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Duloxetine in addition to self-management for painful temporomandibular disorders: a *post hoc* responder analysis of a randomized, placebo-controlled clinical trial*

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Abstract

Aim: To identify the phenotypic characteristics of individuals with temporomandibular disorders (TMD) who may benefit from adding duloxetine to self-management (SM) strategies. Methodology: This was a post hoc exploratory analysis of a randomized, placebo-controlled clinical trial with SM-duloxetine (duloxetine 60 mg/day plus SM strategies for 12 weeks) in adult participants with painful TMD. The primary outcome was the 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 Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials were assessed: pain, psychological, sleep, quantitative sensory testing, and conditioned pain modulation. Relative risk (RR), 95% confidence intervals (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), ≥ 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: Personalized medicine may be implemented in painful TMD management, and phenotype characteristics related to pain and psychological domains may predict which individuals with painful TMD are more likely to respond to the addition of serotonin and norepinephrine reuptake inhibitors to SM strategies to clinically and significantly reduce pain intensity.

Keywords: Temporomandibular Joint Dysfunction Syndrome. Pain management. Duloxetine hydrochloride. Self-management. Phenotype.

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Introduction

Temporomandibular disorders (TMD) are a collective term for a group of musculoskeletal conditions involving pain and/or dysfunction in the masticatory muscles, temporomandibular joints, and associated structures[1]. Painful TMD causes substantial physical, mental, and economic burden.[2,3] Moreover, individuals experience pain disability and low quality of life.[2,4] Due to the multifactorial and biopsychosocial etiology of TMD, patients are treated by a combination of non-pharmacological and pharmacological therapies. Non-pharmacological treatments include self-management (SM) strategies (the core part of treatment), intraoral appliances, physical therapy, and psychotherapy.[5] Pharmacological treatments usually include nonsteroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, anticonvulsants, and tricyclic antidepressants.[5] However, drugs to relieve chronic pain are usually administered for a long time. Thus, adverse events may limit its use. For instance, NSAIDs have gastrointestinal, liver, kidney, and cardiovascular toxicities,[6] whereas titration to higher doses of tricyclic antidepressants is limited by its anticholinergic adverse effects[7]. Thus, it is necessary to find new treatment options for clinicians to choose if other drugs work poorly or are limited by its adverse effects.

Duloxetine is a serotonin and norepinephrine reuptake inhibitor (SNRI) with proven efficacy in treating chronic pain disorders, including fibromyalgia, low back pain, osteoarthritis, and diabetic peripheral neuropathy.[8,9] Our recent randomized, placebo-controlled clinical trial found inconclusive results for the efficacy of duloxetine in addition to SM strategies in individuals with painful TMD due the high dropout rate and characteristics of its sample.[10]

Substantial heterogeneity within a diagnostic category has been suggested as the cause of negative or inconclusive results in pain clinical trials, masking positive results in certain patient subgroups. Such findings have stimulated personalized medicine, which consists of identifying phenotypic characteristics that can predict positive response to a specific treatment.[11] For instance, patients with chronic pain who show early pain reduction, multiple painful sites,[12] and anxiety and depression symptoms[13] are most likely to respond to duloxetine (with significant pain reduction).

Knowing the phenotypic characteristics of individuals with TMD influencing the efficacy of duloxetine in addition to SM strategies can implement personalized medicine that prescribes duloxetine to those most likely to benefit from it. This study conducted a *post hoc* exploratory analysis of our previous randomized, placebo-controlled clinical trial[10] to identify the phenotypic characteristics of individuals with TMD who may benefit from adding SNRIs to SM strategies.

Methodology

Study design and treatment

This study was a *post hoc* exploratory analysis of a randomized, double-blind, placebo-controlled clinical trial of duloxetine in addition to SM strategies to treat painful TMD, which was conducted in Brazil from September 2018 to March 2020 (Brazilian Registry of Clinical Trials # RBR-6pqx4n) and has been previously described.[10] Eligible participants were randomized into 1:1 to duloxetine 60 mg or placebo once daily for 12 weeks. Individuals in the duloxetine group received duloxetine 30 mg/day for one week, followed by 60 mg/day for 11 weeks. Participants in the placebo group received placebo for 12 weeks. Individuals who completed the 12-week treatment period entered a one-week double-blind taper period to minimize discontinuation-emergent adverse events. Moreover, all participants received a SM program including information about TMD etiology and prognostics, nutrition and diet, oral parafunctional behavior control, relaxation techniques for the jaw, sleep hygiene, and encouragement to practice physical exercise. The clinical trial 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 (CAAE 88436318.2.0000.5417). Participants informed their consent before the beginning of the study.

Participants

Overall, 80 male and female participants aged ≥18 years who had painful TMD according to the DC/TMD[1] and showed pain for ≥ three months were included. Uncontrolled systemic disorders, cardiac disorders, neuropathies, history of psychosis or bipolar disorder, treatment with monoamine oxidase inhibitor within 14 days prior to the study, treatment with SNRIs

within 12 months of entering the study, pregnancy or breast-feeding, intolerance to duloxetine or any component of the formulation, and treatment for TMD in the previous three months were chosen as exclusion criteria. To maximize generalizability to clinical practice, the concurrent use of centrally acting medications (constant doses for ≥ 3 months before entry study) and the presence of comorbid conditions commonly related to TMD (e.g., primary headache, neck pain, fibromyalgia, and anxiety and depression disorders) was allowed.[10]

Outcomes

Treatment efficacy in the primary study[10] referred to the change in the 'pain intensity over the past week' from baseline to week 12. Pain intensity was measured by a 0-10 numerical rate scale (NRS). In total, 40 participants in the duloxetine plus SM strategy (SM-duloxetine) group and 38 participants in the placebo plus SM strategy (SM-placebo) group were included in both the primary (intention-to-treat) and this *post hoc* analyses. In the primary study, pain intensity decreased significantly over time in SM-duloxetine and SM-placebo participants, showing 2.1 (95% CI: -3.2, -1.1) and 2.4 (95% CI: -3.3, -1.5) reductions from baseline, respectively, which failed to significantly differ between groups (0.3, 95% CI: -1.1, 1.7; p=0.82).

The primary outcome in this *post hoc* exploratory analysis refers to the proportion of 'responders' to treatment. A 'responder' was defined as a participant showing ≥ 30% reduction in the 'pain intensity over the past week' at week 12. This pain reduction threshold was chosen based on previous studies, which concluded that a ≥ 30% reduction constituted a clinically relevant improvement and correspond to what patients would consider a "moderately important" improvement in pain intensity.[14]

The association of the proportion of responders with five phenotyping domains recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)[11] 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 'pain intensity over the past week.' Severe pain was defined as NRS ≥ 7 and mild to moderate pain, as NRS < 7.[15] TMD-related disability and interference in functioning were assessed using the Graded Chronic Pain Scale (GCPS),[16] which is derived from several variables: characteristic pain intensity, the pain interference score, and pain disability days. Based on two former variables, participants were classified into with (score ≥3) or without disability (score < 3).[16] The Central Sensitization Inventory (CSI)[17] was used to assess central sensitization phenomena (part A) and painful comorbidities (part B). Presence of central sensitization was defined as a CSI total score ≥ 40.[17]

Psychological domain

The Hospital Anxiety and Depression Scale (HADS)[18] was used to measure anxiety and depression symptoms. HADS includes 14 items, seven of which are related to anxiety and seven, to depression, each of which is scored from 0 to 3. The total score for anxiety and depression subscales varies by 0-21 and a score > 8 was defined as showing anxiety or depression symptoms.[18]

Sleep domain

The Pittsburg Sleep Quality Index (PSQI)[19] assess sleep quality over the past month across seven components: quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, sleep medication use, and daytime dysfunction. PSQI total scores vary by 0-21 points and impaired sleep was defined as a total score > 5.[19]

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 patients' masseter muscle according to DFNS recommendations.[20] MPT was assessed using a standardized set of Semmes-Weinstein monofilaments (Touch-Test TM Sensory Evaluators; North Coast Medical) that exert forces from 0.008 to 300 g/mm^2. The monofilaments were applied in a vertical and perpendicular position to the site of examination, and the contact time lasted approximately two 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.[20] 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 applied to a 1-cm^2 area and repeated every 1/s. The monofilament was perceived as "slightly painful" and individually determined for each participant. Participants were asked to rate their pain immediately after the single stimulus and the series of 10 stimuli by using a 0 to 100 NRS. The entire procedure was repeated thrice. TSP was calculated as the mean rating of the three series divided by the mean rating of the three single stimuli[20]. The final test in the QST protocol, the PPT, was performed with a digital dynamometer (Kratos) with a 1-cm^2 probe area and a flat circular-shaped tip. 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 about 0.5 kgf/s.[21] 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.[20]

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). The CPM protocol was detailed the primary study.[10] 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[22] and was defined as normal CPM.

Statistical analysis

This *post hoc* exploratory analysis consisted of all participants included in the intention-to-treat analysis in the primary study.[10] Baseline characteristics are described as means (SD) for continuous variables and as n (%) for categorical variables. For responder analysis, relative risks (RR), 95% confidence intervals (95% CI), and absolute risk reduction (ARR) for responder rates were calculated for each variable in the SM-duloxetine and SM-placebo groups. RR and 95% CI were used to interpret the results. Missing end-of-treatment data were imputed using the modified baseline-observation-carried-forward method.[10] All statistical analyses were conducted on STATISTICA, v. 10 (StatSoft).

Results

Participants' characteristics

Table 1 details participants' characteristics, which have been described previously[10]. In general, treatment groups showed similar baseline characteristics. The sample consisted of women in their mid-30s. Most participants (> 90%) had myalgia and arthralgia diagnoses. Painful TMD was generally of longstanding duration, of moderate to severe intensity, and low disability. The baseline CSI score indicated a central sensitization phenomenon. Most participants (70%) had at least one painful comorbidity, with primary headache, neck pain, and fibromyalgia being the more prevalent. Moreover, the sample showed low levels of anxiety, depression, and catastrophism symptoms but poor sleep quality. Regarding the pain modulation profile, the sample showed enhanced pain facilitation and efficient pain inhibition as per the abnormal values of TSP and negative values of CPM, respectively.

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 at least one 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 pain domain variables (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 of depression (RR 0.65, 95% 0.22, 1.89) — were associated with greater probability of response to treatment (Table 2). Psychological variables were unrelated to responses to SM-placebo (Table 3).

Responder analysis by sleep domain

The presence or absence of sleep disorder were associated with responses to neither SM-duloxetine (RR 0.66, 95% CI 0.29, 1.48) nor 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%

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

CI 0.45, 5.79) or normal PPT (RR 1.75, 95% CI 0.74, 4.09) on their masseter muscle were more likely to respond to SM-duloxetine treatment (Table 2). In the 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 domain

The CPM effect, whether normal or impaired, was associated with the likelihood of response to neither SM-duloxetine (RR 0.49, 95% CI 0.18, 1.28) nor SM-placebo (RR 0.67, 95% CI 0.31, 1.44) (Table 2 and 3).

Discussion

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

This *post hoc* responder analysis associated phenotypic characteristics from pain domain, expressed by presence of severe pain intensity, pain disability, and painful comorbidity with responses to duloxetine in addition to SM strategies. Painful TMD frequently coexist with other painful illness such as headaches, cervical spine dysfunction, fibromyalgia, lower back pain, and irritable bowel syndrome pain, being often categorized as a 'chronic overlapping pain condition.'[23,24] In total, 70% of participants in our analysis showed at least one painful comorbidity, with headache, neck pain, and fibromyalgia being the most prevalent. Evidence endorses the negative impact of painful comorbidities in the clinical course of TMD. Compared to TMD participants without comorbidities, participants with painful comorbidities more likely experience higher TMD pain intensity, duration, and disability and report a history of depression and/

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	0.10
Severe (≥7)	66.6%	66%	(0.56, 3.17)	
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

or anxiety.[25-27] These differences suggest that the presence of painful comorbidities in TMD participants may result from changes in the central nervous system, particularly in reduced activity of descending inhibitory pathways, which amplify pain perception.[23,24] In clinical practice, TMD patients with at least one painful comorbidity, especially for those which duloxetine has already been proven effective (e.g. fibromyalgia, low back pain, osteoarthritis, migraine, and neuropathic pain),[8,9] may benefit from adding duloxetine to conventional strategies of SM.

Another finding was that participants with anxiety

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	-0.35
Severe (7)	47%	80%	(0.26, 0.94)	
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

symptoms were approximately two times more likely to respond to duloxetine in addition to SM strategies than those without them. This finding reflects those of Taylor, et al.[28] (2007) for migraine patients, in which the presence of anxiety may be a positive predictor in treatment with duloxetine. Duloxetine has proven efficacy in the treatment of patients suffering from anxiety disorders.[8] Several psychosocial factors are associated with painful TMD, including anxiety, depression, and somatization.[29] A prospective study has shown affective distress, including anxiety, as a predictor of the incidence of painful TMD.[30] On the

other hand, the persistent pain of TMD might be a link to anxiety disorders as comorbid conditions.[31] While studies in TMD patients have shown that high anxiety and depression scores at baseline are associated with reduced analgesic benefit of treatments (intraoral appliances, NSAIDs, soft diet, cognitive-behavioral therapy, and TMJ hyaluronic acid injection),[32,33] anxiety symptoms may signal individuals with TMD more likely to benefit from adding duloxetine to SM strategies.

Surprisingly, TSP emerged as a possible predictor of responses 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.[34] The finding of a non-specific responder profile to SM-placebo seems to reflect the interaction between placebo effect mediated by patient expectation[35] and the wide mechanism by which SM strategies can improve pain in patients with TMD.[36] Systematic reviews investigating predictors to placebo responses and SM strategies have shown heterogenous results with cognitive constructs such as self-efficacy, locus of control, and "emotionalized" contingency expectations as predictors.[37,38] As we ignore most of those outcomes, this is an important issue for future research.

This *post hoc* responder analysis confirms that combining duloxetine and SM, as any treatment, is not universally effective in all patients. Thus, characteristics which render individual patient more responsive to a specific treatment must be identified.[11] This study showed that the phenotypic characteristics of pain and psychological domains may predict response to duloxetine in addition to SM strategies. TMD is a heterogenous condition, the pain of which stems from a combination of peripheral and central mechanisms. However, central factors may be more relevant in some cases and peripheral factors in others.[39] The core of the pathophysiology of multiple painful comorbidities and mood disturbances, as seen in the TMD responder' profile, mostly stems from the disruption of serotonin and norepinephrine pathways in the central nervous system.[24,40] The pharmacological treatment of clinical conditions with similar pathophysiology involves a global perception of coexisting disorders. Thus, duloxetine is a drug approach that might usefully treat concomitant disorders with parallel pathophysiological pathways such as chronic painful illness and anxiety disorders,[8] which is an advantage for individuals with TMD (avoiding polydrug therapy issues) and a successful cost-effective alternative.

This study has several limitations. First, the small sample size may explain the large CI by predictor phenotypes and its absence of significant associations between CSI, depression symptoms, sleep quality, QST, CPM, and response to SM-duloxetine. The next step is to conduct adequately powerful follow-up studies to confirm these findings. Second, the presence of painful comorbidities was assessed by CSI, part B. A more accurate assessment could be done using the International Classification of Headache Disorders[41] or validated surveys such as the Neck Disability Index[42] and Fibromyalgia Rapid Screening Tool.[43] The strengths of this analysis include the prospective, randomized, placebo-controlled design of the primary study and the assessment of five phenotyping domains in clinical trials of chronic pain recommended by IMMPACT.[11]

Conclusion

This *post hoc* responder analysis of a randomized, placebo-controlled clinical trial suggests that severe pain intensity, pain disability, painful comorbidity, and anxiety symptoms may be important indicators of individuals with painful TMD, who are more likely to derive benefit from adding duloxetine to SM strategies. Personalized medicine may be implemented in painful TMD management, and phenotype characteristics from pain and psychological domains may predict which individuals with painful TMD are more likely to respond to the addition of SNRIs to SM strategies with a clinically significant reduction in pain intensity.

Clinical implication

Personalized medicine may be applied to designing appropriate treatment for individuals with painful TMD, improving analgesic effects and reducing costs.

Phenotypes characteristics from pain and psychological domains can indicate the individuals with painful TMD who are more likely to benefit from adding duloxetine to self-management strategies.

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Conflict of interest

The authors declare no conflict of interest.

Data availability statement

The datasets generated during and/or analyzed in this study are available from the corresponding author upon reasonable request.

Authors' contributions

Ferreira, Dyna Mara Araújo Oliveira: Conceptualization (Equal); Data curation (Equal); Funding acquisition (Equal); Investigation (Equal); Methodology (Equal); Project administration (Equal); Visualization (Equal); Writing – original draft (Equal). **Soares, Flavia Fonseca Carvalho:** Investigation (Equal); Project administration (Equal); Resources (Equal); Visualization (Equal); Writing – review & editing (Equal). **Raimundini, Amanda Ayla:** Data curation (Equal); Investigation (Supporting); Project administration (Supporting); Visualization (Equal). **Costa, Yuri Martins:** Conceptualization (Equal); Data curation (Equal); Formal analysis (Equal); Funding acquisition (Equal); Methodology (Equal); Project administration (Equal); Software (Equal); Validation (Equal); Visualization (Equal); Writing – original draft (Equal); Writing – review & editing (Equal). **Bonjardim, Leonardo Rigoldi:** Conceptualization (Equal); Funding acquisition (Equal); Methodology (Equal); Resources (Equal); Supervision (Equal); Validation (Equal); Visualization (Equal); Writing – review & editing (Equal). **Conti, Paulo César Rodrigues:** Conceptualization (Equal); Funding acquisition (Equal); Methodology (Equal); Project administration (Equal); Resources (Equal); Supervision (Equal); Validation (Equal); Visualization (Equal); Writing – review & editing (Equal).

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