
4TH ANNUAL
CHAIR SUMMIT
Master Class for Neuroscience Professional Development

# HEADACHE — TRICKS OF THE TRADE

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## Disclosures

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# LEARNING OBJECTIVE

Apply best practice strategies for the treatment of migraine into clinical practice.

# MIGRAINE IS A PRIMARY HEADACHE

(No Other Causative Disorder)

# Chart Review: Allison M.

Menu

Calendar

Tests

## BACKGROUND

**Personal:** 35-year-old Caucasian female, life skills counselor for adults with disabilities, married, no children

**Neuropsychiatric History:** Negative psychiatric history (confirmed by spouse)

**Medical History:**
- Healthy, appears stated age
- No chronic illness or allergies
- Was in a car accident as a sophomore in high school where she hit her head, but suffered no severe injury

**Family History:**
- Family history of migraine (Grandmother)
- Family history of breast cancer (Mother, and both Aunts)

**Social History:**
- Social smoker/drinker
- Has many friends, enjoys sports

## TODAY'S VISIT

Severe, sudden onset headaches with associated nausea
- 35 years old
- Married, 6 years; Husband works in sales for phone company
- Works full-time
- Has had to miss work and social events due to these headaches; believes she probably has migraines like her Grandmother did
- Has mild anxiety that she never knows when and where the next time a severe headache will occur and what she will be forced to miss
- Is sensitive to light and sound during headache and prior to onset
- Complains of feeling "tired more often then she should"
- Is stressed about financial concerns and isn't sleeping well

**Physical Findings:** Unremarkable

**Questionnaire and Lab Findings:**
- No aura
- Has been taking opioids for lower back pain
- Labs normal/unremarkable

# Chart Review: Allison M.

## ASSESSMENT AND PLAN

- What is your diagnostic impression?
  - Chronic migraine
- What treatments would you consider?
- What is your response? What do you ask about?
  - How often she is taking opioids for back pain, and how often does she take abortive OTC medications, e.g. Excedrine or Aleve?
- What treatment recommendations do you make?
  - Sumatriptan 50mg BID
  - Address sleep concerns?
- What do you do next? What treatment changes do you consider?
  - Migraine diary (including food intake); follow-up in 3 months
- What do you do next in terms of maintenance?
  - Magnesium and/or feverfew supplements
  - Other?

Menu

Calendar

Tests

◄

## S-N-O-O-P-S

### Headache Red Flags

- **S**ystemic Symptoms (fever, weight loss)
- **N**eurologic Symptoms or abnormal signs (confusion, impaired alertness or conciousness)
- **O**nset: sudden, abrupt or split second
- **O**lder: new onset or progressive headache, especially in patients >50 (giant cell arteritis)
- **P**revious headache history: first headache or new or different headache (change in attack frequency, severity or clinical features)
- **S**econdary Risk Factors (HIV, systemic cancer)

*Developed by David Dodick, MD, Mayo Clinic Scottsdale*

- 80% of “sinus headache” patients meet IHS criteria for migraine
- 85% of “tension/stress” headache patients meet IHS criteria for migraine

Schreiber CP, et al. *Arch Intern Med*. 2004;164(16):1769-1772.
Kaniecki R et al. *CMRO.* 2006;22(8):1535-1544.

# MEDICATIONS AND DRUGS WHICH MAY CAUSE HEADACHE

- Hydralazine, isosorbide dinitrate, nitroglycerin
- Nifedipine
- Enalopril
- Ranitidine, famotidine, cimetidine
- Sildenafil
- Trimethoprim-sulfa, tetracyclines
- Estrogen, progesterone, tamoxifen
- Theophylline
- Pseudoephedrine
- Amphetamines
- Cocaine
- Bupropion

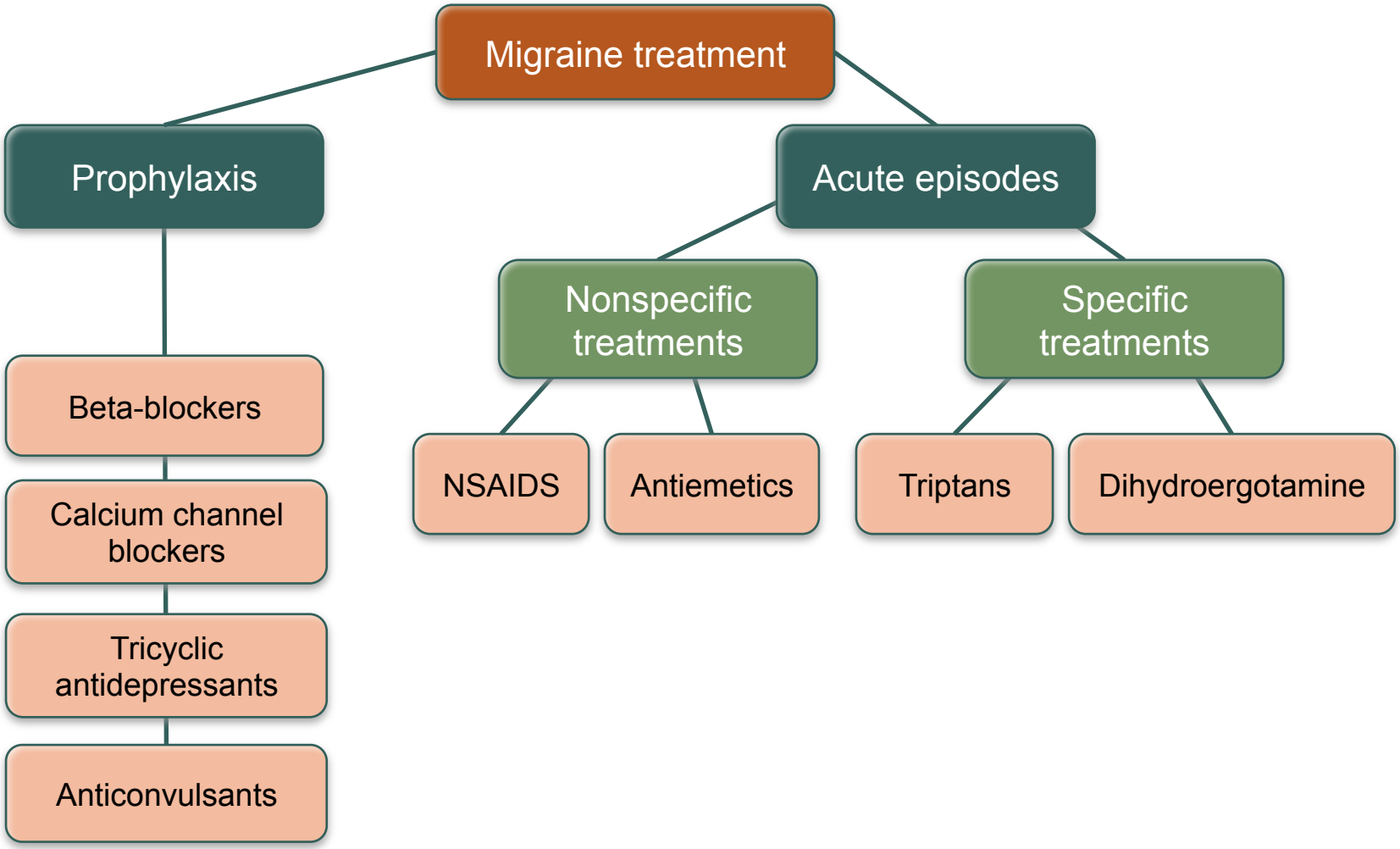
# PATIENT CASE: ALLISON

- Female, 35 years old
- Presents with 4-month history of sudden onset headaches
- No prior history of migraine, denies aura
- BP = 180/95

# PATIENT CASE: ALLISON

- What would be your primary diagnosis and why?

# TREATMENT OF MIGRAINE




Courtesy of: http://www.pharmacologycorner.com.

# OTC ABORTIVE TREATMENTS


Naproxen sodium (220 mg)


Acetominophen (250 mg)
Aspirin (250 mg)
Caffeine (65 mg)


Ibuprofen (200 mg)

# TRIPTAN FORMULATIONS

| Triptan | Tablet | Melt | Nasal | Subcutaneous |
|---|---|---|---|---|
| Almotriptan | 6.25; 12.5 | - | - | - |
| Eletriptan | 20; 40 | - | - | - |
| Frovatriptan† | 2.5 | - | - | - |
| Naratriptan† | 1; 2.5 | - | - | - |
| Rizatriptan | 5; 10 | 5; 10 | - | - |
| Sumatriptan | 25; 50; 100 | - | 5; 10 20 | 4; 6 |
| Zolmitriptan | 2.5; 5 | 2.5; 5 | 5 | - |

* Currently available triptans; doses are in milligrams

† Frovatriptan and naratriptan have longer half-lives than other triptans and may be used for menstrual migraine prophylaxis or for migraine recurrence. Other drugs are shorter-acting and are to be used only in acute headache

From: Gladstein J. *Top Pain Manage*. 2007.

# CONTRAINDICATIONS AND PRECAUTIONS FOR TRIPTANS

- Contraindications
  - Ischemic cardiac disease
  - Cerebrovascular disease
  - Uncontrolled hypertension
  - Use within 24 hours of other triptans or ergots
  - Hemiplegic/basilar migraine
  - Acephalgic migraine

# CONTRAINDICATIONS AND PRECAUTIONS FOR TRIPTANS

- **Precautions**
  - History of risk factors for CAD
  - SSRI use?
- **Risk of serious cardiac event**
  - ~1:1,000,000

# TRIPTAN COMBINATION APPROACHES

- Sumatriptan (85 mg) – naproxen sodium (500 mg)
- Combinations with caffeine or acetaminophen under investigation

# NON-ORAL ALTERNATIVES

- Safe, effective alternatives to oral medications; nausea, vomiting, and gastric stasis may limit the absorption of oral medications
  - Nasal sprays
    - Dihydroergotamine
    - Sumatriptan
    - Zolmitriptan
  - Injections
    - Dihydroergotamine
    - Sumatriptan
  - Needle-free subcutaneous delivery
    - Sumatriptan

# PATIENT CASE: ALLISON

- Treated by PCP with abortive medications for 3 months
- No resolve to date

# PATIENT CASE: ALLISON

- What prophylactic treatment options would you offer?

# WHEN TO USE PROPHYLACTIC THERAPY

- Frequent headaches (3-4 episodes/ month) with risk of medication overuse
- Frequent headaches interfere with quality of life
- Acute medications contraindicated, ineffective, intolerable AEs, or overused
- Hemiplegic migraine or complicated migraine with risk of permanent injury
- Patient preference

# FDA APPROVED PROPHYLACTIC DRUGS

| | |
|---|---|
| Methysergide | 1962 |
| Propranolol | 1976 |
| Timolol | 1995 |
| Divalproex sodium | 1996 |
| Divalproex sodium ER | 2000 |
| Topiramate | 2004 |

# OTHER PROPHYLACTIC AGENTS*

- Antidepressants (NET inhibitors)
  - Amitriptyline, nortriptyline, doxepin
- Antidepressants (MAO inhibitors)
  - Phenelzine
- β-Blockers
  - Atenolol, nadolol, metoprolol
- ACE inhibitors/ angiotensin II receptor antagonists
  - Captopril, lisinopril, candesartan
- Calcium channel blockers
  - Verapamil
- Feverfew
- OnabotulinumtoxinA†

* Not approved by the FDA for prophylactic treatment of migraine
† Approved by the FDA for the prophylaxis of chronic migraine in adults.

# ANECDOTAL MIGRAINE TREATMENTS USED BY MIGRAINE SPECIALISTS*

- Metoclopromide (25-50 mg p.o., 5-10 mg i.v.)
- Solumedrol i.v.
- Dexamethasone p.o.
- Zonisamide
- Toradol (60 mg i.v.)
- Tizanidine (4 mg start; 8-12 mg)
- Memantine

* Not approved by the FDA for the treatment of migraine.

# MEMANTINE REDUCES HEADACHE FREQUENCY IN 28 PATIENTS WITH REFRACTORY MIGRAINE (10-20 MG/DAY)

Headache
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Research Submission

## Memantine in the Preventive Treatment of Refractory Migraine

Marcelo Bigal, MD, PhD; Alan Rapoport, MD; Fred Sheftell, MD; Deborah Tepper, MD; Stewart Tepper, MD

**Objectives.—To assess the efficacy and tolerability of memantine (MEM) in the preventive treatment of refractory migraine.**

**Background.—Glutamate is of importance in migraine pathophysiology and may be related to progression from episodic to chronic mirgraine. Furthermore, individuals with chronic pain often report cognitive problems. MEM has the potential to address both issues, justifying this pilot study.**

**Methods.—We included subjects with refractory migraine (episodic migraine with 8-14 days of headache per month or transformed migraine, who had previously failed at least 2 trials of adequate preventive therapy). Other preventive drugs were allowed if the patient had been on a stable dose for more than 30 days. MEM dose ranged from 10 mg to 20 mg per day. The treatment phase lasted 3 months. The primary endpoint was number of days with headache at month 3. Cognitive performance was assessed with the trail making tests A and B (TMT-A and B). Statistical analyses were performed on the intent-to-treat (ITT) population, using data subjected to the last observation carried forward algorithm. We also conducted per protocol analyses.**

**Results.—In the ITT population (n = 28), monthly headache frequency was reduced from 21.8 days at baseline to 16.1 ($P < .01$) at 3 months. The mean number of days with severe pain was reduced from 7.8 to 3.2 at 3 months ($P < .01$). The mean disability scores were significantly reduced at 3 months, compared with baseline (36.6 vs 54.9, $P < .01$). There was a significant reduction in the time to complete TMT-A at termination vs baseline (28.4 vs 23.2, $P = .02$) and also TMT-B (70.1 vs 50.4, $P = .04$). Side effects were present in 37.5% of the patients; 5.5% dropped out the study because of poor tolerability. Most adverse events were mild.**

**Conclusion.—This study offers preliminary evidence for the use of MEM in the prevention of refractory migraine. Double-blind studies are now required.**

**Key words: refractory migraine, memantine, treatment**

(*Headache* 2008;48:1337-1342)

Many migraineurs who seek care in headache clinics are refractory to treatment.[1-3] Refractoriness is defined based on the chronicity, frequency, and severity of the headaches, as well as on subjects experiencing less than expected benefit from standard therapies.[4,5] Defining refractory migraine (RM) has been the subject of a great deal of interest.[4,6]

**From Merck Research Laboratories and the Albert Einstein College of Medicine – Neurology, Bronx, New York, NY, USA (M. Bigal); UCLA – Neurology, Los Angeles, CA, USA (A. Rapoport); The New England Center for Headache, Stamford, CT, USA (F. Sheftell, D. Tepper, and S. Tepper).**

**Address all correspondence to M. Bigal, MD, PhD, Global Director, Scientific Affairs, Neuroscience, One Merck Drive, PO Box 100, Whitehouse Station, NJ 08889.**

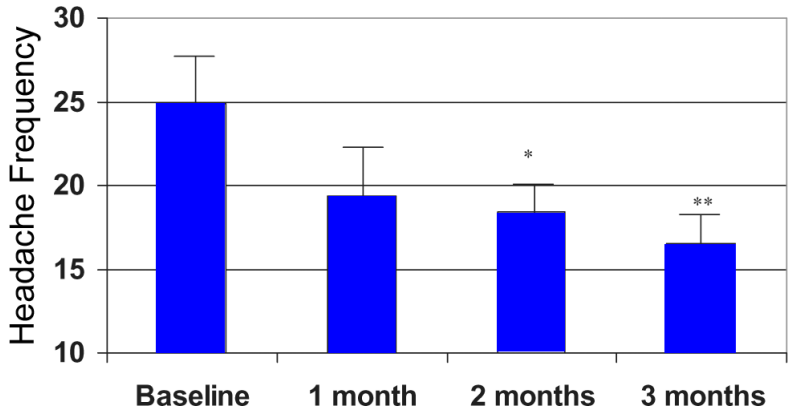
**Accepted for publication January 22, 2008.**

The pharmacological treatment of RM poses a challenge to the physician. Most preventive agents used in this context have not been examined specifically for the treatment of this syndrome.[7-9] Medications for RM are used empirically based on their efficacy in the treatment of episodic migraine,[7,8] and patients are often treated with multiple drugs.[10] As a consequence, side effects, poor compliance, and disappointing outcomes are common. Cognitive symptoms also emerge frequently in this context, either as a consequence of chronic pain[11,12] or of the medications used to treat RM.[13,14]

*Conflict of Interest*: The study was conducted with an independent research grant from Forrest Laboratories. Dr. Bigal is now a full time employee of Merck Research Laboratory.



Open label, uncontrolled



# ON THE HORIZON*. . .

- Dihydroergotamine inhaler
- Ketorolac tromethamine
- CGRP antagonists (Telcagepant, elevated AST)

* Not approved by the FDA for the treatment of migraine.

# PATIENT CASE: ALLISON

- As she progresses, she notes that she has chronic lower back pain and is taking opioids
  - How do you taper patient from opioid?

Schreiber CP, et al. *Arch Intern Med*. 2004;164(16):1769-1772.
Kaniecki R, et al. *CMRO.* 2006;22(8):1535-1544.

# HOW DO YOU DIFFERENTIATE BETWEEN HORMONE-RELATED MIGRAINES AND MEDICATION-OVERUSE HEADACHES (MOH)?

# HORMONES AND MIGRAINE

- Falling estrogen or estrogen withdrawal can trigger migraine
- Migraine often improves during pregnancy (estradiol rising or high); worsen postpartum
- Migraine may worsen with aging (estradiol low)

# MENSTRUAL MIGRAINE

- 50% to 67% of premenopausal females with migraine have attacks consistently during perimenstrual period
- Only migraine without aura
- More severe, disabling, and refractory to abortive medications than non-menstrually related
- Short term prophylactic therapies: naproxen sodium (550 mg bid 6 days before to 7 days after menses)
- Triptans (frovatriptan [2.5 qd or bid], naratriptan [1 mg bid] and zolmiptriptan [2.5 mg bid and 2.5 mg tid]) 4-5 days during the perimenstrual period

# MENSTRUAL MIGRAINE

- Magnesium (360 mg/day), 3-4 days prior to menses
- Diamox 250 mg bid, 3-4 days prior to menses
- Estradiol patches and gels; 100 µg transdermal estradiol patches
- Hormonal contraceptives:
  - Long duration OC (avoid hormone free interval): 24/4 (ethinyl estradiol/desogestrel); extended cycle (levonorgestrel/ethinyl estradiol) 84 days; continuous (levonorgestrel/ethinyl estradiol) 365 days/year
  - Bridge hormone-free interval with transdermal estradiol

# MENOPAUSE

- Migraine may flare at menopause (may last 4 years)
- 30% of women in menopause experience migraine
- Postmenopausal HRT (low-dose estrogen) but consider stroke risk
  - Relatively contraindicated in women with migraine with aura

# MEDICATION-OVERUSE HEADACHE (IHS-2)

- Headache present on ≥ 15 days/month
- Regular overuse for ≥ 3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache
- Headache has developed or markedly worsened during medication overuse
- Headache resolves or reverts to its previous pattern within 2 months after discontinuation of overused medication

# WHAT DRUGS CAUSE MEDICATION OVERUSE?

## All Acute Medications

- Triptans (most common cause in U.S.)
- Opioids (particularly short-acting)
- Butalbital-containing compounds
- Caffeine-containing compounds
- Ergotamine derivative
- Acetaminophen, aspirin, NSAIDs
- Isomethepthene/acetaminophen/ dichloralphenazone (1:2 mixture of antipyrine with chloral hydrate)

# WITHDRAWAL TREATMENT FOR MOH

- Objectives:
  - Detoxify and stop the chronic headache
  - Improve responsiveness to acute or prophylactic drugs
- Abrupt withdrawal leads to quickest resolution (usually 2-10 days)
- ? *Taper* opioids and barbiturates to reduce withdrawal symptoms (worsening headache, nausea, vomiting, hypotension, tachycardia, sleep disturbances, restlessness, anxiety)
- Start prophylactic drugs

# QUESTIONS AND ANSWERS

USF HEALTH

CME Outfitters