

## Answers to Frequently Asked Questions About Migraine

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**Migraine is a common primary headache disorder associated with pronounced disability and hence marked economic and public health implications. Appropriate treatment is warranted to limit the associated disability migraineurs experience. Because of the heterogeneity of migraine, treatment plans must be individualized. The purpose of this article is to provide answers to frequently asked questions regarding the management of migraine.**

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Migraine is a common disabling primary headache disorder associated with considerable reduction in work and school productivity.<sup>1</sup> The current International Classification of Headache Disorders provides diagnostic criteria for different subtypes of migraine disorders.<sup>2</sup> The economic and public health implications of the pronounced disability that migraineurs experience can be substantial. Therefore, proper management is of paramount concern. Pharmacological treatment of migraine is not always straightforward and may involve different strategies, such as acute treatment, preventive treatment, or combined therapy. The optimal therapeutic approach varies depending on each clinical scenario. Questions frequently arise when evaluating and designing a therapeutic plan for a migraineur. The following answers to frequently asked questions occurring in this setting are intended to assist clinicians in treating their patients with this primary headache disorder.

### WHY SHOULD A PRIMARY CARE PHYSICIAN BE INTERESTED IN MIGRAINE?

Estimates of the US population indicate that approximately 30 million Americans (female to male ratio, 3:1) experience migraine. The overall prevalence of migraine in the United States is nearly 1 migraineur per 4 households.<sup>1</sup> Migraine is more common than many other disabling conditions, and the prevalence is greater than that of asthma and diabetes combined. Most migraineurs initially seek

treatment of headache in primary care settings.<sup>3</sup> Furthermore, the vast majority of patients who consult a physician for episodic headaches have migraine.<sup>4</sup> Although the severity of migraine varies among individuals, studies indicate that the median pain intensity is 8 (on a scale of 0 to 10),<sup>5</sup> and the median attack duration is 18 to 24 hours.<sup>6</sup> Almost a third of migraineurs miss at least 1 day of work in a 3-month period.<sup>1</sup> Finally, most patients seek care from a primary care physician.

### WHAT ARE THE CRITERIA FOR THE DIAGNOSIS OF MIGRAINE?

The current International Classification of Headache Disorders provides diagnostic criteria for up to 7 subtypes of migraine.<sup>2</sup> The complete classification is available at the International Headache Society Web site (<http://www.i-h-s.org/>). The criteria for migraine are listed in Table 1. Note that aura is not a requisite for the diagnosis of migraine because two thirds of patients with migraine never experience aura. Clinicians who rely on this symptom to make the diagnosis of migraine will miss many cases.

A brief 3-item self-administered migraine screener (Identification of Migraine) for patients with headache complaints presenting in primary care settings is available and consists of questions on disability, nausea, and photophobia.<sup>7</sup> It is a valid and reliable screening instrument that potentially can improve migraine recognition in primary care. In the Identification of Migraine validation study of patients presenting to their physician with a chief complaint of headache, 3 questions were asked: Are you nauseated or sick to your stomach when you have a headache? Have the headaches limited your activities for a day or more in the last 3 months? Does light bother you when you have a headache? Using this tool, if 2 of 3 answers are affirmative, the positive predictive value of that patient having migraine headache is 93%. If all 3 answers are affirmative, the chance of that patient having migraine is 98%.

### IS THERE A PREFERRED ACUTE MEDICATION TREATMENT FOR PATIENTS WITH MIGRAINE?

Migraine is a heterogeneous disorder that requires an individualized approach; therefore, no preferred approach can be used for all patients. Commonly used nonspecific analgesics for acute migraine attacks include acetaminophen,

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A question-and-answer section appears at the end of this article.

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**TABLE 1. Current Diagnostic Criteria for Migraine Without Aura<sup>2</sup>**

- A. At least 5 attacks fulfilling criteria B-D  
 B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)  
 C. Headache has at least 2 of the following characteristics:  
 1. Unilateral location  
 2. Pulsating quality  
 3. Moderate or severe pain intensity  
 4. Aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)  
 D. During headache at least 1 of the following  
 1. Nausea and/or vomiting  
 2. Photophobia and phonophobia  
 E. Not attributed to another disorder

aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase 2 inhibitors, opiates, and combination analgesics that vary in content but may include any of the following: aspirin, acetaminophen, caffeine, isometheptene, butalbital, or codeine. Occasionally, over-the-counter analgesics alone such as NSAIDs or combination analgesics suffice to abort a migraine attack without a need for a migraine-specific medication. This approach is acceptable as long as limits are placed on their use to prevent medication-overuse headache. Clinicians need to be aware of the existence of migraine-specific drugs, such as triptans and dihydroergotamine, that can be used when nonspecific analgesics do not provide adequate relief. Studies have shown that in most patients these are more efficacious than the nonspecific analgesics, particularly when the attacks result in pronounced disability. Triptans in their various forms appear easier for patients to use with fewer adverse effects compared with dihydroergotamine.

### IS THERE A PREFERRED TRIPTAN?

A response 2 hours after medication has been taken is the most common primary efficacy end point in published clinical trials of triptans.<sup>8</sup> In regard to oral triptans, frovatriptan and naratriptan are less effective using this

parameter compared with the other 5. Oral sumatriptan, zolmitriptan, rizatriptan, almotriptan, and eletriptan all have 2-hour response rates ranging from 57% to 77%.<sup>9</sup> Table 2 lists the triptan agents with dosages and routes of administration. Great interindividual variation exists with respect to patient preference and response rate. Poor response to one triptan does not mean that all triptans will be ineffective. For example, "poor responders" to sumatriptan have obtained good response rates with other triptans.<sup>10</sup> The initial triptan choice is frequently driven by the patient's health insurance formulary to minimize pharmaceutical costs for the patient. When pronounced nausea and vomiting occur early in the attack, a nonoral route such as nasal spray (sumatriptan, zolmitriptan) or subcutaneous injection (sumatriptan) is preferred.

### ARE THERE CONTRAINDICATIONS TO THE USE OF TRIPTANS?

Triptans are a safe class of drugs as long as a careful clinical history is obtained and contraindications are known. Triptans should not be used in the setting of known or suspected ischemic cardiac, cerebrovascular, or peripheral occlusive vascular disease. Uncontrolled hypertension needs to be treated, if present, before a triptan can be prescribed. Triptans should be avoided if other ergot agents or serotonin agonists have been used in the previous 24 hours or if monoamine oxidase inhibitors have been used in the prior 2 weeks.

### WHAT SHOULD BE DONE IF A TRIPTAN FAILS TO PROVIDE ADEQUATE RELIEF?

If relief is inadequate, patients may not be taking triptans early in the attack, when they are most effective. Clinical and experimental evidence suggests that this is at least in part due to central sensitization. This phenomenon appears to occur since the migraine headache persists in almost

**TABLE 2. Administration and Dosages of Triptans**

Triptan	Administration (mg)	Typical dose (mg)	May repeat (h)	Maximal dosage/d (mg)
Almotriptan	Tablet, 6.25, 12.5	12.5	2	25
Eletriptan	Tablet, 20, 40	40	2	80
Frovatriptan	Tablet, 2.5	2.5	2	7.5
Naratriptan	Oral, 1, 2.5	2.5	4	5
Rizatriptan	Oral, 5, 10	10	2	30
	Oral disintegrating tablet, 5, 10	10	2	30
Sumatriptan	Tablet, 25, 50, 100	50-100	2	200
	Nasal spray, 5, 20	20	2	40
	Subcutaneous, 6	6	1	12
Zolmitriptan	Tablet, 2.5, 5	2.5	2	10
	Oral disintegrating tablet, 2.5, 5.0	2.5	2	10
	Nasal spray, 5	5	2	10

80% of patients.<sup>11</sup> A higher dose might be necessary if a lower dose is being used. Furthermore, the heterogeneity of migraine warrants the use of “stratified care” or “rational polytherapy” in which an optimal strategy is designed for each individual patient’s attacks. If vomiting that occurs early in the attack prevents triptan absorption, adding an antiemetic (oral or suppository) such as metoclopramide, prochlorperazine, or promethazine can resolve this problem. Adding an NSAID like naproxen sodium at 550 mg or ketoprofen at 75 mg may increase the success of treatment. A flexible approach is necessary to find the optimal treatment strategy.<sup>12</sup>

#### HOW OFTEN CAN ACUTE MEDICATION BE USED?

Overuse of combination analgesics, opioids, ergot alkaloids, and/or triptans may cause medication-overuse headache.<sup>13</sup> Opioids, butalbital-containing combination analgesics, and aspirin/acetaminophen/caffeine combinations have the highest risk; triptans have moderate risk; and NSAIDs have the lowest risk associated with this problem.<sup>14</sup> We recommend limiting triptan or over-the-counter combination analgesic use to 9 or fewer days a month on average, butalbital-containing analgesics to 3 or fewer days a month, and NSAIDs to 15 or fewer days a month to prevent medication-overuse headache. The limits on butalbital-containing analgesics are due to their high potential for medication-overuse headache.

#### WHAT CAN BE DONE WHEN A HEADACHE RECURS AFTER INITIAL SUCCESSFUL TREATMENT?

If a headache recurs after initial successful treatment, the medication should be repeated. All triptans can be taken multiple times in a 24-hour period as long as the recommended time in-between doses has passed and the maximum daily dosage has not been exceeded. Another approach is to increase the individual dose if it is not at the upper limit allowed. Furthermore, as mentioned earlier, patients may need to try different triptans before finding the most effective one.<sup>9</sup> Delivery of the medication via a different route, ie, nasal or injection, may result in a better response. Finally, rational polytherapy can be used to target symptoms and response to medications. The initial strategy may need to be modified based on results of treatment.

#### WHEN IS PROPHYLACTIC MEDICATION INDICATED?

Preventive treatment should be considered when 1 or more of the following are present: recurring migraines that substantially interfere with the patient’s daily activities despite

acute treatment; frequent headaches (>2 per week); failure, overuse (exceeding the above discussed limits), or contraindication of acute treatment; adverse effects of acute treatment; and/or presence of rare migraine conditions that can potentially cause neurologic damage, such as hemiplegic migraine, basilar migraine, migraine with prolonged aura, or migrainous infarction.<sup>15</sup>

#### WHAT ARE THE GOALS OF MIGRAINE PROPHYLAXIS?

The goals of migraine prophylaxis are to reduce attack frequency, severity, and duration; improve responsiveness to treatment of acute attacks; improve function and reduce disability; and decrease costs of migraine management.<sup>15,16</sup> Timely prophylaxis may impede progression to a more treatment-resistant migraine disorder<sup>17</sup>; however, this remains to be proved.

#### WHAT IS AN “EFFECTIVE” PREVENTIVE AGENT?

Because migraine is a chronic disorder, realistic expectations need to be discussed with patients to prevent frustration and therapeutic failure.<sup>9</sup> With “effective” prophylaxis, an individual patient should expect to obtain a reduction in the frequency of attacks by 50% or more.

#### HOW IS A PREVENTIVE AGENT SELECTED?

Multiple factors are considered in selecting a preventive agent. Optimally, treatment initiation should be with a drug that has proven evidence-based efficacy. Evidence-based guidelines for migraine headache are available at the American Academy of Neurology Web site ([www.aan.com/professionals/](http://www.aan.com/professionals/)) and include a grouping of migraine preventive agents according to efficacy.<sup>15</sup> Table 3 lists commonly used agents. All comorbidities and medications taken for these comorbidities must be cautiously reviewed to prevent adverse outcomes. Preventive agents that can adversely affect comorbid conditions and/or cause unwanted drug interactions should be avoided. One should be vigilant for the presence of “therapeutic opportunities” that could allow the use of a single drug to prevent migraine attacks while also treating a coexisting condition, if present. The combination of painful peripheral neuropathy and migraine is an example of a therapeutic opportunity in which a single drug, such as gabapentin or a tricyclic antidepressant, could be beneficial. Patient preference is of paramount importance. Some prophylactic medications may increase weight, decrease weight, cause sedation, or have other side effects that may or may not be desirable. Women of childbearing age should be

TABLE 3. Commonly Used Migraine Prophylactic Medications

Drug	Initial dose (mg)	Typical total daily dose range (mg)	Adverse effects	
			Common	Serious
Amitriptyline	10	25-150	Weight gain, constipation, sedation	Cardiac dysrhythmias
Nortriptyline	10	25-150	Weight gain, constipation, sedation	Cardiac dysrhythmias
Divalproex sodium	250-500	750-1500	Alopecia, weight gain, nausea, tremor	Pancreatitis, liver failure, thrombocytopenia
Propranolol	40-60	40-240	Depression, fatigue	Bradyarrhythmia
Atenolol	25	50-100	Depression, fatigue	Bradyarrhythmia
Verapamil	80-160	160-480	Edema, constipation	Hypotension, dysrhythmias
Gabapentin	300	900-2400	Edema, sedation, fatigue, dizziness	
Topiramate	15-25	75-200	Paresthesias, fatigue, weight loss	Acute angle closure glaucoma, hyperthermia, metabolic acidosis, nephrolithiasis

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using effective contraception during migraine preventive treatment. This is very important to discuss with patients since unplanned pregnancies may occur while taking migraine preventive treatment. It is generally best to avoid migraine prophylaxis in pregnant women because many commonly used agents are associated with adverse events and/or teratogenicity.

### HOW SHOULD PROPHYLACTIC MEDICATION BE PRESCRIBED?

Preventive agents are usually used one at a time because scientific evidence to support the efficacy of combination therapy is limited. Additionally, use of 2 or more agents often results in more adverse effects than a single agent. Once a preventive agent has been selected, therapy is initiated at a low dose that is increased slowly to reduce the likelihood of adverse effects. Additionally, the dose is slowly increased until the desired clinical effect is obtained or until adverse effects interfere. The minimum effective dose that does not cause intolerable adverse effects is the desired outcome. Of note, the maximum clinical benefit may not be seen until 2 or 3 months after the medication has been used at the target dose. Therefore, a shorter trial should not be considered a failure. Patients should be asked to keep a headache diary to help document response to prophylactic treatment.<sup>9</sup> Occasionally, marked and intolerable adverse effects occur and preclude the completion of a proper trial. When this happens, it may be necessary to change the preventive drug.

### IS BOTULINUM TOXIN EFFECTIVE?

Randomized, double-blind, and placebo-controlled studies using botulinum toxin for migraine prophylaxis have thus far yielded mixed results. Although no indisputable evidence exist that botulinum toxin is effective for migraine

prevention,<sup>19</sup> many headache specialists strongly believe it is effective in a subset of patients. The definite role of botulinum toxin in migraine management has yet to be determined. However, currently, botulinum toxin is routinely part of a headache specialist's armamentarium for migraine prevention. It is injected pericranially, and if beneficial, treatment may be repeated every 3 months since the effect wanes by that time. Adverse effects, including ptosis, frontal muscle weakness, and local pain at the injection site, are primarily mild and temporary.<sup>20</sup> Botulinum toxin is a reasonable option when other more conventional preventive agents have failed because of lack of efficacy, intolerable adverse effects, or contraindications due to comorbidities.

### IS THERE A ROLE FOR COMBINED ACUTE AND PREVENTIVE THERAPY?

The combination of acute symptomatic treatment, prophylaxis, and avoidance of migraine triggers is imperative.<sup>21</sup> The goal of preventive agents is to contain the incidence and vulnerability to individual migraine attacks. Simultaneously, episodic acute treatment is aimed at migraine-related disability during those episodes. Few patients have complete cessation of attacks with prophylaxis alone.

Of note, attacks occurring perimenstrually can be distinctly hard to treat and may not respond to acute analgesics.<sup>22</sup> Severe menstrual migraine often responds better to acute treatment and a preventive agent.<sup>23</sup> The preventive agent can be used in a standard daily dose. Some women will benefit from intermittent "miniprophylaxis" during menses. Medications that have been used effectively in this setting include naproxen sodium, 550 mg twice a day, oral sumatriptan, 25 mg 3 times a day,<sup>24</sup> naratriptan, 1 mg twice a day,<sup>25</sup> or frovatriptan, 2.5 mg once or twice a day.<sup>26</sup> Any one of these medications is typically started 2 days before

the expected onset of headache and continued through the vulnerable period.

### WHAT ARE THE LIMITATIONS IN MIGRAINE MANAGEMENT?

Comorbidities, drug interactions, and adverse effects frequently preclude use of acute and/or preventive therapy in some patients. The cost of some pharmaceuticals can be high, and therefore, they are not an option for some patients. Regarding acute treatment, quantity limits imposed on triptans by health care plans can obstruct optimal migraine therapy.<sup>27</sup> A particular problem unique to women is that of oral contraception since attack frequency and severity may increase, decrease, or not change at all in the setting of initiation of contraception.<sup>28</sup> About a third of women in whom migraines worsen will benefit from discontinuation of the contraceptive.<sup>29</sup> As outlined previously, overuse of acute analgesics may cause medication-overuse headache.<sup>13</sup> The beneficial effect of migraine prophylactics can be abolished in this setting. Fortunately, after successful termination of this pattern of frequent analgesic intake, the efficacy of preventive agents can be seen again.<sup>30</sup> Finally, even when everything is done properly, for unexplained reasons acute or preventive treatment sometimes fails, leading to trial and error with different drugs. Our hope is that further advances in the understanding of the pathophysiology of migraine and the development of new therapies will improve the science of migraine management.

### WHEN CAN PROPHYLAXIS BE DISCONTINUED?

There is no clear evidence to answer this question. However, in our practice, if headaches have been under good control, we usually attempt to taper or even stop the medication after 6 to 12 months. Additionally, this approach was recommended in a recently published expert opinion on this topic.<sup>31</sup> Nevertheless, some patients who have previously experienced frequent disabling attacks and have found a successful agent may choose to continue treatment for longer periods.

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## Questions About Migraine

1. Which *one* of the following statements about migraine is *false*?
  - a. Approximately 1 in 4 households in the United States has at least 1 migraineur
  - b. Migraine is more common than asthma and diabetes combined
  - c. Most patients who consult their physician for episodic headache have migraine
  - d. Almost a third of migraineurs miss at least 1 day of work in a 3-month period
  - e. Among migraineurs, most initially consult a physician for headache in neurology and headache centers
  
2. Which *one* of the following is *correct* regarding the recommended limit for the use of triptans to prevent medication overuse headache?
  - a. 1 day a month
  - b. 3 or fewer days a month
  - c. 9 or fewer days a month on average
  - d. 15 or fewer days a month
  - e. There are no limits
  
3. Which *one* of the following outcomes is *true* regarding an effective migraine prophylactic drug?
  - a. Completely abolishes headaches
  - b. Decreases headache days by 25% or more
  - c. Decreases headache days by 50% or more
  - d. Decreases headache days by 75% or more
  - e. Treats depression simultaneously
  
4. Which *one* of the following statements is *false* regarding migraine prophylaxis?
  - a. Therapy is initiated at a low dose and then increased slowly
  - b. Two or more agents often result in better headache control and tolerability
  - c. The desired clinical benefit may not be seen until after 2 or 3 months
  - d. Overuse of acute analgesics may preclude their efficacy
  - e. The minimum effective dose that does not cause intolerable adverse effects is the desired goal
  
5. In which *one* of the following can discontinuation of migraine prophylaxis be *considered*?
  - a. Once the patient notices benefit
  - b. After 1 to 3 months of good control
  - c. After 3 to 5 months of good control
  - d. After 6 to 12 months of good control
  - e. It can never be discontinued

Correct answers:

1. *e*, 2. *c*, 3. *c*, 4. *b*, 5. *d*