



HEADACHE MANAGEMENT

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Chronic daily headache, Part 2: Treatment strategies

Chronic daily headache (CDH) is a surprisingly common phenomenon, affecting 4-5% of the population^{1,2} and approximately 30 to 40% of patients seen in headache clinics have the condition.³ Treatment can be difficult, especially when — as is often the case — the patient overuses medications and/or has comorbid depression. Table 1 summarizes the procedure advocated by Silberstein *et al* for the initial workup of patients with CDH.⁴

Table 1.

Diagnostic steps for CDH⁴

1

- Exclude secondary causes of headache
- Identify the primary CDH disorder (i.e., transformed migraine, hemicrania continua, new daily persistent headache, or chronic tension-type headache)
- Identify comorbid medical and psychiatric conditions and exacerbating factors (especially medication overuse)

evaluated one to three months after drug withdrawal therapy had been initiated. The mean headache frequency at baseline was 26.9 ± 4.0 days per month. After drug withdrawal therapy, 56% of patients were significantly improved (defined as ≥50% reduction in the number of headache days). The patients were subsequently divided into three categories: group I had ten or fewer headache days per month (n=41), group II had 11-20 headache days per month (n=37), and group III had 21-30 headache days per month (n=23). Treatment with amitriptyline was offered to patients who had not improved after drug withdrawal. Ten of these patients experienced ≥ 50% reduction of headache days on amitriptyline. The investigators concluded that outpatient drug withdrawal therapy is the treatment of choice in patients with CDH and chronic use of symptomatic medications. Furthermore, about 25% of CDH patients will not respond to drug withdrawal therapy alone.

In another study, 25 of 26 children aged 12-18 (mean: 14.2) with CDH related to medication misuse were successfully withdrawn from analgesics.⁷ The adolescents in this study had daily or almost-daily headaches in association with daily or almost daily analgesic intake. Withdrawal led to complete cessation of headaches in 20 patients. In five patients the daily headaches changed to episodic migraines, which were frequent enough in three patients to require prophylactic medication. Only one patient continued to have daily headaches.

When is inpatient drug withdrawal advisable? Seven major factors have been identified for determining whether inpatient treatment is advisable: (1) Degree and intractability of pain, (2) Refractoriness to established regimens, (3) Need for supportive measures, (4) Degree of toxicity and drug dependence, (5) Degree of coping ability, (6) Psychological health considerations, and (7) Comorbid medical disease considerations.⁸ The goals of inpatient treatment of CDH are: (1) Detoxify the patient, (2) Control pain with parenteral therapy, (3) Initiate prophylaxis, (4) Educate the patient, and (5) Establish outpatient pain control.⁴ The detoxification process can be shortened and the patient's symptoms eased through the use of repetitive I.V. dihydroergotamine.^{9,10} Once the CDH cycle is broken, patients tend to revert to their previous headache types. Most detoxified patients do not resume daily anagesic use and continue to do well on long-term follow-up.¹¹

A number of prophylactic medications have been shown to be effective in the management of CDH. Freitag *et al* conducted a retrospective chart review of 642 patients receiving long-term treatment with divalproex sodium for CDH.¹² Of these, 138 were treated solely with divalproex sodium. A ≥ 50% reduction in

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What do patients want from headache therapy?

As we noted in Volume 1, No. 2, CDH is strongly associated with overuse of symptomatic medications, and these medications must be withdrawn before the headaches can be treated effectively.⁵ Indeed, in many patients the headaches improve spontaneously, without additional treatment, once the offending drugs are withdrawn.⁶ For outpatients, drugs may be tapered at a rate of 10% per week, during which a preventive medication (e.g., a long-acting NSAID) may be initiated. The drug withdrawal period may last from three to eight weeks, during which patients should receive education and emotional support. Patients should also understand that the preventive medication is not likely to be fully effective until the drugs are fully withdrawn.⁴

The effect of drug withdrawal in an outpatient population was studied in a retrospective analysis of 101 adults (74 women and 27 men) with CDH and long-term chronic use of symptomatic medications.⁶ The patients (aged 16 to 72; mean: 43) were

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headache frequency was reported for 93 of these patients (67%). No correlation between response and age, sex, and duration of treatment was noted. Adverse events occurred in approximately 35% of patients; none was severe. The investigators concluded that divalproex sodium was safe and effective for prolonged treatment of CDH. In an earlier study, 33 patients with CDH were treated sequentially with divalproex sodium, amitriptyline, amitriptyline plus phenelzine, or methadone.¹³ A $\geq 50\%$ reduction in head-ache days was reported by 22 patients (67%). Most of the positive treatment responses, 17/22 (77%) were attributed to divalproex sodium.

Topiramate, which was approved for migraine in 2003, was evaluated in a double-blind, randomized, placebo-controlled parallel-group study of patients with CDH and analgesic overuse.¹⁴ Patients were randomized in a 1:1 ratio to receive topiramate or placebo. Following an eight-week baseline phase, the study drug was titrated over one week to 50 mg daily. During the final, four-week maintenance phase, patients treated with low-dose topiramate experienced a significantly lower 28-day headache frequency compared to those treated with placebo ($p < 0.0007$).

Botulinum toxin, which had been shown to control pain associated with a variety of neurologic disorders, was studied in a recent double-blind, placebo-controlled trial of 60 patients with CDH.¹⁵ Patients were randomized to botulinum toxin type A 200 U or matching placebo. After evaluation at Week 12, patients were offered botulinum toxin and were similarly followed for another 12 weeks. Over a 12-week period following injections, headache-free days improved in the botulinum toxin group from Week 8 to Week 12 ($p < 0.05$), but did not reach statistical significance for the entire 12-week period. At Week 24 (open label), headache days were fewer in the twice-injected group compared with the once-injected group ($p < 0.05$). The treatment was well tolerated. The investigators concluded that botulinum toxin may help CDH and appears to have a cumulative effect with subsequent injections.

A retrospective chart review suggested that olanzapine, a new atypical antipsychotic drug, may be effective in the treatment of CDH.¹⁶ The investigators reviewed the records of 50 patients with chronic refractory headaches who had been treated with olanzapine for at least three months. All had previously failed treatment with at least four preventive medications. Results showed that treatment produced a statistically significant decrease in headache days from baseline, from 27.5 ± 4.9 to 21.1 ± 10.7 ($p < 0.001$). There was also a significant decrease in headache severity (0 to 10 scale) after treatment, from 8.7 ± 1.6 to 2.2 ± 2.1 ($p < 0.001$). The investigators concluded that olanzapine may be effective in patients with refractory headache, and should receive particular consideration in patients with concomitant mania, bipolar disorder, or psychotic depression.

A number of investigators have stressed the difficulty of treating patients with CDH.⁶ The prolonged and complex process of drug withdrawal and headache stabilization could best be avoided by educating patients (and the general public) about the risks of excessive medication use. Too often, however, patients seek medical help only after the cycle of daily headaches has become firmly established. Clearly, all new patients presenting with chronic headache should be carefully screened for medication overuse.

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Migraine in children

The majority of children who experience chronic headaches have migraines.¹ Migraine symptoms may begin in infancy, but the average age of onset in children is six years.² Estimates of the prevalence of migraine headaches in children of school age range from 4%^{2,3} to 10.6%.¹ Among adults with migraine, 20% reported an onset of their headaches before the age of 10.³ The prevalence of migraine is higher in boys until puberty, after which the prevalence in girls increases rapidly and the female to male ratio reaches 3:1.⁴

Childhood migraines can have distinctive features. The pain is often bilateral, while adult migraines are usually unilateral.⁵ Childhood migraine attacks tend to be briefer than those in adults, often lasting less than an hour. The associated symptoms, such as nausea, vomiting, abdominal pain, and vertigo may be more prominent than the headache itself. Abdominal pain, for example, may be severe enough to lead parents and healthcare professionals to suspect appendicitis.² Nausea and vomiting is especially prevalent in children, occurring in up to 90% of attacks. Other symptoms may include diarrhea, increased micturition, thirst, lacrimation, sweating, shivering, or edema.⁶ A prospective, sequential, observational study found that tension-type headaches and migraines frequently coexist in children with recurrent headache.⁷ In a series of 320 children with recurrent headaches, the investigators found that 124 (38%) had migraine, 57 (18%) had tension-type headache, and 101 (45%) had both migraine and tension-type headache. They noted that the coexistence of migraine and tension-type headaches may represent a distinctive headache type in children.

Diet plays an important role in triggering headaches in children and adolescents. Foods containing caffeine, tyramine, phenylethylamine, histamine, nitrites, or sulfites are major potential offenders.^{8,9} A study of 118 children ages two to 12 years found a higher rate of sleep disturbances in children with migraine compared with healthy controls. Although, the direction of the relationship is unknown, sleep disturbances are known to trigger migraines in some adults.¹⁰

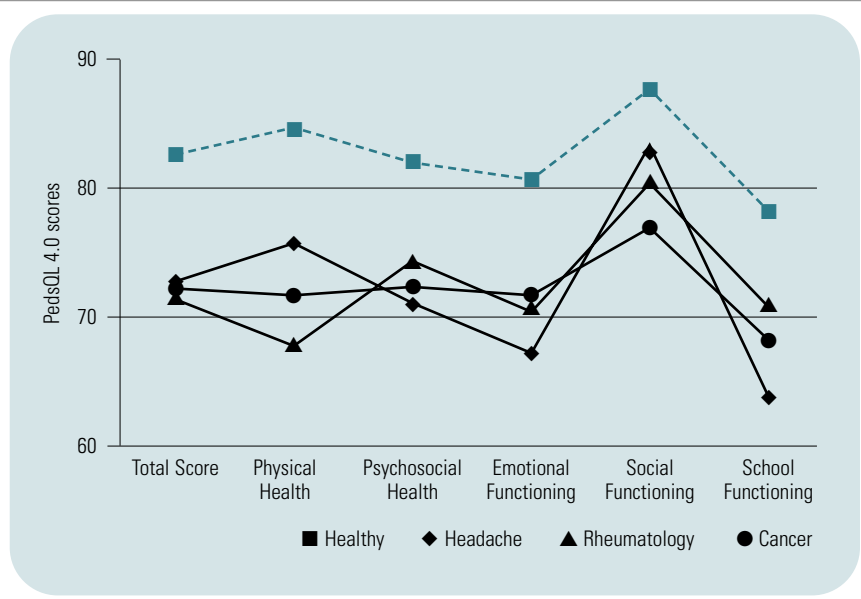
The impact of migraine on children

A recent survey attempted to assess the impact of migraine on the quality of life in children and compare it with the impact of other chronic illnesses.¹¹ The survey was conducted in 572 consecutive patients with a mean age of 11.4 years (± 3.6 years) who presented with headaches at a children's headache center. The children and their parents completed the Pediatric Quality of Life (QOL) Inventory, Version 4.0 and a standardized headache assessment. The results were compared with established norms for both healthy and chronically ill children. Of these children, 99% had a clinical diagnosis of migraine and 40% had chronic daily headaches (CDH). The QOL score for the entire group was lower than for healthy norms (73.1 ± 14.4 vs. 83.0 ± 14.8 , respectively). Children with CDH had the lowest scores (70.5 ± 15.5). The incidence of daily analgesic use in the subgroup of children with CDH was 61.0%.¹¹ The impact on quality of life of children with migraine was similar to that seen for children with arthritis and cancer (Figure 1).

Figure 1.

Pediatric QOL Inventory child self-report score across disease groups

1



Treating childhood migraine

There are few controlled studies of the pharmacologic treatment of migraine in children. From review of available evidence, ibuprofen (7.5 mg/kg) and nasal sumatriptan (5 or 20 mg) are the most effective agents for the treatment of acute pediatric migraine.^{12,13} Both have been shown to be effective in more than one double-blind, placebo-controlled trial. (None of the triptans is approved for use in children under the age of 12.) A randomized, placebo-controlled trial also showed I.V. prochlorperazine to be effective and superior to I.V. ketorolac in the treatment of pediatric migraine.¹⁴ Data from controlled studies are limited and generally poor regarding the use of migraine prophylactic agents in children.¹⁵ Agents that are possibly effective include amitriptyline, propranolol, topiramate, valproate, cyproheptadine, and flunarizine (not available in the U.S.).^{12,13,15,16} One reviewer noted that evaluation of migraine drugs in children may be complicated by a high placebo response rate in a pediatric population.¹²

Childhood migraine attacks tend to be briefer than those in adults, often lasting less than an hour.



What is the natural history of pediatric migraine? *Camarda et al* followed 64 juvenile migraineurs (34 girls and 30 boys) for five years to assess the prevalence and evolution of pediatric migraine over time.¹⁷ Of these subjects, 32 (50%) had migraine without aura, 18 (28.1%) had migrainous disorder, and 14 (21.9%) had headaches that could not be classified. The investigators found that, after five years, migraine with aura persisted in 56.2%, converted to migrainous disorder in 9.4%, converted to headache not classifiable in 3.1%, changed to episodic tension-type headache in 12.5%, and remitted in 18.8%. Migrainous disorder persisted in 11.1%, converted to migraine without aura in 27.8%, converted to headache not classifiable in 5.5%, changed to episodic tension-type headache in 11.1%, and remitted in 35.7%. The investigators concluded that juvenile-onset migraine without aura and migrainous disorder may change in character over time, generally with a favorable prognosis.

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Clinical importance of routes of administration of migraine medications

While medications for migraine prophylaxis are all taken orally, those intended for acute treatment are available in a variety of dosage forms. Patient preference plays a role, certainly, but the administration route may also have clinical importance. The principal medications used for the acute treatment of migraine and their routes of administration are listed in Table 1.

A survey of 500 self-reported migraine sufferers reported that the ability to provide rapid relief of head pain was the most important attribute of a migraine medication.¹ Of nearly equal importance was decreasing the likelihood of headache recurrence. These two desirable attributes account for some of the pharmacokinetic differences among the oral triptans. Oral rizatriptan, with a T-max of 1-1.5 hours, is designed for a rapid onset of action. Frovatriptan, with a 26-hour half-life, is designed to prevent headache recurrence. Thus, it may be possible to match the character of an oral triptan to the typical features of a specific patient's migraines. A meta-analysis of 31 studies showed that the triptans with longer half-lives had lower rates of recurrence.² The migraine-specific medication with the lowest rate of recurrence is DHE (dihydroergotamine mesylate). DHE is available as an intramuscular injection, subcutaneous injection, intravenous infusion, and a nasal spray formulation. Ergotamine/cafeine combinations are available as oral tablets, suppositories; and, with ergotamine alone, as sublingual tablets. Comparative studies of the nasal and injectable dosage forms of DHE confirmed that it has a lower recurrence rate than sumatriptan, but these studies used an older treatment paradigm, in which headaches were treated at moderate to severe intensity.^{3,5}

For some patients, such as those with a very rapid time-to-peak pain, an oral triptan may not act quickly enough. Sumatriptan is available as a subcutaneous injection with a very rapid onset of action. In controlled clinical trials of injectable sumatriptan, onset of relief began as early as 10 minutes after injection.⁶ However, some patients may be unwilling or unable to give themselves injections. For them, a nasal spray formulation may be a good alternative; its onset of action is intermediate between that of oral tablets and a subcutaneous injection. Some patients report onset of relief within 15 to 30 minutes of administration. Sumatriptan and zolmitriptan are both available in nasal spray formulations. While these are easy and convenient to use, some patients find they produce an objectionable aftertaste. Non-oral formulations, such as injectables, nasal sprays, or suppositories may be particularly useful for patients who cannot take tablets because of nausea and vomiting associated with their migraine attacks. Even if the patient is not vomiting, gastroparesis (gastric emptying delay) may occur during a migraine attack, resulting in the failure of oral agents.

Another convenient triptan dosage form is the orally disintegrating tablet (rizatriptan and zolmitriptan). These tablets dissolve very rapidly in the mouth on contact with saliva; they do not need to be taken with water. Sumatriptan is available in an oral tablet that dissolves rapidly in the stomach, but must be taken with water.

Intravenous formulations play an important role in the emergency department (ED) treatment of migraine. Migraine patients who present to emergency departments typically suffer from the "last straw" syndrome; they experience a seemingly endless series of headaches that have not responded to at-home treatment.⁷ These patients usually require rescue with intravenous medications, such as DHE, valproate sodium injection, or prochlorperazine.⁸ Mathew and Kailasam compared the efficacy and safety of valproate sodium injection and intravenous DHE in 66 patients with severe, intractable migraine (transformed migraine).⁹ Thirty-two patients received DHE 0.5 cc plus 5 mg metoclopramide every six hours for two days and 34 patients received valproate sodium injection 500 mg every eight hours for two days. Significant improvement (mild or no headache) was seen in 78% of the valproate patients and 82% of the patients on DHE plus metoclopramide. While the two agents were equally effective, valproate was better tolerated: 52% of the DHE patients reported adverse events, while valproate caused slight dizziness in two patients and lethargy in one patient.

A randomized, double-blind study compared I.V. valproate sodium 500 mg with I.V. prochlorperazine 10 mg infused over two minutes in 40 patients.¹⁰ The primary outcome measure was reduction in pain and nausea at 60 minutes (note that the study cited above measured outcomes after two days of treatment). In this study, valproate failed to elicit significant improvement in pain or nausea scores, while prochlorperazine improved nausea by 15 minutes ($p=0.002$) and pain by 30 minutes ($p<0.001$). At 60 minutes, 15 (79%) of the patients receiving valproate required rescue treatment compared with five (25%) of the patients receiving prochlorperazine ($p<0.001$).

Opioid medications are also useful in the emergency department setting, although many physicians reserve them for patients who have failed on other medications. Opioid analgesics may be helpful in patients who cannot take ergots or triptans or who have comorbid conditions that prevent the use of abortive agents. They are available in a variety of dosage forms (see Table 1).

*For some patients,
such as those with a
very rapid time-to-peak
pain, an oral triptan
may not act quickly
enough.*

Table 1.

Acute migraine medications and their routes of administration

1

Prescription acute medications

- DHE 45[®] (dihydroergotamine mesylate)
- Ergotamine/caffeine
- Depacon[®] (valproate sodium injection)
- Indomethacin
- Meclofenamate
- Midrin[®] (isometheptene mucate/dichloralphenazone/acetaminophen)
- Imitrex[®] (sumatriptan succinate)
- Maxalt[®] (rizatriptan benzoate)
- Amerge[®] (naratriptan HCl)
- Zomig[®] (zolmitriptan)
- Relpax[®] (eletriptan)
- Axert[®] (almotriptan)
- Frova[®] (frovatriptan)

Administration route

- IM, SC, IV, nasal spray (Migranal[®])
- Oral, suppository, sublingual tablet (with ergotamine alone)
- IV
- Oral, suppository
- Oral
- Oral
- Injectable, oral, nasal spray, rapid-dissolving tablet
- Oral, MLT (orally disintegrating tablet)
- Oral
- Oral, ZMT (orally disintegrating tablet), nasal spray
- Oral
- Oral
- Oral

Analgesic/narcotic

- Butalbital/caffeine with aspirin or acetaminophen (marketed under more than one brand name)
- Demerol[®] (meperidine HCl)
- Fiorinal[®] (butalbital, aspirin, and caffeine)
- Fiorinal with Codeine[®] (butalbital, aspirin, caffeine, and codeine phosphate)
- Stadol[®] (butorphanol tartrate)
- Tylenol[®] with Codeine (acetaminophen and codeine phosphate)
- Vicodin[®] (hydrocodone bitartrate and acetaminophen)
- Ketorolac (marketed under more than one brand name)

Administration route

- Oral
- Oral, IM, IV
- Oral
- Oral
- Nasal spray (Stadol[®] NS[™]), IM, IV
- Oral
- Oral
- Oral, IM, IV

Nonprescription acute medications

- Advil[®] Migraine
- Acetaminophen (marketed under more than one brand name)
- Naproxen sodium (marketed under more than one brand name)
- Motrin[®] Migraine Pain
- Exedrin[®] Migraine
- Ibuprofen (marketed under more than one brand name)

Administration route

- Oral
- Oral
- Oral
- Oral
- Oral
- Oral

Table 2.

Alternative formulations for migraine drug delivery
(adapted from Loder)²

2

Formulation

- Parenteral (IV)
- Nasal spray
- Orally disintegrating tablet
- Rapidly dissolving tablet

Advantages

- Good control of delivered dose
- Rapid delivery
- Convenient
- Convenient
- Discreet
- Less aggravation of nausea
- Rapid onset of action

Disadvantages

- Expensive
- Inconvenient
- Nasal irritation
- Absorption uncertain
- Taste
- Taste
- Must be taken with water

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The investigators concluded that fast and complete pain relief are key factors in determining patient satisfaction with treatment. If complete relief is not attained within two hours, the baseline severity of pain and the presence of associated symptoms can also affect a patient's report of satisfaction.

Lipton *et al* conducted a survey of 688 migraine sufferers to determine if they were satisfied with their migraine therapies and, if not, why not.² Migraineurs were asked about demographic characteristics, healthcare behavior, satisfaction with current treatments, and their preferences for various treatment and physician characteristics. Subsequently, a group of 167 physicians attending an educational symposium were asked a series of related questions: (1) Among migraine sufferers not completely satisfied with their usual acute medication, what is the most important reason for their dissatisfaction? (2) What do you think migraine sufferers said were the most important features of an acute migraine medication? (3) What do you think migraine sufferers selected as their first/second choice for a route of administration for an acute migraine treatment? (4) Which of the following qualities did migraine sufferers currently seeing a doctor say were most important to them in a doctor treating their headaches? The responses of the two groups were then compared to determine how well physicians understand the attitudes and preferences of their headache patients.

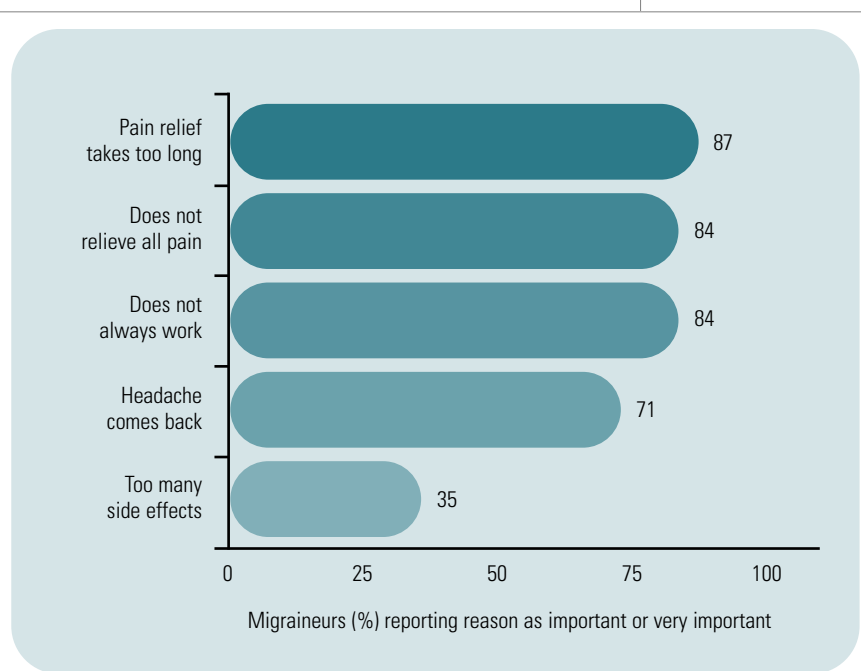
Only 29% of those in the patient survey reported that they were very satisfied with their usual acute treatment for migraine, while 48% were somewhat satisfied. Of the remainder, 7% were neither satisfied nor dissatisfied, 9% were somewhat dissatisfied, and 7% were very dissatisfied. What were the reasons for dissatisfaction? The principle reason was that pain relief took too

What do patients want from their migraine therapy?

What factors influence patient satisfaction with migraine treatment? *Davies et al* conducted an analysis of data from a multiple-attack, crossover study to identify specific components of treatment response that are important from a patient's perspective.¹ Enrolled patients were randomized to receive rizatriptan for three migraine attacks and placebo for the remaining attack or rizatriptan for all four attacks. Satisfaction with treatment was rated at two hours using a seven-point scale. Scores of three or less were defined as satisfaction with treatment. Analyses were performed for all attacks using data from baseline, 30, 60, 90 minutes, and two hours. Outcome measures included pain relief (no pain or mild pain), associated symptoms (photophobia, phonophobia, nausea, and vomiting), and time to relief. Over 97% of patients who reported complete migraine relief at two hours were satisfied with treatment and over 91% of those with no relief at two hours reported that they were not satisfied with treatment. Only 69% who experienced some relief (mild pain at two hours) were satisfied with treatment. Patients who had severe pain at baseline, some relief within one hour, and no associated symptoms at two hours had an 83% probability of being satisfied. Patients with moderate pain at baseline, slower pain relief, and any associated symptoms at two hours had a 53% probability of being satisfied with their treatment.

Figure 1.
Proportion of migraine sufferers reporting reasons for dissatisfaction with their usual migraine treatments

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CHALLENGES IN HEADACHE MANAGEMENT

What do patients want from their migraine therapy?

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long (87%), followed by less than complete pain relief (84%), and doesn't always work (84%). Headache recurrence was an important reason for dissatisfaction in 71%, but side effects were considered important by only 35%.

Participants in the patient survey were then asked to rate the importance of several attributes of acute migraine treatment. The three most important were complete pain relief (87%), lack of recurrence (86%), and rapid onset of pain relief (83%). No side effects (79%), relief of associated symptoms (76%), and route of administration (56%) were somewhat less highly rated. Survey participants who were currently seeing a physician for their migraines were also asked about the physician attributes they considered most important. The most important attribute was a willingness to answer questions (86%), followed by teaches how to treat attacks (72%) and medical expertise in diagnosis and treatment (67%). Understanding/compassion (61%) was the attribute rated very important least often.

When the physicians attending the symposium were subsequently asked to select the attribute that migraine sufferers would consider most important, they correctly chose rapid and complete pain relief. There was one notable contrast between what patients wanted from their physicians and what physicians *believed* patients wanted. Symposium attendees thought that patients rated medical expertise and understanding/compassion as attributes they rated highest in physicians, rather than a willingness to answer questions. The investigators concluded that, although physicians have a good understanding of what migraine patients want from their medications, they do not have a good appreciation for what patients expect from their physicians.

In another survey sponsored by the National Headache Foundation, 2444 adults with migraine were asked about the tolerability of their migraine prescription medications and the impact of medication adverse effects on their self-management of migraine.⁴ Of those surveyed, 1166 met the target criteria for the study and were included in the analysis. Pain relief and

speed of onset were considered to be important product attributes by 75-77% of sufferers. Adverse effects were an important concern: Two-thirds had delayed or avoided taking their medication because of concerns about adverse effects. During the previous six months, these concerns led to a delay in treatment in 37% of treated attacks and to medication avoidance in 44% of untreated attacks, resulting in a worsening of the intensity and duration of pain. Furthermore, 79% expressed an interest in trying new medications with efficacy similar to their current medication, but with fewer adverse effects.

These studies are a reminder that good physician-patient communication is an essential clinical skill. There is growing support for communication skills training at all levels of medical education.³ Good communication is particularly important for the clinician who treats migraine, because the ability to elicit an accurate history and to establish a trusting relationship is essential for accurate diagnosis and effective treatment.

The preceding article gives some idea of the growing therapeutic armamentarium for the acute treatment of migraine. With so many choices available, patient needs, expectations, and preferences have become increasingly important. In addition, support groups encourage migraine patients to play an active role in their treatment, in part by clearly expressing their needs and preferences to their healthcare providers.

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