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CLINICAL TRIAL REPORT

Adding Propranolol to Topiramate is Innefective in Chronic Migraine: In Search of a Better Combination Therapy for Chronic Migraine

Mario Fernando Prieto Peres

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Silberstein SD, Dodick DW, Lindblad AS, et al. Randomized, placebo-controlled trial of propranolol added to topiramate in chronic migraine. Neurology 2012;78(13):976-84 [1].

Rating: •• Of significant importance

Keywords Chronic migraine · Preventive treatment · Randomized clinical trial · Topiramate · Propranolol

Introduction: Chronic migraine (CM) treatment has few options and patients may fail to respond to current therapies. Therefore, it is important to study combination therapy.

Aims: The objective of this trial was to assess the efficacy and safety of adding propranolol to topiramate in chronic migraine subjects inadequately controlled with topiramate alone.

Methods: This was a double-blind, placebo-controlled, randomized clinical trial conducted through the National Institute of Neurological Disorders and Stroke Clinical Research Collaboration, expected to randomize 250 chronic migraine subjects inadequately controlled (≥10 headaches/month) with topiramate (50–100 mg/day) to either propranolol LA (long acting) (240 mg/day) or placebo. Primary outcome was 28-day moderate to severe headache rate reduction at 6 months (weeks 16 to 24), compared with baseline (weeks -4 to 0).

Results: A planned interim analysis was performed after 48 sites randomized 171 subjects. The data and safety monitoring board recommended ending the trial after determining that it would be highly unlikely for the combination to result in a significant reduction in 28-day headache rate compared with topiramate alone if all 250 subjects were randomized. No safety concerns were identified. At study closure, 191 subjects were randomized. The 6-month reduction in moderate to severe 28-day headache rate and total 28-day headache rate for combination therapy vs. topiramate alone was not significantly different: 4.0 vs 4.5 days (moderate to severe 28-day headache rate; $p=0.57$) and 6.2 vs 6.1 days (total 28-day headache rate; $p=0.91$).

Discussion and Editor's Comments

Propranolol, added to topiramate, is ineffective in chronic migraine patients who fail topiramate monotherapy. This is the first trial looking at a combination therapy strategy for CM management. Although it is a negative trial, there is still potential for combination therapy. Below, we highlight reasons why combination therapy in chronic migraine should still be tested in future clinical trials ,and why it may be useful in chronic migraine management.

1. The first aspect to consider in CM management is whether monotherapy is the best first step in treatment. Identifying non-responders by looking at predictive factors such as comorbid conditions may help in deciding on a combination therapy at the beginning of treatment.
2. If monotherapy is in fact the best initial step in CM management, further clinical trials comparing treatments are necessary to establish the first line medication or non-pharmacological treatment.

M. F. P. Peres
Instituto Israelita de Ensino e Pesquisa -Hospital Albert Einstein, Sao Paulo, Brazil

M. F. P. Peres
Department of Neurology, UNIFESP, Escola Paulista de Medicina, Sao Paulo, Brazil

M. F. P. Peres (✉)
Al Joaquim Eugenio de Lima,
881cj 708, Sao Paulo, Brazil
e-mail: marioperes@yahoo.com
URL: http://cefaleias.com.br/

3. When a CM patient fails any given pharmacological treatment, it is probably a different CM population, more severe, refractory and more prone to another medication fail. Non-pharmacological strategies could be a suitable option. If a second medication trial is decided for the patient, the best approach should carefully studied.
4. Adding a beta-blocker to a neuromodulator may not be the best combination strategy. Although different mechanism are covered with these two drug classes, the main issues in chronic migraine management are not considered.
5. Adding a sleeping adjuvant such as an antidepressant (tryciclic, mirtazapina, trazodone, agomelatine), a benzodiazepine (clonazepan, alprazolan), a neuroleptic (quetiapine, olanzapine) or melatonin may restore poor sleep frequently seen in CM.
6. Adding a medication focusing anxiety symptoms and/or disorders very frequently associated with CM is always a need in clinical practice. Topiramate sometimes helps relieve anxiety symptoms, particularly compulsive/feeding behavior, but when it fails, a specific medication or non-pharmacological treatment should be started. Anxiolitics such as benzodiazepines, buspirone, or antidepressants such as SSRIs and SNRIs are good options. Pregabaline may also be used.
7. When a mood disorder is present, whether unipolar depression or one of the bipolar spectrum disorders, an antidepressant or a mood stabilizer may be part of the optimal combination.
8. When and to which CM patients botulinum toxin should be given is also a very important aspect in future clinical trial research.

A common and debilitating condition [2] such as chronic migraine cannot stay with the current scarce options for its management.

Disclosures

No potential conflicts of interest relevant to this article were reported.

References

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2. Queiroz LP, Peres MF, et al. A nationwide population-based study of migraine in Brazil. Cephalalgia. 2009;29(6):642–9.