Taking the Headache Out of Migraine Diagnosis & Management
Session 6: Taking the Headache Out of Migraine Diagnosis and Management

Learning Objectives
- Describe how to use standardized tools to guide you through the appropriate diagnosis and treatment of migraine.
- Describe a stratified care approach to management of migraine in order to tailor therapy to the patient.

Faculty
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Dr Stewart J. Tepper received his bachelor’s degree with honors in psychobiology from Yale University in New Haven, Connecticut. He graduated from Cornell University Medical College in New York, and completed his neurology residency at Harvard University in Boston. Dr Tepper is director of clinical research at the Center for Headache and Pain at the Neurological Institute of the Cleveland Clinic Foundation.

Dr Tepper is a board-certified neurologist with a passionate interest in headache management and patient care. He has authored and co-authored over 150 articles, chapters, videos, books, and monographs. He is co-abstracts editor of the journal *Headache* and co-director of the autumn educational meeting of the American Headache Society.

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Dr Susan Hutchinson received her bachelor’s degree in chemistry magna cum laude from Miami University of Ohio in Oxford, Ohio. She graduated from the Medical College of Ohio in Toledo, and completed her internship and residency in the Department of Family Medicine at the University of California, Irvine, Medical Center, where she is currently an associate clinical professor. Dr Hutchinson is board-certified in family practice, with a subspecialty in headache. She is also director and founder of the Orange County Migraine and Headache Center, also in Irvine.

Dr Hutchinson concentrates on the management of migraine and mood disorders, with a special interest in the relationship of both conditions to hormones. A national speaker on migraine and depression, in February 2003, she was awarded the National Headache Foundation Lectureship Award in recognition of her contribution to headache education. She was designated a Physician of Excellence by the Orange County Medical Association in January 2007. In recent years, Dr Hutchinson has co-authored numerous journal articles and chapters on the subject of migraine.

Faculty Financial Disclosure Statements
The presenting faculty report the following:

Dr Tepper is a member of the advisory board for GlaxoSmithKline and Merck & Co., Inc.; is a consultant to Allergan, Inc.; AstraZeneca Pharmaceuticals LP; Coherex Medical, Inc.; Elan Corporation, plc; Endo Pharmaceuticals; and Forest Laboratories, Inc.; and is a speaker for Allergan, Inc.; AstraZeneca Pharmaceuticals LP; Endo Pharmaceuticals; Merck & Co., Inc.; Ortho-McNeil Pharmaceuticals, Inc.; and Pfizer Inc.

Dr Hutchinson is a member of the advisory board for Endo Pharmaceuticals and GlaxoSmithKline; and is a speaker for Endo Pharmaceuticals; Forest Laboratories, Inc.; GlaxoSmithKline; Merck & Co., Inc.; and Ortho-McNeil Pharmaceuticals, Inc.
**Education Partner Financial Disclosure Statement**
The content collaborators at MedicoAlliance, LLC, have nothing to disclose.

**Drug List**

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<tr>
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<th>Trade</th>
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<tr>
<td>almotriptan malate</td>
<td>Axert</td>
</tr>
<tr>
<td>dihydroergotamine mesylate, USP</td>
<td>Migranal</td>
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<td>divalproex sodium</td>
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<td>sumatriptan succinate</td>
<td>Imitrex</td>
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<td>zolmitriptan</td>
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**Suggested Reading List**


28-year-old female, law school student
Complains of bilateral, moderate in severity, headaches (HAs) with occasional nausea and mild photosensitivity but not phonophobia
Over-the-counter (OTC) analgesics give her partial relief
HAs occur several times/month and started when she began law school 1 year ago

Are these headaches?
1. Tension
2. Migraine
3. Mixed
4. Not enough information to diagnose

Pathophysiology
• Update
Diagnosis
• International Classification of Headache Disorders II
• Pattern recognition
• Brief screeners: ID migraine
• Brief screeners: nausea
Sinister headache
• When to work up for secondary causes
SNOOP
• A mnemonic for secondary workup

Acute treatment
• How to get to the right treatment first time
• The triptans
Preventive treatment
• When to add daily pharmacologic treatment
• US Headache Consortium Guidelines and update
Pathophysiology of Migraine

3 Steps

1. Central generator: cortex or brainstem
2. Peripheral pain mechanisms in the meninges: inflammation and vasodilation
3. Central processing and sensitization

Migraine Neuroanatomy


Pathophysiology of Migraine

Central Generator
- Cortex?
- Brainstem?

Meningeal Events
- Inflammation
- Vasodilation
- Peripheral sensitization

Brainstem Events
- Pain signal to central nervous system (CNS)
- Central sensitization
- Allodynia

Activated neurons and glia release CGRP and substance P

Leads to:
- Vasodilation
- Mast cell degranulation
- Inflammation

Approaches to Diagnosis

- International Headache Society (IHS), International Classification of Headache Disorders II (ICHD-II), 2004
- Pattern recognition
- Brief screeners
International Classification of Headache Disorders

**Migraine Without Aura**

- **Symptoms:**
  - At least 5 episodes, lasting 4-72 hours
  - With any 2 of:
    - Unilateral
    - Throbbing
    - Worsened by movement
    - Moderate or severe
  - With any 1 of:
    - Nausea or vomiting
    - Photophobia and phonophobia

**Secondary Cause:**

- No secondary cause

**Classification:**

- 2+1 = Migraine

**Tension-Type Headache (TTH)**

- **Symptoms:**
  - 10 episodes, 30 min-7 days long
  - With any 2 of:
    - Not unilateral (bilateral)
    - Not throbbing
    - Not worse with movement
    - Not severe (mild to moderate)
  - With both of:
    - No nausea or vomiting
    - Either photosensitivity or phonophobia, or neither (but not both)

**Classification:**

- 2-1 = Episodic tension-type headache

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**IHS (ICHD-II/IHS) Criteria for Migraine/Tension-Type Headache (TTH)**

1.1 Migraine Without Aura (vs episodic TTH)

- At least 5 attacks with
  - At least 2 of the following 4:
    - Unilateral (bilateral)
    - Pulsating (not pulsating)
    - Moderate to severe intensity, inhibits or prohibits activities (mild to moderate)
    - Physical activity aggravates (does not aggravate)
  - At least 1 of the following:
    - Nausea and/or vomiting (no nausea or vomiting)
    - Photophobia and phonophobia (Either or neither, but not both)
  - No evidence on history or exam of disease that might cause headache

1.6 Probable Migraine (Migrainous)

- Missing one of the above criteria

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**Headache Patterns**

- **Vascular**
- **Infectious**
- **Inflammatory/Neoplastic**

**Secondary Headaches**

**Primary Headaches**

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**ID Migraine™ Validated Screener**

During the last 3 months, did you have the following with your headaches?

1. You felt nauseated or sick to your stomach?
   - Yes ___  No ___

2. Light bothered you (a lot more than when you don’t have headaches)?
   - Yes ___  No ___

3. Your headaches limited your ability to work, study, or do what you needed to do?
   - Yes ___  No ___

2/3 for migraine:

- Sensitivity: 0.81
- Specificity: 0.75

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**Nausea**

- **Sensitivity**
- **Specificity**

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**Martin VT, et al. Headache. 2005;45(9):1102-1112.**
Global Prevalence of Episodic Headache Presenting to PCP Based Upon Expert Panel Diary Review

94% migraine/probable migraine

N=377 patients who returned diaries

Migraine + Probable M: 94%

Migraine (N=288) 76%

Probable M (N=67) 18%

Unclassifiable (N=11) 3%

Tension (N=47) 5%

Migraine Prevalence

3 Population-Based Studies

1989

1999

2007


12.1% 5.7%

17.6%

12.6% 6.5%

18.2%

Total Males Females

Algorithm for Headache Diagnoses

Detailed history and examination

Headache alarms (red flags) present

Consider primary headache

Are there atypical features?

Yes

No

Yes

No

Exclude secondary headache using appropriate tests, if necessary

Reconsider secondary headache

Diagnose the primary headache disorder

Atypical features: consider referral

Worrisome Headache Red Flags “SNOOP”

Systemic symptoms (fever, weight loss) or
Secondary risk factors: underlying disease (HIV, systemic cancer)
Neurologic symptoms or abnormal signs (confusion, impaired alertness or consciousness)
Onset: sudden, abrupt or split-second (first, worst)
Older: new onset and progressive headache, especially in older age >50 (giant cell arteritis)
Pattern change: first headache or different, change from
Previous headache history: attack frequency, severity or clinical features


Clinical Pearl

When in doubt, investigate the atypical!

Treatment of Migraine

- Acute
- Preventive
- Medication-overuse headache (MOH)
Strategies for Outpatient Acute Migraine Treatment

- All migraine patients need acute treatment provided
- Selection of medication is based on disability
  - Standard of care for acute therapy: sustained pain-free response, reducing disability, optimally restoring function with minimal adverse events and cost
- Outcome of acute treatment also can be monitored by Migraine Assessment of Current Therapy (Migraine-ACT)

Video Case Study: Part 2

Emily, now in her 3rd year at law school, states her HAs can become worse if she does not take her OTC analgesic soon enough into the HA. Activity worsens her HA, and as a result, she misses running at least once/week. She also is absent from school a few times/month; other times, she attends class with a HA but finds they greatly interfere with her ability to focus and concentrate on her studies. Her Migraine Disability Assessment Scale (MIDAS) score is 22, indicating severe disability.

Audience Response Question #2

The best treatment option for this patient would be?
1. A prescription-strength nonsteroidal anti-inflammatory drug (NSAID), such as naproxen 500 mg
2. Isomethptene/dichloralphenazone/acetaminophen combination
3. Butalbital-containing product
4. A triptan

How to Get the Right Acute Treatment the First Time

- Assess disability, impact, or time loss

Case Study Review: Part 2

MIDAS: Migraine Disability Assessment Scale*

1. On how many days in the last 3 months did you miss work or school because of your headache? [days]
2. How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches? (Do not include days you counted in question 1 where you missed work or school) [days]
3. On how many days in the last 3 months did you not do household work because of your headaches? [days]
4. How many days in the last 3 months was your productivity in household work reduced by half or more because of your headaches? (Do not include days you counted in question 1 where you did not do household work) [days]
5. On how many days in the last 3 months did you miss family, social, or leisure activities because of your headaches? [days]
6. On how many days in the last 3 months did you have a headache? (If a headache lasted more than 1 day, count each day) [days]

Add up the number of days from questions 1-6 (ignore A and B). If the total is above 6, prevention and acute treatments need to be optimized. If the total is above 6, prevention and acute treatments need to be optimized.

Add up the number of days from questions 1-6 (ignore A and B). If the total is above 6, prevention and acute treatments need to be optimized. If the total is above 6, prevention and acute treatments need to be optimized.

Total 40 Days

*Use in waiting room when possible

**MIDAS: Migraine Disability Assessment Scale**

- **MIDAS Grade I**  Little to no disability  Score 0-5
- **MIDAS Grade II**  Mild disability  Score 6-10
- **MIDAS Grade III**  Moderate disability  Score 11-20
- **MIDAS Grade IV**  Severe disability  Score 21+

Useful on initial screening and follow-up visits to assess level of function and determine if change in medication needed.

**How many days in the last 3 months were you at least 50% disabled by your migraines at work, home, school, or recreational activities?**

**Disabilities in Strategies of Care (DISC) Study**

- Compared 3 strategies of migraine management over 6 attacks
- Stratification based on disability (stratified care)
  - MIDAS Grade II: aspirin (ASA) + metoclopramide
  - MIDAS Grade III, IV: triptan (zolmitriptan)
- Step care within attacks
  - ASA + metoclopramide → Assess response at 2 hours
  - Rescue with triptan prn
- Step care across attacks
  - ASA + metoclopramide
  - Assess response after 3 attacks
  - Escalate treatment to triptan if ASA + metoclopramide fails 2/3 or 3/3

**Benefit of Stratified Care Over Step Care**

**Short Cuts to Optimal Acute Treatment of Migraine**

- Most patients in offices complaining of episodic headache have disabling migraine
- Therefore, in the absence of vascular contraindications, most patients complaining of episodic migraine in the office merit a triptan first line
- Since most attacks of migraine begin at mild and progress to disabling, in migraine attacks occurring <10 days/month, use of triptans early in the attack, <60 minutes into the attack, when pain is mild, is most likely to result in a sustained pain-free response (one and done)


**Success Outcome**

Migraine-ACT

<table>
<thead>
<tr>
<th>Impact</th>
<th>Global Assessment of Relief</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are you able to function normally within 2 hours?</td>
<td>Does the HA pain disappear within 2 hours?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Consistency of Response</th>
<th>Emotional Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does your migraine medication work consistently in the majority of your attacks?</td>
<td>Are you comfortable enough with your medication to be able to plan your daily activities?</td>
</tr>
</tbody>
</table>

A Migraine-ACT score of ≤2 suggests a need to switch acute medications

Treatment

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Triptan Groups

Group 1
Fast onset, high potency
- Sumatriptan
- Sumatriptan/naproxen
- Zolmitriptan
- Rizatriptan
- Almotriptan
- Eletriptan

Group 2
Slower onset, lower potency
- Naratriptan
- Frovatriptan


Formulations and Doses of Triptans

Group 1
Fast onset, high potency
- Sumatriptan
  - Subcutaneous 4, 6 mg
  - RT Oral 25, 50, 100 mg
  - Nasal 5, 20 mg
- Rizatriptan
  - Oral 2.5, 5 mg
- Almotriptan
  - Oral 6.25, 12.5 mg
- Eletriptan
  - Oral 20, 40 mg

Group 2
Slower onset, lower potency
- Naratriptan
  - Oral 1.25, 2.5 mg
- Frovatriptan
  - Oral 3.5 mg

Selecting the Triptan
The 3 F's

- Fast vs slow
- Formulation
- Formulary

On the Horizon...

- CGRP-receptor antagonist
- Dihydroergotamine (DHE) inhaler
- AMPA/kainate glutamate–receptor antagonist
- Gap junction inhibitor
- 5-HT1F agonist
- Inducible nitric oxide synthase inhibitor
- Carbon dioxide inhaler

New Triptan-NSAID Combination

- Sumatriptan 85 mg with naproxen sodium 500 mg
- FDA approved April 2008
- Rationale
  - Targets multiple pathways involved in migraine pathogenesis

Selecting the Right Acute Treatment Avoids Chronic Daily Headache (CDH)

- Most CDH evolves from episodic migraine
- Thus, most CDH is transformed migraine (transformed from episodic migraine to daily HA)
- Goal of treatment: sustained pain free, one and done
- The use of suboptimally effective treatment leads to relief but not pain free, recurrence of the same HA, repeat doses, and then overuse
- Most CDH seen in the office is associated with acute medication overuse for episodic migraine (≥10-15 days of use/month)

When to Start Daily Preventive Medication

Video Case Study: Part 3

Emily now works at a prestigious law firm
- She experiences HAs 2-3 times/week, which interfere with her work, personal, and social life; this causes her to worry and lose sleep frequently
- Emily is frustrated and plans to see her PCP but has missed several follow-up appointments
- She recently missed an important client meeting due to a severe HA; the firm is concerned her HAs will impede her ability to successfully carry her full case load

Case Study Review: Part 3

For her headaches, she starts with an OTC combination product (acetaminophen/caffeine/aspirin) and waits to see how the HA evolves before taking her triptan
- Emily takes the OTC product at least 2-3 times/week and the “rescuing” triptan at least 2 times/week
- She often runs out of her #9 allotted triptan tablets/month

Audience Response Question #3

The best treatment option at this time would be?
1. Increase her quantity of triptans/month from #9 to #18
2. Prescribe an NSAID, such as naproxen 500 mg, and instruct her to take this for her milder HAs and “save” the triptan for the more severe HAs
3. Offer her a daily preventive medication
4. Quit her job!
When to Consider Daily Prevention

- Migraine that significantly interferes with the patient’s daily routine despite acute treatment
- Failure of, contraindication to, or troublesome side effects from acute medications
- Special circumstances:
  - Hemiplegic migraine
  - Attacks with a risk of permanent neurological injury

Goals of Preventive Treatment

- Decrease attack frequency (by 50%), intensity, and duration
- Improve responsiveness to acute medication
- Improve function and decrease disability
- Intervene to prevent rebound

Disability/Frequency Issues

- The US Headache Consortium suggests daily prevention with:
  - Migraine that significantly interferes with the patient’s daily routine despite acute treatment
  - ≥ 2 long, significantly disabling attacks/month
  - Infrequent attacks but producing profound disability
  - Failure of, contraindication to, or troublesome side effects from acute medications

- The American Migraine Prevalence and Prevention study (AMPP):
  - As disability increases, headache frequency at which you might intervene with daily prophylaxis decreases

When to Start Daily Preventive Medication

The Frequency Strategy

- Clinic-based study on the development of CDH over 1 year
  - 0-5 vs 6-9 days/month, Odds Ratio (OR) 6.2
  - 0-5 vs 10-14 days/month, OR 20.1 for CDH

Disability/Frequency Issues

- The US Headache Consortium suggests daily prevention with:
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- The American Migraine Prevalence and Prevention study (AMPP):
  - As disability increases, headache frequency at which you might intervene with daily prophylaxis decreases

American Migraine Prevalence and Prevention Study (AMPP) 2007

- AMPP expert consensus
  1. Prevention should be offered:
     - ≥ 5 HA days/month
     - ≥ 3 HA days with at least some impairment
     - ≥ 3 HA days with severe impairment or requiring bed rest
  2. Prevention should be considered:
     - 4-5 migraine days/month with normal functioning
     - 3 migraine days with some impairment
     - 2 migraine days with severe impairment
  3. Prevention not indicated:
     - < 4 HA days/month and no impairment
     - No more than 1 HA/month regardless of impairment
Preventive Therapies for Migraine
US Headache Consortium Guidelines for Migraine Prophylaxis

Group 1
High efficacy, good strength of evidence, low to moderate side effects.
- Amantadine (100-150 mg/day)
- Divalproex sodium (500-1200) mg/day
- Topiramate (100-150 mg/day)
- Flurbiprofen (1000 mg/day)
- Verapamil (120-480 mg/day)
- Botulinum toxin type A (25-100 units/3 months)

Group 2
Medium efficacy, limited strength of evidence, low to moderate side effects.
- Atenolol (25-100 mg/day)
- Naproxen (500-800 mg/day)
- Nimodipine (30 mg/day)
- Verapamil (120-480 mg/day)

Group 3
No scientific evidence of efficacy, but clinically efficacious based on consensus of experience.
- Low to moderate adverse events.
- Frequent or severe adverse events (or safety concerns);
  complex management issues.

- Aspirin (325 mg/day)
- Atenolol (25-100 mg/day)
- Fenoprofen (600 mg three times/day [tid])
- Flurbiprofen (1000 mg two times/day [bid]-tid)
- Fluoxetine (10-80 mg/day)
- Gabapentin (300-2400 mg/day)
- Ketoprofen (75 mg tid)
- Metoprolol (50-200 mg/day)
- Nimodipine (30 mg/day)
- Nicardipine (60 mg/day)
- Nifedipine (30 mg/day)
- Propranolol (20-160 mg/day)
- Topiramate (50-150 mg/day)

Group 4
Medium to high efficacy, good strength of evidence, but side effect concerns.

Group 5
Evidence indicating no efficacy over placebo.
- Acebutolol
- Pindolol
- Carbamazepine
- Nicardipine
- Indomethacin
- Cyproheptadine
- Antidepressants, such as nortriptyline, paroxetine, venlafaxine, doxepin, sertraline, and phenelzine
- Methylergonovine
- Methysergide (discontinued)

Findings of US Headache Consortium

- The following are all somewhat effective in preventing migraine compared with controls:
  - Relaxation training
  - Thermal biofeedback combined with relaxation training
  - Electromyography biofeedback
  - Cognitive-behavioral therapy

Hormonal Approach to Prevent Menstrual Migraine

- Continuous contraception (skip placebo)
- Estradiol patch 0.1 mg perimenstrually to prevent the drop in estradiol
- Transdermal estradiol patches < 0.1 mg not effective at preventing menstrual migraine compared with placebo

Principles for Preventive Treatment

- Start low and increase dose slowly
  - Use long-acting formulation if compliance an issue
  - Adequate trial (2-3 months) at appropriate dosage
- Maximize treatment of comorbidity and avoid interfering and contraindicated medications
- Evaluate therapy
  - Use headache calendar (diary)
  - Attempt to taper and discontinue treatment when headaches well controlled

Randomized Controlled Trials (RCTs) for Prevention Update

- Topiramate, 100 mg, since guidelines, FDA approved (Group 1)
- Venlafaxine, 150 mg (Group 2)
- Lisinopril, 20 mg, 1 RCT since guidelines (Group 2)
- Candesartan, 16 mg, 1 RCT since guidelines (Group 2)
- Butterbur (petasites hybridus), 100-150 mg/d (Group 2)
- Coenzyme Q10, 1 RCT, 300 mg/d (Group 2)

Choose Preventive Medication Based on Pharmacologic Opportunity

- Go for a 2-Fer!
  - Hypertension
    - Beta-blocker, calcium channel blocker, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker
  - Anxiety
    - Beta-blocker
  - Depression and sleep disturbance
    - Tricyclic antidepressant (TCA)
  - Pain disorder
    - Gabapentin
  - Obesity
    - Topiramate
Avoid Medications That Worsen Comorbid Illnesses

- Depression or asthma
  - Beta-blockers
- Obesity
  - TCAs, divalproex

Patient Weekly Diary

<table>
<thead>
<tr>
<th>Day</th>
<th>Sunday</th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
<th>Saturday</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prodrome</td>
<td>Aura</td>
<td>Time of pain onset</td>
<td>Severity of pain</td>
<td>Treatment 1 (dose)</td>
<td>Symptoms (nausea, throbbing, disability)</td>
<td>Treatment 2 (dose)</td>
<td>Treatment 3 (dose)</td>
</tr>
</tbody>
</table>

Prevention

What Goes Wrong

- Wrong drug
- Excessive initial dose
- Inadequate final dose
- Duration of treatment too short
- Combination treatment required
- Non compliance

- The presence of rebound/CDH/MOH nullifies effectiveness of preventive medication
- Expectations unrealistic
- Failure to provide acute medications (triptans) for breakthroughs

Conclusions

- Migraine is common
  - 12% of the general population and 94% of patients complaining of episodic headache in the PCP office
- Secondary headache is less common
  - SNOOP
- All migraine patients need to be provided acute treatment
- Selection of medication is based on disability
- Outcome can also be monitored by Migraine-ACT

Emily Returns

Emily returns 6 weeks after starting daily preventive therapy
- Review of her headache diary shows 1-2 headaches/week
- Many of her headaches are mild and do not require triptan therapy
- She is trying to practice good health habits, is running routinely again, and has not had to miss work for the past 4 weeks!