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Controversies in migraine: monotherapy

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Abstract Migraine patients with frequent and severe headaches need prophylaxis. The most used approach is monotherapy, i.e. one of the available preventive compounds is prescribed to the patient, testing its efficacy and tolerability during a treatment period of some months. Some clinicians use to add a second (or even a third) preventive compound to improve the effects of pharmacological prophylaxis, using an approach that can be defined as polytherapy. In this paper, the main advantages of monotherapy are briefly reviewed, taking into account several aspects: published evidence on polytherapy; the possibility to evaluate the adverse events of the prescribed treatment and to assess its real efficacy; the possibility of addressing different patient's needs, particularly the treatment of comorbidities and the development of an effective patient–physician communication.

Keywords Migraine · Prophylaxis · Monotherapy · Polytherapy · Combination

Introduction

The management of migraine is an important health care issue due to the severity of pain and the presence of relevant associated symptoms and to the occurrence of attacks for several years in most patients, with relevant impact on individuals and on society. Migraine causes disability in daily activities, leads to diminished quality of life, and is characterised by high societal costs [1–5].

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The treatment of migraine patients includes different approaches: avoidance of trigger factors; non-pharmacological therapies; administration of medications. While all migraineurs need appropriate acute treatments to be used to abort individual attacks, patients with severe and/or frequent migraines require also prophylaxis, which requires daily administration of anti-migraine compounds for long periods to reduce headache frequency and improve functioning [6–12].

Prophylaxis of migraine: monotherapy or polytherapy?

Generally, migraine patients are treated with one preventive compound, chosen by the treating clinician among those which are available, and which is usually prescribed for periods of 3–6 months. The minimum suggested trial to assess the benefits of prophylaxis is in fact 2–3 months [6, 7, 11], although many physicians prefer longer treatment periods, which can give more relevant results, as indicated by recently published trials [13, 14]. After such a treatment period, the same or a different compound can be prescribed for a similar or for longer periods, taking into account the efficacy and tolerability of the first prescription as assessed at follow-up visits. This treatment approach can be defined as monotherapy. On the other hand, in clinical practice, some migraine patients are treated with a polytherapy, or combination therapy, which means that they are given two or more preventive compounds at the same time. The basis of this treatment approach in migraine has been reviewed by Krymchantowski and Bigal [15].

Available guidelines on migraine treatment do not explicitly address the problem of monotherapy/polytherapy. An implicit suggestion for using monotherapy may be viewed in the recommendations included in the

Evidence-Based Guidelines for Migraine Headache in the Primary Care Setting, developed by the US Headache Consortium [7]. When discussing the General Principles of Management of Prevention of Migraine, in the Medication Use session, the Authors give the following indications: "A. Initiate therapy with the lowest effective dose. Begin with a low dose *of the chosen pharmacological agent* and increase the dose slowly…B. Give *each treatment* an adequate trial…".

Different aspects may in fact suggest that polytherapy could have some advantages, the most commonly reported being the following: (a) drugs used in migraine prevention are not effective in all the treated patients; (b) some studies reported that the efficacy of some polytherapies in migraine prophylaxis give better results than those achieved in the same patients when using monotherapy; (c) migraine patients often present with comorbid or coexisting condition which may need the prescription of one or more daily treatments.

The aim of the present paper is to briefly discuss the above reported issues, in order to indicate the main reasons for preferring monotherapy as the preferred approach in the pharmacological prophylaxis of migraine. The focus of the present paper is episodic migraine, while discussion of treatment approaches in transformed or chronic migraine is beyond the scope of this article.

Possible advantages of monotherapy

Published international treatment guidelines and specific reviews include extensive reports about the evidence of efficacy of several anti-migraine compounds, based on several published randomised clinical trials [5–12]. However, clinical experience teaches that no single preventive compound is effective in all patients. According to data from clinical trials, headache response (i.e. the proportion of subjects on the given medication achieving a reduction in migraine frequency >50 % as compared to non-treatment periods) of the available compounds is below 50 %. Thus, a relevant proportion of patients is likely to have an insufficient response with one or various compounds.

Some studies have reported that the association of two different anti-migraine compounds may give better results than those obtained with monotherapy, but evidence on polytherapy of migraine is scarce, and not convincing.

Considering the published papers in which episodic migraine patients were studied, a few reports on this topic are available.

Four studies were open-label: in the first study the combination of a beta-blocker + valproate was effective in a series of patients not previously responding to beta blockers, Ca-entry blocker or valproate [16]; in two other studies the associations of atenolol + nortriptyline + flunarizine, and of beta-blocker + topiramate were reported to be superior to monotherapy with the same drugs when used alone, although statistical analyses were not performed [17, 18]; in a recent study [19] the proportions of patients with headache response were not significantly different when prophylaxis with flunarizine or topiramate in monotherapy, and flunarizine + topiramate in combination were evaluated.

Five double-blind studies have been published. In one study, the combination of propranolol and fluoxetine was superior to monotherapy with one of the two compounds [20], but without significant difference at statistical analysis. No difference in efficacy was evident in other two controlled studies: low doses of propranolol and propranolol + nortriptyline gave similar results [21]; polytherapy was not superior to monotherapy in patients treated with topiramate alone, amitriptyline alone or a combination of these drugs, although combination treatment lead to a higher patient satisfaction [22]. Only a recently published trial both the reduction in migraine days and the proportion of patients with headache response were significantly higher in patients in polytherapy with topiramate + nortriptyline than in those in monotherapy with each of these compounds [23]. In another controlled study, a series of patients who experienced at least a 50 % reduction in headache frequency after treatment with either topiramate or valproate, but at the same time reported intolerable adverse events, were switched to the association of the two compounds at sub-optimal daily doses (topiramate 75 mg/day + valproate 500 mg/day): in more than half of the sample tolerability improved "without any decrease in efficacy" [24].

Most of these studies share some characteristics: small clinical samples were enrolled; the studied subjects were often "refractory" to one or more preventive compounds; the drugs which were tested in associations were different across different studies, and some compounds were not among those included in the first or second choice drugs for migraine prophylaxis (such as nortriptyline and fluoxetine) [6, 7, 12].

On the basis of this brief review, it is clear that there is no conclusive evidence of a higher efficacy of polytherapy over monotherapy in the prophylaxis of migraine.

Many migraine patients have comorbid or coexisting conditions: epilepsy, colitis, essential tremor, sleep apnea syndrome, other chronic pain disorders, and, particularly psychiatric (depression, anxiety, bipolar disorder) and cardiovascular (hypertension, Raynaud's syndrome, angina, stroke) disorders [25]. Thus, a proportion of patients with migraine and concurrent medical problems may need two or more drugs. However, the prescription of more than one daily treatment should not be regarded "per

se" as polytherapy of migraine. This situation has been defined as "false polytherapy" in a previously published paper on chronic migraine patients [26], and it may correspond in most cases to what Silberstein et al. [25] defined as therapeutic independence in their review paper on pharmacological approaches to managing migraine and associated comorbidities. This approach is based on the prescription of two or more drugs to a given patient, each compound meant to treat each condition separately. The absolute distinction between patients on a "true" polytherapy (patients in whom all the drugs are prescribed to treat migraine) and those who are on 'false polytherapy'' or are being treated according to therapeutic independence (in whom one compound is prescribed for migraine prevention, and one or more other drugs used on a daily basis aim to treat coexistent conditions) may be not easy in clinical practice with headache patients [26]. The main reason is that many drugs commonly used in migraine prophylaxis are primarily indicated—or have proven efficacy—in other neurological and non-neurological disorders (e.g., valproate for epilepsy, propranolol for hypertension and coronary heart disease).

On the other hand, the fact that most anti-migraine compounds are in fact effective in other conditions may encourage the use of monotherapy, leading to the so-called "two-for-one" strategy. This approach may reduce the number of daily medications in a given patient, limiting possible adverse events, and enhancing patient's compliance and adherence to therapy. However, clinicians must be aware that the use a "two-for-one" strategy may have some risks, which have been systematically discussed by Silberstein et al. [25]. The most common are the risk of treating only one condition; the risk of choosing suboptimal medications. In fact, although one of the two coexisting conditions may be adequately treated with a single compound with potential effects on both migraine and on the other condition, this second illness may require different treatment schedules or daily doses than those used for migraine. Furthermore, the "two-for-one" strategy may lead to the choice of a second- or third-tier line treatment for the coexisting condition or for migraine itself.

Another risk of polytherapy may be related to the problem of adverse events. It is well known that all the drugs commonly used in migraine prophylaxis may cause various side effects [5–12]. In fact, different compounds may be responsible for similar effects: e.g., depression may be caused by propranolol or flunarizine; weight gain may be found in patients on pizotifen, flunarizine, valproate, and amitriptyline. Having a patient on monotherapy enables the physician—and the patient—to evaluate these effects, in order to guide possible changes in daily dose, administration schedule, or withdrawal of a given compound. On the other hand, using polytherapy it could be difficult to assess which of the current treatments needs to be corrected. Furthermore, polytherapy might promote a sum of potential adverse events caused by each of the prescribed compounds.

The use of a single compound may contribute to reduce those factors that are known to negatively influence acceptance of prophylaxis and adherence to the prescribed therapy in clinical practice. This may be particularly evident in those patients who reject the idea of taking a medication each and every day for periods of months, and who are seriously concerned about possible intolerable adverse events [11]. On the other hand, polytherapy may enhance the risk of self-reduction of the prescribed treatments and of withdrawal of medications following trivial side effects.

Concluding remarks

Migraine patients with frequent and severe headaches need daily administration of a preventive compound (prophylaxis). Generally, one preventive compound is prescribed among those that are available, testing its efficacy and tolerability during a treatment period of some months, before prescribing a new therapy, if necessary (monotherapy). However, according to the results of published randomised clinical trials, a considerable proportion of migraineurs who are treated with a given compound may report unsatisfactory results. In clinical practice, some migraine patients are treated with two or more compounds, as some clinicians think that adding a second (or a third) preventive drug may significantly improve the effects of the pharmacological prophylaxis of migraine.

However, polytherapy has not been extensively tested in appropriate clinical trials in migraine patients, and evidence on the real efficacy of the possible association of two or more preventive drugs in migraine prophylaxis is still lacking. For this reason, monotherapy should be the preferred approach in patients with episodic migraine.

As discussed above, monotherapy may have several advantages over polytherapy. It offers the possibility to evaluate accurately the adverse events of a given compound and to assess its real efficacy, allowing the clinician to address the changes needed in the daily dose or in the pattern of administration. Moreover, using a single compound may protect the patient from the potential summing of adverse events or drug interactions.

The results of monotherapy in migraine prophylaxis may be more evident obtained in daily practice as compared to those reported in clinical trials.

The differences in the adverse events profile as well as in the indications for disorders other than migraine which characterise the different anti-migraine compounds give

the chance to tailoring a single preventive compound to the specific patient's needs. Clinicians can obtain optimal results choosing prophylaxis according to patient's characteristics (such as life-style, occupation, preferences), and above all taking into account the possible comorbidities—given the fact that most anti-migraine compounds are effective in conditions other than migraine.

A further aspect that may enhance the satisfaction from a given prophylaxis in clinical practice is the possibility to develop patient–physician communication which has a crucial role in the management of migraine [11]. Also for these aspects, monotherapy seems a better approach than polytherapy, with an easier management of issues related to patient's education and reassurance about possible adverse events and about the daily administration of medications for long periods.

In conclusion, monotherapy seems the most appropriate treatment choice in most episodic migraine patients. Polytherapy should be considered in those patients with proven unsatisfactory response to most available preventive compounds [15, 27]. Before declaring a treatment failure with the monotherapy approach, most—if not all—the first and second line preventive compounds should be tested, and each chosen compound must be used in appropriate daily doses and for adequate time periods.

Conflict of interest The author certifies that there is no actual or potential conflict of interest in relation to this article.

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