

## THE EFFICACY OF GABAPENTIN IN MIGRAINE PROPHYLAXIS: AN OBSERVATIONAL OPEN LABEL STUDY

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**SUMMARY** – Migraine is often a chronic and disabling disorder. The objective of our study was to assess the efficacy and safety of gabapentin in the prophylaxis of migraine in patients refractory to other prophylactic treatments. The study included 67 migraine patients, 55 women and 12 men; 52 patients completed this prospective, open-label study. Patients were given 900-1800 mg of gabapentin in 3 doses; the mean duration of treatment was 7.2 months. Reduction in the number of days with headache, pain intensity and number of acute medications was assessed through patient diary. The mean number of migraine days/4 weeks was reduced from 15.8 to 8.6, yielding a reduction of 7.2 migraine days/4 weeks ( $P=0.001$ ). Pain intensity was reduced by 25% in 14 (26.9%), by 50% in 29 (55.7%) and by 75% in three (5.7%) patients, whereas no improvement was reported by six (11.5%) patients at the end of follow up. A significant reduction was recorded in acute medication use ( $P=0.001$ ). Adverse events were reported by 32/67 (47.8%) patients, in 15 (22.4%) of them causing discontinuation of the drug. The most frequently reported adverse events were drowsiness, dizziness and slowness. Prophylactic treatment with gabapentin was found to be associated with a significant reduction in the number of days with headache, use of acute medications and pain intensity.

**Key words:** *Migraine – therapy; Migraine – prevention and control; Headache – therapy; Headache – prevention and control*

### Introduction

Migraine is a common episodic headache disorder. The prevalence has been estimated to 6%-29% in women and 3%-12% in men<sup>1</sup>. Patients with migraine have a reduced quality of life compared with non-migraine patients<sup>1,2</sup>. Preventive therapy is recommended in migraine patients with frequent, severe, long-lasting attacks, in cases where acute therapy is not efficient, if there is a contraindication to the drug, failure or unbearable side effects from acute treatments, overuse of acute medications, or in special cases such as hemiplegic migraine. Treatment should be chosen individually, taking into

consideration co-morbidities, drug efficacy, adverse reactions, patient preference, availability and costs<sup>3-9</sup>. The drug chosen should be introduced in a low dose and gradually increased, and should be given an adequate trial (at least three months)<sup>10</sup>.

Medications used in migraine prophylaxis come from different pharmacological classes and most have primary indications for other medical conditions<sup>3,5,8</sup>. Beta-blockers and tricyclic antidepressants have been often used as first-line therapy for migraine prevention. Other preventive drugs include pizotifen, flunarizine, and methysergide<sup>10</sup>.

However, in some patients where these medications are contraindicated or that suffer from comorbid diseases, antiepileptic drugs (AEDs) may be offered as an appropriate first-line prophylactic treatment. Gabapentin is among AEDs that have been evaluated for efficacy in migraine and cluster headache prevention<sup>11-15</sup>. Gabap-

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entin has anticonvulsant and analgesic properties and has been used primarily as an adjunctive treatment of partial seizures, but is also accepted for the treatment of neuropathic pain conditions such as diabetic neuropathy, trigeminal neuralgia, and postherpetic neuralgia<sup>16</sup>. Case reports of successful treatment with gabapentin in SUNCT, idiopathic stabbing headache, thunderclap headache and nummular headache have also been published<sup>17-20</sup>.

The aim of this study was to evaluate the efficacy and safety of gabapentin in the prophylaxis of migraine previously successfully or unsuccessfully treated with other prophylactic medications. We also present an overview of trials with the AEDs valproate, gabapentin, topiramate and lamotrigine in the prophylaxis of migraine.

## Patients and Methods

This was an open prospective study that evaluated the efficacy and safety of gabapentin in the prophylaxis of migraine with or without aura in patients attending Headache Clinic at University Department of Neurology. Migraine was defined according to the ICHD-2 criteria<sup>21</sup>.

Patients were included according to the following criteria: migraine attacks with or without aura for at least one year before study entry; and frequency of attacks of three or more *per* month during at least previous three months. Furthermore, patients were included as follows: 1) previous prophylactic treatment with other medications had failed, or was discontinued due to adverse events; 2) patients agreed to take no concurrent prophylactic treatment for headaches (pharmacological or non-pharmacological); 3) patients had no serious concurrent diseases; and 4) patients were willing to be available for follow up for at least 3 months.

Patients were not eligible if noncompliance was likely, if the patient required medication for other medical conditions that might confound the results, women if planning pregnancy or were lactating, or patients with a history of illicit drug or alcohol abuse in the past year. All patients signed their informed consent.

The patients taking other prophylactic medications were told to start gabapentin at 3 weeks of the previous prophylactic drug discontinuation. The majority of patients were taking beta-blockers, tricyclic antidepressants or selective serotonin reuptake inhibitors (SSRIs) for prophylaxis.

Gabapentin was then started at a dose of 300 mg, one capsule at bed time for 5 days, followed by 300 mg twice daily for 5 days, and finally 900 mg daily divided in three doses. During the follow up, the dose was increased if no improvement was recorded at the initial dose of 900 mg. The titration phase was followed by at least a 12-week maintenance phase.

Before initiating gabapentin treatment, patients were asked to keep a headache diary for at least 3 months, which was used to count the average number of days with headache and number of acute medications taken (baseline data). Upon introducing gabapentin in therapy, patients were instructed to keep a diary and note all days with headache, decrease in headache intensity if observed, increase in gabapentin dosage, acute medications taken for severe migraine, and occurrence of adverse events. Patients were told to use their usual therapy for acute attacks.

The primary efficacy endpoint was the change from baseline in the mean monthly (28 days) number of migraine days, decrease in headache intensity and reduction in the mean number of acute medications use. The change in headache intensity was recorded as percentage (no change, decrease by 25%, 50%, 75% or 100%). Assessments of safety and tolerability included physical, neurological and laboratory examinations, and spontaneous reports of adverse events. The patients were included into the study group if they were taking medication for at least 3 months; if they were satisfied with therapy and had no side effects, they continued therapy for up to 12 months if necessary (observational period was therefore expected to be from 3 to 12 months).

On statistical analysis, Wilcoxon's signed rank test was used to compare baseline and end-point values.

## Results

The study included 67 patients, 55 women and 12 men (age  $46 \pm 12$  years). The mean duration of treatment was 7.2 (range 3-12) months. The patients started the treatment according to our instructions, e.g., the dose of gabapentin was increased every five days to a minimal dose of 900 mg daily divided in three doses. The maintenance dose of gabapentin in all patients was in the range from 900 mg to 1800 mg: 29 patients with migraine were taking 900 mg/day, 18 patients 1200 mg/day and five patients 1800 mg/day. The dose of gabapentin was not increased over 1800 mg because either an improvement was achieved or adverse events occurred at this dosage.

In 52 migraine patients that completed the follow up, the mean number of headache days/4 weeks was reduced from 821 (mean 15.8) at baseline to 449 (mean 8.6) at study endpoint evaluation, yielding a reduction of 7.2 migraine days/4 weeks ( $P=0.001$ ), or by 45.3% in headache frequency.

Headache intensity was reduced by 25% in 14 (26.9%), by 50% in 29 (55.7%), and by 75% in three (5.7%) patients, whereas no improvement was reported by six (11.5%) patients at the end of follow up.

Before starting gabapentin, the number of medications was 987 (mean 18.9) tablets/4 weeks. At the end of follow up, the figure fell to 388 (mean 7.4), yielding a reduction of 11.5 tablets/4 weeks ( $P=0.001$ ). A 25% reduction in the use of acute medication was recorded in four (7.6%), by 50% in 28 (53.8%) and by 75% in 14 (26.9%) patients, whereas no change in the use of acute medication was reported by six (11.5%) patients. Accordingly, 88.5% of treated patients reported using less acute medications. Before and during treatment with gabapentin, the patients were using their usual type of acute therapy. The range of gabapentin doses, reduction of headache intensity and reduction of medication use are shown in Table 1.

Adverse events were reported by 32/67 (47.8%) patients and were generally of mild or moderate severity. However, in 15/67 (22.4%) patients, the drug associated adverse events led to discontinuation of the drug and in these patients the efficacy of gabapentin was not evaluated due to the short observational period (less than 3 months). Adverse events were the only reason for discontinuation of the study. The most frequently reported adverse events were drowsiness, dizziness and slowness, followed by constipation, ataxia, swollen face or body, and weight gain. There were no serious adverse

Table 1. (A) Range of gabapentin doses; (B) reduction of pain intensity; and (C) reduction of acute medication use

(A)	Gabapentin dose (mg)			
	900	1200	1800	2400
N=52 (%)	29 (55.8)	18 (34.6)	5 (9.6)	0
(B)	Reduction of pain intensity by %			
	0%	25%	50%	75%
N=52 (%)	6 (11.5)	14 (26.9)	29 (55.7)	3 (5.7)
(C)	Reduction of medication use by %			
	0%	25%	50%	75%
N=52 (%)	6 (11.5)	4 (8.0)	28 (53.8)	14 (26.9)

events. The number of adverse events and withdrawals are shown in Table 2.

## Discussion

Prophylactic therapy for migraine should be based on guidelines from evidence-based medicine. Although double-blind placebo-controlled studies provide unbiased results, they are sometimes difficult to carry out, therefore open-label studies offer additional data on the efficacy of pharmacological or non-pharmacological treatment<sup>3-7</sup>. Trials with AEDs as prophylactic drugs in migraine have shown that certain AEDs can be offered in patients refractory to usual prophylactic treatments.

Valproate and topiramate are approved by the Food and Drug Administration (FDA) for prophylactic treatment of migraine; especially topiramate has been studied in a large number of patients in double-blind placebo-controlled and thus methodologically powerful studies<sup>22-24</sup>. Gabapentin is still omitted from recommendations for headache prevention, mostly due to the lack of double-blind placebo-controlled trials.

Results of our study showed gabapentin to be effective in the prophylactic treatment of migraine in patients refractory to previous prophylactic therapy. We found significant reduction in headache frequency, intensity and medication use during the follow up period. We compared our results with other trials that evaluated the efficacy of AEDs in headache prophylaxis.

Valproate was the first AED recommended for migraine prevention. In controlled studies, divalproex sodium and sodium valproate showed consistent efficacy in reducing headache frequency compared with placebo<sup>25-28</sup>; compared with propranolol, there was no signifi-

Table 2. Adverse events in patients with migraine treated with gabapentin; some patients experienced several adverse events

Adverse event	Migraine (N=67) n (%)
Number of patients with adverse events	32 (47.8)
Drowsiness	15 (22.4)
Dizziness	5 (5.9)
Slowness	8 (11.9)
Constipation	5 (5.9)
Ataxia	2 (3.0)
Swollen face/body	2 (3.0)
Weight gain	2 (3.0)
Withdrawal	15 (22.4)

cant difference in efficacy<sup>29</sup>. Low dosages of valproic acid between 300 and 900 mg were effective in migraine prophylaxis<sup>30,31</sup>. Long-term safety of divalproex sodium was evaluated in an open-label study; the most frequently reported adverse events were nausea, infection, alopecia, tremor, dyspepsia, and somnolence<sup>32</sup>.

In a double-blind, placebo-controlled trial with topiramate up to 200 mg, the mean 28-day reduction in migraine frequency was significant in the topiramate group: from 4.2 (baseline) to 3.0, while in the placebo group the reduction was from 4.1 to 3.8<sup>33</sup>. In another double-blind placebo-controlled study with 100 mg and 200 mg of topiramate, significantly more (54% and 52.3%) topiramate treated patients experienced a 50% or greater reduction in the monthly migraine frequency as compared with placebo treated patients (22.6%)<sup>24</sup>. A similar study showed a mean 28-day migraine frequency reduction by 36% in patients receiving topiramate *vs.* 14% in placebo group; 26% achieved a 50% reduction in migraine frequency *vs.* 9.5% in placebo group; two of 19 topiramate treated patients discontinued treatment due to adverse events<sup>23</sup>. The >50% reduction of headache frequency was recorded in 58.3% of episodic migraine patients and 38.0% of chronic migraine patients on topiramate up to 100 mg twice daily; the mean headache severity was reduced from 6.2 to 4.8 on a 10-point scale; both results were significant<sup>34</sup>. The most common adverse events in topiramate treated patients were cognitive difficulties, weight loss, paresthesias, somnolence, diarrhea, and altered taste, and were present in 26.6%-58.1% of patients<sup>24,33,34</sup>.

A double-blind, crossover clinical trial compared the efficacy of topiramate and sodium valproate in migraine prevention and the two drugs appeared to be equivalent in efficacy and safety; a significant decrease in duration, monthly frequency and intensity of headache occurred in both groups: in valproate group, the mean monthly frequency decreased from 5.4 to 4.0 and in topiramate group from 5.4 to 3.2, while headache intensity decreased from 7.7 to 5.8 and from 6.9 to 3.7, respectively<sup>35</sup>.

In a 12-week open-label study, gabapentin in a dosage of 600-1800 mg was effective in episodic and chronic migraine, headache frequency decreased from 25.2 to 11.6 *per* month and side effects were minimal<sup>12</sup>. A placebo-controlled study in 98 patients receiving gabapentin and 45 placebo showed that gabapentin in a dosage of 1800-2400 mg was effective in reducing the frequency of migraine attacks: the responder rate (50% decrease

in attack frequency) was 46.4% in gabapentin group and 16.1% in placebo group; furthermore, a 4-week migraine headache rate decreased from 4.2 to 2.7 in gabapentin group and from 4.1 to 3.5 in placebo group, yielding a significant difference<sup>14</sup>. Discontinuation rate due to adverse events was 16.3% in gabapentin group (8.2% due to somnolence and dizziness) and 8.9% in placebo group. In one placebo-controlled, double-blind study, gabapentin was not found to be effective<sup>13</sup>. A double-blind, placebo-controlled study including 133 patients with chronic headaches (two thirds had a combination of migraine and tension-type headache) showed that patients taking gabapentin 2400 mg/day had by 9.1% more headache-free days as compared with placebo group; adverse events were reported by 39% and 14% of patients in gabapentin and placebo group, respectively<sup>15</sup>. However, the Cochrane database found limited evidence for the use of gabapentin for acute pain<sup>36</sup>. The most commonly reported adverse events associated with gabapentin in these trials were somnolence, dizziness, drowsiness, ataxia, fatigue and nausea, while weight gain and hair loss were rare<sup>14,15</sup>.

Lamotrigine has been shown to be efficient in the prophylaxis of migraine with aura. Three open-label studies showed that lamotrigine reduced the number of migraine auras and the frequency of migraine attacks. In 13 of 21 patients receiving lamotrigine 100 mg, migraine attacks resolved completely, and one patient was unresponsive to the treatment at the end of third month<sup>37</sup>. In another two studies, lamotrigine significantly reduced the number of migraine auras (from 4.2 to 0.7)<sup>38</sup>, the duration of migraine auras and the frequency of migraine attacks<sup>39</sup>.

Low-dose topiramate (50 mg in 2 divided doses) was demonstrated to be superior in reduction of headache frequency compared to both lamotrigine (50 mg in 2 doses) and placebo; however, in this cross-over study patients were receiving the drug for only one month<sup>40</sup>.

In our study, a significantly lower 28-day migraine frequency was observed: the frequency of mean headache days decreased from 15.9 to 8.6, yielding a reduction of 7.2 days or 45.3%; it was somewhat lower compared to another gabapentin study where the decrease in the frequency of attacks reached 54%<sup>12</sup>. A 50% reduction in migraine frequency was achieved by 61.5% of our patients that were evaluated at the end of the follow up period. In comparison with our results, the response rate of reduction in migraine frequency was lower in a similar study with gabapentin (46.6%)<sup>14</sup> or topira-



mate (54%)<sup>24,34</sup>. A reduction in headache frequency by 83% was observed in a study with lamotrigine<sup>38</sup> and resolution of attacks was observed in 62%<sup>37</sup>, which is much higher compared to our results or even with similar studies.

In our study, headache intensity was reduced by at least 50% in 32/52 (61.5%) patients and by less than 50% in 14/52 (26.9%) patients. In trials with other AEDs, a 25% reduction of headache intensity was observed with valproate and by 46% with topiramate<sup>35</sup>.

The decrease in the frequency and intensity of headache attacks was within the range of results observed in other studies with gabapentin, topiramate and valproate; only studies with lamotrigine showed better results. Most of these studies (double-blind placebo-controlled and open-label studies) have reported significant reduction in headache frequency and intensity, and one (placebo-controlled) study reports unfavorable results<sup>15</sup>.

Most studies evaluated only the decrease in headache frequency and intensity; we also evaluated decrease in the use of acute medication, which is another very important evaluation point in such studies because preventive treatment of migraine reduces the possibility of medication overuse headache. In our study, 88.5% of patients reported using less acute medications.

A high percentage of our patients reported adverse events (47.8%), which is higher compared to a similar study with gabapentin, where 39% of patients reported adverse events<sup>15</sup>. Studies with topiramate showed the rate of adverse events to range from 26.6% to 58.1%<sup>27,29</sup>. In our study, 22.4% of patients discontinued the treatment due to adverse events, which is much higher compared to another study with gabapentin, where the drop-out rate was 8.2%<sup>14</sup>.

Our study suffered from some shortcomings; it was not a placebo-controlled double-blind study and the number of patients was relatively small. We are aware that the study design is crucial in order to minimize bias of the results; trials in migraine prevention should be randomized, preferably in a homogeneous study population, double-blind and placebo-controlled<sup>41</sup>. However, we hope that the results of our study will provide additional information that will help decide on the most preferable preventive medication for the individual patient, especially in patients that have failed to respond to prior trials of preventive medications.

In conclusion, gabapentin treatment in patients with migraine at daily doses of 900-1800 mg resulted in a significant mean reduction of migraine days, reduction in

pain intensity and in the use of acute medications. Although adverse events occurred in a relatively high percentage, the treatment with gabapentin was safe and well tolerated in the majority of patients. Due to a small number of studies with gabapentin as a prophylactic drug for migraine, general recommendations cannot be given yet. Our findings warrant further trials, preferably double-blind placebo-controlled studies in a greater number of patients.

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## Sažetak

## UČINKOVITOST GABAPENTINA U PROFILAKSI MIGRENE: OPSERVACIJSKA OTVORENA STUDIJA

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Migrena je čest poremećaj koji smanjuje kvalitetu života. Cilj ove studije bio je ustanoviti učinkovitost i sigurnost gabapentina u profilaksi migrene kod bolesnika refraktornih na drugu profilaktičnu terapiju. Studija je uključivala 67 bolesnika s migrenom, 55 žena i 12 muškaraca; 52 bolesnika je završilo ovu prospektivnu otvorenu studiju. Bolesnici su uzimali 900-1800 mg gabapentina podijeljeno u 3 doze; prosječno trajanje liječenja je bilo 7,2 mjeseci. Smanjenje broja dana s glavoboljom, intenziteta i broja lijekova u akutnim napadajima procijenjeno je pomoću dnevnika. Prosječan broj dana s migrenom/4 tjedna smanjen je s 15,8 na 8,6, tj. smanjenje za 7,2 dana ( $P=0,001$ ). Intenzitet boli smanjen je za 25% kod 14 (26,9%) ispitanika, za 50% kod 29 (55,7%), za 75% kod 3 (5,7%) ispitanika, dok promjene nisu zabilježene kod 6 (11,5%) ispitanika na kraju razdoblja praćenja. Zabilježeno je i značajno smanjenje broja lijekova koji su se rabili u akutnim napadajima ( $P=0,001$ ). Nuspojave je prijavilo 32/67 (47,8%) ispitanika, od kojih je 15 (22,4%) moralo prekinuti studiju. Najčešće nuspojave su bile pospanost, ošamućenost i usporenost. Profilaktično liječenje gabapentinom kod bolesnika s migrenom dovodi do značajnog smanjenja broja dana s glavoboljom, intenziteta boli i broja konzumiranih lijekova u akutnim napadajima.

Ključne riječi: *Migrena – terapija; Migrena – prevencija i kontrola; Glavobolja – terapija; Glavobolja – prevencija i kontrola*

