



## Analysis of the duration of migraine prophylaxis



Raimundo Pereira Silva-Néto<sup>a,\*</sup>, Kelson James Almeida<sup>a</sup>, Silvy Neri Bernardino<sup>b</sup>

<sup>a</sup> Neurology, Center of Neurology and Headache of Piauí, Teresina, PI, Brazil

<sup>b</sup> Neurophysiology, Hospital Getúlio Vargas, Recife, SP, Brazil

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### ABSTRACT

To determine the minimum duration of migraine prophylaxis, after patients become pain-free. Migraine patients diagnosed according to criteria of International Classification of Headache Disorders-2 were treated prophylactically. After becoming pain-free, they were divided into two equal groups: in group 1, prophylaxis was maintained for another 12 months and in group 2, for 24 months. Each group was followed for more three years after prophylaxis period. Of the 50 patients, 39 (78%) were female and 11 (22%) were male. The age ranged from 18 to 50 years. Before treatment, the attack frequency for groups 1 and 2 was, respectively,  $16.3 \pm 12.8$  and  $16.4 \pm 11.8$  days per month ( $p = 0.769$ ). Patients in groups 1 and 2 have become pain-free, respectively, with  $21.4 \pm 11.2$  and  $16.8 \pm 9.9$  months ( $p = 0.161$ ). During three years without treatment, groups 1 and 2 maintained an annual frequency of respectively 3.2 and 0.5 headache days. Of the patients in group 2, 76.0% (19/25) remained pain-free during follow-up, versus 44.0% (11/25) of group 1, with a significant difference ( $p = 0.001$ ). The best results were obtained when migraine prophylaxis was maintained for 24 months after patients became pain-free.

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### 1. Introduction

There is consensus on migraine prophylaxis based on clinical evidence and personal experience of those who prescribe [1]. Prophylaxis is administered daily for months or years to decrease frequency and intensity of attacks [2]. Beta-blockers, tricyclic antidepressants, calcium channel antagonists, serotonin antagonists and antiepileptics are the main drugs used [1,3].

Prophylaxis of migraine is important to reduce the frequency of attacks and therefore reduce the risk of chronification [4]. In chronic migraine, headache occurs on 15 or more days per month for more than 3 months, which has the features of migraine headache on at least 8 days per month [5].

Few drugs have been tested for the preventive treatment of chronic migraine. Onabotulinum toxin-A [6,7] and topiramate [8–10] have class I studies and evidence level A, and sodium valproate [11], class I study and level evidence B. The duration of preventive treatment for chronic migraine has not been established yet, but there are data demonstrating substantial rate of recurrence in patients treated for one year or less with early suspension of treatment [10,12].

Despite knowledge about prophylactic medications, uncertainty about the duration of treatment remains [13]. Studies suggest maintaining the prophylaxis for 8 to 12 months after reduction in pain parameters exceeds 50% [13,14].

There is another recommendation to maintain prophylactic treatment for at least six months. Then, discontinue it gradually after 75% reduction in frequency and intensity of attacks [1,2,15]. This improvement is observed through a headache diary [16]. If there is recurrence, treatment will be extended for as long as necessary, considering the limitations of each medication [1].

The aim of this study was to determine the minimum duration of migraine prophylaxis, after patients become pain-free [17].

### 2. Patients and methods

This was a prospective study with comparison of groups. The study population comprised all 10,490 migraine patients diagnosed according to criteria of the International Classification of Headache Disorders (ICHD-II) [18] at a headache clinic in the city of Teresina, in northeastern Brazil, from March 2005 to February 2010. Of this population, a total of 1600 patients met the criteria for inclusion and exclusion and were treated by an expert neurologist on headache.

Migraine patients aged between 18 and 50 years, no association with other primary or secondary headaches, using association of atenolol (25 to 50 mg/day), nortriptyline (10 to 20 mg/day) and flunarizine (2.5 to 4 mg/day) and pain-free for more than 90 days were included in the sample. We excluded pregnant patients or who discontinued treatment.

After becoming pain-free, we randomly selected 50 patients. They were divided into two equal groups: in group 1, prophylaxis was maintained for another 12 months and in group 2, for 24 months.

Each group was followed for more three years after the period of prophylaxis. We determined the attack frequency before and after

\* Corresponding author at: Center of Neurology and Headache of Piauí, Rua São Pedro, 2071/304, Teresina, PI 64001-260, Brazil. Tel.: +55 86 3221 9000.

E-mail address: [neurocefaleia@terra.com.br](mailto:neurocefaleia@terra.com.br) (R.P. Silva-Néto).

treatment using a headache diary. Pain-free time and the number of headache days per year during follow-up were defined as end-points.

The Epi Info 7 version 7.0.9.34 for statistical analysis was used. The Kruskal–Wallis and chi-square tests for differences between averages and categorical variables were used respectively, assuming a significance level of 0.05. This study was approved by the Ethics in Research Committee and all patients signed an informed consent.

### 3. Results

The percentage of patients who became pain-free for at least 90 days was 15.2% (1.600 / 10.490). According to prophylaxis groups, distributions by gender, age, initial frequency of attacks and time when patients became pain-free are summarized in Table 1. It was found that groups 1 and 2 did not differ significantly during therapy, although the average time of disappearance of attacks was higher in group 1 than in group 2.

The distribution of patients regarding the initial frequency of attacks and duration of preventive treatment in order to become pain-free for three consecutively months are summarized in Table 2.

During three years of follow-up, a trend of increasing the number of headache days was identified in both groups. However, in group 2, this number was significantly lower than in group 1 (Table 3).

We found that 11 (44.0%) patients in group 1 and 19 (76.0%) in group 2 remained pain-free during three years without prophylaxis (Table 4).

When we observe the temporal behavior of the average of headache days per year in each prophylaxis group, we identified a strong correlation between mean frequency of episodes and duration of prophylaxis (Fig. 1). Group 2 increased the number of headache days in 0.49 per year and was lower than group 1 that was equal to 3.25 per year.

### 4. Discussion

Migraine is a neurovascular disorder and involves abnormal modulatory mechanisms in the brainstem, subcortical and cortical levels to process pain [19,20]. As we know, various neurotransmitters are responsible for the generation of pain. So it's hard to imagine the treatment of migraine with a single drug [21–23].

Prevention of migraine is achieved through the use of prophylactic medication for a long time [13,14]. Generally, neurologists maintain prophylaxis for 6 to 12 months [24]. In this short time, it is hard to imagine a pain-free patient [2,14]. We suggest a longer duration based on our results, in which the time that patients became pain-free ranged from 16 to 21 months. By the way, with a longer duration of prophylaxis, a reduction on the tendency to increase the number of headache days per year was observed.

**Table 1**  
Clinical features of 50 migraine patients, according to prophylaxis groups.

Variables	Groups		p value
	1 (n = 25)	2 (n = 25)	
Gender			0.735 <sup>a</sup>
Female (n; %)	20 (80.0)	19 (76.0)	
Male (n; %)	5 (20.0)	6 (24.0)	
Age (years)			0.299 <sup>b</sup>
Mean (sd)	34.2 (10.4)	37.8 (11.4)	
Variation	19–57	19–57	
Initial frequency of attacks (days/month; sd)	16.3 (12.8)	16.4 (11.8)	0.769 <sup>b</sup>
Minimum and maximum values (days/month)	2–30	2–30	
Time when patients became pain-free (months; sd)	21.4 (11.2)	16.8 (9.9)	0.161 <sup>b</sup>
Minimum and maximum values (months)	6–48	6–48	

Legend: sd – standard deviation.

<sup>a</sup> p value based on the chi-square test.

<sup>b</sup> p value based on the Kruskal–Wallis test.

**Table 2**  
Initial frequency of attacks and duration of prophylaxis until patients become pain-free in 50 migraine patients, according to comparison groups.

	Initial frequency of attacks (days/month)	Duration of prophylaxis (month)
Group I		
Patient 1	10	16
Patient 2	30	22
Patient 3	4	18
Patient 4	4	9
Patient 5	30	22
Patient 6	6	10
Patient 7	2	6
Patient 8	30	26
Patient 9	2	14
Patient 10	30	36
Patient 11	2	9
Patient 12	30	36
Patient 13	4	12
Patient 14	30	48
Patient 15	2	6
Patient 16	4	16
Patient 17	30	24
Patient 18	30	24
Patient 19	30	18
Patient 20	30	28
Patient 21	18	30
Patient 22	5	24
Patient 23	10	36
Patient 24	4	8
Patient 25	30	36
Group II		
Patient 1	5	20
Patient 2	10	28
Patient 3	12	18
Patient 4	2	6
Patient 5	12	22
Patient 6	2	14
Patient 7	2	9
Patient 8	30	18
Patient 9	30	28
Patient 10	30	26
Patient 11	4	10
Patient 12	30	9
Patient 13	8	6
Patient 14	10	10
Patient 15	6	14
Patient 16	10	9
Patient 17	30	28
Patient 18	10	12
Patient 19	16	12
Patient 20	30	10
Patient 21	30	6
Patient 22	2	10
Patient 23	30	48
Patient 24	30	24
Patient 25	30	24

We agree with the experts who consider a reduction to more than 50% as a significant or excellent response to prophylactic treatment. However, a small percentage of patients may completely eliminate headache attacks if prophylaxis is maintained for some years. That is

**Table 3**  
Distribution of the average of number of headache days per year in 50 migraine patients, according to prophylaxis groups.

Headache days per year	Groups		p value
	1 (n = 25)	2 (n = 25)	
After the first year (sd)	5.1 (5.0)	0.4 (0.8)	0.001
After the second year (sd)	6.5 (6.0)	1.1 (2.1)	0.002
After the third year (sd)	8.6 (8.8)	2.1 (3.9)	0.004

Legend: sd – standard deviation.

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