Headache Management Workshop

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This workshop is for you – not for me

- This is a workshop.
- Therefore by definition your participation for online discussion is essential for this workshop to function.
- Translation
- Your participation is required

A migraine attack can have up to four phases, each with many potential symptoms*

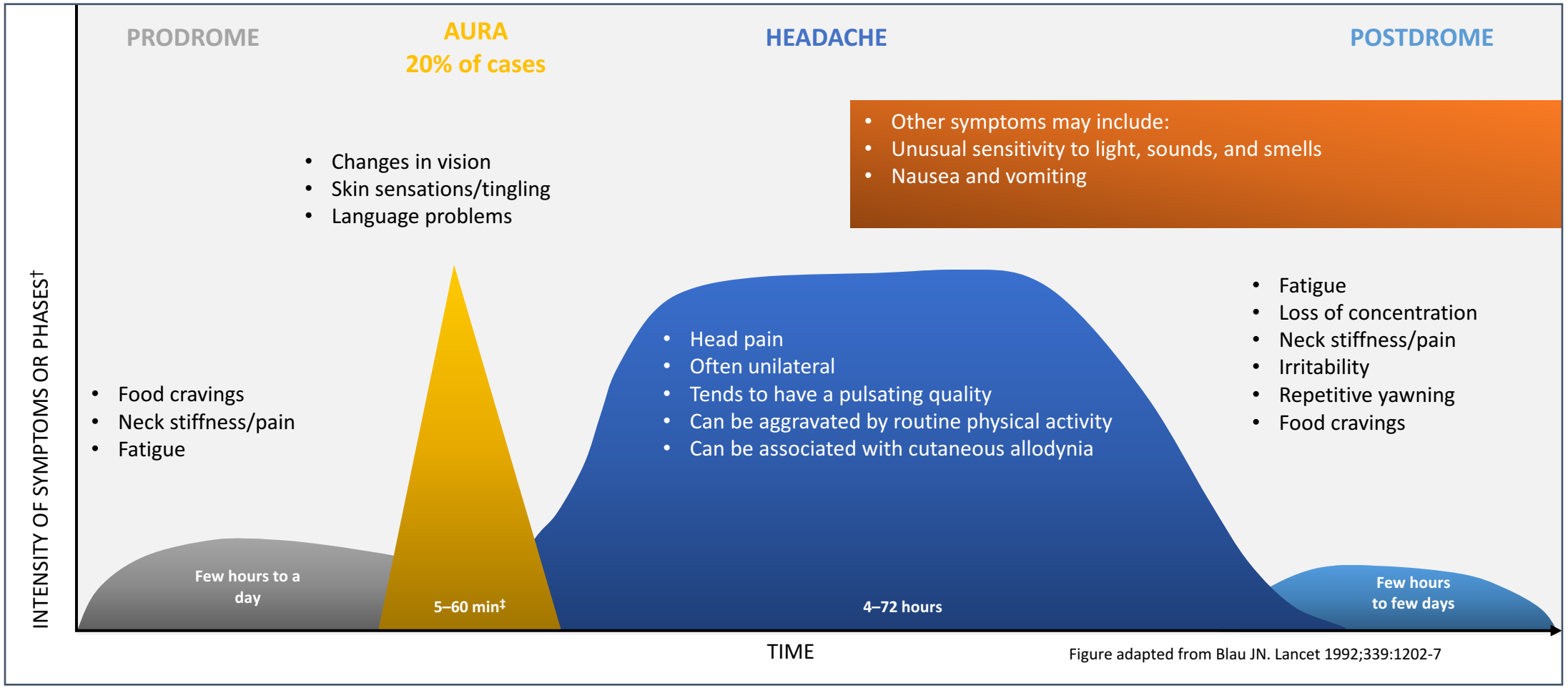


Figure adapted from Blau JN. Lancet 1992;339:1202-7

* Migraine patients may not experience all phases and symptoms shown, and not all possible symptoms are listed. † Illustrative only. ‡ Duration per symptom.

Headache Classification Committee of the International Headache Society (IHS). Cephalalgia 2018;38:1–211; Russell MB et al. Int J Epidemol 1995;24:612-8; Viana et al. Cephalalgia 2013;33:483 90; Giffin et al. Neurology 2016;87:309-13; Lampl C et al. J Headache Pain 2015;16:80; Migraine.com, https://migraine.com/migraine-symptoms/ Accessed 19 Jan 2018.

Migraine is a distinct clinical entity and should not be confused with other primary headache disorders, such as tension-type headache / cluster headache

CHARACTERISTICS	MIGRAINE[1]	TENSION-TYPE HEADACHE[1]	CLUSTER HEADACHE[1]
PAIN INTENSITY / TYPE	Moderate-severe intensity / throbbing	Mild / moderate intensity / pressing-tightening	Severe-very severe intensity / lancinating
HEADACHE LOCATION	Most commonly unilateral	Bilateral	Typically unilateral, around / behind the eye / temple
HEADACHE DURATION	4–72 hours	30 min to 1 week	15–180 mins
HEADACHE FREQUENCY	Variable frequency	Infrequent to daily	1–8 daily during clusters
OTHER SYMPTOMS	Nausea, vomiting, phonophobia, photophobia, pain aggravated by activity	Pericranial tenderness, phonophobia or photophobia, not aggravated by activity	Restlessness, ptosis, eye redness, conjunctival tearing / injection, rhinorrhoea, facial sweating and nasal congestion
DEMOGRAPHICS	Affects 2–3 times more women than men[3,4]	More common in women than men[5]	Affects 3 times more men than women
SEEN BY CLINICIAN	Frequently	Almost never	Rarely[2]

1. Headache Classification Committee of the International Headache Society (IHS). Cephalalgia 2018;38:1–211;
2. Bahra A et al. Acta Neurol Scand 2004;109:175–9; 3. Russell MB et al. Int J Epidemol 1995;24:612–8;
4. Diamond S et al. Headache 2007;47:355–63; 5. Russell MB. J Headache Pain 2007;8:71–6.

Diagnosis of migraine

- Clinical diagnosis – based almost exclusively on the history[1-3]
- Investigations (radiology and laboratory) – usually normal[1,2]
- Clinical examination – usually normal[1,2]
- Diagnostic criteria recently updated – International Classification of Headache Disorders (ICHD3), Cephalalgia, 2018[3]

Migraine without aura. At least five attacks, satisfying A–D below

A. Headache attacks lasting 4–72 hours (when untreated or unsuccessfully treated)

B. Headache has at least two of the following four characteristics:

   1. unilateral location, 2. pulsating quality, 3. moderate or severe pain intensity, 4. aggravation by or causing avoidance of routine physical activity

C. During headache at least one of the following: 1. nausea and / or vomiting, 2. photophobia and phonophobia

D. Not better accounted for by another ICHD3 diagnosis.

1. Katsarava Z et al. Curr Pain Headache Rep 2012;16:86–92;
2. British Association for the Study of Headache. Guidelines for All Healthcare Professionals in the Diagnosis and Management of Migraine, Tension-Type, Cluster and Medication-Overuse Headache 2010;3rd Edition;
3. Headache Classification Committee of the International Headache Society (IHS). Cephalalgia 2018;38:1–211.

Hormonal Factors in Migraine

- The lifetime incidence of migraine is threefold higher among women than men (prevalence 18 vs. 6%), with peak incidence (24%) occurring between 30 and 40 years.
- Often worse around menstruation (periods), pregnancy & menopause
- Hormone manipulation of limited benefit for most patients
- Mirena and progesterone only pill (POP) most commonly used
- Migraine with aura, smoking and combined oral contraceptive pill (COCP) not good combination – significantly higher risk of stroke

Estrogen, migraine, and vascular risk - Neurological Sciences (2018) 39 (Suppl 1):S11–S20

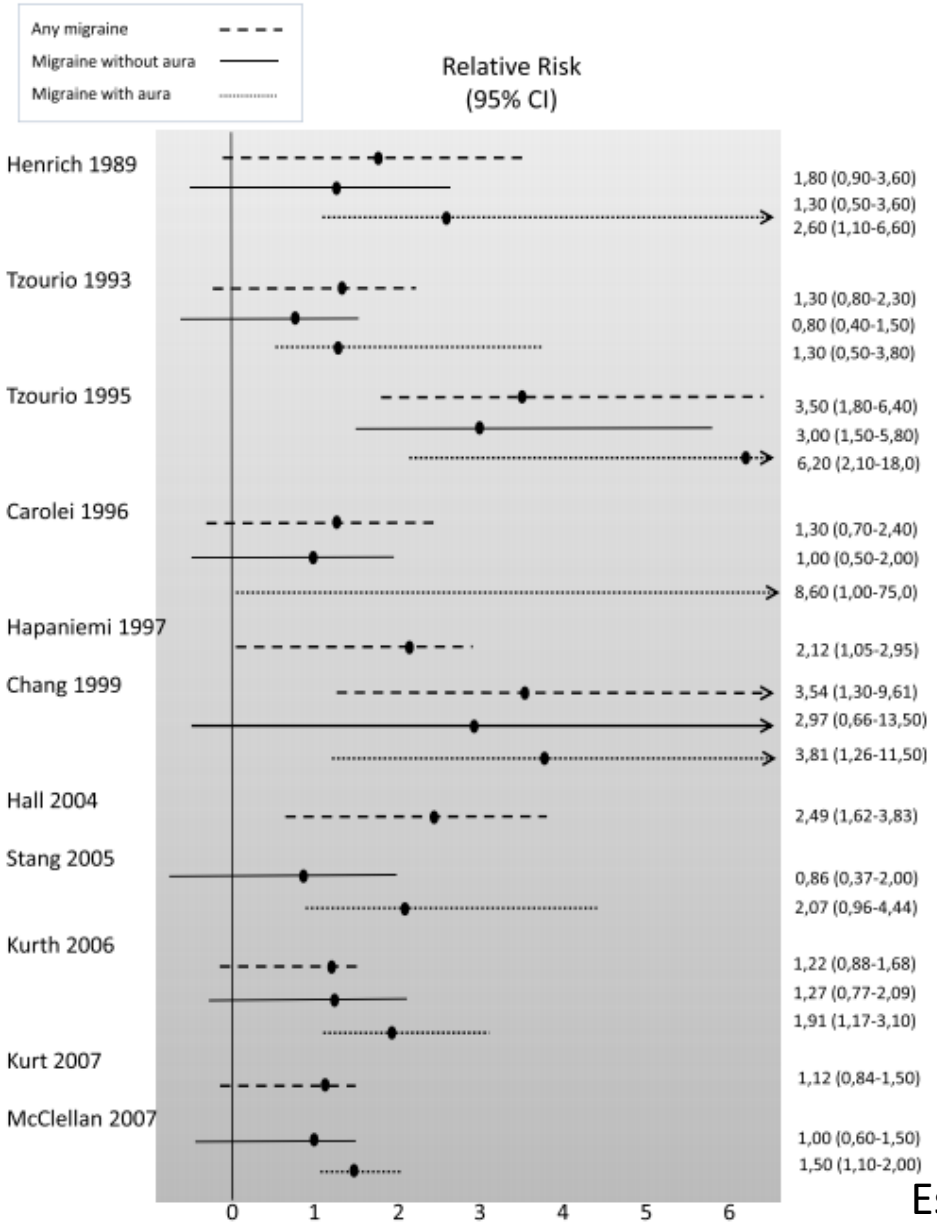


Fig. 1 Association between any migraine, MO and MA with ischemic stroke: data from cohort and case-control studies

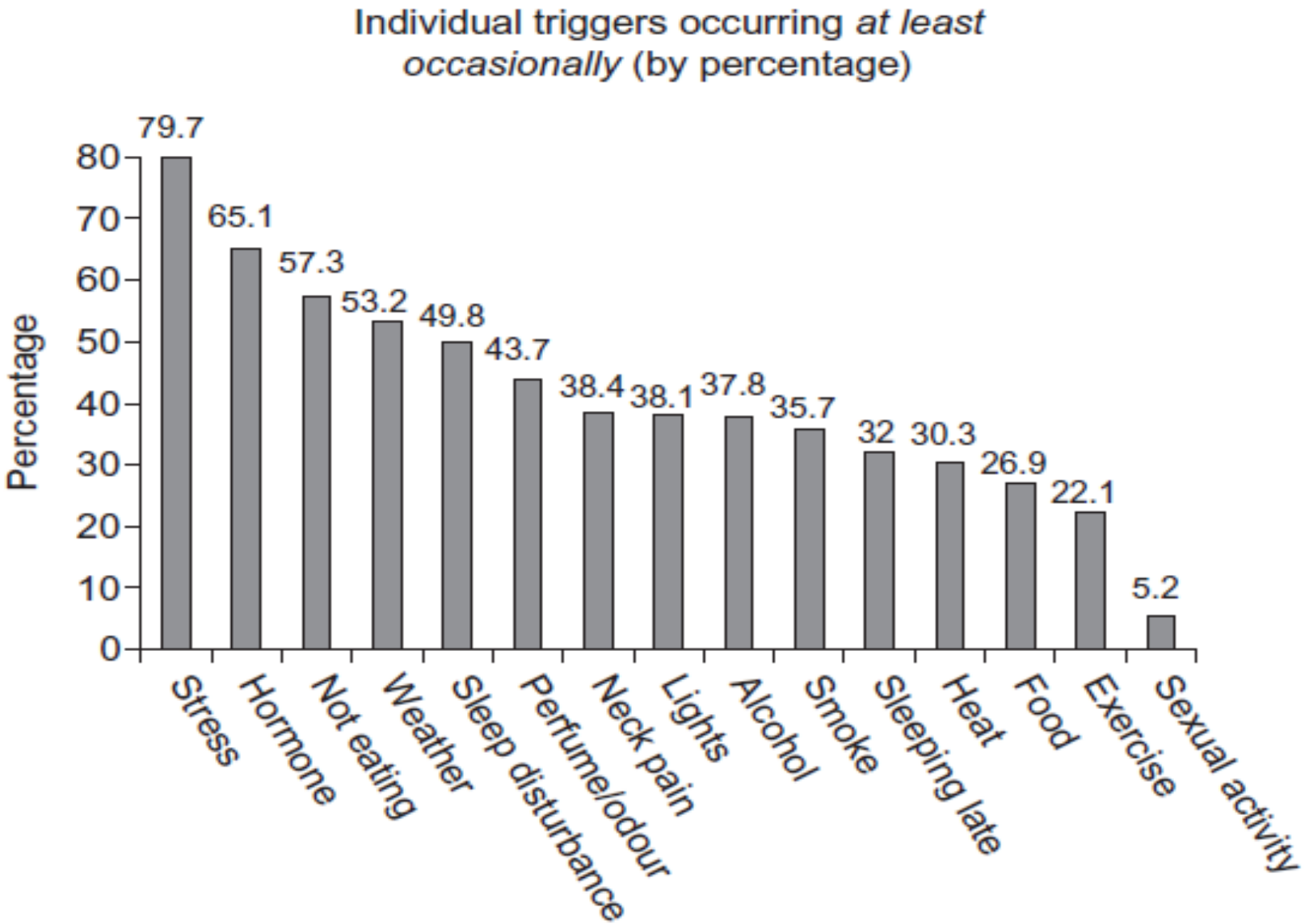
Estrogen, migraine, and vascular risk - Neurological Sciences (2018) 39 (Suppl 1):S11–S20

Question:
The odds ration for having a vascular event in migraine with aura patients who smoke and take OCP is:

A. 3X
B. 5X
C. 7X
D. 9X

Estrogen, migraine, and vascular risk - Neurological Sciences (2018) 39 (Suppl 1):S11–S20

Common migraine triggers



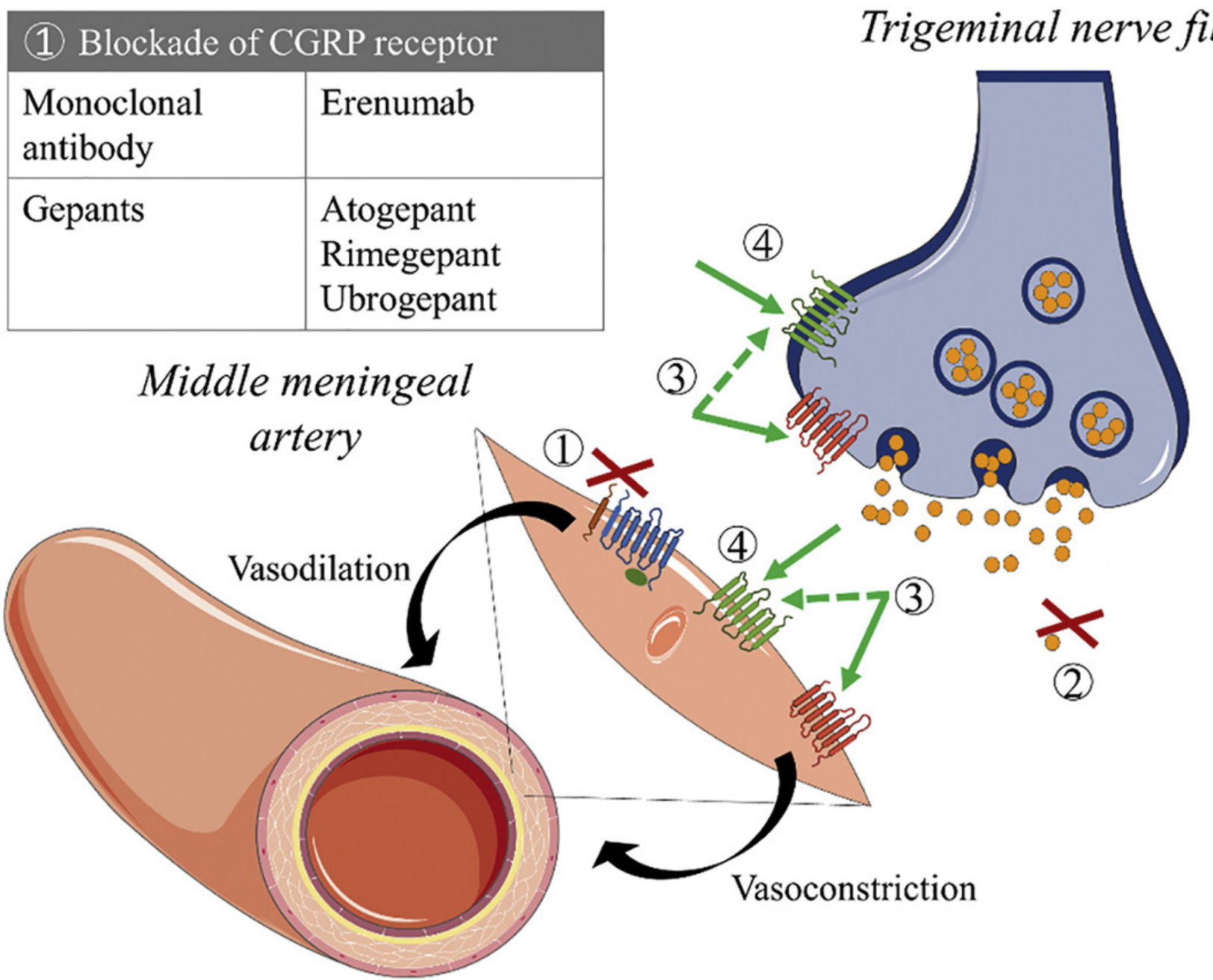
Migraine “ SEEDS”

Key Points

- Sleep: Standard sleep hygiene recommendations to maximize sleep quantity and quality.
- Exercise: 30 to 60 minutes 3 to 5 times a week.
- Eat: Regular healthy meals, adequate hydration, and low or stable caffeine intake.
- Diary: Establish a baseline pattern, assess response to treatment, and monitor analgesia to improve accuracy of migraine diagnosis.
- Stress: Cognitive behavioral therapy, mindfulness, relaxation, biofeedback, and provider-patient trust to minimize anxiety.

Robblee and Starling, Cleveland Clinic Journal of Medicine November 2019, 86 (11) 741-74

① Blockade of CGRP receptor	
Monoclonal antibody	Erenumab
Gepants	Atogepant Rimegepant Ubrogepant



② Blockade of CGRP	
Monoclonal antibody	Eptinezumab Fremanezumab Galcanezumab

③ Stimulation of 5-HT$_{1B/1D(/1F)}$ receptor	
Triptans	Almotriptan Eletriptan Frovatriptan Naratriptan Rizatriptan Sumatriptan Zolmitriptan

④ Stimulation of 5-HT$_{1F}$ receptor	
Ditans	Lasmiditan

Prescribing Migraine Prophylactic Medication in General Practice

For current standard of care optimal efficacy, it is recommended for each preventive agent to:

- Start at a low dose[1]
- Increase the dose in small increments every 2-8 weeks[1]
- Give an adequate trial for 2-3 months at the maximum tolerated dose[1]
- Monitor for overuse of analgesics/painkillers (avoid opiates and codeine containing analgesics as much as possible) [1]
- Discuss contraception with women of childbearing age, and the potential risk of these preventive medications during pregnancy and breastfeeding[1]
- Consider co-morbid medical conditions and aim to use a single medication that may treat multiple disorders if possible (for example, candesartan for migraine and hypertension) [1]
- Revaluate therapy at a reasonable interval of 3-6 months, preferably with the aid of a migraine diary[1]
- After 6 to 12 months of successful prophylactic therapy, consideration should be given to tapering and discontinuing the prophylactic medication in many patients, although others may benefit from a much longer duration of prophylactic therapy. If headache frequency increases as the prophylactic drug dosage is reduced, the dosage can be increased again or the drug restarted if it has been discontinued[2]

1. BASH - Guidelines for All Healthcare Professionals in the Diagnosis and Management of Migraine - 3rd edition (1st revision) 2010 available at www.bash.org.uk
2. Canadian Headache Society Guidelines for migraine prophylaxis, CJNS, vol 39, 2(S2), 2012


RED FLAG

What are the red flags in this patient (This is a real case)

A 24 year old right handed female complains of headache for the past 4 months. Her headache is constant pain that does not throb and does not change with position. She denies photo and phono phobia. She has no prior history of headaches nor is there a family history of migraine. Her family doctor has prescribed her acetaminophen, advil with no relief. She has no fever and no nuchal rigidity. She has been seen in the ED 10 times and treated with IV metoclopramide each time and discharged home. This last visit she was started on amitriptyline. All 6 of her CT scans have been normal.

She is overweight by around 7 kg. Does not smoke. She is working on her PhD.

A copy of her medical record is as follows: (all ED notes are the same)

Ox3. CN normal. No drift. Reflexes 1+. No Babinski.

(Q) What exam can give us the diagnosis?

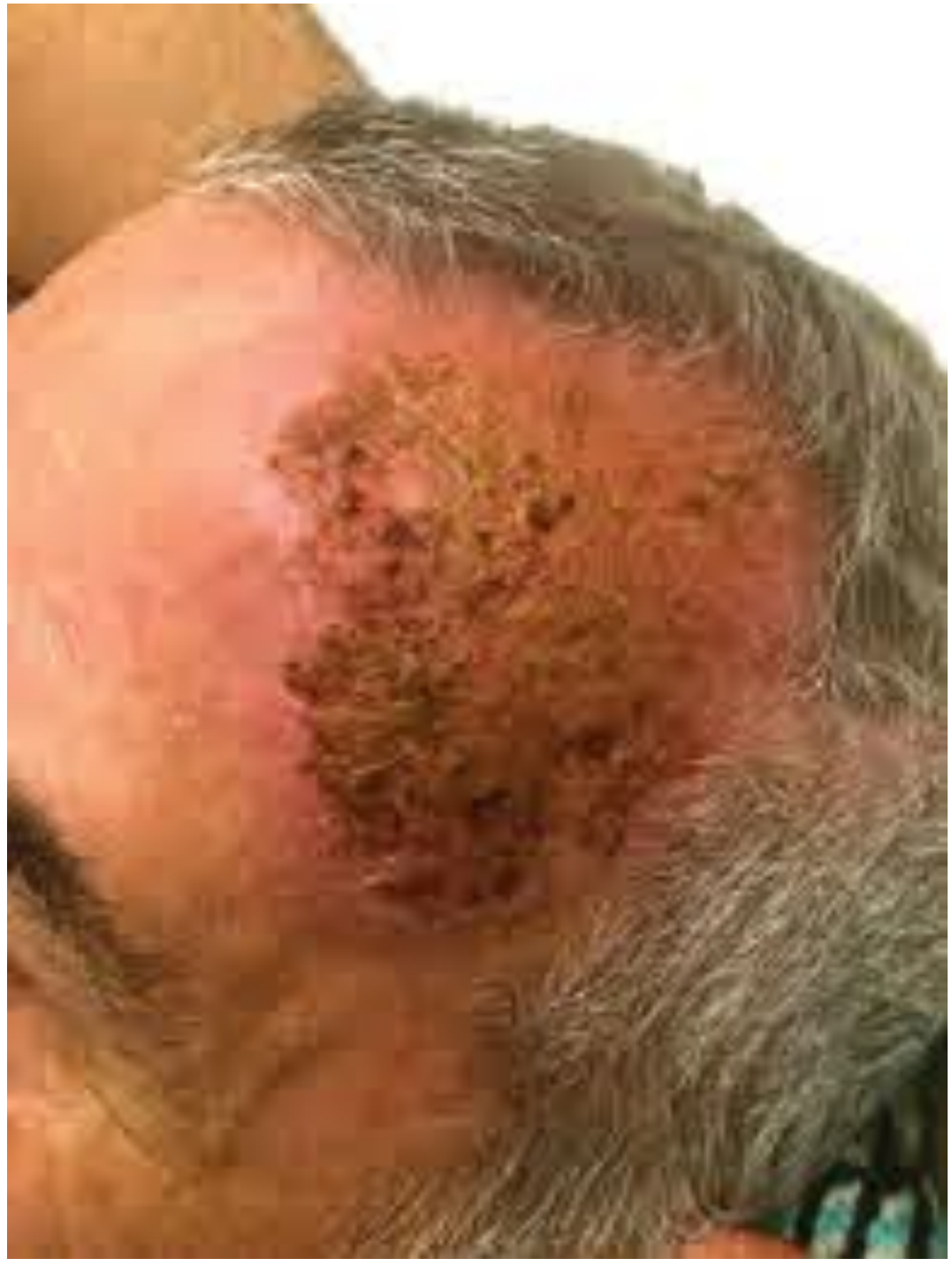
A. MRI Brain
B. CTA angiogram
C. Lumbar Puncture
D. Repeat CT scan of the brain
E. Fundoscopic exam
F. Any 2 of the above

Are there any red flags.

- An 84 year old man with moderate dementia is admitted to geriatrics with fever and subsequently diagnosed with urosepsis. Throughout his stay in hospital (10 days) he has been holding the left side of his head and moaning. He does have a history of migraine. He had no response to Tylenol or ibuprofen and a CT scan of the head was significant for atrophy and moderate microvascular changes. IV metoclopramide was tried and was reported to make him more confused. Given persistent symptoms he subsequently had a CTA of the COW and a Lumbar Puncture all of which were reported as normal.

Q Are there any red flags??

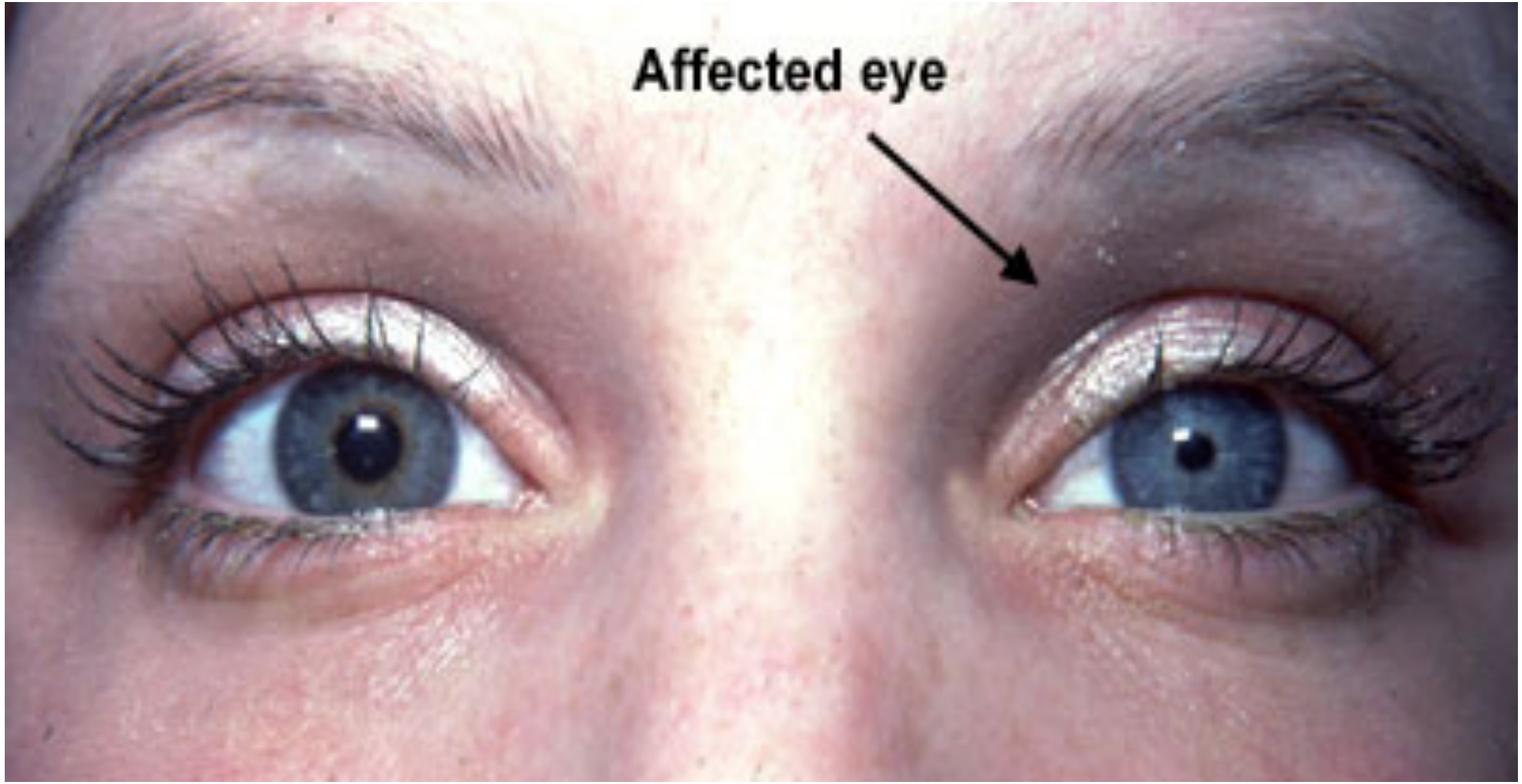
A. Yes
B. No



Q What is the diagnosis

A. Seborrheic Keratosis
B. Shingles
C. Giant Cell Arteritis
D. Psoriatic arthritis

Another true case


Affected eye

Q What is the diagnosis

A. 3rd nerve palsy due to aneurysm
B. 3rd nerve palsy due to cocaine use
C. Vertebral artery dissection
D. Carotid artery dissection
E. Retro orbital lesion

Box 1
Red flags in clinical history or neurologic examination

Clinical signs
- Sudden onset (thunderclap headache)
- Progressive, worsening
- Change from prior headache type
- Refractory to treatment
- Worsening with Valsalva Maneuver, straining, coughing, or sneezing
- Worsens with posture (sitting or standing)

Examination or laboratory findings
- Papilledema
- Peripheral edema
- Hypertension
- Focal neurologic findings (numbness, weakness)
- Fever
- Seizure

Another Case

- 43 year old women comes to see you with a 9 month history of a constant low grade headache pressure. It is not pounding and she has had no phono or photophobia. It is a dull pain that will increase in intensity at times. She feels a buzzing in her ears at times and sometimes feels a pulling sensation in her neck. She has no radicular complaints. She does however complain of interscapular pain at times. She just does not feel right. A CT scan of the brain and MRI of the cervical spine are unremarkable. She has not history of migraine and trial of nsaids, tylenol, aleve, amitryptiline have not helped. A trial of Topamax made her worse. She does not recall how it started. She remembers the family going hiking and loading up the car with heavy bags and the bicycles and feel a couple of weeks later this begun but is really not sure on how it began

What clinical question should be asked as part of the headache history?

Case 1-1

- A 28 year old man with a long history of severe migraine attacks comes in for evaluation. He states that although his headaches respond well to oral sumatriptan 100mg taken earl in the attack, his headaches will recur after 8-12 hours. He has tried taking acetaminophen with codeine for these headaches but obtained only partial relief with this approach.

What are several therapeutic options?

Q What is the best strategy for treating this patient?

A. Take a second dose of sumatriptan

B. Switch triptan to eletriptan 40mg as it has a longer half life.

C. Add Naproxen 550mg to eletriptan

D. Consider using frovatriptan or naratriptan as they have very long half lives

E. All or none of the above.

Case 1-2

A 44 year old woman reported that her sumatriptan 100mg tablets provide only incomplete relief from her migraine attacks. Early treatment of her attacks reduced their severity , but she was still left with mild headaches which remained troublesome for another 12 hours. She also tried rizatriptan, eletriptan, almotriptan and frovatriptan in the past and of all the triptans she found sumatriptan most effective. She was advised to take naproxen sodium 550mg simultaneously with her sumatriptan to enhance the efficacy of her acute treatment. Now despite this she has her typical migraine that has lasted for a 3 days.

What therapeutic options can provide her with relief???

Q Which of the following refractory migraine strategies should be avoided

A. Send her to the Emergency department for metachlopromide and or IM Ketorolac

B. Indomethacin 50-75mg orally or by suppository 50,g – 100mg.

C. Prednisone 60mg on the first day with a rapid taper over 3-4 days or dexamethasone 8 mg first day with rapid taper over 3 days.

D. Treat with opiates

Comment of opiates

- Combination of analgesics with codeine or tramadol are option for rescue medications when triptans fail.
- Opiates should not be used routinely in migraine therapy.
- Opioid use may lead to receptor changes which may make patients with migraine less responsive to other drugs.
- Opioid use frequently associated with medication overuse headache.
- A large randomize double blind cross over trial demonstrated that sumatriptan/naproxen combination was superior to a butalbital, acetaminophen, caffeine combination tablet. *Derosier et al Headache 2012:52(4):530-543*

Cefaly

- 25 yo right handed woman was diagnosed with mifraine without aura at age 16. Until 1 year ago she had headaches 2-3 per month which were rapidly relieved with a “Fiorinal”.
- Over the past year her headaches have steadily increased in frequency and her use of Fiorinal has also increased.
- She presents with 25 days per month of headache, including 12 days per month of severe headache. Her severe headaches were unitlateral (R>L), pulsatile and associated with nausea and photophobia. They lasted 12 hours on average.
- The headaches often awakened her from sleep before her alarm clock went off. They were quite severe if she slept late on the weekends. Even on days when she had no headache, she found it painful to brush her hair or wear a headband. Her scalp was tender on the right even when she had been headache free for 24 hours.

- Exacerbating factors included menses and relation after stress. On severe headache days she too 4-6 fiorinal and on less severe headache days she took 2 tablet per day for a total of 25 days per month.
- She was tried on a TCA earlier in the year but discontinued due to sedation and weight gain.
- Her mother and sister carry a diagnosis of migraine.
- Her family doctor sent her for an MRI, TSH and lyme titer & ESR. All normal.
- She was diagnosed with rebound headache and was asked to gradually taper her fiorinal.
- The patient was unable to do so and was referred to neurology.

What does her scalp tenderness represent?

What headache diagnosis (s) can we give her

Chronic Migraine Definition

Description:

Headache occurring on 15 or more days/month for more than 3 months, which, on at least 8 days/month, has the features of migraine headache.

Diagnostic criteria:

A. Headache (migraine-like or tension-type-like[1]) on ≥15 days/month for >3 months, and fulfilling criteria B and C

B. Occurring in a patient who has had at least five attacks fulfilling criteria B-D for 1.1 *Migraine without aura* and/or criteria B and C for 1.2 *Migraine with aura*

C. On ≥8 days/month for >3 months, fulfilling any of the following[2]:
   1. criteria C and D for 1.1 *Migraine without aura*
   2. criteria B and C for 1.2 *Migraine with aura*
   3. believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative

D. Not better accounted for by another ICHD-3 diagnosis[3;4;5].

Box 1 ICHD-3[1] diagnostic criteria for medication-overuse headache (8.2)

- Headache occurring on ≥15 days/month in a patient with a pre-existing headache disorder.
- Regular overuse for >3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache.*
- Not better accounted for by another International Classification of Headache Disorders (ICHD-3) diagnosis.

*Regular intake of one or more of paracetamol, aspirin and non-steroidal anti-inflammatory drugs on ≥15 days/month AND/OR ergotamine, triptans and opioids on ≥10 days/month.

What therapeutic options would you provide this patient and why?

Key points

- Medication-overuse headache is very common in patients with chronic migraine.
- Medication-overuse headache may occur in patients who take triptans or opiods on >10 days / month or simple analgesics on > 15 days / month for more than 3 months.
- Prevention through doctor and patient education remains the most important treatment strategy.
- Detoxification may take up to 8 weeks and is best achieved with complete withdrawal of acute migraine medications.
- Migraine preventatives, including topiramate and botulinum toxin have been shown to be beneficial in some patients.

Case 1-3

- 25 year old female with well established migraine. She is currently 16 weeks pregnant. Unfortunately, she now has a terrible migraine and calls your office with a very simple question:
- What can I take for my migraine?????

Q What can I take for my migraine?????

A. ASA 325mg
B. Acetaminophen
C. NSAIDS
D. Triptans
E. Codeine
F. B,D,E

Medication	Food and Drug Administration Pregnancy Category	Available Pregnancy Safety Information	Hale's Lactation Risk Rating	Available Lactation Safety Information
Analgesics and NSAIDS				
Acetominophen	B	No increased risk of teratogenic effects, spontaneous abortion, or stillbirth. Case reports of prenatal closure of the ductus arteriosus reported with use during the third trimester; increased risk of early childhood wheezing and asthma reported with frequent maternal use.	L1 (compatible)	Preferred. Infant exposure in breastmilk much lower than typically used therapeutic doses used for infants.
Aspirin	C	Increased risk of fetal/neonatal hemorrhage, perinatal mortality by intrauterine growth restriction, and teratogenic effects with chronic medium to high doses. In third trimester, may cause premature closure of the ductus arteriosus.	L2 (probably compatible)	Other agents strongly preferred. avoid chronic use; with occasional use, monitor infant for hemolysis, prolonged bleeding, metabolic acidosis.
NSAIDs	B (ibuprofen, naproxen, diclofenac) C (indomethacin)	Use restricted to second trimester. Use in first trimester linked to increased risk of spontaneous abortion. Use in third trimester may cause premature closure of the ductus arteriosus. Ibuprofen has the best data for safety.	L1 (compatible): ibuprofen; L2 (probably compatible): diclofenac L3 (no data—probably compatible): naproxen, indomethacin	Adverse events not reported in breastfeeding infants. Avoid in mothers of infants with platelet dysfunction or thrombocytopenia. Best evidence for ibuprofen; poor data for indomethacin.

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(*continued on next page*)

Table 2 (*continued*)

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Medication	Food and Drug Administration Pregnancy Category	Available Pregnancy Safety Information	Hale's Lactation Risk Rating	Available Lactation Safety Information
Butalbital	C	Long history of use in pregnancy. One large study showed possible increase in risk of fetal heart defects when butalbital used in periconceptual period; another large study showed no increase in risk. Withdrawal seizures and barbiturate withdrawal symptoms have been reported in infants after maternal use in the third trimester.	L3 (no data—probably compatible)	Concern for sedation in infant.
Opiates (oxycodone, hydromorphone, hydrocodone, codeine)	C	Either no information regarding risk of fetal malformations or no increase in risk of major congenital malformations; neonatal abstinence syndromes seen after prolonged use in later pregnancy.	L3 (no data—probably compatible): oxycodone, hydrocodone, hydromorphone; L4 (potentially hazardous): codeine	Monitor infants for respiratory depression; avoid codeine in breastfeeding mothers; codeine was associated with 1 fetal death; monitor infants exposed to codeine for sedation, apnea, bradycardia, cyanosis.
Triptans and ergots				
Triptans	C	No increased risk of major congenital malformations; studies conflicting about possible increased risk of premature birth; evidence best for sumatriptan, naratriptan, and rizatriptan.	L3 (no data—probably compatible)	No information available; eletriptan is likely to have lowest concentrations in breastmilk; avoid long-acting triptans (naratriptan and frovatriptan); option to discard pumped milk

Ergots (dihydroergotamine, ergotamine)	X	Increased risk of miscarriage.	L4 (potentially hazardous)	Avoid; may cause gastrointestinal distress and weakness in infant; may suppress milk production.
Antiemetics				
Diphenhydramine	B	No increased risk of major congenital malformations or other adverse outcomes; possible neonatal withdrawal with prolonged maternal use in third trimester.	L2 (probably compatible)	Other agents preferred; monitor for drowsiness or irritability; may reduce milk supply
Metoclopramide	B	Many studies; no increased risk of adverse pregnancy-related outcomes. May cause extrapyramidal signs and methemoglobinemia in neonates with maternal exposure during delivery.	L2 (probably compatible)	Infants may experience intestinal discomfort and gas; monitor infants for extrapyramidal symptoms and methemoglobinemia.
Promethazine	C	Other agents preferred. May cause platelet aggregation inhibition, irritability, or extrapyramidal effects in infants after maternal use within 2 wk prior to delivery.	L3 (no data—probably compatible)	Other agents preferred. May cause sedation or irritability in infants. May interfere with establishment of milk supply.
Prochlorperazine	C	Other agents preferred. May cause infant jaundice, reflex changes, extrapyramidal symptoms, and potentially severe withdrawal effects after maternal use in the third trimester.	L3 (no data—probably compatible)	Effects unknown; other agents strongly preferred.

(continued on next page)

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Table 2
(continued)

Medication	Food and Drug Administration Pregnancy Category	Available Pregnancy Safety Information	Hale's Lactation Risk Rating	Available Lactation Safety Information
Ondansetron	B	No increased risk of major congenital malformations, spontaneous abortion, or stillbirth; studies conflicting about possible increased risk of congenital heart malformations; the balance of evidence suggests against but study quality is challenging.	L2 (probably compatible)	No evidence.
Rescue treatments				
Prednisone	C (D for delayed-release formulations)	Increased risk of cleft lip or cleft palate, low birth weight; risks more strongly associated with chronic rather than episodic use; monitor infants for hypoadrenalism with chronic maternal use.	L2 (probably compatible)	Generally considered compatible with breastfeeding; infant exposure <0.1% of maternal dose; can pump and discard for 4 h if concern remains.
Lidocaine SQ	B	Limited data; existing studies show no increased risk of major congenital malformations; animal studies showed no teratogenic effects.	L2 (probably compatible)	Compatible with breastfeeding.

All information in this table obtained from Micromedex,[53] Natural Medicine,[54] and Reprotox[55] databases and *Hale's Medications & Mother's Milk*.

Now lets say she is having recurrent headaches and requires prophylactic therapy.

- The best prophylactic therapy for migraine during pregnancy is

A. Valproic Acid
B. Amitrityline
C. Propanolol
D. Topiramate
E. Vit B2 200mg BID

Table 3
Commonly used preventive medications for migraine and safety during pregnancy

Medication	Food and Drug Administration Pregnancy Category	Available Pregnancy Safety Information	Hale's Lactation Safety Rating	Available Lactation Safety Information
Antidepressants				
Amitriptyline	C	Second-line choice. Case reports of limb deformities, developmental delay but no causal relationship established. Monitor for infant irritability, urinary retention or constipation with late-term exposure.	L2 (probably compatible)	May be compatible. Report of infant sedation at maternal doses as low as 10 mg/d. Second line for migraine prevention; monitor infant for sedation, poor feeding.
Nortriptyline	C	Less information available than for amitriptyline; risks believed to be the same.	L2 (probably compatible)	Less information available than for amitriptyline; risks believed to be the same.
Venlafaxine	C	Other agents preferred. No increase in fetal congenital malformations; possible increased risk of spontaneous abortion; neonatal seizures, neonatal abstinence syndrome, or serotonergic toxicity possible with maternal use in third trimester.	L2 (probably compatible)	No evidence. Recommend avoidance.
Antihypertensives				
Propranolol	C	First-line choice. Observational studies show small increase in risk of intrauterine growth retardation, small placenta, and congenital abnormalities; neonatal bradycardia, respiratory depression,	L2 (probably compatible)	Compatible with breastfeeding. Monitor infant for bradycardia, hypoglycemia.

Table 3
(continued)

Medication	Food and Drug Administration Pregnancy Category	Available Pregnancy Safety Information	Hale's Lactation Safety Rating	Available Lactation Safety Information
Verapamil	C	No increase in fetal congenital malformations; may cause fetal bradycardia, hypotension, heart block; case report of congenital cardiomyopathy after IV treatment ×2.	L2 (probably compatible)	Compatible with breastfeeding. Exposure <1% of maternal dose.
Candesartan	D	Avoid use. Risk of fetal and neonatal death with second and third trimesters exposure; may cause oligohydramnios, fetal lung hypoplasia, renal failure, skeletal deformations. May cause hypotension, oliguria, hyperkalemia in exposed infants.	L3 (no data—probably compatible)	No evidence. Recommend avoidance
Lisinopril	D	Avoid use. Risk of fetal and neonatal death with second and third trimesters exposure; may cause oligohydramnios, fetal lung hypoplasia, renal failure, skeletal deformations. May cause hypotension, oliguria, hyperkalemia in exposed infants.	L3 (no data—probably compatible)	No evidence. Recommend avoidance

Table 3
(*continued*)

Medication	Food and Drug Administration Pregnancy Category	Available Pregnancy Safety Information	Hale's Lactation Safety Rating	Available Lactation Safety Information
Verapamil	C	No increase in fetal congenital malformations; may cause fetal bradycardia, hypotension, heart block; case report of congenital cardiomyopathy after IV treatment ×2.	L2 (probably compatible)	Compatible with breastfeeding. Exposure <1% of maternal dose.
Candesartan	D	Avoid use. Risk of fetal and neonatal death with second and third trimesters exposure; may cause oligohydramnios, fetal lung hypoplasia, renal failure, skeletal deformations. May cause hypotension, oliguria, hyperkalemia in exposed infants.	L3 (no data—probably compatible)	No evidence. Recommend avoidance.
Lisinopril	D	Avoid use. Risk of fetal and neonatal death with second and third trimesters exposure; may cause oligohydramnios, fetal lung hypoplasia, renal failure, skeletal deformations. May cause hypotension, oliguria, hyperkalemia in exposed infants.	L3 (no data—probably compatible)	No evidence. Recommend avoidance.

Table 3
(continued)

Medication	Food and Drug Administration Pregnancy Category	Available Pregnancy Safety Information	Hale's Lactation Safety Rating	Available Lactation Safety Information
Herbs and supplements				
Coenzyme Q10	N/A	Limited data; a single randomized controlled trial of CoQ10 200 mg daily in the second half of pregnancy did not show increased risk of adverse fetal outcomes.	L3 (no data—probably compatible)	No evidence; recommen
Vitamin B_2	N/A	Safe at physiologic doses; no evidence for use at supraphysiologic doses.	L1 (compatible) at physiologic doses	No evidence for supraph doses.
Feverfew	N/A	Contraindicated; may cause uterine contractions and spontaneous abortion.	N/A	No evidence; recommen
Magnesium	A; D (IV for >5 d)	Prolonged IV magnesium sulfate treatment associated with fetal skeletal abnormalities; oral magnesium not associated with increased risk of congenital malformations, but skeletal defects not specifically assessed.	L1 (compatible)	Safe; levels in breastmil by dietary intake.

All information in this table obtained from Micromedex, Natural Medicine, and Reprotox databases and *Hale's Medications & Mother's Milk*.