10+ Migraine Pearls That May Change Your Practice

Using Old Drugs Well

Alex Crawley, BSP, ACPR
Jackie Myers, BSP

RxFiles Academic Detailing

Presenter Disclosure

- **Faculty:** Alex Crawley
- **Relationships with commercial interests:**
  - **Associate Director of RxFiles Academic Detailing**
  - **Pharmacist at Sturgeon Lake Health Centre**

- **Faculty:** Jackie Myers
- **Relationships with commercial interests:**
  - **Academic Detailer with RxFiles Academic Detailing**
  - **HIV/Addictions Medicine Pharmacist with Saskatchewan Health Authority**

Conflict of Interest

- No industry funding
- RxFiles receives grant from Saskatchewan Ministry of Health through University of Saskatchewan for academic detailing in SK, including a grant specific to detailing on substance use disorders in 2022.
- RxFiles receives revenue from book sales, subscriptions, and conference registrations.

Mitigating Potential Bias

- All RxFiles material has been reviewed by our scientific advisory committee to ensure recommendations are based on evidence accepted to the profession and all scientific research referenced in the materials conforms to generally accepted standards.

Objectives

Migraines: Using Old Drugs Well

Attendees will learn practical tips regarding the primary care management of:

1. Acute Migraines
2. Migraine Prophylaxis
3. Medication Overuse Headache

If time, a brief overview of new CGRP antagonists

Efficacy of standard therapies & combos
(Patients with pain relief at 2 hours, in moderate-to-severe migraine pain)

- Naproxen 500-825mg **45%** vs placebo 28% **NNT=5.8**
- Acetaminophen **52%** vs placebo 32% **NNT=5**
- Ibuprofen 400mg **57%** vs placebo 25% **NNT=3.1**
- Oral triptan, standard dose **57%** vs placebo 32% **NNT=4**
- NSAID + oral triptan **58%** vs placebo 27% **NNT=3.2**
- Oral triptan, high dose **61%** vs placebo 32% **NNT=3.5**
- Acet 1000mg + metoclop 39% vs sumatriptan 100mg 42% (no diff)
- Intranasal triptan, high dose **61%** vs placebo 32% **NNT=3.5**
- Subcut sumatriptan **79%** vs placebo 31% **NNT=2**
- Acet500 + ASA500 + caffeine130 **84%** vs suma 50mg 65% vs placebo **52%** **NNT=3.1**

1. Antiemetics can be used as “boosters”

- Useful beyond just helping with nausea
- Metoclopramide 10mg stat; domperidone 10mg stat
- **Prokinetic agents**: speed up absorption of other simple analgesics
- Expected efficacy: may help an extra 1 in 10 patients (e.g. acetaminophen + metoclopramide as good as triptan alone)

Efficacy of standard therapies & combos
(Patients with pain relief at 2 hours, in moderate-to-severe migraine pain)

- Naproxen 500-825mg **45%** vs placebo 28% **NNT=5.8**
- Acetaminophen **52%** vs placebo 32% **NNT=5**
- Ibuprofen 400mg **57%** vs placebo 25% **NNT=3.1**
- Oral triptan, standard dose **57%** vs placebo 32% **NNT=4**
- NSAID + oral triptan **58%** vs placebo 27% **NNT=3.2**
- Oral triptan, high dose **61%** vs placebo 32% **NNT=3.5**
- Acet 1000mg + metoclop 39% vs sumatriptan 100mg 42% (no diff)
- Intranasal triptan, high dose **61%** vs placebo 32% **NNT=3.5**
- Subcut sumatriptan **79%** vs placebo 31% **NNT=2**
- Acet500 + ASA500 + caffeine130 **84%** vs suma 50mg 65% vs placebo **52%** **NNT=3.1**

2. The highest efficacy triptan is subcutaneous sumatriptan

- Works in up to 80% of patients.
- Useful if vomiting / severe nausea with oral agents as can guarantee absorption.
- Generic TARO product is the easier injection (auto-injector)

https://www.taro.ca/sites/default/files/product-resources/english/TaroSumatriptanEnglishJan2021.pdf

3. Avoid Tylenol #3s for migraines in almost every patient

- Opioids have double the risk of medication overuse headache compared to other agents.
- Caffeine dose is subtherapeutic.
  - ~100mg needed for migraine efficacy; ~15mg in one Tylenol #3 tab
- Acetaminophen dose is often subtherapeutic.
  - Best evidence is for 1000mg of acetaminophen; would need three Tylenol #3 tabs
- Codeine metabolism is unpredictable.
  - ~10% of the population do not adequate activate the codeine into morphine
- But it costs 9 cents a pill, so …

4. Use the low dose of rizatriptan for patients on propranolol.

Propranolol slows rizatriptan metabolism and thus increases levels by ~70%

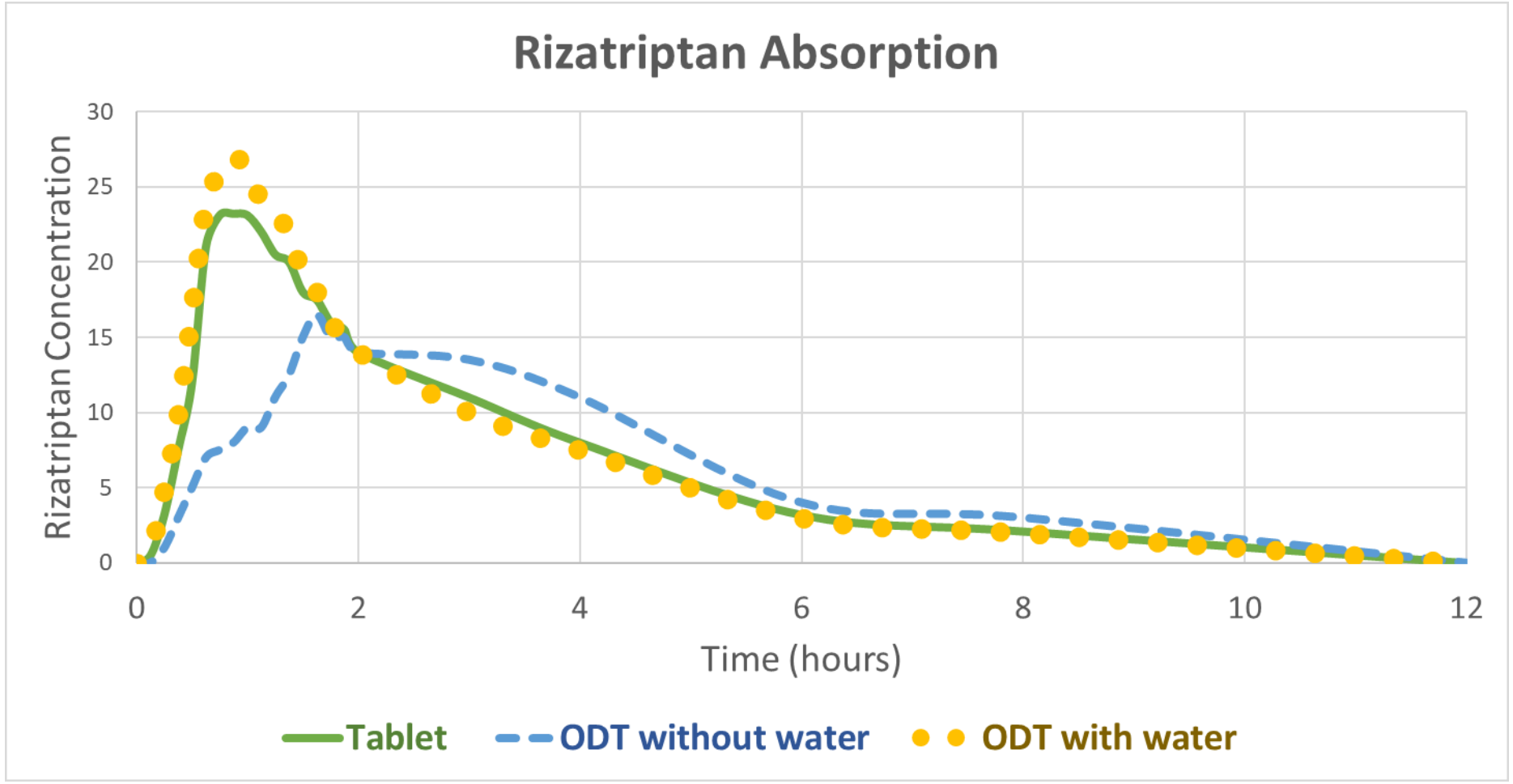
For any patients on propranolol, use rizatriptan 5mg tabs (and not 10mg tabs)

→ or change to a different triptan

→ or change to a different beta blocker

5. Turn “triptan failure” into “triptan success”

- Take triptan at **first sign** of migraine pain.
- **Add an NSAID** to the triptan (or acetaminophen, or metoclopramide)
  - Likely an extra ~20% chance of success with little to no extra side effects
- **Switch triptans**
  - If one triptan fails, switching to a new triptan gives a 25-81% chance of success.
  - Canada 2013 Guidelines: try at least 3 triptans
  - Some experts would say try every single triptan.
- Ensure **adequate absorption** (**oral** vs **ODT** vs **nasal** vs **injectable**)



Swan SK, Alcorn Jr H, Rodgers A, Hustad CM, Ramsey KE, Woll S, Skobieranda F. Pharmacokinetic profile of rizatriptan 10-mg tablet and 10-mg orally disintegrating tablet administered with or without water in healthy subjects: An open-label, randomized, single-dose, 3-period crossover study. The Journal of Clinical Pharmacology. 2006 Feb;46(2):172-8.

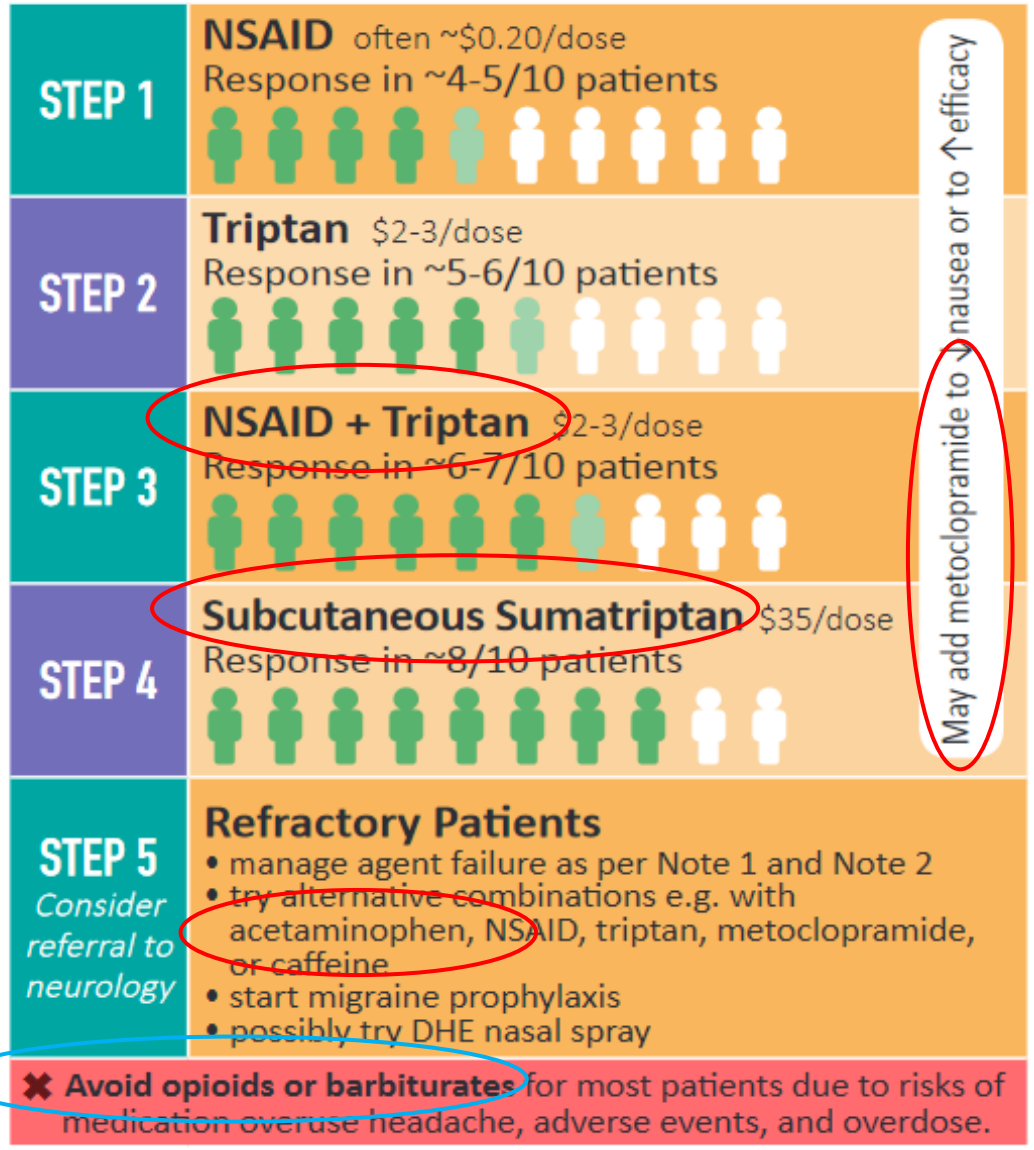
6. Long-acting triptans are also slow-acting triptans.

- For many patients, waiting 1 hour for triptan onset is too long.
- Potentially useful if migraine with very long aura – lots of warning time.
- Potentially useful if fast triptans not tolerated due to nausea

	Drug	Onset	Half-life
FAST	Suma	**Tab**: 30-60min **Subcut**: 10min **Nasal**: 10-15min	~2hrs
FAST	Riza	**Tab/ODT**: 30-60min	2-3hrs
FAST	Zolmi	**Tab/ODT**: 30-60min **Nasal**: 10-15min	2-3hrs
FAST	Almo	**Tab**: 30-60min	3-4hrs
FAST	Ele	**Tab**: 30-60min	~4hrs
LONG	Nara	**Tab**: 1-3 hrs	~6hrs
LONG	Frova	**Tab**: ~2hrs	~25hrs

ACUTE MIGRAINE:
A simplified treatment approach

Response defined as pain relief at 2 hours. Placebo response is ~2-3/10 patients.



7. Taking an NSAID on an empty stomach speeds up absorption.

- e.g. ibuprofen onset ~30 min on empty stomach vs ~60 min with food
- “NSAID with food” perhaps useful if you are a chronic pain patient trying to avoid stomach upset.
  - Less useful if you are a migraine patient looking for quick relief


medSask
YOUR MEDICATION INFORMATION SERVICE

DRUG NEWS

True or False? Nonsteroidal Anti-inflammatory Drugs (NSAIDs) should be taken with food

FALSE: For acute pain when a rapid onset of effect is desired, recommend taking NSAIDs on an empty stomach with a full glass of water. Food delays and may reduce the analgesic effect of

https://medsask.usask.ca/documents/NSAIDS-with-Food.pdf

8. Timolol **eye drops** have emerging evidence for **acute** migraines

- Case reports and one RCT.
  - ↓pain in 82% of patients vs 14% placebo at 20 min
- Too new to be embraced by guidelines
- More RCTs likely to come
- Possible option in those with many contraindications to usual acute drugs.
- **Dose**: 1 drop of 0.5% solution in each eye; may repeat in 10 minutes.
- **Cost**: $1 for a bottle plus dispensing fee

9. Treat at **target dose** for **8-12 weeks** before deciding if prophylaxis is helping.

	Generic/TRADE	Dosing: Initial Dose	Dosing: Target Dose [93]	$/30d (CAD) at target dose
β-BLOCKER	**Propranolol** INDERAL, g 10, 20, 40, 80, 120 mg tab^{S} 60, 80, 120, 160mg LA cap	20mg po BID ↑ weekly	40-**80**mg BID 80-**160**mg LA daily	$18-**26** $40-**58**
β-BLOCKER	**Metoprolol** LOPRESOR, g 25,50,100mg tab; SR 100,200mg	25mg po BID ↑ weekly	50-**100**mg BID 100-**200**mg SR daily	$15-**20** $17-**21**
β-BLOCKER	**Timolol** BLOCADREN, g 5, 10, 20 mg tab^{S}	5mg po BID ↑ weekly	10-**15**mg BID	$32-**43**
TCA	**Amitriptyline** ELAVIL, g 10, 25, 50, 75$^{✗▼}$ mg tab	10-25mg po HS ↑ by 10mg/wk	50-**75**mg HS (100mg if tolerated)	$18-**23** $26
TCA	**Nortriptyline** AVENTYL, g 10, 25mg cap	10-25mg po HS ↑ by 10mg/wk	**50**-75mg HS (100mg if tolerated)	$68-**94** $105
Anticonvulsant	**Topiramate** TOPAMAX, g 25,50$^{✗}$,100, 200mg tab 15, 25mg sprinkle cap	25mg po HS ↑ by 25mg/wk	50mg BID (?100mg HS to ↓AE)	$37
Anticonvulsant	**Divalproex** EPIVAL, g 125, 250, 500mg EC tab	250mg po HS ↑ q1-2wks	500-750mg BID cc (or 250mg AM & 500mg HS to ↓AE)	$65
ACEI/ARB	**Candesartan** ATACAND, g 4, 8, 16, 32mg tab^{S}	8mg po daily ↑ after 1 week	16mg daily	**$17**
ACEI/ARB	**Lisinopril** ZESTRIL, g 5^{S}, 10, 20mg tab	10mg po daily ↑ after 1 week	20mg daily	$18
SNRI	**Venlafaxine** EFFEXOR, g 37.5, 75, 150mg XR cap	37.5mg po daily ↑ q1-2wks	150mg daily	$16
SNRI	**Duloxetine** CYMBALTA, g 30, 60mg cap	30mg daily ↑ after 1-2 wks	60mg daily	$42
CCB	**Flunarizine** SIBELIUM, g 5mg cap ☎▼	5mg po HS ↑ after 1 week	10mg HS	$61
CCB	**Verapamil** ISOPTIN, g 80,120mg IR; 120,180,240^{S}mg SR tab	120mg SR daily with food	240mg SR daily with food	$28
5HT2-Θ	**Pizotifen** SANDOMIGRAN DS 1^{S} mg tab also known as pizotyline	0.5mg po HS ↑ q1-2wks	1.5mg HS	$47

	Generic/TRADE	Dosing: Initial Dose	Dosing: Target Dose [93]	$/30d (CAD) at target dose
Herbal	**Magnesium** oxide ✗ ▼OTC	500mg po daily		**$10**
Herbal	**Magnesium** citrate ✗ ⊗ OTC	300mg po BID		**$12**
Herbal	**Riboflavin** (Vit B_2) ✗ ⊗ OTC	400mg po daily		**$15**
Herbal	**Butterbur** ✗ ⊗ OTC	75mg po BID		$30
Herbal	**Coenzyme Q10** ✗ ⊗ OTC	100mg po TID		$25
anti-CGRP	**Fremanezumab** AJOVY ❄ 225mg syringe ☎	225mg subcut q4wk ***or*** 675mg subcut q12wk		**$630**
anti-CGRP	**Erenumab** AIMOVIG ❄ 70, 140mg pen ✗ ⊗	70-140mg subcut monthly		**$600**
anti-CGRP	**Galcanezumab** EMGALITY ❄ 100,120mg syringe/pen ✗ ⊗	240mg subcut load, then 120mg monthly		**$700**
anti-CGRP	**Rimegepant** NURTEC	75mg po every other day		*USA only*

10. Candesartan is effective for migraine prophylaxis

- **Data for migraine prophylaxis from 2 RCTs:**
  - n=60, 12 wks, candesartan 16mg (**46%** responded) vs placebo (**32%** responded)
  - n=72, 12 wks, candesartan 16mg (**42%** responded) vs propranolol (**40%** responded)
- **New guidelines are jumping on board:**
  - 2020 Va/DOD: ARBs (candesartan or telmisartan) were the **only** migraine prophylactic drugs 'strongly recommended'
  - 2021 American Guidelines: **effective**.

Stovner LJ, et al. A comparative study of candesartan versus propranolol for migraine prophylaxis. Cephalalgia. 2014 Jun;34(7):523-32.
Tronvik E, Stovner LJ, Helde G, Sand T, Bovim G. Prophylactic treatment of migraine with an angiotensin II receptor blocker: RCT. *JAMA.* Jan 1 2003;289(1):65-69.
www.rxfiles.ca/rxfiles/uploads/documents/members/ts-MOH.pdf

10. Candesartan is effective for migraine prophylaxis

- Around **40% of patients** will see their number of migraines per month drop in half.
- Excellent option if also **hypertension**, **post-MI**, **CKD**, etc.
- **Well tolerated** – monitor blood pressure.
  - In trials, up to 1/3 of patients had dizziness at some point, sometimes leading to discontinuation.
- Start at 8mg daily; after 1 week increase to 16mg daily (target dose).

11. Herbal products really do have evidence for migraine prophylaxis.

- **Magnesium**
  - Efficacy in up to 50% of patients (but few trials; **NNT≈5**?)
  - Magnesium oxide 420mg tab (250mg elemental) two tabs daily
  - Magnesium citrate 150mg capsule (150mg elemental) two tabs BID
  - **Watch for**: diarrhea, nausea
  - Magnesium citrate possibly better tolerated (expert opinion)
- **Riboflavin** (Vitamin B_2)
  - Efficacy in up to 50% of patients (but few trials; **NNT≈3**?)
  - Riboflavin 100mg tab, 4 tabs daily (400mg/day)
  - **Watch for**: bright yellow urine

12. Starting prophylaxis can help cure medication overuse headache.

Patients with Medication Overuse Headache

n=120 randomized
n=102 analyzed
80% female
mean age 44 years

52% chronic migraine; 32% episodic migraine + TTH
47% on a triptan (alone or as part of a combo)
mean 25 headache days/month
median 8 migraine days/month

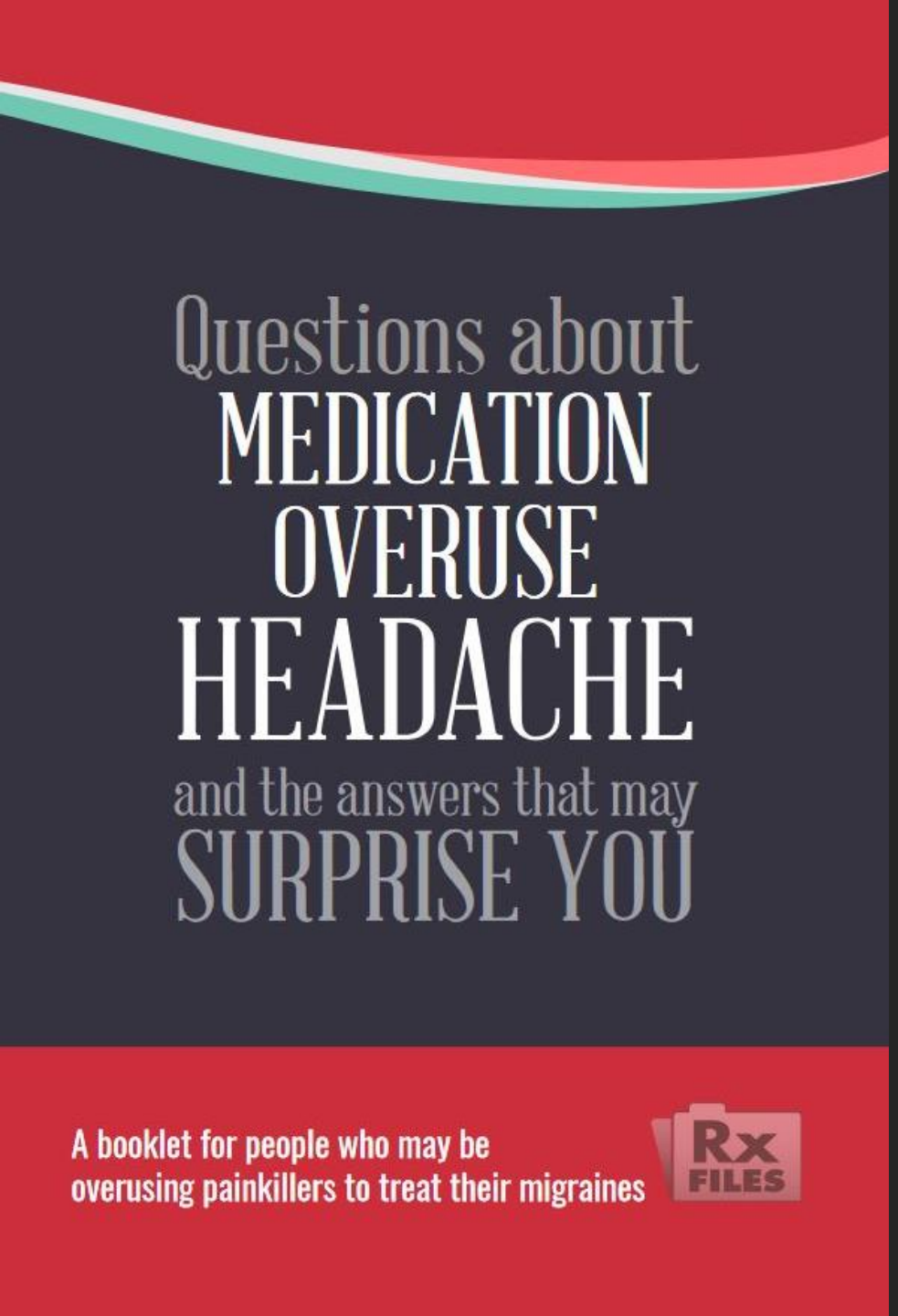
Results after 6 months:

Withdrawal Group	Prevention Group	Withdrawal + Prevention Group
↓ 8.5 headache days per month	↓ 10 headache days per month	↓ 12 headache days per month

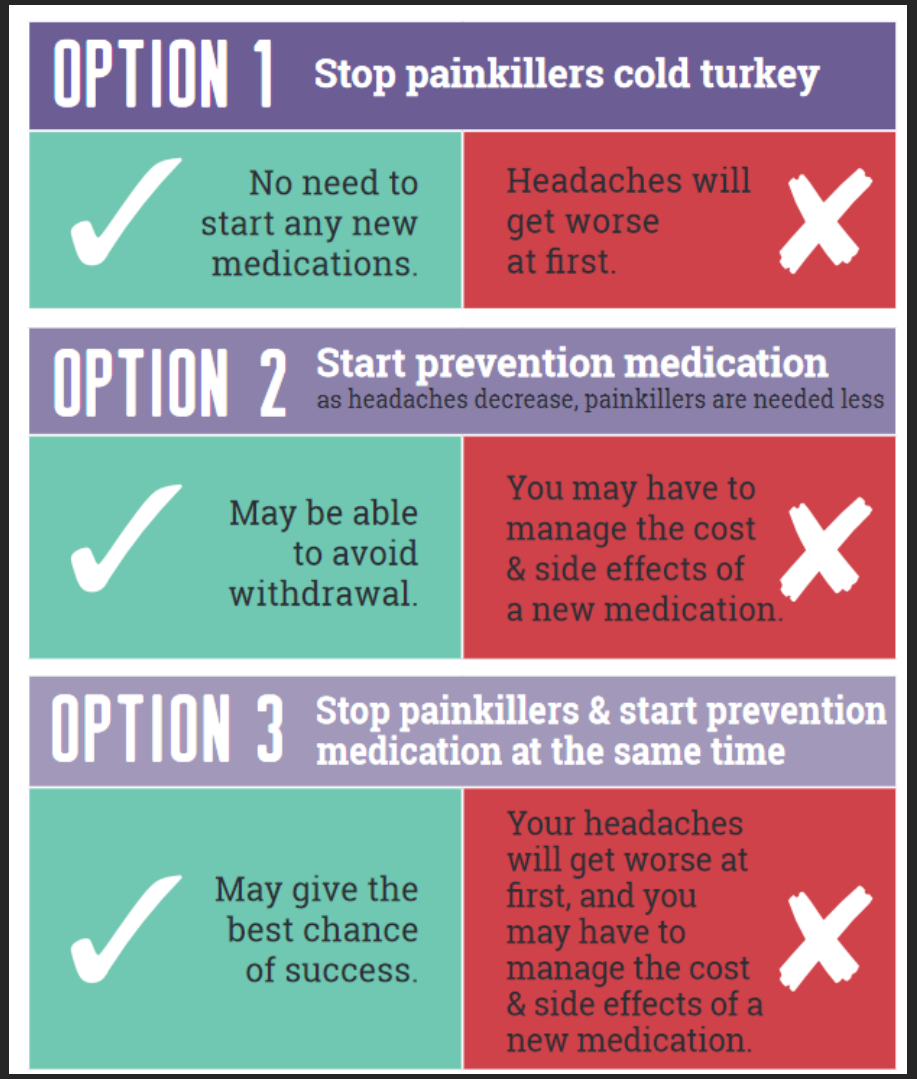
All 3 approaches effective; no statistically significant difference between groups

- Most common prevention therapy started (~50% of pts) was candesartan.
- Limitations include: unblinded; lack of a usual care arm; 15% of patients randomized but not analyzed (i.e. **not** ITT); excluded complex patients (e.g. daily opioid use).

https://www.rxfiles.ca/rxfiles/uploads/documents/members/ts-MOH.pdf



Free to download at www.rxfiles.ca/tools



13. Alex’s favourite headache diary is Migraine Buddy

- It’s free, but they will try hard to sell you a subscription
- Migraine Canada also has an app (but less features)

SUMMARY

- Metoclopramide as a “booster”
- Power of subcutaneous sumatriptan
- Avoid **Tylenol #3**
- **DI**: Propranolol + rizatriptan
- Try at least 3 triptans
- Long-acting triptan = slow-acting triptan
- NSAID on empty stomach in migraines
- Emerging evidence for timolol eye drops
- Prophylaxis: target dose for 8-12 weeks
- Candesartan effective for prophylaxis
- Mg, riboflavin effective for prophylaxis
- Prophylaxis works for medication overuse headache
- Promote headache diaries

BONUS

What about new migraine medications?

2022 Drug Plan Coverage

Selected Biologics for Migraine: Formulary Status & Cost/month												
Province		**BC**	**Alta**	**Sask**	**MB**	**ON**	**QB**	**NB**	**NS**	**PEI**	**NL**	**NIHB**
Fremanezumab **AJOVY**	$630	✖	☎	☎	✖	✖	✖	✖	✖	✖	✖	✖
Erenumab **AIMOVIG**	$600	✖	✖	✖	✖	✖	✖	✖	✖	✖	✖	✖
Galcanezumab **EMGALITY**	$700	✖	✖	✖	✖	✖	✖	✖	✖	✖	✖	✖

✓=full formulary; ✖=not covered; ☎=approval needed

2023 Drug Plan Coverage

Selected Novel Agents for Migraine Prophylaxis: Formulary Status & Cost/month												
Province		**BC**	**Alta**	**Sask**	**MB**	**ON**	**QB**	**NB**	**NS**	**PEI**	**NL**	**NIHB**
Fremanezumab **AJOVY**	$591	☎	☎	☎	✗	✗	☎	☎	☎	☎	☎	☎
Erenumab **AIMOVIG**	$607	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Galcanezumab **EMGALITY**	$608	☎	☎	☎	✗	✗	☎	☎	☎	☎	☎	☎
Eptinezumab **VYEPTI**	$565	✗	☎	☎	✗	✗	☎	☎	☎	☎	☎	☎
Atogepant **QULIPTA**	$630	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗

✓=full formulary; ✗=not covered; ☎=approval needed

Selected Novel Agents for Acute Migraine: Formulary Status & Cost/10 doses												
Province		**BC**	**Alta**	**Sask**	**MB**	**ON**	**QB**	**NB**	**NS**	**PEI**	**NL**	**NIHB**
Ubrogepant **UBRELVY**	$120	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗

✓=full formulary; ✗=not covered; ☎=approval needed

Anti-CGRP

- **Biologics**: CGRP antagonists
  - Fremanezuamb, erenumab, galcanezumab, eptinezumab
  - For migraine prophylaxis
  - Monthly or q12 week options
  - Response in typically around 40% of patients (e.g. **NNT=5**).
  - **AE**: injection site reactions, increased blood pressure
  - Drug coverage requires failure of at least 2 oral agents

- **Small molecules**: CGRP receptor antagonists
  - Atogepant, ubrogepant, rimegepant, zavegepant
  - Some are for migraine prophylaxis, some are for acute migraine, some are for **both**
  - Likely **less effective** than triptans for acute migraine (e.g. **NNT=6-8**), similar to other agents for migraine prophylaxis (e.g. **NNT=3-13**)
  - Well tolerated; none have drug coverage yet

References

- RxFiles Migraine Newsletter (full newsletter also attached to these slides)

  https://www.rxfiles.ca/rxfiles/uploads/documents/members/newsletter-migraine.pdf

Migraines

Spring/Summer 2022

Did you know?

- Metoclopramide and domperidone not only help with the nausea of a migraine attack, they also **enhance analgesia** of acute medications.[6]
- **Candesartan 16mg daily** is now recommended by recent guidelines for migraine prophylaxis.[1,2,3]
- A biologic CGRP-antagonist, subcut **fremanezumab**, is now on EDS for migraine prophylaxis in Saskatchewan and on NIHB for patients who have failed adequate trials of at least 2 oral agents.
- The lowest cost triptan in Saskatchewan is **almotriptan** 12.5mg ($2.35/tab); pill-splitting almotriptan can help reduce cost further for some patients.
- **Propranolol inhibits the metabolism of rizatriptan**. Patients on this combination should only use the 5mg rizatriptan dose (max 10mg in 24hrs) – or switch to a different triptan or beta-blocker.
- During a migraine attack, patients may take **NSAIDs on an empty stomach** to get the fastest possible onset, as food delays NSAID absorption.[8]
- **Orally-disintegrating triptan tablets do not have a faster onset than regular tablets.**[5] However, they may be useful if a patient's nausea is worsened by water.
- Using opioids may **double** the risk of developing medication overuse headache.[11]

TABLE OF CONTENTS

CONNECT WITH US!

www.RxFiles.ca

Migraines are common, with a prevalence of around 10%. Migraines are often undertreated: only ~10% of patients with migraines use a triptan,[4] and only ~30% of patients who might benefit from migraine prophylaxis receive it.[10]

Acute Migraine: Overcoming Medication Failure

Only ~40% of patients with migraines are "very satisfied" with their acute migraine therapy.[4,9]
Fortunately:

- Changing to combination analgesia (e.g. triptan + NSAID) helps ~20% of triptan non-responders.
- Switching triptans helps 25-81% of triptan non-responders (often trial at least 3 triptans).
- Changing to subcutaneous sumatriptan helps ~50% of triptan non-responders.

For more strategies, see our infographic on page 14.

Watch for failure.

Pursue success.

Migraine Prophylaxis: Long Enough at Target Dose

Patients who stop migraine prophylaxis too soon may be missing out on a drug that would have worked well for them. Aim for:

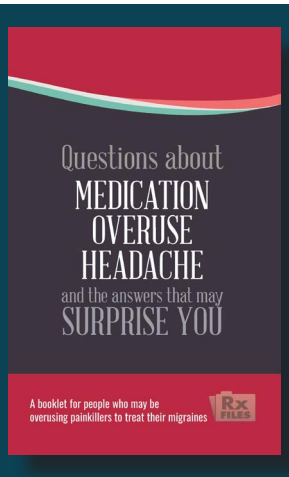
- 8-12 weeks at target dose
- Realistic expectations (e.g. ↓ migraine frequency by 50%)
- A gradual/tolerable dose titration
- Tracking using a headache diary

See our infographic on page 16.

Medication Overuse Headache (MOH) is Treatable

	Monthly Max Amount
Ⓐ triptans or opioids	9 days/month
Ⓑ NSAIDS or acetaminophen	14 days/month
Ⓒ if taking meds from both Ⓐ and Ⓑ	9 days/month (collectively!)

Management of MOH involves stopping or tapering the overused medication(s); initiating migraine prophylaxis can help facilitate this. Help patients pick the best strategy using our infographic on page 15 and our patient booklet.



If you participated in an academic detailing visit, please scan to complete our post-visit evaluation.

CGRP=calcitonin gene–related peptide **MOH**=medication overuse headache

Headache diary 3 months

reproduced with permission of Migraine Canada

DOWNLOAD on www.migrainecanada.org
Want an APP? migrainetracker.ca
Filling a diary is the best way to make the right decisions about your migraines.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Headache **0 1 2 3***																															
Period																															
Preventive Meds																															
Tx:																															
Tx:																															
Tx:																															
Effect of medication																															

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Headache **0 1 2 3***																															
Period																															
Preventive Meds																															
Tx:																															
Tx:																															
Tx:																															
Effect of medication																															

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Headache **0 1 2 3***																															
Period																															
Preventive Meds																															
Tx:																															
Tx:																															
Tx:																															
Effect of medication																															

INSTRUCTIONS: HOW TO FILL MY HEADACHE DIARY?
Write down all your headache according to their severity (1 = mild, 2= moderate, 3 = severe).
ADD a star * if you missed work or needed bed rest. The free line can be used to track anything relevant.
Write the name(s) of preventive meds and indicate the days when you change the doses
Write the names of your acute medications in the Tx squares on the left. Put a check if you used them for each day.
Write codes for efficacy: F=failure, P=partial benefit, S=success, R=recurrence (attacks comes back the same day).

Migraine: Overview CHS 2012 & 2013, AAN 2012, TOP 2016, AHS 2019 & 2021, NICE 2021

A Crawley BSP, M Jin PharmD © www.RxFiles.ca Apr 2022

Background Information

- **Migraine Prevalence**: peaks in midlife, ~10% of Canadians, with females 3-4x more often than males; 5-10% of children & adolescents.
- **Migraine Aura**: flashing lights, blind spots, numbness/tingling in face/extremities, disturbed smell, or difficulty speaking. Experienced by 1 in 3 migraine patients.
- **Medication Overuse Headache**: accounts for ≤50% of pts with chronic migraine.

Identify and address migraine triggers.[45,46]

e.g. stress, meal-skipping (consider food insecurity), foods (e.g. chocolate or soft cheese), alcohol (especially red wine), caffeine withdrawal, dehydration, menstruation, lights/sunlight, erratic sleep, shift work, perfume/odour, obesity, change in barometric pressure.

Red Flag Signs and Symptoms for Acute Headache see also 💻 Online Extras

Emergency (call for ambulance)	Urgent (send for referral)
Worst headache; impairment of speech, sensation, strength, or consciousness; fever or neck stiffness; thunderclap headache (severe peak intensity in seconds to minutes); eye sx (acute angle-closure glaucoma: non-reactive & mid-dilated pupil, red eye, etc.); head trauma.	First ever headache; headache with exercise or sex; new headache if age >50yrs; HIV, cancer, Lyme dx, or pregnancy; papilledema; older adult with cognitive changes.

Acute Migraine: Approach to Therapy

Triptan NNT=2-6 (see: *Which Triptan?* next pg) **max 9 days/month** and/or **NSAID** NNT=3-7 e.g. ibuprofen **max 14 days/month** ± **Antiemetic** e.g. metoclopramide

If ≥3-6 headache days/month, offer prophylaxis

- Unless otherwise stated, **NNT** for acute migraine refers to response (↓ pain) at 2hrs vs placebo.[CHS'13]
- Antiemetics can enhance the efficacy of other agents and may be useful even in the absence of nausea or vomiting.
- Simple analgesia, e.g. NSAIDs alone,[81,82] acetaminophen alone,[83] or acetaminophen + metoclopramide,[84] can be reasonable (especially in milder migraines).[80]
- Ergots (e.g. DHE) are an alternative to triptans, but typically not favoured due to ↑AE and ↓efficacy.
- Failure of standard therapies, or **CI** or **DI**: consider oral acetaminophen or timolol eye drops; consider prophylaxis.
- **Last line**: opioid or butorphanol combinations; reserve due to high risk of tolerance / overuse / dependence.[55]

Special Populations in Acute Migraine

Pediatrics	Use a calendar to identify triggers; consider **ibuprofen** or **acetaminophen**. **Almotriptan** indicated in Canada age ≥12yrs; **rizatriptan** indicated in 🇺🇸 USA age ≥6yrs. (Some evidence also for sumatriptan ≥12yrs).[63]
Pregnancy	Consider **acetaminophen**, **metoclopramide**, **ibuprofen** (2nd trimester only), **sumatriptan** (last resort).
Lactation	Consider **acetaminophen**, **ibuprofen/naproxen**, **metoclopramide**, **sumatriptan**.
Menstrual Migraine	Often ↑ severity/duration and may be harder to treat.[77] May consider pre-emptive **NSAID** (e.g. naproxen 500mg BID) or **long-acting triptan** (nara 1mg BID ☎▼ or frova 2.5mg BID ✗ ⊗)[50] or **estradiol gel** 1.5mg/day, starting ~2 days before menstruation & continuing x ~6 days.[62] Consider daily migraine prophylaxis or CHCs.

Clinical Pearls for Acute Migraine

- **For maximum effectiveness**, take acute medications ASAP (e.g. within 30 min of mild pain).
- **Triptan dosing**: if needing repeat dosing over 24hr, taking the max dose *once* is more effective than a low dose *twice*.
- **Ensure an adequate triptan trial**: try a triptan over 3 attacks, with re-dosing if needed, and/or ↑dose. If still failure, try ≥2 other triptans. See *Which Triptan?* on next page for options.
- **Combination therapy**: more effective than monotherapy (e.g. triptan + NSAID **NNT≈10** vs triptan alone),[24] but also consider potential for AE. Max 9 days/month to prevent MOH.
- **Formulation considerations**: onset of tablet and **ODT** formulations are similar, but **ODT** can be convenient & discrete. **ODT** also useful if water exacerbates nausea. Consider subcut or nasal spray formulations if vomiting is preventing absorption, or if faster relief is desired.
- **Cost considerations**: large variance in cost between triptans; also higher doses can sometimes be lower cost than low doses (e.g. almotriptan 12.5mg tab ↓ cost vs 6.25mg tab).
- **Watch for drug interactions**: especially triptans + ergots; rizatriptan + propranolol.
  Note: risk of serotonin syndrome with triptans, even if triptan + SSRI, is very low (<0.03%).[29]

Medication Overuse Headache (MOH)

MOH: escalating headache frequency, ↑acute med use, ↓efficacy of acute meds.
Prevention of MOH: limit to ≤9 triptan, ≤9 opioid, ≤9 ergot, ≤14 NSAID, ≤14 acetaminophen days/month. With combos (e.g. triptan + NSAID), limit to ≤9 days per month (collectively).
Management of MOH: start prophylaxis &/or withdraw the offending medication.[57] Consider bridge therapy with alternative analgesics: e.g. naproxen,[58] DHE,[59] prednisone,[60] antiemetics.

Migraine Prophylaxis: Approach to Therapy

First Line	About half of patients will respond (↓attacks by 50%) to a beta-blocker, TCA, or topiramate. **Beta-blocker**: esp. propranolol (target 80-**160**mg/day) or metoprolol (target 100-**200**mg/day). **Amitriptyline**: typical target 50-**75**mg HS. **Topiramate**: typical target **100**mg/day (200mg/day studied, but ↑AE and no extra benefit).[65] **Candesartan**: target 16mg/day;[89] well tolerated; likely ↓response vs other first-line agents.
Second Line	**Magnesium** or **riboflavin**: probably effective and few AE, but also ↓ effect size. **CGRP antagonists** (e.g. **fremanezumab**): effective, but reserved due to ↑cost and ↓safety data. **Venlafaxine**: some evidence for benefit, but studies are small; duloxetine alternative to ↓AE. **Nortriptyline**: less studied than amitriptyline, but alternative if ↑AE with amitriptyline. **Flunarizine**: likely effective, but sedating; **verapamil** an alternative but limited data. **Divalproex**: effective, but usually not as well-tolerated as topiramate, & teratogenic.
Third Line	Some evidence for **lisinopril** or **telmisartan**, and alternative **beta-blockers** e.g. bisoprolol.[66-68] **Gabapentin**: evidence for benefit is conflicting; may consider if other comorbidities; target ≥1200mg/day. **Pizotifen**: effective, but ↑AE e.g. weight gain, sedation. **Butterbur**: effective, but quality control issues (e.g. toxic pyrrolizidine alkaloids) may limit use. **Coenzyme Q10**, or **melatonin**: weak evidence, but few AE.

Special Populations in Migraine Prophylaxis

Pediatrics	Most evidence is in kids ≥12yrs; consider **propranolol**, **flunarizine**, ?**amitriptyline**, ?**topiramate**. (**CHAMP**: amitriptyline (1mg/kg/day) or topiramate (2mg/kg/day) ineffective in kids aged 8-17yrs.[69])
Pregnancy	Stop valproate, topiramate, ACEI/ARB. Consider **magnesium**, **propran-/metoprolol**, **ami-/nortriptyline.**
Lactation	Consider **magnesium**, **oral timolol**, **verapamil**, possibly **gabapentin**.

Clinical Pearls for Migraine Prophylaxis

Offer prophylaxis if any one of:	• **≥3-6 headache days/month** • **medication overuse headache** • migraines **severe enough to ↓ quality of life** • attacks **fail to respond** to acute treatment (or **CI** or **DI**).
Goals of prophylaxis therapy:	• ↓ by ≥50% migraine severity or frequency • prevent Medication Overuse Headache (MOH) *Educate patients on realistic expectations.*

- **Start with monotherapy**, at a low dose to minimize AE, and titrate up. Identify & avoid triggers.
- **Increase the prophylaxis dose q1-2wks** until target dose reached, or AE intolerable & persist, or medication becomes effective (whichever comes first). Benefits often take 1-2 months to emerge.
- **Adverse effects typically ↓** within 3-10 days; see RxFiles Anticholinergics for AE management tips.
- **Ensure an adequate prophylaxis trial**: at least 8-12 weeks at target dose (as tolerated).
- **If initial therapy ineffective**, switch agents. If partially effective, usually add an additional first-line agent.
- If prophylaxis therapy is successful, **may consider tapering** after 9-12 months in select pts: e.g. in **teens** or **post-menopausal**. (In one study of teens, ~40% no longer had headaches 10yrs later, especially if no migraine family hx.[61]) Often continue indefinitely in severe cases.
- **Selecting an agent**: individualize; consider comorbidities & AE profile.
  - → e.g. **anxiety/depression/chronic pain**: amitriptyline, nortriptyline, venlafaxine, or duloxetine
  - → e.g. **insomnia**: amitriptyline; **smoking cessation**: nortriptyline
  - → e.g. **hypertension**: candesartan, beta-blocker, or verapamil (or possibly lisinopril or telmisartan)
  - → e.g. **weight loss a strong consideration**: topiramate
- **In some ♀**, long cycle continuous CHC birth control can help ↓migraines but 7x stroke risk if smoking + CHC + aura.[24]

AE=adverse effect **CI**=contraindications **DHE**=dihydroergotamine **DI**=drug interactions **HA**=headache **MOH**=medication overuse headache **NNT**=number needed to treat **CHC**=combined hormonal contraceptive **ODT**=orally disintegrating tab

MIGRAINE: Acute Therapy

L Regier BSP BA, B Jensen BSP, S Downey BSP, A Crawley BSP © www.RxFiles.ca Apr 2022

Generic/TRADE	Usual Dose & MAX	$/6 doses	ADVERSE EVENTS AE / CONTRAINDICATIONS CI / DRUG INTERACTIONS DI / COMMENTS

Triptans: 1st line for **moderate & severe attacks.** Selective 5HT-1 receptor agonists; 2hr response: **NNT=2-6.**[29] ≤40% of all attacks & 25% of all patients do not respond;[74] high recurrence rate (~40% @24hr **IMITREX**). Typically take at earliest onset of migraine pain; taking during aura phase may be too early for some. **Frequent triptan use e.g. >9d/month can cause medication overuse headache** (some suggest 10-18 doses/month is OK; NIHB ▼ max: 12/month; lack of data).[75]

FAST-Acting Triptans

	Usual Dose & MAX	$/6 doses	ADVERSE EVENTS AE / CONTRAINDICATIONS CI / DRUG INTERACTIONS DI / COMMENTS
Sumatriptan IMITREX 25, 50, 100mg DF tab, g ☎▼ 5, 20mg nasal spray ☎▼ 6mg/0.5mL subcut inj ☎▼ **SUVEXX** USA: TREXIMET suma 85mg/naproxen Na+ 500mg tab ✗ ⊗	**Tab:** 50-100mg po; may rpt in 2hr. MAX: 200mg/24hr. **Nasal:** 5mg or 20mg in one nostril; may rpt in 2hr. MAX: 40mg/24hr. **Subcut:** 6mg subcut, may rpt in 1hr; MAX: 12mg/24hr.	$27-28 $117-120 $250	
Rizatriptan MAXALT 5, 10mg tab, g ☎▼ 5, 10mg **ODT wafer**, g ☎▼	**Tab/ODT:** 5mg-10mg po; may rpt in 2hr. MAX: 20mg/24hr. **USA:** ✓kids ≥ 6yrs.	$34	
Zolmitriptan ZOMIG 2.5mg tab, g ☎▼ 2.5mg **RAPIMELT**, g tab ☎▼ 2.5 ✗▼, 5mg nasal spray ☎▼	**Tab/ODT:** 1.25-2.5mg po; may rpt in 2hr; MAX: 10mg/24hr **Nasal:** 2.5-5mg in one nostril; may rpt in 2hr; MAX: 10mg/24hr	$22-33 $207	
Almotriptan AXERT 6.25, 12.5mg tab, g ☎▼	**Tab:** 6.25-12.5mg po; may rpt in 2hr MAX: 25mg/24hr. split 12.5mg tabs = $12	$57-25	
Eletriptan RELPAX 20, 40mg tab, g ✗ ⊗	**Tab:** 20-40mg po; may repeat in 2hr; MAX: 80mg/24hr.	$80	

Drug		Onset	Half-life	Renal dx / CrCl:	Liver dx
FAST	Suma	**Tab**: 30-60min **Subcut**: 10min **Nasal**: 10-15min	~2hrs	no dose change	**Child-Pugh A or B**: 50mg po **Child-Pugh C**: avoid
FAST	Riza	**Tab/ODT**: 30-60min	2-3hrs	**Dialysis**: 5mg	**Child-Pugh B**: 5mg **Child-Pugh C**: avoid
FAST	Zolmi	**Tab/ODT**: 30-60min **Nasal**: 10-15min	2-3hrs	no dose change	**Child-Pugh B or C**: 1.25mg *Tab preferred vs ODT/nasal*
FAST	Almo	**Tab**: 30-60min	3-4hrs	**≤30mL/min**: 6.25mg	**Child-Pugh A or B**: 6.25mg **Child-Pugh C**: avoid
FAST	Ele	**Tab**: 30-60min	~4hrs	no dose change	**Child-Pugh C**: avoid
LONG	Nara	**Tab**: 1-3 hrs	~6hrs	**15-60mL/min**: 1mg **<15mL/min**: avoid	**Child-Pugh A or B**: 1mg **Child-Pugh C**: avoid
LONG	Frova	**Tab**: ~2hrs	~25hrs	no dose change	**Child-Pugh C**: avoid

Which triptan is best for my patient?

- **Fastest relief**: 10-15min for any subcut or nasal formulation; however, these have ↑ **cost**.
- **Best efficacy at 2hr**: likely subcut suma (**NNT=2** at 2hr vs **NNT=3** for oral/nasal suma).[22] [Lowest efficacy at 2hr: nara or frova, due to slow onset.]
- **Best tolerability**: the slow onset of nara or frova results in ↓ nausea and other adverse effects.
- **Best if long-lasting attacks:** nara or frova (long $t_{1/2}$).
- **Best for privacy:** any **ODT** since can take without H_2O.
- **↓ cost**: almo po, suma po, zolmi po, riza po.
- **Useful if vomiting**: any subcut or nasal option, or add antiemetic e.g. metoclopramide.

LONG-Act.

	Usual Dose & MAX	$/6 doses	ADVERSE EVENTS AE / CONTRAINDICATIONS CI / DRUG INTERACTIONS DI / COMMENTS
Naratriptan AMERGE 1, 2.5mg tab, g ☎▼	**Tab:** 1mg or 2.5mg po; may rpt in 4hr; MAX: 5mg/24hr.	$92-51	
Frovatriptan FROVA 2.5mg tab, g ✗ ⊗	**Tab:** 2.5mg po; may repeat in 4hr; MAX: 5mg/24hr.	$97	

- **AE**: **nausea**, facial flushing, tingling, paresthesia; dizziness <10%, fatigue, somnolence, **chest discomfort or tightness ± palpitations** <7% but actual CV events extremely rare;[65] **serotonin syndrome** (very rare). Coronary vasospasm potential: still greatest concern; no agent safer;[8] ♀ with aura ↑risk ⇨ patient selection & counselling important! **Nasal sprays**: poor taste. **Subcut injection**: injection site reactions; overall **NNH=5**.[75]
- **CI**: CV or cerebrovascular dx (risk of MI ~1/5,000,000 migraine attacks treated),[2,17] uncontrolled HTN, PVD, hemiplegic or basilar migraine. **Caution**: ↑CV risk: e.g. ♂ >40yr & ♀ >50yr; **smoker**; ?diabetes, ?sulpha allergy for almo/ele/nara/suma; **ODT**s contain aspartame → caution in PKU pts.
- **DI**: **Do not use within 24hr** of DHE, other ergots, or other triptans (risk of additive vasoconstriction/ coronary vasospasm), MAOIs. **Caution**: multiple serotonergic meds; zolmi: max 5mg/24hr with cimetidine, ciprofloxacin, fluvoxamine; riza: max 10mg/24hr with propranolol. Ele, almo: CYP3A4.
- **M**: Baseline cardiac evaluation/ECG recommended for ♂ >40yr & ♀ >50yr; possible overuse or rebound headache (e.g. ≥10 per month).

ERGOT

	Usual Dose & MAX	$/6 doses	ADVERSE EVENTS AE / CONTRAINDICATIONS CI / DRUG INTERACTIONS DI / COMMENTS
Dihydroergotamine =DHE **MIGRANAL, g** 1mg/ml **injectable** 4mg/ml **nasal** spray = 0.5mg / spray	**Inj**: 0.5-1mg q1hr SC, IM or IV; may rpt q1hr; MAX: 3mg/24hr (6mg/wk). **Nasal**: 1 spray into each nostril stat; may rpt q15min; MAX: 6 spray/24hr (8 sprays/wk) prime pump x4	$51-92 $65 (4 sprays)	2nd-line: **↓ efficacy & ↑ nausea vs triptans.**[36] **Antiemetic recommended**, (e.g. domperidone or **metoclopramide**, ?aprepitant if in-patient)

- **AE**: **nausea** (↑risk vs triptans, consider antiemetic), tingling, paresthesia, drowsiness, dizziness, **chest discomfort** (↓risk vs triptans), diarrhea, muscle cramp, **serotonin syndrome** (very rare). May cause/worsen Raynaud's. Nasal spray: rhinitis, taste disturbance, but ↓ nausea.
- **CI**: CV or cerebrovascular dx, uncontrolled HTN, PVD, hemiplegic or basilar migraine. **Caution**: ↑CV risk: e.g. ♂ >40yr & ♀ >50yr; **smoker**; ?diabetes, þ-porphyria concern. Low risk of medication-overuse headaches.
- **DI**: **Do not use within 12hr** of triptans (24hrs for nara or frova) → risk of additive vasoconstriction/ coronary vasospasm.[6] **Caution**: multiple serotonergic meds (↑serotonin syndrome); **↑Toxicity** (e.g. severe ischemia) of ergot preps with potent CYP 3A4 inhibitors: **clarithromycin, erythromycin, propranolol, protease inhibitors & itra-, posa- & vori-conazole.**
- **M**: Baseline cardiac evaluation/ECG recommended for ♂ >40yr & ♀ >50yr.

Ergots vs Triptans

Intranasal DHE: effective & ↓cost, but inferior to triptans (e.g. 41% DHE vs 53% suma).[25]
Subcut DHE: ?similar profile to nara: slow onset / consider for long-lasting attacks.[7,24]
IV DHE: useful for refractory/overuse headaches, but ↑↑ nausea.[23,32]

- Non-selective 5HT agonist (also α, β, & dopamine).

Other Agents

NSAIDs: Treatment of **mild-moderate** attacks; **NNT=3-7.**[2] Useful also for tension-type headache. **Combo NSAID + triptan** useful (~60% resolution with combo vs ~50% with triptan, & no change in AE).[27,34] Ibuprofen effective in children.[5]

	Usual Dose & MAX	$/6 doses	ADVERSE EVENTS AE / CONTRAINDICATIONS CI / DRUG INTERACTIONS DI / COMMENTS
NSAIDs P1,2P3 L			
Ibuprofen L **ADVIL**	400-800mg q4-6h; MAX 3.2g/24hr OTC	$3	
Naproxen Na+ L **ANAPROX, ALEVE** OTC	550-660mg q12h; MAX 1.5g/24hr ✗ ▼	$7	
ASA L **ASPIRIN**	975mg q4-6h; MAX 4g/24hr OTC ✗ ▼	$3	
ASA/caffeine ANACIN	325/32mg; 3 tabs stat OTC ✗ ⊗	$3	
Naproxen base NAPROSYN	500mg tab or suppository q12h; MAX 1.5g/24hr	$4	
Diclofenac K+ L **CAMBIA**	50mg powder in 30-60mL of H_2O stat ✗ ⊗	$81	
Acetaminophen TYLENOL PL	**Tab**: 1000mg po q4hr; MAX 4g/24hr	$3 ▼ OTC	• Very well-tolerated, but not always effective **NNT=5**; may combine with metoclopramide / NSAIDs.[28] OK in children & adolescents.

- **AE**: Well-tolerated. GI irritation/upset; GI bleed (with chronic use), rash, dizziness, fatigue; acute kidney injury especially if CrCl < 30mL/min.
- **CI**: hypersensitivity (e.g. anaphylaxis, bronchospasm, nasal polyps). **Caution**: CV/renal dx; ↑GI ulcer risk
- **DI**: **↑bleeding** with **anticoagulants/antiplatelets.** May blunt effect of antihypertensives. May displace valproate & older sulfonylureas so ↑ tox, but usually insignificant.
- **M**: **Overuse** (i.e. **>14 days**/mo) **can lead to rebound headache or medication overuse headache.**
- **Which NSAID?** Regular tabs (e.g. ibuprofen, ASA) well-studied and useful. **Fast-acting options**: e.g. naproxen Na+ (not naproxen base), effervescent ASA, ibuprofen liquid gel, diclofenac K+: often 10-20 min quicker onset;[97] this may provide extra benefit to ~1 in 16 patients.[64] Suppository an option if vomiting. **Avoid** enteric-coated or slow-release tabs (too slow). **Avoid** taking NSAIDs with food in acute migraine (slows absorption).

Anti-Emetics. Useful in combo with analgesics for **migraine-induced nausea**, or to **↓ nausea AE of tx**, or to **↑ analgesia efficacy** (e.g. IV metoclopramide **NNT=4** to ↓ pain @<1hr; dexamethasone **NNT=10** to ↓ recurrence @<72hr).[30,31]

DRUG:	metoclopramide MAXERAN	domperidone MOTILIUM [47]	dexamethasone	prochlorperazine STEMETIL [43]	trimebutine MODULON	haloperidol HALDOL	dimenhydrinate GRAVOL, OTC
DOSE:	5-10mg po (10-20mg SC/IV) TID	10mg po;[2] max 40mg/day	4-8mg po (10mg IV) once	10mg po or pr;[2] max 40mg/day	200mg po once.[33] ✗ ⊗	0.5-2mg (5mg IV) q6hr	50mg po (25mg IV) q4-6hr (↓ akathisia w/ MAXERAN)

	Usual Dose & MAX	$/6 doses	ADVERSE EVENTS AE / CONTRAINDICATIONS CI / DRUG INTERACTIONS DI / COMMENTS
Timolol 0.5% eye drops PL	1 drop in each eye; may rpt in 10 min	$11	• **Off-label**; supported by one RCT (↓pain in 82% of pts vs 14% placebo **NNT=2** at 20 min) and case reports;[37,38] very well tolerated and inexpensive.
Lasmiditan REYVOW PL	**Tab**: 50-200mg po; MAX: 1 dose/day	*USA only*	• Selective 5-HT_{1F} agonist; **NNT=6** for 200mg;[42] OK if CV dx; **AE**: dizzy, drowsy, fatigue, paresthesia, ↓HR, caution: alcohol / driving within 8hrs of taking.
Ubrogepant UBRELVY PL	**Tab**: 50-100mg po; may rpt in 2hr	*USA only*	• CGRP receptor antagonists for adult acute migraine; likely less effective than triptans (**NNT=10** rimegepant 75mg; **NNT=11** ubrogepant 100mg, vs placebo).[36] OK if CV disease,[41] & ↓ risk of medication-overuse headache. **AE**: Well-tolerated. nausea, somnolence. **DI**: 3A4 e.g. CBZ, phenytoin, St. John's Wort.
Rimegepant NURTEC PL	**ODT**: 75mg po; MAX: 75mg/day	*USA only*	
Butorphanol 10mg/ml **nasal** spray ✗ ⊗ PL	**Spray**: 1 spray in one nostril; may rpt in 3-5hr; MAX: 16 sprays/24hr prime pump x4	$84 (15 sprays)	• Mixed opioid agonist-antagonist; reserve for rescue treatment or when other treatments ineffective or contraindicated. 1 spray = 1mg. • **AE**: drowsy, nausea/vomiting, nasal irritation, dependency potential. **DI**: CNS depressants, alcohol. Can precipitate withdrawal if on other opioids.
Opioids see Choosing Wisely for cautions e.g. hydromorphone 1-2mg po q6hr $11; morphine 5-10mg po q6hr $11 e.g. **TYLENOL #3** acetaminophen 300mg + codeine 30mg + caffeine 15mg po q6hr $11	PL		• **Avoid** opioids in migraine: high risk of overuse, rebound headache, and dependence → especially with caffeine combos. May be reserved for rescue treatment, or last resort when other agents are ineffective/contraindicated. Short-term use only. May mask pain without affecting pathophysiology. • **AE**: drowsy, dysphoria, nausea, constipation (esp. with codeine). May ↑ risk of chronic HA. **DI**: CNS depressants, alcohol.
Butalbital combos e.g. **FIORINAL** butalbital 50mg + ASA 330mg + caffeine 40mg po q6hr $24	PL		• **Not recommended**: limited evidence that butalbital is effective; can lead to dependence & medication overuse headache.

Migraine headache: consider if recurrent severe disabling headache assoc. with nausea & sensitivity to light & normal neuro exam. Characteristically unilateral[>60%], ?asymmetrical, pulsating, builds up over min-hours, aggravated by routine physical activity. **O_2** x15min; **NNT=8.**[44]

MIGRAINE: Prophylaxis Therapy

most agents ↓ # of days &/or frequency of attacks +/- intensity

L Regier BSP, B Jensen BSP, S Downey BSP © www.RxFiles.ca Apr 2022

	Generic/TRADE	Dosing: Initial Dose	Dosing: Target Dose [93]	$/30d (CAN) at target dose	ADVERSE EVENTS AE / CONTRAINDICATIONS CI / DRUG INTERACTIONS DI / MONITORING M	Comments: Allow 8-12 weeks at target dose for benefit!
β-BLOCKER	**Propranolol** INDERAL, g 10, 20, 40, 80, 120 mg tabς 60, 80, 120, 160mg LA cap	20mg po BID ↑ weekly	40-**80**mg BID 80-**160**mg LA daily	$18-**26** $40-**58**	See also RxFiles: Beta-Blockers. • AE: fatigue, exercise intolerance, ↓HR, ↓BP, coldness of extremities, impotence, ?insomnia, vivid dreams (esp. propranolol). Can mask hypoglycemia symptoms in diabetes. • CI: heart block, decompensated heart failure, severe peripheral vascular dx, uncontrolled asthma (if well-controlled asthma, metoprolol OK to use).[79] • DI: CCBs, clonidine, cimetidine, digoxin, amiodarone. Propranolol ↑ levels of rizatriptan (use 5mg rizatriptan tabs & max 10mg/day).	• Response in 40-80% of pts. Useful if HTN, angina, etc. • Studied, but less data: **nadolol** 80-160mg daily; **atenolol** 100mg daily, **bisoprolol** 5-10mg daily. • Slowly titrating dose helps improve tolerability. • If no response, may switch to alternative β-blocker at equivalent dose (see Online Extras). Otherwise, taper if stopping to prevent tachycardia, etc.
	Metoprolol LOPRESOR, g 25,50,100mg tab; SR 100,200mg	25mg po BID ↑ weekly	50-**100**mg BID 100-**200**mg SR daily	$15-**20** $17-**21**		
	Timolol BLOCADREN, g 5, 10, 20 mg tabς	5mg po BID ↑ weekly	10-**15**mg BID	$32-**43**		
TCA	**Amitriptyline** ELAVIL, g 10, 25, 50, 75✗▼ mg tab	10-25mg po HS ↑ by 10mg/wk	50-**75**mg HS (100mg if tolerated)	$18-**23** $26	• AE: Anticholinergic (e.g. dry mouth, constipation), dizzy, drowsy, fatigue, postural hypotension, ↑weight (e.g. 3kg). Nortriptyline fewer AE than amitriptyline. • CI: severe cardiac, kidney, liver, prostate, thyroid dx; glaucoma; seizures. • DI: MAOI (CI within 14 days), cisapride (CI), clonidine, SSRIs, CNS depressants.	• Response in 40-50% of pts. Taper if discontinuing. • Useful if anxiety, depression, insomnia, chronic pain. • **Nortriptyline** less evidence than amitriptyline & ↑cost, but typically ↓AE and ✓smoking cessation. •
	Nortriptyline AVENTYL, g 10, 25mg cap	10-25mg po HS ↑ by 10mg/wk	**50**-75mg HS (100mg if tolerated)	$68-**94** $105		
Anticonvulsant	**Topiramate** TOPAMAX, g 25,50✗,100, 200mg tab 15, 25mg sprinkle cap	25mg po HS ↑ by 25mg/wk	50mg BID (?100mg HS to ↓AE)	$37	• AE: Sedation, weight **loss** (e.g. 3kg), renal stones 1.5%, paresthesia e.g. tingling. • CI: metabolic acidosis. Ensure contraception (not CHCs!) if ♀ childbearing age. • DI: Many. CHCs, acetazolamide, lithium, valproate, other CNS depressants.	• Response in 40-55% of pts; high drop-out rate e.g. 30%. • Topiramate 200mg/d no better than 100mg/d & ↑AE. • Gabapentin no longer recommended for most pts (evidence for benefit uncertain).[20] May consider in pts with chronic pain, alcohol use disorder, etc. • See also RxFiles: Antiepileptics.
	Divalproex EPIVAL, g 125, 250, 500mg EC tab	250mg po HS ↑ q1-2wks	500-750mg BID cc (or 250mg AM & 500mg HS to ↓AE)	$65	• AE: Sedation, nausea, hair loss, tremor, **weight gain**, rash, ↑LFTs. • CI: Liver dx, porphyria. Ensure contraception (not CHCs!) if ♀ childbearing age. • DI: Many. CHCs, ASA, fluoxetine. Divalproex inhibits CYP2C9.	
ACEI/ARB	**Candesartan** ATACAND, g 4, 8, 16, 32mg tabς	8mg po daily ↑ after 1 week	16mg daily	**$17**	See also RxFiles: ACEIs & ARBs. • AE: ↓BP, ↑K+, cough (esp. lisinopril), rash. **Rare**: AKI, angioedema. • CI: bilateral artery stenosis, hx of angioedema, pre-contrast coronary angiography. • DI: lithium, K+, NSAIDs, K+-sparing diuretics. M: SCr, electrolytes, BP.	• Response in 30-40% of pts and well tolerated.[45] • Useful if also HTN, post-MI, CKD, etc. • Candesartan effective; lisinopril probably effective.[89] • Some evidence for telmisartan 80mg daily.[86]
	Lisinopril ZESTRIL, g 5ς, 10, 20mg tab	10mg po daily ↑ after 1 week	20mg daily	$18		
SNRI	**Venlafaxine** EFFEXOR, g 37.5, 75, 150mg XR cap	37.5mg po daily ↑ q1-2wks	150mg daily	$16	See also RxFiles: Antidepressants. • AE: ↑BP, ↑HR, tremor, agitation, insomnia (take in morning), sweating, nausea, ↓appetite, fatigue, orthostatic hypotension, anticholinergic effects. • DI: MAOI, SSRIs, anticholinergics, CNS depressants. Duloxetine inhibits CYP2D6.	• Venlafaxine probably effective;[89] duloxetine limited data. Less evidence than a TCA, but often better tolerated. Useful if anxiety, depression, chronic pain. • Taper if discontinuing due to risk of withdrawal sx.
	Duloxetine CYMBALTA, g 30, 60mg cap	30mg daily ↑ after 1-2 wks	60mg daily	$42		
CCB	**Flunarizine** SIBELIUM, g 5mg cap ☎ ▼	5mg po HS ↑ after 1 week	10mg HS	$61	• AE: Common. Fatigue, drowsy, weight gain, depression, extrapyramidal sx. Poorly tolerated vs other calcium channel blockers. **Caution**: Parkinson's dx.	See also RxFiles: Calcium Channel Blockers. • **Verapamil** weaker evidence than flunarizine,[85] but better tolerability. Verapamil ✓cluster headache. May ↑ verapamil to 480mg/day if tolerance occurs.
	Verapamil ISOPTIN, g 80,120mg IR; 120,180,240ςmg SR tab	120mg SR daily with food	240mg SR daily with food	$28	• AE: ↓BP, ↓HR, **constipation**, nausea, edema, headache. • CI: heart failure,[90] AV block, low HR. DI: β-blockers. Verapamil inhibits CYP3A4.	
5HT2-Θ	**Pizotifen** SANDOMIGRAN DS 1ς mg tab also known as pizotyline	0.5mg po HS ↑ q1-2wks	1.5mg HS	$47	• AE: **Sedation**, **weight gain** (0.5-4kg at 12wks),[91] nausea, weakly anticholinergic. • **Caution**: DM, CVD, glaucoma, urinary retention, renal dx, hepatic dx. • DI: MAOI, additive effect with other CNS depressants / anticholinergics.	• Response in ~50% of patients.[91] May ↑ to 3mg HS or 2mg BID ($115) if tolerance develops. If stopping, taper to avoid withdrawal (e.g. anxiety, depression, insomnia).
Herbal	**Magnesium** oxide ✗ ▼OTC	500mg po daily		**$10**	• AE: Diarrhea, nausea. • **Caution**: Renal dx. Possibly useful in patients with constipation.	• Response in up to ~50% of patients (but few trials).[92] • **Butterbur** (petasites) effective,[CHS 2012] but reports of impurities (e.g. pyrrolizidine alkaloids leading to hepatotoxicity). • **Feverfew** ineffective.[CHS 2012]
	Magnesium citrate ✗ ⊗ OTC	300mg po BID		**$12**		
	Riboflavin (Vit B_2) ✗ ⊗ OTC	400mg po daily		**$15**	• AE: Well-tolerated. Nausea, diarrhea, bright-yellow urine.	
	Butterbur ✗ ⊗ OTC	75mg po BID		$30	• AE: Burping. M: Ensure commercially prepared product to prevent toxicity.	
	Coenzyme Q10 ✗ ⊗ OTC	100mg po TID		$25	• AE: Few AE. GI upset (<1%). DI: may ↑effect of HTN meds & ↓warfarin effect.	
anti-CGRP	**Fremanezumab** AJOVY ❄ 225mg syringe ☎ ✆	225mg subcut q4wk ***or*** 675mg subcut q12wk		**$630**	Fremanezumab EDS in Sask ☎: only after adequate trial of ≥2 oral classes. • AE: Injection site reactions, constipation (esp. erenumab), hypersensitivity reactions, HTN. CV risk profile unclear (& pts with CV risk were excluded from CGRP-Θ trials). ?Caution in Reynaud's.[98] Store in fridge ❄, but to ↓ injection pain, bring to room temp 30mins pre-injection. Fremanezumab 675mg is given as three consecutive 225mg injections to same body site (three separate pokes). • DI: No known drug interactions. M: BP (first week).	• CGRP-inhibitors; onset in **days** to months. • Response in 40-42% of patients **NNT=5-8**.[96] • Studied in patients where other therapies have failed.[40] • Anti-drug antibodies may form, which ↓efficacy. • Galcanezumab ✓episodic cluster headache (300mg subcut at onset of cluster, max once per month).
	Erenumab AIMOVIG ❄ 70, 140mg pen ✗ ⊗	70-140mg subcut monthly		**$600**		
	Galcanezumab EMGALITY ❄ 100,120mg syringe/pen ✗ ⊗	240mg subcut load, then 120mg monthly		**$700**		
	Rimegepant NURTEC	75mg po every other day		*USA only*	• AE: Well-tolerated. Nausea 3%, somnolence. DI: CYP3A4 substrate.	• Rimegepant **NNT=13** (49% vs 41% placebo) over 12wks.[39]
Other	**Memantine** EBIXA, g 5, 10ςmg tab ✗ ⊗	5mg HS ↑ after 1 week	10mg HS	$67	• AE: Dizzy, drowsy, insomnia, constipation, nausea, ↑BP. • **Caution**: seizures, heart disease. DI: Trimethoprim, antacids, acetazolamide.	• Weak evidence.[89] Response in ~35% of patients.[88] • See also RxFiles: Dementia.
	OnabotulinumtoxinA BOTOX 50, 100, 200 unit inj. ✗ ⊗	155-195 units injected q3 months (PREEMPT protocol; special expertise rq'd)[94]		**$195-242**	• AE: neck pain 7%, muscular weakness 6%, eyelid ptosis 3%, injection site pain 3%. • **Caution**: dysphagia, breathing difficulties, muscle weakness, myasthenia gravis.	• Effective **only if ≥15** headache days/month (chronic migraine).[95] Response: 47% vs 35% placebo **NNT=8**.[94]

Other proposed tx: acupuncture;[18] spinal manipulation; ?transcranial magnetic stimulation, ?melatonin 3mg daily.

✗ =Non-formulary in SK ⊗=not on NIHB ☎=EDS SK ✆=prior approval NIHB ▼=covered NIHB ς =scored tab =↓dose for renal dx =↓dose for liver dx ❄=store in fridge **CGRP**=Calcitonin Gene-Related Peptide **E.C.**=enteric coated **IR**=immediate release **SR**=sustained release

Migraine Prophylaxis – Individualization of Tx – Colour Chart (Adults)

L Regier BSP BA, © www.RxFiles.ca Apr 2022

Considerations	[I] Beta-Blocker	[II] Anticonvulsant		[III] Antidepressant		[IV] CCB		[V] ACEI/ARB Antihypertensive	[VI] CGRP-mAb	[VII] OTC/Herbal[1]	[VIII] Other
Meds with somewhat better evidence **bolded** / *Evidence & patient factors for individualization of therapy*	**Metoprolol Propranolol Timolol**, Atenolol, Bisoprolol, Nadolol	Topiramate [2]	**Divalproex** (Valproate)	**TCA** **Amitriptyline** Nortriptyline	**SNRI** Venlafaxine DULoxetine	Verapamil	Flunarizine (rarely used)	**Candesartan** Lisinopril	**Erenumab Fremanezumab Galcanezumab** (all subcut q4+ wks	**Riboflavin** (B2) **Magnesium** Butterbur Coenzyme Q10 Melatonin?	Comments related to rows and not fitting elsewhere.
Efficacy Evidence [A] Evidence for Benefit In Episodic Migraine	✓✓ *Level A*	✓✓ *Level A*		✓✓ *Level B*	? *Level B*	?	✓	✓✓? *Level B-C*	✓ when refractory to other Tx	? ✓-✓✓ *Level C*	Non-Pharm Tx, Pizotifen, but AEs, Rimegepant po[USA], Memantine?
↓ Migraine/HA frequency by ≥ 50% ~8-12weeks	40-80% responder rate	40-55%		40-50%			✓?	30-40%	40-42%	?	
	NNTs vary: ~4-8; note that the high rate of placebo response in RCTs, and differing populations/methodology limits comparative interpretation.[3,4,5,6] (see notes)										
[A] Effective for other types of headache prevention	✓? Medication overuse headache (MOH)	✓CM, &/or daily HA; ?MOH ? cluster HA Topiramate		✓✓ Tension-type HA, & Mixed Migraine/ Tension; ✓?MOH	✓Tension-type HA	✓✓Verapamil for cluster HA Aura without HA		✓? MOH	✓CM, ?MOH; ✓Galcanezumab for cluster HA	?Melatonin in cluster HA	✓Botox: MOH; CM (≥15 HA/mo); Not indicated for episodic.
If CV Concerns [B] Angina	✓✓			✕ ? if severe		✓✓			?		Presence of CV disease limits acute tx options (triptans, NSAIDS), increasing the importance of prophylaxis.
[B] Cardiac Conduction	✕✕			✕		✕✕	?		?		
[B] Hypertension	✓✓				✕	✓		✓✓	✕ esp. **Erenumab**	✓? Coenzyme Q10	
[B] Hypotension	✕			✕		✕✕		✕			
[B] Other	✓AFib, HF; ✕ PVD			Smoking cessation: Nortriptyline option		Verapamil: ✓AFib; ✕HF		✓ ↓CV risk, HF	? long-term; ? Reynaud	HF, statin pain: ✓?Q10	
Patient Considerations, History & Comorbidities [C] Anxiety/Depression	Comments in notes	?	✓anxiety	✓✓[4]	✓✓		✕		Comment in notes		Role of CBT, etc.
[D] Insomnia	?			✓✓[4]		? uncertain effects				✓? Melatonin,	Caffeine use; ✓Pizotifen
[E] Pain (Chronic/Neuropathic)		✓ Topiramate; other		✓✓	✓ to ✓✓						Monitor for MOH
[F] Seizure disorder		✓✓		✕ ?	✕ ?						
[G] Hepatic			✕			✕ Verapamil				✕ Butterbur see notes	? Dose adjustments
[H] Other/comorbidities	✕ asthma, insulin dependent diabetes	✕ narrow angle glaucoma ✓? mood disorders		✕, narrow angle glaucoma; prostate, thyroid, severe renal	Caution/adjust dose if CrCl <30mL/min	✕Verap: HF, constipation ✓ Flunarizine: vertigo		✓ diabetes ✕ hyperkalemia	✕ Inj site reactions	✓Magnesium: constip; Butterbur: allergic rhin	
[I] ♀ - Pregnancy, current/potential PL	✓? Propranolol ✓? Metoprolol	X Topiramate XX Divalproex		✓?	✕ ?	✓? Verapamil ✕✕Flunarizine		?pre-conception ✕✕	? ✕- long washout pre-conception!	✓?Magnesium ✕ Butterbur	Optimize Non-drug Tx, Migraine often improves in pregnancy
[I] ♀ - Lactation	✓? Propranolol	✕		✓?	✕	✓? Verapamil		✓?	?	✓?Magnesium	
Side Effects [J] Anticholinergic	✓	✓		✕✕	✕	✓		✓	?	✓-✓✓?	Generally *start low, go slow* for better tolerability!
[K] CNS: alertness, dizzy	✕?	✕ to ✕✕		✕ to ✕✕	✕	✓		✓	✓	✓-✓✓?	
[L] Tolerability, overall	✓ to ✕	✓ to ✕	✓ to ✕	✓ to ✕	✓ to ✕	✓ to ✕		✓ to ✓✓?	✓ to ✓✓? new agents	✓-✓✓?	
[M] Weight gain, avoid	?	✓✓	✕	✕	?		✕				✕ Pizotifen
[N] **Cost** Typical cost/month range	✓✓ $12-40	✓ $30-40		✓✓ $20-35	✓-✓✓ $16-40	✓ $28	✕ ☎▼ $35-60	✓ $15-20	✕✕ $600-700 ✗⊗ Fremanezumab: ☎ ✆	✓ to ✕ OTC	✕✕Botox Inj $200 Pizotifen ✗ ▼ $50
[O] **Other**	DI: limit rizatriptan dose if propranolol ?Option in ≥12yo ?✓Timolol Eye Drops	DI: topiramate will reduce CHC efficacy. Valproate, option for prolonged aura. Topiramate: ≥12yo[FDA]		✓ Nortriptyline + Topiramate[7] **RCTs: Avg amitriptyline dose = 80mg/day.** ?Option +CBT in ≥12yo	May combo with a beta-blocker	Flunarizine: effective, but depression & wt gain limit use.		DI: NSAIDs, diuretics	Constipation (SAE with erenumab) **Subcut q4-q12wk** regimen options	Fairly safe options Butterbur: only choose *PA-free* products to avoid hepatic toxicity.	Any agent: option to D/C after 6+ months. Combo tx options in refractory HA.

[P] Menstrual Migraine (MM)	Short-term Cyclic Prevention (Off-Label): NSAIDs [I]	Triptans [II]	Hormonal [III] (Off-Label): e.g.
	Naproxen ~500mg BID **Mefanamic acid** 500mg TID	**Frovatriptan** 2.5mg BID Nara- or Zolmi- triptan	**Extended dosing estrogen/ progestin contraceptives; Short-term cyclic** transdermal estrogen gel 1.5mg (x7 days, starting day -2)
Evidence	✓	✓	Option for MM without aura
Cautions/ Comments	✕ NSAID cautions/AEs ✓Comorbid dysmenorrhea {start ~1-2+ days pre MM; continue ~6-7 days}	✕ Triptan cautions /AEs	✕ Hormonal cautions/AEs/DIs ✓Comorbid dysmenorrhea ✓Provides contraceptive
Cost	✓✓	✕ {frovatriptan ✗⊗}	✓✓

[Q] **Other MM short-term cyclic options: magnesium** (120mg po TID, beginning 15th day of cycle till next cycle).[8]

Important considerations: How a medication is trialed is often just as important as which medication is chosen. 1) **Start low dose and gradually increase** to an effective dose, as tolerated; 2) **Allow ~8-12+ wks** for full effect, then assess; 3) Keep a **headache diary** to allow for accurate evaluation; 4) **Ensure realistic expectations**: an "effective drug" will reduce the *frequency* and/or *impact* of migraine, not eliminate.
See additional notes for various rows and columns in supplementary table that follows (or online).

AE= adverse events **AFib**=atrial fibrillation **CGRP-mAb**=calcitonin gene-related peptide monoclonal antibody **CHC**=combined hormonal contraceptive **CM**=chronic migraine **CNS**=central nervous system **DC**=discontinue **DI**=drug interaction **HA**=headache **HF**=heart failure **MOH**= medication overuse headache **PA**= pyrrolizidine alkaloids **Pl**=placebo **PVD**=peripheral vascular disease **SAE**=serious adverse events **subcut**=subcutaneous. [☎: exception drug status in SK, ✗ =non-formulary in SK, ⊗=non-formulary for NIHB, ▼=full NIHB] **Legend for comparison colour coding:**

✓✓ = An Advantage	✓	Neutral	✕	✕✕ = A Disadvantage

Patient Info Links: Migraine Preventative Medications, What You Should Know; CHS – Patient Tools and Reading

Rows A-B: *Generally, trials were **compared to placebo** (± background treatment); however, there were some small head-to-head trials.*

A: Evidence for Benefit In Episodic Migraine +/- Other Headache[9,10,11] {Effectiveness Levels: **A**=established/***offer***, **B**=probably/***should consider***, **C**=possibly/***may consider***}[12,13,14] Common outcome in trials focuses on migraine/HA **frequency**; however, may also have a potential role in decreasing **intensity/progression** to chronic migraine/QoL	
I	**Beta-Blockers**: Beta-blockers are effective in preventing migraine.[15,16] **Propranolol** and **Timolol** have official indication in Canada. **Metoproplol**, atenolol, bisoprolol and nadolol are also effective. Cochrane SR – Propranolol[17]: N=58, n=5072; adult migraine sufferers, mean age 41; low quality (high drop-out rates, lack of ITT analysis, uncertain allocation concealment, and lack of long-term follow-up); suggest short-term reduction in HA frequency vs placebo, with no effect on HA intensity and a heterogeneous dose response; no clear cut differences with active comparators (flunarizine, other beta-blockers, amitriptyline); adverse effects were somewhat more common in treatment group; overall high certainty of benefit, but low certainty regarding size of benefit. **Benefits often seen in 4-8 weeks; allow 12 weeks**. {e.g. Bisoprolol 5mg po daily, migraine attack frequency/month: baseline **5.6**, run-in phase **4.4**, 1-4wks **3.1**, 5-8 wks **2.5**, 9-12wks **2.3**; 10mg daily dose resulted in similar benefit compared to 5mg daily but had higher adverse event rate (43% vs 35%); overall tolerability was rated as very good by >80% of patients on either drug or placebo.} Beta-blockers may be a treatment option in MOH.[19]
II	**Anticonvulsants**: Both **valproate** (**divalproex**) and **topiramate** are effective and FDA approved for migraine prevention.[2,20] Both are supported by systematic reviews (N=10 & 17; n= 542 & 1737 respectively). Both may reduce HA frequency ≥ 50%.[20] Divalproex more than doubled the proportion of responders vs placebo; **NNT=4**. **Topiramate** effectiveness dose-dependent (100-200mg/day better than 50mg/day), but tolerability also reduced, especially at doses >100mg/day. For most patients, a dose of 100mg/day (50mg BID) may be the sweet spot to balance tolerability and effectiveness. Of interest, quality of life scores were sometimes better even if adverse event rates increased.[22] Topiramate doubled the proportion of responders vs placebo; **NNT=4**. **Topiramate 100mg daily vs Amitriptyline 100mg** daily RCT (good quality): n=347, 26 weeks; showed non-inferiority; change in *least squares mean (LSM) mean monthly migraines* -2.6 vs -2.7; 50% responder rate 56% vs 46% (NS).[23] {Other findings of note: no differences in any 2° efficacy measures; topiramate better for migraine severity functional disability}. Topiramate may also be effective in chronic migraine, MOH and aura without headache. Gabapentin: overall evidence no longer supports any efficacy in migraine prophylaxis.[24] Lamotrigine is not effective in reducing migraine attack frequency, but may reduce migraine with aura.[25,26]
III	**Antidepressants-TCAs**[4,10]**:** TCAs, particularly **amitriptyline** (10-150mg; mean dose in RCTs ~80mg/day), effectively reduce HA severity & frequency, both migraine & tension type; N=37, n=3176; **NNT=8** (note NNT high, in part because placebo rate very high; direct comparative trial data suggests NNT similar to topiramate); **NNH=5**. Additional benefits seen in patients with co-morbid depression and/or insomnia. Limited comparative data suggest similar efficacy between TCAs, topiramate and beta-blockers. Use/ranking partly based on clinical experience. **Nortriptyline** an option clinically. Slow titration of TCAs optimizes benefit & limits AEs. {One network meta-analysis suggested amitriptyline more effective than other migraine prevention options.}[27] TCAs are an option for MOH[28], tension HA & chronic migraine. **SNRIs**: **Venlafaxine** and/or duloxetine may be effective in migraine prevention, however there is limited and weak evidence overall for a significant benefit over placebo. [29] Evidence for SNRIs and SSRIs in preventing tension-type headache is limited and weak.[30] One small RCT (n=60) found venlafaxine 150mg/day reduced days with tension headaches by ≥ 50% (**NNT=3.5**).[31] **Other antidepressants**: Mirtazapine sometimes considered an option for tension-type headache. SSRIs lack evidence for effectiveness in migraine.
IV	**CCBs**: There is some evidence for flunarizine and only weak evidence for verapamil in migraine prevention. They are sometimes included as a 3rd line option in guidelines.[26,32] Verapamil may be effective for prevention of both episodic and chronic cluster headaches (1st line) based on observational and some RCT data.[33] Also an option in aura without headache.[34]
V	**Antihypertensive-ACEI or ARB**: A few, small RCTs provide evidence for the effectiveness of both ARBs (**Candesartan** 16mg daily[35]) and ACEIs (lisinopril 20mg daily[36]) in migraine prevention. {e.g. Candesartan vs placebo RCT, n=60; days with headache 18.5 vs 13.6 over 12 wks., and ~40% of participants had a 50% or greater reduction in migraine days/month.} 2021 AHS Update upgrades candesartan level of efficacy to "established". (Telmisartan 80mg daily also studied but primary results did not show statistical significance.[37]) Their good tolerability, etc., make them an alternative early option, even given somewhat limited evidence. Also consider if an ACEI or ARB is indicated for another reason (e.g. hypertension) or if there are side effect concerns with other alternatives. One comparative RCT found candesartan 16mg/day was similar to propranolol 160mg/day.[38] Candesartan has been used and may be a suitable treatment option for MOH.[39]
VI	**CGRP-mAb**: RCTs, placebo controlled, (range of sample sizes n=174-955) show agents reduce monthly migraine days over 12-24 wks in episodic & chronic migraine.[40] In episodic migraine: - **Erenumab** (ARISE, STRIVE) ↓ monthly migraine days by -1.1 and -1.4 days respectively at 70mg SC q4-weekly dose, and by -1.9 at the 140mg SC q4-weekly dose. - **Fremanezumab**: (HALO-EM) ↓ monthly migraine days overall by -1.5, and during weeks 9-12 by -2.81 at the 225mg SC q4-weekly dose. Similar results seen with 675mg SC q3-months. {A 2020 meta-analysis (N=5, n=3379) found ↓ monthly migraine days by ~2.2 for both chronic and episodic migraine over a 12wk period.[41] } - **Galcanezumab**: (EVOLVE-1, EVOLVE-2) ↓ monthly migraine days by a -1.9 and -2.0 at 120mg SC q4weekly. Similar results seen with 240mg SC q4-weekly. A 2021 systematic review found that **treating 5-8 patients** (ie. **NNT**) with a CGRP-mAb resulted in one patient experiencing a 50% ↓ monthly migraine days compared to placebo.[42] (Variation in NNT reflects different agents, high vs low dose, and populations.) The higher dose options for fremanezumab (675mg vs 225mg/mo) and galcanezumab (120mg vs 240mg/mo) do not result in a higher rate of 50% responders.[43] An indirect comparison of CGRP-mAb's and topiramate for **episodic migraine** prevention concluded that efficacy was likely to be similar, but tolerability ('cognitive', 'sensory & pain') worse with topiramate.[44] A network meta-analysis for both episodic & chronic migraine suggested fremanezumab was the most effective CGRP-mAb after 6wks; erenumab was most effective after 8 and 12wks.[45] CGRP-mAb agents are also somewhat effective for prevention in **chronic migraine** with a mean reduction in monthly migraine days ranging from -1.8 to -2.5. {**$NNT_{50\%}$ = 5-9**[46]} ?Option for MOH. Cluster HA: Galcanezumab may be efficacious in episodic cluster HA, but not chronic cluster HA.[47] Fremanezumab not effective for cluster HA. {CGRP-mAb for vestibular migraine? Possibly.}
VII	**OTC-Herbal/Nutritional Agents: Possibly Effective:** riboflavin[91], magnesium, butterbur, coenzyme Q10. **Conflicting Evidence – unlikely to benefit**: feverfew, melatonin. **Riboflavin** (vitamin B2): In a small RCT (n=55) riboflavin po 400mg/day resulted in reduced frequency of migraine ≥ 50% (54% vs 19%), HA days, & mean severity of HA.[49] Allow 3 months for effect. **Magnesium**: Limited evidence from 3 of 4 small RCTs suggest magnesium supplementation po 400-600mg/day may be effective in preventing migraine.[50] (Best evidence with the higher dose.) **Butterbur**: A few small RCTs suggest that petasites extract of butterbur (75mg po BID) may be effective in reducing migraine frequency vs placebo. However, there are concerns re: hepatotoxic & carcinogenic harms associated with unregulated products that contain pyrrolizidine alkaloids. Avoid unless a reliable, standardized, and pyrrolizidine-free (*PA-free*) product can be obtained.

	Coenzyme Q10: In a small RCT (n=42) coenzyme Q10 100mg po TID resulted in reduced frequency of migraine ≥ 50% over 3 months (48% vs 14%).[51] **Melatonin**: Some studies suggest po 3-4mg/day may have benefit; however, a systematic review (N=4, n=351) concluded evidence not sufficient to support use in migraine.[52] Also small studies in cluster headache prevention with conflicting results; in one trial melatonin 10mg/day reduced analgesic consumption, but not the number of daily attacks.
VIII	**Non-Pharmacologic Tx:**[53] **A) Neuromodulation Handheld Devices:** 1) transcranial magnetic stimulation, 2) external trigeminal nerve stimulation, 3) external vagus nerve stimulation, 4) remote electrical neuromodulation armband**. B) Behavioural Therapies:** 1) mindfulness, 2) biofeedback & cognitive behavioural therapies (muscle stretching, deep breathing, progressive muscle relaxation, relaxation imagery, CBT, thermal feedback). **C) Combination Behavioural + Drug Therapies**: more effective than either alone.[54] (See also section O – VIII). **D) Acupuncture** may help.[55] **Address Lifestyle Factors/Triggers:** a) irregular sleep or too little sleep, b) missed or skipped meals, c) stressful lifestyle, d) excessive caffeine consumption (or variation), e) lack of exercise.[10] Additional factors for special consideration in adolescents: f) adequate hydration, g) physical activity, h) lack of breakfast specifically, i) excessive use of electronic devices/games, j) alcohol/substance use.[56] **Links to useful patient resources**: a) https://migrainecanada.org , b) https://americanheadachesociety.org/**trigger-avoidance**-information/ , c) MyAlbertaHealth **Botox inj:** Systematic review of RCTs (N=28, n=4190) found that botox injection given every 3 months may improve migraine (**particularly chronic vs episodic**).[57] In chronic migraine, the number of migraine days/month was reduced by 2 days in large only trials, and 3.1 days in all trials. The number of participants with non-serious adverse events were increased (60% vs 47%; **NNH=8**). It is not indicated and evidence does not support use in episodic migraine. **Pizotifen**: effective (50% ↓ in frequency) for over 40% of patients, but concerns/contraindications regarding AEs (e.g. CNS, anticholinergic) in patients at risk (e.g. GI obstruction). **Rimegepant**: 75mg po every other day: (**USA**) – effective for **both acute treatment and prevention** of migraine. Studies of regular use for up to a year: ↓ HA/month -4.3, well tolerated, no sign of medication overuse or hepatic toxicity. (However, caution as there could be potential AEs and DIs to watch out for given the limited real-world experience.) **Memantine**: Systematic review of RCTs (N=4, n=183) suggests may be effective in episodic migraine prevention (frequency and severity).[58]
B: If CV Concerns (e.g. Angina, Cardiac Conduction/Heart Block, Hypotension, Hypertension, Other)	
I	**Beta Blockers:** advantageous in the treatment of certain CV conditions (e.g. stable angina, heart failure, atrial fibrillation, hypertension); disadvantageous in the treatment of patients with other CV conditions (e.g. peripheral vascular disease, Reynaud's syndrome, bradycardia, heart block) and those with athletic pursuits.
III	**Antidepressants – TCA**: caution if CV hx (e.g. conduction abnormalities, risk of orthostatic hypotension); effects usually dose-dependent. **SNRIs** may ↑ BP (or occasionally orthostatic hypotension). If patient also a smoker, may consider nortriptyline (target dose ~75mg) which has shown some effectiveness for smoking cessation.[59]
IV	**CCBs – Verapamil:** contraindicated in HF, certain arrhythmias; strong hypotensive effect.
V	**Antihypertensive - ACEI or ARB**: May be highly beneficial in certain cardiovascular diseases (e.g. heart failure, hypertension, cardiovascular risk, etc.)
VI	**CGRP-mAb**: CV safety is uncertain as cardiac patients were excluded from trials. While microvascular complications (worsening Reynaud phenomenon, digital ulcerations, etc.) rare, serious AEs reported.[60] Hypertension, especially with erenumab (FDA warning), has been reported in post-marketing surveillance.[61] (If an issue, HTN often shows up early, e.g. in first week.)
VII	**Riboflavin:** appears safe; **Magnesium**: generally safe when taken orally; **Coenzyme Q10**: likely safe; palpations have been reported. Sometimes used to help manage: statin muscle pain, & HF.[62]
C: Anxiety /Depression	
I	**Beta-blockers:** historically, depression sometimes noted as a side effect, however, best evidence suggests not[63]; some, particularly propranolol, may be effective in treatment of performance anxiety.
II	**Divalproex**: may have a beneficial dual effect and role in patient with a mood disorder and migraine. **Topiramate**: may sometimes cause psychiatric disturbances in patients with previous psychiatric history.
III	**Antidepressants**: may serve a dual role in patients who have both migraine and anxiety/depression.
IV	**Flunarizine**: may actually cause depression, so avoid or monitor for AE.
VII	**CGRP-mAbs**: A post-hoc analysis of the **HALO-CM** study found that fremanezumab was effective in migraine prevention in patients with comorbid depression.[64]
D: Insomnia	
I	**Beta-blockers**: some beta-blockers, especially lipophilic, may adversely affect sleep/sleep quality. {Lipophilicity: propranolol >> timolol = metoprolol = bisoprolol > atenolol = nadolol} see BB Chart
III	**Antidepressants** – **TCA**: may serve dual role in patient with both insomnia and migraine.
VII	**Melatonin**: may serve a dual role in patients who have both migraine and insomnia; possibly effective/helpful for some.
E: Pain, Chronic	
II	**Anticonvulsants**: Topiramate may serve a dual role in patients with neuropathic pain and migraine. Some may consider a role for gabapentin as well (primarily for pain; possible benefit on HA).
III	**Antidepressants**: TCAs and SNRIs may serve a dual role in patients with neuropathic pain and migraine. Patients who also have tension/mixed headaches may also benefit from TCAs.
VIII	**Non-Pharmacologic Tx**: Approaches that emphasize the role of non-pharmacologic interventions e.g. for stress management and exercise, will be important in migraine prevention.
F: Seizure History	
II	**Topiramate and divalproex**: may be advantageous in patients with both migraine and epilepsy given potential to benefit both conditions. Lamotrigine is not effective in reducing migraines, but may ↓ migraine with aura.[26] If stopping, anticonvulsants should be tapered gradually to minimize seizure risk. (Gabapentin may be an option, but little/uncertain benefit in both seizure and migraine.)
III	**Antidepressants**: may lower the seizure threshold, to varying degrees in patients at risk.[65] Caution!
G: Hepatic Impairment	
II	**Divalproex**: contraindicated in severe hepatic disease; hepatic failure/death has occurred, usually within first 6 months; LFTs should be done at baseline & frequent intervals, especially in first 6 months.
IV	**CCBs – Verapamil:** dose may require adjustment; if using, may consider ECG monitoring as CV safety precaution.
VII	**Butterbur**: some formulations contain hepatotoxic pyrrolizidine alkaloids (PA); choose formulations that are regulated and certified "PA-free" in the manufacturing process.

H: Other Comorbidities

I-VI	Medication options may have other relevant indications or contraindications. Always consider any unique patient specific factors.
VII	**Magnesium**: may be effective for constipation, dyspepsia, hypomagnesemia. **Butterbur**: may be effective for allergic rhinitis (hay fever).

I: Pregnancy/Lactation (current or potential - reproductive considerations).[66,67] Seek additional, more detailed/specific information re: options.

-	**NOTE: It is often recommended to gradually taper/discontinue migraine preventative medications prior to a pregnancy, or upon becoming pregnant.** **Lactation: no specific comments below; seek additional sources for more information.**
I	**Beta-blockers**, especially low dose metoprolol and propranolol, may be a reasonable option in pregnancy.
II	**Topiramate** & Pregnancy: a) risk of reduced effectiveness of hormonal contraceptives (consider Depo-Provera, or IUD or CHC + barrier method); b) risk of fetal malformations **Valproate** & Pregnancy: risk of neural tube defects; contraindicated in ♀ of childbearing potential not on effective contraception. **For both topiramate and valproate**, consider folic acid supplement.
III	**Antidepressants**: low dose amitriptyline or nortriptyline may be reasonable options in pregnancy. SNRIs should generally be avoided.
IV	**Verapamil** is an option in pregnancy. **Flunarizine** is contraindicated.
V	**ACEI & ARB**: generally avoid pre-conception & during pregnancy. HTN CDN (GRADE C ACEI, ARB) Consider indications though, may stop upon pregnancy detection if used for nephropathy[DC'18(D)] or HF with reduced EF. Some data suggests ACEI & ARB risk of fetal toxicity during 1st trimester is not greater than other antihypertensives. HTN itself may contribute to fetal toxicity, perhaps not drug therapy.[68,69]
VI	**CGRP-mAb:** lack of data/experience – avoid. {No specific issues have been found; however limited reporting.[70] } Given wash out period is long, **advise stopping at least 5 months prior to conception**.
VII	**OTC-Herbal/Nutritional Agents[1]:** **Riboflavin** (vitamin B2): likely safe at usual dietary amounts; however, safety in pregnancy uncertain at higher doses. Seek additional information. **Magnesium**: likely safe up to 300mg daily; possibly unsafe at higher doses (or if given IV[71]). Seek additional information. **Butterbur**: safety unknown; however, likely unsafe if pyrrolizidine alkaloid (PA) constituents are used (teratogenic, hepatotoxic). **Coenzyme Q10**: possibly safe, however seek additional information. **Melatonin:** safety unknown, possibly unsafe
VIII	**Non-Pharmacologic Tx:** Attempts should be made to optimize non-drug approaches, especially as migraine often improves in pregnancy.

J: Anticholinergic Side Effects (e.g. dry mouth, constipation, etc.)

III	**Antidepressant – TCAs:** commonly cause anticholinergic side effects, which may diminish somewhat with ongoing use; nortriptyline sometimes considered to be less likely than amitriptyline to cause. SNRIs may also cause anticholinergic side effects, however less than TCAs. Some of these side effects may be proactively managed (see link) and/or tolerated (e.g. dry mouth treated with sips of water, OTC saliva substitutes, etc.). Extra caution in older adults.

K: CNS Side Effects (e.g. alertness, dizziness, somnolence, memory, fatigue)

I	**Beta-blockers**: may cause CNS effects; higher risk with propranolol, highly lipophilic compared to most others. {Lipophilicity: propranolol >> timolol = metoprolol = bisoprolol > atenolol = nadolol} see BB Chart
II	**Topiramate**: dose dependent ↑ in CNS side effects may limit therapy, especially for doses >100mg/day. CNS AEs can be minimized by slow titration (1-2 week intervals). Potential CNS AEs include sedative (drowsiness, fatigue), cognitive dysfunction (attention, memory impairment), psychiatric disturbances (behavioural, mood, depression). Valproate also has potential CNS effects (depressive &/or stimulating).
III	**TCA**: dose dependent CNS AEs are well known, but can be minimized by starting low and slowly titrating (1-2 week intervals). Potential for less CNS AEs with nortriptyline.
IV	**CCB**: Flunarizine highly associated with CNS AEs (>20%). If CNS AEs/concerns, may consider verapamil, or agent from alternative class with lower CNS AEs.
VII	**Coenzyme Q10:** usually well tolerated, but some CNS adverse effects have been reported (headache, cognitive decline, depression, falls, etc.).

L: Tolerability, Overall e.g. clinically important adverse events, or adverse events (AEs) leading to discontinuation

I	**Beta blockers:** Some physically active patients may not tolerate if noticing side effects of tiredness and fatigue (~ "body pain" in one trial).
II	**Topiramate:** Systematic Review: N=17, n=1737; AEs usually mild and non-serious. For clinically important adverse events, **NNH=2-25**, depending on trial, and dose; 200mg/day dose less well tolerated. For efficacy and tolerability, the 100mg/day dose hits the sweet spot in clinical trial data.[2] More common AEs: CNS (as per "K – CNS Side Effects" section above), weight loss, paresthesia. Overall tolerability similar between **topiramate 100mg/day vs amitriptyline 100mg** mg/day in RCT (n=331) - AEs (P< 0.05)[23]: Weight increase: 0% vs 14%, -2.7kg vs +2.7kg; Paresthesia: 30% vs 8%; Hypoesthesia: 11% vs 4%; Dry mouth: 7% vs 36%. Cognitive "brain fog" an issue for some. Pts with treatment emergent AEs: 68% vs 76%; Patients with SAE: 4 vs 8. Discontinuation due to AE: no difference. (Approx. 65% tolerated/adhered to tx.) **Divalproex:** side effects common but generally mild. For clinically important adverse events, **NNH=7-14** vs placebo.[20]
III	**TCAs:** AEs worse than placebo, **NNH=5**; however, no difference in withdrawal. **SNRIs:** withdrawals were not improved with SNRIs vs TCAs (and TCAs have much better evidence).[29]
V	**ACEI & ARB**: generally thought to be very well tolerated; however, in a study comparing candesartan vs propranolol, a tolerability advantage was not found (AEs differed; more dizziness with ARB.)[72]
VI	**CGRP-mAb**: common AEs: injection site reactions (sometimes including intense pain on injection), hypersensitivity reactions (within hours or up to a month) and constipation (erenumab). These are newer agents, usually well tolerated, however potential rare/serious adverse events and long-term safety are not available.[73] Of interest, there have been 3 deaths reported in RCTs, none of which are necessarily linked to the medication; however the usual cautions that accompany any relatively new medications, are prudent. In phase II trials, the frequency of AEs ranged from 44-72% in the CGRP-mAb group vs 39-67% in placebo.[40] Serious adverse events (SAE) were seen in 1-2% of patients. Withdrawals due to adverse events (e.g. temperature intolerance, HA/migraine, hypertensive crisis) were infrequent. In a systematic review and network meta-analysis, galcanezumab was associated with more treatment emergent AEs relative to fremanezumab and erenumab.[74] The fact that agents are fairly new, have a limited history of use, and wide ranging effects in the body, give rise to some concerns regarding the uncertainties around long-term safety.[75] However, a 2021 systematic review for NNT and NNH overall suggests a favourable benefit to harm profile (vs propranolol and topiramate) for CGRP-mAbs relative to other agents.[76] For episodic migraine, the CGRP-mAb agent with the best tolerability (least discontinuations due to AEs) was fremanezumab. For chronic migraine, galcanezumab had the most favourable tolerability profile.
VII	**Riboflavin:** well tolerated; infrequent & generally mild gastrointestinal upset possible; counsel patient that use is associated with yellow-orange urine and not to be alarmed. Estimated **NNH=33**.[91]

	Magnesium supplements: associated with diarrhea and GI discomfort, especially with doses >300mg/day. **Butterbur**: less serious: GI upset, burping; more serious: unregulated products containing pyrrolizidine alkaloids have been associated with hepatoxicity & carcinogenicity. Choose *PA-free* products! **Coenzyme Q10**: generally well tolerated.
VIII	**Botox**: non-serious adverse events (e.g. drooping eyelid, muscle weakness) were increased (60% vs 47%); **NNH=8**. Participants may be more likely to stop botox inj compared to oral treatment.[77] **For all agents in row**: generally starting at a low initial dose and gradually titrating up (e.g. every 1-2 weeks) to a potentially effective dose (based on trials) will improve potential for tolerability.

M: Weight Gain[10]

I	**Beta-Blockers**: variable potential effect on weight; occasionally, propranolol may be associated with some weight gain; timolol appears weight neutral.[78]
II	**Topiramate:** associated with weight **loss** and may be an advantage in someone with a prominent weight concern. One good quality RCT compared topiramate 100mg daily vs amitriptyline 100mg daily over 26 weeks. Topiramate was non-inferior and associated with a **2.4kg weight loss compared to a 2.4kg weight gain** with amitriptyline.[23] **Valproate** is associated with possible weight gain.
III	**Antidepressants – TCA:** commonly associated with weight gain (?dose dependant); nortriptyline may cause less weight gain than amitriptyline; SNRIs less likely to cause weight gain than TCAs.

N: Cost

	Costs can sometimes vary greatly depending on which drug within the class and which dose is chosen. See *Migraine: Prophylaxis Therapy* chart to assess chart options. Some of the more common 1st line options are available at relatively low price (e.g. **metoprolol** 100mg/day $17; **amitriptyline** 100mg/day $26). Compare overall cost of medications to prevent HA versus the cost of time/ days lost to headache. One USA pharmacoeconomic analysis found fremanezumab more effective and less costly than erenumab for episodic migraine.[79] Botox not covered for migraine in SK. **CGRP mAbs** are a fairly new and high cost option ($600-700/month), with limited drug plan coverage. They may be particularly useful/reserved for patients refractory to other treatment (e.g. failure of 2 or more previous migraine prophylaxis trials). Note: recently **fremanezumab** 225mg subcut inj (**AJOVY**) added to SK Drug Plan – EDS ☎ status (SK EDS criteria). NIHB ⊗.

O: Other

I	**DI Alert: Propranolol** increases **rizatriptan** levels by 70%; if using together, limit rizatriptan dose to 5mg.[79] **Timolol eye drops**: may also be effective in preventing migraine.
I,II,III	**Nortriptyline + topiramate**: RCT in monotherapy non-responders (<50% ↓in HA frequency at 8wks); n=68; combo-tx more effective than mono-tx (78% vs 37%, over 6 wks; **NNT=2.4**; p=0.04).[80] **Beta-blocker + topiramate**: RCT in monotherapy non-responders; n=58, (57% with MOH); open label; 36/58 (62%) responders; **NNT=4;** 12/58 non-responders, 10/58 DC'd due to AE (**NNH=6**).[81] **Adolescents and Migraine**[82,83] : Topiramate is the only FDA approved agent for migraine prophylaxis in ≥12yo. AAN/AHS options in pediatric migraine prevention: amitriptyline off label + CBT, propranolol off label or topiramate. Limited evidence suggests placebo may work >60%; drug tx often no better. {**CHAMP** Trial: n=328; amitriptyline vs topiramate vs placebo; 50% reduction in HA days, 52% vs 55% vs 60%, all non-statistically significant; however, AEs higher in active tx groups (amitriptyline vs topiramate) fatigue 30% vs 14%, dry mouth 25% vs 12%, paresthesia 31% vs 8%, weight loss 8% vs 0%.} [84] Other options include cyproheptadine, & supplements such as riboflavin, melatonin, magnesium oxide, etc.; however evidence lacking. Caution needed for anticonvulsants in ♀ of childbearing potential (e.g. suitable contraception)!
VIII	**Combination Behavioural + Drug Therapies**: more effective than either alone[1]: migraine days per month: a) beta blocker alone, -2.1; b) behavioural modalities alone, -2.2; c) combination, -3.3.[85] **Combo use of two medications,** when appropriate/needed, **may allow for lower doses and less side effects**, or ↑ effectiveness in patients with migraine refractory to monotherapy. Evidence is largely limited (few clinical trials) and based on expert opinion/experience. (**Useful combos commonly include any two of the following: beta-blockers +/- TCA +/- topiramate +/- candesartan**; valproic acid may also be used with a beta blocker (allowing for lower doses of each); see also Section O - I, II, III just above.) **Option to Taper/DC**: after 6 or more months, if patient's migraines are significantly improved and stable, may trial a gradual taper and possible discontinuation of drug therapy.

P: Menstrual Migraine (MM) – Short-term Cyclic Prevention (Off-Label) – "Mini-prophylaxis"[86]

I	**NSAIDs**: small low quality trials support efficacy and safety in younger women with regular menstrual cycles. **May begin 1-2 days prior to expected onset of migraine/cycle and continue while at risk e.g.~ 5-7 days**. (Option to start NSAID earlier, ~7 days prior to menses, and continue through menses day 6.) Usual NSAID contraindications apply; typical population generally at low risk (e.g. for GI, renal, CV complications). In addition to reducing MM, NSAIDs reduce menstrual pain as well. - **Naproxen** 550mg po BID vs placebo: 1 RCT, n=40, 3 cycles; naproxen group had less HA intensity and duration, and less HA days.[87] (33% were actually migraine free after 2-3 months.) - **Mefanamic acid** 500mg po TID vs placebo: 1 RCT, n=24; 2 cycles, age 18-35 with regular menstrual cycles; significant pain relief – 79% vs 17% (**NNT=1.6**).[88]
II	**Triptans:** systematic review of placebo controlled, crossover RCTs, N=6, n=1999, moderate quality methodology; results support efficacy and safety in women (mean age 36-38) **with regular menstrual cycles.**[89] **May begin 1-2 days prior to expected onset of migraine/cycle and continue while at risk of migraine, e.g.~ 5-7 days**. Typical triptan contraindications and cautions apply. For reduction in MM, reduction in analgesic use to treat MM, and various other endpoints: **Frovatriptan** appears to be more effective than naratriptan. Zolmitriptan is also somewhat effective. - **Frovatriptan** 2.5mg po daily-BID; patient free from MM: **NNT=7.2 and 1.8** for daily, & BID respectively. Most reported AEs were mild-moderate (e.g. nausea, dizziness), & risk of SAE low. - **Naratriptan** 1-2.5mg po BID; for the 1mg po BID dose: **NNT=8** (mean percentage of each cycle without an MRM); higher dose not calculated. There was an ↑ in AEs (e.g. dizziness, dyspepsia), **NNH=11** overall, but not drug specific AEs. - **Zolmitriptan** 2.5mg po BID-TID also studied; 50% reduction in MM: 2.5mg po BID vs placebo: **NNT=5**; 2.5mg TID vs placebo: **NNT=2.5**; 2.5mg TID vs BID: **NNT=5**. AEs: **NNH=8**. AEs included asthenia, dizziness, somnolence, nausea, tightness, dry mouth. Five SAEs were reported; 4 in the zolmitriptan group, 1 in the placebo group (no significant difference in drug specific AEs).
III	**Hormonal: estrogen-progestin contraceptives:** possible **option in menstrual migraine patients who do NOT have aura (note ↑ stroke risk if aura)**; approach will also provide contraception; effective in preventing migraine triggered by estrogen withdrawal. Continuous hormonal strategies may be suitable for some e.g. administration of active pills (e.g. 3-6-12 months) followed by 4-7 day hormone free interval (menses is no different than traditional dosing). Consider obs/gyne referral. (See also RxFiles Combined Oral Contraceptives chart.)

Q: Menstrual Migraine (MM) – Short-term Cyclic Prevention (Off-Label) – Other options/notes

	Other: Magnesium: 120mg po TID starting on day 15 of cycle was effective in RCT over 2 cycles; **Chasteberry**: 40mg/day x3 months possibly effective in open-label, noncontrolled study.[90]

www.RxFiles.ca - April 2022
Dineen Joy, Taisa Trischuk, and Abdul Salama

Migraine FAQs

1. What is the risk of serotonin syndrome when a triptan is prescribed concomitantly with an SSRI?

Combining triptans with SSRIs is unlikely to cause serotonin syndrome in most patients.[1] FDA reports from 1998-2002 state the incidence of serotonin syndrome when using triptans with SSRIs to be rare (<0.03%).[1,2] In addition, the pharmacology underlying serotonin syndrome (5-HT_2 overstimulation) does not match the mechanism of action of triptans (5-HT_{1B} agonists).[1]

- An observational study (2018) concluded that while co-prescriptions of triptans and serotonergic agents have increased over the years, reports of serotonin syndrome have not.[3] A total of 19,017 patients were co-prescribed triptans and antidepressants during the study, serotonin syndrome was suspected in 17 patients and confirmed in only 2 patients.[3] Triptans are not contraindicated when taking SSRIs, however, patients should be informed of the rare possibility of serotonin syndrome and monitor for symptoms (e.g. tremor, agitation).[4]
- Guidance on monitoring for serotonin syndrome: see University of Waterloo: Target Serotonin Syndrome Infographic

2. Which acute migraine medications are safe for use in pregnancy?

Most patients (~60-70%) report improvement in their migraines over the course of pregnancy, while ~5% describe worsening.[6] During pregnancy, there is an increased emphasis on using non-pharmacological treatments to avoid potential harm to the fetus. If pharmacotherapy is required, the fewest number of select medications, for the shortest duration, at the lowest effective dose, should be used.[7,8]

- **Acetaminophen** is the first line agent for pregnancy.[7,8-12] Some **antiemetics** such as **metoclopramide** are also safe for use in pregnancy.[8,9]
- **NSAIDs** (2nd line) may increase spontaneous abortion risk in the 1st trimester,[7,11] and cause neonatal ductus arteriosus closure, pulmonary HTN and renal dysfunction in the 3rd trimester.[7,8,9,11] **Ibuprofen** is the NSAID of choice (2nd trimester).[8,9,11] Avoid **ASA** due to bleeding risk.[7,10]
- **Opioids** (3rd line) can cause AE, neonatal withdrawal, and increased risk of MOH.[8,9,12] Use the lowest effective dose & for shortest duration.
- **Sumatriptan** may be considered when other medications have failed, if benefits outweigh the risks.[11] Although a 2015 meta-analysis showed that **sumatriptan** doesn't increase the risk of congenital malformations, the risks cannot be completely ruled out.[8,11,13] There is less safety data/experience with other triptans.[11] **Triptan** use during the second and third trimesters has been associated with atonic uterus (OR=1.4; 95% CI 1.1-1.8), and blood loss > 500 mL during delivery (OR=1.3; 95% CI 1.1-1.5).[7,11,14] **Ergots** are absolutely contraindicated.[7,9,11,12]

3. Fremanezumab (CGRP antagonist) for migraine prophylaxis: what is the dosing, benefits, risks, and cost?

Fremanezumab (**AJOVY**) is a novel biologic that targets and inhibits CGRP; reducing intracranial vasodilation and improving migraine symptoms.[15] It is approved by Health Canada for the indication of prophylaxis in episodic and chronic migraines.[16]

- **Administration**: Fremanezumab is available as a 225mg pre-filled syringe or auto-injector; dosed 225mg every month or 675mg every 3 months by subcutaneous injection. It is stored in the fridge (2-8°C) and injected at room temperature into the belly, thigh, or upper arm.[16]
- **Efficacy**: Clinical trials have shown a 50% reduction in headache days/month vs placebo (**NNT=5-8**); about 1-2 headache days/month less than baseline.[15,17,18] Benefit was recognized within one month.[15] Development of anti-drug antibodies were seen in <2% of participants,[16] however, the implication on efficacy is uncertain.[15] All trials lasted 12-24 weeks vs placebo, limiting long-term efficacy and safety data.[17]
- **Safety**: The most common AE were injection site pain and erythema (30% and 20%, respectively); rates were similar to placebo.[15] Nausea and dizziness were observed in <10% of participants; no different than placebo.[15] Dropout rates due to AE were low (1-2%).[18] There is no data in pregnancy, pediatrics, those with CV risk factors and hepatic or renal impairment.[15] **Cost**: Fremanezumab^{225mg} ~$630/month ☎ ✆

4. What is the evidence for using ACEIs and ARBs for migraine prophylaxis?

Lisinopril and candesartan are considered level B-C (probably-possibly effective for migraine prophylaxis); with a 30-40% response rate in decreasing headache frequency by ≥50% over ~8-12 weeks.[19,20] These medications may be considered for initial prophylaxis because of their tolerability or if indicated for another reason (e.g. hypertension).

- In a 2003 RCT (n=57), **candesartan 16mg daily** significantly reduced headache frequency (4.5 days/month vs 6.2 days/month on placebo).[19] Additionally, in a 2014 RCT (n=72) comparing candesartan 16mg daily vs propranolol SR 160mg daily vs placebo, candesartan and propranolol were superior to placebo for reducing headache days/month (2.95 & 2.91 vs 3.53, respectively); with candesartan being similar to propranolol.[21] This trial elevated candesartan to "established efficacy" in the 2021 American Headache Society guideline update.[22]
- In a 2001 RCT (n=55), **lisinopril 20mg daily** significantly reduced headache frequency (6.6 days/month vs 7.9 days/month on placebo).[20]

5. What are the risk factors for developing medication overuse headache (MOH)? See MOH infographic pg 15.

MOH is a chronic headache (≥15 days per month) developing as a consequence of regular overuse (>3 months) of acute medication to treat a pre-existing headache condition (migraines and tension-type headaches most common).[24] Prevention is key; **educate all patients** on the risk of conversion to chronic headache when starting any acute analgesics for headaches. Monitor for MOH risk factors including use of symptomatic medications >2 days/week and those with poorly controlled attacks. MOH often decreases the effectiveness of prophylaxis.[22]

- Generally, the risk of MOH is greatest with opioids, barbiturates, and combination analgesics.[25] Triptans and simple analgesics (e.g. NSAIDs) have a low-to-intermediate risk of MOH; simple analgesics are most often overused due to their wide availability and use.[25] Ergots appear to have a low risk, likely due to their decreasing use.[25] CGRP antagonists (e.g. rimegepant) do not appear to be associated with MOH.[22] Limit use of triptans, ergots, combination analgesics, or opioids to ≤9 days/month, and simple analgesics to ≤14 days/month.[11]

5HT= serotonin **ACEI**= angiotensin converting enzyme ⊖ **AE**= adverse events **AHS**= American Headache Society **ARB**= angiotensin II receptor blocker **ASA**= acetylsalicylic acid
CGRP= calcitonin gene related peptide **CV**= cardiovascular **FDA**= Food and Drug Administration **HTN**= hypertension **MOH**= medication overuse headache **NNT**= number needed to treat
NSAID= non-steroidal anti-inflammatory drug **OR**= odds ratio **RCT**= randomized controlled trial **SR**= sustained release **SSRI**= selective serotonin reuptake inhbitor
☎= Exception Drug Status in SK ✆= Prior approval required by NIHB

Target **Serotonin Syndrome**

def. Toxicity caused by excessive serotonin levels that results from a drug overdose or interaction

Assess the patient

Symptoms start within hours to 1 day of increasing a dose or adding a drug

Mild	Moderate	Severe
Nervousness	Hyperreflexia	Fever >38.5°C/101.3°F
Insomnia	Sweating	Confusion/delirium
Nausea/diarrhea	Agitation/restlessness	Sustained clonus/rigidity
Tremor	Inducible clonus	Rhabdomyolysis
Big pupils	Side-to-side eye movements	Death

Assess all drugs

Most cases involve 2 drugs that increase serotonin in different ways – full list on back


Prescription drugs


OTC and natural drugs


Illicit drugs

Rule out

Serotonin syndrome can look like other things; diagnosis requires an accurate drug history

Similar-looking conditions:
- Antidepressant Discontinuation
- Anticholinergic Toxicity
- Malignant Hyperthermia
- Neuroleptic Malignant Syndrome
- Meningitis/Encephalitis
- Drug Overdose
- Alcohol/Benzo Withdrawal

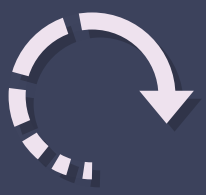
Remind all patients: Non-toxic increases in serotonin can cause anxiety, restlessness and irritability for 1-2 weeks

If you suspect serotonin syndrome

Don't wait, take action – it progresses rapidly


Stop the drug(s)


Refer patient to hospital


once symptoms are gone

Try other drugs or restart low doses slowly

Prevent serotonin syndrome

Stay alert – most cases can be prevented

- ✓ Use lowest effective dose
- ✓ Ask about illicit drug use
- ✓ Check drug monographs for tapering and wash-out periods
- ✓ Follow up 1-2 days after upping a dose or starting a new drug
- ✓ Reassess the need for a serotonin drug yearly
- ✓ Teach patients to recognize serotonin syndrome

AVOID: Group A with Group A or Group A with Group B

CAUTION: TWO or more Group B drugs especially when ONE is used at a high dose

MONITOR: If a patient uses a Group B drug and a second Group B drug is added, start low, increase the dose cautiously, and watch for symptoms for 24-48h after every change

Group A

Non-selective and irreversible MAOi A and B
Isocarboxazid
Isoniazid
Phenelzine
Tranylcypromine

Non-selective and reversible MAOi A and B
Linezolid

Selective and irreversible MAOi B
Selegiline (non-selective at higher doses)
Rasagiline

Selective and reversible MAOi A
Moclobemide
Methylene blue (non-selective at higher doses)

Group B

Antidepressants
Selective Serotonin Reuptake Inhibitors (SSRI): Paroxetine, fluvoxamine, sertraline, citalopram, escitalopram, fluoxetine

Serotonin Norepinephrine Inhibitors (SNRI): Venlafaxine, desvenlafaxine, duloxetine

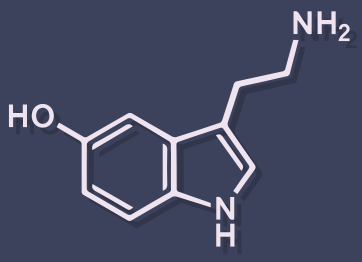
Tricyclic Antidepressants: Clomipramine, imipramine

Opioids and other pain medications
Tramadol, meperidine, methadone, fentanyl (unlikely with morphine, codeine, oxycodone, buprenorphine)

Cough, cold and allergy
Dextromethorphan ("DM"), chlorpheniramine

Natural health products
St. John's wort, L-tryptophan, diet pills

Illicit drugs
Ecstasy (MDMA), amphetamine, cocaine



Commonly listed but unlikely to cause serotonin syndrome
Triptans (e.g., sumatriptan)

Antidepressants: amitriptyline, mirtazapine, trazodone

Antiemetics: 5HT3 receptor antagonists (e.g., ondansetron), metoclopramide

Buspirone, lithium

Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med 2005; 352:1112-20.
Gardner DM. Serotonin Syndrome.
Gillman K. A systematic review of the serotonergic effects of Mirtazapine. Hum Psychopharmacol Clin Exp 2005; 21(2):117-25.
Gillman K. Triptans, serotonin agonists, and serotonin syndrome (serotonin toxicity): a review. Headache 2010; 50(2):264-72.
Gillman K. Monoamine oxidase inhibitors, opioid analgesics and serotonin toxicity. Br J Anaesth 2005 Oct;95(4):434-41.
Gillman K. CNS toxicity involving methylene blue. J Psychopharmacol. 2011 Mar;25(3):429-36.
Harada T et al. Incidence and predictors of activation syndrome induced by antidepressants. Depress Anxiety 2008; 25:1014-19.
Isbister GK et al. Serotonin toxicity: a practical approach to diagnosis and treatment. Med J Aust 2007;187(6):361-5.
Sinclair LI et al. Antidepressant-induced jitteriness/anxiety syndrome: systematic review. Br J Psychiatry 2009; 194:483-90.
Dunkley EJC, Isbister GK, Sibbritt D, Dawson AH, Whyte IM. The Hunter Serotonin Toxicity Criteria. QJM. 2003;96(9):635-642.

Content by Kelly Grindrod, PharmD; Tejal Patel, PharmD; Jamie Kellar, PharmD; Ai-Leng Foong, BSc. Design by Adrian Poon, BA

UNIVERSITY OF WATERLOO
FACULTY OF SCIENCE
School of Pharmacy

ACUTE MIGRAINE: A simplified treatment approach

Response defined as pain relief at 2 hours. Placebo response is ~2-3/10 patients.

STEP 1 — **NSAID** often ~$0.20/dose
Response in ~4-5/10 patients

STEP 2 — **Triptan** $2-3/dose
Response in ~5-6/10 patients

STEP 3 — **NSAID + Triptan** $2-3/dose
Response in ~6-7/10 patients

STEP 4 — **Subcutaneous Sumatriptan** $35/dose
Response in ~8/10 patients

May add metoclopramide to ↓nausea or to ↑efficacy

STEP 5 *Consider referral to neurology*

Refractory Patients
- manage agent failure as per Note 1 and Note 2
- try alternative combinations e.g. with acetaminophen, NSAID, triptan, metoclopramide, or caffeine
- start migraine prophylaxis
- possibly try DHE nasal spray

✖ **Avoid opioids or barbiturates** for most patients due to risks of medication overuse headache, adverse events, and overdose.

➡ Explore migraine triggers and non-pharmacologic options.

➡ Individualize therapy.
- e.g. may consider starting at Step 4 in patients with very rapid attacks or early vomiting.
- e.g. may prescribe both lower & higher intensity options in patients who are able to discern the expected severity of their migraine.

Note 1. Managing NSAID Failure

And/or: escalate to next step of therapy.

- Ensure NSAID is taken at the **earliest** onset of migraine pain and on an **empty stomach** (food delays onset).
- Try a faster-acting NSAID formulation (typically 10-20 minute faster onset than regular tabs).

Selected Faster-Acting NSAIDs

ibuprofen liquid gels
ADVIL LIQUI-GEL OTC, g **$0.15**/dose ✗ ⊗

naproxen sodium
ANAPROX, ALEVE OTC, g **$0.32-0.71**/dose ✗ ▼

diclofenac potassium (fastest oral NSAID)
CAMBIA powder, $11.80/dose ✗ ⊗

Note 2. Managing Triptan Failure

And/or: escalate to next step of therapy.

- Ensure triptan is taken at the **earliest** onset of migraine pain.
- Switch to a different triptan (try at least 3).
- Add acetaminophen, an NSAID, or metoclopramide to triptan therapy.
- Ensure adequate absorption (e.g. switch to nasal or injectable if vomiting up oral dose).
- Fast-acting triptans often preferred, but if tolerability concerns may try a slow-onset triptan (i.e. naratriptan☎▼ or frovatriptan✗⊗).

Fast-Onset Triptans

almotriptan ☎▼
eletriptan ✗ ⊗
rizatriptan ☎▼
sumatriptan ☎▼
zolmitriptan ☎▼

TIPS & TRICKS

- ✓ **Third time's the charm.** Typically try the same triptan for 3 separate migraines before assessing effectiveness. Typically try at least 3 different triptans before giving up on the class (since patient variability to triptans is high).
- ✓ **Acetaminophen (alone or in combinations) can be helpful.** Acetaminophen 1000mg is effective in providing migraine relief (**NNT=5** at 2 hours vs placebo). But acetaminophen is likely less effective than an NSAID at fully aborting a migraine (**NNT=12** at 2 hours vs placebo).
- ✓ Even when combined with an SSRI or SNRI, **triptans are UNLIKELY to cause serotonin syndrome.** Counsel and monitor; see page 12.
- ✓ **Prevent overuse.** The recommended max each month is 9 triptan days, 9 opioid days, 14 NSAID days, 14 acetaminophen days, or 9 days of any acute med if on triptans/opioids with simple analgesics. Track headache patterns and medication days with a headache diary (see page 2).
- ✓ **If nausea:** consider ODT triptan (if nausea exacerbated by water) or add an antiemetic (e.g. metoclopramide). Successful treatment can also relieve nausea!
- ✓ **If vomiting:** consider subcutaneous sumatriptan, intranasal triptan (especially if vomiting comes later in the attack), or NSAID suppository.

Pain relief defined as no pain or mild pain. NSAID onset defined as time to ≥80% of (C_{max}). **DHE**=dihydroergotamine **ODT**=orally disintegrating tablet **NNT**=number needed to treat **NSAID**=non-steroidal anti-inflammatory drug ☎=exception drug status in SK ✗=non-formulary in SK ⊗=non-formulary for NIHB ▼=full NIHB References available at rxfiles.ca/tools. See also www.rxfiles.ca/migraine.

MEDICATION OVERUSE HEADACHE (MOH)

Chronic headache caused by the overuse of acute headache medication that often provides inadequate pain relief.

- **≥15 headache days/month** (in a patient with a pre-existing headache disorder)
- common to wake up with a headache daily

What causes MOH?

A **>9 days/month** of triptans or opioids

B **>14 days/month** of NSAIDs or acetaminophen

C **>9 days/month** of any combo from both **A** and **B**

Withdrawal Symptoms

- Headaches will increase in pain and frequency before they improve.
- Anxiety, nausea, vomiting and problems with sleep can occur.
- Symptoms generally last 2-10 days after stopping the overused medication, but can last up to 2-4 weeks.
- Meaningful improvement in headache frequency is often noticed in 4-8 weeks.

References available at rxfiles.ca/tools.
See also www.rxfiles.ca/migraine.

Breaking the Cycle

1. **RECOGNIZE** MOH
2. **STOP** the overused medications
3. **CREATE** a prevention & treatment plan to avoid relapse

How is MOH treated?

- MOH can be resolved by **stopping the overused medications.**
- Resolution is a return to episodic headaches (<15 days/month); allow 3 months to establish new baseline.
- Evidence is limited when considering options for how to stop overused meds. **Use a patient centered approach to increase the chances of success when choosing between the options to treat MOH.**

TIPS & TRICKS

- **Educate all patients** on the risk of MOH when using any headache medication. This includes effective dosing, proper timing & usage limits of acute analgesics.
- **Prophylactic meds** may become more effective once the overused medications are stopped.
- **Headache diaries** help to detect triggers and track medication use.
- **Non-drug approaches:**
  - manage triggers (e.g. diet, sleep)
  - physical therapy or exercise
  - relaxation techniques
  - cognitive behavioral therapy

VARIABLES TO CONSIDER	OPTION A: Stop the overused medications abruptly	OPTION B: Stop or taper the overused medications while starting prophylactic medication	OPTION C: Start prophylactic medication only (as headaches decrease, overused medications can be decreased)
Need for additional medications	✓ avoids additional long-term meds, cost, & associated adverse events ✓ may start prophylaxis medications later, after withdrawal	✗ ↑ cost and inconvenience (e.g. starting prophylaxis daily) ✗ ↑ potential for adverse events ✗ prophylaxis can take 8-12 weeks to see full benefit; if unsuccessful with option C, may need to initiate withdrawal later	
Risk of withdrawal symptoms	✗ ↑ potential for worsening withdrawal symptoms in the short term		✓ ↓ potential for severe & sudden withdrawal symptoms
Individualization for success	✗ patient may be unable to tolerate withdrawal symptoms	✓ may give the best chance of success (tackles problem from two sides at once) ✓ prophylaxis may ↓ patient's fear of withdrawal	
Risk of MOH relapse	✗ if unsuccessful, may need to initiate prophylaxis	✓ addition of prophylaxis helps prevent MOH from happening again in the future	

CONSIDER BRIDGING STRATEGIES if unable to tolerate withdrawal, temporary medications can be prescribed e.g. naproxen (if not the offending medication), prednisone or antinauseants such as metoclopramide.

AVOID opioids or barbiturates for most patients due to risks of medication overuse headache, adverse events, and overdose. Do not stop these medications abruptly.

Rx FILES

MIGRAINE PROPHYLAXIS is commonly underutilized... who should consider using it?

PATIENT PREFERENCE
- patient prefers prophylaxis for any reason (e.g. based on their occupation)

FREQUENT ATTACKS
- e.g. >6 headache days/month

SEVERELY DISABLING ATTACKS
- especially if >3/month

DIFFICULT-TO-TREAT ATTACKS
- acute treatment doesn't work well, is contraindicated, or causes problems

SETTING UP AN ADEQUATE TRIAL

1. **Initiate** a headache diary.
2. **Start** a migraine prevention drug at a low dose.
3. **Increase** the dose **gradually**, every 1-2 weeks, guided by target dose range, patient response and tolerability.
4. **Remain** at that dose for ~8-12 weeks to assess effectiveness and tolerability.
5. **Assess and decide** whether to continue, increase the dose, or taper/discontinue the drug.

WHICH AGENT IS BEST?

Individualize choice!

BEST EFFICACY DATA drug & target dose

amitriptyline ~50-**75mg/day** at bedtime
propranolol ~80-**160mg/day**
metoprolol ~100-**200mg/day**
topiramate ~**100mg/day**

FEW ADVERSE EFFECTS

candesartan **16mg/day**
magnesium ~500-**600mg/day**
riboflavin ~**400mg/day**

PRESENCE OF COMORBIDITIES

SMOKING	INSOMNIA
may try nortriptyline	may try amitriptyline

HYPERTENSION	CHRONIC PAIN
may try beta-blocker, candesartan, lisinopril, or possibly verapamil	may try amitriptyline, venlafaxine, duloxetine, topiramate, or possibly gabapentin

DEPRESSION/ANXIETY
• may try venlafaxine, duloxetine, or amitriptyline • optimize the role of non-drug approaches e.g. CBT, lifestyle changes

For detailed info on the advantages and disadvantages of various options, see page 6.

CBT=cognitive behavioural therapy **CGRP**=calcitonin gene-related peptide
OTC=over-the-counter **TCA**=tricyclic antidepressant

TIPS & TRICKS

Set realistic expectations
- e.g. ⬇ in migraine days/month by ≥50%; less severe headaches

Use a headache diary
- e.g. paper or smart phone / app
- watch for triggers & track medication effectiveness & tolerability

Be patient – allow time to stabilize on an effective dose
- effectiveness increases with time
- tolerability improves with time

Help to manage side effects
- e.g. advise on OTC saliva substitutes for dry mouth if using a TCA

If trial fails, consider...
- another drug class, and/or
- combo therapy (drug/drug) or (drug/non-drug)
- a CGRP antagonist, e.g. fremanezumab, if failure with 2 or more conventional agents

Rx FILES
References available at rxfiles.ca/tools.
See also www.rxfiles.ca/migraine.

Migraine Newsletter Acknowledgements & References

Acknowledgements: *Migraine Overview* originally written by Debbie Bunka and Margaret Jin; major revisions in 2021 by Alex Crawley. *Migraine Drug Comparison Charts* originally written by Loren Regier, Brent Jensen, and Sharon Downey; redesigned and major revisions by Alex Crawley in 2021 and 2022. Thanks to our reviewers: Debbie Bunka, Taylor Raiche, Eric Landry, Ryan Fung, Jillian Reardon, Katelyn Halpape, Taisa Trischuk, Tahirih McAleer, Brent Jensen, Julia Bareham, Marlys LeBras, Jackie Myers, Abdul Salama, Dineen Joy, Stephanie Zimmer.
Disclosures: No conflicts of interest are reported by the authors.

NEW neuromodulatory devices: electrical trigeminal nerve stimulation; non-invasive vagus nerve stimulation; remote electrical neuromodulation; single-pulse transcranial magnetic stimulation. Option if contraindications or inadequate responses to triptans.[AHS 2021]
Other nonpharmacological approaches: relaxation training; biofeedback; cognitive behavioural therapy

Table 1. Red Flags for Evaluating Acute Headache.

Danger sign or symptoms	Possible diagnoses	Consider the following tests:
First or worst headache of the patient's life	CNS infection, intracranial hemorrhage	Neuroimaging
Focal neurological signs (not typical aura)	Arteriovenous malformation, collagen vascular disease, intracranial mass lesion	Blood tests, neuroimaging
HA triggered by cough, exertion, or sexual intercourse	Mass lesion, subarachnoid hemorrhage	Lumbar puncture, neuroimaging
HA with change in personality, mental status, level of consciousness	CNS infection, intracerebral bleed, mass lesion	Blood tests, lumbar puncture, neuroimaging
Neck stiffness or meningismus	Meningitis	Lumbar puncture
New onset of severe headache in pregnancy or postpartum	Cortical vein/cranial sinus thrombosis, carotid artery dissection, pituitary apoplexy	Neuroimaging
Age > 50 years	Mass lesion, temporal arteritis	Erythorcyte sedimentation rate, neuroimaging
Papilledema	Encephalitis, mass lesion, meningitis, pseudotumor	Lumbar puncture, neuroimaging
Rapid onset with strenuous exercise	Carotid artery dissection, intracranial bleed	Neuroimaging
Sudden onset (maximal intensity occurs within seconds to minutes, **thunderclap headache**)	Bleeding into a mass or arteriovenous malformation, mass lesion (especially posterior fossa), subarachnoid hemorrhage	Lumbar puncture, neuroimaging
Systemic illness with headache (fever, rash)	Arteritis, collagen vascular disease, encephalitis, meningitis	Blood tests, lumbar puncture, neuroimaging, skin biopsy
Worsening pattern	History of medication overuse, mass lesion, subdural hematoma	Neuroimaging
New headache type in a patient with: Cancer, HIV, Lyme disease	**Cancer**: metastasis, tumor; **HIV**: opportunistic infection, **Lyme**: meningoencephalitis	Lumbar puncture, neuroimaging

Table 2. POUND Mnemonic for Diagnosis of Migraine.[78]

P	**P**ulsatile quality of headache	**1 point**
O	**O**ne-day duration of headache (4-72 hours if untreated or unsuccessfully treated)	**1 point**
U	**U**nilateral headache	**1 point**
N	**N**ausea or vomiting	**1 point**
D	**D**isabling intensity of headache	**1 point**

Likelihood of migraine if seen in primary care:
4 or 5 points = 92%
3 points = 64%
0-2 points = 17%

Table 3. Beta-blocker equivalent doses
Note: dosing is only a guide. Ensure adequate follow-up with patients (e.g. heart rate, blood pressure) when switching between beta-blockers.

Drug	Dosage		
	low	**medium**	**higher**
metoprolol	25mg BID	50mg BID	100mg BID
propranolol	20mg BID	40mg BID	80mg BID
nadolol	40mg daily	80mg daily	160mg daily
timolol	5mg BID	10mg BID	15mg BID
atenolol	25mg daily	50mg daily	100mg daily

Migraine Cover Page References

1. **AHS 2021**. Ailani J, Burch RC, Robbins MS, Board of Directors of the American Headache Society. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. Headache: The Journal of Head and Face Pain. 2021 Jul;61(7):1021-39.
2. SIGN 2018 Guidelines. Available from https://www.sign.ac.uk/media/1091/sign155.pdf
3. VA/DoD 2020. Clinical Practice Guideline for the Primary Care Management of Headache. Available from https://www.healthquality.va.gov/guidelines/pain/headache/VADoDHeadacheCPGFinal508.pdf
4. Cooke LJ, Becker WJ. Migraine prevalence, treatment and impact: the canadian women and migraine study. Canadian journal of neurological sciences. 2010 Sep;37(5):580-7.
5. Swan SK, Alcorn Jr H, Rodgers A, Hustad CM, Ramsey KE, Woll S, Skobieranda F. Pharmacokinetic profile of rizatriptan 10-mg tablet and 10-mg orally disintegrating tablet administered with or without water in healthy subjects: An open-label, randomized, single-dose, 3-period crossover study. The Journal of Clinical Pharmacology. 2006 Feb;46(2):172-8.
6. **CHS 2013**. Worthington I, Pringsheim T, Gawel MJ, Gladstone J, Cooper P, Dilli E, Aube M, et al. Canadian Headache Society Guideline: acute drug therapy for migraine headache. Canadian Journal of Neurological Sciences. 2013 Sep;40(S3):S1-3.
7. **CHS 2012**. Pringsheim T, Davenport W, Mackie G, Worthington I, Aube M, Christie SN, Gladstone J, Becker WJ. Canadian Headache Society guideline for migraine prophylaxis. Can J Neurol Sci. 2012 Mar 1;39(2 Suppl 2):S1-59.
8. MedSask. True or False? Nonsteroidal Anti-inflammatory Drugs (NSAIDs) should be taken with food. Available from https://medsask.usask.ca/documents/NSAIDS-with-Food.pdf
9. Lipton RB, Munjal S, Alam A, Buse DC, Fanning KM, Reed ML, Schwedt TJ, Dodick DW. Migraine in America Symptoms and Treatment (MAST) study: baseline study methods, treatment patterns, and gender differences. Headache: The Journal of Head and Face Pain. 2018 Oct;58(9):1408-26.
10. Ailani J, Burch RC, Robbins MS; Board of Directors of the **American Headache Society (AHS)**. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. Headache. 2021 Jul;61(7):1021-1039.

Migraine Overview and Drug Comparison Charts References

1. **CHS 2012**. Pringsheim T, Davenport W, Mackie G, Worthington I, Aube M, Christie SN, Gladstone J, Becker WJ. Canadian Headache Society guideline for migraine prophylaxis. Can J Neurol Sci. 2012 Mar 1;39(2 Suppl 2):S1-59.
2. **CHS 2013**. Worthington I, Pringsheim T, Gawel MJ, Gladstone J, Cooper P, Dilli E, Aube M, et al. Canadian Headache Society Guideline: acute drug therapy for migraine headache. Canadian Journal of Neurological Sciences. 2013 Sep;40(S3):S1-3.
3. Jelinski SE, Becker WJ, Christie SN et al. Clinical features and pharmacological treatment of migraine patients referred to headache specialists in Canada. *Cephalalgia* 2006; 26:578–588.
4. Gawel MJ, et al. A systematic review of the use of triptans in acute migraine. Can J neurol Sci 2001;28:30-41.
5. Lewis D, Ashwal S, Hershey A, Hirtz D, Yonker M, Silberstein S. Practice Parameter: Pharmacological treatment of migraine headache in **children and adolescents**: Report of the American Academy of Neurology Quality Standards Subcommittee and the Practice Committee of the Child Neurology Society. **Neurology. 2004** Dec 28;63(12):2215-24.
6. Diener HC et al. A practical guide to the management and prevention of migraine. Drugs 1998;56:811-24.
7. Pryse-Phillips WE et al. Guidelines for the diagnosis and management of migraine in clinical practice. CAN Med Assoc J 1997;156(9): 1273-87.
8. Ferrari MD et al. Oral triptans in acute migraine treatment: a meta analysis of 53 trials. The Lancet 2001;358: 1668-75.
9. Limmroth V and Michel M. The prevention of migraine: a critical review with special emphasis on B-adrenoceptor blockers. Br J Cin Pharmacol 2001;52:237-43.
10. Brandes J, Saper J, Diamond M, et al. Topiramate for Migraine Prevention: A Randomized Controlled Trial. JAMA 2004;291 965-973.
11. Silberstein SD, Neto W, Schmitt J, Jacobs D; MIGR-001 Study Group. Topiramate in migraine prevention: results of a large controlled trial. Arch Neurol. 2004 Apr;61(4):490-5.
12. Storey JR et al …Headache 2001;41:968-1000.
13. Topiramate (Topamax) for prevention of migraine. Med Lett Drugs Ther. 2005 Jan 31;47(1201):9-10.
Silberstein S, Lipton R, Dodick D, et al. Topiramate treatment of chronic migraine: a randomized, placebo-controlled trial of quality of life and other efficacy measures. Headache. 2009 Sep;49(8):1153-62.
Linde M, Mulleners WM, Chronicle EP, et al. **Topiramate for the prophylaxis of episodic migraine** in adults. Cochrane Database Syst Rev. 2013 Jun 24;6:CD010610. Meta-analysis demonstrates that topiramate in a 100 mg/day dosage is effective in reducing headache frequency and reasonably well-tolerated in adult patients with episodic migraine. This provides good evidence to support its use in routine clinical management. More studies designed specifically to compare the efficacy or safety of topiramate versus other interventions with proven efficacy in the prophylaxis of migraine are needed.
14. Diener HC, Tfelt-Hansen P, Dahlof C, Lainez MJ, Sandrini G, Wang SJ, Neto W, Vijapurkar U, Doyle A, Jacobs D; MIGR-003 Study Group. Topiramate in migraine prophylaxis—results from a placebo-controlled trial with propranolol as an active control. J Neurol. 2004 Aug;251(8):943-50.
15. Diener HC, Rahlfs VW, Danesch U. The first placebo-controlled trial of a special butterbur root extract for the prevention of migraine: reanalysis of efficacy criteria. Eur Neurol. 2004;51(2):89-97. Epub 2004 Jan 28.
Holland S, Silberstein SD, Freitag F, et al. Evidence-based guideline update: **NSAIDs and other complementary treatments** for episodic migraine prevention in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology (AAN) and American Headache Society (AHS). Neurology. 2012 Apr 24;78(17):1346-53.
16. Blumenfeld A. Botulinum toxin type A as an effective prophylactic treatment in primary headache disorders. Headache. 2003 Sep;43(8):853-60.
Chilson CN, Brown SJ. Role of botulinum toxin type a in the prophylactic treatment of migraine headaches. Ann Pharmacother. 2005 Dec;39(12):2081-5. Epub 2005 Nov 1.
Blumenfeld AM, Schim JD, Chippendale TJ. Botulinum toxin type a and divalproex sodium for prophylactic treatment of episodic or chronic migraine. Headache. 2008 Feb;48(2):210-20. Epub 2007 Nov 28. Both BoNTA and DVPX significantly reduced disability associated with migraine; BoNTA had a favorable tolerability profile compared with DVPX.
Naumann M, So Y, Argoff CE, Childers MK, Dykstra DD, Gronseth GS, Jabbari B, Kaufmann HC, Schurch B, Silberstein SD, Simpson DM; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Assessment: Botulinum neurotoxin in the treatment of autonomic disorders and pain (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2008 May 6;70(19):1707-14. Botulinum neurotoxin (BoNT) should be offered as a treatment option for the treatment of axillary hyperhidrosis and detrusor overactivity (Level A), should be considered for palmar hyperhidrosis, drooling, and detrusor sphincter dyssynergia after spinal cord injury (Level B), and may be considered for gustatory sweating and low back pain (Level C). BoNT is probably ineffective in episodic migraine and chronic tension-type headache (Level B). There is presently no consistent or strong evidence to permit drawing conclusions on the efficacy of BoNT in chronic daily headache (mainly transformed migraine) (Level U). While clinicians' practice may suggest stronger recommendations in some of these indications, evidence-based conclusions are limited by the availability of data.
Lipton RB, Varon SF, Grosberg B,et al. OnabotulinumtoxinA improves quality of life and reduces impact of chronic migraine. Neurology. 2011 Oct 11;77(15):1465-72.
Jackson JL, Kuriyama A, Hayashino Y. Botulinum toxin A for prophylactic treatment of migraine and tension headaches in adults: a meta-analysis. JAMA. 2012 Apr 25;307(16):1736-45.
17. Kurth T, et al. Migraine and risk of **cardiovascular** disease in women. JAMA. 2006 Jul 19;296(3):283-91. Erratum in: JAMA. 2006 Jul 19;296(3):1 p following 291. In this large, prospective cohort of women, active migraine with aura was associated with increased risk of major CVD, myocardial infarction, ischemic stroke, and death due to ischemic CVD, as well as with coronary revascularization and angina. (InfoPOEMs: Women suffering from active migraines with aura are at an increased risk of ischemic vascular events, including coronary heart disease and stroke. In general, this correlates to 18 additional cardiovascular events for every 10,000 women per year. Women with active migraine without aura are not at an increased risk of ischemic vascular disease. (LOE = 2b-))
18 Linde K, Streng A, Jurgens S, et al. Acupuncture for patients with migraine: a randomized controlled trial. JAMA. 2005 May 4;293(17):2118-25. . (InfoPOEMs: Acupuncture and sham acupuncture are equally more effective than no treatment in patients with migraine headaches. These results defend the adage that doing something is better than doing nothing. (LOE = 1b)). & Coeytaux RR, Kaufman JS, Kaptchuk TJ, et al. A randomized, controlled trial of **acupuncture** for chronic daily headache. Headache. 2005 Oct;45(9):1113-23.
Linde K, Allais G, Brinkhaus B, Manheimer E, Vickers A, White AR. **Acupuncture** for migraine prophylaxis. Cochrane Database Syst Rev. 2009 Jan 21;(1):CD001218. In the previous version of this review, evidence in support of acupuncture for migraine prophylaxis was considered promising but insufficient. Now, with 12 additional trials, there is consistent evidence that acupuncture provides additional benefit to treatment of acute migraine attacks only or to routine care. There is no evidence for an effect of 'true' acupuncture over sham interventions, though this is difficult to interpret, as exact point location could be of limited importance. Available studies suggest that acupuncture is at least as effective as, or possibly more effective than, prophylactic drug treatment, and has fewer adverse effects. Acupuncture should be considered a treatment option for patients willing to undergo this treatment. Jena S, Witt CM, Brinkhaus B, Wegscheider K, Willich SN. Acupuncture in patients with headache. Cephalalgia. 2008 Sep;28(9):969-79. Epub 2008 Jul 8. Acupuncture plus routine care in patients with headache was associated with marked clinical improvements compared with routine care alone.
Li Y, Zheng H, Witt CM, et al. **Acupuncture** for migraine prophylaxis: a randomized controlled trial. CMAJ. 2012 Jan 9.
Zhao L, Chen J, Li Y, et al. The long-term effect of **acupuncture** for migraine prophylaxis: a randomized clinical trial [online Feb 20, 2017].
JAMA Intern Med. doi:10.1001 /jamainternmed.2016.9378
Xu S, Yu L, Luo X, et al. Manual acupuncture versus sham **acupuncture** and usual care **for prophylaxis** of episodic migraine without aura: multicentre, randomised clinical trial. BMJ. 2020 Mar 25;368:m697
19. Chronicle E, Mulleners W. Anticonvulsant drugs for migraine prophylaxis. Cochrane Database Syst Rev. 2004;(3):CD003226.
20. Mathew NT, Rapoport A, Saper J, et al. Efficacy of **gabapentin** in migraine prophylaxis. Headache. 2001 Feb;41(2):119-28.
Jafarian S, et al. Gabapentin for prevention of **hypobaric hypoxia-induced headache**: randomized double-blind clinical trial. J Neurol Neurosurg Psychiatry. 2008 Mar;79(3):321-3. Epub 2007 Oct 26.

Linde M, Mulleners WM, Chronicle EP, et al. **Gabapentin or pregabalin for the prophylaxis of episodic migraine in adults.** Cochrane Database Syst Rev. 2013 Jun 24;6:CD010609. doi: 10.1002/14651858.CD010609. The pooled evidence derived from trials of gabapentin suggests that it is not efficacious for the prophylaxis of episodic migraine in adults. Since adverse events were common among the gabapentin-treated patients, it is advocated that gabapentin should not be used in routine clinical practice. Gabapentin enacarbil is not efficacious for the prophylaxis of episodic migraine in adults. There is no published evidence from controlled trials of pregabalin for the prophylaxis of episodic migraine in adults.

21. Pringsheim T, Davenport WJ, Dodick D. Acute treatment and prevention of menstrually related migraine headache: evidence-based review. Neurology. 2008 Apr 22;70(17):1555-63
22. Tfelt-Hansen P. Efficacy and adverse events of subcutaneous, oral, and intranasal sumatriptan used for migraine treatment: a systematic review based on number needed to treat. Cephalalgia. 1998 Oct;18(8):532-8.
23. Nagy AJ, Gandhi S, Bhola R, Goadsby PJ. Intravenous **dihydroergotamine** for inpatient management of refractory primary headaches. Neurology. 2011 Nov 15;77(20):1827-32.
24. MacClellan LR, Giles W, Cole J, Wozniak M, Stern B, Mitchell BD, Kittner SJ. Probable migraine with visual aura and risk of ischemic stroke: the stroke prevention in young women study. Stroke. 2007 Sep 1;38(9):2438-45.
25. Boureau F, Kappos L, Schoenen J, Esperanca P, Ashford E. A clinical comparison of sumatriptan nasal spray and dihydroergotamine nasal spray in the acute treatment of migraine. International journal of clinical practice. 2000 Jun 1;54(5):281-6.
26. Rabbie R, Derry S, Moore RA. Ibuprofen with or without an antiemetic for acute migraine headaches in adults. Cochrane database of systematic reviews. 2013(4).
27. Brandes JL, Kudrow D, Stark SR, O'Carroll CP, Adelman JU, O'Donnell FJ, Alexander WJ, Spruill SE, Barrett PS, Lener SE. Sumatriptan-naproxen for acute treatment of migraine: a randomized trial. Jama. 2007 Apr 4;297(13):1443-54.
28. Prior MJ, Codispoti JR, Fu M. A randomized, placebo-controlled trial of acetaminophen for treatment of migraine headache. Headache. 2010May;50(5):819-33.

Derry S, Moore RA, McQuay HJ. Paracetamol (**acetaminophen**) with or without an antiemetic for acute migraine headaches in adults. Cochrane Database Syst Rev. 2010 Nov 10;11:CD008040. Paracetamol 1000 mg alone is an effective treatment for acute migraine headaches, and the addition of 10 mg metoclopramide gives short-term efficacy equivalent to oral sumatriptan 100 mg. Adverse events with paracetamol did not differ from placebo; ``major`` adverse events were slightly more common with sumatriptan than with paracetamol plus metoclopramide.

Derry S, Moore RA. Paracetamol (**acetaminophen**) with or without an antiemetic for acute migraine headaches in adults. Cochrane Database Syst Rev. 2013 Apr 30;4:CD008040.

Paracetamol 1000 mg alone is statistically superior to placebo in the treatment of acute migraine, but the NNT of 12 for pain-free response at two hours is inferior to at of other commonly used analgesics. Given the low cost and wide availability of paracetamol, it may be a useful first choice drug for acute migraine in those with contraindications to, or who cannot tolerate, non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin. The addition of 10 mg metoclopramide gives short-term efficacy equivalent to oral sumatriptan 100 mg. Adverse events with paracetamol did not differ from placebo; serious and/or severe adverse events were slightly more common with sumatriptan than with paracetamol plus metoclopramide.

29. Shapiro RE, Tepper SJ. The serotonin syndrome, triptans, and the potential for drug–drug interactions. Headache: The Journal of Head and Face Pain. 2007 Feb;47(2):266-9.
30. Colman I, Brown MD, Innes GD, Grafstein E, Roberts TE, Rowe BH. Parenteral metoclopramide for acute migraine: meta-analysis of randomised controlled trials. Bmj. 2004 Dec 9;329(7479):1369. Pooling results of 3 trials, metoclopramide reduced pain in 47/88 patients (55%) compared to 30/97 patients on placebo (30%). Two of the trials measured outcomes at 1 hour, and one trial measured outcomes at 30 minutes.
31. Colman I, Friedman BW, Brown MD, Innes GD, Grafstein E, Roberts TE, Rowe BH. Parenteral dexamethasone for acute severe migraine headache: meta-analysis of randomised controlled trials for preventing recurrence. Bmj. 2008 Jun 12;336(7657):1359-61. Pooling 7 trials, dexamethasone prevented migraine recurrence in 114/385 patients (30%) compared to 141/353 patients on placebo (40%) after 24-72 hours.
32. Silberstein SD, Schulman EA, Hopkins MM. Repetitive intravenous DHE in the treatment of refractory headache. Headache: The Journal of Head and Face Pain. 1990 May;30(6):334-9.
33. Rizatriptan vs rizatriptan plus trimebutine for the acute treatment of migraine: a double blind, randomized, cross-over, placebo-controlled study. Cephalgia 2006;26:871-4.
34. Law S, Derry S, Moore RA. **Sumatriptan plus naproxen** for acute migraine attacks in adults. Cochrane Database Syst Rev. 2013 Oct 21;10:CD008541. Combination treatment was effective in the acute treatment of migraine headaches. The effect was greater than for the same dose of either sumatriptan or naproxen alone, but additional benefits over sumatriptan alone are not large. More participants achieved good relief when medication was taken early in the attack, when pain was still mild. Adverse events were more common with the combination and sumatriptan alone than with placebo or naproxen alone.
35. Rozen TD. Emergency department and inpatient management of status migrainosus and intractable headache. Continuum: Lifelong Learning in Neurology. 2015 Aug 1;21(4):1004-17.
36. Ashina M, Buse DC, Ashina H, Pozo-Rosich P, Peres MF, Lee MJ, Terwindt GM, Singh RH, Tassorelli C, Do TP, Mitsikostas DD. Migraine: integrated approaches to clinical management and emerging treatments. The Lancet. 2021 Mar 25.
37. Kurian A, Reghunadhan I, Thilak P, Soman I, Nair U. Short-term efficacy and safety of topical β-blockers (timolol maleate ophthalmic solution, 0.5%) in acute migraine: a randomized crossover trial. JAMA ophthalmology. 2020 Nov 1;138(11):1160-6.
38. Migliazzo CV, Hagan III JC. Beta blocker eye drops for treatment of acute migraine. Missouri medicine. 2014 Jul;111(4):283.
39. Croop R, Lipton RB, Kudrow D, Stock DA, Kamen L, Conway CM, Stock EG, Coric V, Goadsby PJ. Oral rimegepant for preventive treatment of migraine: a phase 2/3, randomised, double-blind, placebo-controlled trial. The Lancet. 2021 Jan 2;397(10268):51-60.
40. Reuter U, Goadsby PJ, Lanteri-Minet M, Wen S, Hours-Zesiger P, Ferrari MD, Klatt J. Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomised, double-blind, placebo-controlled, phase 3b study. The Lancet. 2018 Nov 24;392(10161):2280-7.
41. Mullin K, Hutchinson S, Smith T, Lipton R, Jensen C, Leroue C, Thiry A, Lovegren M, Conway C, Coric V, Croop R. Rimegepant 75 mg for the Acute Treatment of Migraine in Adults With Frequent Migraine: Long-Term Safety and Clinical Improvement Versus Baseline (5054).
42. Kuca B, Silberstein SD, Wietecha L, Berg PH, Dozier G, Lipton RB, COL MIG-301 Study Group. Lasmiditan is an effective acute treatment for migraine: A phase 3 randomized study. Neurology. 2018 Dec 11;91(24):e2222-32.
43. Cohen F, Friedman BW. A randomized study of IV prochlorperazine plus diphenhydramine versus IV hydromorphone for migraine-associated symptoms: A post hoc analysis. Headache: The Journal of Head and Face Pain. 2021 Sep;61(8):1227-33.
44. Ozkurt B, Cinar O, Cevik E, et al. Efficacy of high-flow oxygen therapy in all types of headache: prospective, randomized, placebo-controlled trial. Am J Emerg Med. 2012 May 2.
45. Stovner LJ, Linde M, Gravdahl GB, Tronvik E, Aamodt AH, Sand T, Hagen K. A comparative study of candesartan versus propranolol for migraine prophylaxis: A randomised, triple-blind, placebo-controlled, double cross-over study. Cephalalgia. 2014 Jun;34(7):523-32.
46. Kelman L. The triggers or precipitants of the acute migraine attack. *Cephalalgia* 2007 May; 27(5):394-402
47. MacGregor eA, Wilkinson M, Bancroft K. domperidone plus paracetamol in the treatment of migraine. Cephalalgia. 1993;13: 124-7.
48. Shamliyan TA, Kane RL, Taylor FR. Migraine in Adults: Preventive Pharmacologic Treatments. Comparative Effectiveness Review No. 103. (Prepared by the University of Minnesota Evidence-based Practice Center under Contract No. 290-2007-10064-I) AHRQ Publication No. 13-EHC068-EF. Rockville, MD: Agency for Healthcare Research and Quality; April 2013. www.effectivehealthcare.ahrq.gov/reports/final.cfm.
49. Silberstein SD. Practice parameter: Evidence-based guidelines for migraine headache (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2000; 55(6):754-762.
50. Lipton RB, Scher AI, Kolodner K, et al. Migraine in the United States: epidemiology and patterns of health care use. Neurology. 2002 Mar 26;58(6):885-94. PMID 11914403
51. Lipton RB, Bigal ME, Diamon M, et al. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology. 2007 Jan 30;68(5):343-9. PMID 1726168012.
53. Goadsby PJ, Goldberg J, Silberstein SD. Migraine in pregnancy. BMJ. 2008 Jun 28;336(7659):1502-4.
54. Clinch R. Evaluation of acute headaches in adults. Am Fam Physician 2001;63:685-92.

55. Headache. **Four Things Physicians and Patients Should Question.** July 2020. Accessed from https://choosingwiselycanada.org/headache/
56. Leroux E, Buchanan A, Lombard L, Loo LS, Bridge D, Rousseau B, Hopwood N, Matthews BR, Reuter U. Evaluation of patients with insufficient efficacy and/or tolerability to triptans for the acute treatment of migraine: a systematic literature review. Advances in therapy. 2020 Dec;37(12):4765-96.
57. Carlsen LN, Munksgaard SB, Nielsen M, Engelstoft IM, Westergaard ML, et al. Comparison of 3 treatment strategies for medication overuse headache: a randomized clinical trial. JAMA neurology. 2020 Sep 1;77(9):1069-78.
58. Mathew NT. Amelioration of ergotamine withdrawal symptoms with naproxen. Headache: The Journal of Head and Face Pain. 1987 Mar;27(3):130-3.
59. Raskin NH. Repetitive intravenous dihydroergotamine as therapy for intractable migraine. Neurology. 1986 Jul 1;36(7):995.
60. Evers S, Jensen R. Treatment of medication overuse headache–guideline of the EFNS headache panel. European Journal of Neurology. 2011 Sep;18(9):1115-21.
61. Monastero R, Camarda C, Pipia C, Camarda R. Prognosis of migraine headaches in adolescents: a 10-year follow-up study. Neurology. 2006 Oct 24;67(8):1353-6.
62. Pringsheim T, Davenport WJ, Dodick D. Acute treatment and prevention of menstrually related migraine headache: evidence-based review. Neurology. 2008 Apr 22;70(17):1555-63
63. Ahonen K, Hämäläinen ML, Eerola M, Hoppu K. A randomized trial of rizatriptan in migraine attacks in children. Neurology. 2006 Oct 10;67(7):1135-40.
64. Diener HC, Montagna P, Gacs G, Lyczak P, Schumann G, Zöller B, Mulder LJ, Siegel J, Edson K, Study Group∗. Efficacy and tolerability of diclofenac potassium sachets in migraine: a randomized, double-blind, cross-over study in comparison with diclofenac potassium tablets and placebo. Cephalalgia. 2006 May;26(5):537-47. Diclofenac sachets provided slightly better pain-free efficacy at 2 hrs versus diclofenac potassium tabs, 25% vs 19%, NNT=16.
65. Linde M, Mulleners WM, Chronicle EP, McCrory DC. Topiramate for the prophylaxis of episodic migraine in adults. Cochrane Database of Systematic Reviews. 2013(6).
66. Diener HC, Gendolla A, Fruersenger A, Evers S, Straube A, Schumacher H, Davidai G, Study Group. Telmisartan in migraine prophylaxis: a randomized, placebo-controlled trial. Cephalalgia. 2009 Sep;29(9):921-7.
67. Stovner LJ, Linde M, Gravdahl GB, et al. A comparative study of candesartan versus propranolol for migraine prophylaxis: A randomised, triple-blind, placebo-controlled, double cross-over study. Cephalalgia. 2014 Jun;34(7):523-32.
68. Schrader H, Stovner LJ, Helde G, Sand T, Bovim G. Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomised, placebo controlled, crossover study. Bmj. 2001 Jan 6;322(7277):19.
69. Powers SW, Coffey CS, Chamberlin LA, Ecklund DJ, Klingner EA, Yankey JW, Korbee LL, et al. Trial of amitriptyline, topiramate, and placebo for pediatric migraine. New England Journal of Medicine. 2017 Jan 12;376(2):115-24.
70. Pringsheim T, Davenport WJ, Dodick D. Acute treatment and prevention of menstrually related migraine headache: evidence-based review. Neurology. 2008 Apr 22;70(17):1555-63.
71. **AHS 2019**. American Headache Society. The American Headache Society position statement on integrating new migraine treatments into clinical practice. Headache: The Journal of Head and Face Pain. 2019 Jan;59(1):1-8.
72. **AAN 2012**. Loder E, Burch R, Rizzoli P. The 2012 AHS/AAN guidelines for prevention of episodic migraine: a summary and comparison with other recent clinical practice guidelines. Headache: The Journal of Head and Face Pain. 2012 Jun;52(6):930-45.
73. **NICE 2012** (updated 2021). Carville S, Padhi S, Reason T, Underwood M. Diagnosis and management of headaches in young people and adults: summary of NICE guidance. Bmj. 2012 Sep 19;345.
74. **VA/DoD 2020**. Clinical Practice Guideline for the Primary Care Management of Headache. Available from https://www.healthquality.va.gov/guidelines/pain/headache/VADoDHeadacheCPGFinal508.pdf
75. Derry CJ, Derry S, Moore RA. **Sumatriptan (all routes of administration) for acute migraine** attacks in adults - overview of Cochrane reviews. Cochrane Database of Systematic Reviews 2014, Issue 5. Art. No.: CD009108. DOI: 10.1002/14651858.CD009108.pub2
76. Smith MA and Ross MB. Oral 5HT1 receptor agonists for migraine: comparative considerations. Formulary 1999; 34:324-38.
77. van Casteren DS, Verhagen IE, van der Arend BW, van Zwet EW, MaassenVanDenBrink A, Terwindt GM. Comparing perimenstrual and nonperimenstrual migraine attacks using an e-diary. Neurology. 2021 Oct 26;97(17):e1661-71.
78. Mayans L, Walling A. Acute migraine headache: treatment strategies. American family physician. 2018 Feb 15;97(4):243-51.
79. Morales DR, Lipworth BJ, Donnan PT, Jackson C, Guthrie B. Respiratory effect of beta-blockers in people with asthma and cardiovascular disease: population-based nested case control study. BMC medicine. 2017 Dec;15(1):1-9.
80. Lipton RB, Stewart WF, Stone AM, Láinez MJ, Sawyer JP. Stratified care vs step care strategies for migraine: the Disability in Strategies of Care (DISC) Study: a randomized trial. Jama. 2000 Nov 22;284(20):2599-605.
81. Suthisisang CC, Poolsup N, Suksomboon N, Lertpipopmetha V, Tepwitukgid B. Meta-analysis of the efficacy and safety of naproxen sodium in the acute treatment of migraine. Headache: The Journal of Head and Face Pain. 2010 May;50(5):808-18.
82. Rabbie R, Derry S, Moore RA, McQuay HJ. Ibuprofen with or without an antiemetic for acute migraine headaches in adults. Cochrane database of systematic reviews. 2010(10).
83. Prior MJ, Codispoti JR, Fu M. A randomized, placebo-controlled trial of acetaminophen for treatment of migraine headache. Headache: The Journal of Head and Face Pain. 2010 May;50(5):819-33.
84. Derry S, Moore RA. Paracetamol (acetaminophen) with or without an antiemetic for acute migraine headaches in adults. Cochrane database of systematic reviews. 2013(4).
85. Silberstein SD, Holland S, Freitag F, et al. Evidence-based guideline update: **Pharmacologic treatment for episodic migraine prevention in adults**: Report of the Quality Standards Subcommittee of the American Academy of Neurology (AAN) and American Headache Society (AHS). Neurology. 2012 Apr 24;78(17):1337-45.
86. Diener HC, Gendolla A, Feuersenger A, et al. Telmisartan in migraine prophylaxis: A randomized, placebo-controlled trial. Cephalalgia. Sep 2009;29(9):921-927. PMID: 19250283.
87. Okoli GN, Rabbani R, Kashani HH, et al. Vitamins and minerals for migraine prophylaxis: A Systematic review and meta-analysis. Can J Neurol Sci. Mar 2019;46(2):224-233. https://www.cambridge.org/core/journals/canadian-journal-of-neurological-sciences/article/vitamins-and-minerals-for-migraine-prophylaxis-a-systematic-review-and-metaanalysis/284FF3EC573FA098FB36A302951760D5
88. Shanmugam S, Karunaikadal K, Varadarajan S, Krishnan M. Memantine ameliorates migraine headache. Ann Indian Acad Neurol. 2019;22(3):286-290.
89. **AHS 2021**. Ailani J, Burch RC, Robbins MS, Board of Directors of the American Headache Society. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. Headache: The Journal of Head and Face Pain. 2021 Jul;61(7):1021-39.
90. Page RL, O'Bryant CL, Cheng D, Dow TJ, Ky B, Stein CM, Spencer AP, Trupp RJ, Lindenfeld J. Drugs that may cause or exacerbate heart failure: a scientific statement from the American Heart Association. Circulation. 2016 Aug 9;134(6):e32-69.
91. Fragoso YD, Lopes GC, Santos GM, Carturan P, Martimbianco AL. Pizotifen for the treatment of migraine. A systematic review and meta-analysis. Headache Medicine. 2021 Oct 26:168-81.
92. Rajapakse T, Pringsheim T. Nutraceuticals in migraine: a summary of existing guidelines for use. Headache: The Journal of Head and Face Pain. 2016 Apr;56(4):808-16.
93. **Target dosing for Migraine Headaches** – dosing combined from a variety of sources.
    Pringsheim T, Davenport WJ, Becker WJ. Prophylaxis of migraine headache. Cmaj. 2010 Apr 20;182(7):E269-76.
    CHS 2012. Pringsheim T, Davenport W, Mackie G, Worthington I, Aube M, Christie SN, Gladstone J, Becker WJ. Canadian Headache Society guideline for migraine prophylaxis. Can J Neurol Sci. 2012 Mar 1;39(2 Suppl 2):S1-59.
    TOP 2016. Toward Optimized Practice. Primary Care Management of Headache in Adults, 2nd ed. Available from https://actt.albertadoctors.org/CPGs/Pages/Headache.aspx
    Jackson JL, Shimeall W, Sessums L, DeZee KJ, Becher D, Diemer M, Berbano E, O'Malley PG. Tricyclic antidepressants and headaches: systematic review and meta-analysis. Bmj. 2010 Oct 20;341.
    Linde M, Mulleners WM, Chronicle EP, McCrory DC. Topiramate for the prophylaxis of episodic migraine in adults. Cochrane Database of Systematic Reviews. 2013(6).
    Okoli, George N., et al. Vitamins and minerals for migraine prophylaxis: a systematic review and meta-analysis. Canadian Journal of Neurological Sciences 46.2 (2019): 224-233.
    Ha H, Gonzalez A. Migraine headache prophylaxis. American family physician. 2019 Jan 1;99(1):17-24.
    VA/DoD 2020. Clinical Practice Guideline for the Primary Care Management of Headache. Available from https://www.healthquality.va.gov/guidelines/pain/headache/VADoDHeadacheCPGFinal508.pdf
94. Bendtsen L, Sacco S, Ashina M, Mitsikostas D, Ahmed F, Pozo-Rosich P, Martelletti P. Guideline on the use of onabotulinumtoxinA in chronic migraine: a consensus statement from the European Headache Federation. The journal of headache and pain. 2018 Dec;19(1):1-0.

95. **TOP 2016**. Toward Optimized Practice. Primary Care Management of Headache in Adults, 2nd ed. Available from https://actt.albertadoctors.org/CPGs/Pages/Headache.aspx
96. Trkulja S, Huyghebaert T, Ton J, Svrcek C. Frequent migraines are a headache: Can biologics help? Tools for Practice, August 2021. Accessed 01 Feb 2022 online.
97. RxFiles. Acute Migraine Therapy Infographic
98. Breen ID, Brumfiel CM, Patel MH, Butterfield RJ, VanderPluym JH, Griffing L, Pittelkow MR, Mangold AR. Evaluation of the safety of calcitonin gene-related peptide antagonists for migraine treatment among adults with Raynaud phenomenon. JAMA Network Open. 2021 Apr 1;4(4):e217934-.

Migraine Colour Comparison Chart References

1 Natural Medicines. (2021, March 24). Monographs for riboflavin, magnesium, butterbur, coenzyme q10, melatonin. http://naturalmedicines.therapeuticresearch.com

2 A) Gupta, Adarsh, Can **topiramate** help to prevent episodic migraine in adults?, **Cochrane** Clinical Answers,2016,10.1002/cca.1481. Accessed online 01 Feb 2022 at https://doi.org//10.1002/cca.1481.
B) Linde_M, Mulleners_WM, Chronicle_EP, McCrory_DC. Topiramate for the prophylaxis of episodic migraine in adults. ***Cochrane*** *Database of Systematic Reviews* 2013, Issue 6. Art. No.: CD010610. DOI: 10.1002/14651858.CD010610.

3 Kapusta M, Allan GM. Are **antihypertensive** medications effective for migraine prophylaxis? **Tools for Practice** #52. Available at: https://gomainpro.ca/wp-content/uploads/tools-forpractice/1433184708_updatedtfp52antihypertensivesmigraineprophylaxis.pdf

4 Braschi E (Updated); Allan GM, Levy M (Original). **Antidepressants** for preventing headaches: Which work and how well? **Tools for Practice**, April 2015. Accessed 01 Feb 2022 online

5 Stovner LJ, Linde M, Gravdahl GB, Tronvik E, Aamodt AH, Sand T, Hagen K. A comparative study of **candesartan** versus propranolol for migraine prophylaxis: A randomised, triple-blind, placebo-controlled, double cross-over study. Cephalalgia. 2014 Jun;34(7):523-32.

6 Trkulja S, Huyghebaert T, Ton J, Svrcek C. Frequent migraines are a headache: Can biologics help? Tools for Practice, August 2021. Accessed 01 Feb 2022 online.

7 Krymchantowski AV, da Cunha Jevoux C and Bigal ME. **Topiramate plus nortriptyline** in the preventive treatment of migraine: a controlled study for nonresponders. J Headache Pain 2012; 13(1): 53–59.

8 Facchinetti F, Sances G, Borella P, Genazzani AR, Nappi G. Magnesium prophylaxis of menstrual migraine: effects on intracellular magnesium. *Headache*. 1991;31(5):298-301. doi:10.1111/j.1526-4610.1991.hed3105298.

9 Jackson JL, Cogbill E, Santana-Davila R, et al. A **comparative effectiveness meta-analysis** of drugs for the prophylaxis of migraine headache. PLoS One 2015; 10(7): e0130733.

10 Pringsheim T, Davenport W, Mackie G, Worthington I, Aubé M, Christie SN, Gladstone J, Becker WJ; **Canadian Headache Society Prophylactic Guidelines** Development Group. Canadian Headache Society guideline for migraine prophylaxis. Can J Neurol Sci. 2012 Mar;39(2 Suppl 2):S1-59. PMID: 22683887.

11 Loder E, Burch R, Rizzoli P. The 2012 **AHS/AAN guidelines** for prevention of episodic migraine: a summary and comparison with other recent clinical practice guidelines. Headache. 2012 Jun;52(6):930-45. doi: 10.1111/j.1526-4610.2012.02185.x. PMID: 22671714.

12 Kahriman A, Zhu S. Migraine and Tension-Type Headache. Semin Neurol. 2018 Dec;38(6):608-618. doi: 10.1055/s-0038-1673683. Epub 2018 Dec 6. PMID: 30522135.

13 Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A, Sándor PS; European Federation of Neurological Societies. **EFNS guideline** on the drug treatment of migraine--revised report of an EFNS task force. Eur J Neurol. 2009 Sep;16(9):968-81. doi: 10.1111/j.1468-1331.2009.02748.x. PMID: 19708964.

14 Ailani J, Burch RC, Robbins MS; Board of Directors of the **American Headache Society (AHS)**. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. Headache. 2021 Jul;61(7):1021-1039. doi: 10.1111/head.14153. Epub 2021 Jun 23. PMID: 34160823.

15 A) Holroyd KA, Penzien DB and Cordingley GE. **Propranolol** in the management of recurrent migraine: a meta-analytic review. Headache 1991; 31(5): 333–340.
B) Silberstein SD and Goadsby PJ. Migraine: preventive treatment. Cephalalgia 2002; 22(7): 491–512.

16 Jackson JL, Kuriyama A, Kuwatsuka Y, Nickoloff S, Storch D, Jackson W, Zhang ZJ, Hayashino Y. Beta-blockers for the prevention of headache in adults, a systematic review and meta-analysis. PLoS One. 2019 Mar 20;14(3):e0212785.

17 Linde K and Rossnagel K. **Propranolol** for migraine prophylaxis. **Cochrane** Database Syst Rev 2004; 2: CD003225.

18 van de Ven LL, Franke CL, Koehler PJ. Prophylactic treatment of migraine with **bisoprolol**: a placebo-controlled study. Cephalalgia. 1997 Aug;17(5):596-9. doi: 10.1046/j.1468-2982.1997.1705596.x. PMID: 9251876.

19 Carlsen LN, Munksgaard SB, Nielsen M, et al. Comparison of **3 Treatment Strategies for Medication Overuse Headache**: A Randomized Clinical Trial. *JAMA Neurol.* 2020;77(9):1069–1078. doi:10.1001/jamaneurol.2020.1179.

20 Linde_M, Mulleners_WM, Chronicle_EP, McCrory_DC. **Valproate** (valproic acid or sodium valproate or a combination of the two) for the prophylaxis of episodic migraine in adults. ***Cochrane*** *Database of Systematic Reviews* 2013, Issue 6. Art. No.: CD010611.

21 Mulleners WM, McCrory DC, Linde M. **Antiepileptics** in migraine prophylaxis: an updated **Cochrane** review. Cephalalgia. 2015 Jan;35(1):51-62. doi: 10.1177/0333102414534325. Epub 2014 Aug 12. PMID: 25115844.

22 Gupta A. Can **topiramate** help prevent episodic migraine in adults. **Cochrane Clinical Answers**, 2016. Accessed online 02 Feb 2022.

23 Dodick DW, Freitag F, Banks J, Saper J, Xiang J, Rupnow M, Biondi D, Greenberg SJ, Hulihan J; CAPSS-277 Investigator Group. **Topiramate versus amitriptyline** in migraine prevention: a 26-week, multicenter, randomized, double-blind, double-dummy, parallel-group noninferiority trial in adult migraineurs. Clin Ther. 2009 Mar;31(3):542-59. doi: 10.1016/j.clinthera.2009.03.020. PMID: 19393844.

24 Steiner TJ, Linde M. **Cochrane**, and the truth about **gabapentin** for migraine. Headache. 2014 May;54(5):920-1. doi: 10.1111/head.12360. PMID: 24797486.

25 Steiner TJ, Findley LJ and Yuen AW. **Lamotrigine** versus placebo in the prophylaxis of migraine with and without aura. Cephalalgia 1997; 17(2): 109–112.

26 Diener H-C, Holle-Lee D, Nägel S, Dresler T, Gaul C, Göbel H, et al. Treatment of Migraine Attacks and Prevention of Migraine: **Guidelines by the German Migraine and Headache Society** and the German Society of Neurology. *Clinical and Translational Neuroscience*. 2019; 3(1):3. https://doi.org/10.1177/2514183x18823377.

27 Jackson JL, Cogbill E, Santana-Davila R, Eldredge C, Collier W, et al. (2015) A Comparative Effectiveness Meta-Analysis of Drugs for the Prophylaxis of Migraine Headache. PLOS ONE 10(7): e0130733. https://doi.org/10.1371/journal.pone.0130733.

28 Carlsen LN, Munksgaard SB, Nielsen M, et al. Comparison of 3 Treatment Strategies for Medication Overuse Headache: A Randomized Clinical Trial. *JAMA Neurol.* 2020;77(9):1069–1078. doi:10.1001/jamaneurol.2020.1179.

29 Banzi_R, Cusi_C, Randazzo_C, Sterzi_R, Tedesco_D, Moja_L. Selective serotonin reuptake inhibitors (SSRIs) and serotoninnorepinephrine reuptake inhibitors (SNRIs) for the prevention of **migraine** in adults. ***Cochrane*** *Database of Systematic Reviews* 2015, Issue 4. Art. No.: CD002919.

30 Banzi_R, Cusi_C, Randazzo_C, Sterzi_R, Tedesco_D, Moja_L. Selective serotonin reuptake inhibitors (SSRIs) and serotoninnorepinephrine reuptake inhibitors (SNRIs) for the prevention of **tension-type headache** in adults. ***Cochrane*** *Database of Systematic Reviews* 2015, Issue 5. Art. No.: CD011681.**https://doi.org/10.1002/cca.1481.**

31 Zissis NP, Harmoussi S, Vlaikidis N, Mitsikostas D, Thomaidis T, Georgiadis G, Karageorgiou K. A randomized, double-blind, placebo-controlled study of venlafaxine XR in out-patients with tension-type headache. Cephalalgia. 2007 Apr;27(4):315-24. doi: 10.1111/j.1468-2982.2007.01300.x. Epub 2007 Mar 7. PMID: 17346304.

32 Silberstein SD, Holland S, Freitag F, et al. **Evidence-based guideline update**: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the **American Academy of Neurology and the American Headache Society** [published correction appears in Neurology. 2013 Feb 26;80(9):871]. *Neurology*. **2012**;78(17):1337-1345. doi:10.1212/WNL.0b013e3182535d20.

33 Leone M, D'Amico D, Frediani F, Moschiano F, Grazzi L, Attanasio A, Bussone G. Verapamil in the prophylaxis of episodic cluster headache: a double-blind study versus placebo. Neurology. 2000 Mar 28;54(6):1382-5. doi: 10.1212/wnl.54.6.1382. PMID: 10746617.

34 RS K. Migraine aura without headache: Benign, but a diagnosis of exclusion. *Cleveland Clinic Journal of Medicine.* Vol 722005:6.

35 Tronvik E, Stovner LJ, Helde G, et al. Prophylactic treatment of migraine with an **angiotensin II receptor blocker**: a randomized controlled trial. JAMA 2003; 289(1): 65–69.

36 Schrader H, Stovner LJ, Helde G, et al. Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomised, placebo controlled, crossover study. BMJ 2001; 322(7277): 19–22.

37 Diener HC, Gendolla A, Feuersenger A, Evers S, Straube A, Schumacher H, Davidai G. Telmisartan in migraine prophylaxis: a randomized, placebo-controlled trial. Cephalalgia. 2009 Sep;29(9):921-7. doi: 10.1111/j.1468-2982.2008.01825.x. PMID: 19250283.

38 Stovner LJ, Linde M, Gravdahl GB, Tronvik E, Aamodt AH, Sand T, Hagen K. A comparative study of candesartan versus propranolol for migraine prophylaxis: A randomised, triple-blind, placebo-controlled, double cross-over study. Cephalalgia. 2014 Jun;34(7):523-32.

39 Carlsen LN, Munksgaard SB, Nielsen M, et al. Comparison of 3 Treatment Strategies for **Medication Overuse Headache**: A Randomized Clinical Trial. *JAMA Neurol.* 2020;77(9):1069–1078. doi:10.1001/jamaneurol.2020.1179.

40 **Monoclonal antibodies to prevent migraine** headaches. Ottawa: **CADTH**; 2018 Feb. (CADTH issues in emerging health technologies, issue 167).

41 Gao B, Sun N, Yang Y, Sun Y, Chen M, Chen Z and Wang Z (2020) Safety and Efficacy of Fremanezumab for the Prevention of Migraine: A Meta-Analysis From Randomized Controlled Trials. Front. Neurol. 11:435. doi: 10.3389/fneur.2020.00435.

42 Trkulja S, Huyghebaert T, Ton J, Svrcek C. **Frequent migraines are a headache: Can biologics help? Tools for Practice**, August 2021. Accessed 01 Feb 2022 online.

[43] Diener HC, Förderreuther S, Gaul C, et al. Prevention of migraine with monoclonal antibodies against CGRP or the CGRP receptor: Addition to the S1 guideline: Therapy of migraine attacks and prevention of migraine. Recommendations of the Germany Society of Neurology and the German Migraine and Headache Society. *Neurol Res Pract*. 2020;2:11. Published 2020 Apr 13. doi:10.1186/s42466-020-00057-1.

[44] Overeem LH, Raffaelli B, Mecklenburg J, Kelderman T, Neeb L, Reuter U. **Indirect Comparison of Topiramate and Monoclonal Antibodies Against CGRP or Its Receptor** for the Prophylaxis of Episodic Migraine: A Systematic Review with Meta-Analysis. *CNS Drugs*. 2021;35(8):805-820. doi:10.1007/s40263-021-00834-9.

[45] Masoud AT, Hasan MT, Sayed A, et al. Efficacy of calcitonin gene-related peptide (CGRP) receptor blockers in reducing the number of monthly migraine headache days (MHDs): A network meta-analysis of randomized controlled trials. *J Neurol Sci*. 2021;427:117505. doi:10.1016/j.jns.2021.117505.

[46] Drellia K, Kokoti L, Deligianni CI, Papadopoulos D, Mitsikostas DD. Anti-CGRP monoclonal antibodies for migraine prevention: A systematic review and likelihood to help or harm analysis [published correction appears in Cephalalgia. 2022 Jan;42(1):90]. *Cephalalgia*. 2021;41(7):851-864.

[47] Chan C, Goadsby PJ. CGRP pathway monoclonal antibodies for **cluster headache**. *Expert Opin Biol Ther*. 2020;20(8):947-953. doi:10.1080/14712598.2020.1751114.

[48] Hoskin JL, Fife TD. New Anti-CGRP Medications in the Treatment of **Vestibular Migraine**. *Front Neurol*. 2022;12:799002. Published 2022 Jan 27. doi:10.3389/fneur.2021.799002.

[49] Schoenen J, Jacquy J, Lenaerts M. Effectiveness of high-dose **riboflavin** in migraine prophylaxis. A randomized controlled trial. Neurology. 1998 Feb;50(2):466-70. doi: 10.1212/wnl.50.2.466. PMID: 9484373.

[50] Teigen L, Boes CJ. An evidence-based review of oral **magnesium** supplementation in the preventive treatment of migraine. Cephalalgia. 2015 Sep;35(10):912-22. doi: 10.1177/0333102414564891. Epub 2014 Dec 22. PMID: 25533715.

[51] Sándor PS, Di Clemente L, Coppola G, Saenger U, Fumal A, Magis D, Seidel L, Agosti RM, Schoenen J. Efficacy of coenzyme **Q10** in migraine prophylaxis: a randomized controlled trial. Neurology. 2005 Feb 22;64(4):713-5. doi: 10.1212/01.WNL.0000151975.03598.ED. PMID: 15728298.

[52] Leite Pacheco R, de Oliveira Cruz Latorraca C, Adriano Leal Freitas da Costa A, Luiza Cabrera Martimbianco A, Vianna Pachito D, Riera R. **Melatonin** for preventing primary headache: A systematic review. Int J Clin Pract. 2018 Jul;72(7):e13203. doi: 10.1111/ijcp.13203. Epub 2018 May 24. PMID: 29799148.

[53] Robbins MS. Diagnosis and Management of Headache: A Review. *JAMA*. 2021;325(18):1874–1885. doi:10.1001/jama.2021.1640.

[54] Holroyd KA, Cottrell CK, O'Donnell FJ, Cordingley GE, Drew JB, Carlson BW, Himawan L. Effect of preventive (beta blocker) treatment, behavioural migraine management, or their combination on outcomes of optimised acute treatment in frequent migraine: randomised controlled trial. BMJ. 2010 Sep 29;341:c4871. doi: 10.1136/bmj.c4871. PMID: 20880898; PMCID: PMC2947621.

[55] Linde K, Allais G, Brinkhaus B, Manheimer E, Vickers A, White AR. **Acupuncture** for migraine prophylaxis. ***Cochrane*** *Database Syst Rev*. 2009:CD001218. PM:19160193.

[56] Raucci U, Boni A, Evangelisti M, et al. **Lifestyle Modifications** to Help Prevent Headache at a Developmental Age. *Front Neurol*. 2021;11:618375. Published 2021 Feb 2. doi:10.3389/fneur.2020.618375.

[57] Herd_CP, Tomlinson_CL, Rick_C, Scotton_WJ, Edwards_J, Ives_N, Clarke_CE, Sinclair_A. **Botulinum toxins** for the prevention of migraine in adults. ***Cochrane*** *Database of Systematic Reviews* 2018, Issue 6. Art. No.: CD011616. DOI: 10.1002/14651858.CD011616.pub2.

[58] Mistry VM, Morizio PL, Pepin MJ, Bryan WE, Brown JN. Role of **memantine** in the prophylactic treatment of episodic migraine: A systematic review. *Headache*. 2021;61(8):1207-1213. doi:10.1111/head.14186.

[59] Prochazka AV, Weaver MJ, Keller RT, Fryer GE, Licari PA, Lofaso D. A randomized trial of nortriptyline for smoking cessation. *Arch Intern Med*. 1998;158(18):2035-2039. doi:10.1001/archinte.158.18.2035.

[60] Breen ID, Brumfiel CM, Patel MH, et al. Evaluation of the Safety of Calcitonin Gene-Related Peptide Antagonists for Migraine Treatment Among Adults With Raynaud Phenomenon. *JAMA Netw Open*. 2021;4(4):e217934. Published 2021 Apr 1.

[61] In brief: Hypertension with erenumab (Aimovig). *Med Lett Drugs Ther*. 2021;63(1621):56.

[62] Al Saadi T, Assaf Y, Farwati M, Turkmani K, Al-Mouakeh A, Shebli B, Khoja M, Essali A, Madmani ME. Coenzyme Q10 for heart failure. Cochrane Database of Systematic Reviews 2021, Issue 2. Art. No.: CD008684. DOI: 10.1002/14651858.CD008684.pub3. March 2022.

[63] Ko DT, Hebert PR, Coffey CS, Sedrakyan A, Curtis JP, Krumholz HM. Beta-blocker therapy and symptoms of depression, fatigue, and sexual dysfunction. *JAMA*. 2002;288(3):351-357. doi:10.1001/jama.288.3.351.

[64] Lipton RB, Cohen JM, Galic M, et al. Effects of fremanezumab in patients with chronic migraine and comorbid depression: Subgroup analysis of the randomized **HALO CM** study. *Headache*. 2021;61(4):662-672. doi:10.1111/head.14097

[65] Hill T, Coupland C, Morriss R, Arthur A, Moore M, Hippisley-Cox J. Antidepressant use and risk of epilepsy and seizures in people aged 20 to 64 years: cohort study using a primary care database. *BMC Psychiatry*. 2015;15:315. Published 2015 Dec 17. doi:10.1186/s12888-015-0701-9.

[66] Jarvis S, Dassan P, Piercy CN. Managing **migraine in pregnancy**. *BMJ*. 2018;360:k80. Published 2018 Jan 25. doi:10.1136/bmj.k80.

[67] Drugs in Pregnancy and Lactation. 11th ed. Briggs GE, Freeman RK, Towers CV et al. Williams and Wilkins; Philadelphia, PA: 2017.

[68] Li DK et al. Maternal exposure to **angiotensin converting enzyme inhibitors** in the first trimester and risk of malformations in offspring: a retrospective cohort study. BMJ. 2011 Oct 18;343.

[69] Vasilakis-Scaramozza C, Aschengrau A, Cabral HJ, Jick SS. Antihypertensive drugs and the risk of congenital anomalies. Pharmacotherapy. 2013 May;33(5):476-82.

[70] Noseda R, Bedussi F, Gobbi C, Zecca C, Ceschi A. Safety profile of **erenumab, galcanezumab and fremanezumab** in **pregnancy and lactation**: Analysis of the **WHO pharmacovigilance database**. *Cephalalgia*. 2021;41(7):789-798. doi:10.1177/0333102420983292.

[71] Magnesium – bone damage if IV admin. HIGHLIGHTS OF PRESCRIBING INFORMATION - FDA Accessed Apr 12, 2022 at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020488Orig1s024lbl.pdf

[72] Stovner LJ, Linde M, Gravdahl GB, Tronvik E, Aamodt AH, Sand T, Hagen K. A comparative study of **candesartan** versus propranolol for migraine prophylaxis: A randomised, triple-blind, placebo-controlled, double cross-over study. Cephalalgia. 2014 Jun;34(7):523-32.

[73] Loder EW, Robbins MS. Monoclonal Antibodies for Migraine Prevention: Progress, but Not a Panacea. JAMA. 2018 May 15;319(19):1985-1987. doi: 10.1001/jama.2018.4852. PMID: 29800193.

[74] Wang X, Chen Y, Song J and You C (2021) Efficacy and Safety of Monoclonal Antibody Against Calcitonin Gene-Related Peptide or Its Receptor for Migraine: A Systematic Review and Network Meta-analysis. Front. Pharmacol. 12:649143. doi: 10.3389/fphar.2021.649143.

[75] Urits I, Clark G, An D, et al. An Evidence-Based Review of Fremanezumab for the Treatment of Migraine. *Pain Ther*. 2020;9(1):195-215. doi:10.1007/s40122-020-00159-3.

[76] Drellia K, Kokoti L, Deligianni CI, Papadopoulos D, Mitsikostas DD. **Anti-CGRP monoclonal antibodies** for migraine prevention: **A systematic review and likelihood to help or harm analysis [**published correction appears in Cephalalgia. 2022 Jan;42(1):90]. *Cephalalgia*. 2021;41(7):851-864.

[77] Herd CP, Tomlinson CL, Rick C, et al. **Botulinum toxins** for the prevention of migraine in adults. ***Cochrane*** *Database Syst Rev*. 2018;6(6):CD011616. Published 2018 Jun 25. doi:10.1002/14651858.CD011616.pub2.

[78] Taylor FR. Weight change associated with the use of migraine-preventive medications. Clin Ther. 2008 Jun;30(6):1069-80. doi: 10.1016/j.clinthera.2008.06.005. PMID: 18640463.

Migraine Q&A References

1. Rolan PE. Drug interactions with triptans: which are clinically significant? CNS Drugs. 2012 Nov;26(11):949-57.
2. Shapiro RE, Tepper SJ. The serotonin syndrome, triptans, and the potential for drug-drug interactions. Headache. 2007 Feb;47(2):266-9.
3. Orlova Y, Rizzoli P, Loder E. Association of Coprescription of Triptan Antimigraine Drugs and Selective Serotonin Reuptake Inhibitor or Selective Norepinephrine Reuptake Inhibitor Antidepressants With Serotonin Syndrome. JAMA Neurol. 2018 May 1;75(5):566-572.
4. Evans RW. The FDA alert on serotonin syndrome with combined use of SEROTONIN SYNDROMERIs or SNRIs and Triptans: an analysis of the 29 case reports. MedGenMed. 2007 Sep 5;9(3):48.
5. Sangkuhl K, Klein TE, Altman RB. PharmGKB summary: citalopram pharmacokinetics pathway. Pharmacogenet Genomics. 2011;21(11):769-772.
6. MacGregor EA. Headache in pregnancy. Neurol Clin. 2012 Aug;30(3):835-66.
7. Worthington I, Pringsheim T, Gawel MJ, Gladstone J, Cooper P, Dilli E, Aube M, Leroux E, Becker WJ; Canadian Headache Society Acute Migraine Treatment Guideline Development Group. Canadian Headache Society Guideline: acute drug therapy for migraine headache. Can J Neurol Sci. 2013 Sep;40(5 Suppl 3):S1-S80.
8. Ovadia C. Prescribing for pregnancy: managing chronic headache and migraine. Drug Ther Bull. 2021 Oct;59(10):152-156. doi: 10.1136/dtb.2021.0000dstone J, Cooper P, Dilli E, Aube M 31. Epub 2021 Aug 19.
9. Jarvis S, Dassan P, Piercy CN. Managing migraine in pregnancy. BMJ. 2018 Jan 25;360:k80.
10. Pringsheim T, Davenport W, Mackie G, Worthington I, Aubé M, Christie SN, Gladstone J, Becker WJ; Canadian Headache Society Prophylactic Guidelines Development Group. Canadian Headache Society guideline for migraine prophylaxis. Can J Neurol Sci. 2012 Mar;39(2 Suppl 2):S1-59.
11. Toward Optimized Practice (TOP) Headache Working Group. 2016 September. Primary care management of headache in adults: clinical practice guideline: 2nd edition. Edmonton AB: Toward Optimized Practice. Available from: http://www.topalbertadoctors.org/cpgs/10065.
12. Lee M, Guinn Debra, Hickenbottom S. Headache during pregnancy and postpartum. UpToDate. Retrieved March 2022. Available from: https://www.uptodate.com/contents/headache-during-pregnancy-and-postpartum.
13. Marchenko A, Etwel F, Olutunfese O, *et al*. Pregnancy outcome following prenatal exposure to triptan medications: a meta-analysis. *Headache* 2015;55:490–501.
14. Nezvalová-Henriksen K, Spigset O, Nordeng H. Triptan exposure during pregnancy and the risk of major congenital malformations and adverse pregnancy outcomes: results from the Norwegian Mother and Child Cohort Study. Headache. 2010 Apr;50(4):563-75.
15. Silberstein SD, Dodick DW, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller, T, Grozinski-Wolff MG, Yang R, Ma Y and Aycardi E. Fremanezumab for the Preventative Treatment of Chronic Migraine. N Engl J Med. 2017 Nov 30; 377(22): 2113-2122.
16. Health Canada approval https://health-products.canada.ca/dpd-bdpp/dispatch-repartition.do;jsessionid=2D634AD87BF2DD43008A40DBD7B3E580
17. Trkulja S, Huyghebaert T, Ton J, Svrcek C. Biologics for episodic and chronic migraines. Can Fam Physician 2021;67:911.
18. Gao B, Sun N, Yang Y, Sun Y, Chen M, Chen Z, Wang Z. Safety and Efficacy of Fremanezumab for the Prevention of Migraine: A Meta-Analysis From Randomized Controlled Trials. Front Neurol. 2020 May 19;11:435.
19. Tronvik, E., Stovner, L. J., Helde, G., Sand, T., & Bovim, G. (2003). Prophylactic treatment of migraine with an angiotensin II receptor blocker: a randomized controlled trial. JAMA, 289(1), 65–69. https://doi.org/10.1001/jama.289.1.65
20. Schrader, H., Stovner, L. J., Helde, G., Sand, T., & Bovim, G. (2001). Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomised, placebo controlled, crossover study. BMJ (Clinical research ed.), 322(7277), 19–22. https://doi.org/10.1136/bmj.322.7277.19
21. Stovner, L. J., Linde, M., Gravdahl, G. B., Tronvik, E., Aamodt, A. H., Sand, T., & Hagen, K. (2014). A comparative study of candesartan versus propranolol for migraine prophylaxis: A randomised, triple-blind, placebo-controlled, double cross-over study. Cephalalgia, 34(7), 523-532.
22. Burch, R. C., Ailani, J., & Robbins, M. S. (2021). The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. Headache: The Journal of Head and Face Pain, 62(1), 111–112. https://doi.org/10.1111/head.14245
23. Loder, E., Burch, R., & Rizzoli, P. (2012). The 2012 AHS/AAN Guidelines for prevention of episodic migraine: A summary and comparison with other recent clinical practice guidelines. Headache: The Journal of Head and Face Pain, 52(6), 930–945. https://doi.org/10.1111/j.1526-4610.2012.02185.x
24. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018 Jan;38(1):1-211.
25. Garza, I., Schwedt, T. Medication Overuse Headache: Treatment and Prognosis. UptoDate. Updated July 2021. Accessed Mar 2022.

Acute Migraine Infographic References

Acknowledgements: Written by Alex Crawley. Graphic design by Debbie Bunka. Thanks to our reviewers: Jillian Reardon, Debbie Bunka, Taylor Raiche, Katelyn Halpape, Taisa Trischuk, Tahirih McAleer, Brent Jensen, Julia Bareham, Marlys LeBras, Jackie Myers.
Disclosures: No conflicts of interest are reported by Alex Crawley.

1. Suthisisang CC, Poolsup N, Suksomboon N, Lertpipopmetha V, Tepwitukgid B. Meta-analysis of the efficacy and safety of naproxen sodium in the acute treatment of migraine. Headache: The Journal of Head and Face Pain. 2010 May;50(5):808-18.
2. Law S, Derry S, Moore RA. Naproxen with or without an antiemetic for acute migraine headaches in adults. Cochrane database of systematic reviews. 2013(10).
3. Rabbie R, Derry S, Moore RA, McQuay HJ. Ibuprofen with or without an antiemetic for acute migraine headaches in adults. Cochrane database of systematic reviews. 2010(10).
4. Derry S, Moore RA. Paracetamol (acetaminophen) with or without an antiemetic for acute migraine headaches in adults. Cochrane database of systematic reviews. 2013(4).
5. Law S, Derry S, Moore RA. Sumatriptan plus naproxen for the treatment of acute migraine attacks in adults. Cochrane Database of Systematic Reviews. 2016(4).
6. Derry CJ, Derry S, Moore RA. Sumatriptan (all routes of administration) for acute migraine attacks in adults-overview of Cochrane reviews. Cochrane Database of Systematic Reviews. 2014(5).
7. **CHS 2013**. Worthington I, Pringsheim T, Gawel MJ, Gladstone J, Cooper P, Dilli E, Aube M, et al. Canadian Headache Society Guideline: acute drug therapy for migraine headache. Canadian Journal of Neurological Sciences. 2013 Sep;40(S3):S1-3.
8. **TOP 2016**. Toward Optimized Practice. Primary Care Management of Headache in Adults, 2nd ed. Available from https://actt.albertadoctors.org/CPGs/Pages/Headache.aspx
9. **AHS 2021**. Ailani J, Burch RC, Robbins MS, Board of Directors of the American Headache Society. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. Headache: The Journal of Head and Face Pain. 2021 Jul;61(7):1021-39.
10. Naproxen sodium (anaprox). Pharmacology, pharmacokinetics and drug interactions
Segre, E.J. Journal of reproductive medicine, 1980, Vol.25 (4), p.222-225
11. Todd PA, Sorkin EM. Diclofenac sodium. Drugs. 1988 Mar;35(3):244-85.
12. McNeely W, Goa KL. Diclofenac-potassium in migraine. Drugs. 1999 Jun;57(6):991-1003.
13. Shin D, Lee SJ, Ha YM, Choi YS, Kim JW, Park SR, Park MK. Pharmacokinetic and pharmacodynamic evaluation according to absorption differences in three formulations of ibuprofen. Drug Design, Development and Therapy. 2017;11:135.
14. Marzo A, Dal Bo L, Verga F, Monti NC, Abbondati G, Tettamanti RA, Crivelli F, Uhr MR, Ismaili S. Pharmacokinetics of diclofenac after oral administration of its potassium salt in sachet and tablet formulations. Arzneimittelforschung. 2000 Jan;50(01):43-7.
15. Shapiro RE, Tepper SJ. The serotonin syndrome, triptans, and the potential for drug–drug interactions. Headache: The Journal of Head and Face Pain. 2007 Feb;47(2):266-9.

Medication Overuse Headache Infographic References

Acknowledgements: Written by Taisa Trischuk. Graphic design by Debbie Bunka. Thanks to our reviewers: Alex Crawley, Loren Regier, Debbie Bunka, Jackie Myers, Katelyn Halpape, Jillian Reardon.
Disclosures: No conflicts of interest are reported by Taisa Trischuk.

1. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018 Jan;38(1):1-211. doi: 10.1177/0333102417738202. PMID: 29368949.
2. **TOP 2016**. Toward Optimized Practice (TOP) Headache Working Group. 2016 September. Primary care management of headache in adults: clinical practice guideline: 2nd edition. Edmonton AB: Toward Optimized Practice. Available from: http://www.topalbertadoctors.org/cpgs/10065.
3. **AHS 2021**. Ailani J, Burch RC, Robbins MS, Board of Directors of the American Headache Society. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. Headache: The Journal of Head and Face Pain. 2021 Jul;61(7):1021-39.
4. **CHS 2013**. Worthington I, Pringsheim T, Gawel MJ, Gladstone J, Cooper P, Dilli E, Aube M, Leroux E, Becker WJ; Canadian Headache Society Acute Migraine Treatment Guideline Development Group. Canadian Headache Society Guideline: acute drug therapy for migraine headache. Can J Neurol Sci. 2013 Sep;40(5 Suppl 3):S1-S80. PMID: 23968886.
5. Ashina M, Buse DC, Ashina H, Pozo-Rosich P, Peres MFP, Lee MJ, Terwindt GM, Halker Singh R, Tassorelli C, Do TP, Mitsikostas DD, Dodick DW. Migraine: integrated approaches to clinical management and emerging treatments. Lancet. 2021 Apr 17;397(10283):1505-1518. doi: 10.1016/S0140-6736(20)32342-4. Epub 2021 Mar 25. PMID: 33773612.
6. Carlsen LN, Munksgaard SB, Nielsen M, Engelstoft IMS, Westergaard ML, Bendtsen L, Jensen RH. Comparison of 3 Treatment Strategies for Medication Overuse Headache: A Randomized Clinical Trial. JAMA Neurol. 2020 Sep 1;77(9):1069-1078. doi: 10.1001/jamaneurol.2020.1179. PMID: 32453406; PMCID: PMC7251504.
7. Garza, I., Schwedt, T. Medication Overuse Headache: Etiology, clinical features and diagnosis. UptoDate. Updated Nov 2021. Accessed Mar 2022.
8. Garza, I., Schwedt, T. Medication Overuse Headache: Treatment and Prognosis. UptoDate. Updated July 2021. Accessed Mar 2022.
9. Boes CJ, Black DF, Dodick DW. Pathophysiology and management of transformed migraine and medication overuse headache. Semin Neurol. 2006 Apr;26(2):232-41. doi: 10.1055/s-2006-939924. PMID: 16628534.
10. Katsarava Z, Fritsche G, Muessig M, Diener HC, Limmroth V. Clinical features of withdrawal headache following overuse of triptans and other headache drugs. Neurology. 2001 Nov 13;57(9):1694-8. doi: 10.1212/wnl.57.9.1694. PMID: 11706113.
11. Dodick DW, Silberstein SD. How clinicians can detect, prevent and treat medication overuse headache. Cephalalgia. 2008 Nov;28(11):1207-17. doi: 10.1111/j.1468-2982.2008.01737.x. PMID: 18983588.
12. Cupini LM, et. Al. Medication overuse headache: neurobiological, behavioural and therapeutic aspects. Pain. 2010 Aug;150(2):222-4. Epub 2010 May 23. Review. No abstract available. PMID: 20546999

Migraine Prophylaxis Infographic References

Acknowledgements: Written by Loren Regier. Graphic design by Debbie Bunka. Thanks to our reviewers: Alex Crawley, Taisa Trischuk, Debbie Bunka, Jackie Myers, Katelyn Halpape, Jillian Reardon.
Disclosures: No conflicts of interest are reported by Loren Regier.

1. **TOP 2016**. Toward Optimized Practice (TOP) Headache Working Group. 2016 September. Primary care management of headache in adults: clinical practice guideline: 2nd edition. Edmonton AB: Toward Optimized Practice. Available from: http://www.topalbertadoctors.org/cpgs/10065.
2. **AHS 2021**. Ailani J, Burch RC, Robbins MS, Board of Directors of the American Headache Society. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. Headache: The Journal of Head and Face Pain. 2021 Jul;61(7):1021-39.
3. **CHS 2013**..
4. Pringsheim T, Davenport W, Mackie G, Worthington I, Aubé M, Christie SN, Gladstone J, Becker WJ; **Canadian Headache Society Prophylactic Guidelines** Development Group. Canadian Headache Society guideline for migraine prophylaxis. Can J Neurol Sci. 2012 Mar;39(2 Suppl 2):S1-59.
5. Loder E, Burch R, Rizzoli P. The 2012 **AHS/AAN guidelines** for prevention of episodic migraine: a summary and comparison with other recent clinical practice guidelines. Headache. 2012 Jun;52(6):930-45. doi: 10.1111/j.1526-4610.2012.02185.x. PMID: 22671714.
6. Diener H-C, Holle-Lee D, Nägel S, Dresler T, Gaul C, Göbel H, et al. Treatment of Migraine Attacks and Prevention of Migraine: **Guidelines by the German Migraine and Headache Society** and the German Society of Neurology. *Clinical and Translational Neuroscience*. 2019; 3(1):3.
7. Braschi E (Updated); Allan GM, Levy M (Original). **Antidepressants** for preventing headaches: Which work and how well? **Tools for Practice**, April 2015.
8. Kapusta M, Allan GM. Are **antihypertensive** medications effective for migraine prophylaxis? **Tools for Practice** #52. Available at: https://gomainpro.ca/wp-content/uploads/tools-forpractice/1433184708_updatedtfp52antihypertensivesmigraineprophylaxis.pdf
9. Trkulja S, Huyghebaert T, Ton J, Svrcek C. **Frequent migraines are a headache: Can biologics help**? **Tools for Practice**, August 2021. Accessed 01 Feb 2022 online.
10. **Monoclonal antibodies to prevent migraine** headaches. Ottawa: **CADTH**; 2018 Feb. (CADTH issues in emerging health technologies, issue 167).
11. Schoenen J, Jacquy J, Lenaerts M. Effectiveness of high-dose **riboflavin** in migraine prophylaxis. A randomized controlled trial. Neurology. 1998 Feb;50(2):466-70. doi: 10.1212/wnl.50.2.466. PMID: 9484373.
12. Teigen L, Boes CJ. An evidence-based review of oral **magnesium** supplementation in the preventive treatment of migraine. Cephalalgia. 2015 Sep;35(10):912-22. doi: 10.1177/0333102414564891. Epub 2014 Dec 22.
13. Regier L. Migraine Prophylaxis – Individualization of Tx – Colour Chart (Adults). RxFiles Academic detailing. Published April 2022. Available online at www.RxFiiles.ca/migraine.
14. Prochazka AV, Weaver MJ, Keller RT, Fryer GE, Licari PA, Lofaso D. A randomized trial of nortriptyline for **smoking cessation**. *Arch Intern Med*. 1998;158(18):2035-2039. doi:10.1001/archinte.158.18.2035.