



Acute Migraine Treatment

ACUTE MIGRAINE TREATMENT

Objectives

- Review the general principles and clinical evidence for acute treatment
- Present an approach for selecting and sequencing acute therapies
- Discuss problems that arise in the acute management of migraine
 - Recurrence
 - Consistency

KEY TO SUCCESSFUL MIGRAINE MANAGEMENT

Establish a partnership with the patient

Promote patient education

Establish a treatment plan

- Nature and mechanism of the disorder
- Strategies for identifying and avoiding triggers
- Behavioral management strategies
 - Regular sleep, exercise, meals
 - Stress management, biofeedback
 - Cognitive behavioral therapy

Develop pharmacologic management plan

- Acute treatment
- Preventive strategies

An effective migraine management plan is based on establishing a partnership with the patient. Therapy can be optimized through a management program that encompasses education and behavioral treatments as well as pharmacologic therapy.

Educating patients on the nature and mechanism of their illness will help encourage dialogue and empower the patient to actively participate in his or her own headache management program.

Patients should be encouraged to keep a headache diary for both diagnostic and treatment purposes. Review of the diary may yield previously unrecognized patterns of headache, including migraine triggers. Work with the patient to identify possible triggers, and discuss possible strategies to avoid or minimize exposure.

Behavioral strategies should be initiated, which include establishment of more regular sleep patterns, improvement in diet, and the addition of an exercise program. Patients should be encouraged to participate in behavioral modification programs that have been proven to be successful. These include cognitive-behavioral therapy, stress management, relaxation training, and biofeedback therapy. Although active participation in nonpharmacologic treatment may produce a slower response than pharmacologic treatment, it encourages an active role for patients. These strategies are particularly important when pharmacologic interventions are limited (e.g., comorbid conditions precluding specific migraine drugs).

Pharmacologic treatment of migraine can involve both acute and preventive interventions. Patients with frequent headache may require both approaches. Acute treatment is aimed at aborting the headache, whereas preventive treatment is geared toward reducing the frequency and severity of anticipated attacks.

In summary, education, behavioral management, acute therapy, and preventive therapy (if appropriate) are the cornerstones of good migraine management.

Silberstein SD, Saper JR, Freitag FG. Migraine diagnosis and treatment. In: Silberstein SD, Lipton RB, Dalessio DE, eds. *Wolff's Headache and Other Head Pain*. 7th ed. Oxford, England: Oxford University Press; 2001:121-237.

MIGRAINE TRIGGERS

Physical exertion

Diet

Hormonal changes

Head trauma

Stress and anxiety

Sleep deprivation or excess

Environmental factors

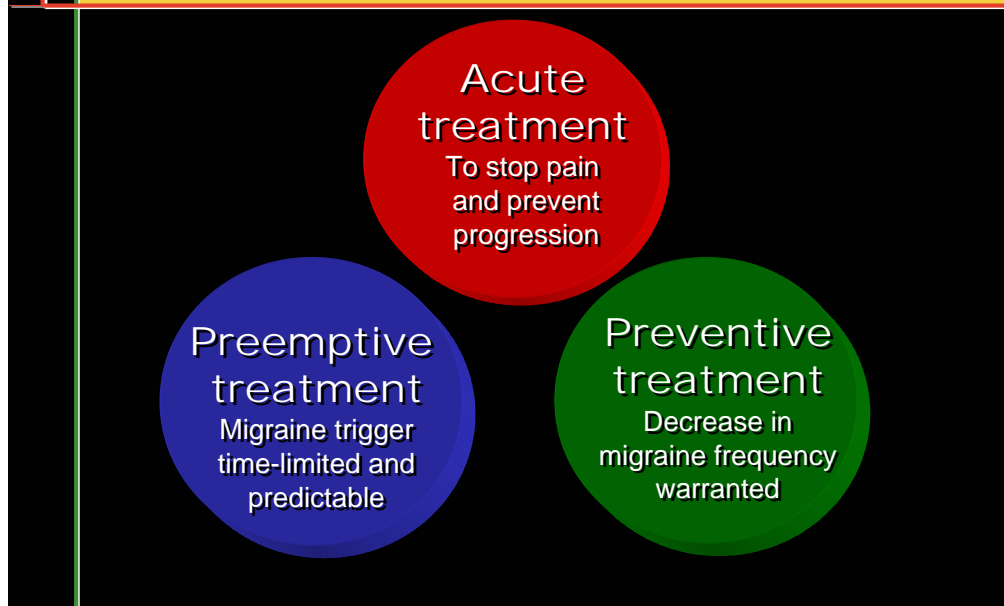
More than in any other headache disorder, migraine sufferers identify triggers. Stress is the trigger most commonly listed by patients. Dietary factors are also frequently reported triggers, although few have been scientifically validated. Although the impact of food triggers probably is not great for the population, their impact could be for the individual. Oversleeping and sleep deprivation are commonly recognized triggers. Patients should maintain a routine bedtime and avoid sleeping in.

Hormonal headaches are triggered by variations in female estrogen levels and possibly other hormonal factors. Noise, bright lights, and fumes are commonly identified migraine triggers. Physical exertion can cause headache of the subtype, exercise-induced migraine.

Silberstein SD, Saper JR, Freitag FG. Migraine diagnosis and treatment. In: Silberstein SD, Lipton RB, Dalessio DE, eds. *Wolff's Headache and Other Head Pain*. 7th ed. Oxford, England: Oxford University Press; 2001:121-237.

Silberstein SD, Lipton RB, Goadsby PJ. *Headache in Clinical Practice*. Oxford, England: Isis Medical Media; 1998.

STRATEGIES FOR MIGRAINE TREATMENT



Treatment can be acute, preemptive, or preventive.

Acute treatment is initiated during an attack to relieve pain and disability and to stop progression of the attack.

Preemptive treatment is used when a known headache trigger exists, such as exercise or sexual activity, and for patients experiencing a time-limited exposure to a trigger, such as ascent to a high altitude or menstruation.

Preventive treatment is maintained for months or even years to reduce attack frequency, severity, and duration.

Patients taking preventive medication can also use acute and preemptive medication.

Silberstein SD. Preventive treatment of migraine: an overview. *Cephalalgia*. 1997;17(2):67-72.

Silberstein SD, Saper JR, Freitag FG. Migraine diagnosis and treatment. In: Silberstein SD, Lipton RB, Dalessio DE, eds. *Wolff's Headache and Other Head Pain*. 7th ed. Oxford, England: Oxford University Press. 2001:121-237.

Silberstein SD, Goadsby PJ. Migraine: preventive treatment. *Cephalalgia*. 2002;22(7):491-512.

ACUTE MIGRAINE MEDICATIONS

Nonspecific

- NSAIDs
- Combination analgesics
- Opioids
- Neuroleptics / antiemetics
- Corticosteroids

Specific

- Ergotamine / DHE
- Triptans



A number of medications are available to treat migraine, and choice depends on the severity and frequency of headaches. These categories of medications include nonspecific and specific treatments.

Nonspecific treatments are those effective for any pain disorder and include nonsteroidal anti-inflammatory drugs (NSAIDs), combination analgesics, opioids, neuroleptics/antiemetics, and corticosteroids.

Specific therapies, such as ergotamine-containing compounds, DHE, and triptans, are effective only for the treatment of migraine and related disorders.

Diener HC, Kaube H, Limmroth V. A practical guide to the management and prevention of migraine. *Drugs*. 1998;56(5):811-824.

ACUTE TREATMENT PRINCIPLES

- Treat early in attack
- Use correct dose and formulation
- Use for a maximum of 2 to 3 days per week
- Stratify treatment
- May be best approach when:
 - Attacks infrequent
 - Preventive medication creates problems
 - Compliance is a problem

The general principles of acute migraine care include the following:

- Treat the headache as early as possible in the attack to reduce the intensity and duration of the attack as well as the accompanying features. Failure to use effective therapy early may increase the pain, disability, and impact of the headache.
- Tailor the treatment to both the individual and the individual attack.
- Use the correct dose and formulation. The route of administration is especially important in patients experiencing severe nausea and vomiting.
- Generally, the use of acute therapy should be restricted to a maximum of 2 to 3 days per week to avoid rebound.
- Everyone needs acute treatment in addition to patient education and, in many cases, nonpharmacologic intervention.
- Consider the addition of preventive therapy for selected patients.
- For patients receiving preventive therapy, provide acute agents to treat breakthrough attacks.

Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2000;55(6):754-762.

Matchar DB. Evidence-based guidelines for migraine headache: pharmacological management of acute attacks. [www.aan.com]. April 25, 2000. Available at: <http://www.aan.com/public/practiceguidelines/03.pdf>.

Lipton RB, Silberstein SD. The role of headache-related disability in migraine management: implications for headache treatment guidelines. *Neurology*. 2001;56(suppl 1):S35-S42.

Lipton RB, Stewart WF, Stone AM, Lainez MJ, Sawyer JP; Disability in Strategies of Care Study group. Stratified care vs step care strategies for migraine: the Disability in Strategies of Care (DISC) study: A randomized trial. *JAMA*. 2000;284(20):2599-2605.

ACUTE TREATMENT PRINCIPLES (CONT'D)

Treat at least two different attacks with same medication before determining efficacy

If treatment ineffective

- Reconsider diagnosis
- Treat early
- Use optimal dose
- Change formulation/route of administration
- Change drug
- Be sure there are no interfering medications or overuse
- Add adjunct

In evaluating therapy, it is important to give sufficient trial to the initial acute medication agent. Treat at least 2 or 3 attacks before judging the effectiveness of the therapeutic choice.

If treatment is not working, consider the following:

Reconsider diagnosis: Secondary headaches, although not as common, may present with clinical signs and symptoms that resemble migraine.

Treat early: Recent studies, both prospective and retrospective, support improved response to triptan therapy when patients treat early in the course of an attack. This is especially pertinent in those who are at risk of developing cutaneous allodynia. Triptans have been shown to be less effective in patients who develop cutaneous allodynia in association with their migraine (summarized in slides below).

Dose and route of administration: If the patient is experiencing some relief from the current medication, would a higher dose be more efficacious? If the patient requires more rapid onset of pain relief, would a nasal spray or an injectable formulation of the present medication suffice?

Choice of drug: If a nonspecific agent, such as a combination analgesic, is being used, would another nonspecific medication, such as an opioid or a specific medication, such as a triptan, be more effective?

Adverse drug interactions: Investigate the use of interfering medications, including other over-the-counter analgesics and medications for depression and heart disease.

Adjunctive therapy: Patients experiencing nausea and vomiting may benefit from the addition of adjunctive antiemetics. Additionally, be sure there are no other medications that may be exacerbating or triggering migraine (e.g., caffeine, herbal preparations, oral contraceptives, among others).

Silberstein SD, Saper JR, Freitag FG. Migraine diagnosis and treatment. In: Silberstein SD, Lipton RB, Dalessio DE, eds. *Wolff's Headache and Other Head Pain*. 7th ed. Oxford, England: Oxford University Press; 2001:121-237.

ASSESSING TREATMENT SUCCESS – FOLLOW-UP

- Severity of disability (MIDAS or HIT-6)
- Duration, intensity, and frequency of attacks
- Use of medical resources
 - Second dose
 - Rescue medication
 - Emergent care / clinic visits
- Incidence of adverse events
- Level of patient satisfaction

Measuring treatment success is important in understanding if the patient is responding to the established treatment plan.

Assessing impact of illness: One way to assess overall treatment plan success is to assess the impact of migraine on the patient's life. This can be done using disability outcomes tools such as the MIDAS questionnaire or the HIT-6 instrument. Specific endpoints to review include number of days missed from work or school, time missed from home and leisure activities, and reduced productivity.

Monitoring migraine features: Also, specific headache features should be assessed at each office visit. The assessment should include a discussion of the average duration of each attack, usual time for attack resolution following treatment, and attack frequency (i.e., achieving a 50% reduction or more in attack frequency). If the patient only achieves partial headache relief (e.g., headache response, 50% reduction in pain), perhaps they are not treating early enough in the course of the attack, the dose may be too low, or the choice of medication may not be correct.

Reviewing use of medical resources: Other ways to assess treatment success include response to a single dose of study medication, such as a triptan, especially if the patient treats early in the course of an attack. Another important factor to evaluate is the use of rescue medications. Patients with migraine run the risk of overusing medications, which can exacerbate their condition.

Evaluating treatment plan tolerability and acceptance: Patients also need to tolerate their medication or else they will not be satisfied with their treatment plan, and may possibly discontinue consulting medical care for the management of their migraine.

ASSESSING EFFICACY

Standard endpoints:

- Pain relief (headache response)
 - Onset of relief (15 minutes; 30 minutes)
 - Duration of pain relief (24 hours)
- Pain-free response
- Recurrence (use of rescue; use of second dose of medicine)
- Return to normal function / activities

Assessing efficacy of treatments can be difficult unless the patient knows what to look for other than overall pain relief. Explain to the patient that pain relief is different than pain-free. Ideally, patients seek a pain-free response, but may only achieve a pain-free status. Pain relief or “headache response” is commonly defined as pain intensity originating at a 3 or 4 pain intensity (4 being severe, 0 being no pain) and going to no pain or mild pain by 2 hours. Other important features is to have the patient track how well their medication worked over a 24-hour period. Do they need rescue or a second dose of study medication? Additionally, patients should monitor their ability to resume normal activities including work, child care, and social or leisure events. Gradual improvements in headache status can be difficult to assess if the patient is not aware of how to monitor improvements or deterioration in migraine patterns. Explaining what to look for and how to track attacks is an important part in determining treatment success or failure.

WHEN TO TREAT MIGRAINE?

Patients may delay taking medication...why?

- Do not know to take medicine early
- May not recognize it as migraine
 - Throbbing, nausea, photophobia
 - Aggravated by activity
- Recognize migraine aura
- Harbor medication so they don't run out / cost

One of the important parts in managing patients with migraine is to help them learn how to manage their own illness. This includes educating them about the cascade of events that occurs with each attack. Understanding that early treatment will improve response to therapy is an important component to also realizing that this approach will lead to less medication use and less disability. Learning how to recognize migraine versus other headache types (e.g., tension-type headache) will also help the patient to know when to take a migraine-specific medication or other analgesic. Preliminary studies have been done that assess the efficacy of giving triptans during an aura. When given during an aura, triptans do not show consistent efficacy in aborting or preventing the migraine. Therefore, until further studies are done, it is also helpful to educate the patient to not take their triptan during the aura phase but rather early in the pain phase of the attack.

MIGRAINE MANAGEMENT

Issues at first visit

Initial Therapy

- Recurrence

Based on attack profile, associated symptoms and level of disability

Back-up Therapy

If Fails

Rescue Therapy

- Follow-up visit

If Fails

The pharmacologic treatment of migraine encompasses several stages. Choice of initial acute therapy depends on the severity and intensity of the migraine, the presence of comorbid conditions, patient preferences, and past therapeutic response profile.

Prescribe initial acute treatment to abort or reverse the progression of headache. Consider the use of one or more medications to treat recurrent headaches.

Provide back-up medication options when initial acute therapy fails.

Rescue therapy is an agent that the patient can use at home to treat breakthrough migraine when other agents, such as initial and back-up medications, have failed to provide relief. Medications of choice include potent opioids such as butorphanol and neuroleptics.

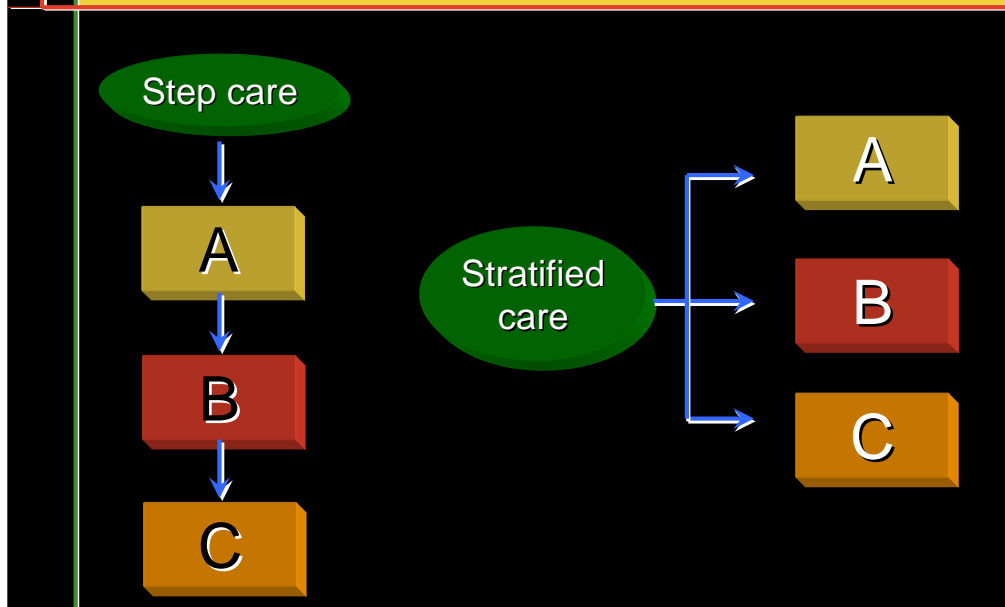
Although rescue medication may not completely eliminate pain and return the patient to normal activities, it may permit the patient to achieve relief without discomfort and a possible visit to the emergency department.

If treatment fails, conduct a thorough follow-up investigation to determine reasons for failure.

Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2000;55(6):754-762.

Matchar DB. Evidence-based guidelines for migraine headache: pharmacological management of acute attacks. [www.aan.com]. April 25, 2000. Available at: <http://www.aan.com/public/practiceguidelines/03.pdf>.

STEP VS. STRATIFIED CARE



There are two strategies for initial therapy: step care and stratified care.

Step care is the use of medications in a sequential order, based on a predetermined plan. Therapy starts with the lowest level of treatment, independent of the characteristics of the attack. This approach to treatment is not necessarily based on the individual needs of the patient. There are two types of step care: between attacks and during an attack. Some managed care companies have attempted to restrict medication choices in a cost-saving attempt to manage plans and not patients.

Stratified care is treatment based on attack characteristics, including peak intensity, time to peak intensity, associated symptoms, and disability. It is also individually tailored to specific patient needs. Stratified care takes into account patient preferences for treatment and allows the patient to select medications for each particular attack.

The advantages to stratified care are that it is more likely to be effective in reducing pain and disability and improving overall patient satisfaction. It also may have the potential to reduce patient drop-out rates and provide improved, cost-effective care through fewer clinic visits and less failed prescriptions. Even with an ideal stratified care plan, treatment of an individual attack may fail and require back-up or rescue medication.

Lipton RB. Disability assessment as a basis for stratified care. *Cephalalgia*. 1998;18:40-46.

BASIS OF STRATIFICATION

- ✓ Headache onset and severity
 - Fast onset may benefit from parenteral therapy
 - Disability predicts treatment needs
- ✓ Symptom profile
 - Prominent nausea and vomiting may require parenteral therapy
- ✓ Headache frequency
 - Consider risk of medication overuse
- ✓ Patient history and preferences
 - Consider adverse events and prior experience

The recently published US Headache Consortium Guidelines recommend using stratified care in a systematic process of diagnosis, patient education, and individualized treatment. These evidence-based guidelines advise clinicians to base their treatment choice on attack frequency, severity, duration, disability, nonheadache symptoms, patient preference, and prior history of treatment response. In stratified care, initial treatment is individualized based on an assessment of the patient's medical needs instead of previously recommended step-care approaches that begin all patients on a nonspecific medication with gradual escalation until they obtain effective relief.

Lipton RB, Silberstein SD. The role of headache-related disability in migraine management: implications for headache treatment guidelines. *Neurology*. 2001;56(suppl 1):S35-S42.

Lipton RB, Stewart WF, Stone AM, Lainez MJ, Sawyer JP; Disability in Strategies of Care Study group. Stratified care vs step care strategies for migraine: the Disability in Strategies of Care (DISC) study: A randomized trial. *JAMA*. 2000;284(20):2599-2605.

ACUTE THERAPIES FOR MIGRAINE: EVIDENCE

GROUP 1: Proven effective with more than one randomized, double-blind, placebo-controlled trial

Specific Medications

- Triptans
- DHE
 - SC, IM, IN, IV (plus antiemetic)

Nonspecific Medications

- Butorphanol IN
- Ibuprofen
- Naproxen sodium
- Prochlorperazine IV
- Droperidol
- Aspirin
- APAP, aspirin, caffeine
- APAP
- Isometheptene
- Opioids

Matchar D et al. AAN, www.aan.com; Silberstein SD. *Neurology*. 2000.

A government-funded meta-analysis of acute migraine therapies permits the categorization of treatments.

Group 1 demonstrated the best evidence for efficacy-consistent statistical significance and moderate-to-large effect size. Group 1a includes migraine-specific therapies, triptans, DHE, and nonspecific prescription therapies, butorphanol IN, ibuprofen, naproxen sodium and prochlorperazine IV. These therapies show substantial empirical evidence and pronounced clinical benefit in migraine.

Naratriptan (Amerge[®])

Sumatriptan SC, IN, PO (Imitrex[®])

Butorphanol IN (Stadol[®])

Prochlorperazine IV (Compazine[®])

Frovatriptan (Frova[®])

Naproxen sodium (Anaprox[®], Naprelan[®], Vicoprofen[®], Aleve[®])

Rizatriptan (Maxalt[®])

Zolmitriptan PO, IN (Zomig[®])

Ibuprofen (Motrin[®])

Eletriptan (Relpax[®])

Almotriptan (Axert[®])

(*Note: Curriculum Developers divided Group 1 into 1a and 1b based on study population)

Lipton RB, Stewart WF, Ryan RE. Efficacy and safety of acetaminophen, aspirin, and caffeine in alleviating migraine headache pain: three double-blind, randomized, placebo-controlled trials. *Arch Neurol*. 1998;55(2):210-217.

Matchar DB, Young WB, Rosenberg JA, et al. Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management of acute attacks. Available from the American Academy of neurology [online]. Available at <http://www.aan.com>. Accessed April 25, 2000.

Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2000;55(6):754-762.

TRIPTANS

Selective 5-HT_{1B/1D/1F} agonists

As a class, relative to nonspecific therapies, triptans provide

- Rapid onset of action
- High efficacy
- Favorable side effect profile

Adverse events and contraindications

Triptans, as a class, represent a significant advancement in the therapeutic management of migraine. These agents have been described as receptor-specific agonists toward serotonin or 5-HT receptors. Specifically, they are selective 5-HT_{1B/1D} agonists having the greatest affinity for these receptors. Blockade of 5-HT₁ receptors has been shown to result in acute migraine relief.

Triptans, relative to nonspecific therapies, including analgesics and NSAIDs, provide rapid onset of action (between 15 minutes and 1 hour, depending on the formulation), are highly effective in relieving migraine pain symptoms, and have a favorable side effect profile. All agents in this class have proven therapeutic efficacy.

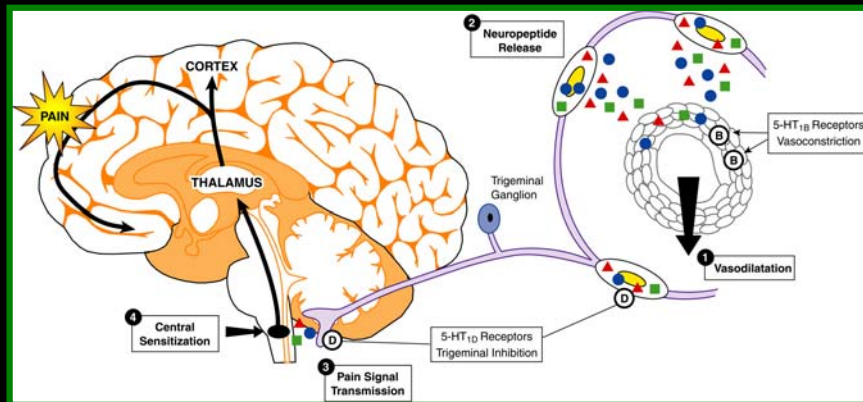
In the majority of patients, the intensity of adverse effects is mild and of short duration. Adverse effects can include chest pressure, flushing, dizziness, drowsiness, and nausea. Patients who are at risk for coronary heart disease, diabetes, obesity, severe uncontrolled hypertension, or hypercholesterolemia should be screened prior to administration of triptans.

Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2000;55(6):754-762.

Silberstein SD, Lipton RB, Goadsby PJ. *Headache in Clinical Practice*. Oxford, England: Isis Medical Media; 1998.

HOW DO SPECIFIC MEDICATIONS WORK?

Trigeminovascular Antimigraine Targets



Hargreaves RJ et al. *Can J Neurol Sci.* 1999. (Modified)

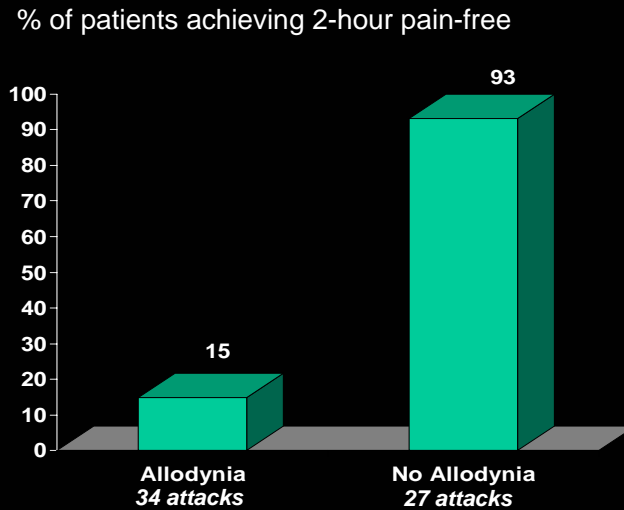
As a group, triptans may affect migraine through a number of proposed mechanisms, which include:

- Vasoconstriction of 5-HT_{1B} receptors on vascular smooth muscle on meningeal, dural, and cerebral arteries, which are dilated and edematous during a migraine attack.
- Activation of the 5-HT₁ receptors on the peripheral terminals of the trigeminal nucleus caudalis, causing neuronal inhibition and blockade of vasoactive neuropeptide release at the trigeminal sensory nerves.
- Inhibition of pain signal transmission in the brainstem trigeminal nucleus caudalis by prevention of sensory neurotransmitter release. Inhibition is through direct action at the 5-HT_{1D} receptors on the central trigeminal nerve terminals.

Hargreaves RJ, Shephard SL. Pathophysiology of migraine—new insights. *Can J Neuro Sci.* 1999;26(suppl 3):S12-S19.

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TRIPTANS AND CUTANEOUS ALLODYNIA



Burstein R et al. *Ann Neurol* 2004.

This study tested the success of triptan therapy when given during the presence vs. absence of cutaneous allodynia (pain resulting from a non-noxious stimulus to normal skin). Cutaneous allodynia is proposed as gradually developing during the course of the migraine attack in the majority of migraine patients. In this study, 31 patients attended a migraine clinic upon three separate occasions: in the absence of migraine (baseline), within the first hour of one attack, and at 4 hours from onset of another attack. Allodynia was identified based on differences between migraine and baseline pain thresholds to both mechanical and thermal stimulation of periorbital skin.

In this study, 34 migraine attacks were associated with allodynia at the time of triptan treatment and 27 attacks were not. Within 2 hours of triptan administration, only 15% (5/34) of attacks achieved a pain-free response to treatment. In patients without cutaneous allodynia, 93% of attacks (25/27) were pain-free at 2 hours.

These results suggest that treatment before the development of cutaneous allodynia may improve response to triptan therapy in some patients.

Burstein R, Collins B, Jakubowski M. Defeating migraine pain with triptans: a race against the development of cutaneous allodynia. *Ann Neurol*. 2004;55(1):19-26.

TRIPTANS: TREATMENT CHOICES

Sumatriptan

- Tablet and fast-disintegrating (25, 50, 100 mg)
- Injection (6 mg)
- Nasal spray* (5, 20 mg)

Zolmitriptan

- Tablet & melt (2.5, 5 mg)
- Nasal spray (5 mg)

Naratriptan

- Tablet (1, 2.5 mg)

Rizatriptan

- Tablet & melt (5, 10 mg)

* Pediatric efficacy shown

Almotriptan

- Tablet (6.25, 12.5 mg)

Frovatriptan

- Tablet (2.5 mg)

Eletriptan

- Tablet (20, 40 mg)

Question and Answer

- Are there differences between the triptans?
- If one triptan fails, will another triptan work?

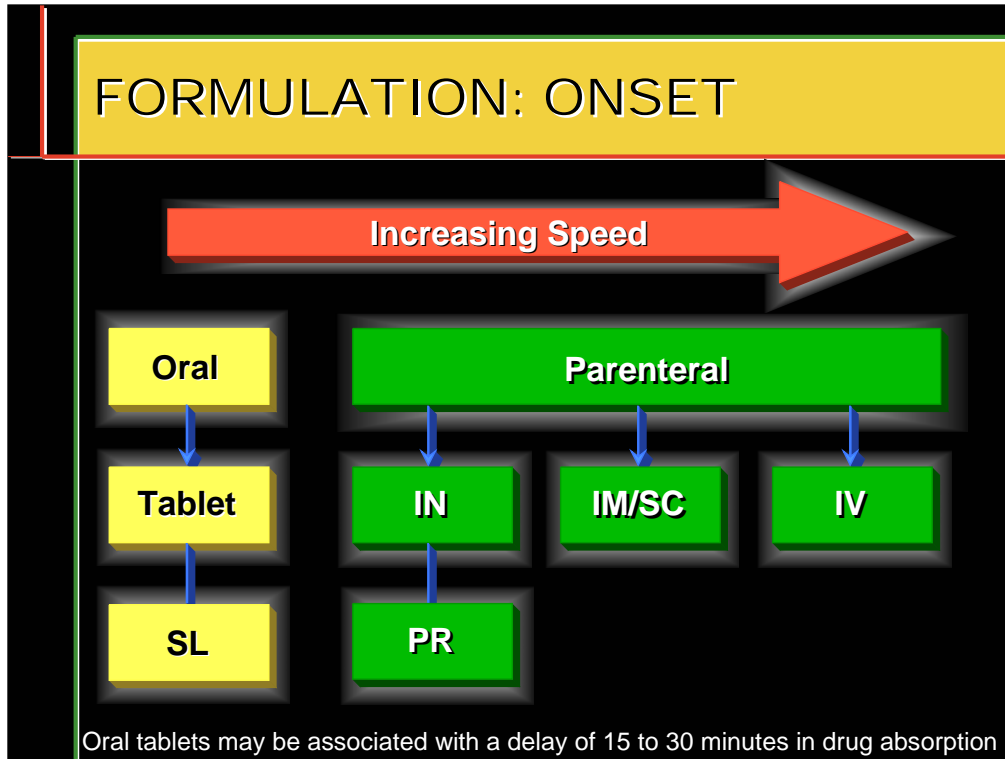
Ferrari MD et al. *Lancet*. 2001.

There are several triptans currently available in the United States. The first is sumatriptan (Imitrex®). The oral formulation is available in 25-mg, 50-mg and 100-mg doses as either an oral tablet or a rapidly-dissolving tablet. Since its introduction in the early 1990s, over 400 million doses of sumatriptan have been given.

- Zolmitriptan (Zomig®), the second product in the triptan class, has a longer half-life than sumatriptan and a more rapid T_{max} . It is available as a tablet, orally disintegrating tablet, and as a nasal spray.
- Naratriptan (Amerge®) has a longer half-life than sumatriptan, and lower recurrence rate. Naratriptan is considered to have lower efficacy than sumatriptan with minimal adverse events.
- Rizatriptan (Maxalt®) has a rapid onset of action and a shorter T_{max} of 1 hour compared to oral sumatriptan. This product is available as a tablet and in a dissolvable wafer form.
- Almotriptan (Axert®) is available as an oral tablet and has a good adverse event profile.
- Frovatriptan (Frova®) is available as a tablet. It, like naratriptan, has a long half-life, low rate of adverse events, and a low recurrence rate.
- Eletriptan (Relpax®) is available as an oral tablet.

Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. Oral triptans (serotonin 5-HT_{1B/1D}) agonists in acute migraine treatment: a meta-analysis of 53 trials. *Lancet*. 2001;358(9294):1668-1675.

Worldwide Product Safety and Pharmacovigilance Document. December 1999.



Oral preparations generally are the least rapidly acting of medications. Onset of action may, for some oral preparations, be delayed by migraine-associated gastroparesis. Among the nonoral formulations, suppositories have the slowest and intravenous drugs the fastest onset of action.

Tfelt-Hansen P, DeVries P, Saxena PR. Triptans in migraine: a comparative review of pharmacology, pharmacokinetics, and efficacy. *Drugs*. 2000;60(6):1259-1287.

Millson DS. Rational migraine management: optimising treatment with the triptans. *Funct Neurol*. 2000;15(suppl 3):182-191.

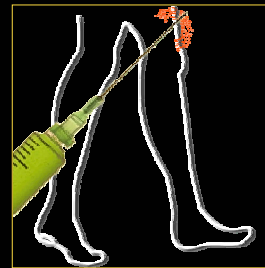
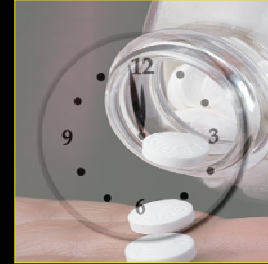
ROUTES OF ADMINISTRATION

Oral therapies: most medications

Nasal sprays: sumatriptan, DHE, butorphanol, zolmitriptan

Injectables (SL, IM, IV)
sumatriptan, DHE, opioids,
injectable NSAIDs, neuroleptics

Suppositories: antiemetics,
ergots, opioids



Migraine medications are available in a number of formulations. It is important to match the formulation to the headache characteristics and the patient's preferences.

Most migraine medications are available as oral formulations. For patients who require a more rapid onset of pain relief, or in whom nausea and vomiting are prominent, there are other options:

- Nasal sprays, which would include sumatriptan, DHE, butorphanol, and zolmitriptan (available in selected countries)
- Parenteral (SC, IM, IV) formulations, such as sumatriptan, DHE, injectable NSAIDs, opioids, and neuroleptics
- Suppositories, including the antiemetics, ergots, and opioids.

Silberstein SD, Lipton RB, Goadsby PJ. *Headache in Clinical Practice*. Oxford, England: Isis Medical Media; 1998.

TREATMENT TIPS FOR ACUTE MANAGEMENT

■ If acute treatment still inadequate:

- Change dose or formulation
- Treat early while headache is mild
- Add adjunctive therapy (e.g., NSAID)
- Try dihydroergotamine (nasal spray, injection)
- Add preventive therapy

■ Screen for exacerbating / interfering medications

- Caffeine or acute medication overuse
- Aggravating medications (e.g., nitroglycerin)

While patients are being evaluated for migraine, several tips may help physicians work with patients to improve headache status. Patients may not recognize exacerbating factors such as regular or high levels of daily caffeine intake. Acute medication, if taken too often or in too high a dose, may also cause headache problems. Women taking oral contraceptives or hormone replacement therapy may experience migraine associated with changing estrogen levels. Other medications, such as nitroglycerin or dipyridamole may also lead to exacerbation of headaches. All medications, vitamins, and over-the-counter remedies should be assessed as possible confounding headache triggers.

Another challenge for many patients and their physicians is that migraine is often a lifelong illness, so treatment plans need to be reviewed continuously. Early intervention after the onset of an attack appears to improve outcomes. Dose adjustment or adding other medications such as an NSAID can be helpful. Routine assessment of sleep hygiene, diet, exercise, concomitant medications, and lifestyle factors will all help identify what may be contributing to migraine.

INCREASING EVIDENCE FOR TREATING EARLY WHEN PAIN IS MILD

- Retrospective studies (sumatriptan, zolmitriptan and almotriptan) support higher pain-free rates when treating while pain is mild
- Retrospective analysis: triptans, ergotamine plus caffeine, and aspirin plus metoclopramide, all provided higher pain-free response. Triptans more effective and less recurrence
- Prospective rizatriptan study: effective at all levels of pain but enhanced benefit if taken while pain is mild

Cady RK et al. *Headache*. 2000. Cady RK et al. *Clin Ther*. 2000.
Hu XH et al. *Headache*. 2002. Winner et al. *Mayo Clin Proc*. 2003.

Treatment with triptans during mild pain produces extremely high pain-free rates (85%–90%). Are the benefits of early intervention shared by all migraine drugs or are they specific to the triptans? Sumatriptan works more effectively when administered early. Aspirin and metoclopramide (ASA + M) work more effectively when administered early, but relative to ASA + M, triptans enhance the benefits of early treatment better than nonspecific therapies. So early intervention generally works better for ASA + M and for ergotamine tartrate (data not shown) but there are incremental benefits from giving triptans. One concern is that early intervention may lead to treatment failure if nonmigraine headaches are treated. So, we wonder what is the relationship of migraine to TTH and do triptans work in phenotypic TTH when they occur in migraine?

Cady RK, Lipton RB, Hall C, Stewart WF, O'Quinn S, Gutterman D. Treatment of mild headache in disabled migraine sufferers: results of the Spectrum study. *Headache*. 2000;40(10):792-797.

Cady RK, Sheftell F, Lipton RB, et al. Effect of early intervention with sumatriptan on migraine pain: retrospective analyses of data from three clinical trials. *Clin Ther*. 2000;22(9):103-148.

Hu XH, Raskin NH, Cowan R, Markson LE, Berger ML; United States Migraine Study Protocol (USMAP) Group. Treatment of migraine with rizatriptan: When to take the medication. *Headache*. 2002;42(1):16-20.

The International 311C90 Long-term Study Group. The long-term tolerability and efficacy of oral zolmitriptan (zolmitriptan, 311C90) in the acute treatment of migraine. An international study. *Headache*. 1998;38:173-183.

Pascual J, Cabarocas X. Within-patient early versus delayed treatment of migraine attacks with almotriptan: the sooner the better. *Headache* 2002;42(1):28-31.

Winner P, Mannix LK, Putnam DG, McNeal S, Kwong J, O'Quinn S, Richardson MS. Pain-free results with sumatriptan taken at the first sign of migraine pain: 2 randomized, double-blind, placebo-controlled studies. *Mayo Clin Proc*. 2003;78:1214-1222.

CONSIDERATIONS FOR TREATING EARLY IN THE ATTACK

Advantages

- May prevent disability
- May reduce headache recurrence and decrease number of tablets used per attack
- May prevent sensitization and allodynia

Disadvantages

- Treating early may lead to over treatment
- To avoid overuse: limit use of acute treatment to no more than 3 days per week

Treating while the pain is mild has a number of potential advantages, which include:

- Avoidance of disability
- Reduction of recurrence
- Reduction of number of tablets necessary to treat each attack
- Prevention of sensitization and allodynia

A disadvantage is the potential for overtreatment and consequent development of chronic daily headache.

To avoid overuse limit acute medication to 3 days or less per week.

ARE TRIPTANS SAFE?

- Serious cardiovascular adverse events are extremely rare (<1/million)
- Chest symptoms rarely due to ischemia
- Usually a tolerability not a safety issue
- Possible mechanisms (need further study)
 - Esophageal spasm
 - Activation of peripheral pain fibers

In patients at low risk for CAD, triptans can be prescribed with confidence, without prior cardiac evaluation. Although serious cardiovascular AEs have occurred after use of triptans, their incidence in clinical trials and clinical practice appears to be extremely low. Over the last decade, millions of patients have successfully used triptans for the acute treatment of migraine.

Chest symptoms are associated with triptans, but are usually not serious and not attributable to ischemia. Possible chest symptoms not related to triptans might include generalized vasospasm, esophageal motility difficulties, pulmonary mechanisms, and changes in skeletal muscle energy metabolism and central sensitization pathways. However, most clinical practice data on triptans are derived from patients without CAD, as these patients were excluded from clinical trials.

TRIPTAN PRESCRIBING

Because of the potential for peripheral arterial constriction, triptans are contraindicated in patients with known CAD and/or—

- Prinzmetal's angina
- High risk for cardiovascular disease
 - Diabetes, obesity, hypercholesterolemia
- Uncontrolled hypertension
- Basilar or hemiplegic migraine
- Pregnancy



Triptans are vasoconstrictors of peripheral blood vessels and, therefore, are contraindicated in patients with ischemic heart disease. As a class, triptans are well tolerated, but precautions are in place to limit their use in high-risk patients including those at risk of cardiovascular disease (obesity, smoking, high blood pressure).

APPROACH TO DIFFICULT HEADACHE PROBLEMS

Problem	Strategy
Pediatric / adolescents	Use NSAIDs, triptans, behavioral therapy (sleep, biofeedback, stress management)
Elderly	Use acetaminophen, COX-2 inhibitors, opioids, atypical neuroleptics
Pregnancy	Use acetaminophen, opioids, corticosteroids, neuroleptics
Adverse effects	Switch triptans, use a different class, lower dose

Silberstein SD et al. *Wolff's Headache and Other Head Pain*. 2001.

These are some difficult headache problems. Some account for patients' dissatisfaction with their medications. Migraine sufferers have high expectations for treatment. They want medications that provide complete pain relief, lack of recurrence, and rapid onset of pain relief.

- With children, studies have suggested that NSAIDs and triptans are somewhat effective, with fast-acting treatments offering some therapeutic benefit (nasal sprays). Nonpharmacological therapies also offer benefit in some patients including sleep, biofeedback, stress management, and physical therapy.
- In cases in which patients experience significant adverse effects, options include switching to naratriptan or to a different class of agents altogether.
- In the elderly, use acetaminophen, COX-2 inhibitors, opioids, and atypical neuroleptics. Try to avoid ergots, DHE, triptans, and NSAIDs.
- During pregnancy use acetaminophen, opioids, corticosteroids, and neuroleptics. Avoid ergots, DHE, and triptans. Limit aspirin and NSAIDs during the third trimester.

Silberstein SD, Saper JR, Freitag FG. Migraine diagnosis and treatment. In: Silberstein SD, Lipton RB, Dalessio DE, eds. *Wolff's Headache and Other Head Pain*. 7th ed. Oxford, England: Oxford University Press; 2001:121-237.

Silberstein SD, Lipton RB, Goadsby PJ. *Headache in Clinical Practice*. Oxford, England: Isis Medical Media; 1998.

HORMONE FLUCTUATIONS AND MIGRAINE

Changes in estrogen levels are associated with migraine in some

- Pregnancy

 - ~33% improve; ~33% deteriorate; ~33% no change

- Hormone replacement / OTCs

- Menopause

Treat with standard acute therapy; hormone therapy adjustments may be needed in some patients

Track migraine frequency, intensity, and response to therapy

Hormone fluctuations in women may be considered a trigger for migraine with some patients experiencing more frequent attacks or more severe attacks. Changes in migraine patterns are not uncommon in women who become pregnant with approximately one third of women reporting improvement in migraine with pregnancy, one other third reporting a deterioration in migraine with pregnancy, and one third reporting not change in headache pattern. Starting or stopping hormone replacement therapy may also lead to changes in migraine status. Therefore, for women who are suspected of having migraine that is associated with such changes in estrogen levels, keeping a monthly diary may help understand predictable times when women are most susceptible to having an attack.

Treatment of migraine that might be associated with estrogen fluctuations is similar to migraine experienced in the absence of estrogen level changes. This includes early intervention with migraine specific or nonspecific medications. Some women may benefit from a short burst of preventive therapy with triptans beginning a few days prior to onset of menses. If migraine is severe and now manageable with acute medications, modifications to hormone therapy may prove helpful. For these patients, consultation with primary care physicians or obstetricians may also be warranted.

RECURRENCE

Recurrence: Return of episodic headache during the same attack following acute treatment

Prevention: Treat early, add NSAID. Use long-duration triptan or DHE

Treatment: Repeat initial acute headache drug that is almost always effective

Tfelt-Hansen P et al. *Drugs*. 2000.; Capobianco DJ, et al. *Headache*. 2001.

Two common terms associated with migraine are *recurrence* and *rebound*.

Recurrence is defined as the return of an episodic headache during the same attack following the use of acute therapy. This superimposed headache may have different characteristics of intensity, severity, and associated features than the primary headache. It may be of migraine or tension-type headache origin.

To prevent recurrence, treat early while pain is mild, add a NSAID, or switch to a long duration triptan or DHE.

To treat recurrence repeat initial acute headache drug; it is almost always effective.

Capobianco DJ, Swanson JW, Dodick DW. Medication-induced (analgesic rebound) headache: historical aspects and initial descriptions of the North American experience. *Headache*. 2001;41(5):500-502.

Tfelt-Hansen P, DeVries P, Saxena PR. Triptans in migraine: a comparative review of pharmacology, pharmacokinetics, and efficacy. *Drugs*. 2000;60(6):1259-1287.

ACUTE MIGRAINE TREATMENT IN URGENT CARE SETTING

Status migrainosus

■ Consider sumatriptan sc

■ Start an IV and hydrate

■ Start repetitive IV treatment

- Antiemetics plus DHE
- Neuroleptics
- Ketorolac 30-60 mg IM
- Opioids
- Corticosteroids
- Magnesium? Valproate?

When a patient presents to an emergency room, they often have already tried their supply of different acute therapies, including rescue medications. One treatment that patients may not try at home is the sumatriptan sc 6 mg. It is important to get the triptan history to see if the patient has either already tried treatment with a triptan, has a contraindication to triptans, or has another medical condition that would prevent additional use of a serotonin agonist. If other medications are needed, it is important to start an IV and hydrate the patient. Antiemetics + DHE, selected neuroleptics, ketorolac IM 30 to 60 mg, selected opioids, and selected corticosteroids have all been proven effective for treatment of status migrainosus. Additionally, some patients have reported benefit from magnesium or valproate.

HEADACHE TREATMENT: NEUROLEPTICS

- IV chlorpromazine (0.1 mg/kg) effective
Avoid orthostatic hypotension: IV fluids and bedrest
- IM (10 mg) and PR (25 mg) prochlorperazine effective
- IM droperidol (1 to 2.5 mg) effective in placebo-controlled, double-blind trials

Neuroleptics for the acute treatment of migraine are often reserved for rescue as they should be given in an emergency room or office setting. Three separate neuroleptics have been studied in clinical trials in headache. These include:

- IV chlorpromazine (0.1 mg/kg) effective
 - Avoid orthostatic hypotension: IV fluids and bedrest
- IM (10 mg) and PR (25 mg) prochlorperazine effective
- IM droperidol (1 to 2.5 mg) effective in placebo-controlled, double-blind trials

Bigal ME, Bordini CA, Speciali JG. Intravenous chlorpromazine in the emergency department treatment of migraines: a randomized controlled trial. *J Emerg Med.* 2002;23(2):141-148.

Brousseau DC, Duffy SJ, Anderson AC, Linakis JG. Treatment of pediatric migraine headaches: A randomized, double-blind trial of prochlorperazine versus ketorolac. *Ann Emerg Med.* 2004;43(2):256-262.

Silberstein SD, Young WB, Mendizabal JE, Rothrock JF, Alam AS. Acute migraine treatment with droperidol: A randomized, double-blind, placebo-controlled trial. *Neurology.* 2003;60(2):315-321.

HEADACHE TREATMENT: OPIOIDS AND BUTALBITAL

WHO USES THEM?

Opioids

- Danger of abuse: restrict use

Butalbital Combination Analgesics

- No placebo controlled studies have established their efficacy in migraine
- Major concerns are overuse, drug-induced headache, and withdrawal
- Use should be limited and carefully monitored

Studies have shown that opioids have demonstrated effectiveness in pain relief of migraine. Guidelines for use include the following:

- Infrequent use in the treatment of moderate-to-severe headaches not responsive to standard medications
- For acute headache when nonopioid medication has failed or is contraindicated, or in the presence of a coexistent disease or lack of diagnosis
- As rescue medication for severe, middle-of-the-night headache
- Pregnancy
- In patients with no history of abuse
- Limit use to 1 or 2 treatment days per week. Set strict limits and prescribe small amounts to avoid overuse. Relax restrictions with menstrual migraine and pregnancy
- Adjust dose to account for difference in bioavailability of formulations

There are no randomized controlled clinical trials that have established the efficacy of butalbital-containing compounds in the treatment of migraine. The AHCPR has conducted a review of 10 separate, controlled trials on the use of butalbital-containing agents for headache treatment. Only 1 trial, which had no placebo arm in the study, was conducted in migraine patients. The trial compared butalbital plus aspirin plus caffeine plus codeine (fiorinal with codeine) to butorphanol NS (stadol NS). Butorphanol was superior at 2 hours, but the treatments were not different at 4 hours. Butorphanol had significantly more adverse events than butalbital combination with codeine.

The major concern of these medications are overuse, drug-induced headache, and withdrawal. Withdrawal symptoms may be minor (e.g., restlessness, anxiety, sleep disturbances, tremulousness, and gastric distress) or major $\geq 400\text{mg/day}$ (e.g., agitation, delirium, psychosis, hypotension, hyperthermia, and seizures).

Withdrawal is more likely with short-acting barbiturates; appears within 1 day and peaks in 2 to 3 days. Use of these agents should be limited and carefully monitored. Limited quantities (24/month) should be prescribed with no refills.

Silberstein SD, Saper JR, Freitag FG. Migraine diagnosis and treatment. In: Silberstein SD, Lipton RB, Dalessio DE, eds. *Wolff's Headache and Other Head Pain*. 7th ed. Oxford, England: Oxford University Press; 2001:121-237.

SUMMARY OF ACUTE MIGRAINE MANAGEMENT

- Make a specific diagnosis
- Assess migraine severity and its impact
- Determine the patient's preferences and needs
- Identify coexistent conditions that influence therapy
- Develop a therapeutic partnership
- Establish realistic expectations
- Agree on treatment plan

Acute migraine management involves a number of important steps.

- Start by making a specific and credible diagnosis based on a complete medical and headache history. The history will provide a comprehensive view of the headaches and any associated conditions or problems. Clearly communicate this diagnosis to the patient.
- Assess the severity of the migraine as a disease—the severity of pain, quality of pain, frequency and timing of headache attacks. Assess what impact the headaches have on the patient's quality of life, both at home and at work or school.
- Take into consideration the patient's therapeutic preferences for treatment, including nonpharmacologic treatment and drug therapy. Treatment should also take into consideration the patient's needs, which may include rapid pain relief, reduction of attack frequency, and ability to tolerate side effects.
- Identify comorbid or coexisting conditions that may limit therapeutic choices. Engage the patient in active dialogue and establish a therapeutic partnership. Work with the patient to develop realistic expectations for management of the migraine.
- Formulate a treatment plan appropriate to the diagnosis, where the intensity of treatment matches the severity of the headache. The treatment plan should consider patient needs, preferences, and any comorbidities.

Silberstein SD, Goadsby PJ, Lipton RB. Management of migraine: an algorithmic approach. *Neurology*. 2000;55(9 suppl 2):S46-S52.

ACUTE CASE DISCUSSION

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ACUTE CASE STUDY

History: 20 y/o female, 2 year history of headache, 4 - 6 h duration, frequency of 3-4/mo

Symptoms: pain (right forehead, eye extending back to occipital region, throbbing, ice picks); nausea (no vomiting); aura (some spots in vision & flashing lights 10 min before headache); sensitivity to light and sound

Triggers: Headaches worse with weather changes, hypoglycemia, sleep deprivation

Medications: taking oral contraceptive; tried a triptan & had some chest "hurting", no relief; lethargy with amitriptyline therapy

Exams: General and neurological were normal; systolic murmur at apex.

This patient has a diagnosis of migraine, which presents on occasion with aura.

Interestingly, although ice-pick headaches can occur as a separate headache type, she finds that they generally occur as part of her migraine. Her symptoms are classical in that she has nausea with occasional vomiting, photophobia, phonophobia, throbbing, and pain. Often, when a patient experiences no vomiting with headache, a diagnosis of "probable migraine" should be considered.

With regard to her current medications, she is on a low dose of oral contraceptives (20 ug). She tried a triptan one time, but it failed to provide relieve and she experienced some traditional "triptan" side effects. In this case, she probably did not need to try amitriptyline as her headache frequency was relatively low. Additionally, she did not tolerate the lethargy.

This patient also was found upon physical exam to have a systolic murmur– PMV or prolapsing mitral valve.

Case presented by Dr. Allan Purdy, Division of Neurology; QEII Health Sciences Centre, April 19th, 2004.

ACUTE CASE DISCUSSION

- What is best therapy at this time?
- She found one triptan failed and not tolerated.. *what should she do?*
- What about the cardiac murmur?
- Should she try other abortive medications, if so what?
- Should she be on oral contraceptive therapy?
- Should she be on any other therapy at this time and if so what?

This patient should try another triptan. It is unclear when in the course of her headache she tried the triptan. If she took it late in the attack, she may have difficulty getting response from any triptan. If the AEs are a concern for her, she may find good tolerability with naratriptan or almotriptan, as they are well tolerated. She also may find that a different formulation may offer benefits, especially if she is nauseated or vomiting.

With additional cardiac work-up, her murmur PMV was confirmed and proven on Echo. There was not an apparent need to specifically treat or pursue. However, given the cardiovascular side effect profile of triptans, it is important to discuss the risks of cardiac valve disorders and use of triptans. Usually, it is not a problem to use triptans in these patients, but she should be aware of her murmur and associated risks of all medications she might take.

Another medication she may find helpful would be analgesics or NSAID's. However, upon further treatment, she found that naratriptan worked fine, but with sumatriptan relief was a little better. She also got used to the "triptan sensation" and it did not frighten her.

Although she reported simple brief visual auras, she could probably continue to take her oral contraceptive therapy. However, the slight increased risk of stroke in women on OCT who also have migraine with aura needs to be addressed with the patient, as part of informed consent.

Lastly, because her migraine is not frequent and she is responding to triptan therapy, now that she knows how to take her medication and what to expect as side effects, she may not need to be tried on preventive therapy. However, she may benefit from other nonpharmacological or other therapies, which routinely should be considered with most migraine patients.

Case presented by Dr. Allan Purdy, Division of Neurology; QEII Health Sciences Centre, April 19th, 2004.