Myofascial Pain: An Open Study on the Pharmacotherapeutic Response to Stepped Treatment with Tricyclic Antidepressants and Gabapentin

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Aims: To evaluate, in an open trial, the pharmacotherapeutic efficacy of tricyclic antidepressant (TCA) drugs and gabapentin in patients with persistent myofascial pain and to identify patient and pain characteristics that may predict treatment outcome. **Methods:** A stepped pharmacotherapeutic protocol was employed. All 42 patients having persistent facial pain with tenderness of regional muscles were first prescribed amitriptyline, but those with side effects were subsequently transferred to nortriptyline. In patients where no response to TCAs was observed, gabapentin was initiated. Outcome was assessed by employing prospective diaries recording pain intensity measured with an 11-point (0–10) verbal pain scale (VPS). Individual characteristics in these patients and their influence on drug response and outcome were analyzed; specifically, patients treated with TCAs were compared with those subsequently treated with gabapentin. Chi-square and *t* tests were used to analyze the data. **Results:** A total of 23 patients responded to TCAs and continued on this regimen, while 19 were resistant to TCAs and were subsequently treated with gabapentin. Their mean (± SD) VPS score at baseline was 6.5 ± 1.9 on an 11-point scale. In TCA-treated patients, 43% showed ≥ 50% reduction in pain intensity. This was achieved with a mean amitriptyline dose of 16 ± 1.1 mg/d and a mean nortriptyline dose of 25 ± 2.1 mg/d. Patients who did not respond to TCAs were characterized by a significantly higher age, more comorbid medical illness, and evidence of more regional pain spread ($P < .05$). In spite of not responding to TCAs, 36.8% of this group showed ≥ 50% reduction in pain intensity following gabapentin therapy at a mean daily dose of 973.7 ± 68.8 mg. Overall, a stepped approach employing TCAs and gabapentin resulted in 54.8% of all treated patients reporting improvements of ≥ 50% in VPS scores. **Conclusion:** This study has demonstrated the good pharmacotherapeutic response of persistent myofascial pain, even in more severe cases. Not being a randomized controlled trial, the results may be biased and should be interpreted with caution. Patients who do not respond to TCAs may be a distinct subgroup and this needs further investigation. The results also suggest that gabapentin, at a lower dose than previously reported, is a good alternative in TCA-resistant patients. *J Oral Facial Pain Headache 2015;29:144–151. doi: 10.11607/ofph.1408*

Key words: *amitriptyline, antiepileptic drug, myalgia, nortriptyline, orofacial pain*

Temporomandibular disorders (TMD) are 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] Typically, persistent myofascial pain (MFP) is located unilaterally, mostly at the angle of the mandible and the preauricular area. Pain is moderate in intensity, dull, pressing; increases on function; and may be associated with limitation in the range of mandibular movement.[3,4]

The etiology of pain and disability in MFP is understood via a biopsychosocial model reflecting a complex interaction between physical, behavioral, social, and psychological factors.[5] In turn, the treatment of MFP is often multimodal.[6,7]

The use of a tricyclic antidepressant (TCA), in particular amitriptyline, is one of the most accepted pharmacologic options. Amitriptyline, or its metabolite nortriptyline, is employed by many as the first choice in pharmacologic treatment of MFP.[8,9] In headache patients with myofascial tenderness, amitriptyline reduces both pain intensity and muscle tenderness.[10] It is well accepted that the analgesic effect of TCA on chronic pain is independent of its antidepressive action[9,11] and appears at significantly lower dosages (10 to 30 mg/d) than those required for depression (75 to 150 mg/d).[9]

While gabapentin is widely used for neuropathic pain in the facial area,[12] historically it has not been utilized for the management of MFP. However, gabapentin is superior to placebo in reducing pain reported by MFP patients.[13] Although this study has not been replicated, clinical experience supports the view that gabapentin is effective for the management of MFP. Gabapentin has therefore become an integral part of the authors' management protocol and has added a further dimension to the treatment of MFP.

Gabapentin has an attractive profile with fewer side effects and drug interactions than amitriptyline. Hepatic enzymes are unaffected and gabapentin has minimum binding capacity to plasma proteins.[14] Furthermore, gabapentin has no anticholinergic effect that typifies and limits the use of amitriptyline. Gabapentin can therefore be an attractive alternative for the treatment of MFP in patients who do not respond to TCA or could not tolerate TCA due to side effects.

The aim of the present study was to evaluate, in an open trial, the pharmacotherapeutic efficacy of TCA drugs and gabapentin in patients with persistent MFP and to identify patient or pain characteristics that may predict treatment outcome. This was an open study and as such suffers from the possibilities of bias and other issues, as explained in the discussion section.

Materials and Methods

All patients were interviewed and examined at the Orofacial Pain Clinic, Faculty of Dentistry, Hadassah–The Hebrew University, Jerusalem. The patients were treated with medications as their sole modality. Over a period of 4 years, 42 such patients attending the clinic were interviewed and data collected at the first visit before medications were prescribed. The resultant data, including a standard pain history, were recorded on an intake form. The institutional review board approved the study and informed consent was obtained from all participating patients.

Patients were asked to rate pain quality and average pain intensity over the previous week. Pain quality was assessed by asking the patients to choose one or more of the following descriptive terms: electrical, stabbing, throbbing, pressure, burning, or any combination of the five terms. These five arbitrary terms are in routine use in the authors' clinic to provide rapid assessment of pain quality.[4,15] Pain intensity was rated by employing a verbal pain scale (VPS) in which 0 was no pain and 10 the worst imaginable pain. For follow-up, pain diaries were employed so that accurate data on the VPS and treatment were available. Regional spread of pain was mapped out onto a diagram of the head and neck, with seven affected areas identified anatomically: preauricular/auricular, angle of the mandible, body of the mandible, maxillary, temporal, suboccipital, and submandibular. These individual areas were awarded a score of 1 and added up to create a score representative of the spread of pain.[16] Pain that began following a clear traumatic event was defined as "posttraumatic" and divided into macrotrauma (road traffic accidents and altercations) and microtrauma (dental surgery: invasive or prolonged interventions).

Patients were also asked a standardized question about whether the pain specifically wakes them from sleep. Answers to this question were carefully interpreted so as to ensure that the patient was reporting awakening specifically related to pain. In this manner random awakenings (to drink water, or for micturition) were excluded; for example, when the patient reported that pain was coincidentally present but had not been the reason for awakening.[15]

Clinical Examination

The masticatory apparatus (TMJs and masticatory muscles) and neck muscles were examined for sensitivity to palpation. The following muscles were examined bilaterally: masseter, temporalis, medial pterygoid, lateral pterygoid, suboccipital group (as one), sternocleidomastoid, and trapezius. Muscle palpation was performed with about 1 to 4 kg of digital pressure.[4,15,17–19] Examiners were calibrated on electronic scales to reliably judge this level of digital pressure. Tenderness to palpation was graded on an ordinal scale: 0 (no pain), 1 (mild), 2 (moderate), and 3 (severe), and the individual scores summated to give the total tenderness score (muscle tenderness score) for each patient.[4,15,20–22] The muscle tenderness score, also known as the total tenderness score in the literature, is commonly used in headache practice for the assessment of pericranial muscle tenderness and adds valuable information beyond the number of involved muscles.[23] The current criteria[19] for the diagnosis of muscle pain require only the examination of the masseter and temporalis muscles bilaterally. However, these patients were examined over a period of 4 years prior to publication of the revised criteria.

Inclusion Criteria and Pain Diagnosis

Diagnoses were established according to the Research Diagnostic Criteria for Temporomandibular Disorders[24]; these have been recently updated.[19] Inclusion criteria comprised a complaint of persistent facial pain, present for a minimum period of 3 months with tenderness in the regional muscles that could reproduce pain. All diagnoses were confirmed by both senior authors (RB, YS).

Exclusion criteria were referred pain from the TMJ and regional pain syndromes such as neuropathic or neurovascular disorders. Patients were also excluded if they suffered from other pain syndromes (eg, fibromyalgia, migraine), refused pharmacotherapy, or had pain originating from the masticatory muscles that was not treated with medications.

Pharmacotherapeutic Protocol

Consistent with the protocol used in the authors' clinic, a stepped pharmacotherapeutic approach was used. Patients diagnosed with MFP with referral were started on amitriptyline 10 mg daily at bedtime and their status was reviewed at 2 weeks. At this or any time during treatment, patients with clinical improvement but intolerable side effects were initially transferred to nortriptyline 12.5 mg daily at bedtime. For both drugs, the dose was subsequently titrated according to the patient's response and reported side effects. A lack of any change in pain intensity following 4 weeks of TCA treatment at a dose of 25 to 35 mg daily was an indication to offer alternate therapy. Patients with a lack of response or intolerable side effects to either of the TCA drugs were transferred to gabapentin. Gabapentin treatment was initiated at 300 mg daily at night, and patients were instructed to increase the dose every third day by 300 mg. The initial target dose was 900 mg taken in three daily doses. Patients experiencing severe side effects or significant improvement during this phase were instructed to stay on the dose that was being prescribed. Following this, patients were titrated on increasing doses of gabapentin as dictated by their response and side effects. At 20 weeks of pharmacotherapy, pain levels were recorded from the pain diaries.

Improvement during treatment was judged as simply a lower pain score. Once the study was completed, the level of improvement was calculated using the pain diaries. Significant improvement was defined as $\geq$ 50% decrease in baseline pain scores.

Patients were not referred to or instructed to perform home care, physiotherapy, or other interventions so as to isolate the effects of pharmacotherapy.

Statistical Analyses

Data were analyzed with SPSS (version 21 for Mac, IBM) with two-tailed α for significance set at .05. Associations between nominal variables were analyzed with Pearson chi-square (χ^2) test. For analysis, data from patients treated with amitriptyline and nortriptyline were pooled into one group referred to as TCA. Differences according to drug response were examined versus the second group, which was finally treated with gabapentin (referred to as GBP). The association between drug response and various demographic and pain-related parameters was analyzed with a *t* test (T). The VPS ratings at baseline and at the end of specific drug therapy were examined with a paired *t* test (paired T). Results in text and tables are expressed as the mean and standard deviation.

Results

Patients and Drug Groups

A total of 176 patients with a diagnosis of MFP with referral[19] were examined during the years 2010 to 2013. Of these, 66 had no satisfactory follow-up and 68 had been treated with no medications or in a multimodal fashion.

Forty-two patients met the inclusion criteria, and all of them initially received amitriptyline. These patients consisted of 31 females (74%) and 11 males (26%), with a mean age ± SD of 37.4 ± 15 years and a mean disease duration of 25 ± 30 months. Of these, 13 patients completed the study period while on amitriptyline. In 14 patients there was no report of any improvement in spite of relatively higher dosages (25 to 35 mg) and they were therefore shifted directly to gabapentin (Fig 1). A further 15 patients reported intolerable side effects at the starting dose (10 mg) and were shifted to nortriptyline. Side effects requiring such drug change occurred at 2 to 4 weeks. Ten of these patients completed the study while on nortriptyline. However, 5 of the 10 did not improve on nortriptyline and were shifted to gabapentin (n = 5). Thus, at the end of the study there were 23 patients who received TCAs (13 amitriptyline + 10 nortriptyline) and 19 patients who received gabapentin (see Fig 1).

To analyze the therapeutic success of TCAs versus gabapentin (ie, reduction in VPS), data from all the patients who had received TCAs (both amitriptyline and nortriptyline) were analyzed together (ie, n = 42) and the data from the 19 patients who were transferred from TCA to gabapentin were analyzed separately. Note that in this manner, patients who subsequently demonstrated resistance to TCAs were included in the analysis of the overall TCA effect.

To examine if the patients who were resistant to the TCAs (n = 19) were in any way different from the patients who responded to the TCAs (n = 23), various factors between the 23 patients who remained

on TCAs (TCA group) and the 19 that were transferred to gabapentin (GBP group) were compared.

Patient Demographics and Comorbidities

The mean patient age of the TCA group (32.7 ± 14 years) was significantly lower than that of the GBP group (43.2 ± 15 years, T: $t = -2.3$, $df = 40$, $P = .02$); Table 1. There were 17 females and 6 males in the TCA group and 14 females and 5 males in the GBP group (χ^2: $P > .05$).

Comorbid medical conditions were reported by 3 patients (13%) in the TCA group and by 9 patients (47.4%) in the GBP group (χ^2: $\chi = 6$, $df = 1$, $P = .01$). Positive reports of chronic pain in other body regions were not significantly different between the TCA and GBP groups (17.4% and 21.1%, respectively, χ^2: $P > .05$). Pain onset associated with trauma was reported by 17.4% of TCA patients and 31.6% of GBP patients, but this was not statistically significant (χ^2: $P > .05$). There was no difference in the distribution of micro- and macrotrauma between the drug groups (χ^2: $P > .05$; Table 1).

Pain-Related Parameters

Baseline VPS was not significantly different between the TCA (6.5 ± 1.9) and GBP (6.7 ± 1.7, T: $P > .05$) groups. Only one patient, from the TCA group, reported pain-related awakenings. Bilateral pain was reported by 69.6% (n = 16/23) of TCA patients and 58% (n = 11/19) GBP patients (χ^2: $P > .05$). None of the pain-quality descriptors or their combinations was significantly different between the two groups (χ^2: $P > .05$). Baseline interincisal mouth opening was not significantly different between the TCA and GBP groups (43.9 ± 8.1 mm versus 39.7 ± 9.9 mm, T: $P > .05$).

Regional pain spread, as measured by the areas involved, was significantly higher in the GBP group (5.1 ± 2.7) relative to the TCA group (3.3 ± 1.9, T: $t = -2.5$, $df = 40$, $P = .02$). Overall muscle tenderness as reflected by the total tenderness score was not significantly different between the TCA and GBP groups (11.4 ± 8.2 versus 13.2 ± 9.7, T: $P > .05$). Duration of disease as measured by months since onset was not significantly different between the TCA and GBP groups (30.3 ± 38.1 months versus 18.5 ± 14.6 months, T: $P > .05$; Table 1).

Treatment Outcomes

Patients treated with TCA. The VPS scores in the TCA group (n = 42) were significantly lower at the end of the treatment period than at baseline (3.9 ± 3.1 versus 6.5 ± 1.9, paired T: $t = 5.01$, $df = 41$, $P < .0001$). The TCAs induced a mean improvement in VPS scores of 36.8% ± 46.1% (range: −50% to 100%; Fig 2a), and 43% of the group (n = 18/42) reported improvements of ≥ 50% in VPS scores. These statistics include data for the patients who were transferred to gabapentin and for those who remained on a TCA until the end of the study period.

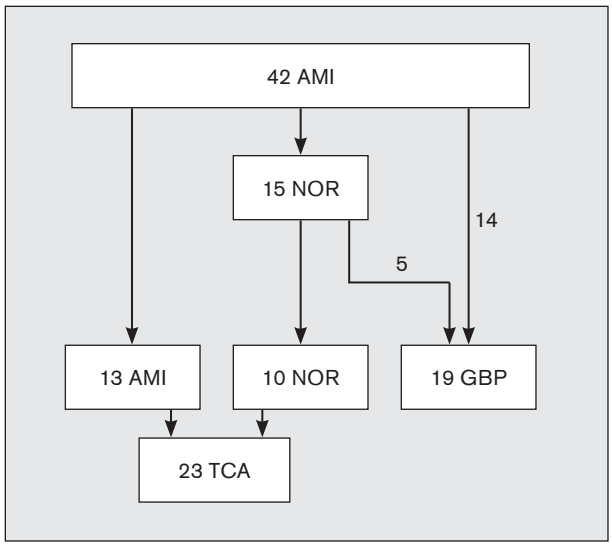

Fig 1 Flowchart of stepped care as delivered in the clinic. All patients were initially treated with amitriptyline (AMI, n = 42). Fifteen patients with subsequent side effects were transferred to nortriptyline (NOR). In patients treated with AMI or NOR, 19 had no response and were transferred to gabapentin (GBP). In total, 23 patients were treated with tricyclic antidepressants (AMI = 13, NOR = 10) and 19 with gabapentin.

Table 1 Demographic and Pain Characteristics

	TCA (n = 23)	GBP (n = 19)	Significance *(P)*
Male / Female	17 / 6	14 / 5	NS
Mean age ± SD (y)	32.7 ± 14	43.2 ± 15	.02
Comorbid medical status	13.3% (n = 3)	47.4% (n = 9)	.01
Body pain	17.4% (n = 4)	21.1% (n = 4)	NS
Disease duration (mo)	30.3 ± 38.1	18.5 ± 14.6	NS
Trauma associated	17.4% (n = 4)	31.6% (n = 6)	NS
Bilateral pain	39.6% (n = 16)	58% (n = 11)	NS
Mouth opening (mm)	43.9 ± 8.1	39.7 ± 9.9	NS
Regional pain spread*	3.3 ± 1.9	5.1 ± 2.7	.02
Tenderness score	11.4 ± 8.2	13.2 ± 9.7	NS

*No. of areas involved.
TCA = tricyclic antidepressant, GBP = gabapentin, NS = not statistically significant.

Patients subsequently treated with GBP. The GBP group (n = 19) included patients who were nonresponsive to TCA treatment. In these patients, VPS scores at the end of gabapentin treatment (4.8 ± 2.1) were significantly lower than at baseline (6.7 ± 1.7, paired T: $t = 5.3$, $df = 18$, $P < .0001$). Gabapentin improved VPS scores by a mean of 28.6% ± 24.3% (range: −23% to 69.2%; Fig 2b), and 36.8% of the group (n = 7/19) reported improvements of ≥ 50% in VPS scores. The mean improvement rates in the

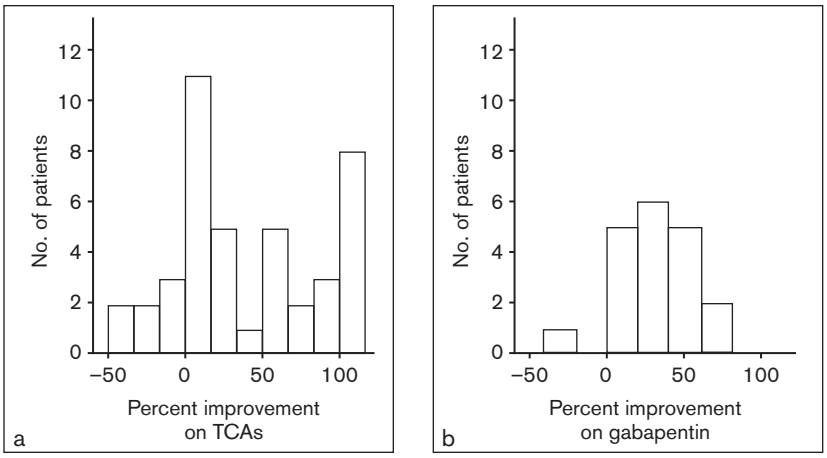

Fig 2 **(a)** Distribution of percent improvement in all patients treated with tricyclic antidepressants (n = 42). This included the 19 patients subsequently treated with gabapentin. **(b)** Distribution of percent improvement in patients treated with gabapentin (n = 19).

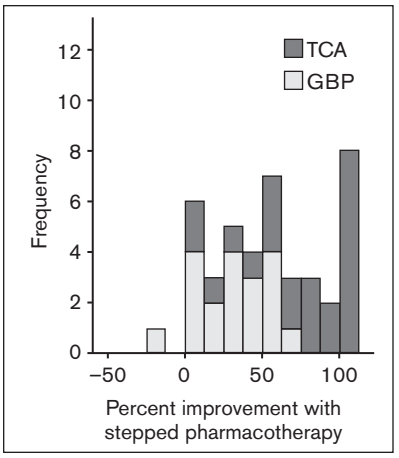

Fig 3 Distribution of percent improvement in all patients treated in the clinic. This included patients receiving TCA treatment for the duration of the study (n = 23) and those transferred to gabapentin (n = 19). The data show the success rate of the pharmacotherapeutic protocol when employed as monotherapy. TCA = tricyclic antidepressant, GBP = gabapentin.

TCA and GBP groups were not significantly different (paired T: $P > .05$).

There were no significant differences in demographic or pain characteristics in the patients who responded to gabapentin (n = 7) and those who did not (n = 12, $P > .05$).

Overall Patient Success with Stepped Care

When the VPS data at the end of treatment were analyzed as one group (ie, VPS values from the TCA and GBP groups analyzed together) so as to reflect success in using both drug modalities, the mean VPS score was significantly lower at the end of treatment (3.1 ± 2.5) than at baseline (6.5 ± 1.9, paired T: $t = 8.3$, $df = 41$, $P < .0001$).

The use of both TCAs and gabapentin resulted in an average improvement in VPS scores of 51.1% ± 35.6% (range: –23% to 100%; Fig 3). Of the 42 patients, 54.8% (n = 23) reported improvement of ≥ 50% in VPS scores. These values reflect the overall success rate of the clinic in providing pain relief by using a stepped-care approach for patients with MFP.

Dosages and Side Effects

The mean amitriptyline dosage in the whole group was 16 ± 1.1 mg/d (range 10 to 35 mg, n = 42). The mean amitriptyline dose was not significantly different between the TCA responders (14.4 ± 7 mg, n = 23) and the TCA nonresponders (ie, GBP group, 17.9 ± 6.5 mg, T: $P > .05$). Side effects were reported by 47.6% (n = 20) of patients who had received amitriptyline; they included tiredness (28.6%), weight gain (9.5%), and both of these side effects (2.4%). Rare side effects included depression, hot flushes, and breathlessness (one each, total 7.1%). The mean nortriptyline dosage in the 15 patients receiving this TCA was 25 ± 2.1 mg/d (range 12.5 to 50 mg), with no significant difference between the TCA (25 ± 10 mg, n = 10) and GBP groups (25 mg ± 0, n = 5, T: $P > .05$). Gabapentin was used in dosages ranging from 300 to 1,800 mg daily with a mean of 973.7 ± 68.8 mg (n = 19); 3 patients (15.8%) complained of tiredness and 2 of weight gain (10.5%). Rare side effects included pruritus and tongue pain (1 patient each, total 10.5%).

Discussion

The Orofacial Pain Clinic participating in this study is a secondary or tertiary referral center and usually attracts therapeutically challenging and severe cases. This explains the focus of the clinic on pharmacotherapeutic and multimodal approaches to management. The mean baseline pain score of 6.5 clearly demonstrates the severity of pain in this patient sample. Similarly, in a previous report on MFP patients from this clinic, the mean pain intensity score was also high at around 7 on a 0 to 10 scale.[18] These pain scores are higher than those in the literature, usually reported as 3 to 5 on a 10-cm visual analog scale.[3,25]

Employing a stepped pharmacotherapeutic protocol with amitriptyline/nortriptyline and gabapentin as monotherapy provided ≥ 50% improvement in pain levels for about 55% of the study population. This is encouraging in such a challenging group of patients. The positive effect of low-dose amitriptyline (10 to 30 mg/d) on MFP has been documented,[9] and amitriptyline has been consistently reported as beneficial for patients with predominantly muscular TMD,[8] posttraumatic MFP,[26] and headache with myofascial tenderness.[10] Amitriptyline may be used at higher doses (eg, 75 mg daily[10]), but severe side effects appear at doses beyond 35 to 50 mg that prevent treatment. In a group of patients with chronic facial pain, an average dose of 25 mg amitriptyline was as effective in its analgesic results as 130 mg.[9] Side effects are dose-dependent, and patients on 25 mg daily of amitriptyline will gain a mean of 3.2 kg over 12 weeks.[27] The risk of sudden death increases by 40% at doses of amitriptyline above 100 mg daily.[28]

Although the protocol employed amitriptyline as first-line therapy, this caused side effects in 36% of patients (n = 15) that were significant enough to warrant a change in medication. Of these patients who were transferred to nortriptyline, none developed significant side effects and 10 completed the study on nortriptyline. This indicates that nortriptyline is the TCA of choice, and the authors' clinical protocol has been adjusted accordingly.

Pharmacotherapy has the advantage of being an inexpensive and rapid modality relative to other accepted options such as active physiotherapy, bite splints, and behavioral interventions. Additionally, with drugs such as amitriptyline and gabapentin, patients often report an immediate improvement in sleep. Combining treatment options may allow for the targeting of specific problems, such as restricted range of motion, and result in even better outcomes.

When assessing treatment outcomes in patients with MFP, the natural history of the disorder should be accounted for. Such patients are characterized by significant fluctuations in reported symptoms and recorded signs.[29,30] Without a randomized controlled design it is possible that some of the patients with good therapeutic outcomes in the present study may have spontaneously improved rather than responded to medication. In one 5-year study, 33% of MFP patients remitted, a further 36% displayed a recurrent pattern, and the remaining 31% displayed a persistent and unremitting clinical course.[30] Their analyses indicated that baseline pain frequency, number of painful palpation sites, and total number of body sites with pain were significant predictors of persistent versus remitted and recurrent cases.[30] Both groups of patients in the present study had a mean disease duration of 25 ± 30 months, which suggests that they may have belonged to the unremitting type of patient profile. This does increase the level of confidence in the present results, but as stated, the lack of a randomized controlled design does limit the conclusions that may be drawn.

In addition, the placebo effect within the groups in the present study remains unknown. However, a previous study[9] observed that amitriptyline was superior to placebo in relieving pain after 4 weeks. Moreover, an early effect after 1 week was not apparent, indicating that the placebo effect on pain is high at the early period of drug administration and then decreases with time. On the other hand, the drug effect increases with time.[9] In the present study, patients were followed up for a total of 20 weeks and based on the above, the placebo effect would be minimal. In long-term investigations such as the present study, regression to the mean needs to be considered before any conclusions can be made.

Nonetheless, there are a number of interesting findings in the present study that have practical applications to the treatment setting. In 36.8% of the 19 patients who were resistant to TCA therapy, gabapentin was able to provide ≥ 50% improvement in pain scores. Gabapentin has been reported to be superior to placebo in reducing reported pain, masticatory muscle hyperalgesia, and the impact of MFP on daily functioning; reduction in muscle tenderness was observed after 8 weeks and the effects on pain appeared only after 12 weeks of therapy at a mean dose of gabapentin of about 3,400 mg daily.[13] In contrast, the present study revealed a significant effect in the gabapentin-responsive patients at a mean dose of about 1,000 mg, but this was also delayed and appeared only after about 6 to 8 weeks. Gabapentin should therefore have a clear place in the treatment of MFP and is an option when TCAs have failed. Even with a delayed onset, it offers an alternative in a situation where few others are available.

The significant differences between the group treated with gabapentin (resistant to TCAs) and the patients who responded to TCAs were increased age, more comorbid chronic medical illnesses, and evidence of more widespread regional pain. Comorbid medical illness is age-dependent, and one of these may therefore have been a related confounding factor. Alternatively, taking all three factors together, the group taking gabapentin may have signified patients at a different disease stage. Comorbid illness is common in patients with MFP and particularly in more severe cases.[31] The more widespread regional pain may indicate more prominent central sensitization. This needs to be tempered by the fact that there were no increased complaints of pain in other body regions and no differences in disease duration and pain severity—all factors that would contribute to or reflect central sensitization.

The pharmacologic mode of action of gabapentin is well suited to situations in which central sensitization is suspected. Gabapentin is thought to act primarily via blockade of L-type calcium channels, which modulate neurotransmitter release, and thus inhibits glutamate release in the spinal cord.[32] Gabapentin is therefore a good choice when central sensitization may be present.[33–35] Since there is evidence of prominent central sensitization in MFP patients,[13,33] gabapentin may be a good option for them, and patients with more regional spread of pain and medical comorbidities also may respond well to gabapentin.

Study Limitations

The major limitation of the present study was that it was not a randomized controlled study and so the results may be biased. A further aspect of studies on patients with MFP is the significant fluctuation of symptoms in this group of patients. Improvement may be due to spontaneous remission of symptoms rather than treatment effects. On the other hand, these patients are a select group with long-lasting pain and other symptoms that may last on average around 2 years. These are possibly the subgroup of MFP patients characterized by persistent unrelenting pain.[29,30] Further limitations include the small sample size and the fact that the analysis focused on only the pain intensity aspect of a chronic pain syndrome that is accompanied by both physical and emotional dysfunction.

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The authors report no conflicts of interest related to this study.

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