Transforming the Interrelationships of Women, their Medical Practitioners and Severe Headaches
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  Contributing Editor – Headache Currents
- Treasurer, National Board for Certification in Headache
Financial Potential COI 2007

- **Research/Publication Grants** –
  - Current/Ongoing: Allergan, Merck, Medtronic, GlaxoSmithKline

- **Consultant Fees & Lecture Honoraria** –
  - Current: AstraZeneca, GlaxoSmithKline, Merck, UpToDate
  - Periodic: Abbott Labs, Allergan, Pfizer
  - Past: Medpointe, Pharmacia, Elan-UCB Pharma

- **Lecture Honoraria** –
  - American Headache Society, American Academy of Neurology, Columbia University, Ortho-McNeil, Primary Care Network, Pri-Med, University of Minnesota, Valeant

- No stocks or family member conflicts

2006 Earned >$10,000 (5), >$25,000 (3), >$50,000 (0)
Rosie’s Headache History
Your History
### Rosie’s Case Scenario

- **Rosie to PCP** - 27y/o “stress” headaches & anxiety

| Frequency: | 3-5 headache days per month |
| Pain Descriptors: | Unilateral (L>R), throbbing & moderate, > 12 hours untreated |
| Starts: | Neck 50%, cheek 30%, frontal 20% |
| Assoc. Symptoms: | Disability, visual flashes and holes, nausea (10%), light sensitivity |
| Antecedents: | Worse with menses |
| Treatments: | OTC analgesics “edge off” – 6 tabs/day |
Rosie’s Diagnosis & Offer

Diagnosis? - Migraine, Tension, Sinus, Menstrual

Rosie’s Offer:

Diagnosis Made: “Mixed Headaches”
Acute: Butalbital compound
Provokers: Not identified; not addressed
Prevention: OCP started
What Rosie Does!

Rosie’s Diagnosis – “Mostly non-migraines”

Rosie Does:

Acute use: “Waits till migraine” ~ 90 minutes

Treatment results: “Doesn’t work!” – pain severe
Worse than usual - “Touching” hurts!
Sleepy, and “Can’t plan my day”
Visual auras ↑ frequency and last longer
What Rosie Needs

- Diagnosis of Migraine - the “mixed” headache syndrome
  Tension Migraine, Sinus Migraine, Menstrual Migraine
- Allodynia Recognized!; Predicts lack of Pain-Free Response
  - Occurs in ½ - ¾ of migraineurs
- Discussion of OCPs, migraine aura and stroke/CVD risk

Rosie’s offer Revisited:

Acute: HA ≤ 9 d/mo treat: “early; mild, whenever possible with migraine-specific therapy”

Provokers: Identified; Counseled modification

Prevention: OCP terminated; preventative started
Does Rosie Have Migraine?

Might You Have Migraine?

Getting the Diagnosis Right
Primary Headaches – Common
Secondary Headaches - Rare

Percentage of population affected in past year

- Tension Headache: 74%
- Migraine Headache: 12%
- Cluster Headache: 0.4%
- Brain Tumor: 0.015%
- Meningitis: 0.01%
- SAH: 0.008%

Of 377 primary care patients reporting a new complaint of recurrent HA, 94% had migraine or probable migraine, according to expert-panel IHS diagnosis of diary data.

Migraine Prevalence: US Female Population

Migraine in Primary Care

Initial patient sample
n=696

Headache patients
n=289 41.5%

Migraine sufferers
n=176 25.3%

Migraine suffersers
n=176

Recognition
n=71 40.3%

Management
n=50 28.4%

IHS migraine 11.21%
IHS probable migraine 14.08%

HIT-6 mean = 59.7
HIT-6 > 60 (severe) = 50%

Vuillaume De Diego E. Cephalalgia 2005;25:184-190
How Migraine Gets Missed

- Letting the uninformed make the diagnosis
- Assigning “Triggers” to headache diagnosis
- Getting fooled by the masks of migraine
  - Autonomic symptoms in migraine
    - Guilt by association
  - Muscle tension in migraine
    - Guilt by location
  - Psychological symptoms and migraine
    - Guilt by mythology
Patterns - What to Assess For

Listen

<table>
<thead>
<tr>
<th>Minutes</th>
<th>Hours/Days</th>
<th>Weeks/Months</th>
<th>Months/Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Infectious</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Inflammatory/Neoplastic</td>
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</table>

Secondary Headaches

Primary Headaches
Impact - What to Assess

Missed:

- Age appropriate responsibilities
  - Decreased performance at work/school
- Family interactions
  - Both leisure and household activities
- Personal life
  - Missed social events
  - Less attention to activities and hobbies
<table>
<thead>
<tr>
<th>Symptom</th>
<th>Likelihood Ratio for Migraine/Probable Migraine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulsating</td>
<td>4/5 = 24 95%CI 1.5 – 388</td>
</tr>
<tr>
<td>4-72 hOurs</td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>3/5 = 3.5 95%CI 1.3 – 9.5</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
</tr>
<tr>
<td>Disabling</td>
<td>2/5 = 0.41 95%CI 0.32 - 0.52</td>
</tr>
</tbody>
</table>

ICHDI-II Migraine

Detsky ME. JAMA 2006;296:1272-83.
ID Migraine™: PIN
Photophobia, Impact, Nausea

- 93% Positive if “yes” answer 2 out of 3 items
- 98% Positive if “yes” answer 3 out of 3 items

Sensitivity | Specificity | PPV
---|---|---
81% | 75% | 93%
98% |   |   

What About? Rosie’s Other Headaches
Recurrent episodes (at least 6 in the past 6 months)
No fever or purulent discharge
No history of abnormal sinus radiographs

How Often Is “Sinus” Headache Really Migraine?

- Migraine with or w/o aura (IHS 1.1, 1.2) 80%
- Migrainous (IHS 1.7) 8%
- Episodic tension-type (IHS 2.1) 8%
- Other 4%

60% of Women Migraineurs Have Menstrual Migraines

- 60% menstrual migraine
  - MRM 46%
  - Pure MM 14%
- 40% non-menstrual migraine

Women With Migraine

Disabling Headaches? – Think Migraine

Migraine

Sinus

Tension

Menstrual

Think Migraine

Courtesy of Primary Care Network
Why Care? About Rosie’s (Your) Headaches
Why Care About Migraine?

- Migraine produces severe disability
- Frequent use of “acute medications” produces chronic headaches
- In some any migraine begets even more frequent migraine (chronically progressive)
- Migraine may produce brain changes
Risk for “Chronic Dailies” with Episodic Migraine

1-year Study

14 per 100 incident CDH
450 migraineurs
(<15 days per month) followed for 1 year

MOH defined as >10 days/month of any acute headache medication

Chronification of Headache
The Frequent Headache Study

CDH incidence (person years): 3/100 in population
14/100 in clinic

Yellow flags* for CDH:
Not readily modifiable
Migraine
Female
Low education
Socioeconomic status
Head Injury

Readily modifiable?
Attack Frequency
Medication Overuse
Obesity
Stressful life events
Caffeine
Snoring (sleep apnea, sleep disturbance)

*Identified by case control and cohort analyses

OCP’s, Migraineurs and Stroke Risk
Variable Effects of OCPs on the Course of Migraine

- 4 DBPC studies - no incidence difference OCP/placebo
- Low dose estrogen OCs - lower headache incidence
- Reported influence of oral contraceptives on frequency and severity of migraine
  - Better: 3-35% of cases
  - Worse: 18-50% of cases
  - No change: 39-65% of cases
- Can trigger the first migraine attack

Systematic Review of OCs on the Course of Migraine

- 2-part systematic review
  - Controls group and prospective cohort studies
  - Trial designs inconsistent – pooling data invalid

Conclusions:
- “There is little indication that OCs have a clinically important effect on headache activity in most women.”

- “Headache that occurs during early cycles of OC use tends to improve or disappear with continued use. No evidence supports the common clinical practice of switching OCs to treat headache.”

Oral Contraceptives and Risk of Stroke

- Lower stroke risk < 50 µg than ≥ 50 µg estradiol
- Increased stroke risk attributed to the estrogen
  - Limited data for progestin-only OCs

Stroke Risk in Migraine Women

- Stroke risk <45 years of age generally very low
  - Estimated 5-10 per 100,000 woman-years
- Stroke risk (odds ratio) increased under age 45
- RR high, but absolute risk low: 17 to 19/100,000
- No evidence for stroke in women over age 45

Influences on Stroke Risk in Migraine

- Migraine: 3
- Migraine with aura: 6
- Migraine plus OC’s: 5 - 17
- Migraine plus OC’s plus smoking: 34

CVD Risk in Migraine Women

10 year followup active migraine to controls
- Migraine without aura ≠ excess CVD risks of any type

Migraine with aura Hazards Ratios
- Major CVD, 2.15  95% CI, 1.58-2.92; P=.001
- Ischemic stroke, 1.91  95% CI, 1.17-3.10; P=.01
- Myocardial infarction, 2.08  95% CI, 1.30-3.31; P=.002
- Coronary revascularization, 1.74  95% CI, 1.23-2.46; P=.002
- Angina, 1.71  95% CI, 1.16-2.53; P=.007
- Ischemic CVD death, 2.33  95% CI, 1.21-4.51; P=.01

Migraine Symptom Relief Revealed
Building Success: The Headache Toolbox

- Education-Biology
- Prevention
- Acute Treatment
- Rescue

Your Toolbox
- Education
- Prevention
- Acute Treatment
- Rescue

Courtesy Primary Care Network
Triptans, DHE & Ketorolac in Interrupting Sensitization

The Race against Time: The Window of Opportunity

Within minutes of a migraine being triggered, the peripheral neurons that innervate meningeal blood vessels become sensitized. If migraine is left untreated, those peripheral pain neurons activate and sensitize central neurons, leading to central sensitization. Central sensitization signifies full-blown migraine; central neurons continually fire and the attack becomes more difficult to treat.

Harvard Research Suggests:
A Sequence of Events Leads to Central Sensitization

The Race to Meaningful Prevention
Prevention
General Principles

Assess your life style/triggers & modify
- ABC’s (D,E,F & G)

You the patient are encouraged to choose by:
- Comfort level: side effects, safety, costs, etc.
- Frequency (Adherence): “I can take this as directed”
- Treat 2 conditions/avoid harming another: i.e. mood
- “Proven Works” - “Proven Effectiveness”
Daily Lifestyles

E
Regular 5-6 days a week of exercise

D
Don’t skip meals! Especially breakfast

C
Caffeine – taper to 2 a day or less

F
Fluids – maintain hydration

A
Regulate Sleep

G
Consider Biofeedback

Structure a treatment plan – & follow the program!
Lifestyle Management

“Best Proven” Identifiable Triggers:

- Sleep
- Stress
- Hormones (in general try not to change)
- Weather (really can’t influence)
- Food (very little evidence)
  - Food triggers are usually not important
  - We encourage “benign neglect”
Lifestyle Management

Highest Priority “New Year’s Resolutions”:

- **Sleep** – 6-8 hours, consistent within 1 hour to bed & rise
- **Exercise** – Any better than none, cardio >>>non-cardio
- **Stress Management** – Biofeedback/relaxation, Cognitive-Behavioral
- **Substance Use** – Taper Caffeine to max 1-6oz cup, eliminate artificial sweeteners, decongestants, smoking
- **Eat** – Fresh, non-processed, Rainbow of Colors, Small amounts spread throughout the day
The Race to Meaningful Acute Relief
Migraine Undertreatment: Key Issues

- Migraineurs not considered for migraine therapy
  - Takes on average 3.5 years to find effective Rx
  - Nearly 5 options before effective treatment

- Prevailing prescriptions for sedating non-migraine-specific drugs with great potential for overuse & end-organ damage

Lipton RB. JAMA 2000;284:2599-2605
Acute Migraine Analgesics (What could be used)

- **Nonspecific:** not mechanistically rational
  - Combination analgesics
  - Opioids
  - Neuroleptics/antiemetics
  - Isomethoheptene

- **Specific:** mechanistically rational
  - NSAIDs
  - Triptans
  - Ergotamine/DHE

Adapted and modified from: Matchar et al. Available at: http://www.aan.com/professionals/practice/pdfs/g/0087.pdf
Acute Migraine Medications (What should be used)

Evidence-based guidelines adopted by AAFP, ACP-ASIM, and the AAN

- **NSAID’s** as first-line therapy
- **Triptans (or dihydroergotamine)** indicated for those who fail to tolerate or respond to NSAID’s

- **No evidence** to support the use of butalbital compounds in acute migraine
- **Little evidence** to support the use of isomethoheptene compounds in migraine
- Opioids “**reserved**” for use when other medications cannot be used”

Acute Headache Prescriptions (What is used)

Migraine Patients with Rx Coverage

<table>
<thead>
<tr>
<th>Prescription Type</th>
<th>% of Patients Receiving Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triptans</td>
<td>41%</td>
</tr>
<tr>
<td>Narcotics/Opioids</td>
<td>59%</td>
</tr>
<tr>
<td>Butalbitals</td>
<td>23%</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>15%</td>
</tr>
<tr>
<td>Ergots</td>
<td>1%</td>
</tr>
</tbody>
</table>

HA Patients with Rx Coverage

<table>
<thead>
<tr>
<th>Prescription Type</th>
<th>% of Patients Receiving Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triptans</td>
<td>7%</td>
</tr>
<tr>
<td>Narcotics/Opioids</td>
<td>77%</td>
</tr>
<tr>
<td>Butalbitals</td>
<td>11%</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>1%</td>
</tr>
<tr>
<td>Ergots</td>
<td>20%</td>
</tr>
<tr>
<td>Other</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

Data from 2003 study, plan with 6.2 million members (640,000 patients coded for headache)
Weighing Early Acute Therapy: Evaluating Nonspecific Therapy

**Nonspecific:**
- Inexpensive
- May be sedating, habit forming
- High rebound risk
- High risk for stomach, kidney damage
- Fail mechanistically

**OTC Combination HA Medications**
- Barbiturates
- Opioids
- Antiemetics
- NSAIDs
- Acetaminophen
- OTC Combination HA Medications
Weighing Early Acute Therapy: Evaluating Specific Therapy

Specific:

- Higher cost to you and insurance
- Nonsedating & non-addictive
- Less rebound headache
- Very low end-organ risk (body damage)
- Rational mechanistic design
About Acute Treatment for Episodic Migraine

- Treat *early*, typically within an hour
- Treat “*mild*” pain, whenever possible
- Expect “*back to normal*” in 2-4 hours
- Expect Consistency - *One and done*; maximum 2 doses in 24 hours
Does My Acute Therapy Work? Migraine-ACT

When you take your treatment,

- Does the headache disappear within 2 hours?
- Are you able to function normally within 2 hours?
- Are you comfortable enough with your medication to be able to plan your daily activities?
- Does your migraine medication work consistently, in the majority of your attacks?

≥1 “No” answers → possible need to change acute medication

About Acute Treatment
“Necessary Limitations”

- Use < 2 days/week on average
  - except if headache limited to menses
- Ideal < 12 tablets per month - maximum 18
- Nearly all drugs have SE’s in all patients
- Narcotics almost never “best” choice!
Why Treatment Fails

- Lack of education/instruction/realistic expectations
- Dx is incorrect: i.e. Chronic HA treated like Episodic
- High frequency of attacks/acute medications/medication overuse HA (MOH)
- Comorbidities
- Non-adherence
- Treatment incorrect
  - Wrong dose
  - Wrong formulation
  - Wrong timing
Migraine

- Is Underdiagnosed & often Ineffectively treated
- Masquerades as many headache types
- May progress in frequency and severity
- Produces brain changes including strokes
- Migraine with aura accrues excess CVD risk
- Without aura and OCs are suitable together
Summary: Optimizing Your Needs

- Getting the Correct Diagnosis /es
- Excellent Communication, inc calendar
- Mutually acceptable “integrated” Rx plan
  - Idealize A-G Lifestyles and Trigger reduction
  - Maximize Prevention to minimize events
  - Optimize but limit acute therapy – typically specific to diagnosis
- Stick with a “successful” plan for the long-haul
Thank You for Your Kind Attention!
Biofeedback & Minimal Contact Therapies
A Sampling of Options

- www.bcia.org (Biofeedback Certification Institute of America)
- www.MHNI.com/CD.html – Alvin Lake
  (Relaxation and Pain Management Strategies for Headache)
- www.healthjourneys.com – Belleruth Naparstek
  Meditation for Optimum Health – Jon Kabat-Zinn
- “Taking Care of Yourself” – Andrew Weil
- “The Art of Effortless Living” – Ingrid Bacci
- www.csh.umn.edu/modules
Triptan Contraindications

- Ischemic heart disease, Prinzmetal’s angina
- Peripheral/cerebral vascular disease
- Uncontrolled hypertension
- Hemiplegic or basilar migraine
- Ergot derivatives (ergotamine, DHE) or other triptans within 24 hours

Agent-specific drug interactions
- MAOI, not SSRI; Eletriptan and potent CYP-3A4 agents
Triptan CVD Safety

- Concerns have arisen because of isolated reports of serious CV events\(^1\)
- Concerns about CV safety are warranted, but exaggerated\(^2\)
- Frequency of CV AEs has been extremely low in postmarketing surveillance data

*Risk with sumatriptan approximately 1 in 2.5 million*

Guidelines

- Triptans are contraindicated in patients with known cardiovascular disease
- Others must be assessed for CV risk before being prescribed triptans
  - **High risk** → triptans contraindicated
  - **Intermediate risk** → more extensive risk evaluation required before triptans
  - **Low risk** → triptans may be prescribed without extensive evaluation

ATP III CV Risk Assessment Guidelines

ATP III* recommends a 2-step process by which numbers of CV risk factors are initially assessed, and if 2 or more are present, Framingham scoring of risk factors is performed.

CV Risk Assessment: Applying ATP III Guidelines

<table>
<thead>
<tr>
<th>ATP III: Major Risk Factors for CHD</th>
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<tbody>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Hypertension (&gt;140/90 or on BP medications)</td>
</tr>
<tr>
<td>High LDL (&gt;159) or low HDL (&lt;40)</td>
</tr>
<tr>
<td>Family hx of premature (man &lt;55; woman &lt;65)</td>
</tr>
<tr>
<td>CHD in first-degree relative</td>
</tr>
<tr>
<td>Age: (men ≥45, women ≥55)</td>
</tr>
</tbody>
</table>

Cardiovascular Risk Assessment

- Patients can be quickly screened for risk factors
  - Those with $\leq 1$ risk factor may be prescribed triptans without more intensive CV evaluation
  - Those with $\geq 2$ risk factors should undergo further testing, including a 10-year risk assessment using Framingham scoring, before a decision is made on triptan use

Consensus Statement on CV Safety of Triptans

- “In patients at low risk of coronary artery disease, triptans can be prescribed confidently without the need for prior cardiac status evaluation.”

Serotonin Syndrome

Symptoms:

- Restlessness, hallucinations, loss of coordination, fast heart rate, rapid changes in blood pressure, increased body temperature, overactive reflexes, spontaneous clonus, nausea, vomiting, diarrhea
Co-Prescriptions

- Merck-Medco insurance from 2000 to 2001
- 65+ million covered
  - 240,000 patients had filled two or more triptan prescriptions within a year
    - ‘Co-prescription’ defined as any fill for a medication that was contraindicated or could potentially adversely interact with a triptan, obtained between and during the first and last triptan fills throughout the study period.
  - 21% (~50,000) taking an SSRI and triptan

Serotonin Syndrome Incidence

Assumptions

- 10% only of actual cases reported
- 85% (250 million) with health insurance in US
- ~200,000 Americans simultaneously exposed to SSRIs and Triptans (based on Tepper data)

Other assumptions

- No change in triptan or SSRI usage rates
- No FDA cases occurring in uninsured patients
- No contribution of SNRIs to the triptan co-prescription

Shapiro R. Neurology Today September 2006
Serotonin Syndrome

- 27 total cases reported
- 8/27 another serotonin agent along with SSRIs and triptan
- 0/27 with triptans alone

- **Annual incidence 0.5-0.9 cases per 1000 patient-months of treatment**
- **Annual incidence <0.03% of patients exposed to SSRIs and triptans**
- **Annual incidence <0.002% of life-threatening events of those similarly exposed**
Serotonin Syndrome (SS)

- FDA July 19th Alert (fine print of the Healthcare Professional Sheet) states:
  - “FDA is considering, but has not reached a final conclusion about this information. FDA intends to update this sheet when additional information or analyses become available.”

- “The FDA advisory is premature and their fine print is very apt.”

- Rarely, SSRIs alone precipitate SS

Serotonin Syndrome (SS)

- Largest prospective study where SS sought
- 1784 patients of a 12,339 cohort -1 year period
- Received sumatriptan SC while taking SSRIs

- NO Serotonin Syndrome events.

Serotonin Syndrome (SS)

- 7 eletriptan clinical trials
- 5992 patients enrolled
- 306 (~5%) also taking SSRIs
- There were no serious adverse events

Managing Risk Factors

- Regular exercise
- Caffeine – taper to 0 ideal or < 2 a day
- Fluids – maintain hydration
- Don’t skip meals! Especially breakfast
- Create a Patient Centered Process
- Regulate Sleep
- Consider Biofeedback

E  G  A  B  C  D  F  H