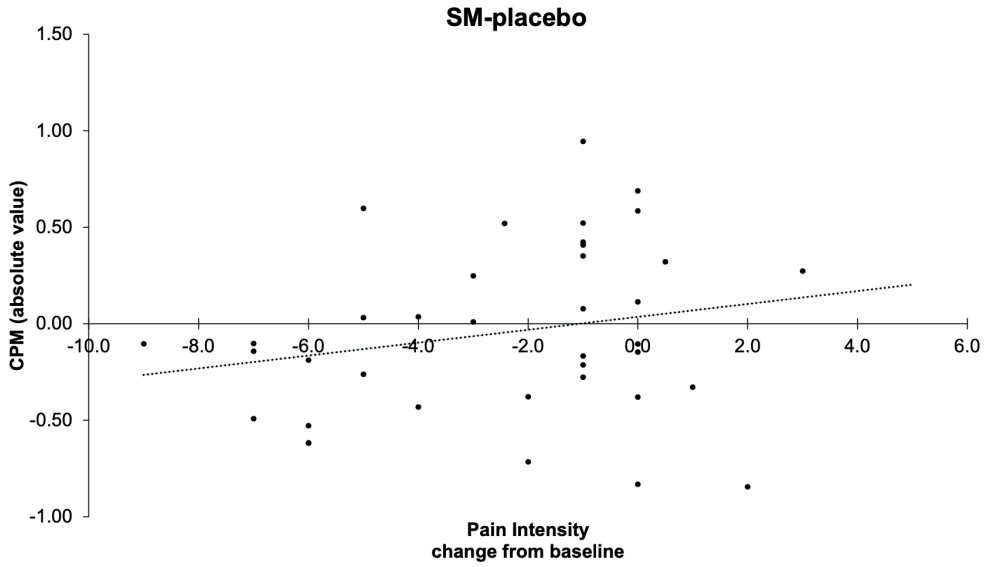


Figure 4. Scatter plots showing the positive correlation between the treatment efficacy and baseline conditioned pain modulation (CPM) for (a) self-management (SM)-duloxetine and (b) SM-placebo. Participants with more efficient CPM (negative values) reported greater pain intensity reduction.

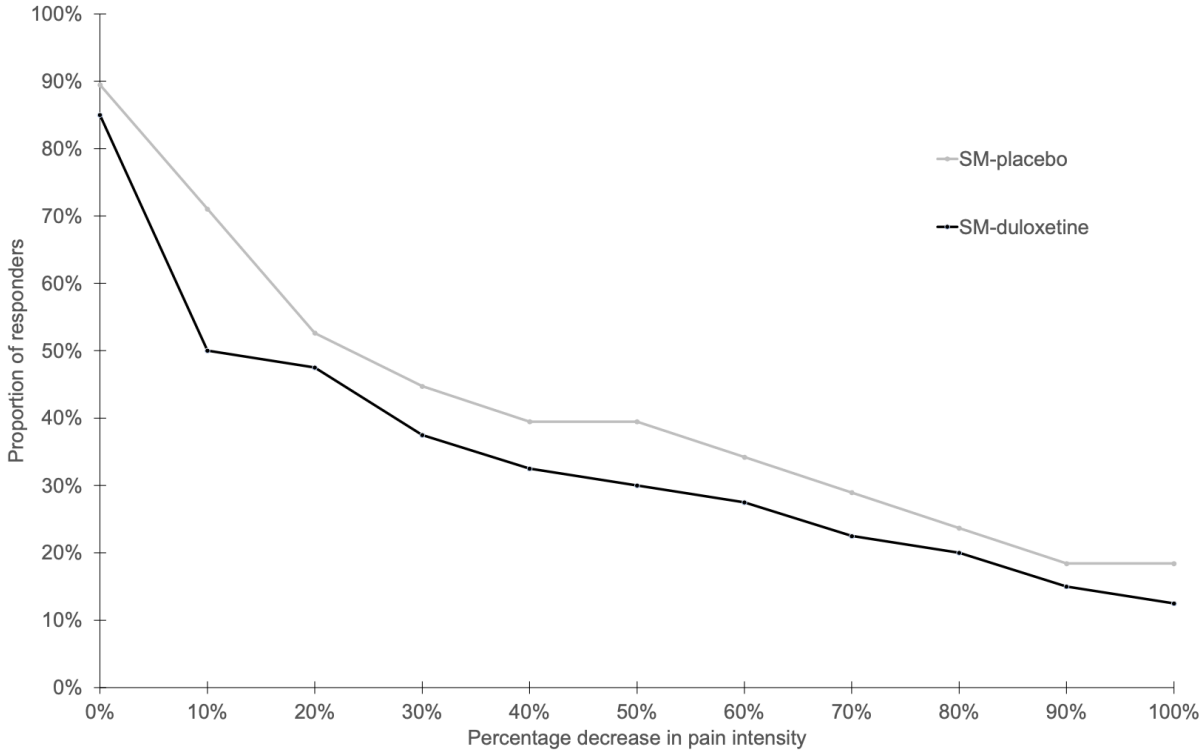


Figure 5. Cumulative proportion of responders to pain intensity for self-management (SM)-duloxetine and SM-placebo. Proportion of responder, plotted on the vertical axis, were calculated by dichotomizing relative reductions from baseline to week 12. Thresholds for dichotomization are shown on the horizontal axis.

Table 1. Baseline demographics and clinical characteristics of participants with chronic temporomandibular disorders treated with self-management (SM)-duloxetine and SM-placebo (ITT population).*

	SM-placebo (n = 38)	**SM-duloxetine (n = 40)**
Age (years)	39.7 (11.2)	38.8 (10.6)
Sex (female)	37 (97.5%)	38 (95%)
Painful TMD		
Number of painful TMD diagnosis,	2.7 (0.5)	2.6 (0.7)
Duration of pain (years)	7.8 (8.9)	7.3 (7.6)
Pain intensity (0 - 10 NRS)	6.9 (1.4)	7.1 (1.6)
Characteristic Pain Intensity (0 - 100 NRS)	68.4 (15.7)	64.5 (15.3)
Pain frequency last 3 months		
≥ 15 days per month	24 (63.2%)	27 (67.5%)
Physical functioning		
GCPS pain disability (0 - 6 scale)	2.1 (1.6)	2.1 (1.9)
PSQI (0 - 21 scale)	9.1 (3.8)	8.9 (4.0)
Presence of ≥1 painful comorbidity	27 (71.1%)	27 (67.5%)
Number of body painful sites (1 - 45 scale)	6.6 (5.3)	7.1 (4.5)
Psychological		
HADS anxiety (0 - 21 scale)	9.1 (4.3)	9.6 (3.7)
HADS depression (0 - 21 scale)	7.2 (4.0)	6.5 (3.3)
Pain Catastrophizing (0 - 52 scale)	29.7 (11.1)	27.7 (13.4)
Concomitant medications		
Antidepressant	2 (5.3%)	4 (10%)
Anticonvulsant	2 (5.3%)	1 (2.5%)
Muscle relaxant	3 (7.9%)	4 (10%)
Benzodiazepines	3 (10.5%)	0 (0%)
Opioid	0 (0%)	2 (5%)
Appetite suppressant (Sibutramine)	0 (0%)	2 (5%)
CPM, absolute value [a]	- 0.045 (0.4)	- 0.046 (0.5)
Stanford Expectations of Treatment Scale		
Positive (1-7 scale)	5.3 (1.4)	5.2 (1.1)
Negative (1-7 scale)	3.2 (1.7)	3.2 (1.5)

* Data are means (SD) or numbers (%).

[a] Negative value means pain inhibition along the protocol.

CPM= Conditioned Pain Modulation test, GCPS=Graded Chronic Pain Scale, HADS= Hospital Anxiety and Depression Scale, ITT= intention to treat, NRS= numerical rate scale, PSQI= Pittsburg Sleep Quality Index, TMD= temporomandibular disorder

Table 2. Summary of primary and secondary outcomes (ITT population).

	SM-placebo (n=38)	SM-duloxetine (n=40)	*p Value*
Primary Outcomes			
Pain Intensity, mean (95% CI)	-2.4 (-3.33, -1.51)	-2.1 (-3.16, -1.07)	
Difference vs SM-placebo, mean (95%CI)		0.3 (-1.1, 1.7)	0.820
≥ 30% reduction in Pain Intensity			
Subject achieving response, n (%)	17 (44.7)	15 (37.5)	0.645
Number needed to treat		14.3	
≥ 50% reduction in Pain Intensity			
Subject achieving response, n (%)	15 (39.5)	12 (30)	0.476
Number needed to treat		11	
Characteristic Pain Intensity, mean (CI)	-23 (-31.30 to -14.74)	-13.3 (-19.78 to -6.85)	
Difference vs SM-placebo, mean (95%CI)		9.7 (20.3, -0.9)	0.115
Secondary Outcomes			
PGIC score dichotomized			
Better improvement, n (%)	32 (84)	35 (89)	0.709
Physical Functioning			
GCPS pain disability, mean (SD)	-1.3 (1.7)	-1.0 (2.0)	0.423
PSQI, mean (SD)	-2.8 (2.7)	-0.6 (3.7)	0.003
Body painful sites, mean (SD)	-0.7 (3.4)	-1.8 (4.3)	0.205
Psychological Functioning			
HADS Anxiety, mean (SD)	-1.4 (2.8)	-0.7 (2.5)	0.269
HADS Depression, mean (SD)	-0.6 (2.8)	-0.1 (2.2)	0.374
Pain Catastrophizing, mean (SD)	-7.9 (9.5)	-2.4 (5.0)	0.001

CI= confidence interval, ITT= intention to treat, SM= self-management, GCPS= Graded Chronic Pain Scale, HADS= Hospital Anxiety and Depression Scale, SD= standard deviation, PGIC= Patient Global Impression of Change, PSQI= Pittsburg Sleep Quality Index.

Table 3. Multiple linear regression model for the prediction of treatment efficacy with mean pain intensity as outcome.

Predictor (at baseline)	**B Coefficient**	**Beta**	**t**	***p Value***
Pain intensity	- 0.68	-0.33	-3.05	0.003
CPM	1.63	0.23	2.14	0.035
Body painful sites	0.09	0.15	1.36	0.177
HADS Depression	0.03	0.03	0.27	0.789
PSQI	0.06	0.07	0.58	0.561

CPM= Conditioned Pain Modulation test, HADS= Hospital Anxiety and Depression Scale, PSQI= Pittsburg Sleep Quality Index.

Table 4. Adverse events in participants with chronic temporomandibular disorder treated with self-management (SM)-duloxetine and SM-placebo (all participants randomized).

	N de participants (%)*		
	SM-placebo (n=40)	**SM-duloxetine (n=40)**	***P* *(Fisher)***
Adverse events	26 (65%)	36 (90%)	0.014
Death	0 (0%)	0 (0%)	
Serious adverse events	0 (0%)	2 (5%)	0.493
Discontinuations due to an adverse event	2 (5%)	9 (22.5%)	0.047
Specific Adverse Events			
Nausea	7 (17.5%)	21 (52.5%)	0.002
Drowsiness	9 (22.5%)	17 (42.5%)	0.093
Headache	13 (32.5%)	16 (40%)	0.642
Dry mouth	2 (5%)	10 (25%)	0.025
Dizziness	9 (22.5%)	10 (25%)	0.999
Dyspepsia	7 (17.5%)	10 (25%)	0.585
Constipation	2 (5%)	9 (22.5%)	0.047
Insomnia	2 (5%)	7 (17.5%)	0.154
Loss of appetite	1 (2.5%)	5 (12.5%)	0.200
Weakness	1 (2.5%)	4 (10%)	0.358
Altered taste	0 (0%)	4 (10%)	0.115
Diarrhea	3 (7.5%)	4 (10%)	1.000
Diaphoresis	0 (0%)	4 (10%)	0.115
Decrease blood pressure	0 (0%)	4 (10%)	0.115
Loss of libido	0 (0%)	4 (10%)	0.115
Vomit	1 (2.5%)	3 (7.5%)	0.615
Palpitation	0 (0%)	3 (7.5%)	0.240
Irritability	3 (7.5%)	3 (7.5%)	1.000
Menstrual dysregulation	2 (5%)	1 (2.5%)	1.000
Memory problems	0 (0%)	2 (5.2%)	0.493
Anxiety	2 (5%)	0 (0%)	0.493
Bruxism	0 (0%)	2 (5%)	0.493

* Data represent participants with at least 1 episode of an adverse event during the study. If an individual had multiple types of adverse events, he/she was counted once for each type. If an individual had a type of adverse events many times, he/she was counted once for that type.
Only adverse events with an incidence greater than 5% in any treatment group were computed.

Supplementary Material

Table S1. Additional baseline clinical characteristics of participants with chronic TMD treated with self-management (SM)-duloxetine and SM-placebo (ITT population).

	N of participants (%)	
	SM-placebo (n=38)	**SM-duloxetine (n=40)**
TMD diagnosis		
Arthralgia only	1 (2.6)	0 (0)
Myalgia only	0 (0)	4 (10)
Arthralgia and myalgia	10 (26.3)	4 (10)
Arthralgia and headache	0 (0)	1 (2.5)
Myalgia and headache	4 (10.5)	8 (20)
Arthralgia and myalgia and headache	23 (60.5)	23 (57.5)
Painful comorbidity		
Headache (TTH, migraine)	21 (55.2)	24 (60)
Neck pain	6 (15.8)	4 (10)
Fibromyalgia	5 (13)	5 (12.5)
Irritable bowel syndrome	0 (0)	4 (10)
Rheumatoid arthritis	1 (2.6)	2 (5)
Tendonitis	3 (7.9)	3 (7.5)
Sinusitis	1 (2.6)	3 (7.5)

[a] Only comorbidities with an incidence greater than 5% in any treatment group were computed.

ITT= intention-to-treat, TMD= temporomandibular disorder, TTH= tension type headache

Table S2. Multiple linear regression model for the prediction of treatment efficacy with characteristic of pain intensity (CPI) as outcome.

Predictor (at baseline)	**B Coefficient**	**Beta**	**t**	***p Value***
CPI	- 0.58	-0.37	-3.66	< 0.001
CPM	16.74	0.32	3.15	0.002
Body painful sites	1.14	0.23	2.26	0.027
HADS Depression	0.09	0.01	0.13	0.897
PSQI	1.00	0.16	1.42	0.159

CPM= Conditioned Pain Modulation test, HADS= Hospital Anxiety and Depression Scale, PSQI= Pittsburg Sleep Quality Index.

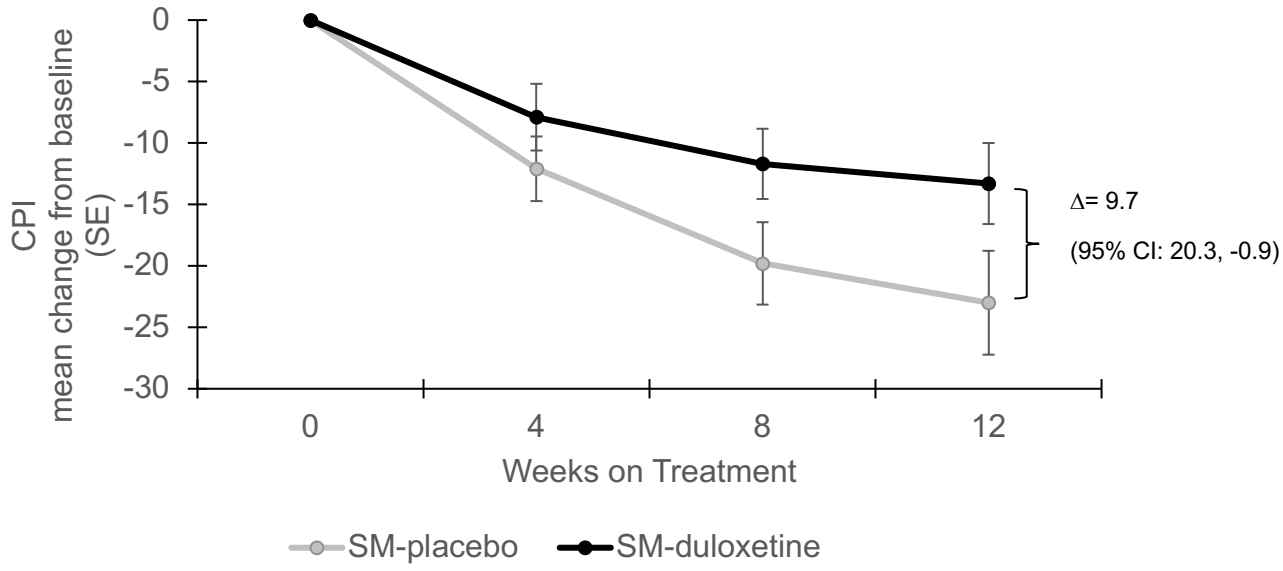
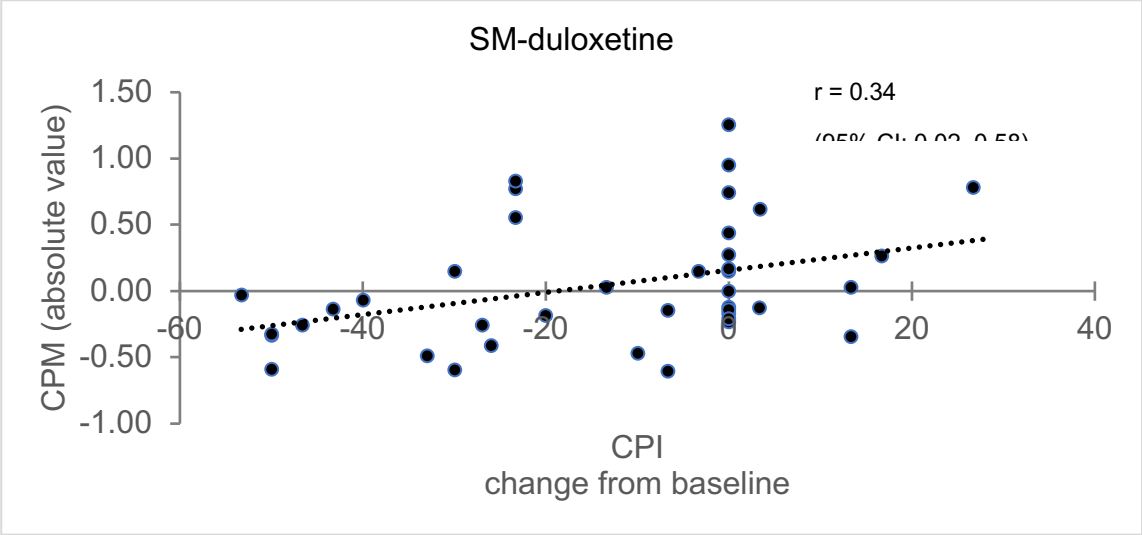


Figure S1. Change in the characteristic pain intensity (CPI) from baseline to week 12 for self-management (SM)-duloxetine and SM-placebo groups. Mean and standard error (SE) shown.

(a)



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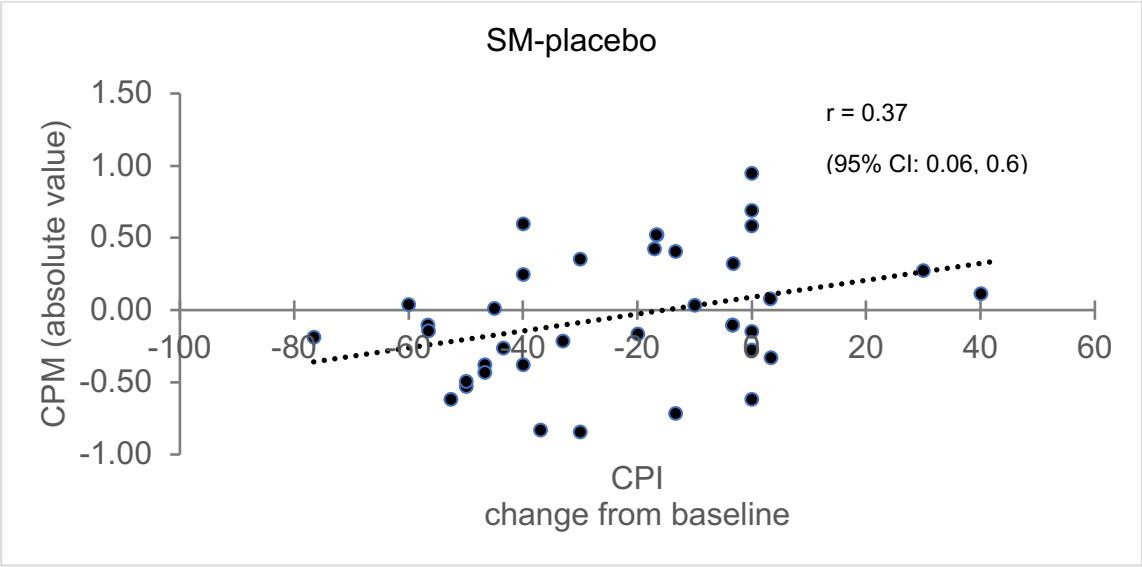

Figure S2. Scatter plots showing the positive correlation between the treatment efficacy and baseline conditioned pain modulation (CPM) for (a) self-management (SM)-duloxetine and (b) SM-placebo. Participants with more efficient CPM (negative values) reported greater pain reduction in characteristic pain intensity (CPI).

2.2 ARTICLE 2

This article was written according to *Journal of Oral Rehabilitation* instructions and guideline for article submission (Annex B).

Possible predictors of response to duloxetine in addition to self-management for chronic temporomandibular disorders: an exploratory analysis of a randomized controlled trial

Predictors of duloxetine plus self-care for TMD

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Abstract

Background: Adding duloxetine to self-management strategies (SM-duloxetine) has demonstrated inconclusive efficacy for chronic painful temporomandibular disorder (TMD). SM-duloxetine, like many pain treatments, is more effective in some individuals than in others, thus identifying predictors of treatment response is a priority area for research. **Objective:** To examine predictors of response to SM-duloxetine for chronic TMD. **Methods:** This was a post hoc analysis from a randomized, placebo-controlled trial of SM-duloxetine (duloxetine 60 mg/d plus SM program for 12 weeks) in adults' participants with chronic TMD. Primary outcome was proportion of responders to treatment (individuals with ≥ 30% reduction in pain intensity) in SM-duloxetine and SM-placebo group at week 12. For responder analysis, five phenotyping domains recommended by IMMPACT were assessed: pain, psychological, sleep, quantitative sensory testing and conditioned pain modulation. Relative risk (RR), 95% confidence interval (CI) and absolute risk reduction were calculated. **Results:** Among participants treated with SM-duloxetine, severe pain intensity (RR 1.33, 95% CI: 0.56, 3.17), pain disability (RR 1.30, 95% CI: 0.63, 2.67), presence ≥ 1 painful comorbidity (RR 1.48, 95% CI: 0.57, 3.79) and anxiety symptoms (RR 1.80, 95% CI: 0.75, 4.34) were associated with greater likelihood of response to treatment. Among individuals treated with SM-placebo, only temporal summation of pain was associated with greater likelihood of response to treatment. **Conclusion:** TMD individuals with severe pain intensity, pain disability, painful comorbidity or anxiety symptoms may be more likely to derive benefit from adding duloxetine to SM strategies with a clinically significant reduction in pain intensity.

Keywords: Temporomandibular joint dysfunction syndrome, chronic pain, duloxetine hydrochloride, self-management, double-blind method, treatment outcome

1. BACKGROUND

Pain in the temporomandibular joint, masticatory muscle and associated structures that persist for more than 3 months is considered chronic painful temporomandibular disorders (TMD)[1, 2]. Chronic TMD causes substantial physical, mental and economic burden[3, 4]. Moreover, patients experience pain disability and low quality of life[3, 5]. The exact pathophysiological mechanisms of painful TMD are currently unclear, although it is thought to be a combination of peripheral and central mechanisms[6]. It is known that TMD comprise a heterogenous population with varying manifestation of pain areas, pain sensitivity, somatosensorial profile, psychological profile and comorbidities associated[7-9]. Thus, clinicians struggle to identify the optimal treatment option for individual patients with TMD.

The management of chronic TMD involve a combination of non-pharmacological and pharmacologicall therapies. Non-pharmacological treatments include a variety of interventions such as self-management (SM),intraoral appliances, physical therapy and psychotherapy [10]. Pharmacological treatments usually include nonsteroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, anticonvulsants and tricyclic antidepressants[10]. Drugs for relief of chronic pain usually are administer for a long time and may have its use limited by adverse events. For instance, NSAIDs have gastrointestinal, liver, kidney and cardiovascular toxicities[11], while titration to higher doses of tricyclic antidepressants is limited by its anticholinergic adverse effects[12]. Thus, it is necessary to find new treatment options for clinicians to choose in the condition of other drugs do not work well or are limited by its adverse effects.

Duloxetine is a serotonin and norepinephrine reuptake inhibitor (SNRI) with demonstrated efficacy in the treatment of chronic pain disorders including fibromyalgia, low back pain, osteoarthritis, and diabetic peripheral neuropathy[13, 14]. Our recent work has shown inconclusive results for efficacy of duloxetine in addition to SM strategies (SM-duloxetine) in individuals with chronic TMD. Moreover, approximately 40% of participants treated with SM-duloxetine experienced moderate pain reduction (decrease ≥30%).

As SM-duloxetine was neither completely effective nor worked for every patient, identifying predictors of treatment response is a priority area for research. If factors influencing SM-duloxetine efficacy are known, personalized medicine can be implemented in which duloxetine is prescribed in addition to SM to those most likely to

benefit from it. Clues regarding possible predictors of duloxetine response have been described in chronic pain population. For instance, in patients with early pain reduction, multiple painful sites[15], anxiety and depression symptoms[16], duloxetine appeared to be more effective than placebo.

In this study, we conducted an exploratory post hoc analysis of our previous clinical trial to identify subgroups of TMD participants that may benefit from duloxetine in addition to SM strategies.

2. METHODS

Study Design and Treatment

This was a post hoc exploratory analysis of a randomized, double-bind, placebo-controlled trial of duloxetine in addition to SM strategies for treatment of participants with chronic painful TMD (Brazilian Clinical Trials Registry # RBR-6pqx4n). Details of the study are described in the primary publication. Eighty participants with TMD were randomized 1:1 to duloxetine 60 mg or placebo once daily for 12 weeks. Participants in the duloxetine group received duloxetine 30 mg/day for 1 week, followed by 60 mg/day for 11 weeks. Participants in the placebo group received placebo for 12 weeks. Individuals that completed the 12-week treatment period entered in a 1-week double-blind taper period to minimize discontinuation-emergent adverse events. Moreover, all participants were treated with a SM program including information about TMD aetiology and prognostics, dietary advice, use of reminders to avoid oral behaviors, techniques for relax jaw, keep good cervical posture, as well as sleep hygiene and encouragement to practice physical activities. The clinical trail was conducted in accordance with the Declaration of Helsinki and approved by the Human Research Ethics Committee of the Bauru School of Dentistry, University of São Paulo, Brazil. Participants provided informed consent before start the study.

Participants

Inclusion criteria included: (1) individuals ≥ 18 years age (male and female), (2) diagnosis of painful TMD according to DC/TMD[1] (i.e., arthralgia, myalgia and headache attributed to TMD), (3) pain present for ≥ 3 months. Major exclusion criteria included presence of uncontrolled systemic disorders, cardiac disorders, neuropathies, history of psychosis or bipolar disorder, treatment with monoamine oxidase inhibitor within 14 days

previous, treatment with SNRIs within 12 months of study entry, pregnancy or breast-feeding, intolerance to duloxetine or any component of the formulation and treatment for TMD in the last 3 months. To maximize generalizability to clinical practice, we did not exclude individuals with continuous use of centrally acting medications (constant doses for ≥ 3 months before entry study) and present comorbid conditions commonly related to TMD (e.g., primary headache, neck pain, fibromyalgia, anxiety and depression disorders).

Outcome

In the primary study, the treatment efficacy was the change in the 'pain intensity over the past week' from baseline to week 12. The pain intensity was measured by 0-10 numerical rate scale (NRS). Forty participants in SM-duloxetine group and thirty-eight participants in SM-placebo group were included in both the primary analysis (intention-to-treat analysis) and this post hoc analysis. In the primary study, pain intensity decreased significantly over time with participants on SM-duloxetine and SM-placebo, reporting reductions from baseline of -2.1 (95% CI: -3.2, -1.1) and -2.4 (95% CI: (-3.3, -1.5), respectively, but did not differ significantly between groups (0.3, 95% CI: -1.1, 1.7; p = 0.82).

In this post hoc analysis, the primary outcome was the proportion of participants 'responders' to treatment. A 'responder' was defined as a participant demonstrating ≥ 30% reduction in the 'pain intensity over the past week' at week 12. We selected this pain reduction threshold based on previous studies concluding that ≥ 30% reduction constituted a clinically relevant improvement and correspond to what patients would consider a "moderately important" improvement in pain intensity[17].

Responder analysis

The association of the proportion of responders with five phenotyping domains recommended by IMMPACT[18] was assessed for participants receiving SM-duloxetine and SM-placebo. The variables were measured at baseline and dichotomized based on reference values according to each measure tool.

Pain Domain

A 0-10 NRS was used to assess the 'pain intensity over the past week'. Severe pain was defined as NRS ≥ 7 and mild to moderate pain NRS < 7 [19]. TMD-related disability and interference in functioning were assessed using the Graded Chronic Pain Scale (GCPS)[20]. The GCPS grade is derived from several variables: the characteristic pain intensity, the pain interference score and pain disability days. Based on two former variables, participants were classified into: with disability (score ≥3) or without disability (score < 3)[20]. The Central Sensitization Inventory (CSI)[21] was used to assess the presence of central sensitization phenomena (part A) and painful comorbidities (part B). Presence of central sensitization was defined as CSI total score ≥ 40[21].

Psychological Domain

The Hospital Anxiety and Depression Scale (HADS)[22] was used for measure anxiety and depression symptoms. HADS includes 14 items, seven related to anxiety and seven related to depression, each scored between 0 and 3. The total score for anxiety and depression subscales vary from 0-21 and a score > 8 was defined presence of anxiety or depression symptoms[22].

Sleep Domain

Pittsburg Sleep Quality Index (PSQI)[23] assess sleep quality over the past month across seven components: quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use sleep medication and daytime dysfunction. PSQI total score vary from 0-21 points and impaired sleep was defined as total score > 5[23].

Quantitative Sensory Testing (QST) Domain

Mechanical pain threshold (MPT), temporal summation of pain (TSP) and pressure pain threshold (PPT) were assessed, in this order, on the masseter muscle according to DFNS' recommendations[24]. MPT was assessed using a standardized set of Semmes-Weinstein monofilaments (Touch-Test TM Sensory Evaluators; North Coast Medical) that exert forces between 0.008 g/mm^2 and 300 g/mm^2. The monofilaments were applied in a vertical and perpendicular position to the site of examination, and the contact time was approximately 2 seconds. Participants were asked to verbally report the first sharpness/pinprick sensation. The final MPT threshold was the geometric mean of

five series of ascending and descending stimulus intensities.[24] To evaluate pain facilitation, TSP was performed with the same set of Semmes-Weinstein monofilaments. For this test, the perceived intensity of a single pinprick stimulus was compared to a series of 10 repetitive pinprick stimuli of the same physical intensity repeated a 1/s applied within an area of 1 cm^2. The monofilament was perceived as "slightly painful" and individually determined for each participant. The participant was asked to give a pain rating immediately after the single stimulus and the series of 10 stimuli by using a 0 to 100 NRS. The entire procedure was repeated three times. TSP was calculated as the mean rating of the three series divided by the mean rating of the three single stimuli[24]. The final test in the QST protocol, the PPT, was performed with a digital dynamometer (Kratos) with a probe area of 1 cm^2 and flat circular-shaped tip. The participants were instructed to press a button at the first painful sensation. The PPT was determined as the arithmetic mean of three series of ascending stimulus intensities, each applied as a slowly increasing ramp of that were applied with an increasing ramp of approximately 0.5 kgf/s [25]. QST parameters were transformed into *z* values according to the following expression: $Z = (value_{patient} - mean_{controls}) / SD_{controls}$. A z-score outside ± 1.96 was defined as somatosensory abnormality[24].

Conditioned Pain Modulation (CPM) Domain

To assess pain inhibition, a CPM-sequential paradigm was performed using PPT on the masseter muscle as test stimulus (TS) and immersion of the contralateral hand in cold-water as conditioning stimulus (CS). Details of the CPM protocol are described in the primary study. The CPM effect was calculated as the difference between the TS_{before} and TS_{after} the CS. Pain inhibition along the protocol was represented by a negative value[26]. At present, there are no published normative data for CPM, thus, an increase in PPT after the CS, which corresponds to a normally functioning endogenous pain inhibition system[27, 28], was defined as normal CPM.

Statistical analysis

The post hoc analysis consisted of all participants include in the intention-to-treat analysis described in the primary study. Baseline characteristics are described as mean (SD) for continuous variables and n (%) for categorical variables. For the responder analysis, relative risk (RR), 95% confidence intervals (95% CIs) and absolute risk

reduction (ARR) for the responder rate were calculated for each variable in SM-duloxetine and SM-placebo group. RR and 95% CI was used for interpretation of results. Missing end-of-treatment data were imputed using modified baseline-observation-carried-forward method[29]. All statistical analyses were conducted using STATISTICA, v 10 (StatSoft).

3. RESULTS

Study participants

The baseline characteristics were similar between SM-duloxetine and SM-placebo groups (Table 1). TMD pain was of longstanding duration, moderate intensity and low disability. Most of participants (70%) had at least one painful comorbidity, with primary headache, neck pain and fibromyalgia the more prevalent. The baseline CSI score indicate presence of central sensitization phenomenon. In addition, participants showed high anxiety symptoms and poor sleep quality. Regard the pain modulation profile, the sample presented enhanced pain facilitation and efficient pain inhibition as demonstrated, respectively, by abnormal values of TSP and negative values of CPM.

Responder analysis by pain domain

Among participants treated with SM-duloxetine, individuals with severe pain intensity (RR 1.33, 95% CI: 0.56, 3.17), pain disability (RR 1.30, 95% CI: 0.63, 2.67) or presenting at least 1 painful comorbidity (RR 1.48, 95% CI: 0.57, 3.79) were more likely to respond to treatment than participants with mild to moderate pain, without pain disability or pain comorbidity (Table 2). The response to SM-placebo was similar regardless of variables within pain domain (Table 3).

Responder analysis by psychological domain

Among individuals treated with SM-duloxetine, symptoms of anxiety (RR 1.80, 95% CI: 0.75, 4.34) but not symptoms of depression (RR 0.65, 95% 0.22, 1.89), were associated with greater probability of response to treatment (Table 2). Psychological variables were not associate with response to SM-placebo (Table 3).

Responder analysis by sleep domain

The presence or absence of sleep disorder was not associated with response to SM-duloxetine (RR 0.66, 95% CI 0.29, 1.48) neither to SM-placebo (RR 0.85 95%CI: 0.40, 1.82) treatment (Table 2 and 3).

Responder analysis by QST domain

Responder analysis of z-score for QST data suggest that participants with an abnormal TSP (RR 1.62, 95% CI 0.45, 5.79) or normal PPT (RR 1.75, 95% CI 0.74, 4.09) on masseter muscle were more likely to respond to SM-duloxetine treatment (Table 2). In SM-placebo group, abnormal TSP was associated with greater likelihood of response to treatment (RR 1.44, 95% CI 0.53, 3.92) (Table 3).

Responder analysis by CPM

The CPM effect, whether normal or impaired, was not associated with likelihood of response to SM-duloxetine (RR 0.49, 95% CI 0.18, 1.28) neither to SM-placebo (RR 0.67, 95% CI 0.31, 1.44) (Table 2 and 3).

4. DISCUSSION

This is the first analysis to examine the effect of five phenotyping domains - pain, psychological, sleep, QST and CPM - on the response to duloxetine in addition to SM strategies for treatment of chronic TMD. The main finding was that severe pain intensity, pain disability, painful comorbidity or anxiety symptoms were indicative of the likelihood of response to SM-duloxetine at 12 weeks of treatment. Our results could assist clinicians in predicting and considering adding duloxetine to SM strategies for individuals with chronic TMD in favor of those presenting specific pain and psychological profiles.

An interesting finding is that the level of pain intensity, presence of pain disability and ≥ 1 painful comorbidity may predict the likelihood of response to SM-duloxetine. TMD frequently coexist with other painful illness such as headache, cervical spine dysfunction, fibromyalgia, lower back pain, irritable bowel syndrome pain being often categorised as one of the 'chronic overlapping pain conditions'[7, 30]. Seventy percent of participants included in our analysis presented at least 1 painful comorbidity, with headache, neck pain and fibromyalgia being the most prevalent, which is like previous studies[31]. Compelling evidence endorses the negative impact of other painful

comorbidities in the clinical course of TMD. Compared to TMD participants without comorbidities, participants with painful comorbidities are more likely experiencing higher TMD pain intensity, duration, disability and report a history of depression and/or anxiety[32-34]. These differences suggesting that the presence of painful comorbidities in TMD participants may signify a more complex disorder. Duloxetine is effective for treatment of many pain conditions that usually coexist with TMD, although there are no randomized controlled trials of duloxetine for primary headache[35].

In this post hoc responder analysis, participants with anxiety symptoms were approximately two times more likely to respond to SM-duloxetine. These results reflect those of Taylor *et al*.[36] in migraine patients. Duloxetine has well-demonstrated efficacy in the treatment of patients suffering from anxiety disorders[13]. Several psychosocial factors are associated cross sectionally with chronic TMD, including levels of anxiety, depression and somatization[37]. Prospective analysis has shown affective distress, including anxiety, as predictor of incidence of painful TMD[38]. On the other hand, the persistent pain of TMD might be a link to anxiety disorders as comorbid conditions[39]. While studies in TMD patients have shown that high anxiety and depression scores at baseline are associated with reduced analgesic benefit of treatments (standard conservative care, cognitive-behavioral therapy and TMJ hyaluronic acid injection)[40, 41], anxiety symptoms may signal TMD individuals more likely to benefit from duloxetine in addition to SM strategies.

As expected, duloxetine was not universally effective in all participants, and the reasons for its selective efficacy remains unknown. One possible reason for this may be that the mechanisms of pain in these individuals differ. Most of chronic TMD patients present pain caused by multiple/mixed mechanisms, both peripheral nociceptive and central (i.e., generated, exacerbated, and/or maintained by central nervous system mechanisms), however central factors may be more relevant in some cases and peripheral factors in others[6]. The responder profile to SM-duloxetine found in our study is similar to global symptoms cluster identified by OPPERA study[8]. TMD individuals in the global symptoms cluster present general pain sensitivity, high levels of pain, functional limitation, comorbid conditions and high psychological distress[8]. Perhaps participants responding to SM-duloxetine experience more central pain due to presence of global symptoms and thus, may be more responsive to treatments that target such central mechanisms.

Given these considerations, the cause of duloxetine's selective effect may lie within the central nervous system. The core of the pathophysiology of multiple painful comorbidities and mood disturbances is mostly due to the disruption of serotonin and norepinephrine pathways in the central nervous system[30, 42]. The pharmacological treatment of clinical conditions with similar pathophysiology involves a global perception of coexisting disorders. In this sense, duloxetine is monotherapy approach that might be useful to treat concomitant disorders with parallel pathophysiological pathways[13] such as TMD, painful comorbidities and anxiety disorders, which is an advantage for patients (avoiding polytherapy issues) and a successful cost-effective alternative.

TSP emerged as possible predictor of response to SM-duloxetine and was the only predictive variable of response among participants treated with SM-placebo. A pragmatic explanation for this result could be related to the low reliability of TSP[43]. The finding of a non-specific responder profile to SM-placebo seems reflect the interaction between placebo effect mediated by patient expectation[44] and the wide mechanism by which self-care interventions can improve pain in patients with TMD[45]. Systematic reviews investigating predictors to placebo response and SM strategies have shown heterogenous results with cognitive constructs such as self-efficacy, locus of control, and "emotionalized" contingency expectations as predictors[46, 47]. We did not measure most of those outcomes, therefore this is an important issue for future research.

This study has several limitations. First, although the results suggest that some variables within pain and psychological domains were the only variables that can predicts SM-duloxetine response, the sample size of responders may have been too small to detect significant associations between CSI, depression symptoms, sleep quality, QST, CPM and response to SM-duloxetine. The next step is to conduct adequately powered follow-up studies to confirm these findings. Second, presence of painful comorbidities was assessed by CSI, part B. A more accurate assessment could be done using the International Classification of Headache Disorders[48] or validated surveys like Neck Disability Index[49] and Fibromyalgia Rapid Screening Tool[50]. The strengths of this analysis include the prospective, randomized, placebo-controlled design of the original study and the assessment of five phenotyping domains in clinical trials of chronic pain recommend by IMMPACT[18].

5. CONCLUSION

This post hoc analysis of a randomized placebo-controlled trial suggests that severe pain intensity, presence of pain disability, painful comorbidity or anxiety symptoms may be an important indicator of chronic TMD individuals who are more likely to derive benefit from adding duloxetine to SM strategies. Both pain and psychological profiles assessed in baseline may predict which individuals with chronic painful TMD are more likely to respond to duloxetine in addition to SM strategies with a clinically significant reduction in pain intensity.

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Table 1. Baseline characteristics of participants with chronic temporomandibular disorders enrolled in a randomized, placebo-controlled trial of duloxetine in addition to self-management treatment[§].

	SM-duloxetine (n = 40)	**SM-placebo (n = 38)**
Age (years)	38.8 (10.6)	39.7 (11.2)
Sex (female)	38 (95%)	37 (97.5%)
TMD pain		
Duration of pain (years)	7.3 (7.6)	7.8 (8.9)
Pain intensity (0 - 10 NRS)	7.1 (1.6)	6.9 (1.4)
Pain disability (0 - 6 scale)	2.1 (1.9)	2.1 (1.6)
Presence of ≥1 painful comorbidity	27 (67.5%)	27 (71.1%)
Central sensitization inventory	48.1 (13.8)	49.7 (16.2)
Psychological		
HADS anxiety (0 - 21 scale)	9.6 (3.7)	9.1 (4.3)
HADS depression (0 - 21 scale)	6.5 (3.3)	7.2 (4.0)
Sleep		
PSQI (0 - 21 scale)	8.9 (4.0)	9.1 (3.8)
QST, z-score		
MPT	1.88	1.81
TSP	4.46	4.16
PPT	0.40	0.70
CPM, absolute value[¶]		
Masseter	- 0.046 (0.5)	- 0.045 (0.4)

[§] Data are means (SD) or numbers (%).

[¶] Negative value means pain inhibition along the protocol.

CPM= Conditioned Pain Modulation test, HADS= Hospital Anxiety and Depression Scale, MPT= mechanical pain threshold, PPT= pressure pain threshold, PSQI= Pittsburg Sleep Quality Index, QST= Quantitative Sensory Testing, SM= self-management, TMD= temporomandibular disorder, TSP= temporal summation of pain

Table 2. Response rate of ≥ 30% reduction in pain intensity for participants with chronic temporomandibular disorders treated with duloxetine in addition to self-management for 12 weeks.

Domain	SM-Duloxetine		Relative risk (95% CI)	Absolute risk reduction
	Responders (n= 15)	Non responders (n= 25)		
Pain				
Pain intensity				
Mild to moderate (< 7)	33.3%	44%	1.33 (0.56, 3.17)	0.10
Severe (≥ 7)	66.6%	66%		
Pain disability				
Without (< 3)	46.7%	76%	1.30	0.14
With (≥ 3)	53.3%	24%	(0.63, 2.67)	
Pain Comorbidities				
Without	27%	40%	1.48	0.14
At least 1	73%	60%	(0.57, 3.79)	
Central Sensitization				
Without (< 40)	40%	24%	0.64	-0.18
With (≥ 40)	60%	76%	(0.29, 1.40)	
Psychological				
HADS Anxiety				
Without (≤ 8)	33.4%	56%	1.80	0.21
With (> 8)	66.6%	44%	(0.75, 4.34)	
HADS Depression				
Without (≤ 8)	80%	68%	0.65	-0.14
With (> 8)	20%	32%	(0.22, 1.89)	
Sleep				
Normal (PSQI ≤ 5)	33.3%	20%	0.66	-0.17
Impaired (PSQI > 5)	66.6%	80%	(0.29, 1.48)	
QST				
MPT				
Normal	60%	52%	0.81	-0.07
Abnormal	40%	48%	(0.35, 1.85)	
TSP				
Normal	13.4%	24%	1.62	0.15
Abnormal	86.6%	76%	(0.45, 5.79)	
PPT				
Normal	80%	92%	1.75	0.26
Abnormal	20%	8%	(0.74, 4.09)	
CPM				
Normal (< 0)	73.4%	48%	0.49	-1.1
Impaired (≥ 0)	26.6%	52%	(0.18, 1.28)	

CPM= Conditioned Pain Modulation test, HADS= Hospital Anxiety and Depression Scale, MPT= mechanical pain threshold, PPT= pressure pain threshold, PSQI= Pittsburg Sleep Quality Index, QST= Quantitative Sensory Testing, SM= self-management, TSP= temporal summation of pain

Table 3. Response rate of ≥ 30% reduction in pain intensity for participants with chronic painful temporomandibular disorders treated with placebo in addition to self-management for 12 weeks.

Domain	SM-Placebo		Relative risk (95% CI)	Absolute risk reduction
	Responders (n=17)	Non responders (n= 21)		
Pain				
Pain intensity				
Mild to moderate (< 7)	53%	20%	0.50 (0.26, 0.94)	-0.35
Severe (≥ 7)	47%	80%		
Pain disability				
Without (< 3)	70.6%	57.2%	0.71	-0.15
With (≥ 3)	29.4%	42.8%	(0.31,1.60)	
Pain Comorbidities				
Without	35.3%	19.1%	0.65	-0.21
At least 1	64.7%	80.9%	(0.33, 1.29)	
Central Sensitization				
Without (< 40)	46%	34%	0.74	-0.14
With (≥ 40)	64%	76%	(0.36, 1.51)	
Psychological				
HADS Anxiety				
Without (≤ 8)	58.8%	38.1%	0.63	-0.20
With (> 8)	41.2%	61.9%	(0.30,1.30)	
HADS Depression				
Without (≤ 8)	82.4%	47.7%	0.36	-0.37
With (> 8)	17.6%	52.3%	(0.12, 1.05)	
Sleep				
Normal (PSQI ≤ 5)	29.4%	23%	0.85	-0.08
Impaired (PSQI > 5)	70.6%	77%	(0.40,1.82)	
QST				
MPT				
Normal	63%	58%	0.88	-0.05
Abnormal	47%	52%	(0.43, 1.80)	
TSP				
Normal	28%	28.6%	1.44	0.15
Abnormal	82%	71.4%	(0.53, 3.92)	
PPT				
Normal	100%	81%	-	-
Abnormal	0%	19%		
CPM				
Normal (< 0)	64.7%	47.6%	0.67	-1.13
Impaired (≥ 0)	35.3%	52.4%	(0.31, 1.44)	

CPM= Conditioned Pain Modulation test, HADS= Hospital Anxiety and Depression Scale, MPT= mechanical pain threshold, PPT= pressure pain threshold, PSQI= Pittsburg Sleep Quality Index, QST= Quantitative Sensory Testing, SM= self-management, TSP= temporal summation of pain

3 FUNDAMENTED DISCUSSION

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The main findings of this thesis were as follows: 1) there was no beneficial effect of duloxetine in addition to SM strategies for the primary outcome of pain intensity and most of the secondary outcomes, 2) a more efficient CPM at baseline was associated with a greater pain intensity reduction after 12 weeks of treatment, regardless the treatment group (article 1) and 3) phenotypes, e.g., severe pain intensity, pain disability, painful comorbidity and anxiety symptoms, were indicative of the likelihood of response to SM-duloxetine (article 2).

In this randomized clinical trial, after 12 weeks of treatment, both treatment groups presented a clinically relevant improvement (≥ 30% reduction in the pain intensity)[17]. However, combing duloxetine with SM strategies did not improve pain intensity. Other researchers have noted similar findings in TMD patients. The use of tizanidine or cyclobenzaprine in addition to SM was not more effective than placebo for the management of patients with myofascial jaw pain upon awakening[18]. Moreover, the simultaneous use of occlusal splint device and SM in myofascial TMD patients did not present additional effect after 3 months of treatment, although it was associated with an earlier improvement of pain intensity[19].

Reasons for this lack of effect are not clear but may be related to the SM effect size or to methodological aspects of the study. SM strategies involving psychoeducation, as used in our study, can influence individual's cognitive, behavioural and emotional responses that modulate peripheral and central pain processing[6]. Those strategies present a medium to very large effect sizes[20] and therefore, might have masked the treatment effects of duloxetine. Moreover, participants in SM-duloxetine group reported more AEs and lower improvement in sleep quality and pain catastrophizing compared with SM-placebo after 12 weeks of treatment. Duloxetine 60 mg increased sleep fragmentation and substantially reduced REM sleep, even with morning dosing[21]. It's known that a poor sleep quality may worsen pain catastrophizing which in turn may worsen pain or refrain pain improvement[22]. Thus, the sleep fragmentation seen with duloxetine is concerning and its analgesic efficacy may be limited by the negative physiological effect on sleep.

Methodological aspects can also explain the negative finding. The sample size calculation considered a moderate difference in the pain intensity between SM-duloxetine and SM-placebo and assuming a dropout rate of 20%. Attrition was high (32%), although similar to that reported for other recent clinical trials in chronic pain[23]. Finally, considering the 95% CI

of the mean difference in pain intensity between the groups and the pain intensity reduction associated with duloxetine for musculoskeletal pain disorders from a meta-analysis of RCTs[8], our investigation is perhaps better interpreted as inconclusive rather than a negative trial.

This study demonstrated that TMD participants with more efficient CPM at baseline reported the greater reduction in pain intensity after 12 weeks, regardless the treatment group. Thus, it can be suggested that CPM can identify a clinically relevant subgroup of TMD individuals who can obtain better analgesia with SM strategies. Obviously, the placebo effect, natural history of the disease and regression towards the mean may also have an important role in the effectiveness of treatment. Our findings agree with previous studies investigating the association between baseline CPM and analgesic response, with a more efficient CPM at baseline predicting more pain relief in knee osteoarthritis patients treated with nonsteroidal anti-inflammatory drugs[16] and in chronic low back pain patients treated with opioids[24]. On the other hand, our outcome is contrary to that of Yarnitsky et al.[15], who found a better analgesic response to duloxetine in neuropathic pain patients with a less efficient CPM at baseline. Such differences may be related to the observed lack of additional effect of duloxetine to SM strategies, pathophysiological differences between both diseases or the absence of placebo group in Yarnitsky et al. study[15]. Therefore, it is possible that ability of an impaired CPM to predict treatment analgesic response may be dependent on the overlap between CPM mechanisms and the therapy mechanisms, like SNRIs[15].

Regard the post hoc responder analysis, severe pain intensity, presence of pain disability, ≥ 1 painful comorbidity and anxiety symptoms were associated with the likelihood of response to SM-duloxetine, while no significant predictor was found to SM-placebo treatment. As expected, duloxetine was not universally effective in all participants and the reasons for its selective efficacy remains unknown. One possible reason for this may be the different mechanisms of pain in in these individuals. Most of chronic TMD patients present pain caused by multiple/mixed mechanisms, both peripheral nociceptive and central, however central factors may be more relevant in some cases and peripheral factors in others[25]. The responder profile to SM-duloxetine found in our study is similar to global symptoms cluster identified by OPPERA study[26]. TMD individuals in the global symptoms cluster present general pain sensitivity, high levels of pain, functional limitation, comorbid conditions and high psychological distress[26]. Perhaps participants responding to SM-duloxetine experience more central pain due to presence of global symptoms and thus, may be more responsive to treatments that target such central mechanisms.

Given these considerations, the cause of duloxetine's selective effect may lie within the CNS. The core of the pathophysiology of multiple painful comorbidities and mood disturbances is mostly due to the disruption of serotonin and norepinephrine pathways in the central nervous system[27,28]. The pharmacological treatment of clinical conditions with similar pathophysiology involves a global perception of coexisting disorders. In this sense, duloxetine is monotherapy approach that might be useful to treat concomitant disorders with parallel pathophysiological pathways[7] such as TMD, painful comorbidities and anxiety disorders, which is an advantage for patients (avoiding polytherapy issues) and a successful cost-effective alternative.

The strengths of our study include use of validated diagnostic criteria to select participants with TMD and the inclusion of participants with possible psychiatric disorders, painful comorbidities and taking commonly used medications, which make the study sample representative of the TMD population seeking treatment. One limitation, however, is that the attrition was higher than anticipated. Thus, it is possible that the current study was not adequately powered to detect a minimal clinically meaningful difference between SM-duloxetine when compared with SM-placebo. Future investigations should examine these effects in larger samples. This study also lacks a placebo and duloxetine as comparator arms, which may have allowed for comparison of duloxetine efficacy as monotherapy for chronic TMD. Finally, the relatively short duration is also another limitation.

4 CONCLUSIONS

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There is no beneficial effect of adding duloxetine to SM strategies for treatment of chronic TMD, although high attrition and CI interpretation preclude firm conclusions. Nonetheless, efficient CPM was associated with a better treatment response to SM strategies. Furthermore, it was shown that phenotypes, e.g., severe pain, pain disability, pain comorbidities and anxiety symptoms, may predict which TMD individuals are more likely to derive benefit from adding duloxetine to SM strategies. Thus, this pragmatic randomized clinical trial was able to demonstrate the feasibility of applying patient phenotyping assessment to predict short-term treatment response in chronic TMD individuals, which can contribute to the development of mechanism-based treatments of orofacial pain.

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For PAIN authors, Wolters Kluwer offers two publication routes, Gold and Green, for articles that have funder-mandated open access policies. Specific policies may vary. Descriptions of the Gold and Green options are provided below.

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The manuscript must contain an Abstract (unstructured, 250 words), Introduction (500 words), Methods (no word limit), Results (no word limit), Discussion (1,500 words), Acknowledgments, and References .

File format should be Microsoft Word, and manuscript pages should be numbered.

Title page. The title page should include the following: (i) complete title (preferably no chemical formulas or arbitrary abbreviations); (ii) full names of all authors; (iii) complete affiliations of all authors; (iv) the number of text pages of the entire manuscript (including pages containing figures and tables) and the actual number of figures and tables; (v) the author to whom correspondence should be sent and this author's complete mailing address, telephone number, fax number, and e-mail address, and, if available, institutional URL.

Acknowledgments. Place acknowledgments at the end of the text before the reference list and specify the following: (1) contributions that need acknowledging but do not justify authorship; (2) acknowledgments of technical help; (3) acknowledgments of financial and material support, specifying the nature of the support; (4) financial arrangements that may represent a possible conflict of interest.

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References. Cite literature references in the text using bracketed numbers that correspond to the alphabetized and numbered reference list as follows: "Pain is made worse if you hit the already injured site [15]." For multiple references in the text, please use the format [number,number] (with a comma and no spaces). For example: [2,4,28,33].

- All references cited in the text must be listed at the end of the paper. They should be numbered, double spaced, and arranged alphabetically by first author last name.

- All authors must be listed in the references; the use of et al. is not acceptable.

- References must be complete, including initial(s) of author(s) cited, title of paper, journal, year of publication, and volume and page numbers.

- For citations of books, the following uniform sequence should be maintained: author(s), title of article, editor(s), complete title of book, place of publication, publisher, year, and page numbers.

- Journal titles should be abbreviated according to the National Library of Medicine's Index Medicus. Please refer to the NLM website's FAQ on how to find Index Medicus journals: www.nlm.nih.gov/services/aim.html.

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- For manuscripts containing citations that are in press, authors must have electronic copies immediately available in case reviewers/editors request these materials.

- URLs should be included for all references that are publicly accessible via the Internet.

Examples:

[1] Adams CWM. Neurohistochemistry. Amsterdam: Elsevier, 1965.

[2] Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. Eur J Pain 2005;9:463-84.

[3] Eccles R. Understanding the symptoms of the common cold and influenza. Lancet Infect Dis 2005;5:718-25.

[4] Turner JA. Coping and chronic pain. In: Bond MR, Charlton JE, Woolf CJ, editors. Pain research and clinical management. Proc. VIth World Congress on Pain, Vol. 4. Amsterdam: Elsevier,; 1991. pp. 219-227.

Figure legends. Provide each illustration with a title and an explanatory legend. The title should be part of the legend; do not reproduce the title and legend on the figure itself. Legends should appear on a separate page at the end of the manuscript. Each legend should be numbered consecutively with Arabic numerals (i.e., Fig. 1, Fig. 2, etc.), and should begin with the number of the illustration to which they refer. Explain all symbols and abbreviations used in the figure.

Tables. Tables, with their captions and legends, should be intelligible with minimal reference to the text. Tables of numerical data should each be typed (double spaced) on a separate page, numbered in sequence with Arabic numerals (i.e., Table 1, Table 2, etc.), provided with a title/heading, and referred to in the text as Table 1, Table 2, etc. Provide a detailed description of its contents and any footnotes below the body of the table.

Upload figures and tables as separate files.

ANNEX B – Guideline for Journal of Oral Rehabilitation:

JOURNAL OF ORAL REHABILITATION

HOME | ABOUT | CONTRIBUTE | BROWSE

Author Guidelines

Sections

1. SUBMISSION

Authors should kindly note that submission implies that the content has not been published or submitted for publication elsewhere except as a brief abstract in the proceedings of a scientific meeting or symposium.

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Progressing Towards Transparency

Authors now have the option to choose transparent peer review when submitting their article. A transparent peer review workflow shows readers the process behind editorial decision making, increases accountability, and helps recognize the work of editors and peer reviewers.

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2. AIMS AND SCOPE

Journal of Oral Rehabilitation is an international journal for those active in research, teaching and practice in oral rehabilitation and strives to reflect the best of evidence-based clinical dentistry. The content of the journal also reflects documentation of the possible side-effects of rehabilitation, and includes prognostic perspectives of the treatment modalities.

Journal of Oral Rehabilitation aims to be the most prestigious journal of dental research within all aspects of oral rehabilitation and applied oral physiology. It covers all diagnostic and clinical management aspects necessary to re-establish a subjective and objective harmonious oral function.

The focus for the journal is to present original research findings; to generate critical reviews and relevant case stories, and to stimulate commentaries and professional debates in Letters to the Editor. We will invite relevant commercial interests to engage in the journal in order to make it the international forum for debate between dental clinical dental clinical sciences and industry, which share a common goal: to improve the quality of oral rehabilitation.

We would particularly like to encourage the reporting of randomised controlled trials.

Keywords: dental disease, dental health, dental materials, gerodontology, oral health, oral medicine, oral physiology, oral prostheses, oral rehabilitation, restorative dentistry, TMD.

3. MANUSCRIPT CATEGORIES AND REQUIREMENTS

i. Original Research

Original articles that describe cases require parental/patient consent. For cohort studies, please upload a copy of your IRB approval.

Word limit: 5,000 words maximum, excluding abstract and references.
Abstract: 250 words maximum; must be structured, under the sub-headings: Background, Objective(s), Methods (include design, setting, subject and main outcome measures as appropriate), Results, Conclusion.
References: Maximum of 50 references.
Figures/Tables: Total of no more than 6 figures and tables.

ii. Reviews

Structured summary giving information on methods of selecting the publications cited.

Word limit: 5,000 words maximum, excluding references.
References: No limit
Figures/Tables: Total of no more than 6 figures and tables.

iii. Case Reports

Only exceptional reports that have important education or safety messages will be considered. Our current rejection rate is 90%. Conclude with 3 learning points for our readers. All case reports require parental/ patient consent for publication.

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References: Maximum of 5 references.
Figures/Tables: Total of no more than 1 figure or table.

We work together with Wiley's Open Access journal, *Clinical Case Reports*, to enable rapid publication of good quality case reports that we are unable to accept for publication in our journal. Authors of case reports rejected by our journal will be offered the option of having their case report, along with any related peer reviews, automatically transferred for consideration by the *Clinical Case Reports* editorial team. Authors will not need to reformat or rewrite their manuscript at this stage, and publication decisions will be made a short time after the transfer takes place. *Clinical Case Reports* will consider case reports from every clinical discipline and may include clinical images or clinical videos. *Clinical Case Reports* is an open access journal, and article publication fees apply. For more information please go to www.clinicalcasesjournal.com.

iv. Correspondence

Letters to the editor are encouraged, particularly if they comment, question or criticize original articles that have been published in the journal. Letters that describe cases require parental/ patient consent for publication.

Word limit: 1,500 words maximum, excluding references.
References: Maximum of 5 references.
Figures/Tables: Total of no more than 1 figure or table.

4. PREPARING THE SUBMISSION

All submissions to Journal of Oral Rehabilitation should conform to the uniform requirements for manuscripts submitted to biomedical journals, drawn up by the International Committee of Medical Journal Editors (ICMJE) see http://www.icmje.org/.

Parts of the Manuscript

The manuscript should be submitted in separate files: main text file; figures. The main manuscript file can be submitted in Microsoft Word (.doc or .docx) or LaTex (.tex) format.

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The text file should be presented in the following order:

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iii. The full names of the authors with institutional affiliations where the work was conducted, with a footnote for the author's present address if different from where the work was conducted;
iv. Acknowledgments;
v. Abstract (structured);
vi. Keywords;
vii. Main text;
viii. References;
ix. Tables (each table complete with title and footnotes);
x. Figure legends; must be added beneath each individual image during upload AND as a complete list in the text;
xi. Appendices (if relevant).

Figures and supporting information should be supplied as separate files.

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Please refer to the journal's authorship policy the Editorial Policies and Ethical Considerations section for details on eligibility for author listing.

Acknowledgments

Contributions from anyone who does not meet the criteria for authorship should be listed, with permission from the contributor, in an Acknowledgments section. Financial and material support should also be mentioned. Thanks to anonymous reviewers are not appropriate.

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Authors will be asked to provide a conflict of interest statement during the submission process. For details on what to include in this section, see the section 'Conflict of Interest' in the Editorial Policies and Ethical Considerations section below. Submitting authors should ensure they liaise with all co-authors to confirm agreement with the final statement.

Abstract

Structured abstracts or summaries are required for some manuscript types. For details on manuscript types that require abstracts, please refer to the 'Manuscript Types and Criteria' section.

Keywords

Please provide six keywords. Keywords should be taken from those recommended by the US National Library of Medicine's Medical Subject Headings (MeSH) browser list at www.nlm.nih.gov/mesh.

Main Text

The main body must contain sections on background, methods, results and conclusions, with the appropriate heading.

References

All references should be numbered consecutively in order of appearance and should be as complete as possible. In text citations should cite references in consecutive order using Arabic superscript numerals. For more information about AMA reference style please consult the AMA Manual of Style

Sample references follow:

Journal article
1. King VM, Armstrong DM, Apps R, Trott JR. Numerical aspects of pontine, lateral reticular, and inferior olivary projections to two paravermal cortical zones of the cat cerebellum. J Comp Neurol 1998;390:537-551.

Book
2. Voet D, Voet JG. Biochemistry. New York: John Wiley & Sons; 1990. 1223 p.

Internet document
3. American Cancer Society. Cancer Facts & Figures 2003. http://www.cancer.org/downloads/STT/CAFF2003PWSecured.pdf Accessed March 3, 2003

Tables

Tables should be self-contained and complement, not duplicate, information contained in the text. They should be supplied as editable files, not pasted as images. Legends should be concise but comprehensive – the table, legend, and footnotes must be understandable without reference to the text. All abbreviations must be defined in footnotes. Footnote symbols: †, ‡, §, ¶, should be used (in that order) and *, **, *** should be reserved for P-values. Statistical measures such as SD or SEM should be identified in the headings.

Figure Legends

Legends should be concise but comprehensive – the figure and its legend must be understandable without reference to the text. Include definitions of any symbols used and define/explain all abbreviations and units of measurement.

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Although authors are encouraged to send the highest-quality figures possible, for peer-review purposes, a wide variety of formats, sizes, and resolutions are accepted. Click here for the basic figure requirements for figures submitted with manuscripts for initial peer review, as well as the more detailed post-acceptance figure requirements.

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Note: if data, scripts, or other artefacts used to generate the analyses presented in the paper are available via a publicly available data repository, authors should include a reference to the location of the material within their paper.

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The following points provide general advice on formatting and style.

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The list of authors should accurately illustrate who contributed to the work and how. All those listed as authors should qualify for authorship according to the following criteria:

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3. Given final approval of the version to be published. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content; and
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