Expert Opinion

Bending the Rule of Monotherapy for Migraine Prevention?

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Most of us prescribe polytherapy for prevention for intractable migraine and may have our own favorite combos. And yet, there is an amazing dearth of studies to guide such a common clinical problem.

CLINICAL HISTORY

A 32-year-old woman had migraine without aura 8 times per month. After taking propranolol long acting 160 mg daily for 4 months, the frequency was 6 times monthly. She had previously been on monotherapy with therapeutic doses of amitriptyline, topiramate, and extended release divalproex sodium without benefit.

Questions.—Would the patient benefit from the addition of a second preventive medication? What is the evidence for combined therapy for migraine prevention?

EXPERT COMMENTARY

Pharmacological prevention of migraine is of crucial importance for the treatment of patients who are experiencing frequent attacks. The use of preventatives should be obligatory for those migraine patients with more than one migraine attack per week, so as to try to restore a reasonable quality of life and avoid the development of analgesic overuse. Unfortunately, however, the case of this young migrainous woman unresponsive to several sequential preventatives is far from rare in daily clinical practice. Migraine preventatives with well-demonstrated efficacy include β-blockers, the neuromodulators valproate, topiramate and, possibly to a lesser degree, flunarizine and amitriptyline. This rather long list of drugs does not mean that an ideal preventive treatment for migraine is available. In the best case scenario, we can expect that about 50% to 60% of patients improve with these medications. In clinical practice, almost a quarter of patients cannot tolerate these drugs and about half of those who notice some benefit also experience adverse events, especially weight gain and central nervous system side effects.[1] Therefore, and agreeing with the repeated contention that monotherapy should be the rule in migraine prevention,[2] what should we do with the at least one-third of cases coming to our clinics who either cannot tolerate or do not improve on *any* of the preventatives?

Very probably, the explanation for this insufficient efficacy and tolerability of current preventatives is that their mechanisms of action are not truly specific, but indirect and partial, in terms of migraine pathophysiology. Think, for instance, of migraine as a potential channelopathy: none of the already available drugs are specific for a particular channel but act either on a variety of them (eg, topiramate or flunarizine) or partially on the theoretical consequences of channel malfunctioning (eg, β-blockers or amitriptyline). In summary, the mechanisms of action of the current preventative drugs are nonspecific, partial and different.

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That being so, why not break the rule of monotherapy and try to combine these drugs in resistant patients? Hypothetically, drugs acting at different levels of the migraine pathophysiological cascade could have summatory effects for the preventive treatment of this condition. This approach will not sound as new to neurologists. We prescribe combined therapy, based on the same reasoning of complementary mechanisms of action, in a variety of neurological conditions, such as epilepsy, Parkinson's disease, etc. No rigorous clinical trials, however, have yielded convincing evidence of the additive effects of a second or third preventative drug for migraine. In a recent open trial, we explored whether combining a β-blocker and sodium valproate could lead to an advantage in efficacy in 52 patients with migraine previously resistant to the two medications in monotherapy for 2 to 3 months.[3] Combination therapy appeared to be a good migraine preventive in over 50% of previously resistant migraine cases. Such a strategy, though, could also increase side effects, while potential interactions are not fully understood.[2] In our trial, 20% of our patients were unable to tolerate even usually low doses of the two drugs when used in combination. In any case, from our results combining two treatments appears to be a conceptually reasonable option for the preventive treatment of resistant migraine patients.[3]

When should the use of combined treatment be considered and which combinations? We think that combined treatment should be prescribed only after the patient has not responded to two consecutive adequate trials (therapeutic doses for at least 6 weeks) of two of the "major" preventatives (especially β-blockers and neuromodulators), so long as that tolerability is not a problem. Regarding potential combinations, a β-blocker together with amitriptyline at night is an adequate option for those migraine patients experiencing interictal, tension-type-like headaches.[4] For "purer" migraine patients and to maximize compliance, we would recommend a β-blocker in a morning dose (eg, nadolol, atenolol, or long-acting propranolol) plus a neuromodulator at night (topiramate or extended release valproate). In refractory cases with tolerability problems on these combinations, other usually forgotten options, such as riboflavin[5,6] or magnesium,[7] at adequate doses, could also be tried. Lamotrigine is one further combination option in case relevant auras still remain.[8] In summary, with no current ideal drug for migraine prevention and with nothing very promising on the horizon, the combination of these preventatives is an option to explore in clinical practice for those patients who have shown no clear effect on appropriate monotherapy. It would be very recommendable to design in the future controlled clinical trials testing these potential advantages of combination preventive therapy in resistant patients. The same is true for symptomatic treatment, where at least 20% of patients do not respond either to triptans or NSAIDs separately and some recent, preliminary trials (and daily experience) suggest that these refractory patients can benefit from their combination.[9,10]

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