Nortriptyline Compared to Amitriptyline for the Treatment of Persistent Masticatory Myofascial Pain

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Aims: To evaluate and compare the pharmacotherapeutic efficacies of two tricyclic antidepressant (TCA) drugs for masticatory myofascial pain (MFP): nortriptyline (NOR) and amitriptyline (AMI). **Methods:** Fifty patients with chronic MFP were included in the study; 30 were medicated with AMI only, and 20 took NOR after discontinuing AMI due to adverse effects. Pain diaries recording verbal pain scores (VPS) were utilized to compare posttreatment scores to baseline scores. Chi-square and *t* tests were used to analyze the data. **Results:** Across both groups, the mean ± standard deviation VPS score at the end of treatment (2.92 ± 3.2) was significantly lower compared to baseline (6.4 ± 1.75; $P < .0001$) and was a clinically meaningful (≥ 50%) difference. Initial VPS scores were similar in the AMI and NOR groups (6.27 ± 1.92 and 6.78 ± 1.98). At the end of the study, NOR patients reported a lower final VPS compared to AMI patients (2.83 ± 3.06 vs 4.55 ± 2.92; $P = .039$). The 50% improvement rate with NOR treatment was better than with AMI treatment ($P = .036$). The same maximal dosages were used by the patients who achieved a ≥ 50% success rate (20.96 ± 5.036 mg) than those who did not (21.667 ± 5.036 mg). **Conclusion:** TCAs are effective in reducing pain in patients with chronic MFP. NOR seems more effective and better tolerated than AMI, but due to study limitations, more data are needed to confirm these results. *J Oral Facial Pain Headache 2019;33:7–13. doi: 10.11607/ofph.1886*

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Temporomandibular disorders (TMD) are musculoskeletal pain conditions characterized by pain and dysfunction in the temporomandibular joint (TMJ) and/or masticatory muscles and represent the most common chronic orofacial pain condition.[1,2] According to the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD),[3] masticatory myofascial pain (MFP) represents the myalgia aspect of TMD. Typical myofascial pain is unilateral, of moderate intensity and dull pressing quality, and tends to increase with function.[4,5] Pain is usually self-limited with complete remission of symptoms, and conservative reversible treatment is the preferred strategy.[6,7] Primary treatment options include self-administered or professional physiotherapy, soft diet, parafunctional habit modification, and moist heat and/or ice therapy.[6,8,9] Occlusal appliance therapy is also a useful adjunct for some MFP patients.[10,11] However, MFP can become chronic and persistent in about one third of patients, and long-term pharmacotherapeutic treatment is often an essential component of management in these cases.[12]

Tricyclic antidepressants (TCAs) are among the most accepted pharmacologic treatment options. Amitriptyline (AMI) is the most studied TCA and is frequently the drug of choice for MFP treatment, with doses ranging from 10 to 35 mg daily.[13–17] TCAs are metabolized in the liver[17] and their analgesic effects are thought to be mediated primarily by a central inhibition of serotonin (5-HT) and noradrenaline reuptake.[18,19] However, further modes of action include increased endogenous brain opioid levels[20,21]; N-Methyl-D-aspartate (NMDA) antagonist effects[22]; sodium, calcium, and potassium channel blockage[23]; upregulation of GABA receptor expression[24,25]; and histamine and cholinergic receptor blockage.[26]

The analgesic effect of a TCA on chronic pain is independent of its antidepressive action,[13,27] and its effective analgesic dose in chronic pain treatment is significantly lower than that used for depression.[13] Adverse effects (AE) are common but usually mild, and chronic administration of 25 mg AMI daily is not associated with significant reductions in patient processing or task-performing capacity.[28] Common AEs include sedation, palpitations, nausea, dry mouth, constipation, dizziness, tiredness and fatigue, and weight gain due to increased appetite. A mean weight gain of 3.2 kg was measured in patients taking 25 mg of AMI for 3 months.[29] These non–life-threatening side effects may compromise compliance.

The serious concerns with TCA include an increased risk of upper gastrointestinal (GI) bleeding[30] and a 40% increased risk of sudden cardiovascular-related death with dosages of ≥ 100 mg of amitriptyline or an equivalent TCA dose.[31]

Nortriptyline (NOR) is an active metabolite of AMI and is de-methylated in the liver.[32] It has antidepressive activity, but its main use is for neuropathic pain.[33] The milder side effects of NOR make it an attractive alternative to AMI in MFP patients who cannot tolerate AMI due to AEs.[34,35] To the best of the authors' knowledge, no head-to-head comparisons between NOR and AMI have been reported in the treatment of patients with MFP or TMD.

The aims of the present study were to evaluate and compare the efficacies of AMI and NOR for treatment of patients with chronic MFP in terms of pain reduction and AEs.

Materials and Methods

Patients were interviewed and examined at the Orofacial Pain Clinic, The Hebrew University, Hadassah School of Dental Medicine, Jerusalem. This tertiary clinic mostly manages patients when treatment fails in the community. A total of 50 patients were recruited between 2011 and 2015. Primary and resultant data were recorded on the intake form. The study was approved by the Hadassah Hospital Helsinki International Review Board committee. Informed consent was obtained from all participants. Demographic data, including gender, age, and medical status, were also recorded.

Patients were asked to rate pain quality and pain intensity during the week before the appointment. Pain intensity was rated on a verbal pain scale (VPS) on which 0 represented no pain and 10 the worst imaginable pain. Pain quality was assessed by asking patients to choose one or more of the following descriptive terms routinely used in the clinic: electrical; stabbing; throbbing; pressure; burning; or a combination of the five.[5,16,36] Patients recorded VPS data in pain diaries, and the number of patients with a reduction of at least 50% in VPS from baseline was calculated based on these data. A 50% reduction as a cut-off for therapeutic success is a standard and accepted therapeutic outcome indicating clinical significance. The presence of systemic (eg, nausea or dizziness) or autonomic (eg, tearing or skin flushing) symptoms was recorded. Regional spread of pain was mapped on a diagram of the head and neck, and five areas were identified anatomically: preauricular/auricular; angle of the mandible; maxillary; temporal/frontal; and suboccipital. These areas were recorded, and sites in which pain was present were awarded a score of 1. The total score was termed number of surfaces (NOS), which represents the pain spread, with a maximum score of 10.[16] Pain that began following a clear traumatic event was defined as posttraumatic and classified as macrotrauma (eg, road traffic accidents and altercations) or microtrauma (eg, dental surgery; invasive or prolonged interventions). Patients were also asked whether the pain specifically wakes them from sleep (using a standardized question).

Clinical Examination

The masseter and temporalis muscles and the TMJ were examined bilaterally. Passive opening of the mouth was recorded in millimeters. Muscle and joint palpation were performed with about 2 kg of digital pressure (previous examiner calibration).[3,5] Tenderness to palpation was graded on an ordinal scale for each patient at each site: 0 = no pain; 1 = mild; 2 = moderate; and 3 = severe. The sum of muscle tenderness scores (0 to 12) was defined as the muscle index.

Inclusion Criteria and Pain Diagnosis

The inclusion criteria were complaint of persistent facial pain present for at least 3 months that matched the published myalgia criteria of the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD),[37] updated in 2014 to the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD).[3]

Exclusion criteria were other pain syndromes; refusal of pharmacotherapy; or treatment with nonpharmacologic means.

Pharmacotherapeutic Protocol

The clinic employed a stepped pharmacotherapeutic protocol.[16] Patients diagnosed with MFP began treatment with 10 to 35 mg of AMI daily at bedtime. In patients with intolerable AEs, the medication was changed to 12.5 to 50 mg of NOR daily at bedtime. The dosage of both medications was titrated according to patient response and reported side effects.

Patients tolerating AMI and taking it as a sole treatment were compared to those who took NOR after stopping AMI (Fig 1).

A minimum of 8 weeks of pain levels while on pharmacotherapy were recorded in the pain diaries. Patients were not referred to professional physiotherapy, but were instructed to do home care physiotherapy. No other interventions were performed.

Statistical Analyses

Therapeutic success (≥ 50% reduction in pain) was descriptively presented as frequency and percentage, and VPS scores as mean and standard deviation (SD). Univariate analyses of differences between independent VPS variables were analyzed with *t* tests, and differences in therapeutic success were analyzed using chi-square test for nominal independent variables and *t* test for numeric variables. Odds ratios (ORs) were calculated using binominal logistic regression when comparing success vs nonsuccess, and independent variables that were found to be significant in the univariate analysis were adjusted by age and gender. SPSS 21.0 software was used. Statistical level of significance was set at $P < .05$.

Results

A total of 50 patients met the inclusion criteria: 13 males (26.0%) and 37 (74%) females. The mean age of the included patients was 36.33 ± 14.89 years (range: 16 to 53 years), and the mean pain duration was 19.76 ± 14.67 months (range: 3 to 54 months). Thirteen (26.0%) patients had known associated medical comorbidities (eg, migraine and fibromyalgia). Thirty (60%) reported mostly unilateral pain, and 20 (40%) bilateral pain. Overall, 3.66 ± 2.28 surfaces (NOS) were involved. Forty-four (88%) of the patients reported pressure pain quality. Eight (16%) reported systemic and 10 (20%) autonomic signs of any kind. The masseter muscle was significantly more painful to palpation than the temporalis muscle across both groups (1.74 ± 0.91 vs 1.07 ± 0.92, respectively; $P < .001$).

Thirty patients (60%) completed the study with AMI treatment, while 17 patients who had reported side effects were switched to NOR. Three additional patients started and completed the study on NOR due to previous AEs from treatment with AMI. Overall, 20 patients completed the trial on NOR (40%, Fig 1). AEs included tiredness, daytime sleepiness, and weight gain. No differences were found between the AMI and NOR groups in terms of age, background medical status, dominant unilateral pain, possible trauma, quality of pain, or awakening from sleep (Table 1). The gender distribution was significantly different between groups ($P = .03$), with more females in the AMI group compared to the NOR group; this point was addressed and adjusted in the regression analysis (Table 2). Mean maximal drug dose for all patients was 21.30 ± 7.46 mg, with 25 ± 7.02 mg for NOR and 18.83 ± 6.78 mg for AMI ($P < .003$). Baseline mean VPS of the NOR group did not differ from the AMI group (6.78 ± 1.93 vs 6.27 ± 1.92, respectively).

The therapeutic success rate of the NOR group was significantly better than the AMI group ($P = .036$). In addition, the final VPS in the NOR group was lower

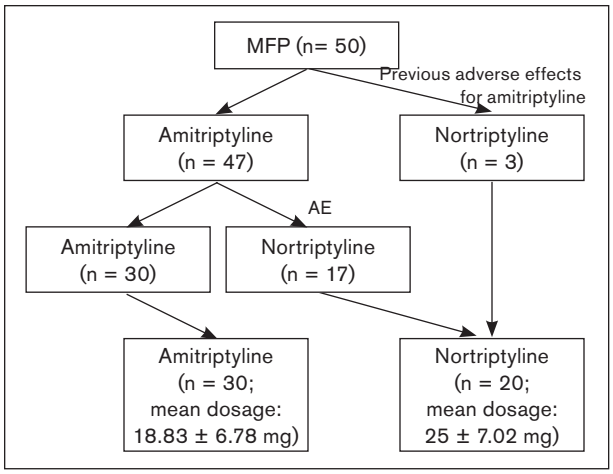

Fig 1 Participant flowchart.

Table 1 Characteristics of Nortriptyline (NOR) and Amitriptyline (AMI) Groups

	Total, n (%)	NOR, n (%)	AMI, n (%)	*P* value[a]
Gender				
Female	37 (74)	2 (10.0)	11 (36.7)	.034
Male	13 (26.0)	18 (90)	19 (63.3)	
Medical status				
Healthy	37 (74.0)	14 (70.0)	23 (76.6)	.428
Pain-related disability	13 (26.0)	6 (30)	7 (23.3)	
Dominant side				
Both sides	20 (40)	12 (60)	8 (40)	.617
Unilateral	30 (60)	18 (60)	12 (60)	
Trauma				
No trauma	39 (78)	17 (85)	22 (73.3)	.456
Microtrauma	5 (10)	2 (10)	3 (10)	
Macrotrauma	6 (12)	1 (5)	5 (16.7)	
Characteristics				
Pressure	44 (88)	16 (80)	28 (93.3)	.164
Stabbing	12 (24)	3 (15)	9 (30)	.191
Burning	4 (8)	3 (15)	1 (3.3)	.170
Pulsating	6 (12)	2 (10)	4 (13.3)	.544
Waken from pain				
Yes	13 (26)	3 (15.0)	10 (33.3)	.131

[a]Chi-square test.

Table 2 Binominal Regression Analysis of Therapeutic Success of Amitriptyline (AMI) vs Nortriptyline (NOR)

					95% CI for OR	
	B	SE	*P*	OR	Lower	Upper
NOR	2.07	0.88	.02	7.95	1.41	44.94
Gender	−0.71	0.77	.36	0.49	0.11	2.23
Dose	−0.08	0.05	.13	0.93	0.84	1.02
Medical status	2.35	0.90	.02	10.44	1.81	60.28
Constant	−0.71	1.20	.55	0.49		

All parameters found to be statistically significant in the univariate analysis were included in the regression analysis. After adjustment for dose and gender, significant factors were NOR (*P* = .02; OR = 7.95) and medical status (*P* =.02; OR = 10.45). SE = standard error; OR = odds ratio; CI = confidence interval.

Table 3 Therapeutic Success Rate (50% Reduction in Pain) and Drug Dosages Among Groups

	Baseline VPS	Final VPS	*P* value[a]	Drug dose	Patients ≥ 50% (within group), %
TCA	6.4 ± 1.75	2.92 ± 3.2	< .001	21.30 ± 7.46	52
AMI	6.27 ± 1.92	4.55 ± 2.92	.043	18.83 ± 6.78	40
NOR	6.78 ± 1. 93	2.83 ± 3.06	< .001	25 ± 7.02	70
P value[a]	NS	.039		.003	.036

TCA = tricyclic antidepressants (AMI + NOR); AMI = amitriptyline; NOR = nortriptyline; VPS = verbal pain scale.
[a]*t* test.

Table 4 Comparison of Numeric Variables According to Therapeutic Success Rate (≥ 50% Pain Reduction)

Success	All groups (n = 50)	Mean	*P value*[a]
Age (y)	36.33 ± 14.89		
< 50%		40.292 ± 16.09	NS
≥ 50%		32.673 ± 12.98	
NOS	3.66 ± 2.28		
< 50%		4.083 ± 2.45	NS
≥ 50%		3.269 ± 2.09	
Muscle index	1.40 ± 0.77		
< 50%		1.369 ± 0.73	NS
≥ 50%		1.437 ± 0.81	
Masseter tenderness to palpation (VPS)	1.74 ± 0.91		
< 50%		1.65 ± 0.83	NS
≥ 50%		1.83 ± 0.99	
Temporalis tenderness to palpation (VPS)	1.07 ± 0.93		
< 50%		0.09 ± 0.91	NS
≥ 50%		1.05 ± 0.96	
Duration of pain (mo)	19.76 ± 14.67		
< 50%		17.500 ± 14.12	NS
≥ 50%		21.846 ± 15.14	
Baseline VPS	6.4 ± 1.75		
< 50%		6.917 ± 1.76	NS
≥ 50%		6.058 ± 1.68	
Mouth opening (mm)	42.68 ± 8.93		
< 50%		41.583 ± 10.00	NS
≥ 50%		43.692 ± 7.90	
Drug dosage (mg)	21.30 ± 7.46		
< 50%		21.67 ± 5.30	NS
≥ 50%		20.96 ± 5.03	

NOS = number of surfaces; VPS = verbal pain scale.
[a]Comparison between ≥ 50% success (n = 26) and < 50% (n = 24); *t* test.

than the final VPS in the AMI group (2.83 ± 3.06 vs 4.55 ± 2.92, respectively; *P* = .039). The final VPS minus baseline VPS (ΔVPS) of the 26 patients from the AMI group (4 were missing final VPS) was lower than the ΔVPS in the NOR group (2.53 ≥ 3.66 vs 4.32 ≥ 2.53, respectively; *P* = .057). A total of 70% of the NOR group reached more than 50% improvement, with a final mean VPS of 1.000 ± .0377; only 51% of the AMI group reached a 50% improvement, with a final mean VPS of 2.711 ± 2.785.

Of the total cohort, 26 (52%) reported a ≥ 50% reduction in pain. The overall mean VPS at the end of treatment (2.92 ± 3.2) was significantly lower than at baseline (6.4 ± 1.75) (*P* < .0001) (Table 3).

No difference was found when comparing maximal drug dose of patients who had ≥ 50% success rate (20.96 ± 5.036) to patients who did not attain this level of improvement (21.67 ± 5.036) (Table 4). There was no significant difference in demographics, pain characteristics, or muscle pain index between patients who responded to NOR or AMI (Table 1) and those who did not respond to either medication (Tables 4 and 5).

Discussion

This study took place in a referral center that treats challenging and severe persistent cases. The mean baseline VPS score of the MFP patients was 6.4 ± 1.75, with a mean pain duration of 19.76 ± 14.67 months. These scores are higher than

the reported pain scores of 3 to 5 for MFP patients.[4] Chronicity is typical in severe MFP,[4,12] as observed in this cohort. Additionally, 26% of the patients in the present study had comorbid pain-related diseases; eg, fibromyalgia or migraine. This may suggest a systemic pain condition with underlying mechanisms of central sensitization or disturbed conditioned pain modulation,[38] which is common in more severe cases of MFP.[15] Of the patients included in the present study, 40% had bilateral pain, which is more common in MFP patients with generalized pain conditions, such as fibromyalgia or trauma, and is usually noted in more severe cases.[39,40] Mean spread of pain involved 3.66 ± 2.28 areas, indicating pain spread and referral, which may predict poorer therapeutic outcomes.[16]

Consequently, the present study focused on a group of patients with severe MFP that may require long-term pharmacologic prophylactic treatment. Studies estimate that up to 11%[41] or up to one-third[6] of all MFP patients experience such severe symptoms.

AMI has been consistently reported as beneficial for patients with masticatory myofascial pain,[14] and analgesic effects of low-dose AMI (10 to 30 mg/day) have been documented.[13] Although AMI is effective for MFP pain control, there are AEs at this low dosage—such as tiredness or weight gain—that have caused many patients to stop treatment. AMI's active metabolite, NOR, has a milder AE profile[34] and thus may be used at higher doses. NOR has been utilized for patients in psychiatric medicine and for other types of pain, especially neuropathic pain,[42] but no studies have been performed regarding NOR for MFP treatment. NOR and AMI have been compared for other disorders, such as depression[43,44] and postherpetic neuralgia,[34] but these comparisons were carried out at much higher doses than used in the present study. Interestingly, the choice to use AMI or NOR in different pain centers seems geographical and mostly based on expert opinion and personal experience rather than on efficacy.[45]

Table 5 Comparison of Nominal Variables According to Therapeutic Success Rate (≥ 50% Pain Reduction)

	Total	≥ 50%	< 50%	*P* value[a]
Gender				
Female	13 (26.0)	5 (19.2)	8 (33.3)	NS
Male	37 (74.0)	21 (80.8)	16 (66.7)	
Medical status				
Healthy	37 (74.0)	23 (88.5)	14 (58.3)	.024
Pain-related disease[b]	13 (26.0)	3 (11.5)	10 (41.7)	
Dominant side				
Both sides	20 (40)	9 (34.6)	11 (45.8)	NS
Unilateral	30 (60)	17 (65.4)	13 (54.2)	
Trauma				
No trauma	39 (78)	21 (80.8)	18 (75)	NS
Microtrauma	5 (10)	2 (7.7)	3 (12.5)	
Macrotrauma	6 (12)	3 (11.5)	3 (12.5)	
Characteristics				
Pressure	44 (88)	23 (88.5)	21 (87.5)	NS
Stabbing	12 (24)	7 (26.9)	5 (20.8)	NS
Burning	4 (8)	3 (11.5)	1 (4.2)	NS
Pulsating	6 (12)	3 (11.5)	3 (12.5)	NS
Waken from pain				
Yes	13 (26)	6 (23.1)	7 (29.2)	NS

[a]Comparison between ≥ 50% success (n = 26) and < 50% success (n = 24); chi-square test.
[b]Fibromyalgia, migraine, rheumatoid arthritis.

The overall therapeutic success rate (≥ 50% improvement) of TCA (AMI and NOR groups) was 52%, and the reduction in pain scores was significant. This suggests that TCAs are reasonably effective in the treatment of severe MFP. However, 40% of patients treated by AMI had AEs that limited dose adjustment and needed higher mean NOR dosages. Consequently, NOR achieved a significantly higher success rate in the treatment of MFP in terms of ≥ 50% pain reduction, as well as mean VPS reduction. Even though the mean dosage was significantly higher in the NOR group, it is possible that the mean plasma levels of the pharmacologically active elements were comparable.[46]

Study Limitations

While NOR seemed to be better tolerated at a higher dosage than AMI and the therapeutic results seemed to be better for the latter, these results should be carefully considered. The present study was not a randomized controlled trial, and the patients who received NOR were treated first with AMI, not randomly assigned to NOR treatment. Also, the groups of patients were relatively small and not fully balanced. Furthermore, the findings regarding severe MFP patients in the present study may not be applicable to the majority of MFP patients. Finally, there were significantly more females in the AMI group, and this was only partly solved by regression analysis.

Conclusions

It seems that TCAs are effective in about 50% of MFP patients with chronic MFP, high baseline pain scores, and high comorbidity. The somewhat better results achieved with NOR may be due to the ability to utilize a higher dose than AMI with less AEs. Nevertheless, the authors are unable to make any clinical recommendations at this

stage due to the study limitations mentioned above. A well-designed prospective study comparing NOR and AMI in MFP patients is therefore warranted.

Acknowledgments

The authors report no conflicts of interest.

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