Arch Neurosci. 2014 October; 1(3): e19083. DOI: 10.5812/archneurosci.19083

Published online 2014 October 01. **Research Article**

Long-Term Prophylaxis of Migraine

Francesco Raudino [1,*]

[1]Department of Neurology, Valduce Hospital, Como, Italy

*Corresponding author: Francesco Raudino, Department of Neurology, Valduce Hospital Via Dante n. 11 22100 Como, Italy. Tel: +39-31264109, E-mail: fraudino@hotmail.com

Received: December 21, 2013; **Revised:** December 25, 2013; **Accepted:** December 29, 2013

Background: Only few studies evaluated the long-term effectiveness of the prophylactic therapy of migraine.
Objectives: In this study we evaluate the optimal length of the prophylaxis in migtaineurs.
Patients and Methods: The length of the prophylactic therapy was evaluated in 68 outpatients with migraine without aura. The drugs dosage was adjusted upon clinical response while maintaining the aim of reducing the headaches frequency by at least 75%. Following a minimum of three months of well-being, a gradual tapering of the tested drug was attempted; whenever this resulted in worsening conditions, the original dosage was restored. The follow-up lasted from a minimum of one year to a maximum of five years.
Results: The prophylaxis mean length was 15.4 ± 15.3 months, ranging from two to 60 months; 33 (48.5%) patients with migraine required longer than one year of prophylaxis. In 14 (36.8%) patients with migraine who worsened after withdrawal of the prophylaxis, the drug previously effective became ineffective when prescribed again.
Conclusions: According to the recent studies, a significant number of patients require longer prophylaxis than usually advised by the guidelines. Besides, in a significant number of patients, one drug previously effective became ineffective if prescribed again after suspension.

*Keywords:*Migraine Disorders; Long-Term Migraine Prophylaxys

1. Background

Headaches often have a floating and unpredictable course, which raises uncertainty about the treatment length and timing of interruption. Pharmacologic trials usually evaluate the drugs effectiveness for only a few months, typically three to six months, while only few studies evaluate the effectiveness over a longer period. Existing guidelines also show some discrepancies. The 2001 Italian guidelines (1), the 2004 American guidelines for children and adolescents (2), and the 2006 European Federation of Neurological Societies (EFNS) guidelines (3) contain no information about the prophylaxis period length. The Canadian Headache Society suggests that an effective prophylaxis "should be continued for an adequate period, usually several months" (4) whereas the 2000 American guidelines for adults (5) and the British Association of Headache (6) advise standard treatment of three to six months after adequate control of the headache. The Switzerland Headache Society advises a minimum treatment of six months(7), whereas French guidelines (8) and the European Headache Federation (9) advise a treatment for eight to 12 months. Besides, recent data with topiramate suggest the necessity of longer treatment periods for a significant number of patients (10-12). In the daily practice, the decision of continuing rather than discontinuing the prophylaxis is often influenced by the patients' expectations, their attitude towards drugs, and their tolerance to pain.

2. Objectives

The current study followed a sample of patients with headache to evaluate their prophylaxis period length and the possible changes of symptoms after suspension of prophylaxis.

3. Patients and Methods

The study included 75 consecutive patients with migraine referred to a neurological outpatient clinic. Sixty-four were females and 11 were males with the mean age of 40.9 ± 12.4 years (range, 18-66 years). The diagnosis was made according to the International Headache Society criteria (13). The study excluded any patient younger than 18 years of age, with a history of cluster headache, pregnant or nursing women, those with any serious medical or psychiatric disorders, or those who took any drugs that might interfere with the migraine treatment. The frequency of headaches was evaluated using daily records and the pain intensity was assessed by Visual

Implication for health policy/practice/research/medical education:
A significant number of patients require longer prophylaxis than usually advised by the guidelines. Besides, in a significant number of patients one previously effective drug became ineffective if prescribed again after suspension. If confirmed, these results might help the physicians to manage the patients with migraine.

Analogue Scale (VAS). Follow-up visits were appointed every three to four months. The drugs were prescribed by taking the previous pharmacological history and the possible presence of other illnesses into account. The initial drug prescription was at the lower end of the recommended dosage range and the dosages was subsequently increased in the absence of troublesome side effects. Abortive medications, namely analgesics or triptans, were allowed. The drugs dose was adjusted according to the clinical response with the aim of reducing the headaches frequency by at least 75%. Whenever the drug proved to be effective after a minimum of three months of well-being, a gradual tapering of the drug was attempted; whenever the headache worsened, the previous dosage was restored. When the drug proved to be ineffective after three months of full dosage, a second trial with a different drug was initiated. The follow-up period lasted from a minimum of one year to a maximum of five years.

4. Results

Sixty-eight patients fulfilled the criteria for migraine without aura, three for migraine with aura, and four for chronic migraine. Because the small number of patients with aura and with chronic migraine, the patients were allocated in one group. Mean number of migraine days was 7.4 ± 5.1 per month (range, 2-20 days). Mean migraine duration was 21.4 ± 18.3 hours (range, 3-72 hours) and mean VAS was 7.5 ± 1.9 (range, 2-10).

At the first visit session, 22 patients had never tried a prophylactic treatment while the remaining 53 had previously undergone at least one therapy. The previous prophylaxis in these patients was topiramate in six patients, flunarizine in 25 patients; amitriptyline in 14 patients, propanolol and paroxetine each one in four patients. This prophylaxis proved ineffective in 35 patients; the improvement was equal or below 50% in 17 patients and it was discontinued in one patient because of the side effects. The mean duration of the preceding prophylaxis was 4.7 ± 3.9 months (range, one to 20 months).

Of the 75 patients examined, 39 were treated with an antiepileptic drug: 30 with topiramate at the dosage of 50-150 mg/day; six with lamotrigine at the dosage of 75-100 mg/day; three with valproic acid at the dosage of 500-1.000 mg/day. Twenty-two patients were treated with flunarizine at the dosage of 5-10 mg/day, two patients with amitriptyline at the dosage of 10-30 mg/day, 12 patients with propranolol at the dosage of 60-120 mg/day. The mean length of the prophylaxis period was 15.4 ± 15.3 months; the range of the prophylaxis period was from one to six months in 31 patients, from seven to 12 months in 12 patients, from 13 to 18 months in seven patients, and longer than 18 months in 25 patients.

Fifty patients were treated continuously for a mean period of 10.2 ± 12.4 months (range, 2-60 months) whereas 25 patients attempted once or twice to stop the prophylaxis. In this group, the mean length of well-being was 3.1 ± 4.6 months (range, ten days to 24 month). Renewing the prophylaxis with the same drug proved to be ineffective in 14 patients; in this group, the mean time between the stop and restart of the prophylactic treatment was 3.6 ± 5.2 months.

5. Discussion

In the literature, the length of the pharmacological trials typically varies from few weeks to few months; only few studies evaluated a drug effectiveness for longer than six months. Most studies are finalized at evaluating the drug safety. Regarding propranolol (14), a Cochrane review found clear evidence that propranolol was more effective than placebo in the short-term interval treatment of migraine whereas there was a lack of evidence on the long-term effects. Diamond et al. (15) continued the prophylaxis for six to 12 months in 148 patients with good response to propranolol; at the one to two months follow-up after the discontinuation of the drug, only 11% of the patients had rebound headaches. Wober and Coll. (16) followed up 64 patients treated with flunarizine, propranolol, or metoprolol for migraine to investigate the effectiveness of the prophylaxis. After three to six months of treatment, only three out of 19 patients treated with beta-blockers experienced reduction of migraine frequency by at least 50% for the entire 18 months follow-up, whereas the remaining 16 patients treated with beta-blockers experienced an increase in the migraine frequency after one to 15 months (mean, 4.4 months). Thirteen out of 45 patients treated with flunarizine experienced a reduction of migraine frequency by at least 50% for the entire follow-up, whereas the remaining 32 patients had an increase in the frequency of migraine after one to 28 months (mean, 7.2 months).

Bono and Coll (17) studied the long-term effectiveness of flunarizine in 120 patients; 72% of patients reported a minimum improvement of 60% after a three to nine months treatment. All 71 patients treated for one year and all 18 patients treated for two years were asymptomatic at the follow-up; at the first and second year follow-up, seven out of 13 and 18 out of 26 patients, respectively, interrupted the prophylaxis and reported having headache.Martinez-Lage et al. (18) treated 64 patients with flunarizine 10 mg/day for six months; 54% after three and 66.9% after six months of prophylaxis reported improvement; at the sixth month follow-up, 65% of the patients reported having experienced some improvement. Colucci D'Amato et al. (19) treated 67 patients with flunarizine 10 mg/day for one year; the frequency was reduced by about half in one to three months (average, 1.5 months). At the follow-up, 11 (16.4%) patients had overcome migraine and 49 (73.1%) patients had improvement of about 50%. Finally, Nuti and Coll. (20) treated 25 patients with flunarizine 10 mg/day and 25 patients with nimodipine 40 mg TDS for six months. Flunarizine was more efficacious than nimodipine and the efficacy after discontinuation lasted 8.4 ± 4

months in the group treated with flunarizine and 4.9 ± 3.5 months in the group treated with nimodipine. Data regarding the long-term use of valproic acid are quite scanty. Silberstein and Coll. (21) enrolled 163 patients who completed one or two randomized, double-blind, placebo-controlled studies evaluating the safety and efficacy of the divalproex for the prophylaxis of migraine in an open study for a total treatment period of up to three years. Patients experiencing a reduction in migraine by more than 50% ranged from 49% during the first three months to 70% at the end of the study; nonetheless, these data suffered from limited validity as only 33% of the patients completed the study. Indisputably, topiramate is the most studied drug. In an eight-month open-label extension large, 26-weeks trials, randomized, double-blind, placebo-controlled studies Rapoport and Coll (10) enrolled 567 patients, 159 on placebo and 408 on topiramate. (correct; the paper is extension of two trials and reports final results) Patients on topiramate in the double-blind study had a reduction in the number of headaches from 5.5 ± 2.3 per month to 3.4 ± 2.6 per month; therapy with topiramate for up to 14 months further reduced this number to 2.2 ± 2.4 per month. Diener and Coll (11) assessed the effects of discontinuing topiramate after a treatment of six or twelve months. Sustained benefit was found following the discontinuation of topiramate after six months although the number of migraine days increased. The authors suggested that patients should be treated for six months although some might require a 12-months treatment. Pascual and Coll (12) reached similar results; about half of 109 patients attending a specialized clinic because of their frequent migraine needed preventive treatment with topiramate for more than one year. Nelles and Coll (22) studied 366 patients treated with topiramate for at least six months; 183 patients continued the prophylaxis for one year. The median number of days with migraine decreased from six days at baseline to 1.2 days at month six to 0.7 day at month twelve. A double-blind study found the lamotrigine to be ineffective in migraine (23); however, in another small study, it was effective in tackling migraine (24).

The amitriptyline was used both in migraine and in tension-type headaches; however, most studies are short with only few of them reaching a six months period length (25). The amitriptyline proved effective in both types of headaches although the patients in the first month of treatment showed milder improvements in comparison to the patients treated for six months. The present paper tried to evaluate the prophylaxis length of cephalalgia and the reasons influencing therapeutic decisions. It was an observational study. For obvious reasons, randomized clinical trials cannot last several years hence useful information needs to be retrieved from the clinical practice. Because the patients' expectations play an important role in real-world practice, clinical decisions are not always in complete agreement with guidelines. Some remarks regarding the guidelines observance are in order. In clinical trials, drugs are usually considered effective when they reduce the frequency of headaches by at least 50%. However, since in daily practice the patients often judge this result as unsuccessful, we considered a drug to be effective only if it induced an improvement of at least 75%. The second remark related to the decision of starting and continuing the prophylaxis, which largely depended upon the patients' expectations, attitudes towards drugs, and tolerance to pain. For these reasons, a prophylactic treatment was started in patients with sporadic headache (two headaches per month) and the analysis included patients who stopped the prophylaxis after a short period. The third observation concerned the choice of drugs; drugs with proven efficacy were prescribed with the exception of patients who had already tried these drugs without any advantage or with serious side effects. In these cases, second- or third-line drugs, like lamotrigine, were prescribed. The first observation on the data related to their great variance; the standard deviations for many of the outcome measures were close to 100%. This result were likely related to the large degree of heterogeneity of sample with respect to the frequency and intensity of the headache. The length of the prophylaxis period varied greatly. Whereas in some patients the response was almost immediate likely because a placebo effect, the prophylaxis lasted much longer in other patients. The interlacement between headache and psychological problems is a well-known phenomenon. Since this study lacks a formal psychiatric diagnosis, it fell short of judging the weight of psychological problems as provocative factors of the headache or as codeterminants the patients' attitudes towards the prophylaxis.

The most interesting result of this study was the number of patients (42.6 %) who needed prophylaxis for more than one year. Clearly, this was a quite small study; moreover, patients who were grouped together were not exactly similar. Consequently, these results need to be confirmed by bigger and more homogeneous series. Nevertheless, these results were in agreement with more recent studies on topiramate, which have shown that a significant number of patients required a longer prophylaxis period than usually advised period in the guidelines. Another interesting point was the frequency of relapses after the suspension of the prophylaxis. In some patients, the well-being period lasted up to 24 months although in some cases the headache reappeared after few months or even few days. In addition, if some cases of early relapses could be judged as rebound headaches, in a significant number of patients the pain reappeared shortly after the interruption of the prophylaxis. Granella and Coll. (26) reported that only 15% of the patients were long-term responders. Hence, in the daily practice, patients must be followed-up after the interruption of the prophylaxis and considering the opportunity of renewing the therapy is necessary. In the series here analyzed, a drug previously effective became ineffective when prescribed again in 36.8% of patients. This is a well-known phenomenon (15)

that has not been examined in details but may provide some interesting insights for future research.

This work shows some important criticisms as the relatively small number of the patients, the great variance of the frequency as well as severity of the headaches, and consequently, the outcome measures. Besides, the guidelines have not been always followed regarding the decision to start the prophylaxis; hence, the choice of the drugs, the evaluation of their efficacy, and a formal psychiatric diagnosis is lacking. However, this was an observational study in the real world where following strict scientific criteria is not always possible. Therefore, despite some drawbacks, the results are worthy of interest and may be confirmed in more wide series.

Acknowledgements

None declared.

Authors' Contribution

Single author.

Financial Disclosure

There was not any relevant financial interests or financial conflicts within the past five years and for the near future.

Funding/Support

No funding or support.

References

1. Gallai V, Sarchielli P. Diagnostic and therapeutic guidelines for migraine. Italian Society for the Study of Headaches (SISC). *J Headache Pain.* 2001;**2**(1):s125–s9.
2. Lewis D, Ashwal S, Hershey A, Hirtz D, Yonker M, Silberstein S, et al. Practice parameter: pharmacological treatment of migraine headache in children and adolescents: report of the American Academy of Neurology Quality Standards Subcommittee and the Practice Committee of the Child Neurology Society. *Neurology.* 2004;**63**(12):2215–24.
3. Members of the task, force , Evers S, Afra J, Frese A, Goadsby PJ, Linde M, et al. EFNS guideline on the drug treatment of migraine - report of an EFNS task force. *Eur J Neurol.* 2006;**13**(6):560–72.
4. Pryse-Phillips WE, Dodick DW, Edmeads JG, Gawel MJ, Nelson RF, Purdy RA, et al. Guidelines for the diagnosis and management of migraine in clinical practice. Canadian Headache Society. *CMAJ.* 1997;**156**(9):1273–87.
5. Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* 2000;**55**(6):754–62.
6. British Association for the Study of Headache: Management of Migraine.. *Management of migraine. Guidelines for All Healthcare Professionals in the Diagnosis and Management of Migraine, Tension-Type, Clusture and Medication-Overuse Headache.* 3rd ed; 2007.
7. Swiss Headache Society.. *Headache and facial neuralgia. treatment recommendations.* 2010. Available from: http://www.headache.ch.
8. Graud G, Lantri-Minet M, Lucas C, Valade D. French guidelines for the diagnosis and management of migraine in adults and children. *Clin Ther.*;**26**(8):1305–18.
9. Steiner TJ, Paemeleire K, Jensen R, Valade D, Savi L, Lainez MJ, et al. European principles of management of common headache disorders in primary care. *J Headache Pain.* 2007;**8 Suppl 1**:S3–47.
10. Rapoport A, Mauskop A, Diener HC, Schwalen S, Pfeil J. Long-term migraine prevention with topiramate: open-label extension of pivotal trials. *Headache.* 2006;**46**(7):1151–60.
11. Diener HC, Agosti R, Allais G, Bergmans P, Bussone G, Davies B, et al. Cessation versus continuation of 6-month migraine preventive therapy with topiramate (PROMPT): a randomised, double-blind, placebo-controlled trial. *Lancet Neurol.* 2007;**6**(12):1054–62.
12. Pascual J, El Berdei Y, Gomez-Sanchez JC. How many migraine patients need prolonged (>1 year) preventive treatment? Experience with topiramate. *J Headache Pain.* 2007;**8**(2):90–3.
13. Headache Classification Subcommittee of the International Headache S. The International Classification of Headache Disorders: 2nd edition. *Cephalalgia.* 2004;**24 Suppl 1**:9–160.
14. Linde K, Rossnagel K. Propranolol for migraine prophylaxis. *Cochrane Database Syst Rev.* 2004(2):CD003225.
15. Diamond S, Kudrow L, Stevens J, Shapiro DB. Long-term study of propranolol in the treatment of migraine. *Headache.* 1982;**22**(6):268–71.
16. Wober C, Wober-Bingol C, Koch G, Wessely P. Long-term results of migraine prophylaxis with flunarizine and beta-blockers. *Cephalalgia.* 1991;**11**(6):251–6.
17. Bono G, Manzoni GC, Martucci N, Baldrati A, Farina S, Cassabgi F, et al. Flunarizine in common migraine: Italian cooperative trial. II. Long-term follow-up. *Cephalalgia.* 1985;**5 Suppl 2**:155–8.
18. Martinez-Lage JM. Flunarizine (Sibelium) in the prophylaxis of migraine. An open, long-term, multicenter trial. *Cephalalgia.* 1988;**8 Suppl 8**:15–20.
19. Colucci D'Amato C, Colucci D'Amato A, Alfano V, Giordano E, Marmo E. Flunarizine in long-term migraine prophylaxis: clinical evidence. *J Med.* 1990;**21**(3-4):201–7.
20. Nuti A, Lucetti C, Pavese N, Dell'Agnello G, Rossi G, Bonuccelli U. Long-term follow-up after flunarizine or nimodipine discontinuation in migraine patients. *Cephalalgia.* 1996;**16**(5):337–40.
21. Silberstein SD, Collins SD. Safety of divalproex sodium in migraine prophylaxis: an open-label, long-term study. Long-term Safety of Depakote in Headache Prophylaxis Study Group. *Headache.* 1999;**39**(9):633–43.
22. Nelles G, Schmitt L, Humbert T, Becker V, Sandow P, Bornhoevd K, et al. Prevention of episodic migraines with topiramate: results from a non-interventional study in a general practice setting. *J Headache Pain.* 2010;**11**(1):33–44.
23. Steiner TJ, Findley LJ, Yuen AW. Lamotrigine versus placebo in the prophylaxis of migraine with and without aura. *Cephalalgia.* 1997;**17**(2):109–12.
24. Gupta P, Singh S, Goyal V, Shukla G, Behari M. Low-dose topiramate versus lamotrigine in migraine prophylaxis (the Lotolamp study). *Headache.* 2007;**47**(3):402–12.
25. Jackson JL, Shimeall W, Sessums L, De Zee KJ, Becher D, Diemer M, et al. Tricyclic antidepressants and headaches: systematic review and meta-analysis. *BMJ.* 2010;**341**.
26. Granella F, Cavallini A, Sandrini G, Manzoni GC, Nappi G. Long-term outcome of migraine. *Cephalalgia.* 1998;**18 Suppl 21**:30–3.