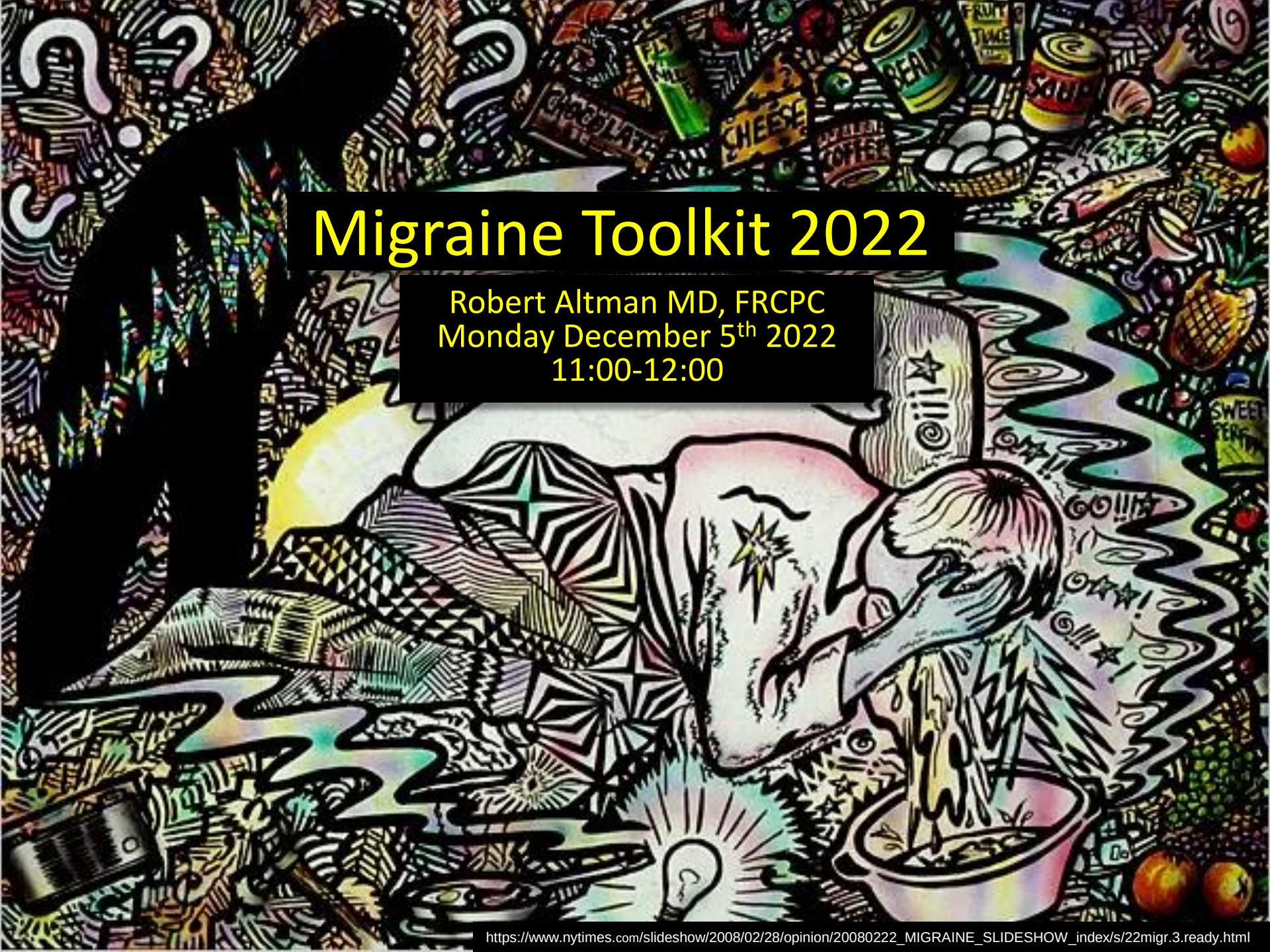
Migraine Toolkit 2022
Robert Altman MD, FRCPC
Monday December 5th 2022
11:00-12:00
https://www.nytimes.com/slideshow/2008/02/28/opinion/20080222_MIGRAINE_SLIDESHOW_index/s/22migr.3.ready.html

Disclosures

- None.

Learning Objectives for Today

- Be aware of **RED FLAGS**.
- Essentials on **history** and **exam**.
- Be **secure** in your diagnosis.
- Rare to get '***quick fixes***' in migraine medicine. Patience and planning.
- Many options / resources exist beyond **triptans**.
- Have a well stocked and organized "**toolkit**" and know ***all options*** for therapies – both pharmacological and non-pharmacological.
- Take **ownership** of your cases.
- Power of the **follow-up**.
- Migraine / cephalalgia is a chronic (episodic) medical condition with considerable burden / impact on **QOL**, so it deserves the time.
- **Empower** your patients.

Red Flags for 'Serious' Headaches

Common Sense

<u>Always</u> justifies a work-up for secondary causes

- Any new onset >50yo
- Immunocompromised host (i.e, HIV+, any oncology patient)
- Signs/symptoms of raised ICP
  - Pulsatile tinnitus, TVOs, CN VI palsy (diplopia)
- Thunderclap onset
- **Exam**: ***any*** focal findings, papilledema, pupillary abnormalities, change in mental status, visual fields, ataxia, fever or constitutional symptoms

FOCUSED PHYSICAL EXAM FOR A HEADACHE CONSULT

Examination

- Vitals signs (**BP**)
- Mental status
- Visual fields
- **Fundoscopy**
- **Pupils**
- **Blind spot assessment (for pseudotumor)**
- **EOM**
- **Cx ROM, TA palpation, GON/LON palpation**
- Neck ROM, nucchal rigidity (Kernig, Brudzinski)
- Screen for lateralizing signs (pronator drift, fine finger movements, reflexes, tone, coordination)

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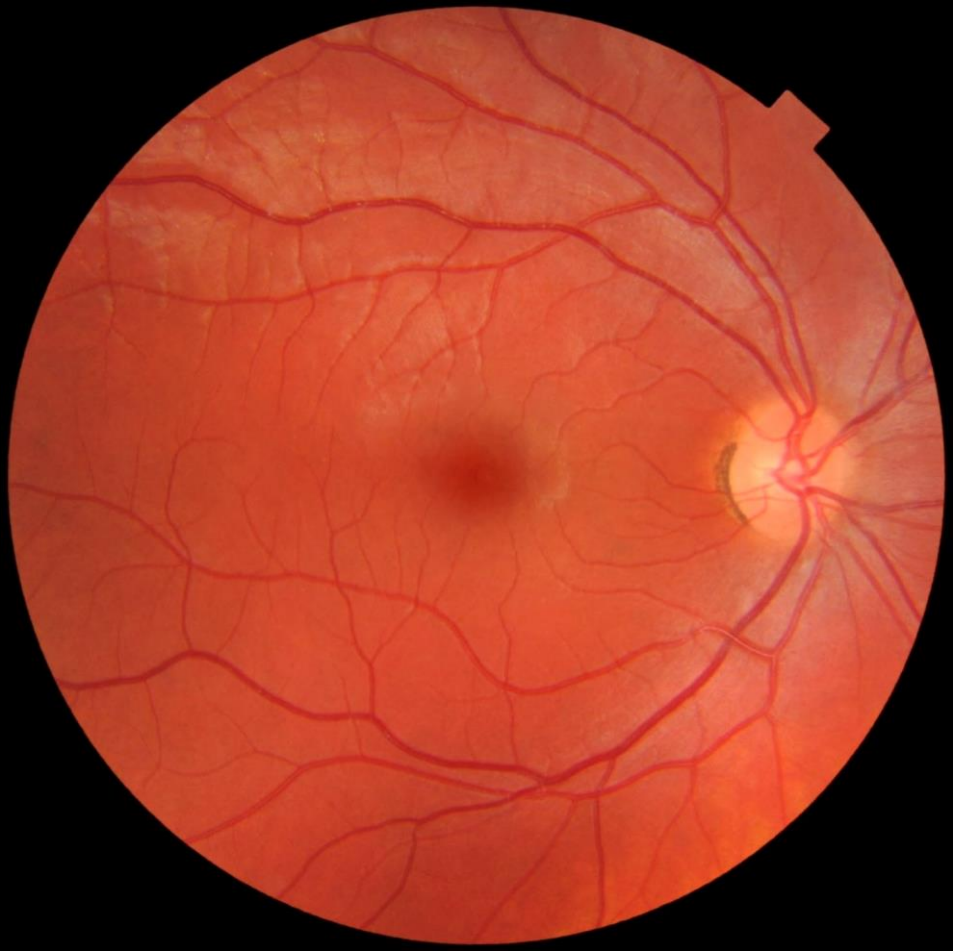
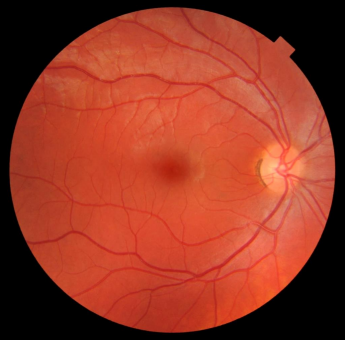
Normal Fundi



Papilledema

Normal

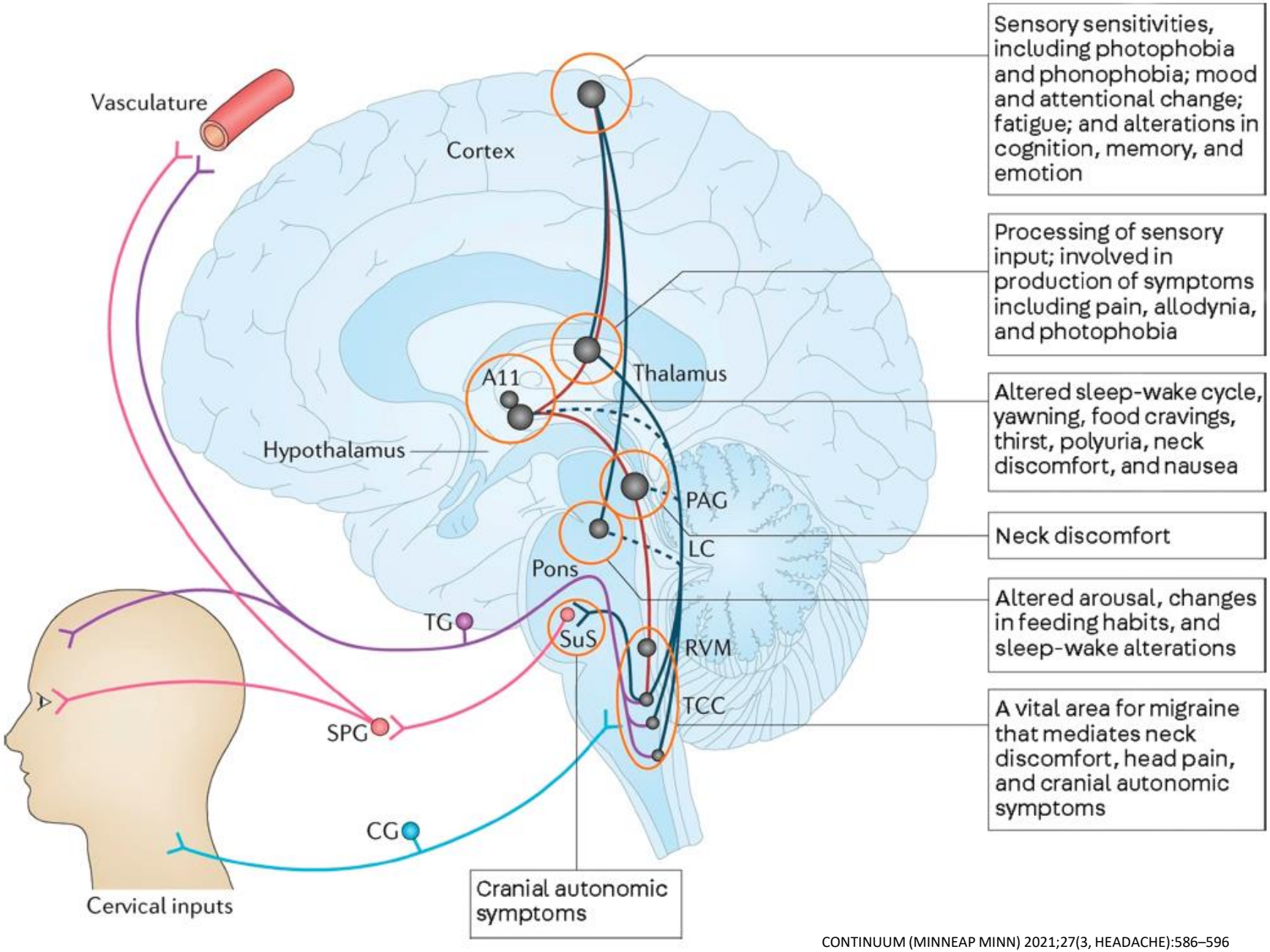


Migraine 101

“Migraine is an inherited disorder of sensory processing, but many aspects of the underlying basis of this disorder still remain unknown”

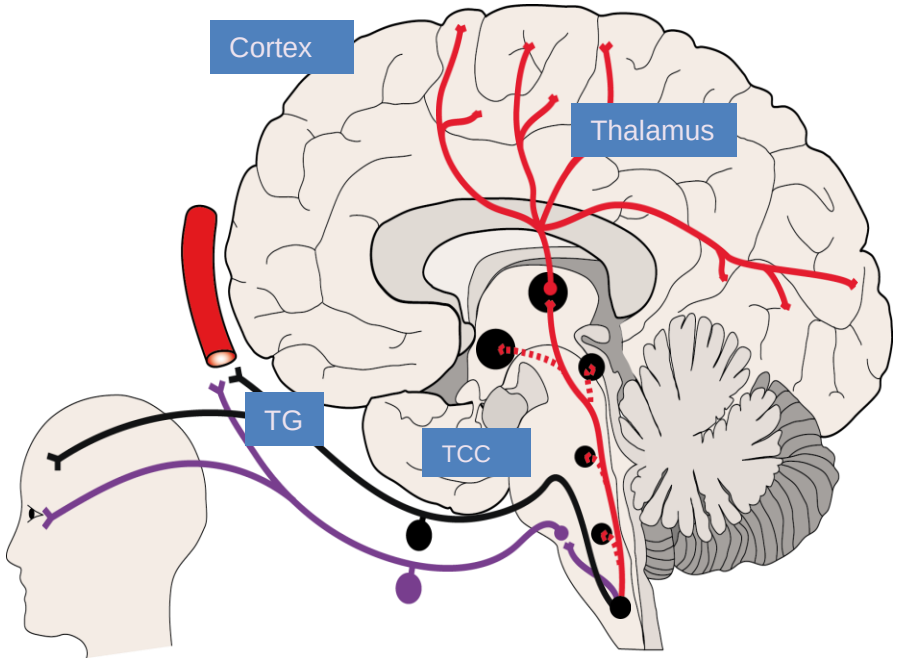
Definition

- ***Primary*** headache syndrome per IHS
  - Secondary being related to structural lesion(s) / infections
- Not *fully* understood
- Partly genetic, partly environmental influences
- "*Vascular* theory" of vasodilatation **no longer accepted** as sole explanation.
  - Appears to be an **epiphenomenon** (in a cascade of neuro-inflammatory changes)
- Primarily **neuronal dysfunction**
  - Culminates in physiological changes intracranially and extracranially
    - Implication of multiple neurochemicals; **serotonin**, calcitonoin gene related peptide (**CGRP**), **neurokinin A**, **substance P** etc



CONTINUUM (MINNEAP MINN) 2021;27(3, HEADACHE):586–596

Migraine is primarily a disorder of nervous system excitability[1–3]



- TGVS activation causes release of various neuropeptides at the meninges:[1,3]
  - **Calcitonin**
  - **CGRP**
  - Neurokinin A
  - Substance P
- These peptides can induce **neurogenic inflammation**[2,4]
- **Vasodilation** may occur but is not required for migraine pain[1,2]

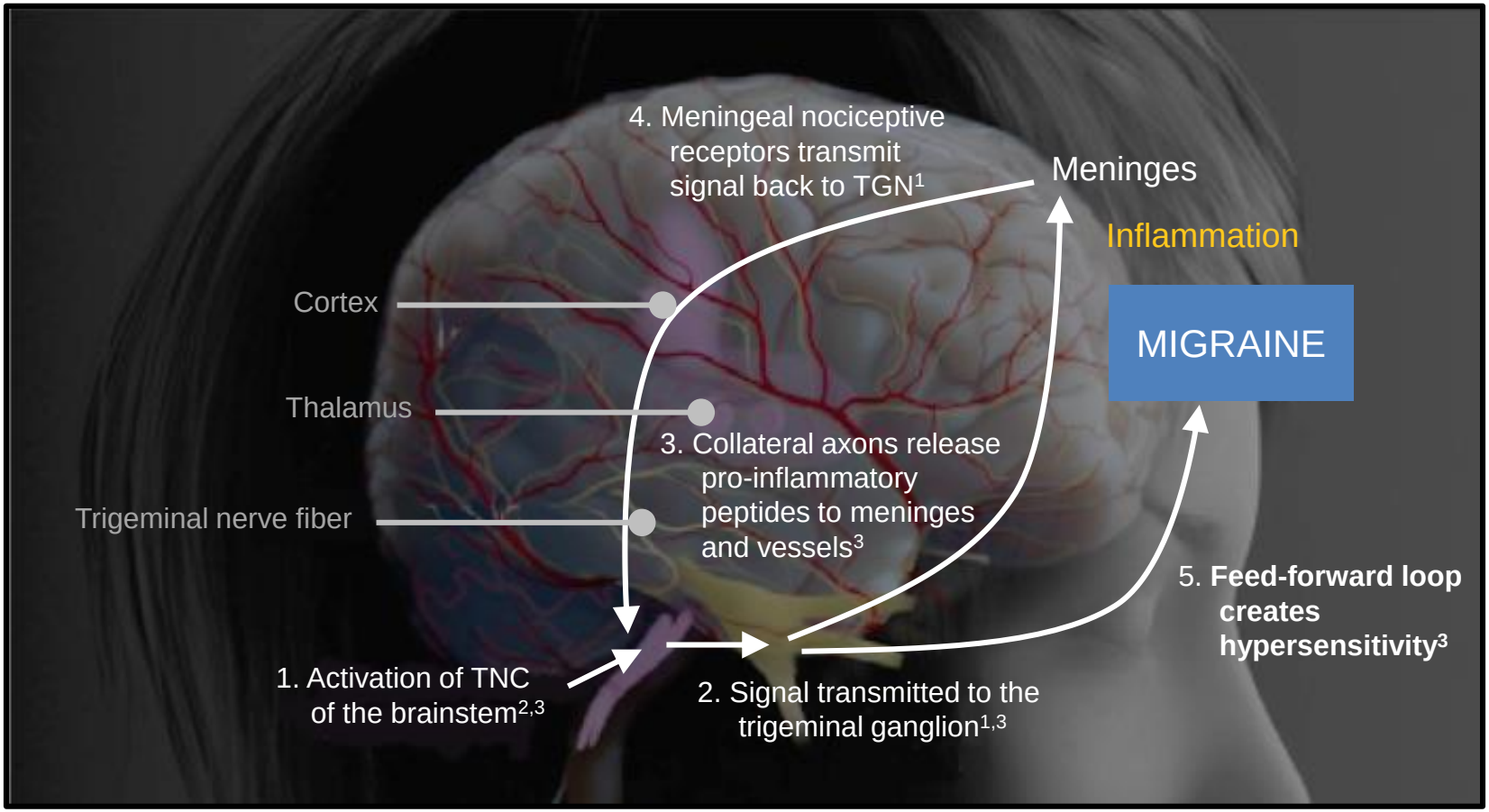
Image adapted from Holland PR, et al. 2014[6]

- Inflammation and dysregulation contribute to a **feed-forward loop**, causing migraine[5]

CGRP, calcitonin gene-related peptide; TCC, Trigeminocervical complex ; TGG, trigeminal ganglion; TGVS, trigeminovascular system

1. Burgos-Vega C, et al. Prog Mol Biol Transl Sci. 2015;131:537–64; 2. Raddant AC, Russo AF. Expert Rev Mol Med. 2011;13:e36; 3. Russo AF. Annu Rev Pharmacol Toxicol. 2015;55:533–52; 4. Pietrobon D, Moskowitz MA. Annu Rev Physiol. 2013;75:365–91; 5. Eising E, et al. BMC Med. 2013;11:26; 6. Holland PR, et al. Cephalalgia. 2014;34(10):725–44.

A **feed-forward loop** in the TGVS creates a state of **hypersensitivity**[1] and **sustained pain**



TGN, trigeminal nerve; TGVS, trigeminovascular system; TNC, trigeminal nucleus caudalis

1. Demarquay G and Mauguière F. Headache. 2016;56:1418–38; 2. Akerman S, et al. Br J Pharmacol. 2002;137:62–8; 3. Capuano A, et al. Mol Pain. 2009;5:43.

Pathophysiology

- Migraine involves activation of peripheral and central components of the trigeminal system
- Complex role of **CGRP** in migraine pathophysiology may involve multiple processes in both the CNS and in the periphery, including
  - Neuropeptide release
  - Vasodilation
  - Nociceptor sensitization
  - Inflammation
- **Trigeminovascular** input from the meningeal vessels passes through the **trigeminal ganglion** and synapses on **second-order** neurons in the brainstem before being relayed to the **sensory cortex**

CGRP, calcitonin gene-related peptide; CNS, central nervous system

migraine simplified.

Pounding pain, photo/phonophobia, nausea, vomiting, etc.

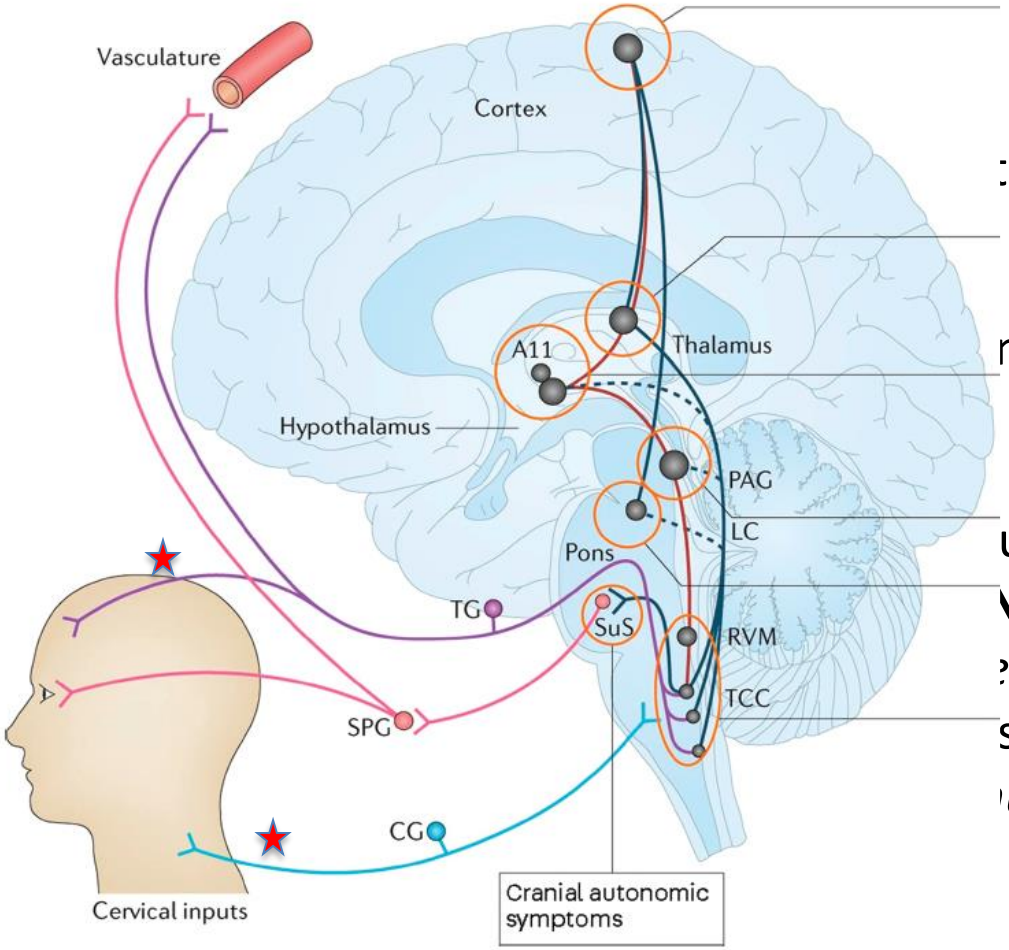
Trigger in susceptible host (genetically determined)
?dietary
?stress
?hormonal
?cervicalgia
?weather changes

Our interventions: Triptans, CGRPa, NSAIDs, anti-emetics, GON block, Botox etc.

What anatomical <u>structures</u> causes pain in the head and neck region?

Cranial Pain Sensitive Structures

- **Intracra**
  - Vessel
    - Art
      an
      siz
    - *Me*
    - *La*
    - *Du*
  - Dura /
    - Ne



id artery and all

mbrane

us nerves

N/LON

s and facet joints

s

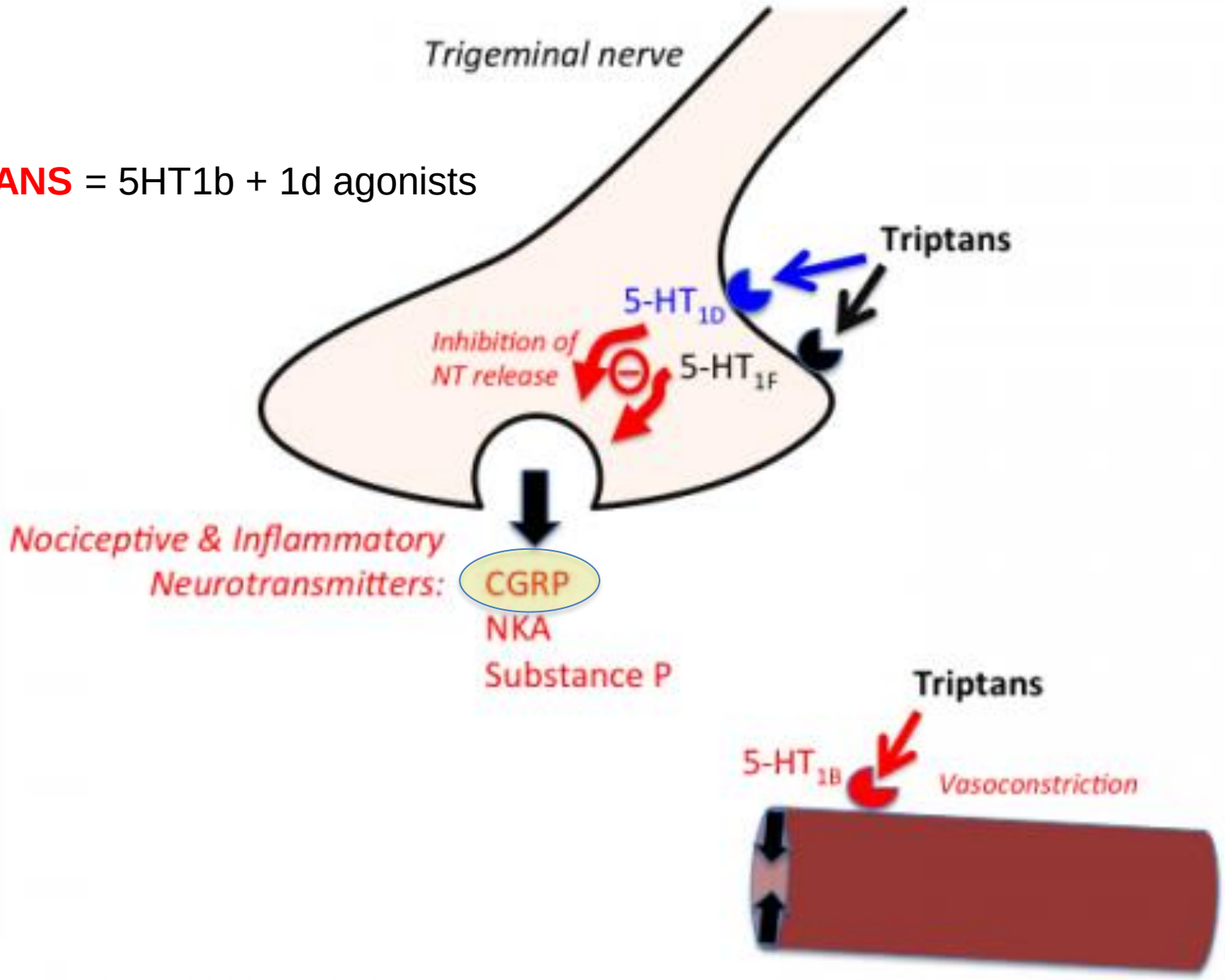
uses

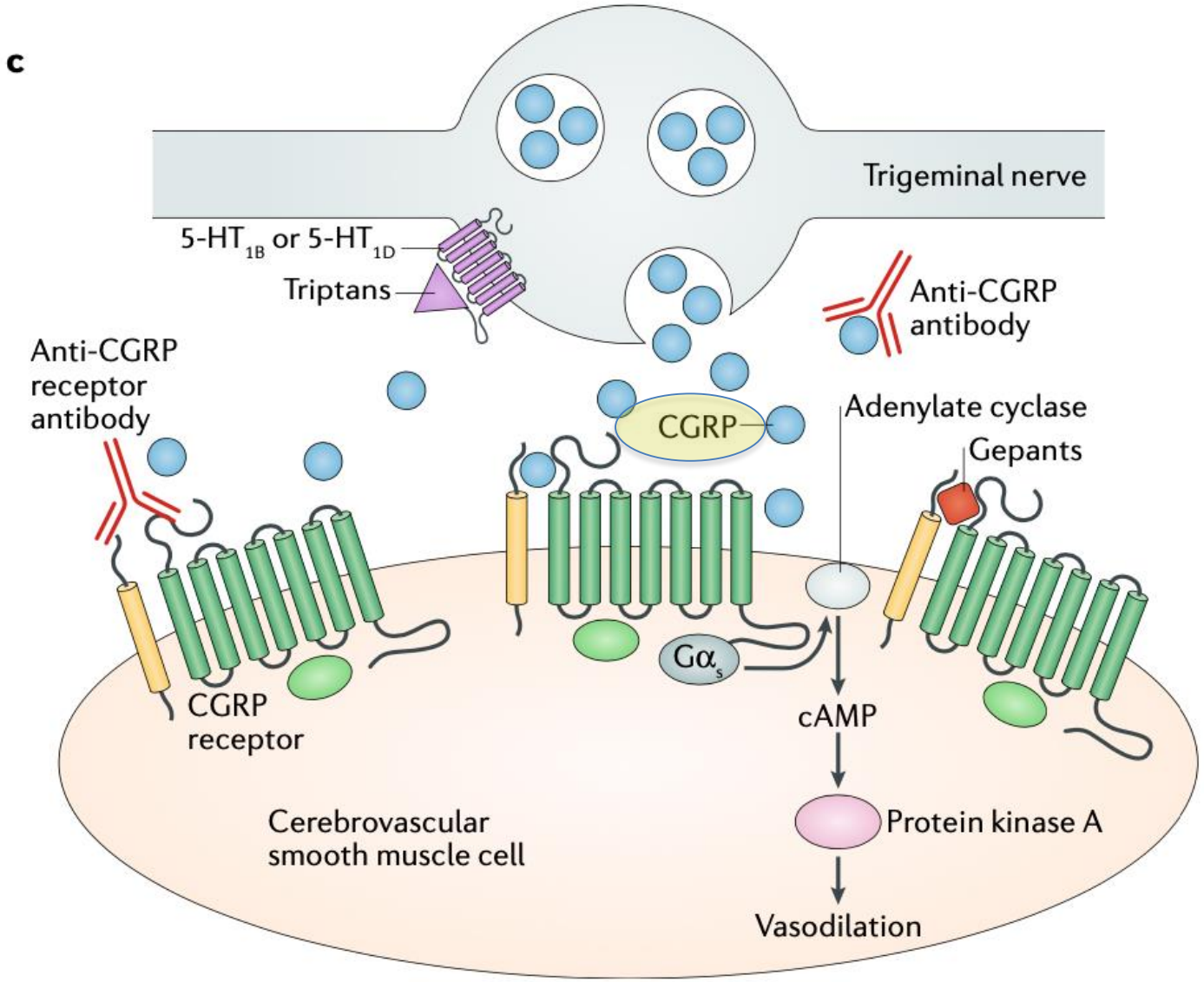
Targeted Migraine Therapies

- One should appreciate the roles of serotonin receptors **5HT1b, 5HT1d** (**7** total; *Sumatriptan, Rizatriptan, Eletriptan, Zolmitriptan, Almotriptan, Naratriptan, Frovatriptan*) - first one on the was market Suma in **1991**.
- **CGRP** antagonist (*Erenumab - Aimovig*) - Health Canada approved 2018 – on market as of Jan **2019**.
- **5HT1f** agonist (*Lasmiditan - Reyvow*) – FDA approved Oct **2019** - not in Canada yet.

Proposed Mechanisms for Triptan Effect on Migraine

TRIPTANS = 5HT1b + 1d agonists





Nat Rev Neurol. 2018 Jun;14(6):338-350. doi: 10.1038/s41582-018-0003-1.

Epidemiology of Migraine

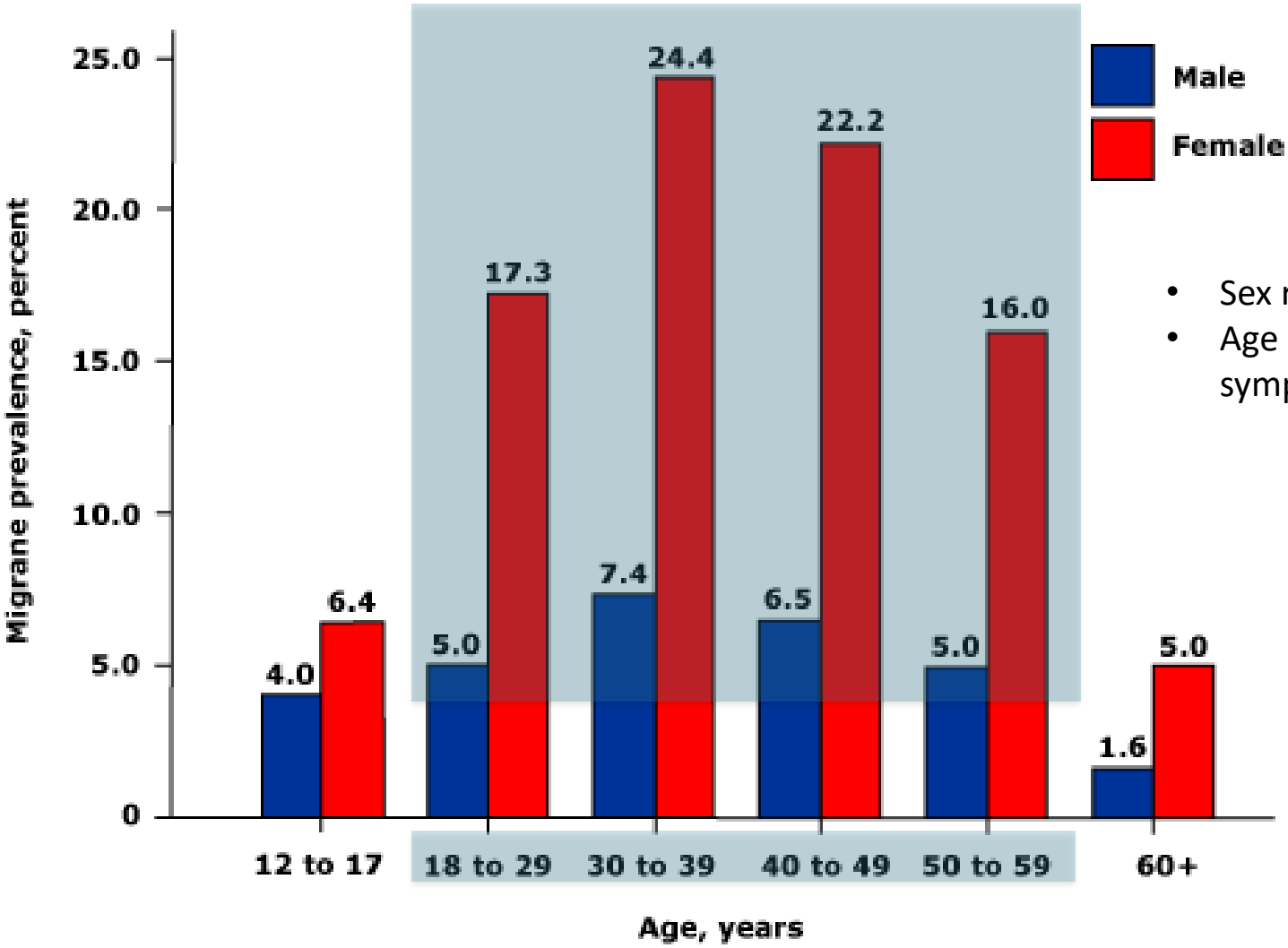
- 4,000,000 Canadian “sufferers”
- Worldwide prevalence ≈ 10%
- Canadian data
  - 23-26% of women
  - 7.8-10% of men
- Sex asymmetry **3:1**
- Significant **disability**
- Reduce **health-related QOL**
- Listed 19th overall in the WHO; “years lived with disability”

Epidemiology of Migraine

- Most people (and MDs) self-diagnose and treat
- Most people (and MDs) do not consider headaches serious
  - *Mostly episodic, does not cause death and are not contagious*
- **4 hours** spent on average in **undergraduate medical education (globally)**

UpToDate®

Prevalence



- Sex ratio
- Age of maximal symptoms

Neurology 2007; 68:343.

IHS diagnostic Criteria: Migraine without Aura (MO)

"5,4,3,2,1 rule"

A. ≥ **5** attacks fulfilling B-D
B. **4-72 (3d)** hrs (untreated or unsuccessfully treated)
C. ≥ **2** of the following
    1. Unilateral*
    2. Pulsatile
    3. Moderate or severe pain
    4. Worsened by physical exertion or avoids activities which would worsen h/a
D. ≥ **1** of the following
    1. Nausea and/or vomiting
    2. Phono *and* photophobia
E. Not attributed to another disorder

IHS: Migraine with Aura (MA)

A. ≥ **2** attacks fulfilling **B-D**

B. Aura consisting of at ***≥ 1*** of the following, but **no motor** weakness
   1. fully reversible visual symptoms including positive features (**eg**, flickering lights, spots or lines) and/or negative features (**ie**, loss of vision)
   2. fully reversible sensory symptoms including positive features (**ie**, pins and needles) and/or negative features (**ie**, numbness)
   3. Fully reversible dysphasic speech disturbance
   4. Motor
   5. Brainstem
   6. Retinal

C. ***≥3*** of the following:
   1. At least one aura symptom spreads ≥ 5 mins
   2. Two or more aura symptoms occur in succession
   3. Each individual aura symptom lasts 5-60 minutes
   4. at least one aura symptom is unilateral (i.e, dysphasia)
   5. at least one aura symptom is positive (visual scintillations, or tingling)
   6. the aura is accompanied, or followed within 60 minutes, by headache

D. Not attributed to another disorder[2]

Migraine "***Associations***"

- **Medical conditions**:
  - PFO (R→L shunting)
  - *Hypotension* or hypertension
  - Mitral valve prolapse
  - Raynaud's phenomenon
  - Asthma
  - Irritable bowel syndrome
  - Depression, anxiety

Search for them on your **Hx**; *relevant* and *may* help *solidify your diagnostic impression* that the h/a in front of you is migraine.

- **Clinical**:
  - Multiple chemical sensitivity
  - Joint / ligamentous hyperlaxity
  - Motion sickness
  - Childhood equivalents:
    - Cyclic vomiting (in periods of stress)
    - Recurrent torticollis
    - Abdominal crises
  - Vasovagal syncope
  - Vertigo (BPPV or vestibular neuronitis)
  - Catamenial flare-ups (premenstrual); cyclic **drop** in estorgen.

TOOLKIT

Non-pharmacological

Trigger diary, hydration, stress management, sleep hygiene, exercise, cold towel, sunglasses

Pharmacological

Abortive, prophylactic

Acetaminophen, NSAID, triptans, D2 blockers, CGRP antagonists, gepants

Procedures / Interventions

ONB, SPG blocks, Botox, TENS machine

*Classic **"Triggers"***

- **Foods**
  - Red wine, beer
  - Marinated, pickled or fermented foods, aged cheeses
  - Chocolate
  - Citrus fruits
  - Figs, raisins, papayas, avocados (especially when overripe), red plums
  - **Nitrites**: hot dogs, bacon, smoked meats
  - Salty foods
  - MSG (soy sauce, meat tenderizers, seasoned salt)
- **Drugs**
  - Nitroglycerine
  - Calcium channel blockers
  - Anti-depressants
  - If you take excessive “over-the-counter” Tylenol, Advil, Ibuprofen, Excedrin, Aleve etc.
- **Cortisol**
  - Stress or “stress let-down,” such as on weekends or vacation

Classic Triggers 2

- **Habits / Life-style**
  - Sleep deprivation, or excessive sleep
    - Fatigue
  - Dehydration from overexertion, excessive diuretics (tea/coffee) or inadequate water/electrolytes
  - Fasting / skipping meals
  - Excessive eyestrain
    - Flashing lights – neon lights (prolonged exposure), movie theaters, flickering lights
- Strong odours (perfumes, colognes, aftershave, smoke, smog)
- High altitude or airplane travel

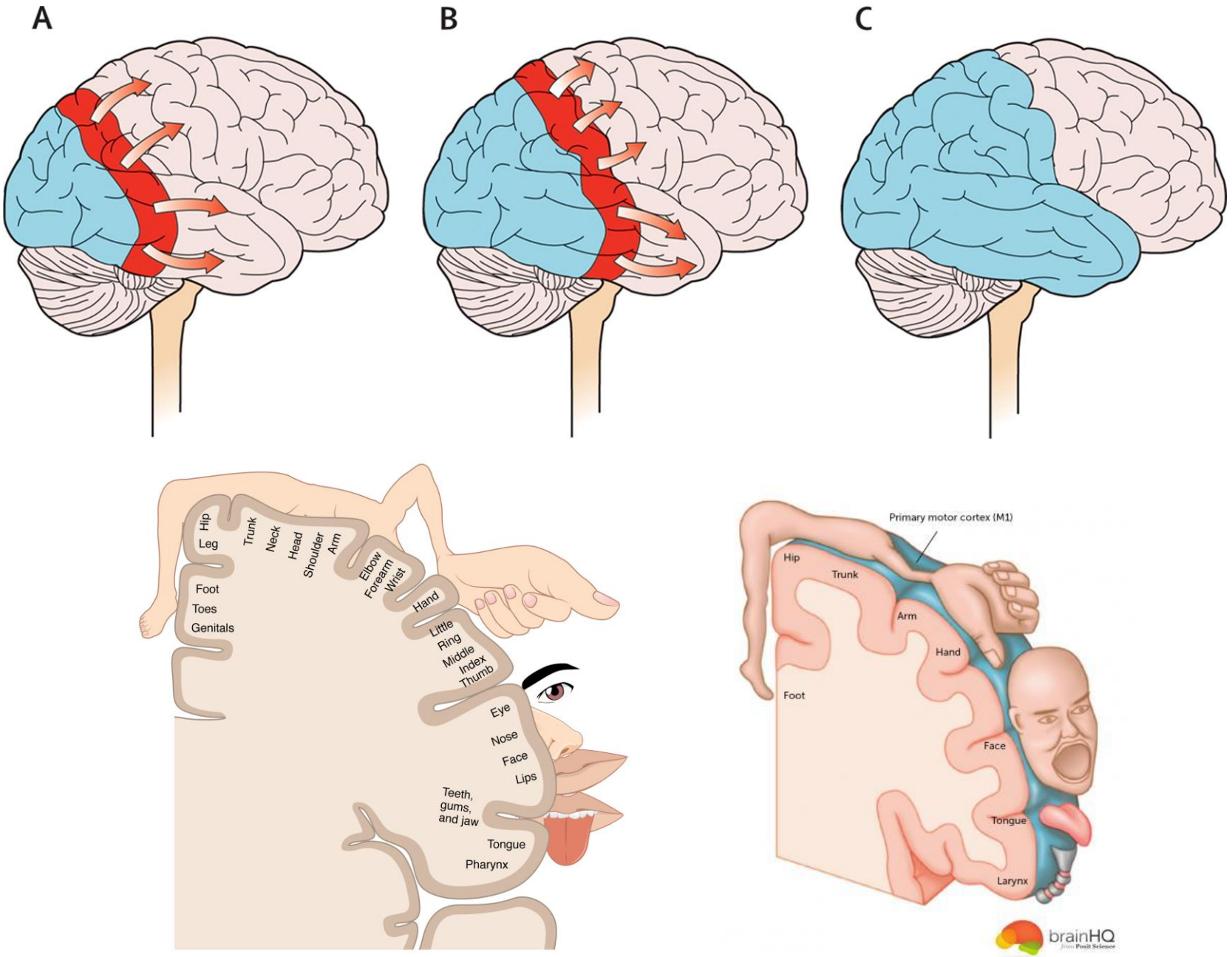
- **Change in barometric pressure / seasonal changes**
  - *Especially **fall** and **spring***
- **Hormonal**
  - **Fluctuations in estrogen (dropping levels)**
  - Menstrual period (unless on regular 28/28 oral contraception)

4 Phases of Migraine (1/4)

- **Prodrome** (better established in chronic MO)
  - Can last up to 12 hrs preceding headache
    - Fatigue
    - Scalp sensitivity
    - Photosensitivity, photosensitivity
    - Trouble concentrating, word finding difficulties
    - Nausea
    - Moody; irritable, hyperactive, sad-depressive
    - Weakness
    - Lethargic

4 Phases of Migraine (2/4)

- **Aura (30% ensuing after prodrome)**
  - 15-60 minutes
  - Visual, sensory, dysphasic speech
    - Positive or negative phenomena
  - Pathophysiologically
    - Cortical **excitation** followed by **depression** (spreading depression)
      - 2-3 mm/min
      - Wave of depolarization / refractory period
      - *Occipital* → parietal → *temporal*
      - *Hemianopia*→somatosensory phenomena→dysphasic speech
      - Corresponds to regional hypoperfusion (above the ischaemic threshold)) followed by hyperaemia


A
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Trunk
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Head
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Arm
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Forearm
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Ring
Middle
Index
Thumb
Eye
Nose
Face
Lips
Teeth, gums, and jaw
Tongue
Pharynx
Primary motor cortex (M1)
Hip
Trunk
Arm
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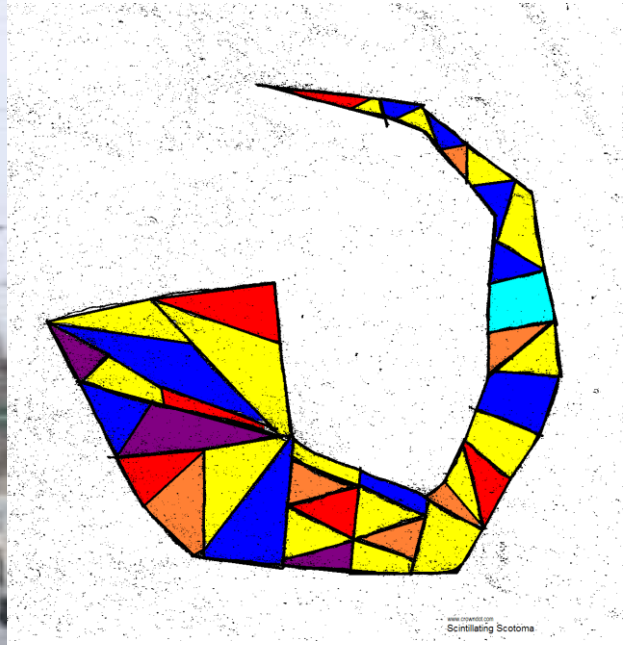
ЮРИДИЧНІ ПОСЛУГИ
АДВОКАТИ


Scintillating Scotoma

Visual Aura

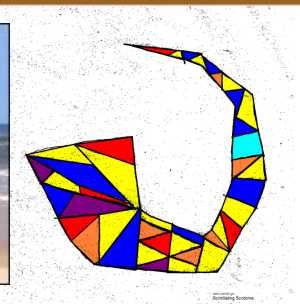
Migraine aura vs. TIA

TABLE 2

Visual symptoms of migraine aura vs transient ischemic attack (TIA)

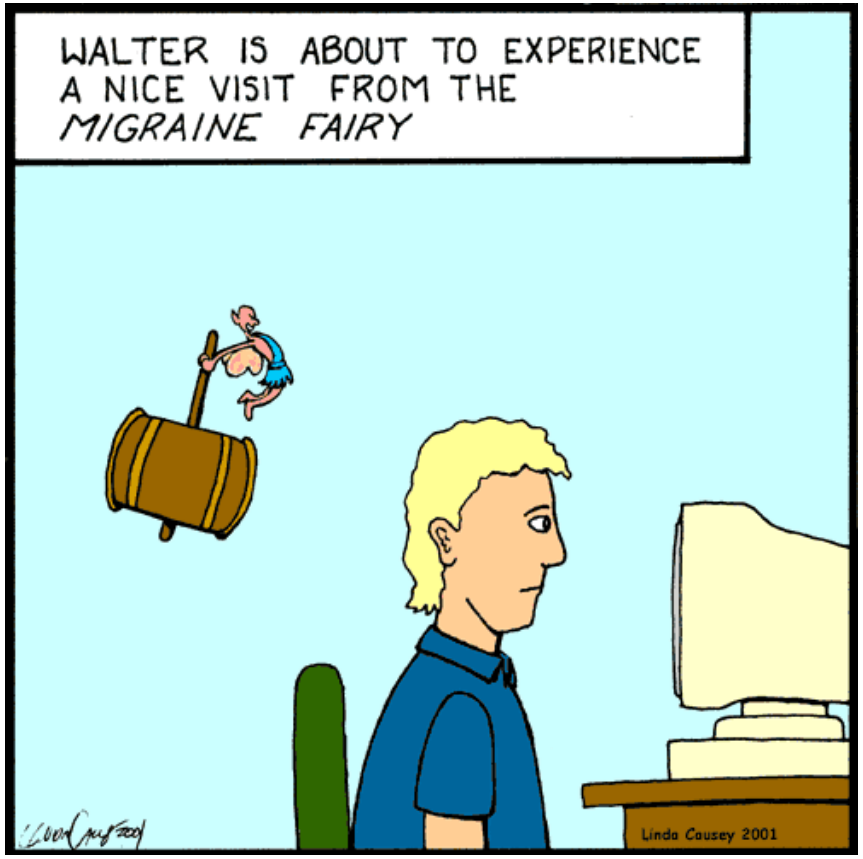
FEATURE	MIGRAINE AURA	TIA
Duration	15–30 minutes	3–10 minutes
Quality	Dynamic, bright, multicolored Forms geometric patterns	Static, dark Dimming of vision

Grey curtain descending



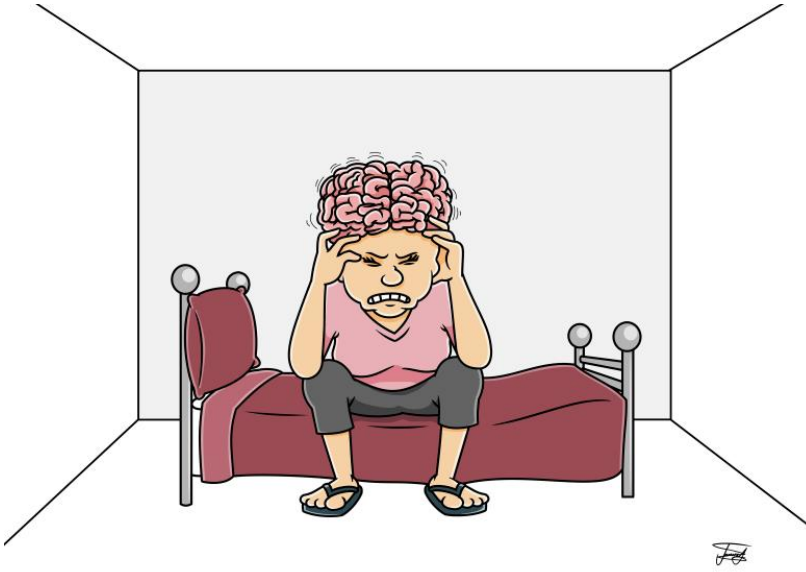
4 Phases of Migraine (3/4)

- **Migraine headache (cephalgia)**
  - Phenotypically described by IHS criteria
- Chances are a unilateral headache, incapacitating and not-daily; is *migraine* until proven otherwise.



4 Phases of Migraine (4/4)

- **Postdrome**
  - 60% of the time
  - Less common in rare, episodic migraineurs
  - Can last up to 25 hours
  - People just don’t feel “right”, sometimes until the next day.
  - Usually compounded by **AE** of symptomatic therapies (Triptans).



Abortive Therapies

Abortive Therapies

- Step or **stratified** approach
- Options
  - Non-specific analgesics: Tylenol 1000mg, Caffeine
  - NSAIDs: Advil, Motrin, Aleve, *Excedrin* (combo Tylenol, aspirin and caffeine), aspirin, Naproxen, Cambia (Diclofenac powder).
  - Prokinetic agents: Domperidone, Maxeran, stemitil
  - Triptans: 7 total to chose from
  - Opiods: Empracet
  - Barbituates , sedatives: Fiorenal, fioracet etc

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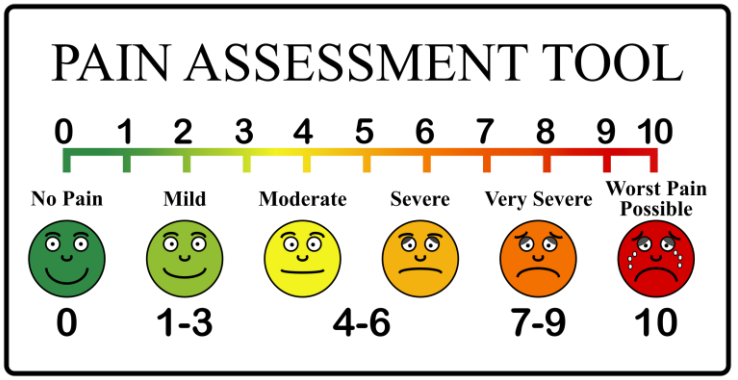
General Rules

"Stratified approach"



- Mild 1-3; Does it need Rx at all?
- Moderate 4-6; Is this a migraine or TTH?
  - Can usually treat with adequate doses NSAID
- Severe 7-10; "Migraine quality" pain, **no hesitation**
  - Start with triptan +/- D2 blocker +/- NSAID (Advil liquigel or Naproxen 500mg)
  - If severe nausea (unable to keep down Rx's)
    - SC, IN injectable triptans
    - PR Gravol

General Rules

1. Treat **early**
   - Within 10-15 minutes
   - **Don't** "tough it out"
     - **Don't** "wait until I get home from work"
2. Combination therapies ***always*** superior.
   - Synergy (triptan, NSAID, D2 antagonist)
   - Know the MOA of what you are prescribing
3. Know what headache your treating / targeting with what Rx.

TOOLKIT

Non-pharmacological

Trigger diary, hydration, stress management, sleep hygiene, exercise, cold towel, sunglasses

Pharmacological

Abortive, prophylactic

Acetaminophen, NSAID, triptans, D2 blockers, CGRP antagonists, gepants

Procedures / Interventions

ONB, SPG blocks, Botox, TENS machine

Acute Migraine Pearls

- Oral triptans are divided into two groups:
  - **Fast onset** with high efficacy at 2 hours
    - while **sumatriptan, zolmitriptan, rizatriptan, almotriptan (axert), and eletriptan (relpax)** have fast onset of action
  - **Slow onset** with lower response rate at 2 hours.
    - Naratriptan (amerge) and frovatriptan (Frova) are slow-onset triptans with longer ½ life in system.
- Migraineurs whose symptoms **evolve rapidly** are more appropriately treated with **fast onset** triptans.

The Seven Canadian Triptans

Sumatriptan (Imitrex)	injection (6) nasal spray (20) oral (50, 100)
Naratriptan (Amerge)	oral (2.5)
Zolmitriptan (Zomig)	oral (2.5) oral wafer (2.5) nasal spray (5)
Rizatriptan (Maxalt)	oral (5, 10) oral wafer (5, 10)
Almotriptan (Axert)	oral (12.5)
Eletriptan (Relpax)	oral (20, 40)
Frovatriptan (Frova)	Oral (2.5)

Migraine - Acute

- Triptans
  - *Maxalt = Rizatriptan (5 or 10 mg po) 
  - *Axert = Almotriptan (6.25 or 12.5 mg po)
  - *Relpax = Eletriptan (20 or 40 mg po)
  - %Amerge = Naratriptan (1 or 2.5 mg PO)
  - Imitrex = Sumatriptan (50 or 100 mg po)
  - Zomig = Zolmitriptan (2.5mg po/IN [or 5.0mg]/RapidMelt)

Triptans

- MOA = **5HT1B** and **5HT1D** agonists
- "Effective" (mild or no pain) in 2/3 attacks in 2/3 individuals
- **Absolute CI to triptans**:
  - Hemiplegic or basilar migraine
  - Hypersensitivity reaction or previous adverse reaction
  - Ischemic CAD, PVD, ischemic bowel disease
  - Coronary artery vasospasm (including Prinzmetal angina); history of stroke or transient ischemic attack
  - Uncontrolled HTN
  - Prinzmetal angina
  - Use of other triptan or ergot derivative in previous 24 h
  - MAO-A inhibitor in last 2/52
  - Canadian labeling: Valvular heart disease or cardiac arrhythmias (especially tachycardias); ophthalmoplegic migraine; severe hepatic impairment.

Name	Route(s)	Dose	Max Daily	Tmax (hours)	T1/2 (hours)	S/E
Sumatriptan (imitrex)	SQ **PO** *Nasal spray* PR	6mg, may rpt in 60mn 25, 50, 100mg 5, 50 mg 25mg	12 mg 200 mg 40 mg 50 mg	0.17 1.5 1.5 1.5	2 2 1.8 1.8	Chest pressure Flushing Tingling Dizziness Limb heaviness Nausea
Rizatriptan (maxalt)	**PO**	5, 10mg	30mg	1.0	2	
Zolmitrptan (zomig)	**PO** *Nasal spray*	2.5, 5mg 2.5, 5mg	10mg 10mg	1.5 3-4	3 3	
Eletriptan (Relpax)	**PO**	20, 40mg	80mg	1.4	6.3 (80mg dose)	
Almotriptan (Axert)	**PO**	6.25, 12.5 mg	25mg	2.5	3.1	
Naratriptan (Amerge)	**PO**	1, 2.5mg	5mg	2	5.5	
Frovatriptan (Frova)	**PO**	2.5mg	7.5mg	3	25.7	

Warn your patients but be weary of nocebo.

Better tolerability, lower efficacy

Lower recurrence rates

ER strategies

- IV fluid bolus for all (500-1000 cc NS)
- IV Maxeran for all (10 mg iv)
- Decadron 10 mg IV
  - Oral taper in ensuing days not unreasonable
- DHE (dihydroergotamine) = “Migranal”
  - **5HT1D** agonist (similar to **triptan**)
    - Also interacts with central adrenergic and Da receptors
  - Usual ER dose 1mg IV
  - Must *premedicate* with anti-emetic for IV administration; as will trigger severe nausea
  - Potent vasoconstrictor (venoconstriction)
- Can also consider MgSO4
- Consider Toradol

Prophylactic Therapies

- When to start = clinical judgment
  - Some guidelines stipulate >1 major attack per week (4 per month), or approximately 3 per month that fail to respond adequately to symptomatic therapies.
- Step (**1**)
  - Trigger avoidance and lifestyle modification
- Step (**2**)
  - Evaluate all co-morbidities
    - "Targeted" therapy
- Step (**3**)
  - Ask patient preference
  - Have they been on anything before or has a friend/relative had success with one particular agent (increase likelihood of **compliance** and likely **success**)

Do Not Start

Unless…

- Patient agrees to perform a headache log (journal)
  - Your only way to track objective improvement
- Improvement ***will*** occur (provided dx correct) – METRICS of CONTROL are:
  - *Intensity*
  - *Frequency of attacks*
  - *Response to adequate doses of abortive therapies*
- ***Explicitly*** indicate this at first visit and encourage "sticking to the plan"

Setting Expectations

- Set *realistic* expectations
- Must wait *minimum* of 1-3 months to note improvements
  - Instruct patients to be patient
  - Migraine is a chronic medical condition.
  - Make parallel to:
    - Diabetes
    - Cardiac disease
    - HTN

Practical Point

Choice of agent

Let the comorbidity guide you…

- **Hypertension or CAD**
  - Propranolol*, Nadolol, Lisinopril or Candesartan
- **Essential tremor**
  - Propranolol
- **Insomnia**
  - Amitriptyline* (or any TCA)
- **Mood disorder**
  - Venlafaxine, Amitriptyline, Valproic Acid
- **Seizure disorder**
  - Topiramate*, Valproic Acid, Gabapentin
- **Pregnant or trying to conceive**
  - Magnesium (citrate)
- **Obesity or desired weight loss**
  - Topiramate

Those that tolerate poorly all Rx's

Polypharmacointolerant / resistant

- Who bring in a list of **15 allergies**…
- **Naturals**:
  - Riboflavin 400 mg DIE
  - Magnesium citrate 450-600mg DIE
  - Coenzyme Q10 100 mg TID
  - Butterbur 50 mg BID
  - Melatonin 3-5 mg HS
- **Prescription Rx** with low AE profile:
  - Propranolol (low dose; 10-20 mg BID)
  - Lisinopril, Candesartan
- **Interventions**
  - GON block
  - Botox (in chronic migraineurs)
  - TENS machine
  - SPG block (MNI and MGH)
  - Acupuncture

CMAJ Guidelines (2010)

Table 2: Guide to choosing migraine prophylactic drugs

First-line agents	Second-line agents	Third-line agents
Amitriptyline or Nortriptyline Propranolol Nadolol	Topiramate Gabapentin Venlafaxine Candesartan Lisinopril Magnesium Butterbur Coenzyme Q10 Riboflavin	Flunarizine Pizotifen Divalproex sodium
Special considerations	Appropriate agents	
Hypertension or cardiovascular disease	Propranolol, nadolol, lisinopril, candesartan	
Initial insomnia	Amitriptyline	
Mood disorder	Amitriptyline, venlafaxine	
Seizure disorder	Topiramate, divalproex sodium, gabapentin	
Pregnant or trying to conceive	Magnesium	
Obese	Topiramate	
Poor tolerance of medication side effects	Riboflavin, coenzyme Q10, butterbur, propranolol, lisinopril, candesartan	

Table 1: Prophylactic medications for migraine by quality of supporting evidence, clinical impression of efficacy, and adverse effects

Medication Starting dosage (dosage range)	Quality of evidence*	Impression of efficacy†	Adverse effects	
			Frequency‡	Adverse effect (incidence, %)
Divalproex sodium[9,10,18–21] 250 mg BID (500–1500 mg/d)	A	Effective	Frequent at higher doses§	Nausea (15%–46%), somnolence (7%–30%), tremor (13%–16%), dizziness (20%)
Topiramate[11,22–27] 25 mg QHS (50–200 mg/d)	A	Very effective	Frequent, especially at higher doses**	Paresthesias (34%–56%), weight loss (5%–11%), altered taste (5%–20%), anorexia (8%–17%), fatigue (9%–24%), memory impairment (4%–15%)
Gabapentin[28,29] 300 mg BID (900–3600 mg/d)	B	Effective	Occasional	Somnolence (25%), dizziness (26%), asthenia (22%)
Amitriptyline[30–33] or Nortriptyline 10 mg QHS (20–50 mg QHS)	B	Very effective	Occasional	Dry mouth (35%–69%), drowsiness (20%–35%)
Venlafaxine[34,35] 37.5 mg OD (75–150 mg OD)	B	Effective	Occasional	Nausea (23%–45%), vomiting (30%), drowsiness (12%–14%)
Propranolol[36] 20 mg BID (40–160 mg/d)	B	Effective	Infrequent	Fatigue (22%), reduction of heart rate and blood pressure (common)
Nadolol[37,38] 80 mg OD (80–240 mg OD)	B	Effective	Infrequent	Drowsiness (13%)
Flunarizine[39–47] 5 mg OD (5–10 mg OD)	B	Effective	Occasional	Sedation (7%–10%), weight gain (15%–21%)
Verapamil[48,49] 40 mg TID (40–80 mg TID)	C	Somewhat effective	Infrequent	Mild constipation (43%)
Lisinopril[50] 20 mg OD (no range)	B	Effective	Infrequent	
Candesartan[51] 16 mg OD (no range)	B	Effective	Infrequent	
Pizotifen[52–56] 0.5 mg TID (1.5–3 mg/d)	B	Effective	Occasional	Weight gain (21%–41%), sedation (37%–50%)
Botulinum toxin type A[57–64] 100 U (no range)	A	Ineffective	Infrequent	
Riboflavin[65,66] 400 mg OD (no range)	A	Somewhat effective	Infrequent	
Magnesium[67,68] 300 mg OD (300–600 mg/d)	B	Somewhat effective	Occasional	Soft stools and diarrhea (20%)
Feverfew[69–72] 6.25 mg TID (6.25–18.75 mg TID)	B	Ineffective	Infrequent	
Coenzyme Q10[73] 100 mg TID (no range)	B	Effective	Infrequent	
Butterbur[74,75] 50 mg BID (100–150 mg/d)	A	Effective	Infrequent	Burping (25%)

Table 9: Summary of recommendations*

Recommended For Use in Episodic Migraine** (Use)		
	Recommendation	
Drug	**Recommendation Strength**	**Quality of Evidence**
Topiramate	Strong	High
Propranolol	Strong	High
Metoprolol	Strong	High
Amitriptyline or Nortriptyline	Strong	High
Nadolol	Strong	Moderate
Gabapentin	Strong	Moderate
Candesartan	Strong	Moderate
Butterbur	Strong	Moderate
Riboflavin	Strong	Low
Coenzyme Q10	Strong	Low
Magnesium citrate	Strong	Low
Divalproex	Weak	High
Flunarizine	Weak	High
Pizotifen	Weak	High
Venlafaxine	Weak	Low
Verapamil	Weak	Low
Lisinopril	Weak	Low
Not Recommended for Use in Episodic Migraine (Do not use)**		
Botulinum toxin type A	Strong	High
Feverfew	Strong	Moderate

*Utilizing Grade Criteria; ** Migraine with headache on less than 15 days a month.

TOOLKIT

Non-pharmacological

Trigger diary, hydration, stress management, sleep hygiene, exercise, cold towel, sunglasses

Pharmacological

Abortive, prophylactic

Acetaminophen, NSAID, triptans, D2 blockers, CGRP antagonists, gepants

Procedures / Interventions

ONB, SPG blocks, Botox, TENS machine

Non-pharmacological

- Acute
  - Rest
  - Ice
  - Tiger Balm, other topical ointments OTC
- Chronic / prophylaxis
  - Lifestyle hygiene
    - Stress management, biofeedback, meditation
    - Sleep schedule
    - Dietary triggers
    - Exercise
    - Hydration status

Cefaly Anti-Migraine:

TENS to trigeminal nerve

TOOLKIT

Non-pharmacological

Trigger diary, hydration, stress management, sleep hygiene, exercise, cold towel, sunglasses

Pharmacological

Abortive, prophylactic

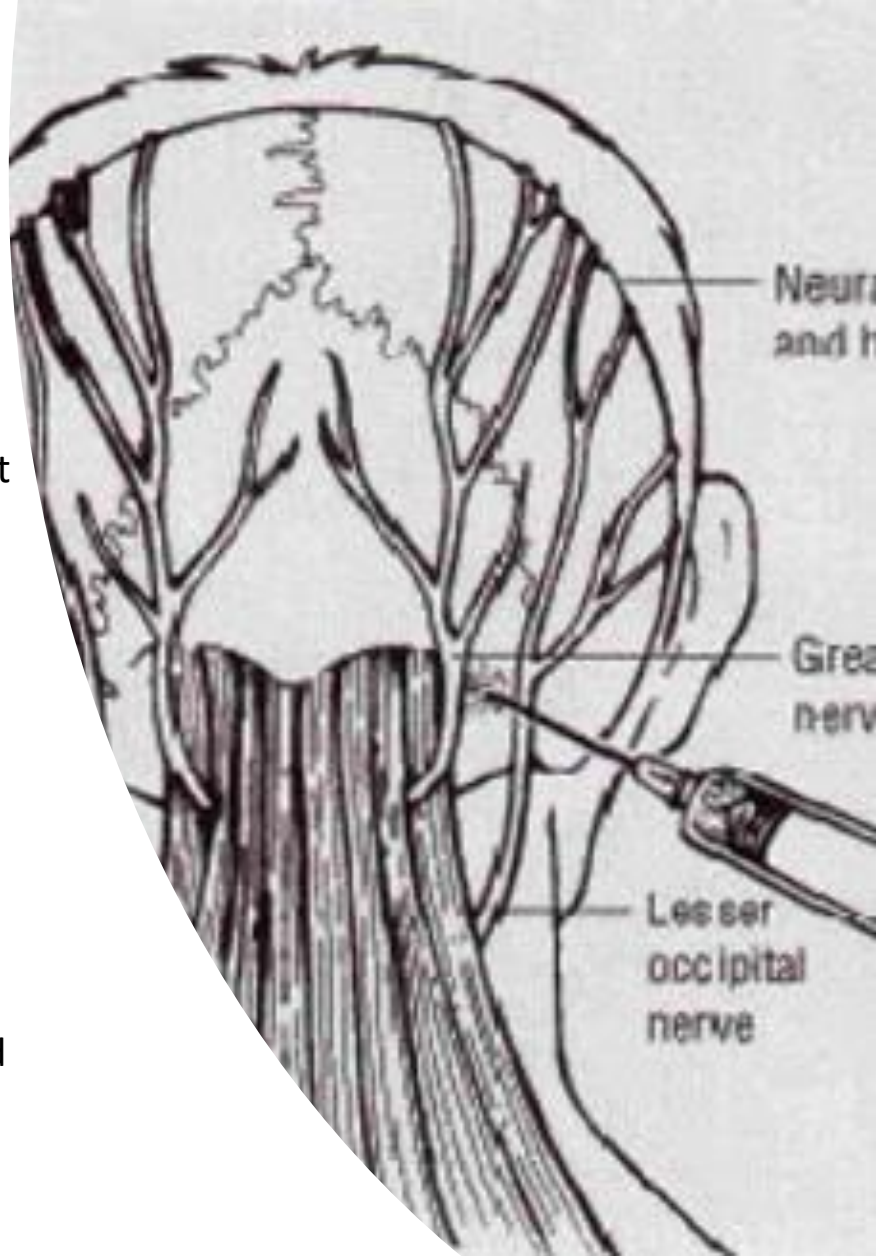
Acetaminophen, NSAID, triptans, D2 blockers, CGRP antagonists, gepants

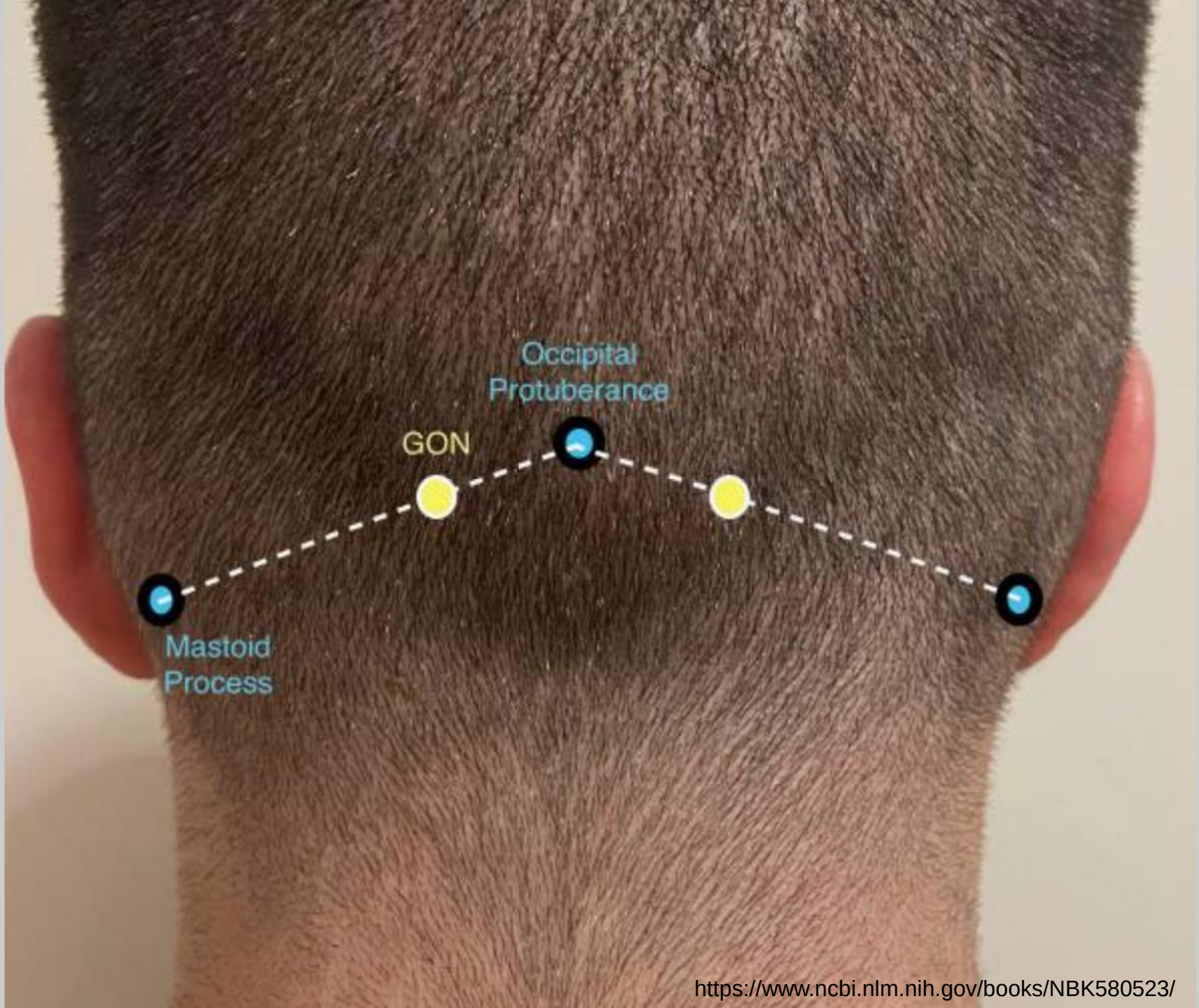
Procedures / Interventions

ONB, SPG blocks, Botox, TENS machine

Greater / Lesser Occipital Nerve Block

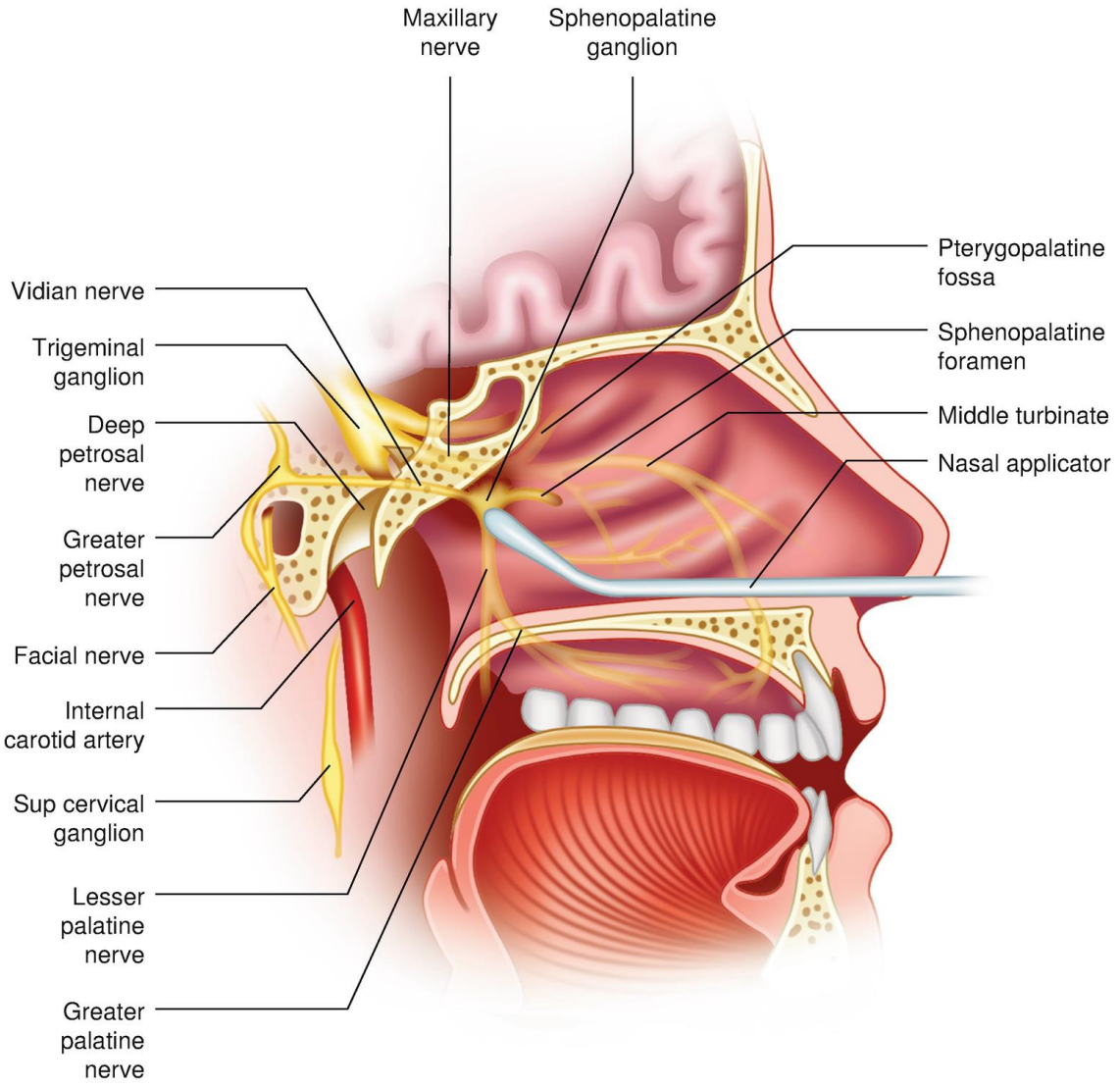
- Done in office or ER with Xylocaine 1 to 2% +/- Depot Medrol 40mg
  - 3 CC's total (2 CC's Xylo, 1 CC Medrol)
  - Local pressure / tamponade for 30-60 seconds, and massage mixture into soft tissues
- Can break **cycle** of pain if exquisitely tender on exam
  - If provoking pain in migraine patient
- Post concussive, cervicogenic or cluster headaches too all respond.
- Consistent evidence for efficacy
  - Anecdotally I try it in patients with migraine and focal suboccipital pain – referred pain to TCC which feeds into cycle of pain.
- Remains an option in pregnancy





https://www.ncbi.nlm.nih.gov/books/NBK580523/

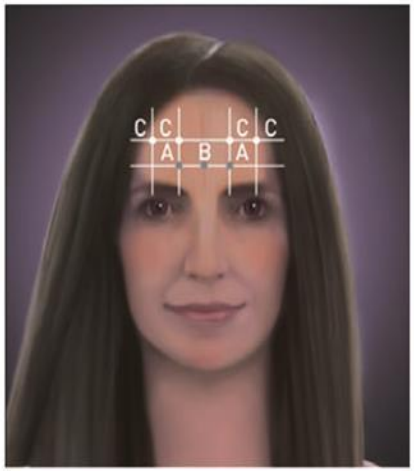
SPG block (sphenopalatine ganglion block)



https://link.springer.com/chapter/10.1007/978-3-030-85047-0_52

Botox

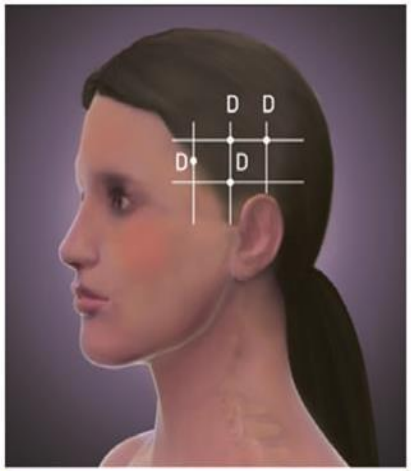
31 injections (5 Botox-A units per injection, for a total of 155 units)



A. Corrugator
5 U each side

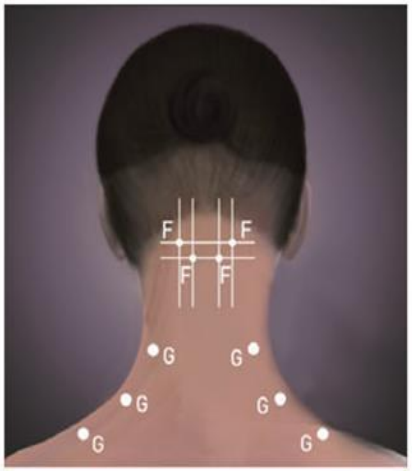
B. Procerus
5 U (one site)

C. Frontalis
10 U each side



D. Temporalis
20 U each side

E. Occipitalis
15 U each side



F. Cervical paraspinal
10 U each side

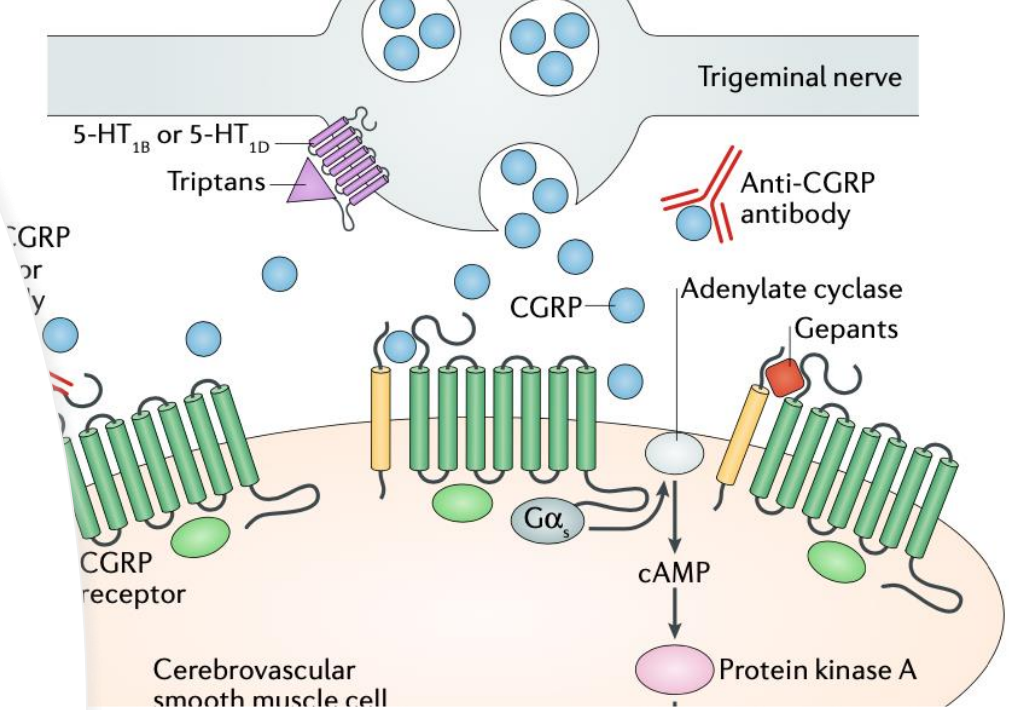
G. Trapezius
15 U each side

Erenumab (CGRP receptor antagonist)

- Aimovig
- Approved in Canada
- Strictly for **prophylactic** use
- To qualify for “Quick Start” program via Novartis
  - Must have ≥ 8 migraine days per month and have failed at least 2 prophylactic agents (different classes).

Erenumab

- 70, 140 mg doses
- SC injection once monthly
- Most common AE's:
  - Constipation (10%), injection site reaction(s), URTIs
- Some "super responders"
  - exact phenotype to be determined.



Practical Limitations

- RAMQ and private insurers will usually **not** reimburse both CGRP-A and Botox unfortunately.
- Difficult to understand why when the drugs have completely different MOA.
- Common use Rx's with multiple differing (MOA) in chronic diseases.
  - Diabetes, HTN, Epilepsy etc

"AJOVY"
(fremanezumab)
injection 225 mg/1.5 mL

COMPARISON OF SELECT THERAPIES INDICATED IN MIGRAINE PREVENTION*,1–4

	INDICATION	MECHANISM OF ACTION	DOSAGE FORMS / STRENGTHS	RECOMMENDED DOSE AND FREQUENCY		HALF-LIFE
PrAJOVY® (fremanezumab)[1] **TEVA**	Indicated for the prevention of migraine in adults who have at least 4 migraine days per month.	Fremanezumab is a humanized monoclonal antibody that binds to calcitonin gene-related peptide (CGRP) ligand and blocks its binding to the receptor.	SC INJECTION Single-use prefilled autoinjector (225 mg/1.5 mL)  Single-use prefilled syringe (225 mg/1.5 mL) 	Two subcutaneous dosing options are available to administer the recommended dosage: MONTHLY DOSING: 225 mg (1 injection) QUARTERLY DOSING: 675 mg (3 separate injections of 225 mg one after another) every 3 months		30 DAYS
PrAIMOVIG® (erenumab)[2] **NOVARTIS**	Indicated for the prevention of migraine in adults who have at least 4 migraine days per month.	Erenumab is a recombinant human monoclonal antibody that competes with CGRP for binding to the CGRP receptor and antagonizes CGRP receptor function. It has no significant activity at adrenomedullin, calcitonin, and amylin receptors. CGRP is a neuropeptide that modulates nociceptive signalling and a vasodilator that has been associated with migraine pathophysiology.	SC INJECTION Single-dose prefilled autoinjector (70 mg/mL or 140 mg/mL) 	The recommended dose of AIMOVIG® is 70 mg once monthly. Some patients may benefit from a dose of 140 mg once-monthly administered as one subcutaneous injection of 140 mg.		28 DAYS
PrEMGALITY® (galcanezumab)[3] **LILLY**	Indicated for the prevention of migraine in adults who have at least 4 migraine days per month.	Galcanezumab is a humanized IgG4 monoclonal antibody that binds calcitonin gene-related peptide (CGRP) and prevents its biological activity. Galcanezumab targets CGRP with high affinity (KD = 31 pM) and does not bind to the CGRP receptor or related peptides adrenomedullin, amylin, calcitonin, and intermedin.	SC INJECTION Single-use prefilled pen (120 mg/mL)  Single-use prefilled syringe (120 mg/mL) 	The recommended dose is an initial (loading) dose of 240 mg (administered as two consecutive subcutaneous injections of 120 mg) followed by once-monthly doses of 120 mg (one injection).		27 DAYS
PrVYEPTI® (eptinezumab)[4] **LUNDBECK**	Indicated for the prevention of migraine in adults who have at least 4 migraine days per month.	Eptinezumab is a humanized immunoglobulin G1 (IgG1) antibody that binds to human calcitonin gene-related peptide (CGRP) ligand with picomolar affinity and blocks its binding to the CGRP receptor. Eptinezumab is highly selective and does not bind to any of the related neuropeptides amylin, calcitonin, adrenomedullin, and intermedin.	IV INFUSION 100 mg/mL solution in a single-use vial		The recommended dose is 100 mg administered by IV infusion every 12 weeks. Some patients may benefit from a dosage of 300 mg administered by IV infusion every 12 weeks.	29 DAYS

TOOLKIT – Principals and Practice

empowerment

confidence by treating MD will translate to patient

Non-pharmacological

trigger diary, hydration, stress management, sleep hygiene, exercise, cold towel, sunglasses

patience

Pharmacological

abortive, prophylactic

Acetaminophen, NSAID, triptans, D2 blockers, CGRP antagonists, gepants (GCRP R antagonists)

compassion and acceptance

Procedures / Interventions

ONB, SPG blocks, Botox, TENS machine

A few added pearls…

ALWAYS screen for **MOH –** frequently comorbid.

Provide patient with "**protocol**" about what to use, when - to be reinforced at each visit.

Time off work -offending activity / trigger avoidance may be necessary.

Medication Overuse Headache (MOH)

- Probably ***the*** most "missed" diagnosis in doctor's office
- Strict criteria exist
- Felt to be a "rebound" phenomenon (i.e, brain is craving OTC analgesia)
- Recognition is key, as cannot achieve success if treat as simple migraine
- OTC (Tylenol, Advil, Aspirin)
  - ≥14 days per month (14 "headache" days)
- Prescription (Triptans, narcotics, Fiorenal, Excedrin etc)
  - ≥9 days per month
- *Least likely* to cause rebound = **Naproxen**

MOH

- Does **not preclude** Dx of migraine
- Most frequent story is
  - *Undertreated* migraineur who self-treats (unsuccessfully), or told by walk-in MD (or ER) to take OTC Rx's.
    - Final diagnosis *usually*:
      1. **MOH due to OTC analgesic abuse-overuse**
      2. **Episodic migraine +/- aura**

- Signal for utility of CGRP antagonists in MOH
  - Should not dissuade you from using it.

Migraine - Conclusions

- Know the diagnostic criteria
- **Stratify** the therapy(ies) to the intensity of the pain (and dysfunction of the patient)
  - Abortive strategies
  - Prophylactic strategies [pharmacologic / non-pharmacological]
- Targeted procedures (ONB, SPG block, Botox)
  - Know they exist, often effective, and know who does them
- **Do not miss MOH (usually comorbid)**
- There will **always** be patient who seem refractory to everything (minority)
  - Education, counseling, multimodal approach and **setting realistic expectations and goals (frequency, intensity, response to abortive Rx's)**

Last word

- Migraine is a chronic condition which require follow-ups, no quick solutions.
- Demand for ‘migraine’ assessment/management far exceeds the capacity for neurology; and will likely never be met.
- Empowering community MDs is part of the solution and knowing who / when to refer.
- Referrals at times placed exceedingly prematurely after insufficient abortive / prophylactic trials and typically either due to (**a**) patient insistence to see a ‘specialist’ or (**b**) insufficient time by primary MD (we won’t go there) and follow-ups.
- CRDS protocols are quite firm.

CRDS

Headache	☐ Migraine *(Prerequisite: failed an abortive treatment such as Triptan and 2 prophylactic treatments, history of attempted treatments (agent, dose, effectiveness and duration) (Recommended: specify reason for failure)*	**D**
	☐ Suspected cluster headache (Horton) *(Prerequisite: justify autonomic manifestation)*	**C**
	☐ Trigeminal neuralgia *(Prerequisiste: justify paroxysmal pain, facial involvement, trigger zone) (Recommended: attempt treatment with Carbamazepine)*	**C**
	☐ Other type of headache *(Prerequisite: justify suspected diagnosis)*	**E**

Thank you for your attention

Questions?

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References

3 primary references

All Canadian based content

65 Pages CJNS (2011)
86 Pages CJNS (2013)
10 Pages CMAJ (2010)

Excellent References

CMAJ REVIEW

Prophylaxis of migraine headache

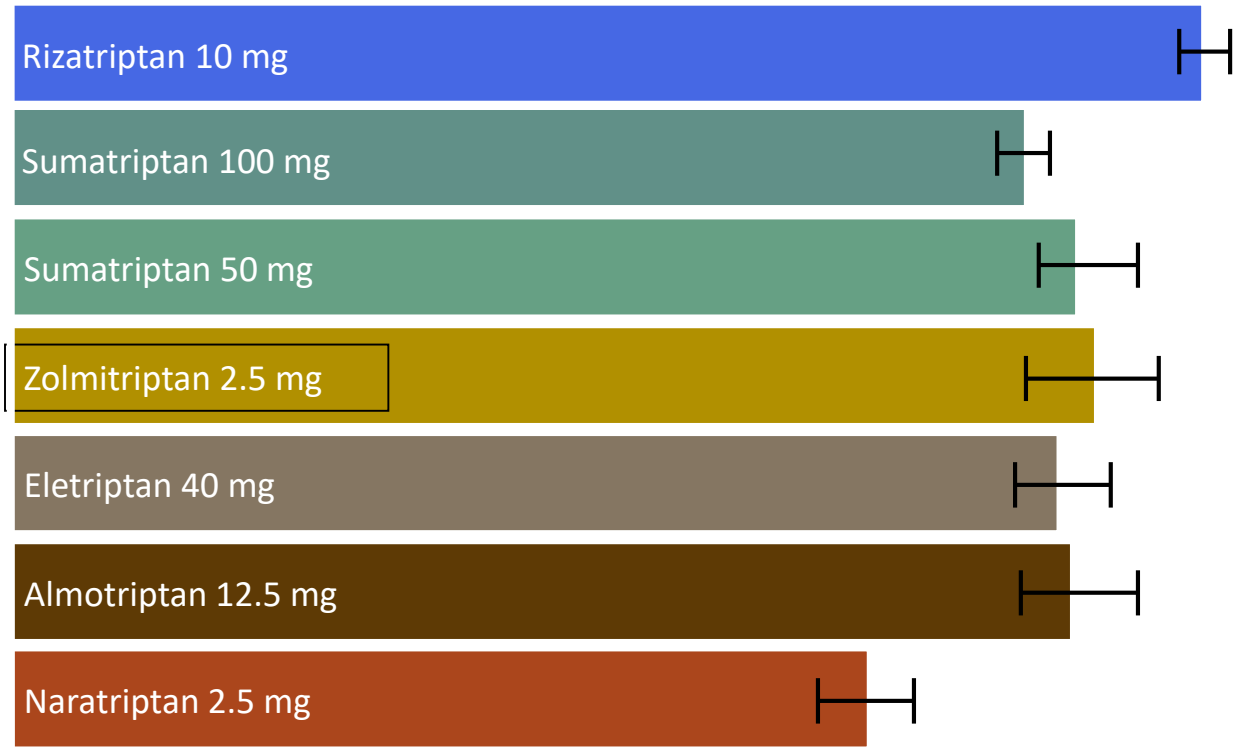
Tamara Pringsheim MD MSc, W. Jeptha Davenport BA MD, Werner J. Becker MD

April 2010
CMAJ

CANADIAN NEUROLOGICAL SCIENCES FEDERATION
FÉDÉRATION DES SCIENCES NEUROLOGIQUES DU CANADA
The journal
Canadian Journal of Neurological Sciences
Volume 39 / Number 2 / Supplement 2 / March 2012

March 2012
(prophylaxis)
Sept 2013
(abortive)
CJNS

Relief of Migraine Pain

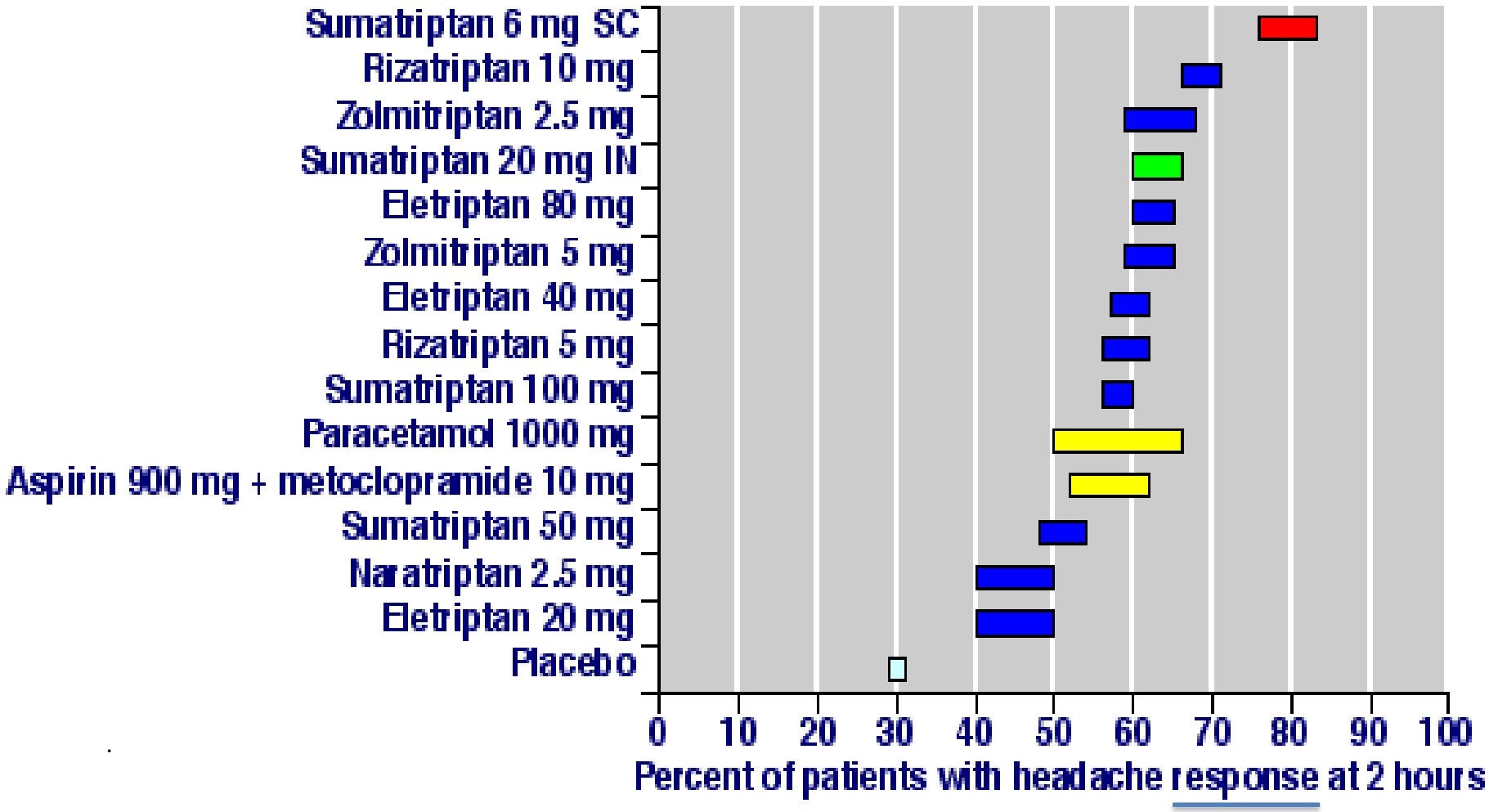


Headache **relief** at 2 hours* (95% CI)

% Patients (N=24,089)

Adapted from Ferrari MD et al. *Lancet* 2001;358:1668-1675.
*Comparison of recommended initial doses in SPC and standard comparator in the meta-analysis (sumatriptan 100 mg).

Systematic reviews of comparable trials



http://www.jr2.ox.ac.uk/bandolier/index.html accessed April 2007

Migraine Prophylaxis: Doses

Class/drug	Usual starting dose & titration	Recommended target dose	Avoid or use with caution* for patients with:	May be preferred in patient with:	Adverse Effects*
Antiepileptics:					
Divalproex sodium (also valproic acid or sodium valproate)	250 mg/d for 1 week, then 250 mg BID for 1 week, then 250 mg in am & 500 mg at bedtime; ↑ weekly by 250 mg, if needed	750-1500 mg/d (divided BID)	Liver disease, bleeding disorders, alcoholism, obesity; avoid in pregnancy (human teratogen); small risk of encephalopathy when combined with topiramate	Epilepsy, mania, anxiety	Nausea/vomiting, tremor, weight gain, alopecia, ↑ hepatic enzymes, neural tube defects (if used during pregnancy)
Topiramate	15 or 25 mg/d; ↑ by 15 mg weekly or 25 mg every 1-2 weeks	100 mg/d (at bedtime) or 50 mg BID; up to 200 mg/d may be used, if needed & tolerated	Kidney stones, kidney failure, angle closure glaucoma, pregnancy; small risk of encephalopathy when combined with valproate	Epilepsy, obesity, mania, anxiety, essential tremor, alcohol dependence	GI (nausea, anorexia); renal calculi; paresthesias; acute glaucoma; CNS (dizziness, tremor, sedation, cognitive impairment, depression); weight loss; metabolic acidosis
Gabapentin	300 mg/d & ↑ by 300 mg every 3-5 days, or start with 300 mg TID & ↑ weekly by 300 mg	1200-1500 mg/d (divided TID); up to 1800 mg/day may be used, if needed & tolerated	Kidney failure	Epilepsy, mania, anxiety, insomnia	Drowsiness, dizziness
Antidepressants:					
TCAs: Amitriptyline (or nortriptyline. Note: nortriptyline has no controlled trial evidence for efficacy)	10 mg/d (bedtime or 1 h before); ↑ by 10 mg every 1-2 weeks	20-40 mg/d (bedtime); up to 100-150 mg/d may be used, if needed & tolerated	Heart block, significant CV disease, urinary retention, uncontrolled glaucoma, prostate disease, mania	Insomnia, depression, anxiety, neuropathic pain, co-morbid tension-type headache	Weight gain, drowsiness, confusion, anticholinergic effects (dry mouth, constipation), ↓ seizure threshold, sexual dysfunction cardiovascular effects
SNRIs: Venlafaxine extended release	37.5 mg once daily for 1 week; ↑ weekly by 37.5 mg (may ↑ weekly by 75 mg)	150 mg/d (once daily)	Hypertension, kidney failure	Depression, anxiety	Nausea/vomiting, sexual dysfunction, drowsiness, dizziness, blurred vision

Migraine Prophylaxis: Doses

Class/drug	Usual starting dose & titration	Recommended target dose	Avoid or use with caution* for patients with:	May be preferred in patient with:	Adverse Effects*
Antihypertensives: Beta-blockers:					
Propranolol	20-40 mg BID; ↑ by 20 mg BID every 1-2 weeks	80–160 mg/d (divided BID or LA form once daily)	Asthma, heart block, CHF, hypotension, bradycardia, Raynaud's, peripheral vascular disease, insulin-dependent diabetes, depression, sexual dysfunction	Hypertension, angina	Fatigue, reduced exercise tolerance, bradycardia, CHF, hypotension, bronchospasm, impotence, sleep disturbance
Nadolol	20-40 mg/d (morning); ↑ by 20-40 mg every 1-2 weeks	80–160 mg/d once daily	See Propranolol	See Propranolol	See Propranolol; may have fewer CNS side effects
Metoprolol	50 mg BID	100-200 mg/d (divided BID or SR form once daily)	See Propranolol	See Propranolol	See Propranolol
Calcium Channel Blockers:					
Flunarizine	5-10 mg/d (at bedtime); ↑ to 10 mg/d in 1-2 weeks (if start with 5 mg/d)	10 mg/d (at bedtime)	Depression, Parkinson's	Dizziness, vertigo	Weight gain, depression, drowsiness, extrapyramidal effects
Verapamil (not recommended for routine use because of low quality evidence for efficacy)	40 mg TID; ↑ to 80 mg TID over 1-2 weeks; SR: start with 160 mg/d; ↑ to 240 mg/d (divided BID) over 1-2 weeks	240 mg/d (divided TID; SR divided BID); doses > 480 mg/d not recommended	Constipation, hypotension, severe CHF, bradycardia, heart block, arrhythmias; avoid concomitant use with beta-blockers	Hypertension, angina	Constipation, peripheral edema, AV conduction disturbances
Antihypertensives: ACEIs/ARBs:					
Candesartan	8 mg/d, ↑ to 16 mg/d in 1 week (once daily)	16 mg/d (once daily)	Hypotension, pregnancy (especially 2nd & 3rd trimesters); monitor K if used with K-sparing diuretics	Hypertension	Hypotension, dizziness
Lisinopril	10 mg/d (once daily)	20 mg/d (once daily)	Hypotension, pregnancy (especially 2nd & 3rd trimesters); monitor K if used with K-sparing diuretics	Hypertension	Hypotension, dizziness, fatigue, non-productive cough, angioedema (rare)

Migraine Prophylaxis: Doses

Class/drug	Usual starting dose & titration	Recommended target dose	Avoid or use with caution* for patients with:	May be preferred in patient with:	Adverse Effects*
Vitamins/minerals/herbals:					
Riboflavin	400 mg/d (or 200 mg BID)	400 mg/d (once daily or divided BID)	None	None	Yellow discolouration of urine (benign)
Coenzyme Q10	100 mg TID	300 mg/d (100 mg TID to minimize GI adverse effects)	Hypotension	Hypertension	GI upset
Magnesium citrate	300 mg (elemental magnesium) BID	300 mg (elemental magnesium) BID	Kidney failure, diarrhea	Constipation	Diarrhea, GI upset
Butterbur (*Petasites*)	75 mg BID	75 mg BID	None	Allergic rhinitis	GI (burping)
Serotonin antagonists:					
Pizotifen (pizotyline)	0.5 mg at bedtime for 1 week; 0.5 mg BID for 1 week; 0.5 mg TID, ↑ up to 4 mg/d, if needed	1.5- 4 mg/d (1 mg BID is good target); full dose can be given at bedtime	Obesity	Insomnia	Drowsiness, weight gain (can be significant)