UPDATE ON MIGRAINE: SPECIAL CONSIDERATIONS FOR HORMONALLY INFLUENCED MIGRAINE

Jan Lewis Brandes, MD, MS
Nashville Neuroscience Group
Assistant Clinical Professor
Department of Neurology
Vanderbilt University
Nashville, Tennessee
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Conflicts of Interest/Affiliations

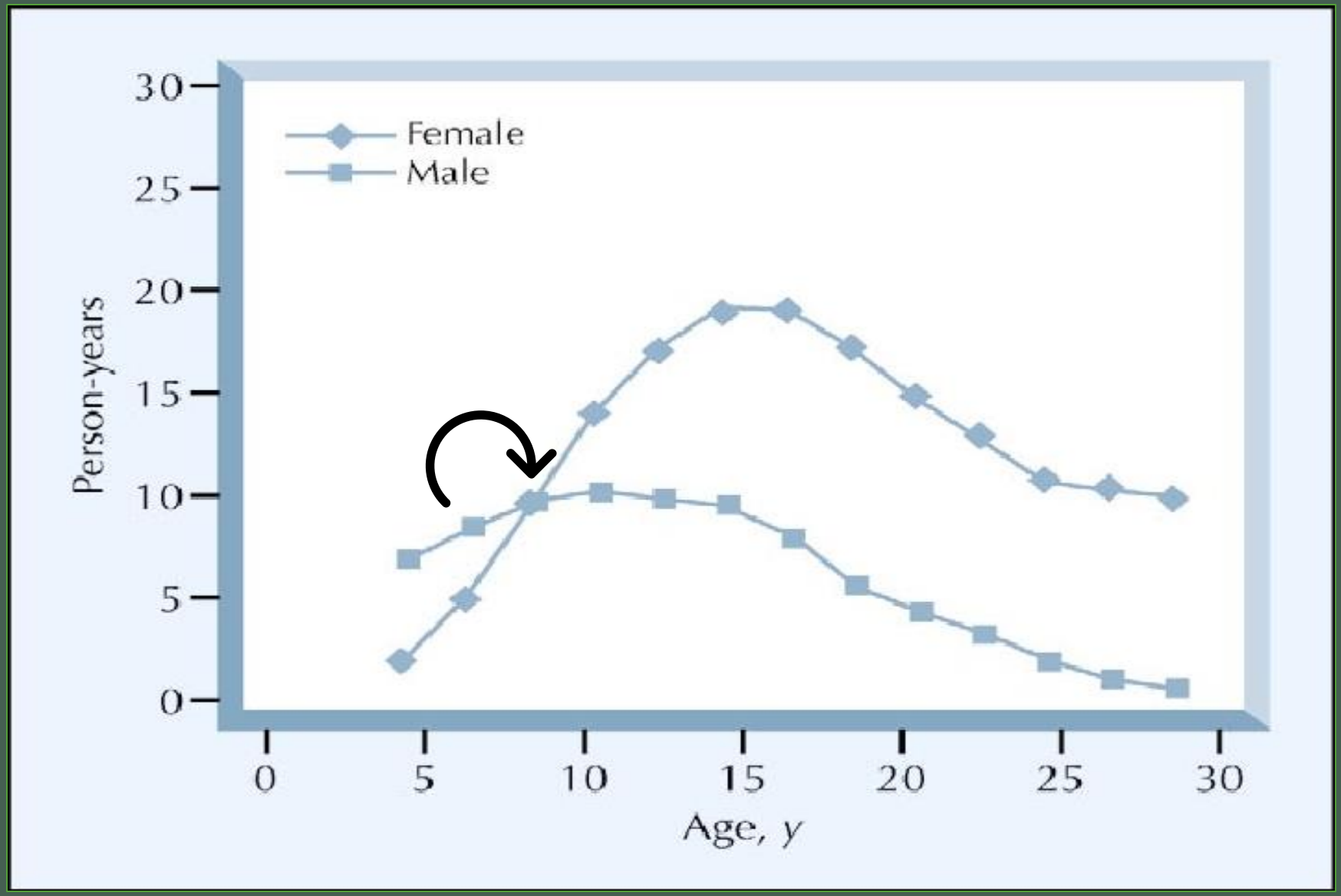
- Eli Lilly/Syneos
- National Headache Foundation

Prevalence of Migraine

- Over 30 million migraineurs in US[1]
- Migraine 3 times more common in women than men during reproductive years[1]
  - Believed to be associated with hormonal fluctuations in women; no comparable fluctuations in androgens are observed in men[2]
  - Prevalence in women rises after puberty and falls in postmenopausal period[1]
  - 51% to 55% of women with migraine report menstruation as trigger for migraine[2,3]
- Two main types of estrogen-mediated migraine[2]
  - Estrogen ***withdrawa***l and migraine without aura
  - ***High*** estrogen and migraine with aura

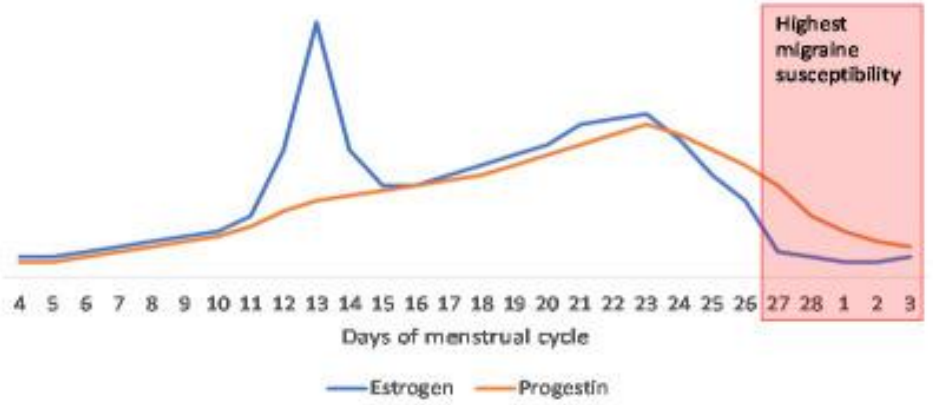
1. Lipton RB. *Headache*. 2001;41:638-645. 2. MacGregor EA. *Neurology*. 2004;63:351-353. 3. Couturier E. *Cephalalgia*. 2003;23:302-308.

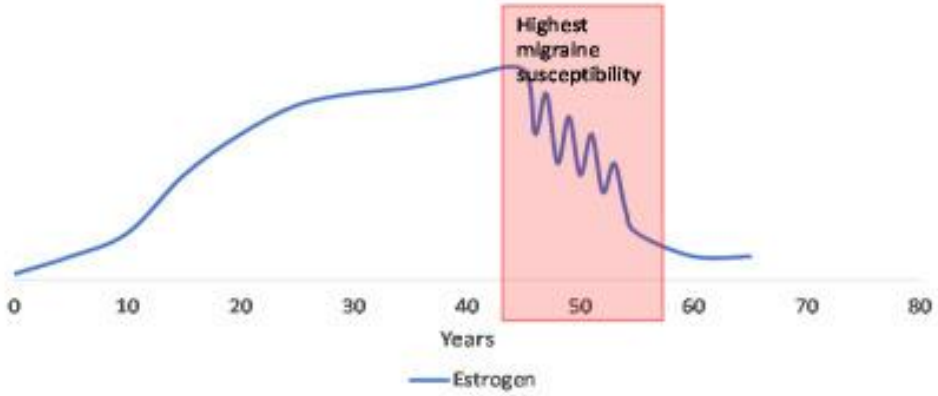
Incidence of Migraine by Sex and Age



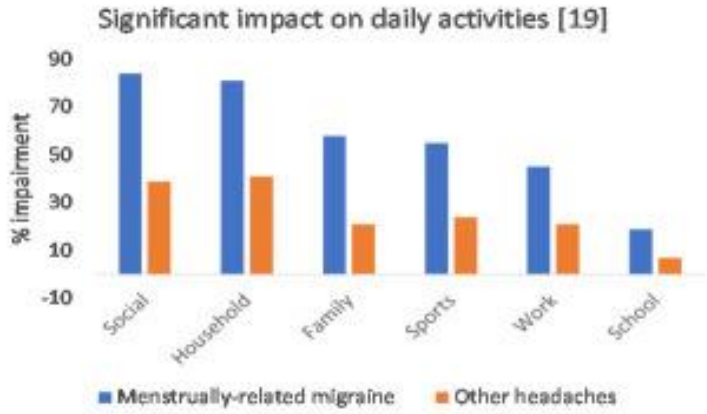
Bigal,Marcelo, Richard Lipton. Migraine at All Ages. **Current Pain and Headache Reports** 2006, **10:**207–213

Levels of sex hormones during the menstrual cycle and during the years of women's lives





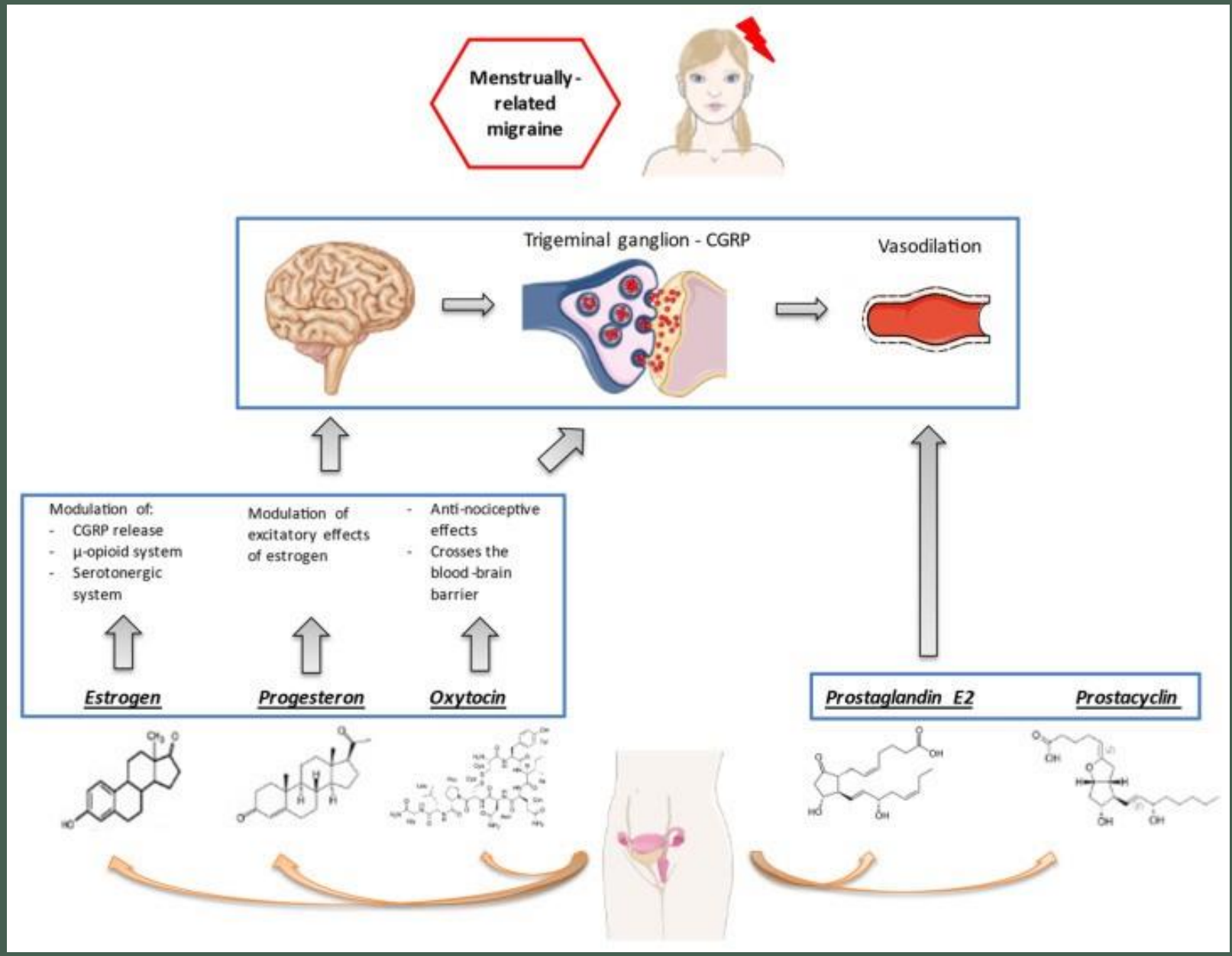
Quality of life impairment with migraine



Adapted from R Ornello, 2021, J Clinical Med. and Couturier EGM, Cephalalgia, 2003.

Female Sex Hormones and Pathogenesis of Menstrual Migraine

from
Ornello, R
J Clin Med
2021,10,2263



My daughter just missed school because of headache which began with her menstrual period.
What do I tell her?

Menstrual Migraine: Epidemiology

- Among women with migraine:
  - 11% have onset of migraine at menarche[1]
    - More likely to experience menstrual migraine[2]
  - 14% have migraine only with menses[3]
  - 60% have migraine with menses and at other times during menstrual cycle[3]
- Risk of migraine is elevated during first 3 days of menstruation, and with ovulation[4]

1. Granella F, et al. *Headache*. 1993;33:385-389. 2. Welch KMA. *Cephalalgia*. 1997;17(suppl):12-16.

3. Epstein MT, et al. *Lancet*. 1975; 1:543-547. 4. Johannes CB, et al. *Neurology*. 1995;45:1076-1082.

Characteristics of Menstrual Migraine

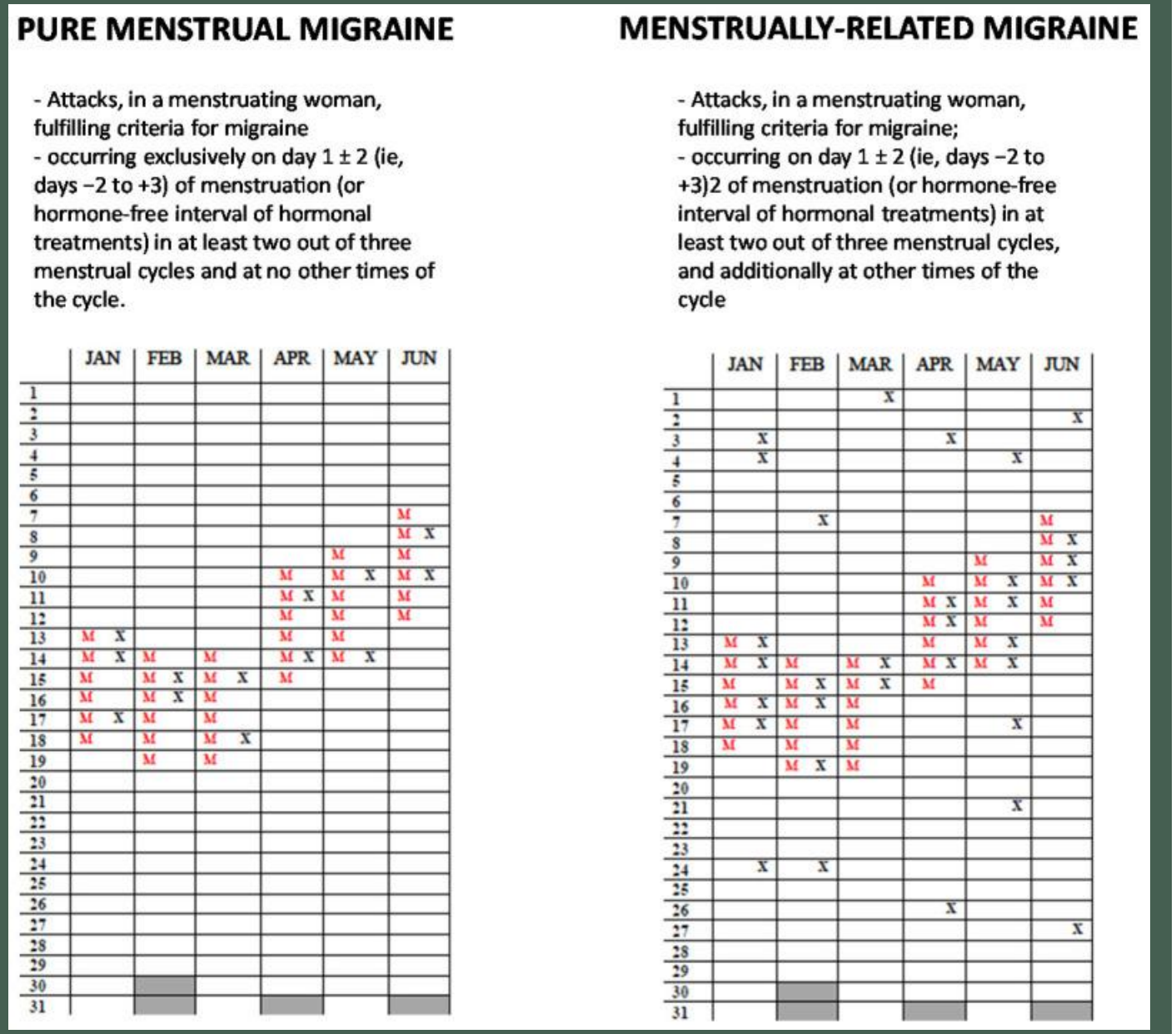
- Migraine without aura, but not always
- Severe intensity
- Long duration (up to 72 hours)
- High recurrence rate
- Greater work-related disability compared to non-menstrually related migraine
- Predictable timing

Allais G. *Neurol Sci*. 2004;25:S229-S231.

Pure vs. Non-Pure… maybe, …Solely

Figure 2 Example of headache diary of patient with pure menstrual and menstrual-related migraine. The Xs represent headache days; M's represent reported menstruation days.

Ornello R, De Matteis E, Di Felice C, Caponnetto V, Pistoia F, Sacco S. Acute and Preventive Management of Migraine during Menstruation and Menopause. J Clin Med. 2021 May 24;10(11):2263. doi: 10.3390/jcm10112263. PMID: 34073696; PMCID: PMC8197159.



PURE MENSTRUAL MIGRAINE

- Attacks, in a menstruating woman, fulfilling criteria for migraine
- occurring exclusively on day 1 ± 2 (ie, days −2 to +3) of menstruation (or hormone-free interval of hormonal treatments) in at least two out of three menstrual cycles and at no other times of the cycle.

	JAN	FEB	MAR	APR	MAY	JUN
1						
2						
3						
4						
5						
6						
7						M
8						M X
9					M	M
10				M	M X	M X
11				M X	M	M
12				M	M	M
13	M X			M	M	
14	M X	M	M	M X	M X	
15	M	M X	M X	M		
16	M	M X	M			
17	M X	M	M			
18	M	M	M X			
19		M	M			
20						
21						
22						
23						
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27						
28						
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30						
31						

MENSTRUALLY-RELATED MIGRAINE

- Attacks, in a menstruating woman, fulfilling criteria for migraine;
- occurring on day 1 ± 2 (ie, days −2 to +3)2 of menstruation (or hormone-free interval of hormonal treatments) in at least two out of three menstrual cycles, and additionally at other times of the cycle

	JAN	FEB	MAR	APR	MAY	JUN
1			X			
2						X
3	X			X		
4	X				X	
5						
6						
7		X				M
8						M X
9					M	M X
10				M	M X	M X
11				M X	M X	M
12				M X	M	M
13	M X			M	M X	
14	M X	M	M X	M X	M X	
15	M	M X	M X	M		
16	M X	M X	M			
17	M X	M	M		X	
18	M	M	M			
19		M X	M			
20						
21					X	
22						
23						
24	X	X				
25						
26				X		
27						X
28						
29						
30						
31						

Two Hit Process: Rapid Estrogen Decline + Trigger

Caffeine – taper to 1 a day or less

Fluids – maintain hydration 8 - 8oz glasses

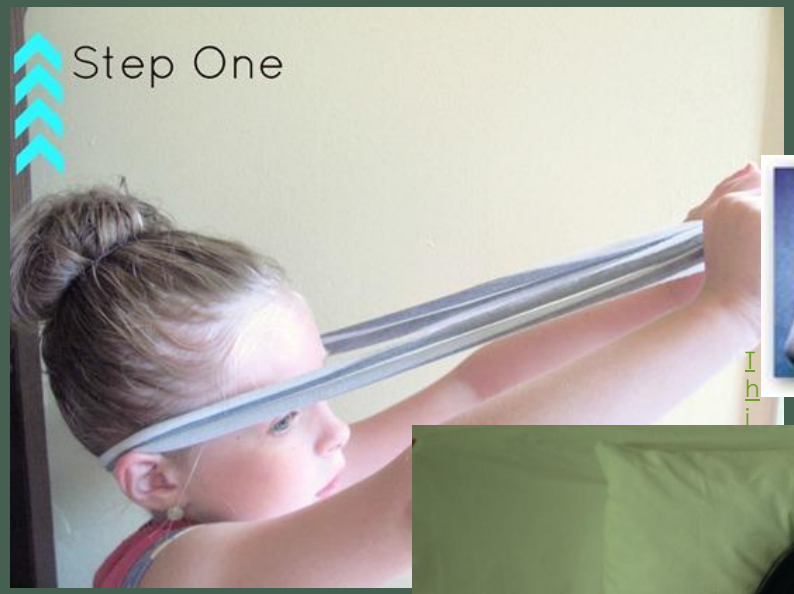
Don't skip meals, especially breakfast

Structured treatment plan – follow the program!

Regulate sleep – same time to bed and rise each day

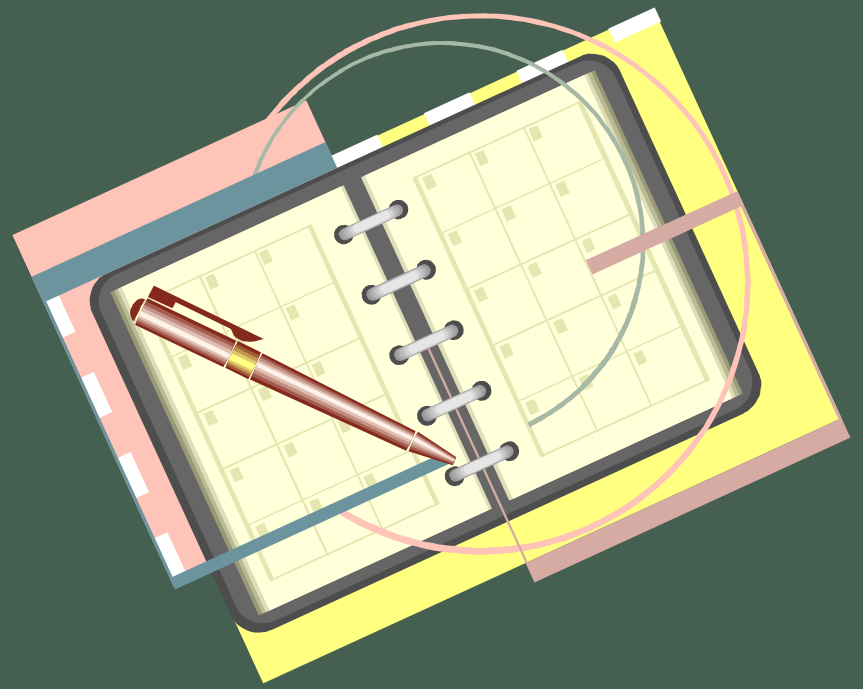
Regular exercise – 30 min/day 5 days/week

How can I manage my debilitating menstrual migraine?

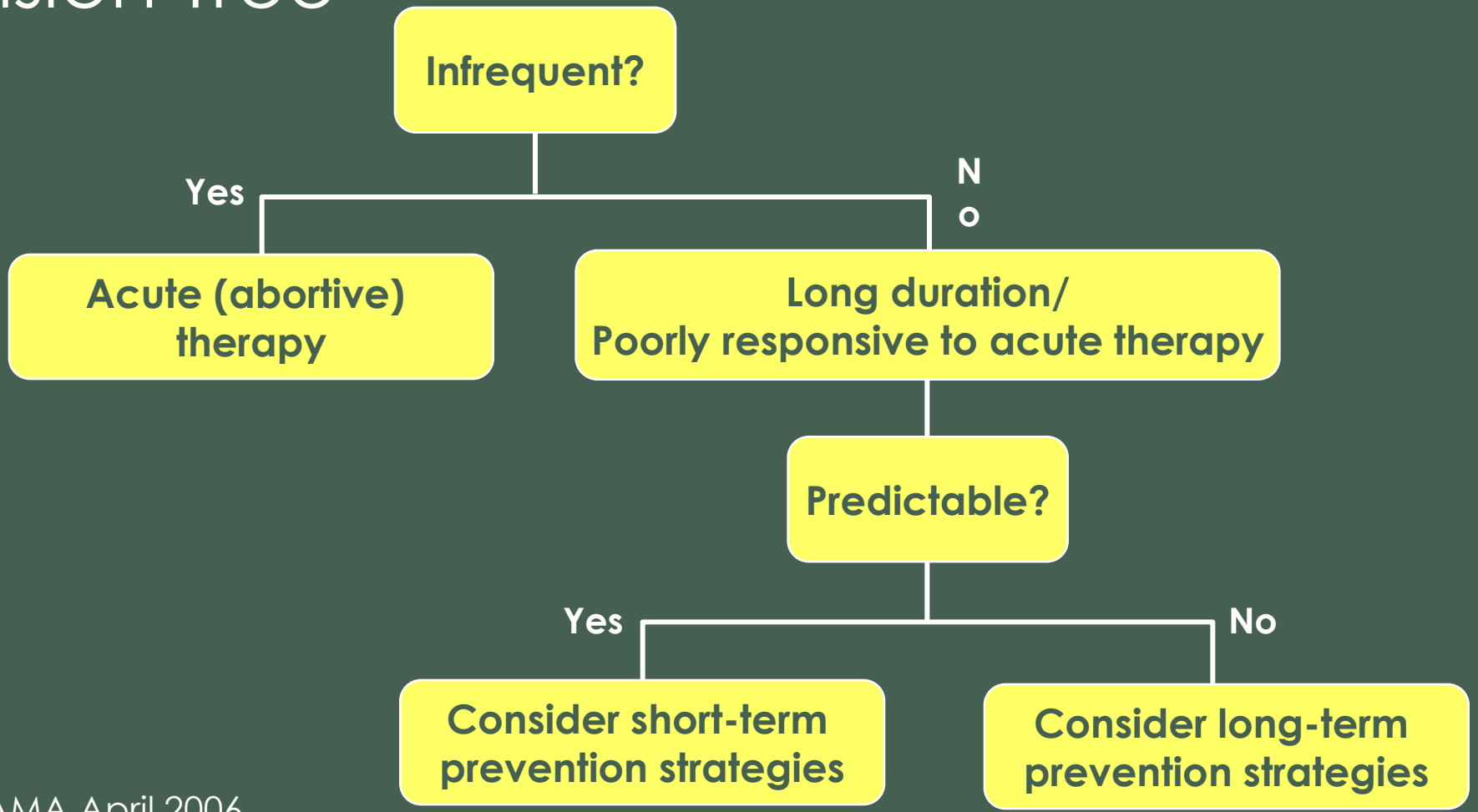


Evaluation and Management of Menstrual Migraine

- Diary to determine headache
  - Frequency and onset
  - Menstrual cycle
  - Triggers in addition to menses
  - Response to therapy



Menstrual Migraine Pharmacologic Treatment Decision Tree



Brandes JL JAMA April 2006.

Therapeutic Options and Management Strategies

- Acute (abortive) Therapy
  - Aborts pain and migraine-associated symptoms after headache begins
- Short-Term Prevention
  - Prevents recurring migraine attacks which are typically associated with menses
- Long-Term Continuous Prevention
  - Aimed at preventing the onset of pain
    - Ongoing prevention may be used for patients who experience migraine throughout cycle or with concomitant medical conditions
- Education/Behavior Modification

Acute Treatments

NSAIDs/Combinations[1]
- Naproxen Sodium 500-550mg, max 1375mg/day
- Diclofenac powder for oral solution 50mg, max 50mg/day. Tabs 50mg, max 150mg/day
- Acetaminophen 250mg/aspirin 250mg/caffeine 65mg, 2 capsules, max 8caps/day

Triptans[2]
- Almotriptan 6.25-12.5mg, max 25mg/day
- Eletriptan 40mg, max 80mg/day
- Zolmitriptan PO, intranasal 5mg, 10mg/day
- Naratriptan 2.5mg, max 5mg/day

Rizatriptan 10mg, max 30mg/day
Sumatriptan PO, intranasal, subcutaneous
Sumatriptan 85/Naproxen 500mg 1 tab, max 2 tabs/day
Frovatriptan 2.5mg, mg, max 7.5mg/day

Ergots[1]
- Dihydroergotamine intranasal 0.5mg, max 4mg/day subcutaneous 0.5-1mg max 3mg/day , IM injection 0.5-1mg max 3mg/day

Gepants
Atogepant 10-30-60mg
Ubrogepant 50-100mg
Rimegepant 75mg

Ditans
Lasmiditan 100mg-200mg

Anti-emetics
- Metoclopramide 5-10mg
- Ondansetron 4-8mg PO, ODT
- Prochlorperazine 10mg PO, max 40mg/day/suppositories 10-25mg, max 50mg/day

1. Becker, Werner. Acute Migraine Treatment. Continuum (Minneap Minn) ;21 (4)953-972 2. MacGregor, Anne. Migraine Management During Menstruation and Menopause. Continuum (Minneap Minn) 2015;21(4):990–1003

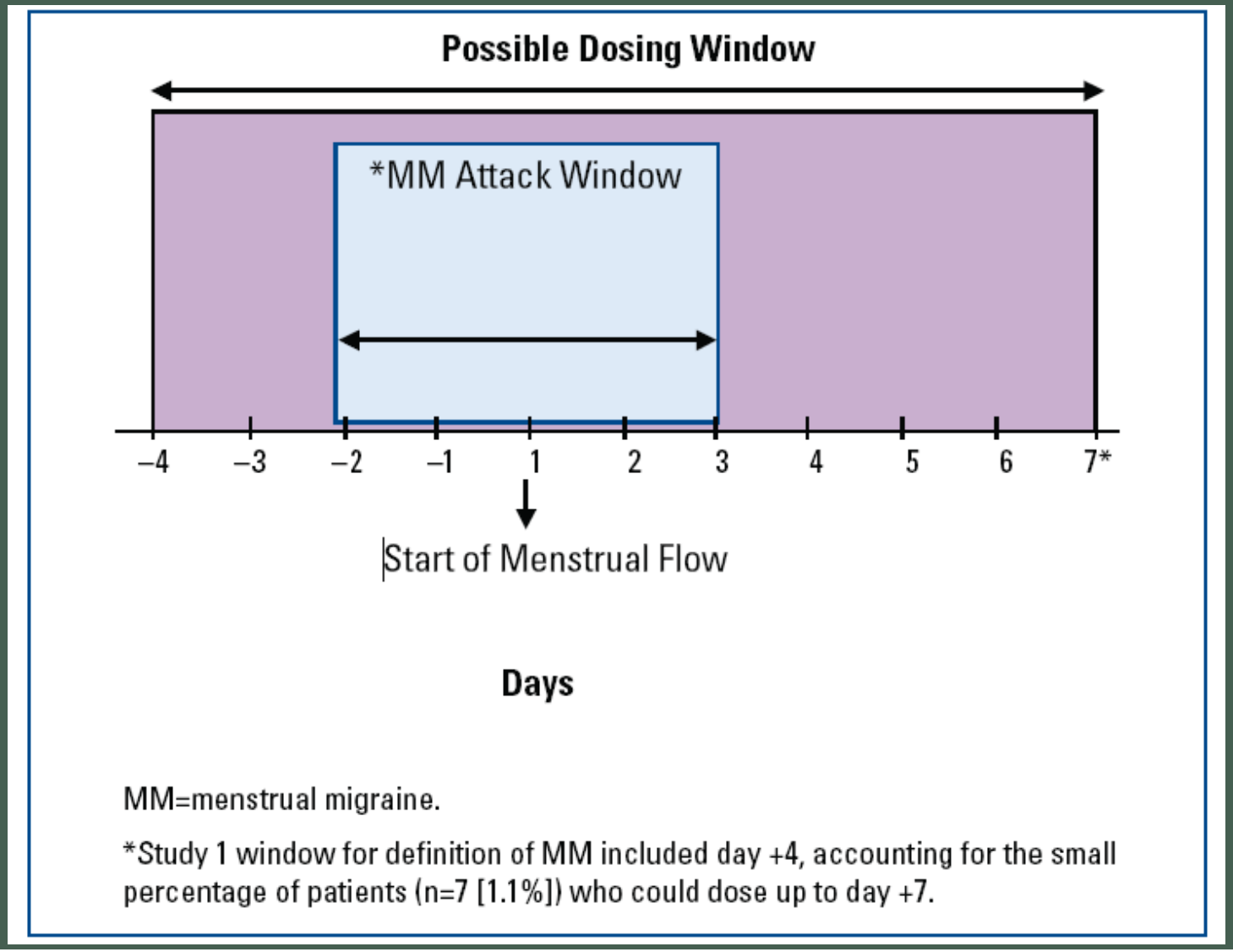
Non-Invasive Neuromodulation Device Options

- Transcutaneous Supraorbital Neurostimulator – sending electrical pulses through forehead to stimulates the supraorbital nerves which transmit that signal to the brain
- Single Pulse Transcranial Magnetic Stimulator – a magnet using split-second impulses to interrupt the electrical activity during migraine attacks
- Vagus Nerve Stimulator - handheld device sending mild electrical pulses to interrupt migraine
- Other devices are controlled through a phone app, transmitting weak electrical pulses to stop migraine; one activating stimulation in the vestibular nerve

1.

What if my menstrual migraine gets better when I treat, but comes back?

Dosing Strategies in Short Term Prevention of Menstrual Migraine



MM=menstrual migraine.

*Study 1 window for definition of MM included day +4, accounting for the small percentage of patients (n=7 [1.1%]) who could dose up to day +7.

Short Term or "Mini" Prevention with *somewhat* predictable menstrual cycles

NSAIDs

- ***Naproxen*** 550mg [1]
  - BID 7-14days
  - Start the week before onset of menses
- Flurbiprofen 100mg
  - BID x7 days
    - Start 2days prior to onset of menses

Triptans

- ***Frovatriptan*** 2.5-5mg[1]
  - 5mg BID 2days prior to onset of menses, then 2.5mg BID for total of 6days
- Naratriptan 1mg[2]
  - 1mg BID x5days
  - Start 2days prior to onset of menses
- Zolmitriptan 2.5mg[2]
  - 2.5mg BID
  - Start 2days prior to onset of menses

1. MacGregor, Anne. Migraine Management During Menstruation and Menopause. Continuum (Minneap Minn) 2015;21(4):990–1003
2. Epocrates for Apple iOS (Version 5.1) [Mobile application software]. Retrieved from http://www.epocrates.com/mobile/iphone

CGRP-Abs & Influence on Menstrual Migraine

- Erenumab subgroup analysis of women with self-reported history of MRM[1]
- Endpoints
  - Reduction in monthly migraine days
  - Reduction in days which acute migraine specific medication was used
- STRIVE episodic migraine trial 3
- Erenumab was found to be equally effective in reducing monthly migraine days and improving the 50% responder rate in women with and without a history of MRM[1]
- Ornello showed that women with chronic migraine on erenumab had headaches more commonly in menstrual than in premenstrual or non-menstrual days. This pattern was similar in responders and non-responders to the treatment 4

Galcanezumab post-ad hoc analysis looked at self reported menstrual migraines (2days prior to and 3 days after onset of menses)[2]

- Migraine headache days were reduced both within the peri-menstrual period as well as outside the peri-menstrual period[2]

1.Pavlovic,Jelena, Koen Paemeleire, et al. Efficeacy of Erenumab in Women with and without a History of Menstraully-Related Migraine. Neurology Apr 2018,90(15 supplement) P4.096
2. Data on file, Eli Lilly and Company
3, Pavlovic JM et.al The Journal of Headache and Pain. 21, 03 August 2020. 4. Ornello R et.al Brain Sci 2021 mar; 11(3): 370.

CGRP Levels in Menstruating Women

- *Significantly higher levels of calcitonin gene-related peptide* (CGRP) with regular menstrual cycles during the menstrual cycle
- Fluctuations in estrogen lead to activation of the trigeminovascular system and subsequent release of CGRP, contributing to the high prevalence of migraine in females of child-bearing age
- CGRP concentrations in plasma and tear fluid of women with and without migraine under three hormonal conditions:

    episodic migraine with regular menstrual cycles

    episodic migraine while on combined oral contraceptives (no change in CGRP)

    postmenopausal women with episodic migraine (no change in CGRP)

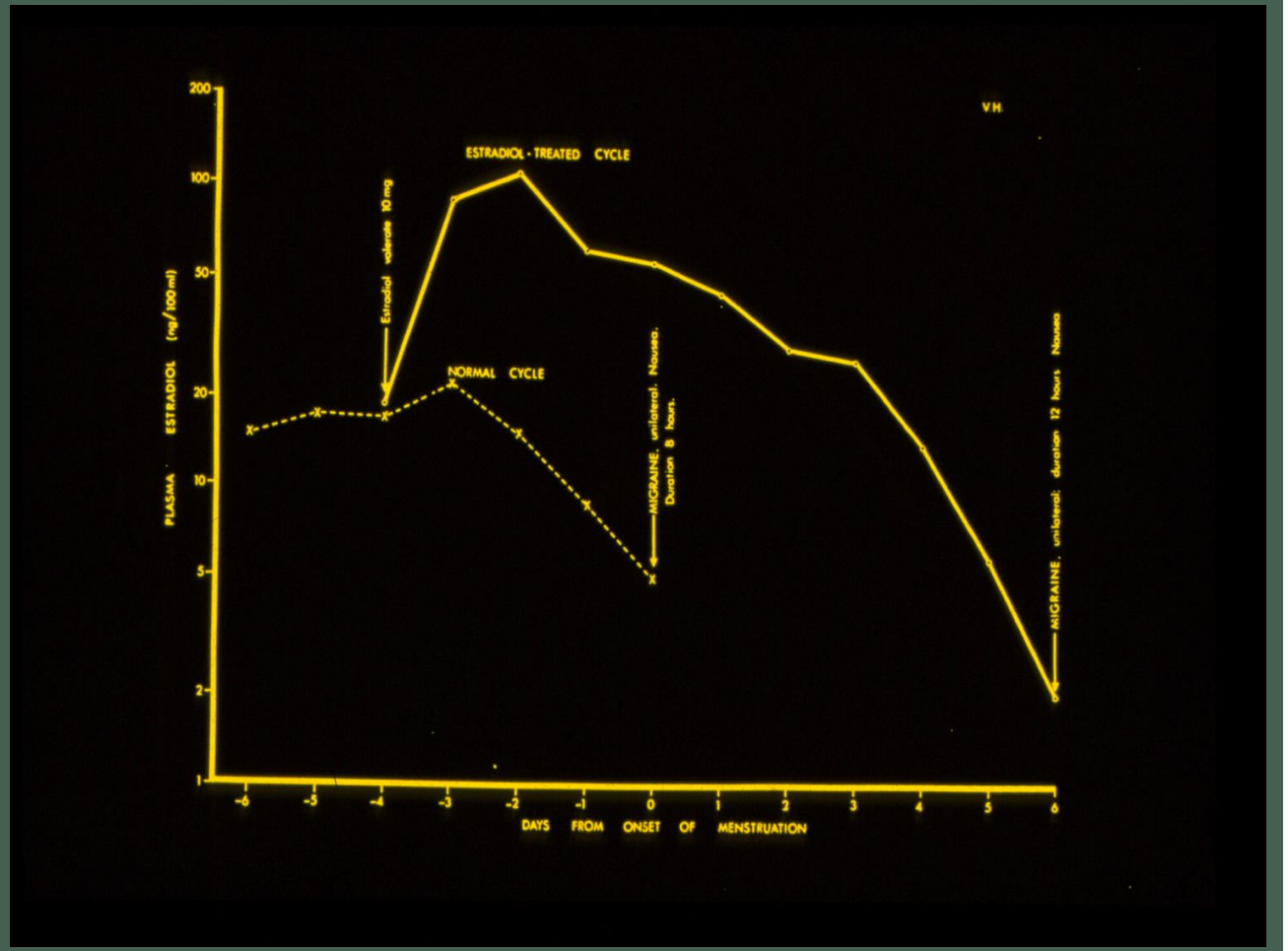
No correlation found between estrogen and progesterone concentrations and CGRP in plasma and tear fluid

These *observed fluctuations* –not absolute levels – of sex hormones ***appear to be more important in their influence on CGRP and therefore, migraine pain***

Raffaelli B, Storch E, Overeem LH, *Neurology*. 2023 April 25; 100 (17): e1825-d1835

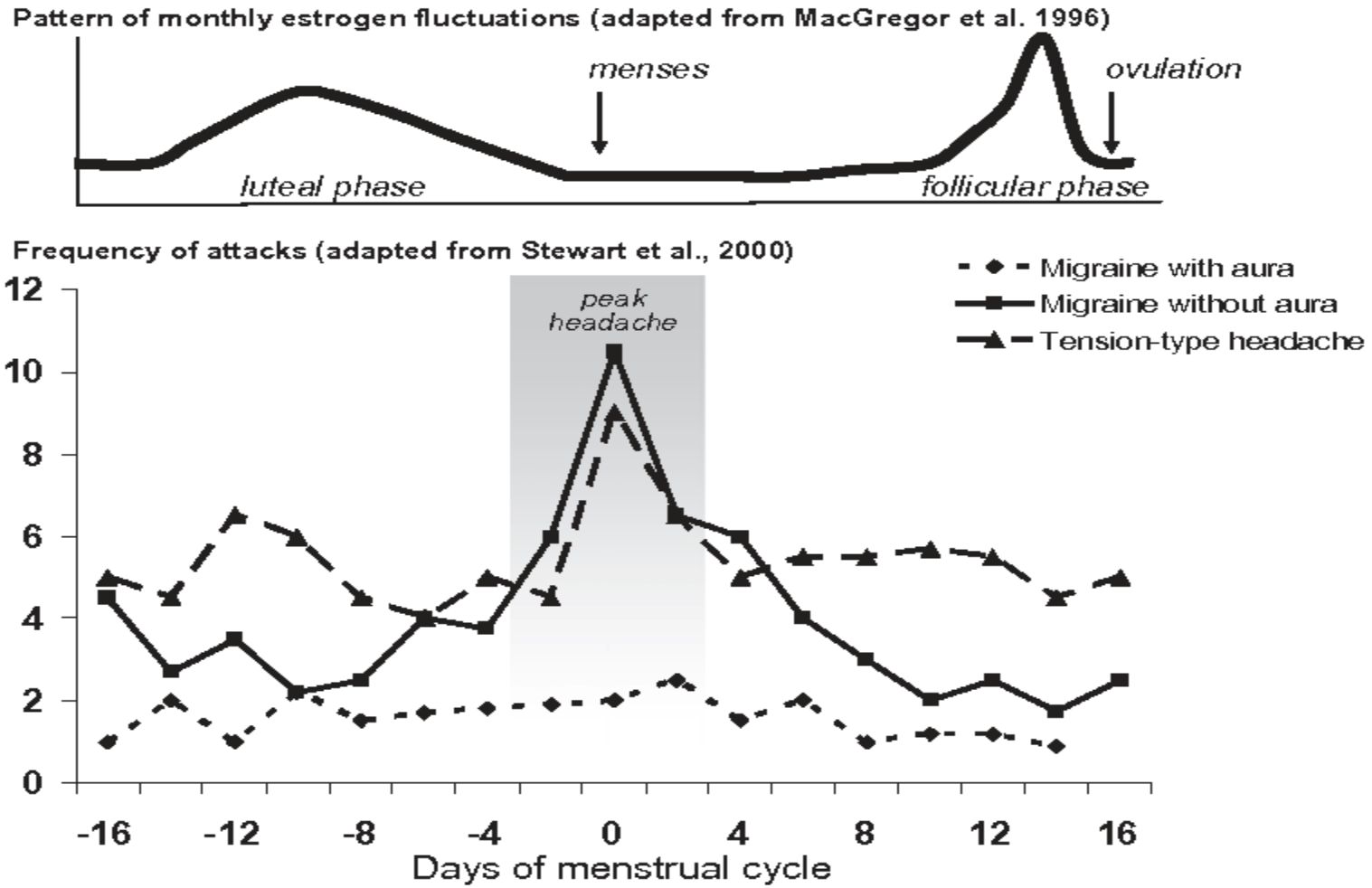
What happens if I am still suffering?

Can I use hormonal therapies, like continuous oral contraceptives or add estrogen?



Somerville, B. Neurology. 1972: 22:355-365.

Relationship of Headache to Circulating Estrogen



Migraineurs and the Use of Combination Hormonal Contraceptives

- Evaluate stroke risk factors and treat when present
- Take family history for hypercoagulable state
- Identify migraine with aura; check hypercoagulable status
- Women who smoke should stop before CHCs
- Consider progestin-only OC pills or non-hormonal therapy in women at increased risk

OCPs for Prophylaxis of Menstrual Migraine

- Lack of consensus, lack of RDBPC trials
- Migraine improves in one third of patients, worsens in one third, remains unchanged in one third offered OCPs
- Strategies, if used:

  Shorten placebo days

  Continuous use
  - three consecutive packs of active pill followed by pill-free interval
  - irregular bleeding
- Precaution/contraindications
  - ***Aura, age, smoking, vascular risk factors***

Silberstein S. *Semin Headache Management*. 1998;3:1-8. Loder, E. In: *Advanced Therapy of Headache*. Eds. Rapoport AM, Purdy RA, Sheftell FD. 1999. Chapter 6.

Percutaneous Estradiol Gel for Short Term Prophylaxis of Menstrual Migraine

Study	Patients	Design	Results
de Lignieres et. al, 1986	20	DBPC, crossover	Reduction in migraine frequency, duration, severity
Dennerstein et. al, 1988	22	DBPC	Significant reduction in occurrence of moderate or severe migraine
MacGregor et. al, 2006	42	DBPC	22 women benefited, but 15 experienced post gel HA

de Lignieres B, et al. *BMJ*. 1986;293:154.

Dennerstein L, et al. *Gynecol Endocrino*;1988;2:113-120.

Other hormonal strategies for menstrual migraine

- Peri-menstrual estrogen supplementation
  - Best evidence is for the patch
  - Dose seems to make a difference (100 mcg better than 50 mcg)
  - Can also use continuous oral contraceptives
    - Not first-line treatment unless patient desires contraception or has endometriosis

- Oophorectomy not advised
  - Abrupt surgical menopause may worsen headaches
  - Use of GNRH analogues plus add-back estrogen not effective

Aura vs. Frequency of Aura

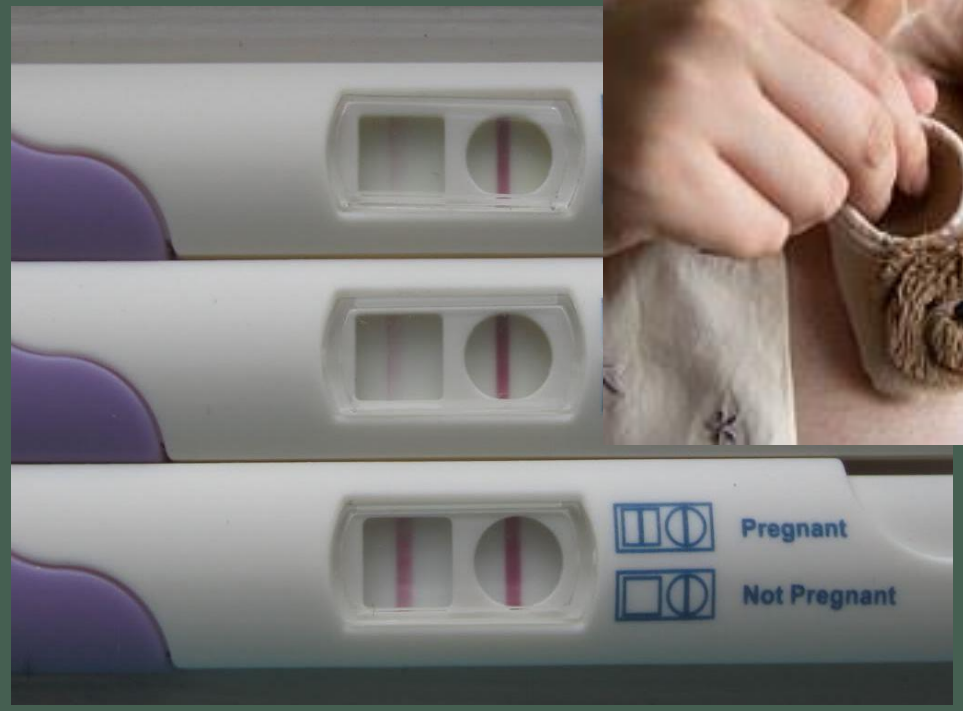
- Longitudinal Women's Health Study [1]
  - 27,798 women >45years old
  - MwA conferred an increased risk of CvD (including stroke) that varied with frequency of aura
    - Aura <one a month conferred a two-fold increased risk compared to women w/o migraine.
    - Risk increased more than four-fold with aura frequency exceeded once a week.

1. Kurth T, Slomke MA, Kase CS, et al. Migraine, headache, and the risk of stroke in women: A prospective study. Neurology. 2005;64:1020-1026.

World Health Organization	American College of Obstetrics and Gynecology	International Headache Society
Recommend complete avoidance of combination contraceptives for women with migraine with aura regardless of age. There is no restriction for migraine without aura[1]	Recommends using alternative forms of contraceptives in certain populations of women over 35 who smoke or have migraine with "focal neurological signs"[2]	Advises that low-dose estrogen containing contraception may be prescribed in women who have simple visual aura[3]

1.US Medical Eligibility Criteria for Contraceptive Use, 2010. Adapted from the WHO Medical Eligibility for Contraceptive Use, 4th Edition. CDC MMWR May 28, 2010/Vol. 59.
2.ACOG Practice Bulletin No 110: Noncontraceptive uses of hormonal contraceptives. Obstet Gynecol. 2010;115:206-218.
3International Headache Society Taskforce. Recommendations on the risk of ischaemic stroke associated with use of combined oral contraceptives and hormone replacement therapy in women with migraine. Cephalalgia 2000;20:155-6.
Hutchinson, Susan. Use of Oral Contraception in Women with Migraine. https://americanheadachesociety.org/wp-content/uploads/2018/06/Hutchinson-Contraceptives.docx.

How do I manage my migraine while I'm trying to achieve pregnancy?



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Management Around Time of Conception

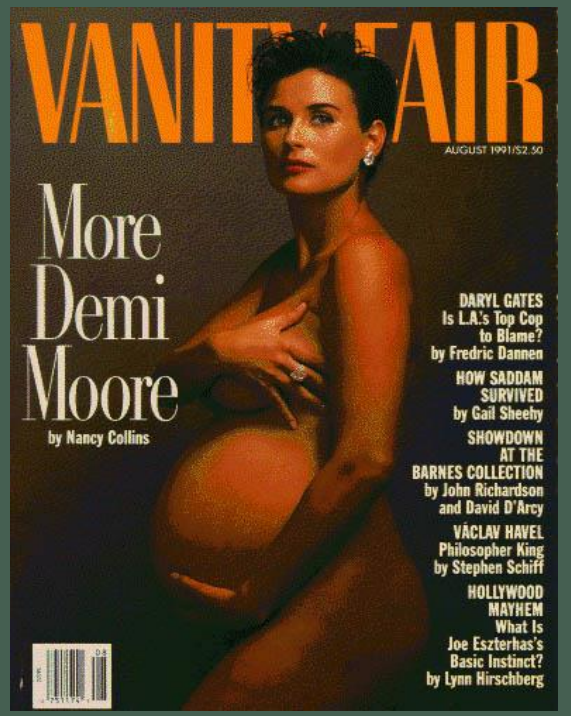
- Change to “acceptable” prophylaxis
- Add folate 1-4 mg per day
- Begin magnesium 360mg/qd - 400mg/BID (avoid iv and high dose after conception because of concern about fetal bone abnormalities
- Vitamin B2 400mg/qd
- Transcranial direct current stimulation
- Non pharmacological therapy
- Pre-ovulation: usual Rx
- Post-ovulation:
  - analgesics, opioids, antiemetics, corticosteroids

Wickman F, et.al J Neurol Sci. 2015, 354, 103-109. Facchinett, F et.al Headache 1991, 31 298-30.

What will I do if my migraine worsens during pregnancy?

Migraine Management During Pregnancy
Accentuate non-pharmacological treatments

- Rest
- Biofeedback
- Ice/Heat
- Massage
- Trigger avoidance
- Exercise
- Neuromodulation or neurostimulation



Can I use triptans during my pregnancy?

- Currently 3 published prospective comparative studies confirmed **no increased risk of major malformations with exposure to sumatriptan during pregnancy** [1]
- Two subsequent systematic reviews also found no association between teratogenicity and use of sumatriptan during pregnancy[1]
- **Pregnancy registry** data are available for 3 **triptans-sumatriptan, naratriptan, and rizatriptan**.
  - To date, the risk of major malformations has been reported to be similar to the baseline risk in the general population (1-3%) [1]
- Interpret with caution
  - Small sample sizes
  - Insufficient power to reliably detect an increase in major malformation

1. Duong,Silvia, Pina Bozzo, et al. Safety of triptans for migraine headaches during pregnancy and breastfeeding. Canada Fam Physician. 2010 Jun;56(6): 537-539.

Migraine Medications – associated risk during pregnancy

- Category B Acetaminophen, Caffeine, Cyproheptadine, diphenhydramine, memantine, metoclopramide, ondansetron, lidocaine
- Category C Triptans, promethazine, narcotics, NSAIDs up to 32 weeks of pregnancy, butalbital, aspirin (first trimester), propranolol, nadolol, SSRI and SNRI antidepressants (except paroxetine), amitriptyline, onabotulinum
- Category D Valproic acid, topiramate, nortriptyline, imipramine, lithium, paroxetine
- Category X Ergots
- Minimal evidence for gepants or ditans but please enroll in their registries!!!
- New labeling system, begun in 2015, still does not provide definitive "yes" or "no" answers in most cases; clinical interpretation is still required on a case by case basis (The Pregnancy and Lactation Labeling Final Rule, PLLR)

Tepper D. Headache April 2015. Parikh SK et.al Progress in Brain Research, 255, 2020, 275-309. https://www.drugs.com/pregnancy-categories.html#.

Procedures/Devices during Pregnancy

Peripheral nerve blocks-considered safe as risk to fetus is low given peripheral location and lack of central effects[1]

greater occipital, auriculotemporal, supraorbital, and supratrochlear)
Lidocaine (FDA category B)
>Bupivacaine (FDA category C[1]
Steroid - some avoid due to potential risk of accelerating fetal lung development

Sphenopalatine ganglion blocks- pregnancy risk category?

- **Onabotulinum toxin A-**pregnancy risk category C[1]
  - Lack of well-controlled human studies during pregnancy
  - Large molecule which *should* not cross placenta[2]
  - Discussion risk vs. benefits with patients
- **Transcutaneous supraorbital neurostimulation** and **single pulse transcranial magnetic stimulation-** theoretically should be safe in pregnancy[2]
- **Trigger Point Injections**
- **Dry Needling**

1.Wells, Rebecca, Dana Turner. Managing Migraine During Pregnancy and Lactation. Curr Neurol Neurosci Rep (2016) 16:40
2. Robbins, Matthew. Migraine in Pregnancy. American Headache Society. https://americanheadachesociety.org/news/migraine-pregnancy-qa-dr-matthew-robbins/

Preventive Therapy During Pregnancy

- C Beta-blockers

  Propranolol, metoprolol, nadolol, *labetalol*

- C Tricyclic antidepressants

  Amitriptyline (*nortriptyline* D)

- D Topiramate, lithium, paroxetine, valproate (known for neural tube defects)

- B Cyproheptadine, memantine, metoclopramide, caffeine, diphenhydramine

- Rescue: Steroids/Odansetron/Diphenhydramine

- No data on gepants or CGRP monoclonal Abs for migraine prevention

- ***Please enroll*** your patients in pregnancy registries if they inadvertently take gepants, lasmiditan, or a CGRP monoclonal antibody for migraine

Migraine Pregnancy Registries

- Lasmiditan: www.migrainepregnancyregistry.com 833-464-4724
- Rimegepant: Migraine Observational Nurtec Pregnancy Registry (MONITOR) 877-366-0324
- Erenumab: Genesis Pregnancy Registry 833-244-4083
- Fremanezumab: Teva Migraine Pregnancy Registry 833-927-2605
- Galcanezumab: PASS www.migrainepregnancyregistry.com 833-464-4724

- PUSH FOR PATIENTS TO REGISTER and BE FOLLOWED!!!

How will I treat my headaches while I'm breastfeeding?

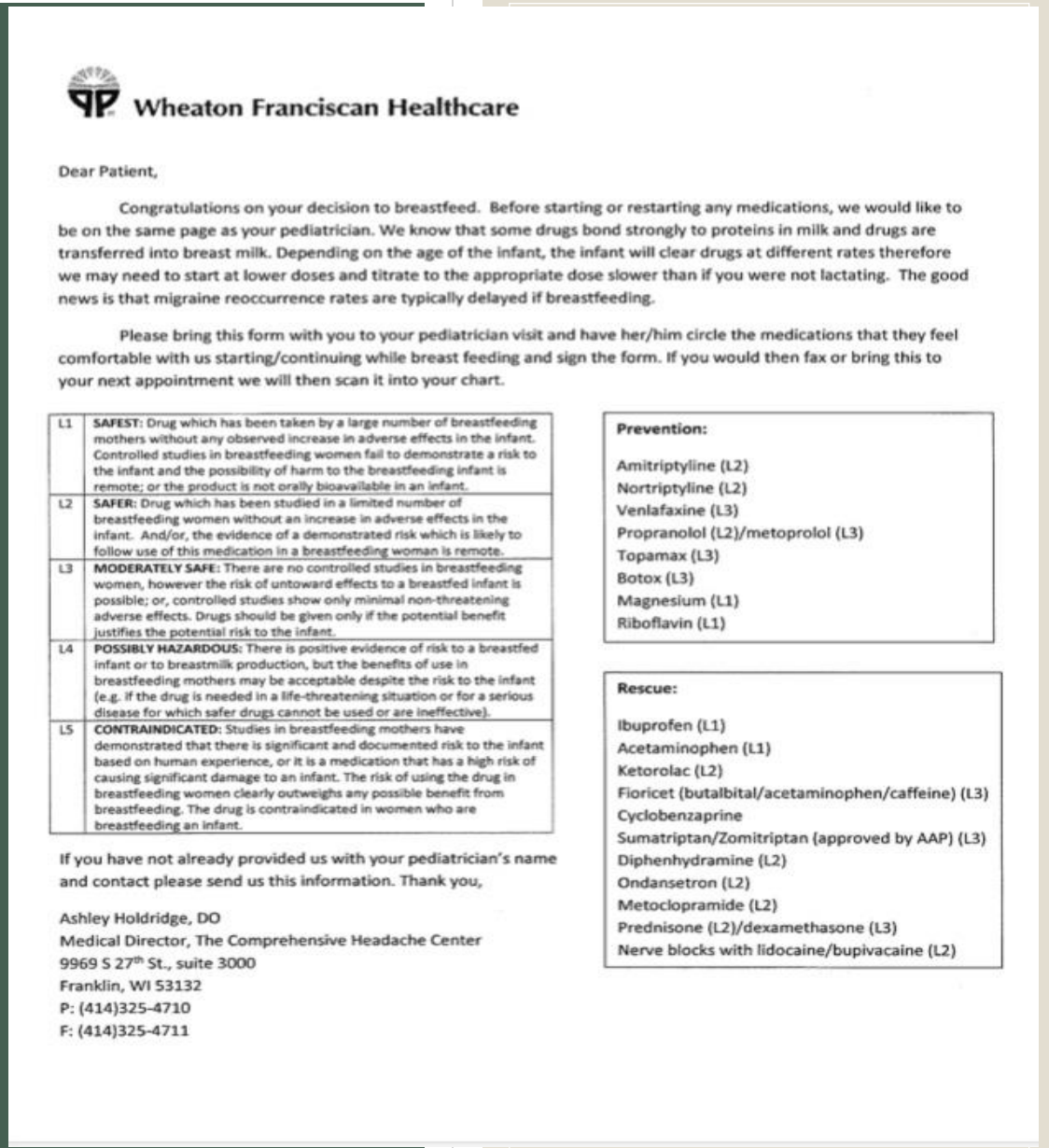
Table 2. Workplace structural support provided for breastfeeding (*N*=14)

Structural support for breastfeeding	*n* (%)
Occupational health programme	8 (57.1)
Onsite/nearby crèche	2 (14.3)
Private space and room	2 (14.3)
Written breastfeeding policy	4 (28.6)
Refrigerator for breastmilk storage	5 (35.7)
Breastfeeding counselling for staff	1 (7.1)
Educational material for pregnant and new mothers	5 (35.7)
Educational material for expecting fathers	5 (35.7)
Routinely promote benefits of breastfeeding to employees	2 (14.3)

Lactation

- Important to have this conversation prior to conception and before delivery and to be on the same page as pediatrician.
- National Library of Medicine's Drugs and Lactation Database (LactMed)
- Dr. Hale's lactation risk categories
- Considerations:
  - Delaying feeding to allow clearance of drug
  - "Pumping and Dumping"
- If starting prevention, start lower and go slow as most drugs transfer to breast milk
- Age of infant is important
  - premature infants clear drugs less efficiently than full term[1]
  - At approximately 7months, the infant will be clearing drugs at a rate similar to adults[1]

1.Diamond, Seymour, Merle Diamond. "Menstrual Migraine". Headache and Migraine Biology and Management, Elsevier AP, 2015, 128



Wheaton Franciscan Healthcare

Dear Patient,

Congratulations on your decision to breastfeed. Before starting or restarting any medications, we would like to be on the same page as your pediatrician. We know that some drugs bond strongly to proteins in milk and drugs are transferred into breast milk. Depending on the age of the infant, the infant will clear drugs at different rates therefore we may need to start at lower doses and titrate to the appropriate dose slower than if you were not lactating. The good news is that migraine reoccurrence rates are typically delayed if breastfeeding.

Please bring this form with you to your pediatrician visit and have her/him circle the medications that they feel comfortable with us starting/continuing while breast feeding and sign the form. If you would then fax or bring this to your next appointment we will then scan it into your chart.

L1	**SAFEST:** Drug which has been taken by a large number of breastfeeding mothers without any observed increase in adverse effects in the infant. Controlled studies in breastfeeding women fail to demonstrate a risk to the infant and the possibility of harm to the breastfeeding infant is remote; or the product is not orally bioavailable in an infant.
L2	**SAFER:** Drug which has been studied in a limited number of breastfeeding women without an increase in adverse effects in the infant. And/or, the evidence of a demonstrated risk which is likely to follow use of this medication in a breastfeeding woman is remote.
L3	**MODERATELY SAFE:** There are no controlled studies in breastfeeding women, however the risk of untoward effects to a breastfed infant is possible; or, controlled studies show only minimal non-threatening adverse effects. Drugs should be given only if the potential benefit justifies the potential risk to the infant.
L4	**POSSIBLY HAZARDOUS:** There is positive evidence of risk to a breastfed infant or to breastmilk production, but the benefits of use in breastfeeding mothers may be acceptable despite the risk to the infant (e.g. if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
L5	**CONTRAINDICATED:** Studies in breastfeeding mothers have demonstrated that there is significant and documented risk to the infant based on human experience, or it is a medication that has a high risk of causing significant damage to an infant. The risk of using the drug in breastfeeding women clearly outweighs any possible benefit from breastfeeding. The drug is contraindicated in women who are breastfeeding an infant.

If you have not already provided us with your pediatrician's name and contact please send us this information. Thank you,

Ashley Holdridge, DO
Medical Director, The Comprehensive Headache Center
9969 S 27th St., suite 3000
Franklin, WI 53132
P: (414)325-4710
F: (414)325-4711

Prevention:

Amitriptyline (L2)
Nortriptyline (L2)
Venlafaxine (L3)
Propranolol (L2)/metoprolol (L3)
Topamax (L3)
Botox (L3)
Magnesium (L1)
Riboflavin (L1)

Rescue:

Ibuprofen (L1)
Acetaminophen (L1)
Ketorolac (L2)
Fioricet (butalbital/acetaminophen/caffeine) (L3)
Cyclobenzaprine
Sumatriptan/Zomitriptan (approved by AAP) (L3)
Diphenhydramine (L2)
Ondansetron (L2)
Metoclopramide (L2)
Prednisone (L2)/dexamethasone (L3)
Nerve blocks with lidocaine/bupivacaine (L2)

Hale Lactation Risk Categories

- **L1 SAFEST** – Drug has been taken by many breastfeeding women without evidence of adverse effects in nursing infants OR controlled studies have failed to show evidence of risk.
- **L2 SAFER** – Drug has been studied in a limited number of breastfeeding women without evidence of adverse effects in nursing infants.
- **L3 MODERATELY SAFE** – Studies in breastfeeding have shown evidence for mild non-threatening adverse effects OR there are no studies in breastfeeding for a drug with possible adverse effects.
- **L4 POSSIBLY HAZARDOUS** – Studies have shown evidence for risk to a nursing infant, but in some circumstances the drug may be used during breastfeeding.
- **L5 CONTRAINDICATED** – Studies have shown significant risk to nursing infants. The drug should NOT be used during breastfeeding.

Commonly Used Migraine Treatments during Lactation

Acute

- Acetaminophen (L1)
- Ibuprofen (L1)
- Ketorolac (L2)
- Diclofenac (L2)
- Diphenhydramine (L2)
- Ondansetron (L2)
- Metoclopramide (L2)
- Naproxen (L3)
- Sumatriptan/Zolmitriptan approved by AAP (L3); rizatriptan and eletriptan
- Butalbital/acetaminophen/caffeine (L3)
- Codeine (L4)

Prevention

- Magnesium (L1)
- Riboflavin (L1)
- Amitriptyline/Nortriptyline (L2)
- Venlafaxine (L2)
- Metoprolol/Propranolol (L2)
- Topiramate (L3)
- Botox (L3)

Epocrates Essentials for Apple iOS (Version 5.1) [Mobile application software]. Retrieved from http://www.epocrates.com/mobile/iphone/essentials; Drugs.com, May 17, 2023.

I'm still having periods but now I'm having hot flashes, too, and my migraines are worse. Why and what do I do?

…Now you are in ***perimenopause***,
with:
-Fluctuating estrogen levels
-Falling estrogen levels
-Loss of orderly pattern of estrogen and progesterone secretion
-Irregularity of menstrual cycle

Options in Perimenopause

- Stratified acute attack therapy
- Short term menstrual migraine prevention
- Conventional prevention
- Adjunctive hormonal therapy regimens: contraceptive or hormone replacement

Does her migraine appear to have a hormonal influence?

- Establish her trend during: menses, pregnancy, breakthrough bleeding, uterine ablation
- Determine her hormonal status
- Consider recently FDA approved fezolinetant for vasomotor symptoms, if hormonal therapy is contraindicated
- Review her overall risk factors for vascular events:
  malignancy, osteoporosis, CHD, stroke, hx of thrombosis
- Consider hormonal therapies:
  solely: if only dealing with hormonal influence on HA
  dually: if *non*-hormonally triggered attacks prominent and/or if **no response** to hormonal tx

Offer Hormonal Therapy when….

- Hormonal fluctuations appear to be a major triggering event for migraine
- High risk for colon cancer
- Significant perimenopausal symptoms: hot flashes, mood disorders, insomnia, cognitive changes
- High risk for fracture

How will hormone replacement therapy affect my migraine?

- HRT has a variable influence on migraine:
  - Improvement (45%)
  - Worsening (46%)
  - No change (9%)
- Lowest dose estrogen
- Progesterone if uterus intact

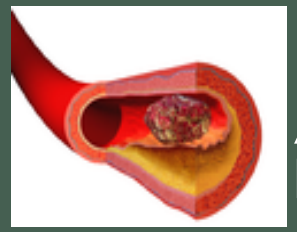
MacGregor EA. Is HRT giving you a headache? *Br Migraine Assoc Newsletter* 1993:19-24.

Tailoring Estrogen Replacement Therapy for Perimenopausal Migraine

- Oral –***not*** recommended
- **Transdermal** 50 mcg/day
  - Climara® or ClimaraPro weekly
  - Estraderm®, Vivelle q3d
  - Compounded drops/gel
  - Aim for a level of 50-70 pg/ml
- Intramuscular -- controversial
- Continuous – ***not*** intermittent dosing

Ensure that adequate estrogen dose is given to avoid endogenous fluctuations

Too high a dose, coupled with endogenous estrogen surges may result in symptoms of estrogen excess



Always consider hypercoagulopathy

Will my migraine get better after menopause?

Occurrence

Postmenopausal women:13.7% had headache

-82% before menopause

-62% migraine without aura

-Remainder tension type headache

-None had migraine with aura

Prognosis

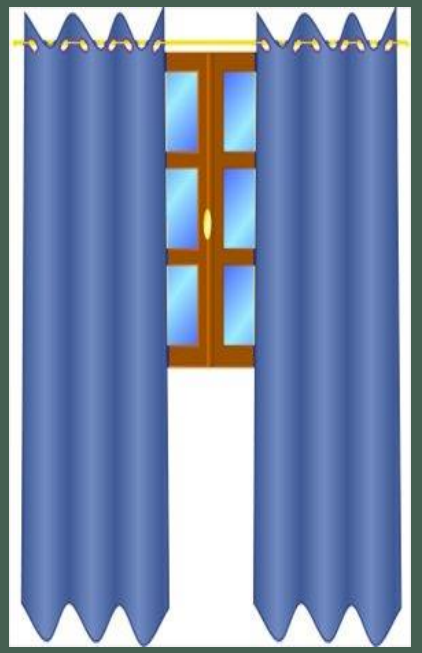
Physiologic menopause 2/3 *improved*

Surgical menopause 2/3 *worsened*

Nerl et al,1993

the "critical" window

- for estrogen benefit, brain animal models
  suggest that estrogen
  initiation at ***perimenopause***
  is necessary to observe
  the benefits of --neuroprotection
  -- cognition
  --in some, migraine quiescence



This may explain the results showing lack of beneficial cardiovascular/neural effect in the WHI study, where the average age of subjects was 63-65 years, well past their menopause

Sherwin 2007, Maki 2007, Suzuki 2007, Zhang 2009

Reassurance from Women's Health Initiative

- No link was found between migraine hx and risk for stroke, MI, and other CVD was found in postmenopausal women
- 71,441 woman between 50-79 years of age, of whom 10.7% had migraine
- Pavlovic et al 2019, found that after 22 yr of longitudinal followup:
- 211 incident strokes in migraine/1943 strokes in women w/out migraine
- Trend continued across composite CVD events – angioplasty, CABG, CAD, DVT, PE

Exacerbation of Migraine on HRTx

Treatment Options

- Switch from one type of estrogen to another (e.g., Premarin, conjugated equine estrogen, most commonly used preWHI, may increase headache)
- Change the dosing regimen; consider combination patch
- Increase or decrease the dosage
- Change the route of administration
- Consider adjunctive therapy, especially CGRP Mabs for prevention
- Cessation of hormonal therapy

Open Label Studies

- Tamoxifen
- Danazol
- Combination of phytoestrogens
- Exception: 60mg soy isoflavones
  100mg dong quai
  50mg black cohash
- Combination showed some reduction in 49 women, but precludes studying single effect

Folk Remedies for Perimenopausal Symptoms

- Bee pollen
  - Combination of "male and female" hormones
    - Dose: 3 Bee pollen pills (500 mg) a day
- Grated nutmeg
  - Mix 1 ounce of grated nutmeg in 1 pint of Jamaican rum
    - Dose: 2 tsp TID
- Cucumber
- Garden Sage
- Motherwort
  - Contains "beneficial" hormones

Approaches to Management of Hormonally Influenced Migraine

- Identify relationship between migraine and hormonal change
  - Thorough history, careful diary
- Reassurance and education
- Pharmacological measures to treat acutely and prevent migraine
- Trigger avoidance
- Overall wellness
  - exercise, balanced diet, smoking cessation, sleep hygiene, hydration, structured emotional and physical support !!
  - Encourage clinical trial participation and pregnancy registries!