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Analgesic action of gabapentin on chronic pain in the masticatory muscles: A randomized controlled trial

Pablo Kimos [a], Catherine Biggs [a,b], Jennifer Mah [b], Giseon Heo [c], Saifudin Rashiq [d], Norman M.R. Thie [a], Paul W. Major [c,*]

[a] TMD/Orofacial Pain Clinic, Department of Dentistry, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alta., Canada
[b] Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alta., Canada
[c] Orthodontic Graduate Program, Department of Dentistry, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alta., Canada
[d] Department of Anesthesiology and Pain Medicine, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alta., Canada

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Abstract

Chronic masticatory myalgia (CMM) can be defined as constant pain in the masticatory muscles for more than 6 months and is influenced by the central nervous system. The antiepileptic agent gabapentin acts centrally and is used for managing different types of chronic pain conditions. The objective of this study was to evaluate the analgesic action of gabapentin on CMM. In this 12-week randomized controlled clinical trial 50 patients were randomly allocated into two study groups: 25 received gabapentin and 25 received placebo. The outcome measures utilized were pain reported on a VAS (VAS-pain), Palpation Index (PI) and impact of CMM on daily functioning reported on a VAS (VAS-function). Thirty-six patients completed the study. Gabapentin showed to be clinically and statistically superior to placebo in reducing pain reported by patients (gabapentin = 51.04%; placebo = 24.30%; $P = 0.037$), masticatory muscle hyperalgesia (gabapentin = 67.03%; placebo = 14.37%; $P = 0.001$) and impact of CMM on daily functioning (gabapentin = 57.70%; placebo = 16.92%; $P = 0.022$). It can be concluded from this study that gabapentin is effective for the management of CMM.

Keywords: Gabapentin; Chronic muscle pain; Orofacial pain; Masticatory muscles; TMD; Antiepileptic agents

1. Introduction

Orofacial pain affects millions of people every year. It has been reported that 40% of all chronic pain cases seen in pain clinics are located in the craniofacial and cervical regions (Donaldson and Kroening, 1979). The study of orofacial pain encompasses a variety of conditions, including temporomandibular disorders (TMD), facial neuropathic pain and headaches. TMD are musculoskeletal disorders of the masticatory system. Chronic masticatory myalgia (CMM) is part of the myogenous disorders under the TMD family.

The pathophysiology of CMM and other chronic musculoskeletal conditions is not completely understood, and it is thought to be a problem with a multifactorial pathophysiology. Like other chronic muscle pain problems such as fibromyalgia, CMM is thought to be highly influenced by central nervous system (CNS) effects associated with central sensitization (Sessle, 1995). CMM becomes a central pain perception problem, rather than a local muscle tissue injury (Carlson et al., 1998). However, peripheral and psychogenic

* Corresponding author. Tel.: +1 780 492 7696; fax: +1 780 492 1624.
E-mail address: major@ualberta.ca (P.W. Major).

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factors have also been suggested to influence this condition (Kinney et al., 1992; Butt et al., 1998; Carlson et al., 1998; Hedenberg-Agnusson et al., 2001; Yap et al., 2002).

CMM often presents with constant pain in the masticatory muscles with no periods of intermission, which increases with mandibular function (Dworkin and LeResche, 1992). No inflammatory signs are present. CMM usually interferes with daily activities such as talking, eating or laughing. In many cases, an overlap between CMM and fibromyalgia is found (Plesh et al., 1996; Aaron and Buchwald, 2003).

Pharmacological approaches are often used to control pain and provide patients with better daily functioning. Tricyclic antidepressants (TCAs) have been widely used to treat chronic pain problems of myogenous origin, such as fibromyalgia and chronic TMD (Diamond and Baltes, 1971; Pilowsky et al., 1982; Goldenberg et al., 1986; Sharav et al., 1987; Zitman et al., 1990; O'Malley et al., 2000; Heymann et al., 2001). Antiepileptic agents and opioid drugs have also been used to manage chronic orofacial pain.

Gabapentin is a new generation antiepileptic agent, which acts in the central nervous system (CNS). This medication has been used to manage different chronic pain conditions (Rowbotham et al., 1998; Serpell, 2002) including orofacial pain problems, such as trigeminal neuralgia, migraine headaches and atypical facial pain (Schachter and Sauter, 1996; Cerbo et al., 1997; Lucier and Franm, 1997; Sist et al., 1997a,b; Khan, 1998; Merren, 1998; Valzania et al., 1998; Childs et al., 2000; Di Trapani et al., 2000; Fragoso and Carrazana, 2000; Mathew et al., 2001; Moretti et al., 2002; Spira and Beran, 2003).

To date, there are no clinical trials reported in the literature evaluating the analgesic efficacy of gabapentin specifically on CMM. Although there are a few published reports regarding the use of gabapentin on myogenous pain (van Deventer and Bernard, 1999; Gustorff et al., 2002; Nguyen and Lawrence, 2004), higher levels of evidence are required to support the clinical use of gabapentin in orofacial pain conditions, including CMM. Therefore, we have conducted a randomized controlled trial (RCT) to assess the analgesic action of gabapentin on chronic pain in the masticatory muscles.

2. Materials and methods

2.1. Study design

This study was a double-blind, randomized controlled clinical trial. A computer-generated randomization code list was utilized to randomly allocate patients in two study groups. For double-blinding purposes, concealed randomization and the according allocation were implemented by a research assistant. Neither the patients nor the main investigator was aware of the random group allocation.

One group received gabapentin and the other group received placebo. For double-blinding purposes the active and placebo medications were packed in identical looking capsules by the pharmaceutical company that donated the study medication. Both, active medication and placebo capsules were packed in identical clear bottles labelled according to Investigational Pre-Packing Control Records, established by Section C.05.011 of the Food and Drug Regulations. These labels did not affect the blinding process because neither the investigator nor the patients were aware of the medication codes. Non-used capsules of gabapentin and placebo were destroyed at the end of the trial by the Department of Pharmacy at the University of Alberta.

This clinical trial ran for 12 weeks. It was carried out in the TMD/Orofacial Pain Clinic, Department of Dentistry at the University of Alberta. Scores derived from outcome measures were recorded by the same investigator (PK), who ran all the tests involved in this study. On the initial visit baseline scores were recorded and the study medication was provided. Patients were expected to return for two follow-up visits and one final visit every 30 days after the initial appointment. At each visit, data derived from the outcome measures were recorded. The final visit was at week 12.

2.2. Patients

The protocol for this study was approved by the University of Alberta Human Research Ethics Board and by Health Canada. Sample size calculation identified a sample size of 50 patients to obtain a power of 0.80. Females from 18 to 45 years old were recruited because TMD problems are significantly prevalent in this population group (Solberg et al., 1979; Pullinger et al., 1988; Von Korff et al., 1988; Agerberg and Inkapool, 1990; Dworkin et al., 1990; De Kanter et al., 1993; Magnusson et al., 1993; de Leeuw et al., 1994).

Subjects for this clinical trial were recruited from four main sources. Patients from the existing patient pool and patients seeking treatment at the TMD/Orofacial Pain Clinic were considered for participating in the study. In addition, dentists and physicians within the city of Edmonton and surrounding areas were contacted by mail requesting referral of patients who presented symptoms of CMM for screening at the TMD/Orofacial Pain Clinic. Newspaper advertisements in Edmonton and poster advertisements at the University of Alberta Campus were also utilized to recruit subjects. Subjects coming from any of these three sources were screened by the main investigator to verify if they met our inclusion/exclusion criteria prior to being enrolled in the study.

The following inclusion criteria were utilized:

- Diagnosis of masticatory muscle pain based on the diagnostic classification of Dworkin and LeResche (Dworkin and LeResche, 1992), "patients must present constant pain or ache in their masticatory muscles, face, and preauricular area or inside the ear at rest or during function."
- Masticatory muscle pain for at least 6 months.

- Chronic masticatory muscle pain not attributable to recent acute trauma or previous infection.
- Chronic pain in the masticatory muscles not attributable to an active inflammatory cause.
- Moderate to severe baseline score of 50 mm or greater using a 100 mm VAS. According to Collins et al. (1997) moderate pain is considered to be approximately 30 mm in the 100 mm VAS. In this study it was decided to set a minimum baseline score of 50 mm in order to be able to identify a clinically significant difference after treatment.
- Pain upon palpation in at least three of the following points proposed by Fricton and Schiffman (1986, 1987) and Fricton et al. (1988): Temporalis (anterior, medial and posterior bellies). Masseter (deep belly, and the inferior and anterior portion of the superficial belly).

The following exclusion criteria were also applied:

- Clinical evidence of inflammatory TMD;
- Pregnant or nursing females;
- Epilepsy, cardiac, renal or hepatic disorders;
- History of intolerance to gabapentin or to any of the components of the formulation;
- Dental or periodontal disease, oral pathology lesions, oral infection, or neuropathic facial pain;
- Patients wearing an occlusal splint appliance for less than 6 months were excluded.

Subjects were asked to discontinue any pain medications such as muscle relaxants, anti-inflammatories or combination drugs (i.e., acetaminophen and narcotics). In those cases in which an analgesic medication was required to be discontinued, patients were asked to return for a second visit after a washout period. The washout period was based on the half-life of the drug. If subjects were taking other medications (such as TCAs, benzodiazepines, specific serotonin re-uptake inhibitors (SSRIs)) on a regular basis for more than 2 months, they were allowed to participate in the study as long as there were no changes in dosage of these medications during the course of the trial. In addition, other medications that could influence pain, such as hypnotics, were not allowed to be introduced during the course of the study.

2.3. Objectives and null hypotheses

The primary objectives of this study are described as follows:

- To compare the effectiveness of gabapentin versus placebo on reducing pain intensity reported by subjects with CMM, after 12 weeks.
- To compare the effectiveness of gabapentin versus placebo on reducing palpable tenderness in masticatory muscles, in subjects with chronic masticatory myalgia after 12 weeks.

The secondary objective of this study was to compare the effectiveness of gabapentin versus placebo on reducing the impact of chronic pain on daily functioning, reported by these subjects after 12 weeks.

Our null hypotheses are described as follows:

- Gabapentin is equally or less effective than placebo for reducing chronic masticatory muscle pain intensity reported by subjects.
- Gabapentin is equally or less effective than placebo for reducing pain on extraoral palpation of the masticatory muscles in those subjects experiencing chronic masticatory myalgia.
- Gabapentin is equally or less effective than placebo for reducing the impact of chronic masticatory myalgia in the patient's daily functioning.

2.4. Outcome measures

Three outcome measures were evaluated at the initial visit (baseline), at week 4 (second follow-up visit), at week 8 (third follow-up visit) and at week 12 (final visit).

2.4.1. VAS-pain

CMM pain intensity reported on a 10 cm VAS (VAS-pain). Subjects were asked to report the average pain intensity experienced in the previous week on a VAS. The validity and reliability of these methods for determining pain intensity have been confirmed (Scott and Huskisson, 1976; Chapman and Syrjala, 1990; Wewers and Lowe, 1990; Jensen and Karoly, 1992). The VAS utilized was 100 mm long with both ends labelled with the two extreme boundaries of pain sensation: "no pain", at one end and "worst pain imaginable" at the other end. Moderate pain was considered to be over 30 mm, and severe pain over 54 mm (Collins et al., 1997). A pain reduction of 30% on the 100 mm VAS from the baseline pain score was considered to be clinically significant (Farrar et al., 2001).

2.4.2. Palpation Index (PI)

The number of tender sites in the masticatory muscles was recorded before and after the study. Six sites were palpated bilaterally in this study: anterior temporalis, medial temporalis, posterior temporalis, superior masseter, inferior masseter, and deep masseter. These palpation sites have been validated for research purposes (Fricton and Schiffman, 1986, 1987; Fricton et al., 1988). The patient's response was recorded to be positive if it was reported below the normal threshold value for the palpated site. A response was considered negative when reported to be equal to or higher than the normal threshold value of the palpated site. The normal pain threshold values for the masticatory muscles utilized in this trial were based on those reported by Chung et al. (1992) obtained from healthy females (mean age 22.9 years) with no TMD or orofacial pain conditions. A value of "1" was assigned to positive responses and "0" to negative responses. The difference between the number of total positive responses at the initial visit and final visit (week 12) was obtained. An algometer was utilized to perform palpation. This instrument allows the application of pressure over a specific area at a constant, invariable rate, thereby approaching standardization (Lasagna, 1962). Clinical inter-reliability and validity of pressure algometry have been reported (Reeves et al., 1986; Fischer, 1987; Brown et al., 2000; Visscher et al., 2004).

2.4.3. VAS-function

Although not a primary objective of this study, CMM interference with daily function was also assessed in order to have a general idea if gabapentin therapy may also help by improving daily functioning. This was recorded on a 10 cm VAS (VAS-function). Patients were trained to understand that one end of the scale represented no impact at all and the other end was representative of extreme or severe impact, reflecting disability.

2.5. Medication dosing

Gabapentin was administered until adequate pain control was reached or unacceptable side effects limited titration (Mao and Chen, 2000; Backonja and Glanzman, 2003). In order to avoid side effects, provide adequate pain control, and diminish as much as possible the number of drop outs from the study; the minimum effective dose for each patient was determined. Patients were started on 300 mg per day and the dose was increased by 300 mg every 3 days until pain was controlled with no adverse effects. The maximum dose was 4200 mg. Data from previous clinical trials suggest that doses higher than 1200 mg per day may have increased efficacy in some patients, but at the same time there is the chance of increasing the appearance of minor side effects (Pharmel Inc., 2002). Therefore, subjects in this study received a weekly follow-up phone call by a pharmacy research assistant in order to help them reach their minimum effective dose and monitor for possible side effects. Follow-up phone calls were directed to both study groups (patients taking gabapentin and placebo) in order to keep patient's blinding uncompromised.

If the study medication had to be discontinued for any reason, dosage was gradually decreased 300 mg every 3 days. In the case of undesirable side effects, specific complaints were recorded, and the subject was expected to continue their clinical trial appointments for further evaluation, regardless if they had withdrawn from the study. Once a patient finished the trial, the same protocol to taper down the dosage by 300 mg every 3 days was followed to discontinue the medication. This final segment of the study was performed by a research assistant and not from the main investigator due to blinding purposes.

Acetaminophen 500 mg was utilized in this study for breakthrough pain in those cases where subjects needed pain control between gabapentin doses, or if the study medication was not having an analgesic effect. They were instructed to take it as needed every 6 h, with a maximum of eight tablets (4000 mg) per day. Subjects were requested to keep a calendar of times and amounts of escape medication use.

2.6. Statistical analysis

Statistical analysis involved four parts. The first part consisted of a one way MANOVA to compare means between gabapentin and placebo groups in each outcome measure and detect the presence of a difference between them. The mean proportion (percentage) of the difference from the baseline scores (at the initial visit) to the final visit (week 12) was compared for the VAS-pain and the VAS-function. For the PI such means were not expressed in terms of percentage of reduction but in terms of number of tender sites in the masticatory muscles. The second part involved a Pearson correlation analysis to evaluate the association between reported pain on the VAS and the PI. The third part consisted of a Repeated Measures ANOVA to compare the mean reduction scores of the three outcome measures throughout each one of the four study visits. LSD was performed as a post hoc test to compare study groups at each fixed time. Finally, a Chi-square *t*-test was performed to compare side effects between gabapentin and placebo groups.

The data derived from this study were analyzed by intent-to-treat analysis. The intent-to-treat population included those subjects who, once randomized, had evidence of taking at least one dose of the study medication and provided at least 1 follow-up evaluation, regardless of withdrawing from the study before week 12.

3. Results

A total of 50 female subjects (mean age 33.58 years) were enrolled in the clinical trial. Patients were recruited in a period of 10 months. Thirty-six (72%) patients completed the study at week 12. From the 36 subjects who completed the trial, 19 (38%) were in the gabapentin group and 17 (34%) in the placebo group. From the 14 (28%) subjects who dropped out the clinical trial, 7 (14%) subjects were noncompliant with the dosing and the scheduled appointments; 4 (8%) subjects stopped taking the study drug (gabapentin or placebo) due to side effects; and 1 (2%) subject had mild adverse reactions but were unsure if these were related to the study drug. One (2%) subject found out she was pregnant after the beginning of the trial, so she was advised to discontinue the medication immediately. Finally 1 (2%) subject was removed from the study for starting a new pain medication. The total number of drop outs and patients analyzed on each visit is illustrated in Fig. 1.

Some of the subjects in our sample had overlap with other reported muscle pain conditions. In the 25 subjects of the gabapentin group 14 (56%) reported constant tension headache; 12 (48%) poor sleep quality; 11 (44%) recurrent headaches; 4 (16%) neck pain; 2 (8%) migraines; and 1 (4%) fibromyalgia. In the 25 subjects in the placebo group 10 (40%) reported constant tension headaches; 7 (28%) recurrent tension headaches; 5 (20%) poor sleep; 4 (16%) migraines; and 3 (12%) reported neck pain.

The intent-to-treat population consisted of a total of 44 (88%) subjects. Twenty-four (48%) subjects were in the gabapentin group and 20 (40%) received placebo. Six (12%) subjects attended only for the initial visit when medication dosing was started. They did not provide any follow up visit and no observation could be measured. Therefore, no analysis could be made for these subjects.

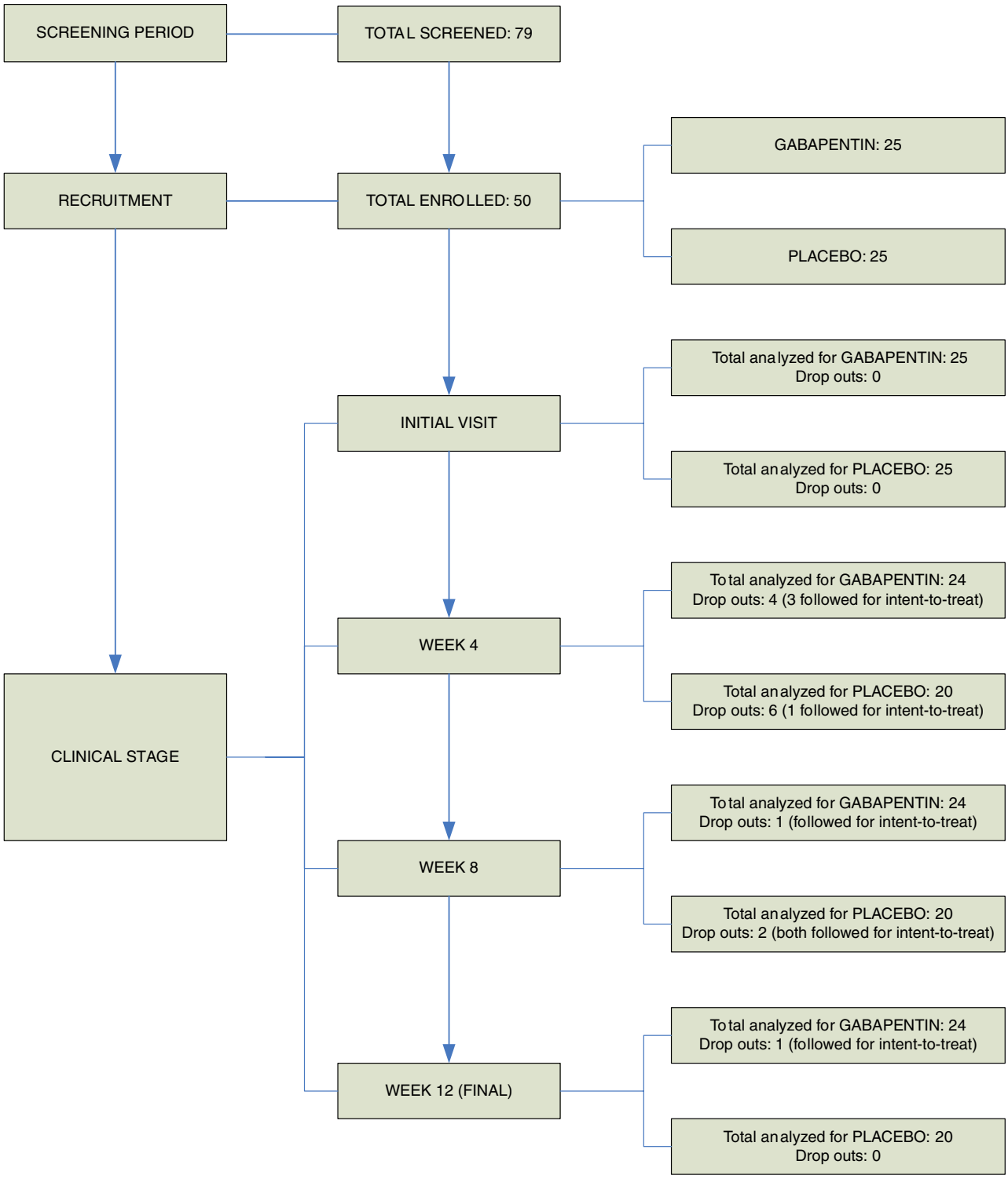

Fig. 1. Patient flow during the clinical trial. Total patients analyzed in the study are indicated for each study visit. The number of drop outs, including those followed for intent-to-treat analysis, is indicated for each study visit.

Patients were asked to discontinue pain medications during the trial. However, some of them were taking tricycle antidepressants (TCA) or specific serotonin reuptake inhibitors (SSRI) on a regular basis for more than 2 months previous to enrolling in the study. These medications could not be stopped due to other medical or psychological conditions. No changes in the dosage of these medications were allowed during the trial. No patients were on TCAs in the gabapentin group, although 2 patients (10%) in the placebo group were tak-

Table 1
Mean (M) and standard deviation (SD) of the proportion of scores reductions from baseline (initial visit) to the final visit (week 12)

Outcome measure	VAS-pain % reduction	PI reduction	VAS-function % reduction
Gabapentin	51.04 (SD = 38.89)	6.46 (SD = 4.11)	52.61 (SD = 42.42)
Placebo	24.30 (SD = 43.54)	1.90 (SD = 5.02)	18.63 (SD = 55.22)
P-value	0.037	0.002	0.026
F-value	4.625	10.946	5.323

ing this kind of medication. Regarding SSRIs, 8 patients (33%) were found to be taking them on a regular basis in the gabapentin group and 5 (25%) in the placebo group.

One way MANOVA detected an overall difference between study groups in at least one of the three outcome measures ($P = 0.018$, $F = 3.752$). Further on, subjects in the gabapentin group demonstrated a clinically and statistically significant reduction reported on the VAS-pain of 51.04% in comparison to 24.30% in the placebo group ($P = 0.037$, $F = 4.625$). The mean baseline number of tender palpation sites in the masticatory muscles was 9.50 in both study groups. However, at week 12 the number of tender sites was reduced from 9.50 to 3.04 in the gabapentin group, in comparison to the placebo group in which it was only reduced to 7.60 tender sites. The mean reduction of number of tender sites was 6.46 in the gabapentin group against 1.9 in the placebo group ($P = 0.002$, $F = 10.946$). Finally, the reduction of the impact of CMM on daily functioning reported on the VAS-function was measured to be 52.61% in subjects taking gabapentin, in comparison to a 18.63% reduction in the placebo group ($P = 0.026$, $F = 5.323$). Table 1 illustrates these results. Unfortunately, numerous subjects were not compliant with completing their escape medication calendar and further analysis of use of escape medication as a secondary evaluation of pain control was not feasible.

A correlation analysis was performed to determine if a direct association was present between VAS-pain and the PI variables in the intent-to-treat population. A positive correlation between the two variables was detected with a Pearson correlation value of 0.70 in the gabapentin group and 0.63 in the placebo group. This indicates that pain reduction increases simultaneously in the VAS-pain and PI.

A Repeated Measures ANOVA was performed to compare the means of the response to the study medications for both study groups during the 12-week period for each variable evaluated (Figs. 2–4). Within this statistical test a comparison between study groups on each visit was performed in order to detect at what point in time during the trial a significant difference appeared between both groups. Regarding main effects between groups, gabapentin demonstrated statistically lower VAS pain scores at week 12 ($P = 0.026$), lower PI scores at week 8 and week 12 ($P < 0.001$) and improved VAS-function at week 8 ($P = 0.013$). Main effects of time were shown to be significant in the three outcome measures: VAS-pain $P < 0.001$, $F = 18.553$; PI $P = 0.001$,

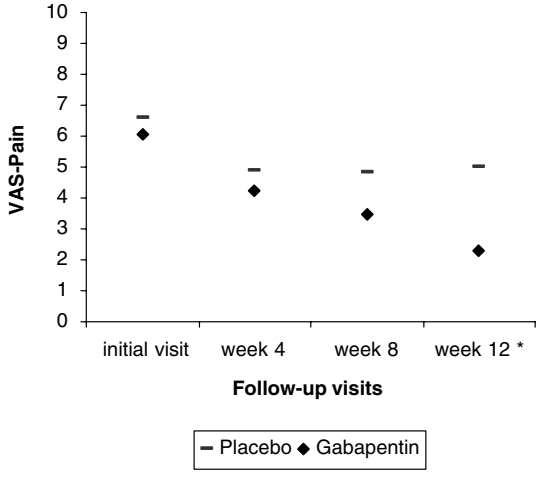

Fig. 2. 12-week progress for VAS-pain (intent-to-treat analysis). (–) Placebo mean at the initial visit (SD: ±1.21), week 4 (SD: ±2.00), week 8 (SD: ±2.37) and week 12 (SD: ±2.67). (♦) Gabapentin mean at the initial visit (SD: ±1.27), week 4 (SD: ±2.17), week 8 (SD: ±2.12) and week 12 SD: ±2.37). (*) Statistically significant difference between study groups (week 12, $P = 0.026$).

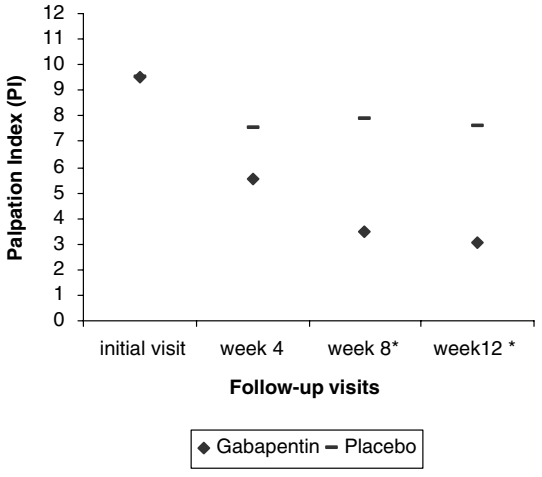

Fig. 3. 12-week progress for PI (intent-to-treat analysis). (–) Placebo mean at the initial visit (SD: ±2.06), week 4 (SD: ±3.51), week 8 (SD: ±3.81) and week 12 (SD: ±4.29). (♦) Gabapentin mean at the initial visit (SD: ±2.06), week 4 (SD: ±3.43), week 8 (SD: ±3.28) and week 12 (SD: ±3.85). (*) Statistically significant difference between study groups (at week 8 and week 12, $P < 0.001$).

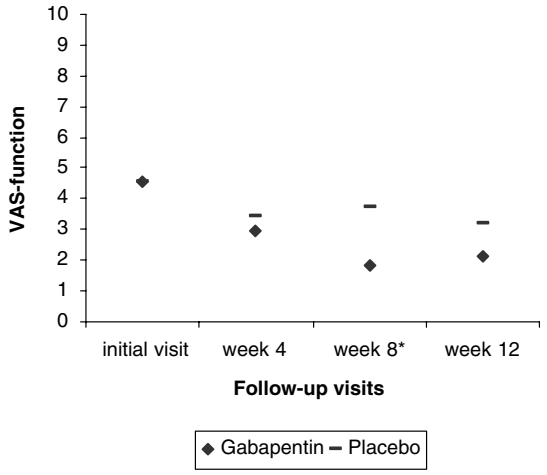

Fig. 4. 12-week progress for VAS-function (intent-to-treat analysis). (–) Placebo mean at the initial visit (SD: ±2.18), week 4 (SD: ±2.47), week 8 (SD: ±2.48) and week 12 (SD: ±2.84). (♦) Gabapentin mean at the initial visit (SD: ±2.87), week 4 (SD: ±2.58), week 8 (SD: ±2.22) and week 12 (SD: ±2.50). (*) Statistically significant difference between study groups (week 8, $P = 0.013$).

$F = 25.135$; and VAS-function $P < 0.001$, $F = 11.714$. Finally, the Repeated Measures ANOVA did not detect statistically significant interactions between time and study groups for VAS-pain ($P = 0.425$) and VAS-function ($P = 0.076$), except for PI ($P = 0.004$). The number needed to treat (Cook and Sacett, 1995) was calculated to be (-) 3.43, suggesting that approximately 4 patients must receive gabapentin therapy in a period of 12 weeks to produce a clinically significant reported pain reduction in one of them, who would not have improved if they had not received such therapy.

Side effects were reported based on the 50 subjects who enrolled in the study, including those who dropped out of the study. A Chi-square *t*-test did not detect significant differences between gabapentin and placebo for these side effects (Table 2).

Table 2
Incidence of adverse side effects for gabapentin and placebo groups

Side effect reported	Gabapentin ($n = 25$)	Placebo ($n = 25$)	*P*-value
Dizziness	28% ($n = 7$)	8% ($n = 2$)	0.69
Drowsiness	28% ($n = 7$)	20% ($n = 5$)	0.37
Memory and cognitive impairment	16% ($n = 4$)	4% ($n = 1$)	0.17
Dry Mouth	12% ($n = 3$)	4% ($n = 1$)	0.30
Fatigue	12% ($n = 3$)	8% ($n = 2$)	0.50
Ataxia	4% ($n = 1$)	Not reported	–
Diarrhea	4% ($n = 1$)	4% ($n = 1$)	0.75
Constipation	4% ($n = 1$)	Not reported	–
Weight gain	4% ($n = 1$)	Not reported	–
Chest tightness	4% ($n = 1$)	Not reported	–
Numbness	Not reported	4% ($n = 1$)	–
Accelerated heart beat	Not reported	4% ($n = 1$)	–

4. Discussion

Physiological pain is generally short-lasting, has a protective role, and is usually quickly resolvable. However, sometimes pain may become persistent (chronic) with no biological role. Indeed, rather than simply being a symptom of a disease or injury, it could be considered a disease itself involving CNS perception disorders, psychological implications, and sleep disturbances. CMM, as a chronic pain condition, is not easily treated and resists traditional treatment. This study demonstrated that gabapentin is a useful treatment option to provide analgesia and anti-hyperalgesia in the pharmacological management of CMM.

The results of this study reject our null hypotheses. In this clinical trial gabapentin appears to have a statistically significant difference with the control group at week 12 for the VAS-pain (Fig. 2). For the PI a statistical difference appears at week 8 and it is maintained up to week 12 (Fig. 3). At these points the gabapentin dose was approximately 3300 mg/day to 3600 mg/day. This could be considered a threshold dose for analgesic efficacy in CMM. Maximum dose at week 12 according to our titration protocol was 4200 mg/day. However, the mean dose in the actual study was 3426.31 mg/day at week 8 and 3315.78 mg/day at week 12. The fact that a statistical difference appeared at week 8 and week 12 for the PI and VAS-Pain, respectively, may be related to the time that this drug takes to produce its analgesic effect in CMM. There is no consensus in the literature regarding the time required by the drug to produce its effect. It can range from weeks to several months when treating intractable pain conditions and varies from patient to patient (Reisner and Pettengill, 2001).

The fact that a statistically significant analgesic effect of gabapentin appeared at week 8 on VAS-function but was not maintained up to week 12 may be due to the measuring tool utilized. Measuring daily function was not the main objective of this study and a VAS was utilized for this purpose. Since this tool has not been validated to measure impact of CMM on daily functioning, these results should be interpreted with caution.

In terms of side effects and dose titration, gabapentin did not cause side effects that were severe enough to prevent dose titration. In those cases in which side effects appeared during dose titration, they subsided within a few days and were easily managed. This allowed following the continuation of the dose titration protocol until a therapeutic dose was achieved. Subjects who achieved partial pain control or no pain control at all were at the maximum dose proposed (4200 mg/day) and further dose titration could not be continued to determine if an increased analgesic effect is observable. Further research on gabapentin therapy for CMM or other chronic musculoskeletal disorders like fibromyalgia

should address this question using doses higher than 4200 mg/day.

Gabapentin has been shown to have central sites of pharmacological action, including calcium channels and possibly NMDA receptors (Gee et al., 1996; Taylor et al., 1998; Gu and Huang, 2001, 2002; Luo et al., 2002). These pharmacological targets seem to also be involved in the pathophysiology of CMM (Sessle, 1995, 1999; Mense and Simons, 2001). The results of this clinical trial support the hypothesis that CMM may have important CNS effects (Sessle, 1995) as one of the mechanisms that influence this condition. However, there are also a few recent reports suggesting the analgesic action of gabapentin in peripheral sites (Carlton and Zhou, 1998; Pan et al., 1999) and in postoperative pain (Dahl et al., 2004). Further research is required on the pathophysiology of CMM and gabapentin's analgesic mechanism of action. Additional research regarding the peripheral action of this drug and its effect on acute pain is also required before making definitive conclusions.

There are no previously published studies in the literature evaluating the analgesic effect of gabapentin on any type of chronic TMD. Central-acting pharmacological agents most commonly utilized for managing chronic masticatory muscle pain are TCAs.

Unfortunately, previously published studies regarding TCA treatment in TMD did not provide statements regarding the frequency of side effects and associated withdrawals. However, it is known that the dose of TCA is usually limited by anticholinergic side effects, such as dry mouth, constipation, blurred vision and urinary retention (Dionne, 1997; Pettengill and Reisner-Keller, 1997). Cardiovascular side effects such as postural hypotension or serious ventricular arrhythmias can also occur, especially in those subjects with pre-existing heart disease (Dionne, 1997; Pettengill and Reisner-Keller, 1997). One RCT performed by Heymann et al. (2001) comparing the analgesic effect of amitriptyline and nortriptyline in subjects with fibromyalgia reported the incidence of side effects for both medications. The number of side effects of gabapentin reported in our trial was slightly lower than that reported by Heymann et al.

A major advantage of gabapentin over TCA is its lack of major interactions with other drugs (Goa and Sorkin, 1993; Pharmel Inc., 2002; Pfizer Pharmaceuticals Ltd., 2003). There are no known drug interactions with gabapentin, whereas TCAs can cause severe CNS toxicity if administered along with monoamine oxidase inhibitors (MAOI) (Kreisberg, 1988). TCA drugs are also known for potentiating the effect of alcohol and probably of other sedatives (Kreisberg, 1988). TCAs inhibit the uptake of epinephrine by sympathetic nerve endings and can potentiate the cardiovascular effects of epinephrine. Therefore, from a dental practice perspective, caution should be taken with patients taking TCAs when using epinephrine contained in local anesthetics and gingival retracting cords (Dorris and Taylor, 1984; Kreisberg, 1988).

When choosing pharmacotherapy, the side effect profile and interaction of the treatment medication with other medications should be considered. Based on this trial, gabapentin should be considered as another treatment option for CMM with a cleaner drug interaction profile and fewer side effects than TCAs.

The results of this clinical trial suggest that gabapentin may be effective in the treatment of other chronic musculoskeletal problems. Like CMM, fibromyalgia represents chronic muscular problems that has CNS and peripheral influences, psychological implications and sleep disturbances (Geenen and Jacobs, 2001) and may also respond to gabapentin therapy. This treatment approach is supported by one study which reported that gabapentin was effective in 35% of subjects with intractable chronic musculoskeletal pain (Gustorff et al., 2002). In addition, an open-label pilot study showed that gabapentin in combination with a topical lidocaine patch 5% was effective in decreasing chronic low-back pain levels (White et al., 2003). However, to date, there are no clinical trials evaluating the analgesic efficacy that gabapentin may have on specific chronic musculoskeletal disorders. Further clinical trials performed in a well-controlled fashion are required to begin exploring the analgesic action of gabapentin in chronic musculoskeletal disorders.

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