CLINICAL PRACTICE

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Migraine

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A 23-year-old woman presents with five episodes of headache during the past 2 months. Each episode began with yawning, sensitivity to light, and a depressed mood that was followed by the gradual onset of neck pain that spread to the occipital region and eventually to the retro-orbital region on the right side. The pain became incapacitating over a period of 1 to 2 hours and was associated with nausea and sensitivity to light and sound. With two of the episodes, she had jagged lines in her vision for 15 minutes as the neck pain was beginning; with all the episodes, she had severe fatigue and difficulty concentrating and finding words. The headache lasted approximately 24 hours, and, after resolution, she had several hours of residual neck soreness, fatigue, and depressed mood. How would you evaluate and treat this patient?

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THE CLINICAL PROBLEM

Migraine is highly prevalent and is the seventh leading cause of time spent disabled worldwide,[1] yet it has received relatively little attention as a major public health issue. It may begin early in childhood, but its prevalence increases steeply at 10 to 14 years of age and continues to increase until 35 to 39 years of age, after which it gradually decreases, particularly among women after menopause. Migraine is two to three times as common in women as in men[2]; the prevalence at its peak among women is more than 25%. Attacks of migraine occur with a broad spectrum of frequency and severity; for some persons it is an occasional problem that can be effectively managed, but for many it is frequent, incapacitating, and refractory to current therapy. As many as 1 in 25 women may have chronic migraine with headache on more than 15 days per month.[3] Migraine is a common cause of lost work and disrupted family relationships and is associated with a reduced quality of life.[4] It is also associated with increased risks of several other disorders, including asthma, stroke, anxiety and depression, and other pain disorders.[2,5]

Although often simplistically characterized as a "bad headache," a migraine attack typically includes a variety of premonitory symptoms that may occur hours before the headache begins and postdromal symptoms that last for hours after the headache ends. Yawning, mood change, light sensitivity, neck pain, and fatigue are common premonitory symptoms that may persist during and after the headache (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Aura symptoms may include visual disturbances (e.g., wavy lines or bright or dark spots), other sensory changes (e.g., numbness or tingling), language dysfunction, and vertigo. Cutaneous allodynia (the experience of normal touch as

KEY CLINICAL POINTS

MIGRAINE

- Migraine is underdiagnosed; recurrent headache that is associated with sensitivity to light, nausea, or a reduced ability to function is most likely migraine, regardless of other headache characteristics.
- Management should include establishing an accurate diagnosis, identifying and modifying potential exacerbating factors (including medications), developing a plan for the treatment of acute attacks, and determining whether preventive therapy is warranted.
- Therapies for acute migraine (e.g., triptans, nonsteroidal antiinflammatory drugs, and antiemetic agents individually or in combination) should be taken as early as possible after the onset of a migraine attack.
- Preventive therapies (e.g., beta-blockers, candesartan, tricyclic antidepressants, and anticonvulsant agents as well as botulinum toxin for chronic migraine) should be considered on the basis of the frequency and severity of attacks, response to medications for acute migraine, and coexisting conditions.
- Recent clinical trials support the efficacy of new therapies targeting calcitonin gene–related peptide (CGRP) for the treatment of acute migraine and for migraine prevention.

uncomfortable) is also a common component of a migraine attack. Patients may not recognize or spontaneously report these symptoms, but when asked to record them, they can often identify the onset of an attack several hours before a headache occurs[6] and realize that the disabling features of an attack often outlast the headache.[7] Some presumed triggers of migraine may be manifestations of the premonitory phase of a migraine attack; food, light, sound, and odor triggers that are identified by patients may in some cases be early symptoms of gastrointestinal and sensory sensitivity that are part of the attack.

The diverse and highly variable symptoms of migraine reflect complex alterations in the functioning of the nervous system.[8,9] Changes in the activity of multiple brain regions during migraine attacks have been visualized with functional imaging techniques and quantified with the use of clinical electrophysiological techniques.[10,11] These studies reveal activation of the hypothalamus, thalamus, brain stem, and cortex corresponding with various symptoms of a migraine attack, including those occurring before and after headache. The long-standing concept of migraine as primarily a vascular disorder, in which headache is caused by dilation of blood vessels and is throbbing in quality due to the vascular pulse, has been refuted by substantial evidence during the past two decades.[12,13] It is now clear that constriction of blood vessels is not a required mechanism of therapies for migraine.[12] Although migraine is associated with an increased relative risk of stroke and cardiovascular disease,[14,15] the mechanisms underlying this association remain uncertain, and it is exceedingly rare for cerebral ischemia or infarction to occur during a migraine attack.

STRATEGIES AND EVIDENCE

The clinical approach to patients with migraine includes making a correct diagnosis, identifying and removing exacerbating factors, establishing a plan for the treatment of acute attacks, and determining whether daily therapy to prevent attacks is warranted.

DIAGNOSIS

The *International Classification of Headache Disorders* (ICHD) provides detailed criteria for the diagnosis of different types of headache.[16] Many persons with migraine have not received a correct diagnosis, in part because of a traditional focus on the severity and quality of pain as the primary diagnostic criterion. Although migraine headache is characteristically severe, unilateral, and throbbing, it may also be moderate, bilateral, and constant in quality. The features of migraine other than headache, particularly sensitivity to light and sound, nausea, and interference with the ability to function, may be more useful in diagnosis than the character of the headache[17] (Table 1). Other common migraine symptoms, including aura, cognitive dysfunction, dizziness, and fatigue, may lead physicians to order brain imaging, yet this is generally unnecessary if symptoms have a gradual onset and are transient (Table 2). Neck pain is another common symptom of migraine,[18] but it is frequently misinterpreted as a manifestation of a disorder in the cervical spine, often leading to unnecessary scans of this region.[19] Patients or physicians frequently believe

that migraine is related to sinus disease, whereas the majority of patients who receive a diagnosis of "sinus headache" in fact have migraine.

LIFESTYLE FACTORS

Skipped meals, irregular caffeine intake, irregular sleep, and stress are commonly identified as migraine triggers. Migraine attacks are more common before and during the menstrual period in women. These observations reinforce the concepts that migraine attacks may be precipitated by environmental or hormonal change and that day-to-day consistency of diet, caffeine intake, sleep, and exercise is a sensible approach to reducing migraine frequency. There are, however, no randomized trials of lifestyle modifications to support the efficacy of any specific approach, such as caffeine withdrawal or dietary restrictions.

EXACERBATING MEDICATIONS

Multiple medications can exacerbate migraine, including oral contraceptives, postmenopausal hormone therapy, nasal decongestants, selective serotonin-reuptake inhibitor antidepressants, and proton-pump inhibitors. In some patients, the frequency and severity of attacks can be dramatically reduced by adjusting or discontinuing these medications. In addition, regular use of analgesic medications, particularly opioids and barbiturate–caffeine–analgesic combinations, can increase migraine frequency and severity, even when taken only once or twice a week.[20] This exacerbation cannot be explained simply by tolerance, dependence, or addiction but rather is a direct adverse effect on migraine. Withdrawing the frequently used medication can result in marked improvement, but this may require substantial time and effort, and in some patients, inpatient treatment is needed.[21]

TREATMENT OF ACUTE MIGRAINE

Medications that are commonly used in the management of acute migraine, their effects (vs. placebo) in randomized trials, and common or serious adverse effects are reviewed in Table 3. Triptans (selective activators of the 5-hydroxytryptamine [5-HT], or serotonin, receptors of type 1B, 1D, and 1F) are effective in aborting an attack in the majority of patients with migraine, but clinical trials indicate that a minority of patients are pain-free by 2 hours. This may in part be due to the fact that in most clinical trials, the dosing of therapies for acute migraine occurs when pain is already moderate or severe. Nonetheless, in clinical practice, a substantial percentage of patients report dissatisfaction with triptans because of a slow or incomplete response.[36,37] For some, the addition of a nonsteroidal antiinflammatory drug (NSAID) (including nonprescription preparations), or taking one of these medications independently, can be effective (Table 3).[22,24] Multiple ergotamine preparations are available, and intravenous dihydroergotamine in particular is a mainstay of treatment for refractory migraine in urgent care or inpatient settings (Table 3).[22,27]

Antiemetic agents are important adjunctive therapies, particularly for patients with substantial nausea, a disabling symptom that may be a predictor of a poor therapeutic response.[28] Parenteral administration of antiemetics may be a useful approach in the emergency department.[23] Intranasal, subcutaneous injectable, rectal suppository, or other nonoral preparations of therapies for acute migraine may be able to achieve

Table 1. Diagnostic Criteria for Migraine.*

Disease Classification
Migraine without aura (ICHD-3)
At least five attacks fulfilling the following criteria:
Headache attacks lasting 4–72 hr (untreated or unsuccessfully treated)
Headache has at least two of the following four characteristics:
Unilateral location
Pulsating quality
Moderate or severe pain intensity
Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
During headache, at least one of the following:
Nausea and vomiting
Photophobia and phonophobia
Headache is not better accounted for by another ICHD-3 diagnosis
Migraine (ID Migraine validation study)
During the past 3 mo, at least two of the following with headaches:
Nausea or sickness to stomach
Sensitivity to light (a lot more than when one did not have headaches)
Limited ability to work, study, or do what one needed to do for at least 1 day

* The diagnostic criteria for migraine without aura are from the *International Classification of Headache Disorders*, third edition (ICHD-3).[16] The simplified criteria for diagnosis of migraine were shown in the ID Migraine validation study to have a high positive predictive value (93% in a primary care setting).[17]

Table 2. Typical Features of Migraine versus "Red Flags" That Warrant Further Diagnostic Evaluation.

Feature
Typical features of migraine
History of multiple stereotypical attacks lasting 4–72 hr
No symptoms between attacks
Gradual onset of headache, neck pain
Vision, sensory, and language symptoms begin and progress gradually and last ≤1 hr (typical aura)
Yawning, neck pain, sensory sensitivity, fatigue, and mood change before and after headache
Family history of headache
Features suggestive of secondary headache
New onset of headache (particularly in persons older than 50 yr of age)
Headache lasting >72 hr
Vision, sensory, and language symptoms lasting >1 hr
Very sudden onset of headache or neurologic symptoms
Abnormal neurologic examination
Associated fever, systemic illness

therapeutic levels more quickly than oral preparations and are indicated if nausea and vomiting are a feature of migraine attacks.[22,24]

Administration of therapies for acute migraine early in an attack, before symptoms are severe, is associated with better efficacy than later administration.[36,38] It is therefore important to educate patients to recognize premonitory symptoms so that they can initiate treatment as soon as pain begins, or even beforehand (although in nearly all clinical trials of treatments for acute migraine, the treatments are administered when the pain is moderate or severe). Patients commonly withhold treatment until later in an attack because of concerns regarding adverse effects or the cost of medications; these concerns should be addressed if the maximal benefit of therapy for acute migraine is to be achieved. Insurance companies in the United States typically limit the number of triptan doses that a patient may receive per month, but these limitations are not evidence-based. The primary concern with frequent triptan use is not safety but rather the potential development of medication-overuse headache, which the ICHD, third edition, defines as more than 10 days per month of triptan use in a person who has 15 or more days of headache per month.[16]

PREVENTIVE THERAPY FOR MIGRAINE

The decision to initiate preventive therapy should be based on a number of factors, including attack frequency and severity, responsiveness to medications for acute migraine, and coexisting conditions. There is no evidence supporting a specific "threshold" migraine frequency for which preventive therapy is clearly warranted, although it is generally agreed that preventive therapy should be considered if migraine occurs at least once per week or on 4 or more days per month. Identifying a preventive therapy that is both effective and has few side effects in patients with migraine remains challenging. All currently available preventive medication therapies for migraine were initially developed for other indications and have been secondarily adopted as treatments for migraine. Antihypertensive agents (e.g., beta-adrenergic blockers and candesartan), anticonvulsant agents (e.g., topiramate and divalproex sodium), and tricyclic antidepressants (e.g., amitriptyline and nortriptyline) are standard preventive therapies for migraine (Table 4). For some patients, these agents can be highly effective, although the average difference in headache days per month between preventive therapies and placebo has been small in clinical trials.[39,41] Adverse effects are common for most of the preventive therapies, and patients often report an initial response that "wears off" despite increasing doses. Adherence to treatment is generally poor.[51]

OnabotulinumtoxinA is a Food and Drug Administration (FDA)–approved therapy for the prevention of chronic migraine, defined as headache occurring on more than 15 days per month, with migraine features on at least 8 of those days. There is limited evidence to support the use of nonprescription agents — including coenzyme Q10, riboflavin, magnesium, melatonin, and petasites — but these agents are nonetheless widely used because of their acceptable side-effect profile.[46] Without clear biologic or phenotypic predictors of response to specific preventive treatments, the choice of a preventive therapy for migraine is largely based on the side-effect profile and coexisting conditions. For example, for patients with hypertension, a beta-blocker or candesartan may be warranted; for those with insomnia, a tricyclic antidepressant may be considered; and for patients who are obese, topiramate may be appropriate.

"Neuromodulation" approaches, which are

Table 3. Selected Therapies for Acute Migraine.*

Class	Specific Treatments	Reported Mean Therapeutic Effects†	Common or Serious Adverse Effects	Comments
Triptans[26]	Almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan	Pain relief by 2 hr, 16–51%; pain-free by 2 hr, 9–32%; free of headache for 24 hr, 9–27%	Chest or facial muscle tightness, lightheadedness; contraindicated in patients with coronary artery disease	Response to and side-effect profile of different triptans varies in individual patients; nasal or subcutaneous delivery may be more effective than oral delivery in patients with nausea or vomiting
Ergots[27,28]	DHE nasal spray, DHE injection	Pain relief by 2 hr, 20–40% (for DHE nasal spray; limited evidence)	Nausea, dizziness; contraindicated in patients with peripheral vascular disease or coronary artery disease	Intravenous DHE is commonly used for refractory migraine
Acetaminophen[29]		Pain relief by 2 hr, 19%; pain-free by 2 hr, 9%	Minimal with intermittent use	May be more effective in combination with antiemetic agent
NSAIDs[30]	Aspirin, diclofenac, ibuprofen, ketorolac, naproxen	Pain relief by 2 hr, 17–29%; pain-free by 2 hr, 7–20%	Gastric irritation, excessive bleeding	May be effective individually or have additive benefit when taken with triptan; different oral preparations (effervescent or powder) may have improved efficacy
Combinations[31,32]	Acetaminophen–aspirin–caffeine, sumatriptan–naproxen	Pain relief by 2 hr, 10–17% (limited evidence); pain-free by 2 hr, 20–30%	Same as with NSAIDs and triptans	Caffeine-containing preparations may have increased potential for overuse; combination therapy is more effective than individual agents in some patients
Antiemetic agents[23,29,30]	Chlorpromazine, metoclopramide, prochlorperazine	Pain relief by 2 hr with oral metoclopramide (plus aspirin or acetaminophen), 23%; pain relief by 1–2 hr with intravenous delivery in emergency department, 24–67%	Sedation, restlessness (akathisia), dystonic reactions	Phenothiazines plus metoclopramide have benefit for headache as well as nausea; ondansetron is commonly used for nausea, but evidence is lacking
Single-pulse TMS[33]	SpringTMS	Pain-free by 2 hr, 17%	No clinically significant adverse effects	Handheld device for patient-delivered therapy; currently FDA-approved for treatment of acute migraine with aura
CGRP receptor antagonists[34,35] (under investigation)	Rimegepant, ubrogepant	Pain-free by 2 hr, 14–18%	None reported; safety studies are ongoing	Phase 2 studies have been completed

* Shown are therapies that have high-quality supporting evidence or are highly recommended in guidelines from the American Headache Society,[22,23] the Canadian Headache Society,[24] and the European Federation of Neurological Societies[25] as well as other Food and Drug Administration (FDA)–approved or emerging therapies. Citations are for primary trial data within guidelines except as noted; trials were of variable quality. All approaches are FDA-approved for the treatment of acute migraine except antiemetics and calcitonin gene–related peptide (CGRP) receptor antagonists. DHE denotes dihydroergotamine, NSAIDs nonsteroidal antiinflammatory drugs, and TMS transcranial magnetic stimulation.

† Values are the percentage of patients with pain relief or freedom from pain after a single dose of the treatment minus the percentage with pain relief or freedom from pain after placebo administration. In most cases, therapy was administered when pain was already moderate or severe.

Table 4. Selected Preventive Therapies for Migraine.*

Class	Specific Treatments	Reported Mean Monthly Therapeutic Effects†	Common or Serious Adverse Effects	Comments
Tricyclic antidepressants[41]	Amitriptyline, nortriptyline	Data not available	Dry mouth, sedation, weight gain, urinary retention	Low doses are typically used (10 to 50 mg); may be useful in patients with insomnia
Beta-blockers[42,43]	Metoprolol, nadolol, propranolol,‡ timolol‡	Headache days, –0.4 (meta-analysis for propranolol)	Hypotension, exercise intolerance, sexual dysfunction	May be useful in patients with hypertension, tachycardia, or anxiety
Anticonvulsant agent[44]	Topiramate‡	Episodic migraine days, –1.1 to –1.3; chronic migraine days, –1.5 to –3.3	Paresthesias, weight loss, cognitive dysfunction, depression	Also used for weight loss; preparations with various half-lives are available
Anticonvulsant agent[45]	Divalproex sodium‡	Migraine days, –2.6; migraine attacks, –0.6 to –3.4	Tremor, weight gain, hair loss, fetal neural-tube defects	May be efficacious, but adverse effects limit its use
Candesartan[43]		Headache days, –0.7 to –1.7; migraine days, –0.6 to –1.1	Dizziness	Side effects are generally acceptable
Flunarizine[41]		Migraine attacks, –1.2 to –1.8	Sedation, weight gain, depression	Not available in the United States
Nonprescription therapies[46]	Coenzyme Q10, magnesium, melatonin, petasites, riboflavin	Migraine attacks: –1.1 with coenzyme Q10, –0.5 to –0.9 with magnesium, –0.8 with petasites or riboflavin	Diarrhea with magnesium	Side effects are generally acceptable, but current evidence of efficacy is poor
Botulinum toxins[47]	OnabotulinumtoxinA‡	Chronic migraine headache days, –1.4 to –2.3; migraine days, –1.5 to –2.4	Muscle weakness, headache	Delivered by subcutaneous injection at multiple sites; approved for chronic migraine only
Supraorbital nerve stimulation[48]	Cefaly device‡	Migraine days, –2.1	Local discomfort, skin irritation	Headband with forehead stimulation; applied for 20 min daily
Monoclonal antibodies targeting CGRP or its receptor[49,50] (under investigation)	Eptinezumab, erenumab, fremanezumab, galcanezumab	Episodic migraine headache days, –1.0 to –1.2; high-frequency episodic migraine days, –2.8; days with chronic migraine headache, –2.5; hr with chronic migraine headache, –30.4	Injection-site reactions; safety studies are ongoing	Multiple phase 3 trials have been completed; administered subcutaneously or intravenously every 1 to 3 mo; rapid onset of efficacy; rates of response of 75% and in some cases 100% have been reported

* Shown are therapies that have high-quality supporting evidence or are highly recommended in guidelines are from American Academy of Neurology and the American Headache Society,[39,40] the Canadian Headache Society,[41] and the European Federation of Neurological Societies[25] as well as other FDA-approved or emerging therapies. Citations for primary clinical-trial data are included in these guidelines except where noted. All studies were of episodic migraine unless otherwise specified. Episodic migraine is defined as less than 15 headache days per month; chronic migraine is defined as 15 or more headache days per month, with migraine features on at least 8 of those days.

† Values are the number of migraine attacks, or number of days or hours with symptoms, per month with the treatment minus the number with placebo; negative values indicate a benefit with the treatment. The mean monthly effect (typically after 3 months of treatment) is summarized.

‡ These therapies have been approved by the FDA as preventive therapies for migraine.

based on the concept that migraine can be aborted or prevented by the stimulation of peripheral nerves or the brain, are other potential therapies. Single-pulse transcranial magnetic stimulation[33] is now approved by the FDA as a treatment for acute migraine and as a preventive treatment, whereas supraorbital nerve stimulation[48] is approved as a preventive treatment. More experience with these approaches is needed to guide their appropriate use relative to pharmacologic approaches in clinical practice.

AREAS OF UNCERTAINTY

The causes of migraine remain incompletely understood. Migraine commonly runs in families, but specific genetic mechanisms have been elusive. Population studies have identified at least 38 different gene polymorphisms that are associated with migraine.[52] However, the contribution of these polymorphisms in individual patients with migraine is uncertain.

The nature and source of neurochemical mediators that trigger migraine attacks are being actively investigated. Migraine is associated with the release of a number of neurotransmitters and neuromodulators, including the neuropeptides calcitonin gene–related peptide (CGRP)[53] and pituitary adenylate cyclase–activating peptide (PACAP).[54] Administration of these peptides can provoke migraine attacks in susceptible persons,[55] suggesting a causative role.

Small-molecule antagonists of the CGRP receptor have shown efficacy as therapies for acute migraine.[34,35] Monoclonal antibodies to CGRP or its receptor have shown consistent efficacy as preventive therapies for migraine in multiple large phase 2 and phase 3 clinical trials[49] (Table 4). These monoclonal antibodies will probably soon be under consideration by the FDA for approval for clinical use as preventive therapies.

GUIDELINES

Guidelines regarding treatments for acute migraine and preventive therapies have been produced by the American Headache Society, the American Academy of Neurology, the Canadian Headache Society, and the European Federation of Neurological Societies.[22-25,39,41] These guidelines vary somewhat in their recommendations, in part because they are based not only on data from clinical trials but also on expert opinion. The recommendations in this article are generally consistent with these guidelines, although only therapies that are supported by high-quality evidence or are highly recommended are discussed.

CONCLUSIONS AND RECOMMENDATIONS

The young woman described in the vignette has migraine with and without aura. If her neurologic examination is normal, there is no indication for an imaging study, given that she has had multiple episodes of typical duration with complete resolution of symptoms between episodes and no "red flags," such as an abrupt onset of symptoms, fever, concurrent clinically significant illness, or persistent headache between attacks. Many practitioners reflexively order an imaging study when attacks include neurologic symptoms in addition to headache, but such symptoms are characteristic of migraine. Current medications should be reviewed as possible exacerbating factors. Consistency of lifestyle factors (diet, caffeine intake, sleep, and exercise) should be encouraged, and a strategy for the treatment of acute attacks with triptans, NSAIDs, antiemetics, or a combination of these agents should be developed, with an emphasis on treating as early as possible after migraine onset. The frequency and severity of migraine attacks should be monitored to assess whether preventive therapy may be indicated; options include a beta-blocker, candesartan, a tricyclic antidepressant, an anticonvulsant (topiramate or divalproex sodium), or onabotulinumtoxinA (if headache occurs ≥15 days per month). This choice should be informed by coexisting conditions and potential adverse effects. Paper or electronic symptom diaries can be very helpful in assessing the clinical course of migraine and the response to therapies. If pharmacologic therapies are ineffective or have unacceptable side effects, neuromodulation approaches should be considered.

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REFERENCES

1. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016;388:1545-602.
2. Vetvik KG, MacGregor EA. Sex differences in the epidemiology, clinical features, and pathophysiology of migraine. Lancet Neurol 2017;16:76-87.
3. Natoli JL, Manack A, Dean B, et al. Global prevalence of chronic migraine: a systematic review. Cephalalgia 2010;30:599-609.
4. Abu Bakar N, Tanprawate S, Lambru G, Torkamani M, Jahanshahi M, Matharu M. Quality of life in primary headache disorders: a review. Cephalalgia 2016;36:67-91.
5. Minen MT, Begasse De Dhaem O, Kroon Van Diest A, et al. Migraine and its psychiatric comorbidities. J Neurol Neurosurg Psychiatry 2016;87:741-9.
6. Giffin NJ, Ruggiero L, Lipton RB, et al. Premonitory symptoms in migraine: an electronic diary study. Neurology 2003;60:935-40.
7. Giffin NJ, Lipton RB, Silberstein SD, Olesen J, Goadsby PJ. The migraine postdrome: an electronic diary study. Neurology 2016;87:309-13.
8. Hansen JM, Goadsby PJ, Charles AC. Variability of clinical features in attacks of migraine with aura. Cephalalgia 2016;36:216-24.
9. Charles A. Migraine: a brain state. Curr Opin Neurol 2013;26:235-9.
10. Chong CD, Schwedt TJ, Dodick DW. Migraine: what imaging reveals. Curr Neurol Neurosci Rep 2016;16:64.
11. Magis D, Vigano A, Sava S, d'Elia TS, Schoenen J, Coppola G. Pearls and pitfalls: electrophysiology for primary headaches. Cephalalgia 2013;33:526-39.
12. Amin FM, Asghar MS, Hougaard A, et al. Magnetic resonance angiography of intracranial and extracranial arteries in patients with spontaneous migraine without aura: a cross-sectional study. Lancet Neurol 2013;12:454-61.
13. Ahn AH. On the temporal relationship between throbbing migraine pain and arterial pulse. Headache 2010;50:1507-10.
14. Timm FP, Houle TT, Grabitz SD, et al. Migraine and risk of perioperative ischemic stroke and hospital readmission: hospital based registry study. BMJ 2017;356:i6635.
15. Kurth T, Winter AC, Eliassen AH, et al. Migraine and risk of cardiovascular disease in women: prospective cohort study. BMJ 2016;353:i2610.
16. Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders, 3rd edition (beta version). Cephalalgia 2013;33:629-808.
17. Lipton RB, Dodick D, Sadovsky R, et al. A self-administered screener for migraine in primary care: the ID Migraine validation study. Neurology 2003;61:375-82.
18. Ashina S, Bendtsen L, Lyngberg AC, Lipton RB, Hajiyeva N, Jensen R. Prevalence of neck pain in migraine and tension-type headache: a population study. Cephalalgia 2015;35:211-9.
19. Gil-Gouveia R, Oliveira AG, Martins IP. The impact of cognitive symptoms on migraine attack-related disability. Cephalalgia 2016;36:422-30.
20. Bigal ME, Lipton RB. Excessive acute migraine medication use and migraine progression. Neurology 2008;71:1821-8.
21. Diener HC, Holle D, Solbach K, Gaul C. Medication-overuse headache: risk factors, pathophysiology and management. Nat Rev Neurol 2016;12:575-83.
22. Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: the American Headache Society evidence assessment of migraine pharmacotherapies. Headache 2015;55:3-20.
23. Orr SL, Friedman BW, Christie S, et al. Management of adults with acute migraine in the emergency department: the American Headache Society evidence assessment of parenteral pharmacotherapies. Headache 2016;56:911-40.
24. Worthington I, Pringsheim T, Gawel MJ, et al. Canadian Headache Society Guideline: acute drug therapy for migraine headache. Can J Neurol Sci 2013;40:Suppl 3:S1-S80.
25. Evers S, Afra J, Frese A, et al. EFNS guideline on the drug treatment of migraine — revised report of an EFNS task force. Eur J Neurol 2009;16:968-81.
26. Cameron C, Kelly S, Hsieh SC, et al. Triptans in the acute treatment of migraine: a systematic review and network meta-analysis. Headache 2015;55:Suppl 4:221-35.
27. Nagy AJ, Gandhi S, Bhola R, Goadsby PJ. Intravenous dihydroergotamine for inpatient management of refractory primary headaches. Neurology 2011;77:1827-32.
28. Eller M, Gelfand AA, Riggins NY, Shiboski S, Schankin C, Goadsby PJ. Exacerbation of headache during dihydroergotamine for chronic migraine does not alter outcome. Neurology 2016;86:856-9.
29. Derry S, Moore RA. Paracetamol (acetaminophen) with or without an antiemetic for acute migraine headaches in adults. Cochrane Database Syst Rev 2013;4:CD008040.
30. Kirthi V, Derry S, Moore RA. Aspirin with or without an antiemetic for acute migraine headaches in adults. Cochrane Database Syst Rev 2013;4:CD008041.
31. Goldstein J, Hagen M, Gold M. Results of a multicenter, double-blind, randomized, parallel-group, placebo-controlled, single-dose study comparing the fixed combination of acetaminophen, acetylsalicylic acid, and caffeine with ibuprofen for acute treatment of patients with severe migraine. Cephalalgia 2014;34:1070-8.
32. Law S, Derry S, Moore RA. Sumatriptan plus naproxen for the treatment of acute migraine attacks in adults. Cochrane Database Syst Rev 2016;4:CD008541.
33. Lipton RB, Dodick DW, Silberstein SD, et al. Single-pulse transcranial magnetic stimulation for acute treatment of migraine with aura: a randomised, double-blind, parallel-group, sham-controlled trial. Lancet Neurol 2010;9:373-80.
34. Marcus R, Goadsby PJ, Dodick D, Stock D, Manos G, Fischer TZ. BMS-927711 for the acute treatment of migraine: a double-blind, randomized, placebo controlled, dose-ranging trial. Cephalalgia 2014;34:114-25.
35. Voss T, Lipton RB, Dodick DW, et al. A phase IIb randomized, double-blind, placebo-controlled trial of ubrogepant for the acute treatment of migraine. Cephalalgia 2016;36:887-98.
36. Seng EK, Robbins MS, Nicholson RA. Acute migraine medication adherence, migraine disability and patient satisfaction: a naturalistic daily diary study. Cephalalgia 2016 August 3 (Epub ahead of print).
37. Lipton RB, Buse DC, Serrano D, Holland S, Reed ML. Examination of unmet treatment needs among persons with episodic migraine: results of the American Migraine Prevalence and Prevention (AMPP) Study. Headache 2013;53:1300-11.
38. Goadsby PJ, Zanchin G, Geraud G, et al. Early vs. non-early intervention in acute migraine — 'Act when Mild (AwM)': a double-blind, placebo-controlled trial of almotriptan. Cephalalgia 2008;28:383-91.
39. Silberstein SD, Holland S, Freitag F, Dodick DW, Argoff C, Ashman E. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology 2012;78:1337-45.
40. Holland S, Silberstein SD, Freitag F, Dodick DW, Argoff C, Ashman E. Evidence-based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology 2012;78:1346-53.
41. Pringsheim T, Davenport W, Mackie G, et al. Canadian Headache Society guideline for migraine prophylaxis. Can J Neurol Sci 2012;39:Suppl 2:S1-S59.
42. Linde K, Rossnagel K. Propranolol for migraine prophylaxis. Cochrane Database Syst Rev 2004;2:CD003225.
43. Stovner LJ, Linde M, Gravdahl GB, et al. A comparative study of candesartan

versus propranolol for migraine prophylaxis: a randomised, triple-blind, placebo-controlled, double cross-over study. Cephalalgia 2014;34:523-32.
44. Linde M, Mulleners WM, Chronicle EP, McCrory DC. Topiramate for the prophylaxis of episodic migraine in adults. Cochrane Database Syst Rev 2013;6:CD010610.
45. Linde M, Mulleners WM, Chronicle EP, McCrory DC. Valproate (valproic acid or sodium valproate or a combination of the two) for the prophylaxis of episodic migraine in adults. Cochrane Database Syst Rev 2013;6:CD010611.
46. Tepper SJ. Nutraceutical and other modalities for the treatment of headache. Continuum (Minneap Minn) 2015;21 (4 Headache):1018-31.
47. Aurora SK, Dodick DW, Turkel CC, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. Cephalalgia 2010;30:793-803.
48. Schoenen J, Vandersmissen B, Jeangette S, et al. Migraine prevention with a supraorbital transcutaneous stimulator: a randomized controlled trial. Neurology 2013;80:697-704.
49. Hou M, Xing H, Cai Y, et al. The effect and safety of monoclonal antibodies to calcitonin gene-related peptide and its receptor on migraine: a systematic review and meta-analysis. J Headache Pain 2017;18:42.
50. Tepper S, Ashina M, Reuter U, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Neurol 2017; 16:425-34.
51. Hepp Z, Dodick DW, Varon SF, Gillard P, Hansen RN, Devine EB. Adherence to oral migraine-preventive medications among patients with chronic migraine. Cephalalgia 2015;35:478-88.
52. Gormley P, Anttila V, Winsvold BS, et al. Meta-analysis of 375,000 individuals identifies 38 susceptibility loci for migraine. Nat Genet 2016;48:856-66.
53. Goadsby PJ, Edvinsson L, Ekman R. Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. Ann Neurol 1990;28:183-7.
54. Zagami AS, Edvinsson L, Goadsby PJ. Pituitary adenylate cyclase activating polypeptide and migraine. Ann Clin Transl Neurol 2014;1:1036-40.
55. Ashina M, Hansen JM, Olesen J. Pearls and pitfalls in human pharmacological models of migraine: 30 years' experience. Cephalalgia 2013;33:540-53.

Supplementary Appendix

This appendix has been provided by the author to give readers additional information about his work.

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Supplementary Appendix

Table of Contents

Figure S1. A migraine attack is a complex neurological event leading to a variety of symptoms that may precede, accompany, and follow headache. The different phases of a migraine attack may be overlapping, and the symptoms may be highly variable between patients, or from one attack to the next in an individual patient. Cutaneous allodynia refers to the experience of normal touch as uncomfortable.

Timeline of a Migraine Attack

4-72 hours