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 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.

Abstract

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

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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 | 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 |
|--------------------------------|-------------------------------------------------|------------------------------------------------------------------|
| At least 3 severe attacks in 30 days | | |
| Attacks last more than 4 hours, or prolonged aura is present | | |

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 ly in patients resistant to more simple treatments, it is 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].

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.
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**   | 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 (propranolol) |
| **Calcium-channel blockers** | Verapamil A-V block, hypertension, 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 prolongation, mania | Panic disorders, depression, anxiety 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, hemorrhagic diatheses, asthenia, tremors, obesity, pregnancy
- Gabapentin Asthenia, dizziness, pregnancy, lactation

Notes:
- Atenolol, propanolol, metoprolol and nadolol

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