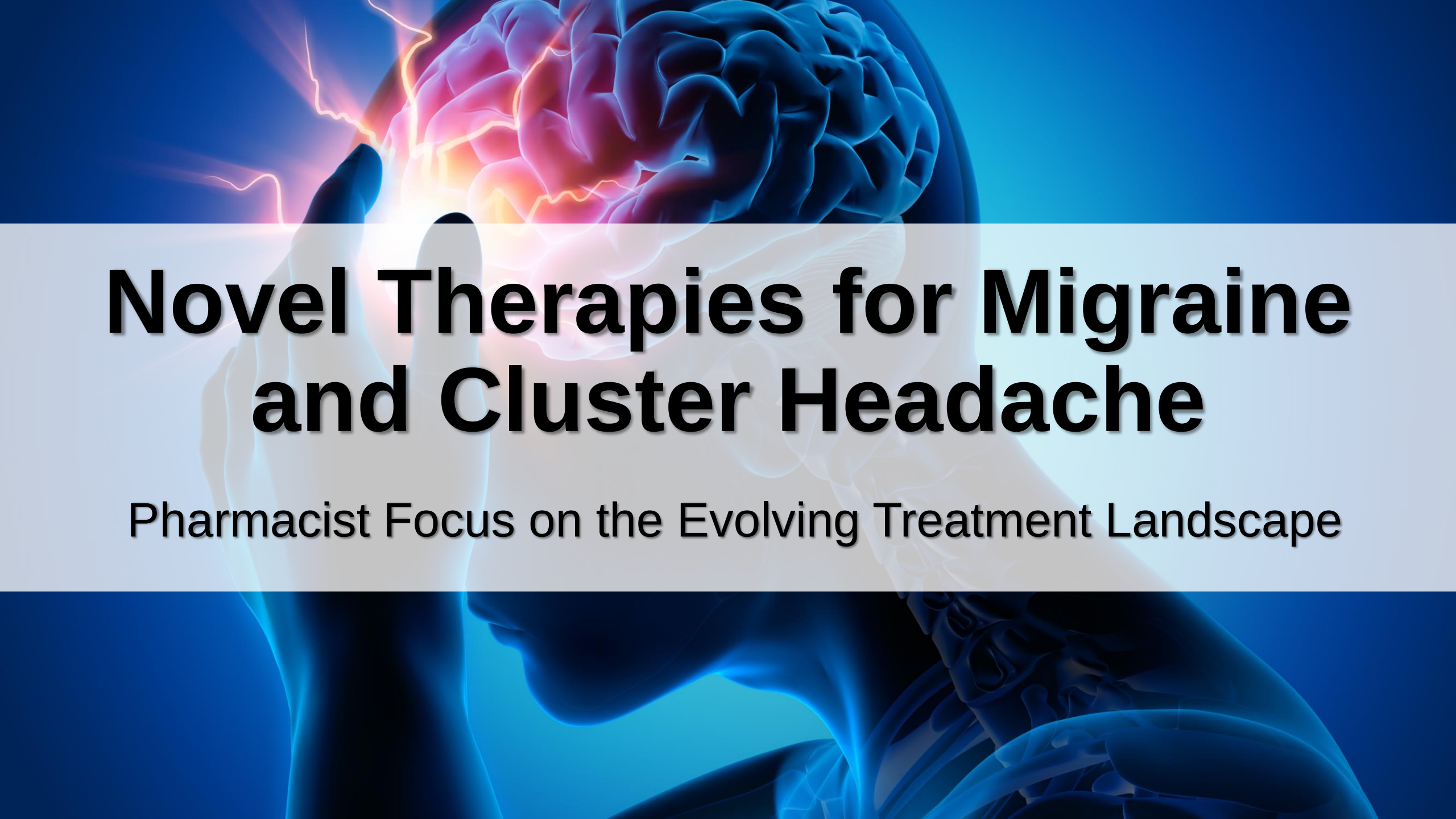

Novel Therapies for Migraine and Cluster Headache

Pharmacist Focus on the Evolving Treatment Landscape

This educational activity is sponsored by Postgraduate Healthcare Education, LLC and is supported by an educational grant from Lilly USA, LLC.

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Disclosures

Dr. Smith has disclosed that he has served as a Consultant for Amgen, Biohaven, Impel NeuroPharma, Lilly, Lundbeck, Theranica, and Vorso; a Clinical Investigator for Amgen, Allergan, Biohaven, electroCore, Impel NeuroPharma, Lilly, Lundbeck, Novartis, Satsuma, Theranica, and Vorso; on the Speaker's Bureau for Amgen, Allergan, Biohaven, and Lilly; and is a Major Shareholder of UnitedHealth Group.

The clinical reviewer, **Michele A. Faulkner, PharmD**, **FASHP**, has no actual or potential conflict of interest related to this program.

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UAN: 0430-0000-20-136-H01-P
Credits: 1.0 hour (0.1 CEU)
Type of Activity: Application

Learning Objectives

- **Describe** the distinctive features of migraine and cluster headache, including symptoms and triggers
- **Explain** important differences between the available treatment options for migraine and cluster headache, including mechanism of action, adverse effects, drug-drug interactions, and dosing/route of administration
- **Recommend** optimal treatment strategies for patients with migraine and cluster headache
- **Demonstrate** pharmacist-driven strategies to provide patient-centered care for patients with migraine and cluster headache

Migraine and Cluster Headache

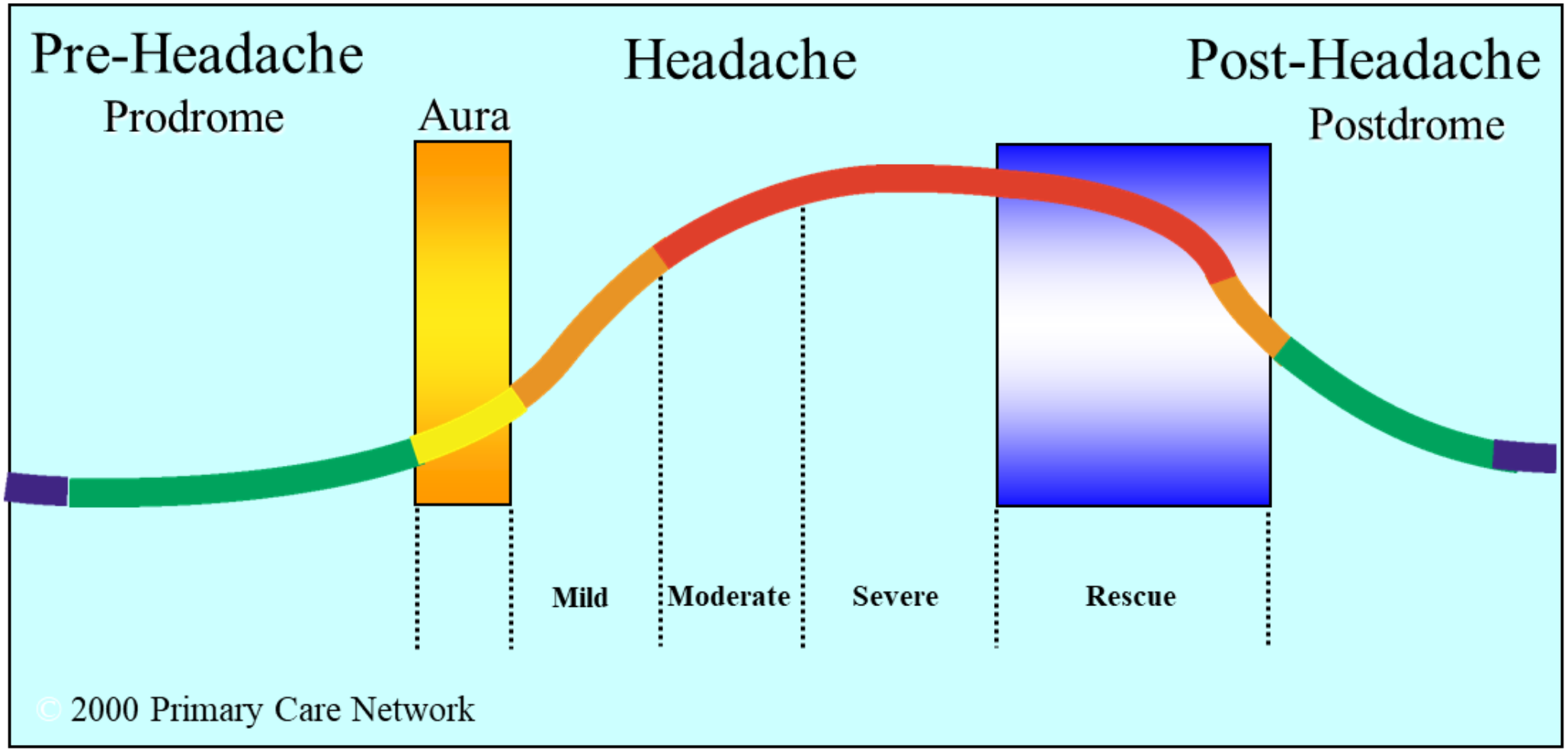
- Disabling primary headache disorders
- Once referred to as “vascular headaches”
- Major causes of disability and lost productivity
- Some shared pathways and neuroanatomical areas of dysfunction
- Distinct clinical presentations and therapeutic considerations

What Is Migraine?

- A tendency (likely inherited) for the brain to lose control of its inputs
- A disorder of brain sensory processing that cycles
- Influenced by both genetics and the environment
- Characterized by relapsing and remitting episodes of neurovascular dysfunction that may be incapacitating
- Symptoms include a complex of head pain and other neurologic and systemic symptoms
- Four possible phases: prodrome (premonitory), aura, headache, and postdrome

Goadsby, et al. *Physiol Rev.* 2017;97(2):553-622.

Migraine Phases



What Is Cluster Headache?

- A trigeminal autonomic cephalalgia (TAC)
- Characterized by periods of frequent, extremely painful, strictly unilateral, short-lasting headache attacks
- Accompanied by ipsilateral autonomic symptoms
- May include a sense of restlessness and agitation (or both)
- May have a hereditary component
- Involves synchronized abnormal activity in the hypothalamus, trigeminovascular system, and autonomic nervous system
- Frequently manifests with circadian pattern

Hoffman and May. *Lancet Neurol*. 2018;17(1):75-83.

Epidemiology

- Migraine
  - 39 million people with migraine in the US (12% of the population)
  - Over 1 billion people worldwide
  - 18% of women, 6% of men, 10% of children experience migraines
  - Most common between the ages of 18 and 44 years
  - Almost 90% of these patients have a family history of migraine
- Cluster Headache
  - Pooled lifetime prevalence is approximately 0.1% (300-500K people with cluster headache in the US)
  - Male-to-female ratio is 2.5:1
  - Most common in patients in their 30s to 50s

https://migraineresearchfoundation.org/about-migraine/migraine-facts

Burden of Migraine

- Migraine is the third most prevalent illness in the world
- Nearly 1 in 4 US households includes someone with migraine
- Migraine is the sixth most disabling illness in the world
- On any given day, over 150,000 people are incapacitated with a migraine attack in the US
- Every 10 seconds, someone in the US goes to the emergency room (ER) complaining of head pain
- 1.2 million ER visits are for acute migraine attacks annually
- Health care and lost productivity costs associated with migraine are estimated to be as high as $36 billion annually in the US
- More than 157 million workdays are lost each year in the US due to migraine

https://migraineresearchfoundation.org/about-migraine/migraine-facts

Burden of Cluster Headache

- Mean total cost of a cluster headache period is $5136 per patient
- Mean total cost of chronic cluster headache is 5.4 times higher than episodic ($15,589 vs. $2904, *P* < .001)
- 27% of patients feel that cluster headache has limited their career
- 40% have changed their work pattern
- 20% have changed their place of employment
- 10% have lost a job due to the disease

Vinding. *Cephalalgia*. 2007;27(3):263-270.

Diagnostic Criteria

Migraine and Cluster Headache

ICHD-3 Diagnostic Criteria

- According to the International Classification of Headache Disorders, 3rd ed (ICHD-3), migraine has 2 major types
- **1.1 Migraine without aura** is a clinical syndrome characterized by headache with specific features and associated symptoms
- **1.2 Migraine with aura** attacks are consistent with the 1.1 characteristics above but have the added characteristic of transient focal neurological symptoms that usually precede or sometimes accompany the headache

https://ichd-3.org

ICHD-3 Diagnostic Criteria

1.1 Migraine without aura

- Diagnostic criteria:
  - A. At least 5 attacks fulfilling criteria B-D
  - B. Headache attacks lasting 4-72 h (untreated or unsuccessfully treated)
  - C. Headache has at least 2 of the following 4 characteristics:
    - Unilateral location
    - Pulsating quality
    - Moderate or severe pain intensity
    - Aggravation by or causing avoidance of routine physical activity (eg, walking)
  - D. During headache at least 1 of the following:
    - Nausea and/or vomiting
    - Photophobia and phonophobia
  - E. Not better accounted for by another ICHD-3 diagnosis

https://ichd-3.org

ICHD-3 Diagnostic Criteria

1.2 Migraine with aura

- Diagnostic criteria:
  - A. At least 2 attacks fulfilling criteria B and C
  - B. One or more of the following fully reversible aura symptoms:
    - Visual
    - Sensory
    - Speech/language
    - Motor*
    - Brainstem*
    - Retinal*
  - C. At least 3 of the following 6 characteristics:
    - At least 1 aura symptom spreads gradually over ≥5 minutes
    - 2 or more aura symptoms occur in succession
    - Each individual aura symptom lasts 5-60 minutes
    - At least 1 aura symptom is unilateral
    - At least 1 aura symptom is positive
    - Aura is accompanied, or followed within 60 minutes, by headache
  - D. Not better accounted for by another ICHD-3 diagnosis

** Represent rare "complicated" migraine subtypes that require special management consideration.*

https://ichd-3.org

ICHD-3 Diagnostic Criteria

1.3 Chronic Migraine

- Diagnostic criteria:
  - A. Headache (migraine-like or tension-type-like) on ≥15 days/month for >3 months, and fulfilling criteria B and C
  - B. Occurring in a patient who has had at least 5 attacks fulfilling criteria for *1.1 Migraine without aura* and/or criteria for *1.2 Migraine with aura*
  - C. On ≥8 days/month for >3 months, fulfilling any of the following:
    - Criteria for *1.1 Migraine without aura*
    - Criteria for *1.2 Migraine with aura*
    - Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative
  - D. Not better accounted for by another ICHD-3 diagnosis

https://ichd-3.org

ICHD-3 Diagnostic Criteria

3.1 Cluster Headache

- Diagnostic criteria:
  - A. At least 5 attacks fulfilling criteria B-D
  - B. Severe or very severe unilateral orbital, supraorbital, and/or temporal pain lasting 15-180 minutes (when untreated)
  - C. Either or both of the following:
    - At least 1 of the following symptoms or signs, ipsilateral to the headache:
      - conjunctival injection and/or lacrimation
      - nasal congestion and/or rhinorrhea
      - eyelid edema
      - forehead and facial sweating
      - miosis and/or ptosis
    - A sense of restlessness or agitation
  - D. Occurring with a frequency between 1 every other day and 8 per day
  - E. Not better accounted for by another ICHD-3 diagnosis

https://ichd-3.org

ICHD-3 Diagnostic Criteria

3.1.2 Chronic Cluster Headache

- Diagnostic criteria:
  A. Attacks fulfilling criteria for *3.1 Cluster Headache*, and
  B. Occurring without a remission period, or with remissions lasting <3 months, for at least 1 year

ICHD-3 Diagnostic Criteria

8.2 Medication Overuse Headache (MOH)

- Formerly called “rebound headache”
- Diagnostic criteria:
  A. Headache occurring on ≥15 days/month in a patient with a preexisting headache disorder
  B. Regular overuse for >3 months of 1 or more drugs that can be taken for acute and/or symptomatic treatment of headache
  C. Not better accounted for by another ICHD-3 diagnosis

Pathophysiology

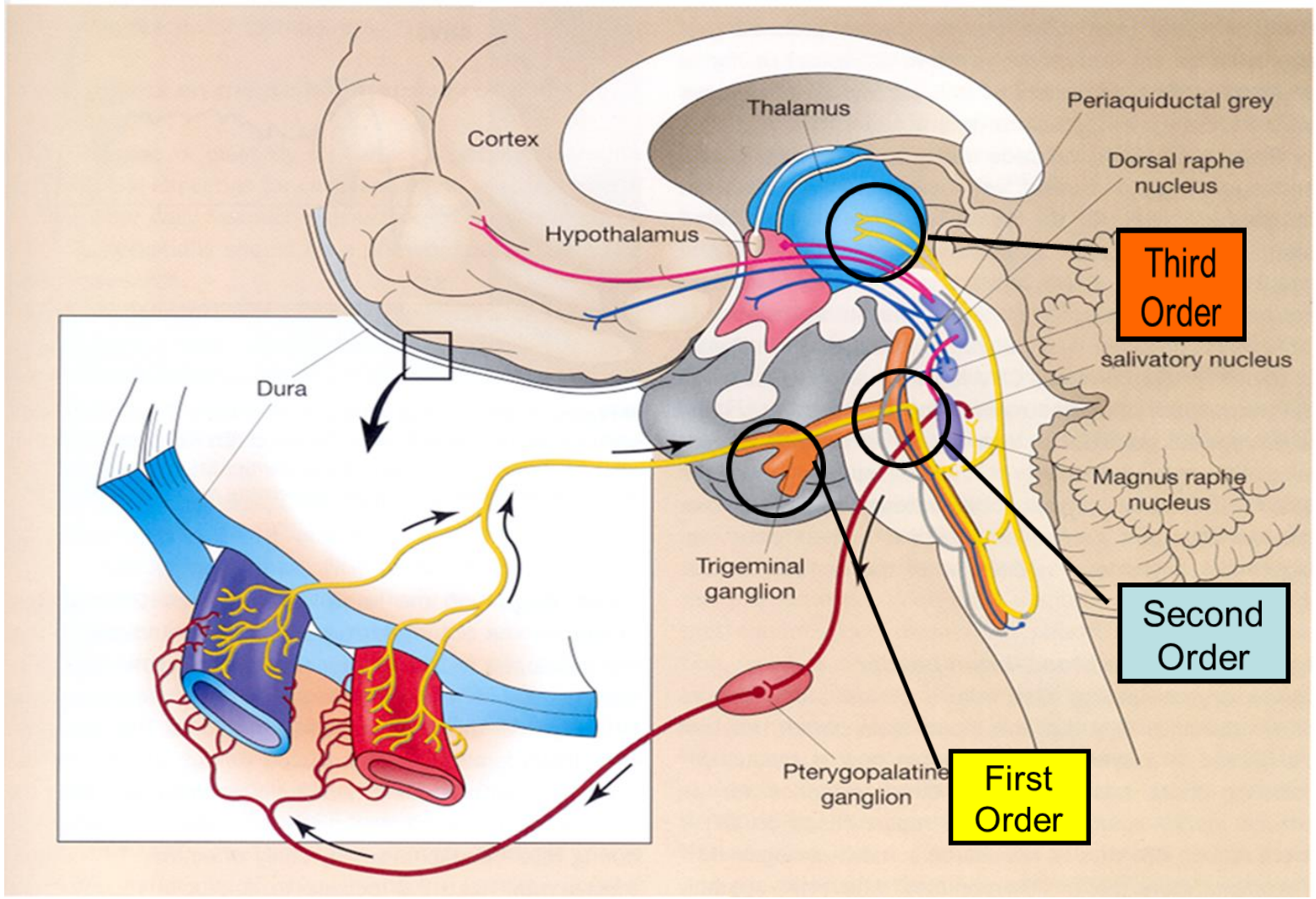
Migraine and Cluster Headache

Migraine Pathophysiology

- Genetically determined abnormalities in neuronal ion channels
- Increased CNS sensitivity to internal and external stimuli
  - Cortical spreading neuronal depolarization (aura)
  - Increased plasma extravasation
  - Neurogenic inflammation
  - Enhanced trigeminal nociceptive transmission
- Hypothalamic modulation abnormalities
  - Dysautonomia
- Impaired descending pain inhibition/modulation (brainstem)

Goadsby. *Ann Indian Acad Neurol*. 2012;15(suppl 1):S15-S22.

Migraine Pathophysiology



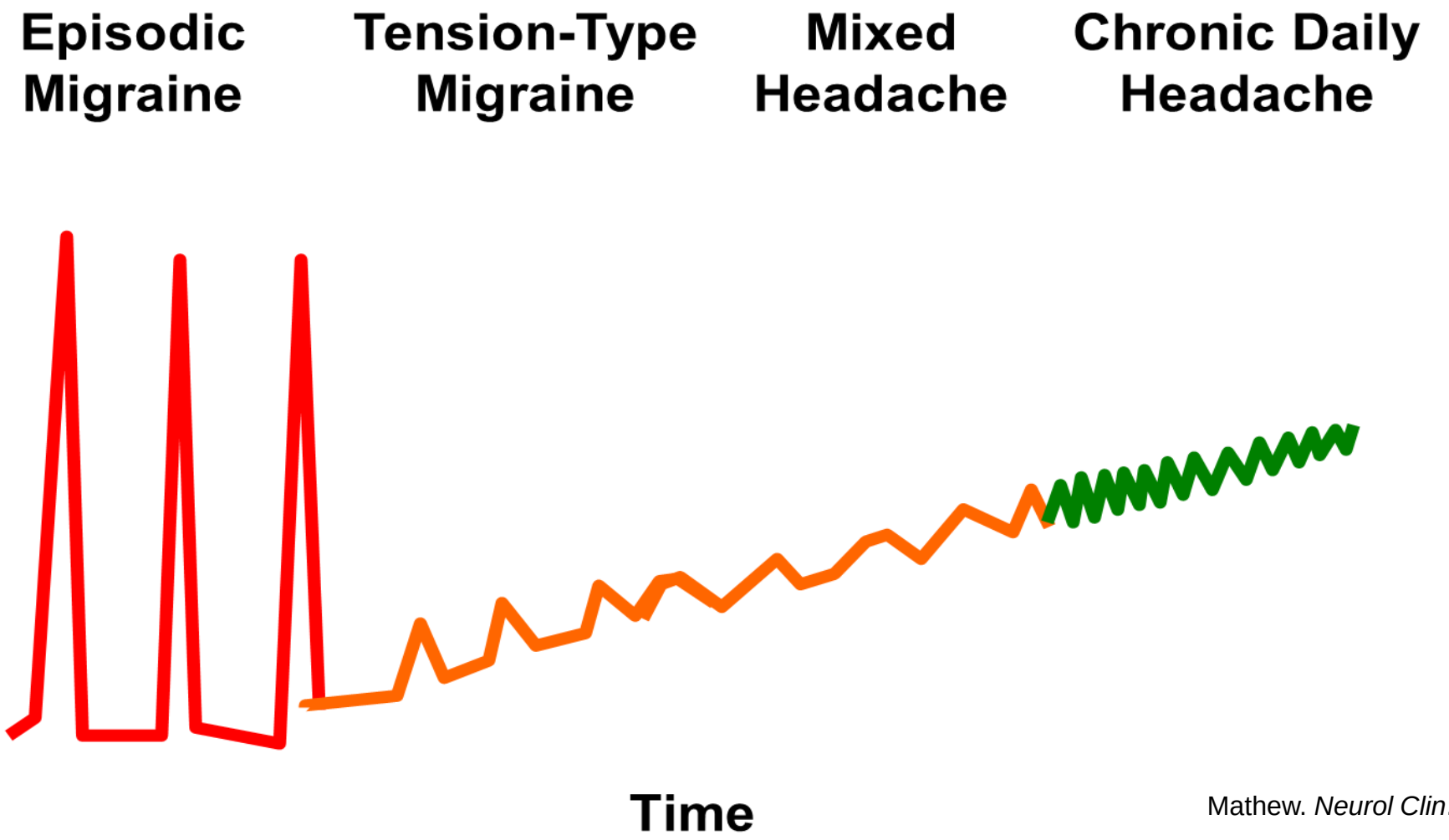
Silberstein, et al. *Headache in Clinical Practice*. 2002.

Migraine Pathophysiology

- Prolonged or uncontrolled migraine activity
  - Upregulation of 5-HT2 receptors (pronociceptive), especially with MOH
  - Central sensitization
  - Allodynia
  - Neuroplasticity
    - Glial cell activation (especially with opioid use)
    - Increased migraine chronicity
  - Oxidative injury/apoptosis of descending pain inhibition/modulation

Welch, et al. *Headache*. 2001;41:629-637.
Srikiatkhachorn, et al. *Headache*. 1998;38(7):534-539.
Goadsby. *Ann Indian Acad Neurol*. 2012;15(suppl 1):S15-S22.

Transformation of Migraine



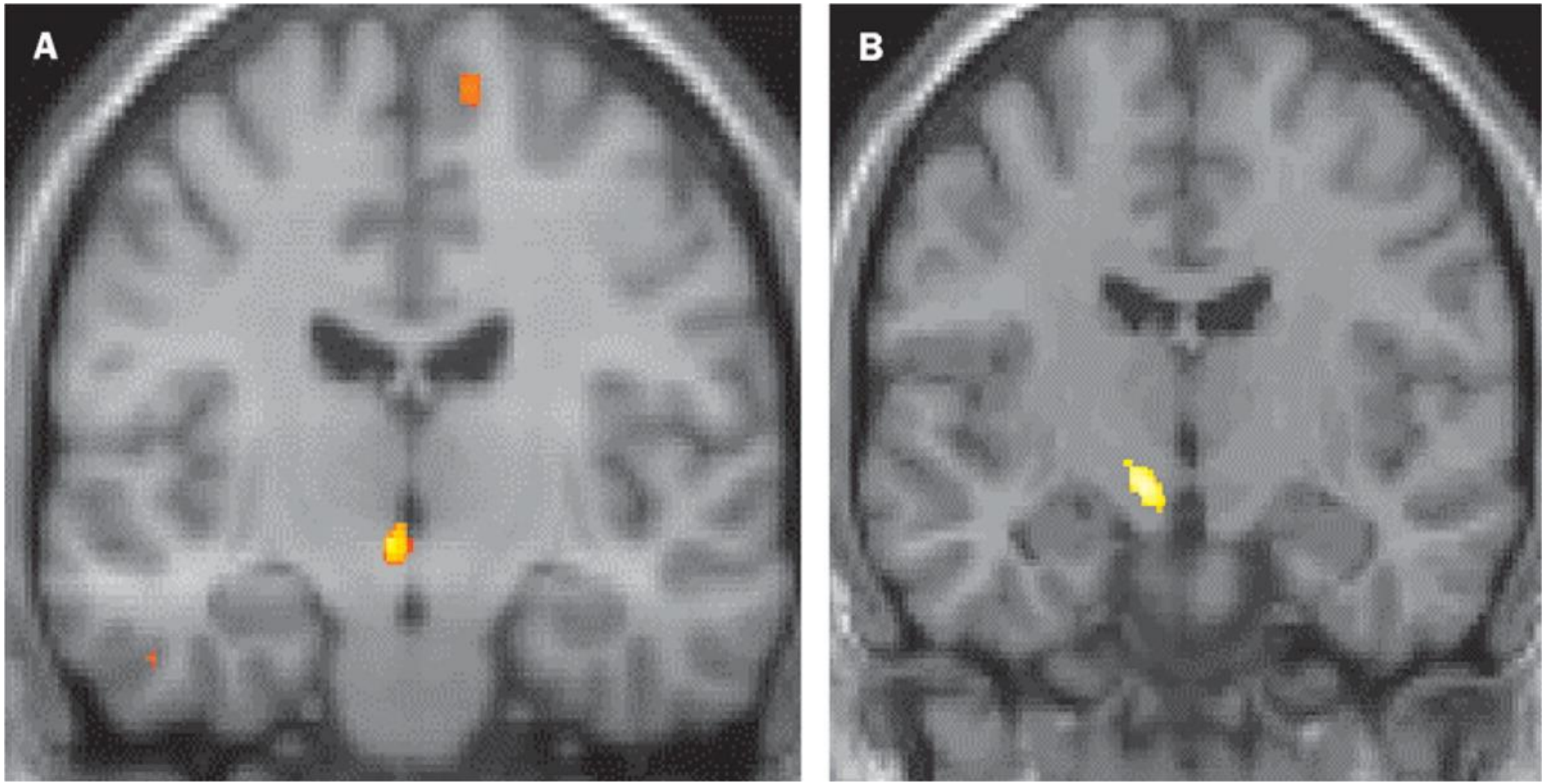
Mathew. *Neurol Clin*.1997;15(1):167-186.

Cluster Headache Pathophysiology

- Not fully understood
- Involves vascular dilation, trigeminal nerve stimulation, and circadian effects
- Histamine release, an increase in mast cells, and autonomic nervous system activation may also contribute
- Activation of the posterior hypothalamic nuclei on functional imaging
- Autosomal dominant inheritance in about 5% of patients
- Having a first-degree relative with cluster headache increases the risk 14- to 39-fold

Nesbitt and Goadsby. *BMJ*. 2012;344:e2407.

Cluster Headache: Hypothalamic Activation



May. *Lancet*. 2005;366(9488):843-855.

Traditional Guideline-Recommended Therapies

Acute Treatment and Prophylaxis of Migraine and Cluster Headache

Traditional Guideline-Recommended Migraine Therapies

- Acute treatments
  - NSAIDs
  - Triptans
  - Ergots
- Preventive treatments
  - Tricyclic antidepressants
  - Antiepileptic drugs
  - Beta-blockers
  - OnabotulinumtoxinA (chronic migraine only)

US Headache Consortium.

Acute Treatments for Migraine

- US Headache Consortium Guidelines
- Acute Medications
  - Use migraine-specific agents
    - As first-line treatment in patients with moderate or severe headache
  - Select a nonoral route of administration for migraine associated with severe nausea or vomiting
  - Consider a self-administered rescue medication for severe migraine that fails to respond to other treatments
  - Guard against MOH

US Headache Consortium.

NSAIDs for Migraine

- Ibuprofen (400 mg q6h prn)
- Naproxen (440 mg q12h prn)
- Special NSAID formulations by prescription
  - Diclofenac potassium for oral solution (Cambia), 50 mg/packet
  - Ketorolac tromethamine nasal spray (Sprix), 15.75 mg/spray (not specifically indicated for migraine, but commonly used)
  - Celecoxib oral solution (Elyxyb), 120-mg unit dose
- Renal, cardiovascular, gastrointestinal, hematologic, skin reaction warnings
- Drug interactions: ACE inhibitors, diuretics, anticoagulants/ antithrombotics, others

FDA package inserts.

Triptans

- Serotonin receptor agonists (5-HT1B/1D)
- Reduce sterile inflammation of dura/vasculature
- Reduce nociceptive signaling through trigeminal and other ascending afferents
- Induce vasoconstriction of cerebral vessels

Triptan package inserts.

Triptan Contraindications

- Cardiovascular disease, high cardiovascular risk, coronary spasm
- Wolff-Parkinson-White syndrome or other cardiac accessory conduction disorders
- History of stroke, TIA, or hemiplegic/basilar migraine (brainstem aura)
- Peripheral vascular disease
- Ischemic bowel disease
- Uncontrolled hypertension
- Recent (within 24 hours) use of another triptan or an ergot
- Concurrent or recent (past 2 weeks) use of MAOIs
- Hypersensitivity to triptans (angioedema and anaphylaxis seen)
- Severe hepatic impairment

Triptan package inserts.

Triptan Precautions/Concerns

- Most common adverse reactions (≥2% and >placebo) include:
  - Paresthesia
  - Warm/cold sensation
  - Pain, tightness, or pressure in the chest, neck, or throat
  - Vertigo
  - Malaise/fatigue
- Serotonin syndrome (SSRIs, SNRIs)
- MOH
- Pregnancy (based on animal data) may cause fetal harm

Triptan package inserts.

Triptans: Available Agents

- Sumatriptan
  - SC injection (6 mg and 4 mg, Imitrex STATdose)
  - SC injection (3 mg, Zembrace SymTouch)
  - Needle-free injection (6 mg, Sumavel DosePro)
  - Tablet (25 mg, 50 mg, and 100 mg, Imitrex)
  - Nasal spray (5 mg and 20 mg, Imitrex)
  - Nasal spray with absorption enhancer (10 mg, Tosymra)
  - Sumatriptan/naproxen combination tablet (85 mg/500 mg, Treximet)

Sumatriptan package inserts.

Triptans: Available Agents

- Zolmitriptan (Zomig)
  - Tablet (2.5 mg and 5 mg)
  - Orally disintegrating tablet (2.5 mg and 5 mg)
  - Nasal spray (2.5 mg and 5 mg)
- Naratriptan (Amerge)
  - Tablet (1 mg and 2.5 mg)
- Rizatriptan (Maxalt)
  - Tablet (5 mg and 10 mg)
  - Orally disintegrating tablet (5 mg and 10 mg)
  - 5 mg, if taking propranolol

Triptan package inserts.

Triptans: Available Agents

- Almotriptan (Axert)
  - Tablet (6.25 mg and 12.5 mg)
- Frovatriptan (Frova)
  - Tablet (2.5 mg)
  - 26-hour half-life
- Eletriptan (Relpax)
  - Tablet (20 mg and 40 mg)
  - Highly bioavailable orally
  - CYP450 3A4 metabolism; be careful with macrolides and antifungal agents
  - P-glycoprotein (P-gp) pump substrate

Triptan package inserts.

Ergot Derivatives

- Ergotamine tartrate
  - 1-mg tablets, capsules, and sublingual form
  - Frequently in combination with 100-mg caffeine
  - Risk of ergotism, MOH, and fibrotic complications
  - Max 6 mg/attack, 10 mg/week; drug holiday recommended periodically
- Dihydroergotamine mesylate (DHE 45)
  - Injection IV, IM, or SC (usual dose 1 mg), up to 3 doses per week
  - Nasal spray (Migranal), 2-mg dose
  - Nausea, bad taste, fibrosis
  - Advantageous when MOH or rebound headaches are suspected?
  - No oral dosage available in the US
- All ergot derivatives are contraindicated in pregnancy, known risk of fetal harm (Category X)

FDA package inserts.

Traditional Guideline-Recommended Migraine Therapies: Prophylaxis

- US Headache Consortium Guidelines
- Consider preventive treatment for migraine patients in any of the following situations:
  - Migraine attacks are frequent (≥4 migraine headache days per month) and/or the attacks interfere with patients' daily routines even with acute treatment
  - There is contradiction to, failure, or overuse of acute treatments
  - Acute treatments lead to adverse events
  - Oral treatments should be offered for migraine prevention
  - Start oral treatments at a low dose and titrate slowly
  - Give oral treatments for at least 8 weeks to optimize therapeutic response (or discontinue when adverse events occur)

US Headache Consortium.

Migraine Prophylaxis

- Preventive therapies
  - Beta-blockers (propranolol, timolol, metoprolol)
  - Tricyclic antidepressants (especially amitriptyline)
  - Antiepileptic drugs (divalproex, topiramate)
  - Venlafaxine
  - Candesartan*
  - Lisinopril*
  - OnabotulinumtoxinA (chronic migraine only, ≥15 headache days/month)

* *Level C evidence.*

US Headache Consortium Guidelines.

Estemalik and Tepper. *Neuropsychiatr Dis Treat*. 2013;9:709-720.

Cluster Headache Therapies

- Acute treatment
  - Oxygen, high flow (10 L/min) inhaled via non-rebreather mask, 3-5 min prn
  - Triptans
    - SC sumatriptan (3-6 mg prn; max = 12 mg/24 h)
    - IN sumatriptan (20 mg spray prn; max = 40 mg/24 h)
    - IN zolmitriptan (2.5-5 mg spray prn; max = 10 mg/24 h)
  - Octreotide (Sandostatin), vasoconstrictor, for triptan failure
- Short-term preventive
  - Prednisone 60 mg x 3 days and taper off over 2 weeks
- Preventive
  - Verapamil ≥240 mg/day
  - Lithium carbonate 300-450 mg hs, especially for chronic cluster
  - Topiramate 25-200 mg daily

Gooriah, et al. *Ther Clin Risk Manag*. 2015;11:1687-1696.

Novel Treatments for Migraine and Cluster Headache

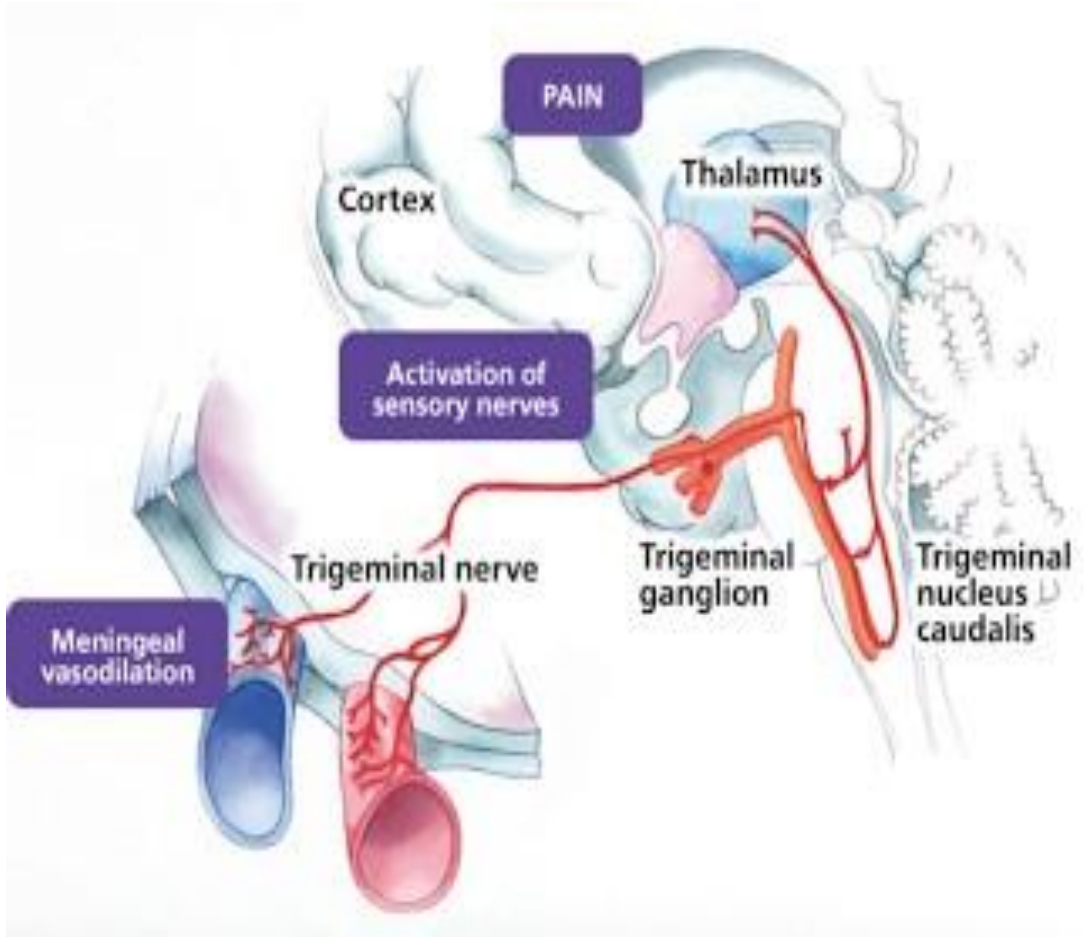
Acute Treatment and Prophylaxis

Novel Treatments for Acute Management of Migraine

- 5-HT1F agonists (“ditans”)
  - Lasmiditan (Reyvow)
- Oral calcitonin gene-related peptide (CGRP) receptor blockers (“gepants”)
  - Ubrogepant (Ubrelvy)
  - Rimegepant (Nurtec)
- Neuromodulation devices
  - Noninvasive vagus nerve stimulator (nVNS, gammaCore)
  - External trigeminal nerve stimulator (eTNS, Cefaly)
  - Remote electrical neuromodulation (REN, Nerivio)

FDA package inserts.

Lasmiditan Mechanism of Action



Treatments	Lasmiditan	Triptans
Primary Site of Action	Trigeminal Pathway	Blood Vessels
Receptor	5-HT_{1F}	5-$HT_{1B/1D}$
CNS Penetrant	Yes	No
Vasoconstrictor	No	Yes

Reyvow.com/hcp/moa

Lasmiditan

- 5-HT1F agonist
- Centrally penetrant
- Migraine abortive effect when dosed within 4 hours of onset
- Approved doses: 50 mg, 100 mg, and 200 mg
- 1 dose per 24 hours (repeat dose no benefit)
- Only comes in 50-mg and 100-mg tablets
- Schedule 5 (C-V) controlled substance
- 8-hour postdose driving restriction
- No vasoconstriction
- No contraindications

Lasmiditan package insert.

Lasmiditan Metabolism and Drug Interactions

- Tmax = 1.8 hours, delayed 1 hour by high-fat meal
- $T_{1/2}$ = 5.7 hours
- Plasma protein binding = 55% to 60%
- Metabolism via ketone reduction, multiple other pathways
- No active metabolites
- 66% of dose recovered as metabolites excreted in urine
- No CYP450 adjustments necessary
- Drug interaction studies with propranolol, sumatriptan, and topiramate show no drug interaction potential
- Substrate of P-gp and in vitro inhibitor of P-gp breast cancer resistance protein (BCRP)

Lasmiditan package insert.

Lasmiditan Adverse Events

Table 1: Adverse Reactions Occurring in ≥2% and at a Frequency Greater than Placebo in Studies 1 and 2

Adverse Reaction	REYVOW 50 mg N=654 %	REYVOW 100 mg N=1265 %	REYVOW 200 mg N=1258 %	Placebo N=1262 %
Dizziness	9	15	17	3
Fatigue[a]	4	5	6	1
Paresthesia[b]	3	7	9	2
Sedation[c]	6	6	7	2
Nausea and/or Vomiting	3	4	4	2
Muscle Weakness	1	1	2	0

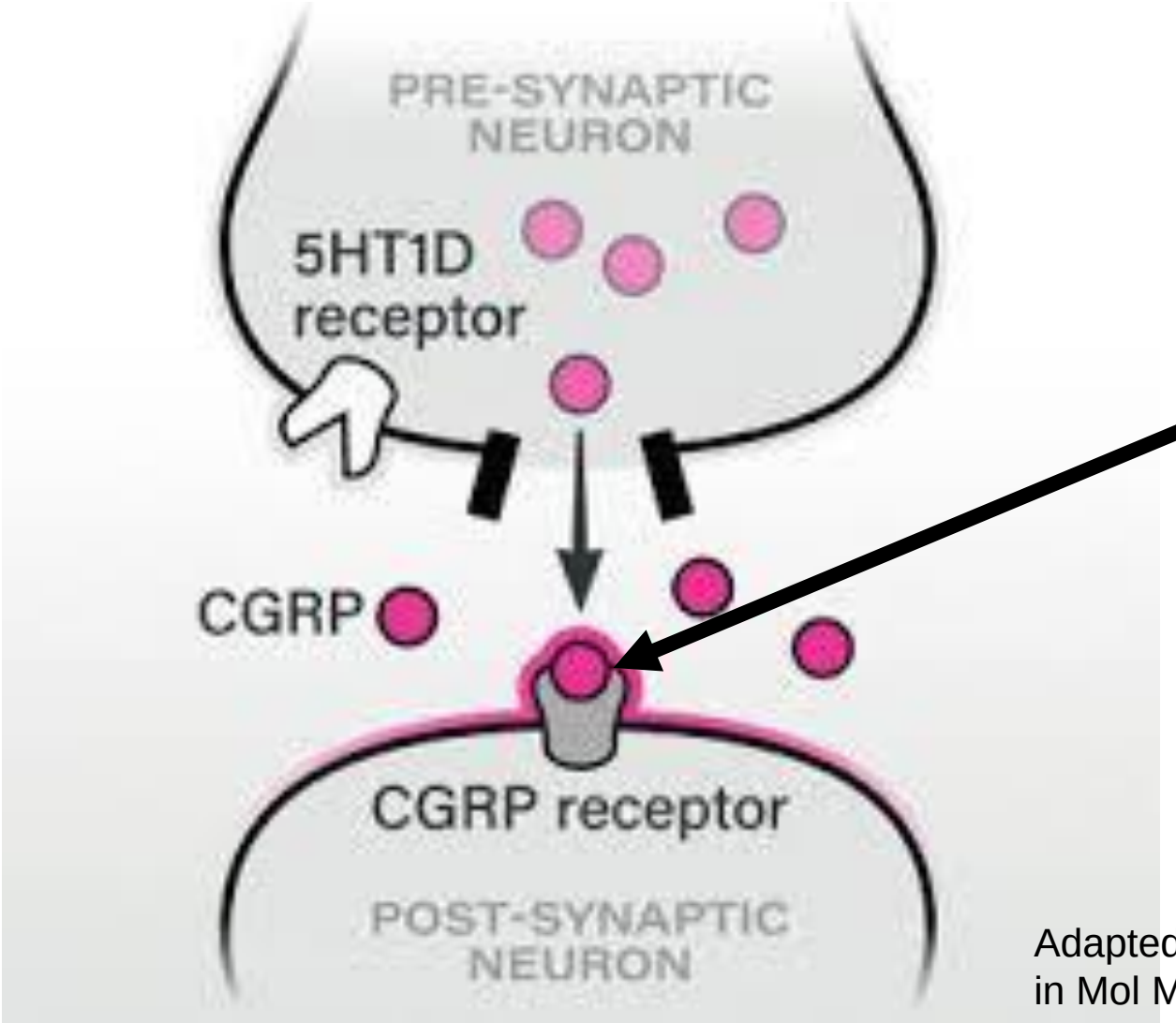
[a] Fatigue includes the adverse reaction related terms asthenia and malaise.

[b] Paresthesia includes the adverse reaction related terms paresthesia oral, hypoesthesia, and hypoesthesia oral.

[c] Sedation includes the adverse reaction related term somnolence.

Lasmiditan package insert.

Ubrogepant and Rimegepant Mechanism of Action



Postsynaptic Receptor Blockade Trigeminal Nerve

Adapted from Radant & Russo. Exp Rev in Mol Med. 2011.

Ubrogepant

- Orally administered CGRP receptor blocker
- Small molecular weight pharmacotherapeutic
- Indicated for acute treatment of migraine attacks in adults (≥18 y)
- 50-mg and 100-mg tablets marketed
- Second dose within 24 hours allowed if not effective by 2 hours

Ubrogepant package insert.

Ubrogepant Metabolism and Drug Interactions

- Tmax = 1.5 hours, delayed 2 hours by high-fat meal
- $T_{1/2}$ = 5-7 hours
- Plasma protein binding = 87%
- Metabolism mainly via CYP3A4
- Two glucuronide conjugates, inactive
- Substrate of BCRP and P-gp
- Avoid use with strong CYP3A4 inducers and within 24 hours of strong CYP3A4 inhibitors
- Reduce dose with moderate CYP3A4 inhibitors and BCRP and/or P-gp inhibitors

Ubrogepant package insert.

Ubrogepant Adverse Events

	PBO (%) (N = 984)	50 mg (%) (N = 954)	100 mg (%) (N = 485)
Nausea	2	2	4
Somnolence*	1	2	3
Dry mouth	1	<1	2

** Includes sedation and fatigue.*
Abbreviation: PBO, placebo.

Ubrogepant package insert.

Rimegepant

- Orally disintegrating tablet (ODT), Zydis technology
- Indicated for acute migraine treatment in adults (≥18 y)
- 75 mg as a single dose on or under the tongue
- Only one dose/dosage form marketed
- Single dose per day, repeat dosing no benefit
- Clinical trial data and FDA label support dosing up to 15 days/mo
- No MOH concerns
- Only adverse event to affect 2% of subjects = nausea (placebo 0.4%)
- Mild mint flavor

Rimegepant package insert.

Rimegepant Metabolism and Drug Interactions

- Tmax = 1.5 hours, delayed 1 hour by high-fat meal
- $T_{1/2}$ = 11 hours
- Plasma protein binding = 96%
- 77% of dose excreted unchanged
- Some metabolism via CYP3A4 and CYP2C9 (plasma metabolites <10% of dose)
- Substrate of BCRP and P-gp
- Avoid use with strong CYP3A4 inhibitors
- Avoid redosing within 48 hours when used with moderate CYP3A4 inhibitors
- Avoid use with BCRP and/or P-gp inhibitors

Rimegepant package insert.

American Headache Society Position Statement on Novel Acute Therapies

- Requirements that should be met before starting novel therapies (gepants, ditans, neuromodulation):
  - Patients who have failed 2 oral triptans, or
  - Have experienced intolerance to triptans, or
  - Have contraindications to triptans
- Coverage should be provided until at least 2 attacks are treated
- For neuromodulation, consideration should be given for patients who prefer nondrug therapies

AHS. *Headache*. 2019;59(1):1-18.

Novel Agents for Preventive Treatment of Migraine

- CGRP monoclonal antibodies (MAbs)
  - Erenumab (Aimovig)
  - Galcanezumab (Emgality)
  - Fremanezumab (Ajovy)
  - Eptinezumab (Vyepti)
- All approved for prophylaxis of both episodic and chronic migraine
- Approved for adults only

CGRP MAb package inserts.

CGRP MAb Dosing

- Erenumab, 70 mg or 140 mg SC monthly (starting dose per clinical judgment)
- Galcanezumab, 240 mg loading dose (120 mg x 2) followed by 120 mg SC monthly
- Fremanezumab, 225 mg SC monthly or 675 mg SC (225 mg x 3) quarterly
- Eptinezumab, 100 mg or 300 mg IV infusion quarterly

CGRP MAb package inserts.

CGRP MAb as a Class

- MAbs do not substantially cross the blood-brain barrier; probably work peripherally for the most part
- All are metabolized via the reticuloendothelial system (macrophage phagocyte system); no hepatic or renal elimination
- No identified drug interactions
- All have infrequent reports of hypersensitivity reactions in trials and postmarket experience
- All have reported small numbers of injection site reactions
- “Super-responders” identified for all 4, with >75% reduction in migraine days achievable in many patients
- No negative impact on immune system

CGRP MAb package inserts.

Differences Among the Agents

- Erenumab
  - Fully human antibody (others are “humanized” antibodies)
  - Specific for the CGRP receptor (others bind the CGRP ligand)
  - Clinical trials showed adverse events of constipation in 3% (postmarket reports of rare but severe constipation)
  - New onset or worsening of hypertension reported in postmarket surveillance
- Galcanezumab
  - Only MAb with a recommended loading dose
  - FDA approved for treatment of episodic cluster headache as well
- Fremanezumab
  - 2 dosing regimens, monthly or quarterly
- Eptinezumab
  - IV administration only (others are SC that may be self-administered)
  - Has data showing relief from migraine pain within 2 hours of administration
  - Nasopharyngitis in 8% of study subjects on 300 mg dose (6% in placebo arm)

CGRP MAb package inserts.

American Headache Society Position Statement on CGRP MAbs

- Patient must have migraine with or without aura
- Must be an adult with ≥4 migraine days per month
- Must have failed a 6-week trial of at least 2 traditional oral therapies with Level A or B evidence (ineffective or not tolerated)
- Patients with 4 to 7 monthly migraine days should also have at least moderate disability (MIDAS* = 11 or more)
- Chronic migraine patients (≥15 monthly migraine days), may alternatively have demonstrated failure to onabotulinumtoxinA, at least 2 rounds of injections (155 units total per treatment round)

** MIDAS: migraine disability assessment.*

AHS. *Headache*. 2019;59(1):1-18.

Novel Agents for Acute and Preventive Treatment of Cluster Headache

- CGRP MAbs
  - Galcanezumab (Emgality)
    - FDA approved for treatment of episodic cluster headache
    - 300 mg SC (100 mg x 3) given monthly until cluster period is over
    - Prefilled syringe only, no autoinjector for this dose
- Neuromodulation devices
  - Noninvasive vagus nerve stimulator (nVNS), gammaCore
    - Preventive
    - Acute management

FDA package inserts.

Neuromodulation Devices

Some Provided Through Specialty Pharmacies

Noninvasive Vagus Nerve Stimulation (nVNS)

- FDA authorized for:
  - Acute treatment of migraine attacks
  - Preventive treatment of migraine
  - Acute treatment of cluster headache attacks
  - Preventive treatment of cluster headache
- Requires electrode gel application
- Stimulate over carotid pulse area

gammaCore package insert.

gammaCore (nVNS)

gammacore.com

External Trigeminal Nerve Stimulator (eTNS)

- Indicated for:
  - Acute treatment of migraine (60-minute stimulation)
  - Prophylaxis of migraine (20-minute stimulations daily)
- Stimulates branches of the trigeminal nerve
  - Supratrochlear
  - Supraorbital
- Hands-free operation
- Disposable electrodes good for 20 stimulations each
- Recently approved for OTC status

Cefaly package insert.

Cefaly (eTNS)

cefaly.com

Remote Electrical Neuromodulation (REN)

- FDA indicated for acute treatment of migraine
  - Episodic (≤14 headache days per month)
  - Chronic (≥15 headache days per month)
- Stimulator applied to upper arm
- Controlled by phone app
- 45-minute treatment
- 12 uses per electrode device

Nerivio package insert.

Nerivio (REN)

theranica.com

Neuromodulation Device Limitations

- Should not be used in patients with:
  - Implanted electronic devices
  - Pacemakers
  - History of seizures
  - History of vagotomy (nVNS)
  - Metallic hardware near area of stimulation
  - Trauma or lack of skin integrity in the area
  - Cochlear implants

FDA package inserts.

Traditional Nonpharmacologic Care

Migraine

Biobehavioral Interventions

- Consider biobehavioral interventions for patients who:
  - Prefer nonpharmacologic interventions
  - Have inadequate response, poor tolerance, or medical contraindications to specific pharmacologic treatments
  - Are pregnant, lactating, or planning to become pregnant
  - Have a history of acute medication overuse
  - Exhibit significant stress or deficient stress-coping skills
- Level A evidence for:
  - Progressive relaxation
  - Biofeedback
  - Cognitive behavioral therapy

AHS. *Headache*. 2019;59(1):1-18.

Physical-Manipulative Therapies

- Randomized controlled trials suggest possible benefit from:
  - Massage therapy
  - Physiotherapy
  - Relaxation
  - Chiropractic spinal manipulative therapy

Chaibi. *J Headache Pain*. 2011;12(2):127-133.

The Pharmacist’s Role

Migraine and Cluster Headache

Pharmacist Considerations in Migraine and Cluster Headache

- OTC medications
  - Not appropriate for cluster headache, except melatonin 10 mg hs
  - NSAIDs (simple and combination analgesics) are appropriate for first-line therapy for migraine
  - Suspect MOH if patients use medications more than 2 days per week regularly (detox program may be required)
- Herbals/nutraceuticals
  - Magnesium oxide 400-550 mg bid
  - Riboflavin 400 mg bid
  - CoQ10 150 mg daily

Peres and Rozen. *Cephalalgia*. 2001;21(10):993-995.
https://www.migrainetrust.org/living-with-migraine/treatments/supplements-and-herbs/

Recognizing Headache “Red Flags”

- When should patients seek medical help?
  - Sudden onset headache, “thunderclap” headache
  - Headache onset with exertion, cough, intercourse, valsalva
  - Stiff neck/fever
  - Focal neurologic signs or symptoms, especially if persistent
  - Seizure, loss of consciousness
  - Onset before the age of 5 years or after the age of 50 years
  - Headache in patient with history of cancer or immune compromise
  - Headache never goes away

https://americanmigrainefoundation.org/resource-library/headache-red-flags/

Patient Counseling for Prescription Therapies

- Expected effects of the medication
- Dosing/administration
- Adverse effects
- Drug interactions
- Encourage adherence
- Encourage headache diary
- Advise healthy lifestyle (sleep, hydration, exercise, stress management, avoidance of triggers/risk factors)
- Ensure adequate communication with prescriber

Questions and Answers

Thank You!