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REVIEW

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Clinical considerations preliminary to application of the Italian Society for the Study of Headache's guidelines regarding migraine prophylactic treatment

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Abstract The main goals of prophylactic treatment for migraine are to decrease headache attack frequency, length and intensity, to improve the efficacy of symptomatic drugs, to reduce their need, and to prevent pain chronicization. Therefore, the choice of a prophylactic drug and the modality of treatment is not easy and often not adequately supported by literature data nor by current national and international guidelines. Moreover, the response of the migraine patient to treatment is often unforeseeable. The aim of this short review is to provide some practical suggestions to the physician regarding how to decide when to begin a migraine prophylactic treatment and how to apply the specific guidelines of the Italian Society for the Study of Headache.

Key words Drugs • Evidence-based medicine • Guidelines • Migraine • Prophylaxis • Pharmacological treatment

Introduction

This paper provides some clinical suggestions regarding the prescription of prophylactic headache treatment. The paper is directed to primary care physicians and to algologists who do not currently manage headache, and is based on the scientific evidence as summarized in the clinical guidelines elaborated by the Italian Society for the Study of Headache [1, 2].

Indication for migraine prophylaxis: what should be achieved?

The main goals of prophylactic treatment for migraine are to decrease headache attack frequency, length and intensity, to improve the efficacy of symptomatic drugs, to prevent the frequent intake of analgesic and specific migraine drugs, and to prevent the episodic headache from turning into chronic headache [2, 3]. Therefore, clinical evaluation of the patient, regarding the frequency, length and intensity of their headache attacks, is preliminary to the evaluation of treatment efficacy. In randomised clinical trials, a good answer to prophylactic treatment is evaluated as a 50% responder rate in 50% of the treated subjects [4, 5].

In everyday clinical practice, we often observe that in the vast majority of patients migraine does not have a constant trend and its time-related evolution depends on trigger factors often contingent and not foreseeable in the single subject. Only an adequately compiled headache diary concerning the previous months can reveal eventual pain cycles and help in deciding the preventive treatment start time and length [6]. If this record is not available, we believe that there is a risk of prescribing an ineffective drug too long or, quite the opposite, of discontinuing the treatment before the time necessary to observe the desired response to a potentially effective drug.

Adequate therapeutic choices are not easy, even when specific guidelines are available. First of all, it is necessary to decide if, when and how to begin a prophylactic treatment, but on this point there are no absolute indications [2].

Some useful parameters to help in this choice are summarised in Table 1. However, deciding not to treat is a therapeutic choice and therefore it needs a rigorous scientific approach. Each prescription decision requires the physician to decide specific efficacy and safety goals at the treatment beginning and to periodically re-evaluate the patient during the therapy [7]. To monitor the patient, we can employ both quantitative and qualitative indexes. Headache index, evaluating migraine attack length and intensity or the number of headache days, and the analgesic and specific migraine drug intake are good quantitative indexes, while accompanying symptoms, analgesic drug efficacy and patients' quality of life are examples of qualitative indexes [2, 8]. The treatment results will obviously depend on the baseline characteristics of the patients and of their migraine attacks and they are not always those expected from the results of the main clinical trials used to define the guidelines [9].

Table 1 Indications for prophylactic treatment of migraine

Migraine attack characteristics
At least 3 severe attacks in 30 days
Attacks last more than 4 hours, or prolonged aura is present
Symptomatic medications are ineffective or the patient does not tolerate their side effects
Patient's quality of life is decreased by migraine in an unacceptable way, even if symptomatic medications are effective and well tolerated

To relate the results of a treatment given in usual clinical practice to those found in the scientific literature, guidelines should clearly indicate the inclusion and exclusion criteria applied to select the patients for whom the results are reported [10]. Randomised clinical trials provide objectives and systematic data on drug efficacy and safety, but they are often inadequate to guide the therapeutic choices in the "real world" outside the aseptic and ideal setting where they are carried out [11, 12].

The choice of the "right" drug: some practical advice

In selecting a drug for prophylactic treatment, the most important parameters to consider are the drug's efficacy, tolerability and safety after prolonged assumption, known contraindications to the drug, possible pharmacological interactions, and the acceptability by the patient [13]. Table 2 reports some elements that are still not clearly defined in the scientific literature and thus not evidence-based regarding migraine prophylactic treatment [14]. Monotherapy is undoubtedly preferable, although in special cases, especially in patients resistant to more simple treatments, it possible to use drug associations (Table 3) [2]. However, even if commonly used, their efficacy and safety have not been adequately demonstrated in well carried out and specifically designed clinical trials [15].

Table 2 Evidence-based medicine and migraine prophylactic treatment: some points not yet clearly defined

Predictive factors of effectiveness of the different drugs in specific patient sub-categories
Strategies to start and to discontinue the treatment
Minimal and maximal lengths of the pharmacological prophylaxis
Efficacy and inefficacy predictive factors for repetition of the same drug
Indications for the sequential use of drugs of the same pharmacological class or of different classes

Table 3 Drug combinations used in migraine prophylaxis

Possible combinations
Antidepressants and beta-blockers
Antidepressants and calcium-channel blockers
Antidepressants and valproic acid
Beta-blockers and flunarizine
Combinations used with caution
Beta-blockers and verapamil

A rational therapy requires not only an accurate diagnosis but also a good comprehension of the disease's physiopathology [16, 17]. Because migraine pathogenesis is not well known, specific and resolutive therapies have not been developed either. Drugs employed in prophylaxis are only partially efficacious and the treatment result is often unsure and unforeseeable [18].

From our everyday experience, we know that the preventive drug theoretically more efficacious in a patient may not be the most appropriate drug for treating all the phases of the patient's migraine. Efficacy, safety, indications and contraindications of a drug do not have absolute value, but they depend on the migraine attack intensity and frequency and on the patient's characteristics. While a prophylactic drug is ineffective, a drug of another therapeutic class or the combination of drugs different could be [19].

Tables 4 and 5 present some recommendations useful, respectively, for the physician and the patient regarding prophylactic treatment [20, 21]. Not only is the choice of drug problematic, but also the modality of a preventive treatment. In fact, to obtain the patient's compliance to the treatment and to accelerate the therapeutic response it is theoretically advantageous to rapidly increase the dose to the full dosage.

Table 4 Our main recommendations for physicians who prescribe a migraine prophylaxis

Chose the drug considering the eventual medical or psychiatric co-morbidity (there is no well established order to follow in prescribing the different prophylactic drug classes)
Prefer monotherapy in order to more easily evaluate both efficacy and side effects (especially the causal relationship) of the employed drug
Continue therapy for the time required to verify drug efficacy (encourage patients to follow the treatment even if the benefit is not immediate) and then prolong it for a variable time on the basis of the drug used and the patient's characteristics
Obtain patient compliance by explaining frequent drug side effects and by using long-acting formulations (reducing the number of daily doses can improve patient compliance)
Explain to the patient that an excessive use of analgesic and specific migraine drugs can reduce the efficacy of prophylactic treatment
Remember that the efficacy of prophylactic treatment decreases after some months and that further prophylatic cycles give hardly the same results as the first
Evaluate the usefulness of reducing the dosage to the minimal effective dosage or of slowly tapering it when the desired benefit has been obtained
Verify periodically the efficacy of therapy and the patient's compliance by monitoring the headache diary
Re-evaluate the diagnosis in case of resistance to treatments with drugs of different pharmacological categories, if the attack frequency is always elevated, when the patient excessively uses symptomatic drugs or if the migraine characteristics change

Table 5 Explanations that can be given to a patient who has to begin migraine prophylaxis

The aims of prophylactic treatment are to decrease the headache attack frequency, length and intensity, to improve the efficacy of symptomatic drugs, to reduce their need, and to prevent the episodic headache from turning into a chronic headache
Patient co-operation is indispensable, and the therapy must be followed according to the physician's prescription, even for many months
Sometimes side effects appear before the therapeutic effect, which usually begins after several weeks of treatment (sometimes even after 2–3 weeks)
Often side effects are only transient and disappear within the first few days of treatment
Usually the prophylactic treatment does not completely eliminate migraine attacks: often it decreases the frequency, but not the intensity

On the other hand, in this way we increase the risk that the patient develops side effects and discontinues the treatment before experiencing its benefit [22]. Thus, slow dose escalation is generally recommended (this does not apply, for instance, to flunarizine). It is generally agreed, instead, that the treatment has to be interrupted slowly, tapering the dosage to avoid rebound symptoms, and that the dosage should rapidly be re-increased if migraine immediately worsens. However, this event is infrequent, because most drugs employed in migraine prophylaxis have a carryover effect that continues after treatment interruption [23].

Comorbidities and drug-drug interactions

Medical and psychiatric co-morbidities significantly influence the choice of prophylactic drug. The coexistence of a second illness imposes the physician to exclude those medications that are contraindicated as, for example, beta-blockers in asthmatic patients [24]. In Table 6, we report the most relevant contraindications and indications. In patients with psychiatric co-morbidity, the prescription of one drug to treat both pathologies could be a suitable solution. However, drugs with double indications are few, and the employment of two different specific drugs has the advantage of allowing the independent modulation of the doses on the basis of the desired effect [25]. Finally, it is important to remember that drug combinations are always a possible cause of pharmacokinetic and pharmacodynamic interactions (partially avoidable selecting the drugs to associate on the basis of the more widely known contraindications), and these treatments must be constantly monitored to speedily recognise eventual interactions [16].

Drugs can interact at many levels and cause addictive toxicity that is specific and often not foreseeable based on the knowledge of the single agents. It is an ingenuity to presume that there is no interaction between two drugs only because no previous toxicity data have been reported [26]. It is especially relevant to remember the possibility of pharmacological interactions even between compounds used for acute and prophylactic treatment of headache. Sumatriptan and rizatriptan are metabolised selectively by the monoamine oxidases (MAO) so that they may interact only with MAO inhibitors, rarely employed in Italy [27, 28]. Other triptans are metabolised partially or totally by the cytochrome P450 system, so that inhibitors or inducers of

the specific metabolising isoforms could cause some pharmacological interactions. However, the main reported interaction between drugs assumed for symptomatic treatment and prophylactic drugs is that between propranolol and zolmitritpan. The drug-drug interaction is, however, not clinically significant when patients use a dose of 2.5 mg, as usually done in Italy [29]. From a pharmacodynamic point of view, the co-assumption of a triptan and a serotoninergic drug, like most antidepressant drugs used in headache prophylaxis, increases the risk of developing a serotoninergic syndrome [30]. So, the drugs to begin a prophylactic treatment has to be adequately chosen even considering the risk of pharmacodynamic and pharmacokinetic interactions with drug usually assumed for symptomatic headache treatment.

Table 6 Preventive management of migraine: main relative contraindications and indications for the choice of drugs in comorbid conditions. Only drugs available on the Italian market with levels of evidence A and B and known clinical effectiveness as reported in the guidelines of the Italian Society for the Study of Headache [1, 2] are listed

Drug class	Contraindications	Indications
Beta blockers[a]	Congestive heart failure, bradycardia, arterial hypotension, peripheral vascular diseases, asthenia, depression, dizziness, asthma, emphysema, insulin-dependent diabetes, pregnancy, lactation	Angina pectoris, hypertension, tachycardia, anxiety, panic attack, essential tremor (proporanolol)
Calcium-channel blockers		
Verapamil	A-V block, hypotension, constipation, bradycardia	Asthma, hypertension, tachycardia, stroke, prolonged aura
Nimodipine	Abdominal discomfort, gastroesophageal reflux, hypotension, tachycardia	Asthma, hypertension, bradycardia
Flunarizine, cinnarizine	Asthenia, depression, obesity, parkinsonisms, pregnancy, lactation	Asthma
Antidepressants		
Amitriptyline	Drowsiness, obesity, constipation, urinary retention, bradycardia, QT prolungation, mania	Panic disorders, depression, anxiey disorders, tension-type headache, depression, Horton's syndrome
Fluoxetine	Asthenia, insomnia, dyspepsia, tremors	Same as for amitriptyline
Pizotifen	Asthenia, obesity, pregnancy, asthenia, glaucoma, prostatic hypertrophy	Same as for amitriptyline
Antiepileptics		
Valproic acid	Liver disease, hemorragic diatheses, asthenia, tremors, obesity, pregnancy	Prolonged or atypical migraine
Gabapentin	Asthenia, dizziness, pregnancy, lactation	Neuropathic pain

[a] Atenolol, propanolol, metoprolol and nadolol

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