CLINICAL CASES

Case: Ms. MC

Ms. MC: Profile

- 30-year-old female, nurse
- Diagnosed with migraine without aura 3 years ago
- No other significant medical history
- Has been taking the same estroprogestative oral contraceptive (estroprogestative: levonorgestrel, 0.15 mg + ethinylestradiol, 0.03 mg for the last 7 years

Ms. MC: History

- One-year history of migraine without aura attacks exclusively during menstruation
  - Attacks are long lasting (4 days)
- Acute treatment with sumatriptan
  - Immediate efficacy (pain-free within 3 hours)
  - Relapse within 12 hours after initial intake each day
  - Needs to take 8 triptan doses in 4 days to relieve pain
- Significant negative impact on quality of life
  - Anxious anticipation of menstrual periods

Discussion Questions

BASED ON THE CASE PRESENTATION, WHAT WOULD YOU CONSIDER IN YOUR DIFFERENTIAL DIAGNOSIS?

WHAT FURTHER HISTORY WOULD YOU LIKE TO KNOW?

WHAT TESTS OR EXAMINATIONS WOULD YOU CONDUCT?

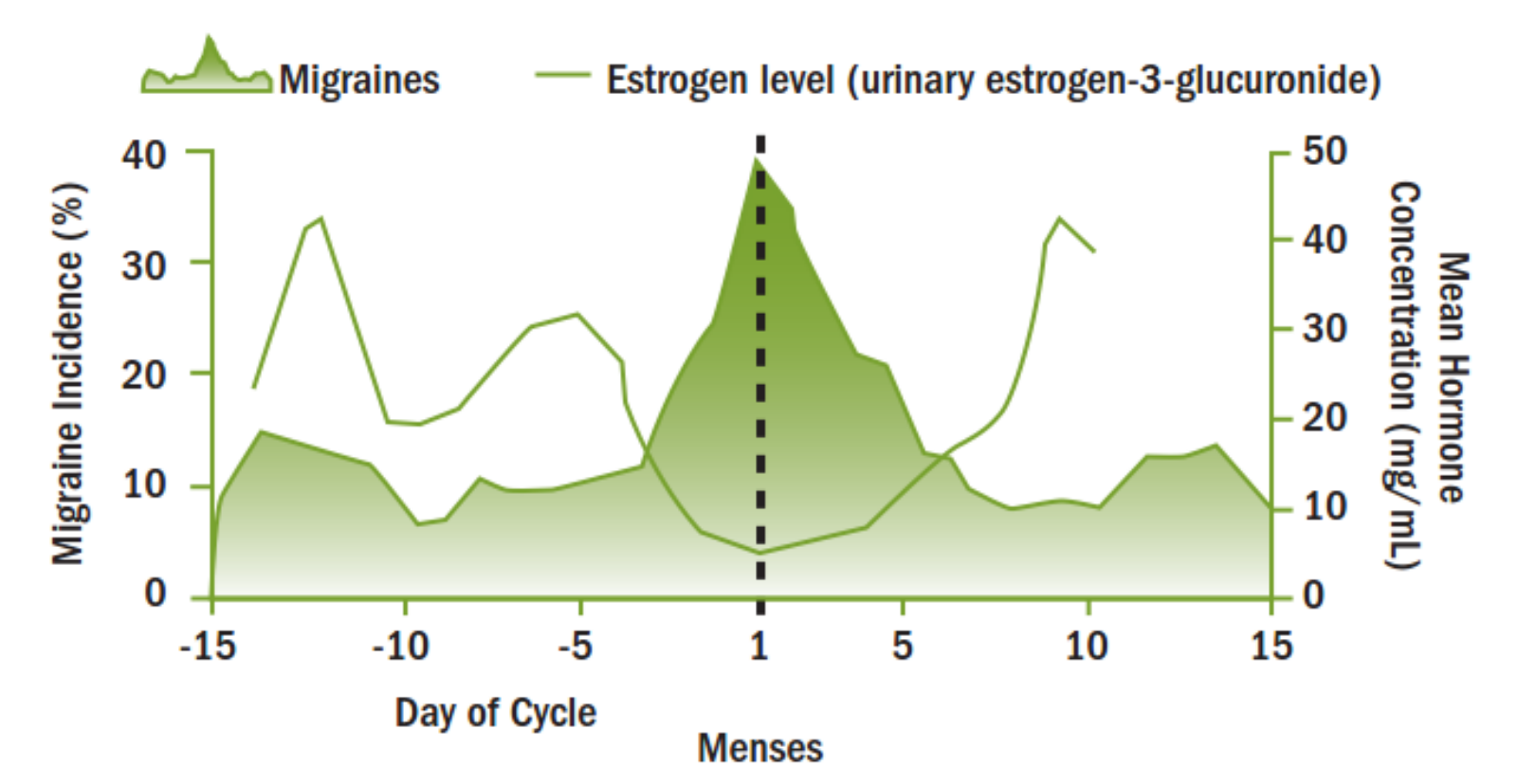
Menstrual Migraine

- ~60% of female migraine sufferers have menstrual migraines
- Reduced estrogen at menstruation can trigger migraine
- Menstrual migraines may be more persistent, painful, and resistant to treatment than migraines that occur at other times
- ICHD criteria: Migraine without aura occurring between 2 days prior and 3 days after the onset of menses and in 2 of 3 menstrual cycles
  - Some women experience migraine perimenstrually
- Headache diary should be used to record timing of menstrual migraines

ICHD = International Classification of Headache Disorders

Menstrual migraine: breaking the cycle. Available at: http://practicingclinicians.com/cms/wb/PCEv3/site/hs09_pdfs/migraine.pdf. Accessed 14 December, 2014.

Estrogen Levels and Menstrual Migraine



Menstrual migraine: breaking the cycle. Available at: http://practicingclinicians.com/cms/wb/PCEv3/site/hs09_pdfs/migraine.pdf. Accessed 14 December, 2014.

Discussion Question

WOULD YOU MAKE ANY CHANGES TO THERAPY OR CONDUCT FURTHER INVESTIGATIONS?

Ms. MC: Further Tests/Examinations

- In this clinical case there is no need for further tests.
- If desired, a diary could be filled to confirm the reality of pure menstrual migraine.

Discussion Question

WHAT WOULD BE YOUR DIAGNOSIS FOR THIS PATIENT?

IHS Diagnostic Criteria for Menstrual Migraine

A. Attacks, in a menstruating woman, fulfilling criteria for migraine without aura

B. Attacks occur exclusively on day 1+2 (*i.e.*, days 2 to +3)[1] of menstruation in at least two out of three menstrual cycles and at no other times in the cycle

Link to IHS Diagnosis of Menstrual Migraine

1The first day of menstruation is day 1 and the preceding day is -1; there is no day 0
IHS = International Headache Society
Headache Classification Committee of the International Headache Society (IHS). *Cephalalgia*. 2013;33(9):629-808.

Ms. MC: Diagnosis

- This patient has pure menstrual migraine
- Her attacks are difficult to treat
- She has recurrence of pain even with treatment with triptans

Discussion Question

WHAT TREATMENT STRATEGY WOULD YOU RECOMMEND?

Pharmacological Treatments for Menstrual Migraine

Acute	Short-term Preventative	Long-term Preventative
• NSAIDs • Acetaminophen + Aspirin + caffeine • Triptans	• NSAIDS • Triptans • Estrogen transdermal patches/gel	• Hormonal* • Beta-blockers • Calcium channel blockers • Tricyclic antidepressants • Anticonvulsants

*Long duration oral contraceptives, gonadotropin-releasing hormone antagonists NSAID = non-steroidal anti-inflammatory drug

Martin VT. Menstrual migraine: new approaches to diagnosis and treatment. Available at: http://www.americanheadachesociety.org/assets/1/7/Vincent_Martin_-_Menstrual_Martin.pdf. Accessed March 26, 2015.

Ms. MC: Treatment

Step 1: Acute Treatment Optimization

- Determine if triptan is taken early enough in the attack (within 1 hour of onset while pain is of mild intensity)
  - If not, try the same triptan, stressing the need to take it early in the attack
- If early treatment is ineffective, try a triptan + NSAID combination
- Alternatively, try a different triptan
  - Evidence is weak, particularly for triptans with long half-lives

NSAID = non-steroidal anti-inflammatory drug

Ms. MC: Treatment

Step 2: Prevention of Menstrual Migraine Attacks

- Sequential prevention by estradiol or triptan
  - If menstrual cycle is regular and patient is adherent to therapy
- Continuous estroprogestative oral contraceptive or pure progestative oral contraceptive
  - With the agreement of the patient's gynecologist

Discussion Question

WOULD YOU MAKE ANY CHANGES TO THERAPY OR CONDUCT FURTHER INVESTIGATIONS?

Case: Mrs. LT

Mr. LT: Profile

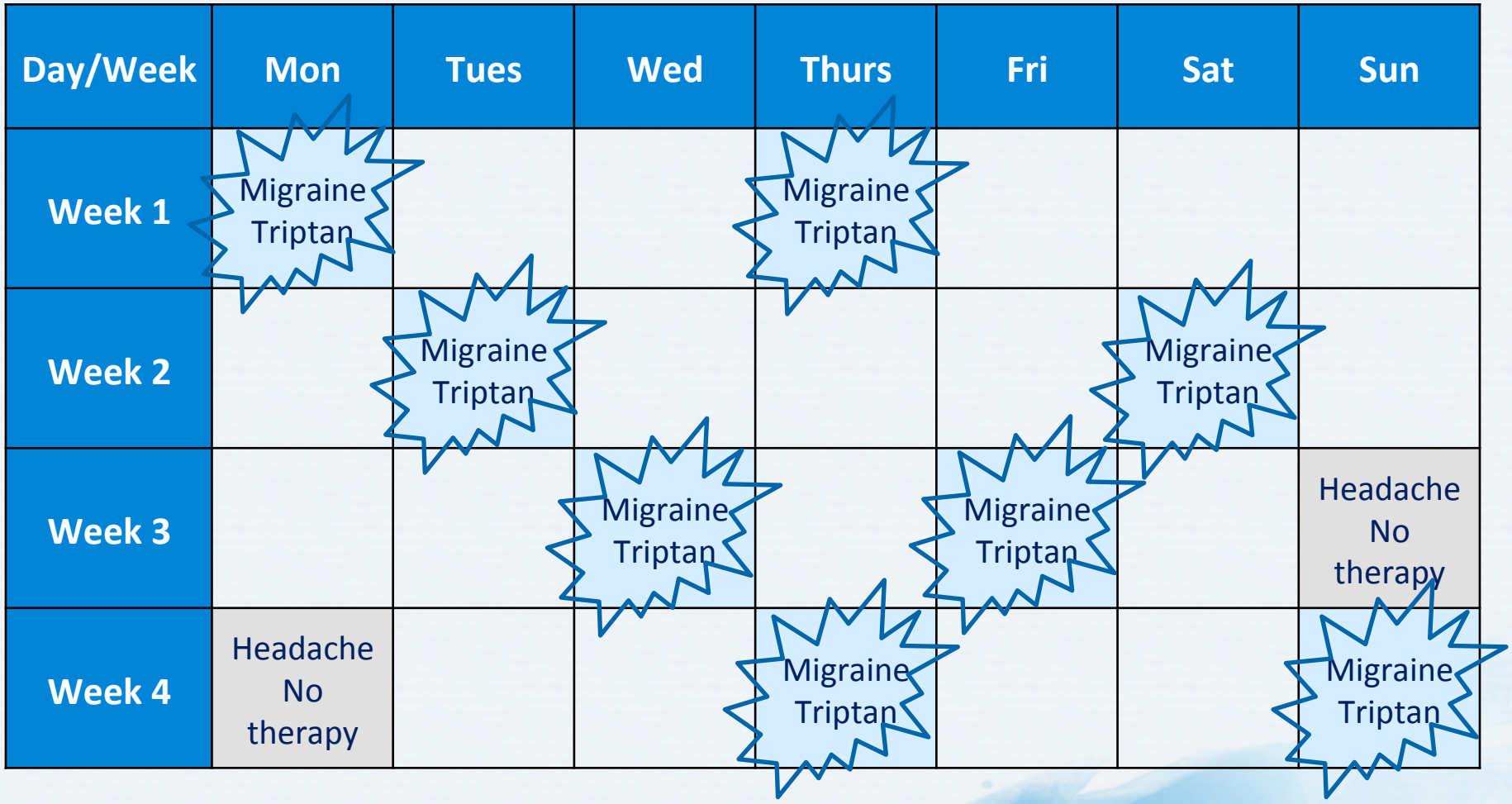
- 48-year-old female, **executive secretary**
- Diagnosed with migraine without aura 20 years ago
- Mild generalized anxiety
- Non-active asthma
- Overweight (BMI = 26.4 kg/m^2)
- Confirmed menopause since 1 year
- She has non-active asthma (asthma in childhood)

BMI = body mass index

Mr. LT: History

- 20-year history of migraine without aura attacks
- Frequency of attacks is increasing

Mrs. LT's Headache Diary



Mr. LT: History

- Patient has been using a triptan for acute treatment
- HIT-6 score = 58
- HAD Anxiety score = 9 (mild anxiety)
- HAD Depression score = 3 (no depression)
- Very good quality of life without avoidance behavior

HAD = Hospital Anxiety and Depression

Tools to Assess Impact of Migraine

Test	Comments
MIDAS (Migraine Disability Assessment)	• 5-item tool • Scores number of days of inactivity due to migraine in the past 3 months
Headache Impact Test™-6 (HIT-6)	• Covers 6 categories • Useful in clinical practice and research
Headache Needs Assessment (HANA)	• 7-item self-administered tool • Can help identify which patients require treatment
Short Form 36® (SF-36®)	• 36 items covering physical and mental components of health • Generic measuring tool to identify quality of life issues

Stewart WF *et al. Neurology.* 2001;56(6 Suppl 1):S20-8; Kosinski M *et al. Qual Life Res.* 2003;12(8):963-74; Cramer JA *et al. Headache.* 2001;41(4):402-9; Ware, JE Jr. Available at: http://www.sf-36.org/tools/SF36.shtml.

HIT – Headache Impact Test

- Helps patients communicate the severity of their headache pain to their health care provider
- Helps to
  - Determine impact of headaches on patient's life
  - Better communicate the information to the health care provider
  - Track the patient's headache history and response to therapy over time

Kosinski M *et al. Qual Life Res.* 2003;12(8):963-74.

Headache Impact Test™-6 (HIT-6)

This questionnaire was designed to help you describe and communicate the way you feel and what you cannot do because of headaches.

To complete, please circle one answer for each question.

1. When you have headaches, how often is the pain severe?

Never	Rarely	Sometimes	Very Often	Always

2. How often do headaches limit your ability to do usual daily activities including household work, work, school, or social activities?

Never	Rarely	Sometimes	Very Often	Always

3. When you have a headache, how often do you wish you could lie down?

Never	Rarely	Sometimes	Very Often	Always

4. In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches?

Never	Rarely	Sometimes	Very Often	Always

5. In the past 4 weeks, how often have you felt fed up or irritated because of your headaches?

Never	Rarely	Sometimes	Very Often	Always

6. In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities?

Never	Rarely	Sometimes	Very Often	Always

COLUMN 1 (6 points each)	+	COLUMN 2 (8 points each)	+	COLUMN 3 (10 points each)	+	COLUMN 4 (11 points each)	+	COLUMN 5 (13 points each)

To score, add points for answers in each column.
To find out what your score means, see sidebar.
Please share your HIT-6 results with your doctor.

Total Score

Higher scores indicate greater impact on your life.

Score range is 36–78.

Score >60 indicates patient is severely impacted or impaired by migraines

Kosinski M *et al. Qual Life Res.* 2003;12(8):963-74.

Hospital Anxiety and Depression Scale - Anxiety

Question	Frequency	Score
I feel tense or "wound up"	Most of the time A lot of the time Occasionally Not at all	3 2 1 0
I get a sort of frightened feeling as if something awful is about to happen	Very definitely and quite badly Yes, but not too badly A little, but it doesn't worry me Not at all	3 2 1 0
Worrying thoughts go through my mind	A great deal of the time A lot of the time From time to time, but not often Only occasionally	3 2 1 0
I can sit at ease and feel relaxed	Definitely Usually Not often Not at all	0 1 2 3
I get a sort of frightened feeling like "butterflies" in the stomach	Not at all Occasionally Quite often Very often	0 1 2 3
I feel restless as I have to be on the move	Very much indeed Quite a lot Not very much Not at all	3 2 1 0
I get sudden feelings of panic	Very often indeed Quite often Not very often Not often at all	3 2 1 0

Zigmond AS, Snaith RP. *Acta Psychiatr Scand.* 1983;67:361-70.

Discussion Questions

BASED ON THE CASE PRESENTATION, WHAT WOULD YOU CONSIDER IN YOUR DIFFERENTIAL DIAGNOSIS?

WHAT FURTHER HISTORY WOULD YOU LIKE TO KNOW?

WHAT TESTS OR EXAMINATIONS WOULD YOU CONDUCT?

Mr. LT: Further Tests/Examinations

- In this clinical case there is no need for further tests.
- The only thing that could possibly be proposed is to confirm normality of the clinical examination.

Discussion Question

WHAT WOULD BE YOUR DIAGNOSIS FOR THIS PATIENT?

Mr. LT: Diagnosis

- This patient has the beginnings of medication overuse headache
- There is an indication for preventative treatment

IHS Diagnostic Criteria for Medication Overuse Headache

A. Headache occurring on ≥15 days/month in a patient with a pre-existing headache disorder

B. Regular overuse for >3 months of ≥1 drugs that can be taken for acute and/or symptomatic treatment of headache

C. Not better accounted for by another ICHD-3 diagnosis

Link to IHS Diagnosis of Medication Overuse Headache

IHS = International Headache Society

Headache Classification Committee of the International Headache Society (IHS). *Cephalalgia*. 2013;33(9):629-808.

Medication Overuse Headache (MOH)

- New or worsening of existing headache develops in association with medication overuse
- Headache on ≥15 days/month for >3 months due to overuse of acute medications
  - About 50% of people have MOH
- Most patients improve after withdrawal of the overused medication

Headache Classification Committee of the International Headache Society (IHS). *Cephalalgia.* 2013;33(9):629-808.

IHS Classification of Medication Overuse Headaches

- Ergotamine-overuse headache
- Triptan-overuse headache
- Simple analgesic-overuse headache
- Opioid-overuse headache
- Combination-analgesic-overuse headache
- Medication-overuse headache attributed to multiple drug classes not individually overused
- Medication-overuse headache attributed to unverified overuse of multiple drug classes
- Medication-overuse headache attributed to other medication

IHS = International Headache Society

Headache Classification Committee of the International Headache Society (IHS). *Cephalalgia*. 2013;33(9):629-808.

Prescribing Triptans and Monitoring Use

- Most effective if taken early in a migraine attack
- Should not be taken during aura phase
- Dose should **not** be repeated if there is no response
  - Dose can be repeated after 2-4 hours if there was initial relief from the migraine and it has reoccurred
- Avoid using triptans for ≥10 days/month

A triptan should be taken early during a migraine attack

A triptan should not be taken during the aura phase

In absence of a response, the dose of triptan should not be repeated

Best Pract J. 2014;62:28-36.

Triptans - Precautions

- Limit use to ≤2 days/week
- Do not use within 24 hour of ergotamine derivatives, other triptans, or methysergide
- Screen for asymptomatic cardiac disease in patients at risk
- Common adverse events:
  - Transient feelings of pain or tightness in the chest or throat
  - Tingling
  - Heat
  - Flushing
  - Heaviness or pressure
  - Drowsiness
  - Fatigue
  - Malaise

IM = intramuscular; IV = intravenous; SC = subcutaneous

American Headache Society. Brainstorm. 2004. Available at: http://www.americanheadachesociety.org/assets/1/7/Book_-_Brainstorm_Syllabus.pdf. Accessed 04 December,

Discussion Question

WOULD YOU MAKE ANY CHANGES TO THERAPY OR CONDUCT FURTHER INVESTIGATIONS?

Discussion Question

WHAT TREATMENT STRATEGY WOULD YOU RECOMMEND?

Preventative Therapies in Migraine

- For episodic migraine, the AHS Guidelines[1] list the following preventive agents as having Level A Evidence:
  - Anti-epilepsy drugs: divalproex sodium, sodium valproate, topiramate
  - Beta blockers: metoprolol, propranolol, and timolol
- In the EU, flunarazine is felt to have top level evidence[2]
- Recent studies place candesartan as Level A evidence[3,4]
- Some supplements, vitamins, and herbs have evidence for effectiveness[5]
- For chronic migraine, botolinumtoxinA has top level evidence[6,7]
- None of these preventive agents was developed for migraine prophylaxis

AHS = American Headache Society

1. Silberstein SD *et al. Neurology.* 2012;78:1337-45; 2. Evers S *et al. Eur J Neurology*. 2006:13: 560-72;
3. Tronvik E *et al. JAMA*. 2003;289:65-69; 4. Stovner LJ *et al. Cephalalgia.* 2014; 34:523-32; 5. Holland S *et al. Neurology*. 2012;78:1346-53; 6. Diener HC *et al. Cephalalgia*. 2010;30:804-14.

Treatment

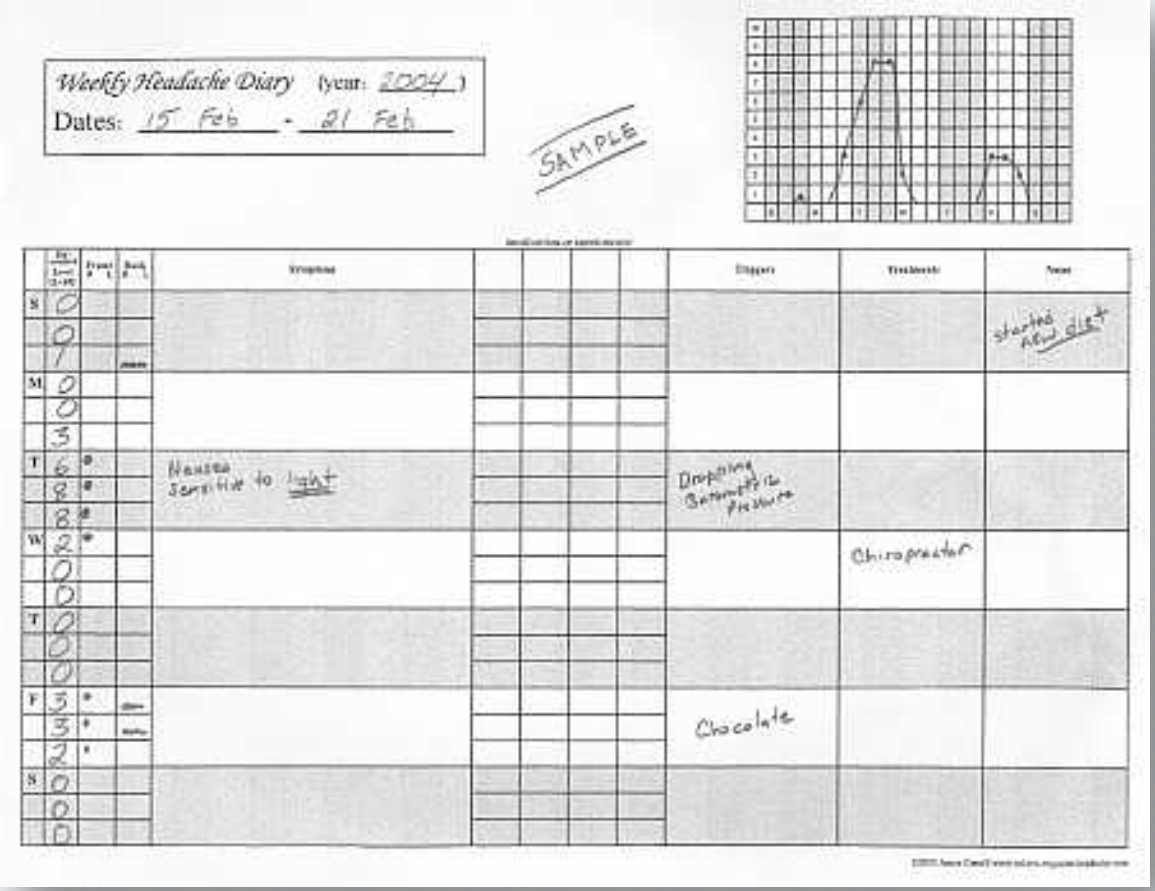
- Why start preventative therapy in a woman who has good quality of life?
- Prevention of medication overuse headache diary/headache diary with high frequency EM (episodic migraine) and beginning of medication overuse (regular use of triptan 2 days/week)
- Which drug should be used as preventative therapy?
  - Must consider any comorbidities
    - Beta-blockers are contraindicated (she has asthma)
    - Topiramate is indicated because she is overweight

NSAID = non-steroidal anti-inflammatory drug

Treatment

- Objective of preventative therapy: reduce number of headache days and days with acute migraine drug use by **≥50%**
- How can the efficacy of preventative therapy be evaluated?
  - Use a headache diary

Headache Diary



Patients should record:

- Date, time of onset and end
- Preceding symptoms
- Intensity on scale
- Suspected triggers
- ANY medication taken, including over-the-counter medication – note dosage taken, how many pills the patient took that day
- Relief (complete/partial/none)
- Relationship to menstrual cycle

American Headache Society, 2004. Available at: http://www.americanheadachesociety.org/assets/1/7/Book_-_Brainstorm_Syllabus.pdf; National Institute for Health and Care Excellence, 2012. Available at: http://www.nice.org.uk/CG150.

Discussion Question

WOULD YOU MAKE ANY CHANGES TO THERAPY OR CONDUCT FURTHER INVESTIGATIONS?

Case: Ms. MC

Ms. MC: Profile

- 42-year-old female court stenographer
- Comes to the clinic complaining of daily headache
  - Has some type of headache every day
- Taking ASA/acetaminophen (paracetamol)/caffeine combination tablets daily for the pain
- Headaches wax and wane from mild (1/3) to moderate (1/3) to severe (1/3)
- Headaches vary in location from bilateral to unilateral to posterior
- Often awakens with severe headache and neck pain

ASA = acetylsalicylic acid (Aspirin)

Ms. MC: History

- Family history of migraine
- History of motion sickness since childhood
- Began to have non-menstrual headaches in her 20s
  - Headaches lasted 1-2 days
  - Headaches were moderate to severe
  - Headaches got worse with activity
  - Bilateral or unilateral; no predominant side
  - Throbbing, nausea, photophonophobia
- Treated attacks using ASA/acetaminophen (paracetamol)/caffeine combination
  - Two tablets gave relief but did not render her pain free
  - Invariable recurrence → would take at least 6 tablets/day for the 1-2 days of each attack

ASA = acetylsalicylic acid (Aspirin)

Ms. MC: History

- Headache frequency increased when she was in her 20s and 30s
  - Monthly → twice monthly → twice weekly
- By her mid- to late-30s she was experiencing headache >15 days per month
  - At least 4 hours daily
- Increased intake of ASA/acetaminophen (paracetamol)/caffeine tablets

ASA = acetylsalicylic acid (Aspirin)

Discussion Questions

BASED ON THE CASE PRESENTATION, WHAT WOULD YOU CONSIDER IN YOUR DIFFERENTIAL DIAGNOSIS?

WHAT FURTHER HISTORY WOULD YOU LIKE TO KNOW?

WHAT TESTS OR EXAMINATIONS WOULD YOU CONDUCT?

Ms. MC: Medical History

- Imaging: normal MRI
- Labs: normal
- Physical exam: normal
- Neurological exam: normal

Ms. MC: Medication History

- Numerous acute medications have not worked for her
  - Sumatriptan
  - Metoclopramide + ASA
  - Diclofenac
- Currently using ASA/acetaminophen (paracetamol)/ caffeine combination tablets

ASA = acetylsalicylic acid (Aspirin)

Discussion Question

WHAT WOULD BE YOUR DIAGNOSIS FOR THIS PATIENT?

Ms. MC: Diagnosis

- Medication overuse headache
  - Combination-analgesic-overuse headache subtype

IHS Diagnostic Criteria for Medication Overuse Headache

A. Headache occurring on ≥15 days/month in a patient with a pre-existing headache disorder

B. Regular overuse for >3 months of ≥1 drugs that can be taken for acute and/or symptomatic treatment of headache

C. Not better accounted for by another ICHD-3 diagnosis

Combination-analgesic-overuse headache subtype:

- Regular intake of ≥1 combination-analgesic medications on ≥10 days/month for >3 months

Link to IHS Diagnosis of Medication Overuse Headache

IHS = International Headache Society

Headache Classification Committee of the International Headache Society (IHS). *Cephalalgia*. 2013;33(9):629-808.

IHS Classification of Medication Overuse Headaches

- Ergotamine-overuse headache
- Triptan-overuse headache
- Simple analgesic-overuse headache
- Opioid-overuse headache
- **Combination analgesic-overuse headache**
- Medication-overuse headache attributed to multiple drug classes not individually overused
- Medication-overuse headache attributed to unverified overuse of multiple drug classes
- Medication-overuse headache attributed to other medication

IHS = International Headache Society

Headache Classification Committee of the International Headache Society (IHS). *Cephalalgia*. 2013;33(9):629-808.

Discussion Question

WHAT TREATMENT STRATEGY WOULD YOU RECOMMEND?

Ms. MC: Treatment

- Establish preventive medication, either a daily medication or botulinumtoxinA.
- Wean the overused medications as prevention is added.
- Provide a migraine-specific medication such as a triptan for use on severe attacks, limited to no more than 2 days per week.
- Instruct Ms. MC not to treat low level headaches
- Provide behavioral support during this period

Tepper SJ. *Continuum Lifelong Learning Neurol.* 2012;18(4):807–822.

Ms. MC: Follow up

- Providing regular follow up is very important.
- Ms. MC was started on topiramate, was able to tolerate it at 100 mg, and was provided eletriptan for use for her attacks.
- By 3 months, she was no longer having daily headaches, but had discrete episodic attacks of migraine without aura every 7-10 days, with a sustained pain-free response from the eletriptan.

Ms. MC: Work Up

- This patient had a long history of episodic migraine and a clear description of transformation to daily headache with increased combination analgesic intake.
- She had had chronic migraine for years, stable and without change.
- Her exam was normal and she had had a normal MRI in the past, during the time of daily headaches.
  - Therefore, further workup was not necessary before initiating the treatment.

Case: Ms. HT

Ms. HT: Profile

- 24-year-old female nurse
- Comes to the clinic complaining of headaches

ASA = acetylsalicylic acid (Aspirin)

Ms. HT: History

- Onset of headaches in childhood
- Family history of headache and motion sickness
- Headaches:
  - Episodic, lasting 1 to 3 days (usually at least 2 days), occurring 1 to 2 times per week (usually twice), with an average of at least 10 headache days per month
  - Generally moderate in intensity
  - No antecedent visual or sensory aura; no nausea
  - Bilateral with severe neck pain
    - Often, neck, pain for hours precedes a full blown attack
  - Non-throbbing, but are worse when she bends over or climbs stairs
- Often awakens with her headaches
- Headaches do not respond very well to ibuprofen or other over-the-counter analgesics
- Pattern and frequency of her headaches has not changed in at least 2 years, and her exam is entirely normal.

Discussion Questions

BASED ON THE CASE PRESENTATION, WHAT WOULD YOU CONSIDER IN YOUR DIFFERENTIAL DIAGNOSIS?

WHAT FURTHER HISTORY WOULD YOU LIKE TO KNOW?

WHAT TESTS OR EXAMINATIONS WOULD YOU CONDUCT?

Discussion Question

WHAT WOULD BE YOUR DIAGNOSIS FOR THIS PATIENT?

Classification of Migraine

Migraine without aura

- Recurrent attacks
- Attacks and associated migraine symptoms last 4-72 hours

Migraine with typical aura

- Visual and/or sensory and/or speech/language symptoms but no motor weakness
- Gradual development
  - Each symptom lasts ≤1 hour
- Mixture of positive and negative features
- Complete reversibility

Chronic Migraine

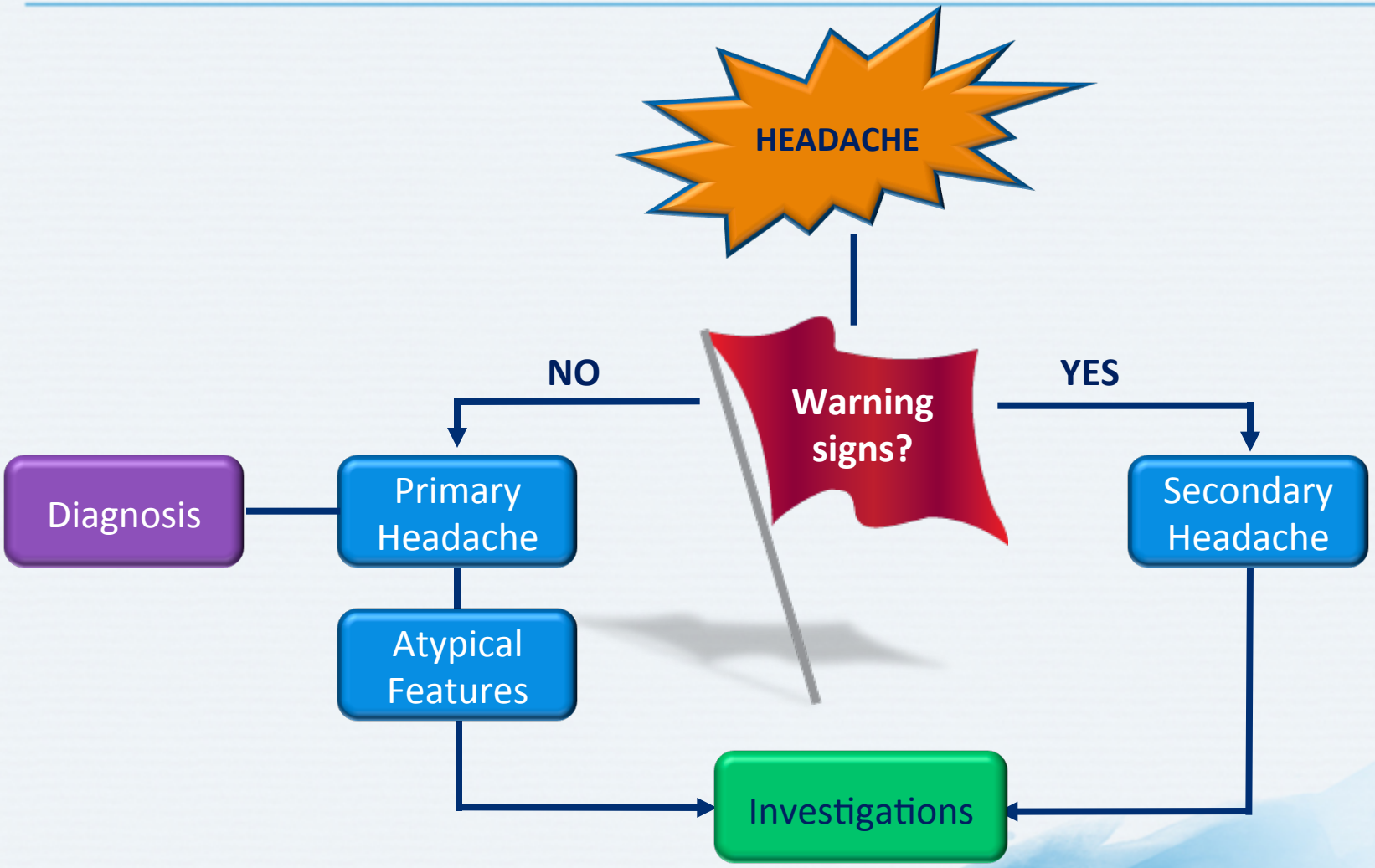
- In a patient with previous episodic migraine
- Headache on ≥15 days/month for >3 months
- Headache has features of migraine on ≥8 days/month

Headache Classification Committee of the International Headache Society (IHS). *Cephalalgia*. 2013;33(9):629-808.

Discussion Question

WHAT TREATMENT STRATEGY WOULD YOU RECOMMEND?

Diagnostic Evaluation for Migraine



Adapted from Silberstein SD *et* al. *Headache in Clinical Practice.* 2nd ed. London: Martin Dunitz; 2002.
American Headache Society. Brainstorm. 2004. Available at: http://www.americanheadachesociety.org/assets/1/7/Book_-_Brainstorm_Syllabus.pdf. Accessed 04 December,

IHS Diagnostic Criteria for Migraine without Aura

A. At least five attacks fulfilling criteria B to D

B. Headache attacks lasting 4 to 72 hours (untreated or unsuccessfully treated)

C. Headache has ≥2 of the following characteristics

1. Unilateral location
2. Pulsating quality
3. Moderate or severe pain intensity
4. Aggravation by or causing avoidance of routine physical activity (*e.g.*, walking or climbing stairs)

D. During headache ≥of the following

1. Nausea and/or vomiting
2. Photophobia and phonophobia

3. Not better accounted for by another ICHD-3 diagnosis

Link to IHS Diagnosis of Migraine without Aura

IHS = International Headache Society

Headache Classification Committee of the International Headache Society (IHS). *Cephalalgia*. 2013;33(9):629-808.

Diagnosis: How Ms. HT Fulfills the IHS Criteria

A. **At least five attacks** fulfilling criteria B to D

B. Headache attacks lasting 4 to 72 hours (untreated or unsuccessfully treated)
   - **Hers last 6 hours to one day**

C. Headache has ≥2 of the following characteristics

1. Unilateral location
2. **Pulsating quality**
3. **Moderate** or severe pain intensity
4. **Aggravation by or causing avoidance of routine physical activity (*e.g.*, walking or climbing stairs)**

D. During headache ≥of the following

1. Nausea and/or vomiting
2. **Photophobia and phonophobia**
3. Not better accounted for by another ICHD-3 diagnosis

IHS = International Headache Society

Headache Classification Committee of the International Headache Society (IHS). *Cephalalgia*. 2013;33(9):629-808.

Notes on Ms. HT's Diagnosis of Migraine without Aura

1. Location does **not** determine diagnosis
   - Neck pain is very common in migraine, and often precedes head pain as a prodrome[1-3]
2. Stress is a very common trigger for migraine[4]
3. Moderate pain can occur in migraine, and is part of the ICHD-3 criteria[5]
4. Migraine is bilateral 40% of the time[6]
5. Episodic disabling headache is usually migraine[7]

1. Blau JN, MacGregor EA. *Headache*;34:88-90; 2. Kaniecki RG. *Neurology* 2002;58 (Suppl 6): S15-20; 3. Calhoun AH *et al. Headache.* 2010;50:1273-7; 4. Kelman L. *Cephalalgia*. 2007;27:394-402; 5. ICHD-3 Beta. *Cephalalgia* 2013; 33:629-808; 6. Lipton RB *et al*. *Headache.* 2001;41:646-57; 7. Tepper SJ *et al. Headache* 2004;44:856-64.

Ms. HT: Acute Treatment

- **Treatment goal**: sustained pain-free response
- Oral triptan for her daytime attacks
- Non-oral triptan for the migraines upon wakening

Preventative Therapies in Migraine

- For episodic migraine, the AHS Guidelines[1] list the following preventive agents as having Level A Evidence:
  - Anti-epilepsy drugs: divalproex sodium, sodium valproate, topiramate
  - Beta blockers: metoprolol, propranolol, and timolol
- In the EU, flunarazine is felt to have top level evidence[2]
- Recent studies place candesartan as Level A evidence[3,4]
- Some supplements, vitamins, and herbs have evidence for effectiveness[5]
- For chronic migraine, botolinumtoxinA has top level evidence[6,7]
- None of these preventive agents was developed for migraine prophylaxis

AHS = American Headache Society

1. Silberstein SD *et al. Neurology.* 2012;78:1337-45; 2. Evers S *et al. Eur J Neurology*. 2006:13: 560-72;
3. Tronvik E *et al. JAMA*. 2003;289:65-69; 4. Stovner LJ *et al. Cephalalgia.* 2014; 34:523-32; 5. Holland S *et al. Neurology*. 2012;78:1346-53; 6. Diener HC *et al. Cephalalgia*. 2010;30:804-14.

EFNS Guidelines for Initiating Prophylactic Therapy for Migraine

Consider and discuss prophylactic drug when:

- Quality of life, business duties, or school attendance are severely impaired
- Patient experiences 2 or more attacks per month
- Migraine attacks do not respond to acute drug treatment
- Frequent, very long, or uncomfortable auras occur

Migraine prophylaxis is regarded as successful if the frequency of migraine attacks per month is decreased by ≥50% within 3 months

EFNS = European Federation of Neurological Societies

Evers S *et al. Eur J Neurol.* 2009;16(9):968-81.

Ms. HT: Treatment

- With a stable pattern of ICHD-3 migraine without aura and a normal exam, no imaging study or further work up is necessary.
- Ms. HT was offered oral sumatriptan for headaches beginning during the day and subcutaneous sumatriptan for headaches full blown upon awakening.
- Her headache frequency is high, so candesartan 16 mg at bedtime was offered for prevention.
- She did well, with a 50% reduction in headache frequency and was able to reliably treat each attack with either oral or subcutaneous sumatriptan or use of both sequentially.

ICHD = The International Headache Classification

Case: Ms. LG

Ms. LG: Profile

- 8-year-old female
- 8-month history of headache

Discussion Questions

WHAT FURTHER HISTORY WOULD YOU LIKE TO KNOW?

WHAT TESTS OR EXAMINATIONS WOULD YOU CONDUCT?

WHAT RED FLAGS WOULD YOU LOOK FOR?

Ms. LG's Headache Characteristics

- Bilateral, frontal non-throbbing severe headache that comes on in the later part of the morning
  - Attack frequency: twice per month
- The girl wants to lie down in a dark, quiet place and not run around
- She feels better after sleeping

Ms. LG: History

- Born at term
- Colicky as a baby
- Episodes of unexplained abdominal pain for about a year at age six
- No other medical problems
- Normal development
- Happy at school
- Mother has a headache with her menses
- Physical examination is normal

Pediatric Migraine

- Migraines are common in children
- Increase in frequency with increasing age
- Approximately 6% of adolescents experience migraine
- Mean age at onset: girls = 10.9 years; boys = 7.2 years
- Diagnosis is challenging because symptoms can vary significantly throughout childhood
- Not all adolescents will experience headaches throughout their lives
  - Up to 70% will experience some continuation of persistent or episodic migraines

Lewis D *et al. Neurology*. 2004;63:2215-24; Winner P. Pediatric and Adolescent Migraine. Available at: http://www.americanheadachesociety.org/assets/1/7/Paul_Winner_-_pediatric_and_Adolescent_Migraine.pdf. Accessed March 31, 2015.

Key Features for Diagnosis of Pediatric Migraine

- Duration tends to be shorter than in adults
- May be as short as 1 hour but can last 72 hours
- Often bifrontal or bitemporal rather than unilateral pain
- Children often have difficulty describing throbbing pain or levels of severity
- Using a face or numerical pain scale can be helpful
- Children often have difficulty describing symptoms
  - Symptoms often have to be inferred from the child's behavior
- Consider associated symptoms (difficulty thinking, fatigue, lightheadedness)

Winner P. Pediatric and Adolescent Migraine. Available at: http://www.americanheadachesociety.org/assets/1/7/Paul_Winner_-_pediatric_and_Adolescent_Migraine.pdf. Accessed March 31, 2015.

Red Flags in the Diagnosis of Pediatric Migraine

- Increasing frequency and/or severity over several weeks (<4 months) in a child <12 years of age
  - Even more important in children <7 years of age
- A change of frequency and severity of headache pattern in young children
- Fever is not a component associated with migraine at any stage – especially in children
- Headaches accompanied by seizures
- Altered sensorium may occur in certain forms of migraine but it is not the norm
  - Needs attention to determine appropriate assessment and intervention

Winner P. Pediatric and Adolescent Migraine. Available at: http://www.americanheadachesociety.org/assets/1/7/Paul_Winner_-_pediatric_and_Adolescent_Migraine.pdf. Accessed March 31, 2015.

Discussion Question

WHAT WOULD BE YOUR DIAGNOSIS FOR THIS PATIENT?

Ms. LG: Diagnosis

- Ms. LG has **migraine without aura.**

Discussion Question

WHAT TREATMENT STRATEGY WOULD YOU RECOMMEND?

Ms. LG: Treatment

- Ms. LG was advised to treat her headaches using simple analgesics, such as acetaminophen (paracetamol) or ibuprofen.

Treatment of Pediatric and Adolescent Migraine

- Management includes a comprehensive approach: pharmacologic + non-pharmacologic therapies
- Review dietary triggers
- Avoid caffeine overuse
- Avoid head trauma
- Wear protective headgear whenever appropriate
- Behavior modification
- Exercise protocols
- Proper sleep

Lewis D *et al. Neurology*. 2004;63:2215-24; Winner P. Pediatric and Adolescent Migraine. Available at: http://www.americanheadachesociety.org/assets/1/7/Paul_Winner_-_pediatric_and_Adolescent_Migraine.pdf. Accessed March 31, 2015.

Pharmacotherapies for Pediatric and Adolescent Migraine

- Acute therapies should be used as soon as it is clear the headache is migraine
  - Ibuprofen and sumatriptan nasal spray are effective
  - Acetaminophen (paracetamol) is probably effective
- Almotriptan is the only triptan currently approved by the FDA for treatment of migraine in patients ≥12 years of age
- Analgesics or acute medications should not be used >2 times per week unless patient is under medical supervision
- Supplementation with magnesium, riboflavin, and coenzyme Q10 may be helpful
- No medication currently approved by FDA for migraine prophylaxis in children
  - Some studies have shown topiramate to be effective

Lewis D *et al. Neurology*. 2004;63:2215-24; Winner P. Pediatric and Adolescent Migraine. Available at: http://www.americanheadachesociety.org/assets/1/7/Paul_Winner_-_pediatric_and_Adolescent_Migraine.pdf. Accessed March 31, 2015.

Case: Mrs. PA

Mrs. PA: Profile

- 43-year-old female who works at home
- Twice-monthly attacks of disabling headache over the last two years

Discussion Questions

WHAT FURTHER HISTORY WOULD YOU LIKE TO KNOW?

WHAT TESTS OR EXAMINATIONS WOULD YOU CONDUCT?

WHAT RED FLAGS WOULD YOU LOOK FOR?

Mrs. PA's Headache Characteristics

- Bilateral, frontal throbbing severe pain, worsened with movement
- Nausea
- No sound or light sensitivity
- Cranial allodynia during attacks
- No aura
- Bilateral nasal congestion and lacrimation with attacks
- Attacks last 1-2 days and occur twice a month

Ms. PA: History

- Her mother had menstrual headache.
- Ms. PA's physical exam is normal.

Mrs. PA: Migraine Medication History

- Current uses ASA (Aspirin) with modest benefit
- Has used paracetamol, ibuprofen, naproxen, and sumatriptan 50 mg (oral) without useful effect
- Takes propanolol 80 mg daily for mild hypertension
  - Hypertension is well controlled
- Headache around puberty with menses for 5 years

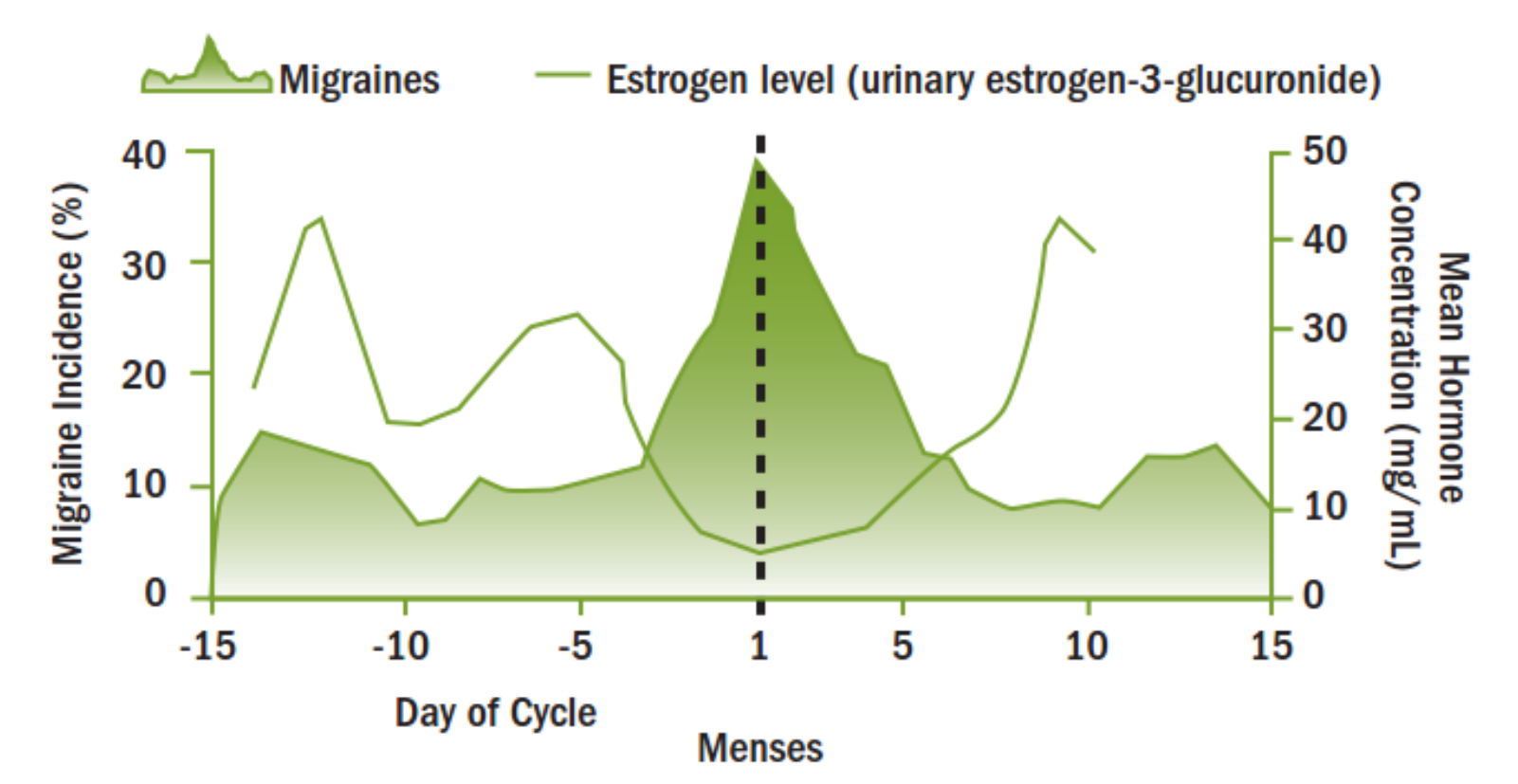
Menstrual Migraine

- ~60% of female migraine sufferers have menstrual migraines
- Reduced estrogen at menstruation can trigger migraine in many women
- May be more persistent, painful, and resistant to treatment than migraines that occur at other times
- ICHD criteria: Migraine without aura occurring between 2 days prior and 3 days after the onset of menses and in 2 of 3 menstrual cycles
  - Some women experience migraine perimenstrually
- Headache diary should be used to record timing of menstrual migraines

ICHD = International Classification of Headache Disorders

Menstrual migraine: breaking the cycle. Available at: http://practicingclinicians.com/cms/wb/PCEv3/site/hs09_pdfs/migraine.pdf. Accessed 14 December, 2014.

Estrogen Levels and Menstrual Migraine



Menstrual migraine: breaking the cycle. Available at: http://practicingclinicians.com/cms/wb/PCEv3/site/hs09_pdfs/migraine.pdf. Accessed 14 December, 2014.

Discussion Question

WHAT WOULD BE YOUR DIAGNOSIS FOR THIS PATIENT?

Mrs. PA: Diagnosis

- Ms. PA has **migraine without aura.**

Discussion Question

WHAT TREATMENT STRATEGY WOULD YOU RECOMMEND?

Mrs. PA: Treatment

- Rizatriptan (10 mg po) or eletriptan (40 mg po) could be prescribed to Mrs. PA.

Mrs. PA: Follow-up

- Mrs. PA should be followed up in two to three months to see how her treatment is working.

Case: Ms. MY

Ms. MY: Profile

- 21-year-old female office secretary
- Complains of a left-sided throbbing headache
- Symptoms started at age 15
  - Have occurred once or twice a month since then
- Notices flashes of white light followed by a unilateral pulsating headache after a few minutes during her episodes
- Prefers to stay in a dark, quiet room
- Adequate rest, sleep, and mefenamic acid or ibuprofen have failed to relieve her headaches in the last 3 months
  - She would only get partial relief from the NSAIDs

NSAID = non-steroidal anti-inflammatory drug

Discussion Questions

WHAT FURTHER HISTORY WOULD YOU LIKE TO KNOW?

WHAT TESTS OR EXAMINATIONS WOULD YOU CONDUCT?

WHAT RED FLAGS WOULD YOU LOOK FOR?

Ms. MY: History

- No weakness, numbness or dizziness
- Unremarkable past history
- Unremarkable neurologic exam
- Ms. MY is not taking any medications or oral contraceptives
- Her mother reportedly also had throbbing headaches during adolescence

Discussion Question

WHAT WOULD BE YOUR DIAGNOSIS FOR THIS PATIENT?

Ms. MY: Diagnosis

- This patient has migraine with aura

Discussion Question

WHAT TREATMENT STRATEGY WOULD YOU RECOMMEND?

Ms. MY: Treatment Strategy

- Neurologist recommends that the patient take a triptan
- Patient indicates she wants to take only over-the-counter medications because they used to help her
- Her neighbour advised her to take a coxib
  - Ms. MY is considering doing this in her next migraine attack

Discussion Question

WHAT TREATMENT STRATEGY WOULD YOU RECOMMEND?

Ms. MY: Recommended Treatment Strategy

- Since patient presents with migraine headache once or twice a month with NSAID failure, recommended therapy according to CHS guidelines for acute migraine therapy would be:
  - NSAID + triptan rescue
  - Triptan

CHS = Canadian Headache Society; NSAID = non-steroidal anti-inflammatory drug

Worthington I *et al. Can J Neurol Sci.* 2013;40(5 Suppl 3):S33-S62.

Ms. MY: Follow Up

- Regular follow up with attending physician is recommended to assess treatment efficacy
- Any changes in the character of headache or the presence of red flags warrants immediate reassessment

Case: Ms. BD

Ms. BD: Profile

- 25-year-old female sales agent
- Diagnosed with migraine headache
- Migraines started around age 13
- Migraines are intermittent unilateral throbbing headaches
- Occur 3 to 4 times per year
- No aura
- During attacks, Ms. BD becomes nauseated and vomits several times
  - This restricts the use of oral medications

Ms. BD: History

- No comorbid conditions
- Neurologic exam is unremarkable

Discussion Questions

WHAT FURTHER HISTORY WOULD YOU LIKE TO KNOW?

WHAT TESTS OR EXAMINATIONS WOULD YOU CONDUCT?

WHAT RED FLAGS WOULD YOU LOOK FOR?

Ms. BD: Further History

- No family history of chronic headaches, intracranial tumors, or lesions
- Not a smoker, not an alcoholic beverage drinker, denies drug use

Ms. BD: Further Testing

- Stable headache
- Normal neurologic examination
- Nausea and vomiting
  - May be a sign of increased intracranial pressure
  - Midline lesions may not show any focal neurologic deficit and present only with headache, nausea and vomiting
- Imaging may be done – ideally cranial MRI with contrast

Ms. BD: Red Flags

- Nausea and vomiting in this present case
- Particular attention to character, intensity of headaches and accompanying manifestations (*e.g.*, new kind of headache [non-throbbing, progressive]
  - Such severe intensity for the first time (from usual VAS 4 to 7 to VAS 8 to 10)
  - Accompanied by diplopia, lateralizing signs and altered consciousness

VAS = Visual Analog Score

Discussion Question

WHAT TREATMENT STRATEGY WOULD YOU RECOMMEND?

Choosing a Triptan

- All triptans have similar efficacy
  - Base choice on patient preference
- Patients often prefer oral therapy
  - **Vomiting and nausea may preclude use of oral treatment →consider subcutaneous or nasal formulations**
- Patients who do not respond to one triptan may respond to a different one
  - Try an alternative triptan in a subsequent attack
- Patients who do not respond to oral triptans should be encouraged to try subcutaneous formulations

Best Pract J. 2014;62:28-36.

Triptans: Treatment Choices

Sumatriptan
- Tablet and fast-disintegrating
- Injection
- Nasal spray

Zolmitriptan
- Tablet and melt
- Nasal spray

Naratriptan
- Tablet

Rizatriptan
- Tablet and melt

Almotriptan
- Tablet

Frovitriptan
- Tablet

Eletriptan
- Tablet

Ferrari MD *et al. Lancet*. 2001;358(9294):1668-75; Worldwide Product Safety and Pharmacovigilance Document. December 1999.

Pharmacokinetic Properties of Triptans

Triptan	Onset of Efficacy (min)	Time to Peak Levels (h)	Lipophilicity	Bioavailability (%)	Elimination $t_{1/2}$ (h)	Elimination Routes
Almotriptan	45-60	1.5-2.5	Unknown	80	3.5	Hepatic (active metabolite) Renal, MAO, CYP
Eletriptan	60	1.3.-2.8	High	50	4-5	Hepatic (active metabolite) CYP
Frovatriptan	Up to 4 hours	2-4	Low	24-30	26	Hepatic, CYP
Naratriptan	Up to 4 hours	2-3.5	High	63-73	5-6	Hepatic, renal, CYP
Rizatriptan	30	1	Moderate	45	2-2.5	Hepatic, MAO, renal
Sumatriptan	45-60	2-3	Low	14	2-2.5	Hepatic, MAO
Zolmitriptan	45-60	1-1.5	Moderate	40-48	2.5-3	Hepatic (active metabolite) MAO, CYP

Rizatriptan provides the fastest onset of efficacy

CYP = cytochrome hepatic system; MAO = monoamine oxidase A

Belvís R *et al. Recent Pat CNS Drug Discov.* 2009;4(1):70-81.

Prescribing Triptans and Monitoring Use

- Most effective if taken early in a migraine attack
- Do not take during aura phase
- Dose should not be repeated if there is no response
  - Dose can be repeated after two to four hours if there was initial relief from the migraine and it has reoccurred
- Avoid using triptans for ≥10 days/month

A triptan should be taken early during a migraine attack

A triptan should not be taken during the aura phase

In absence of a response, the dose of triptan should not be repeated

Best Pract J. 2014;62:28-36.

Triptans: Contraindications

- Pregnancy
- Lactation
- Ischemic stroke
- Ischemic heart disease
- Prinzmetal's angina
- Raynaud's disease

- Uncontrolled hypertension
- Severe liver or renal failure
- Familial hemiplegic migraine
- Basilar migraine
- Ergotamine therapy
- MAOI therapy

MAO = monoamine oxidase

Belvís R *et al. Recent Pat CNS Drug Discov.* 2009;4(1):70-81.

Ms. BD: Follow Up

- Cranial imaging
- Assess response to treatment
- Changes in the character of headache and the presence of other red flags warrant reassessment

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