#CHAIR2019

11TH ANNUAL

CHAIR SUMMIT

CME Outfitters

Master Class for Neuroscience Professional Development

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CME Outfitters

Individualizing Care in Migraine: From Prevention to Acute Management

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Learning Objective 1

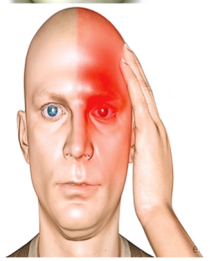
Incorporate evidence-based tools and strategies into routine practice to improve the differential diagnosis of migraine.

IHS Classification ICHD-3

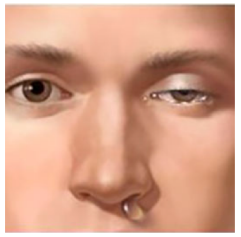
Migraine

- Frequency and duration ≥ 5 attacks lasting 4-72 hours
- Pain criteria: ≥ 2 of
  - Unilateral
  - Pulsating
  - Moderate or severe intensity
  - Aggravation by routine physical activity
- Associated symptoms: ≥ 1 of
  - Nausea and/or vomiting
  - Photophobia and phonophobia
- Not attributable to another disorder

Tension-type



Trigeminal autonomic cephalalgia



Unilateral, side-locked (mostly) with cranial parasympathetic features

IHS Classification ICHD-3. https://www.ichd-3.org/1-migraine/.

ID Migraine Validated Screener

During the last 3 months

- Does light bother you when you have a headache? (Photophobia=P)
- Has a headache limited your activities for a day or more in the last three months? (Impairment=I)
- Are you nauseated or sick to your stomach when you have a headache? (Nausea=N)

***PIN* the diagnosis**

Sensitivity 93% (2/3); 98% (3/3)

Lipton RB, et al. *Neurology*. 2003;61:375-382.

The History: SNOOP4

- Systemic symptoms (fever, weight loss) or Secondary risk factors (HIV, cancer)
- Neurologic symptoms (or signs)
- Onset: abrupt, peak <1 min
- Older: >50 (GCA; glaucoma, cardiac cephalgia)
- Previous headache history (new or change in pattern/progression)
- Postural (worse in upright/supine position)
- Precipitated by Valsalva (exertion)
- Pulsatile tinnitus (diplopia, transient visual obscurations)
- Pregnancy

Dodick DW. *Semin Neurol*. 2010;30(1):74-81.

Learning Objective 2

Integrate safety and efficacy data on novel strategies for migraine prevention and acute treatment into treatment decisions.

Triptans Transformed Migraine Care

OPINION

The most transformative drugs of the past 25 years: a survey of physicians

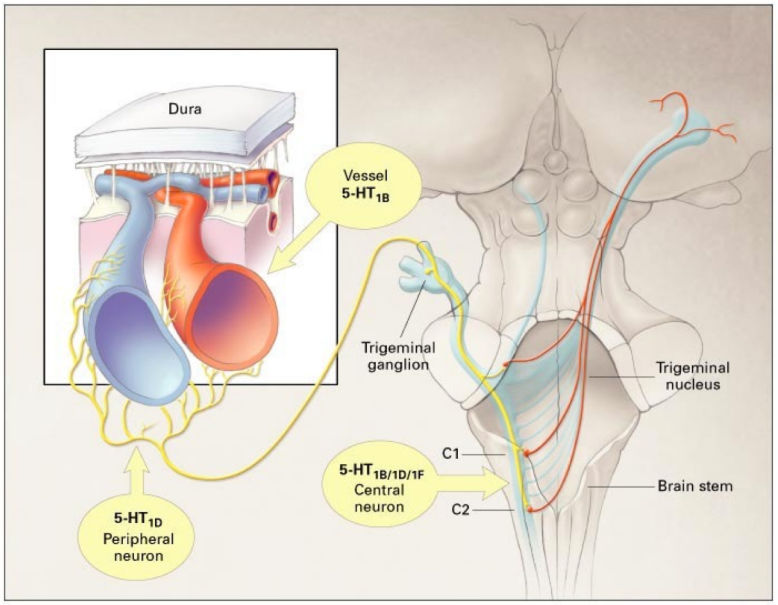
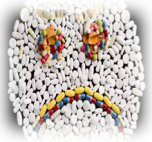


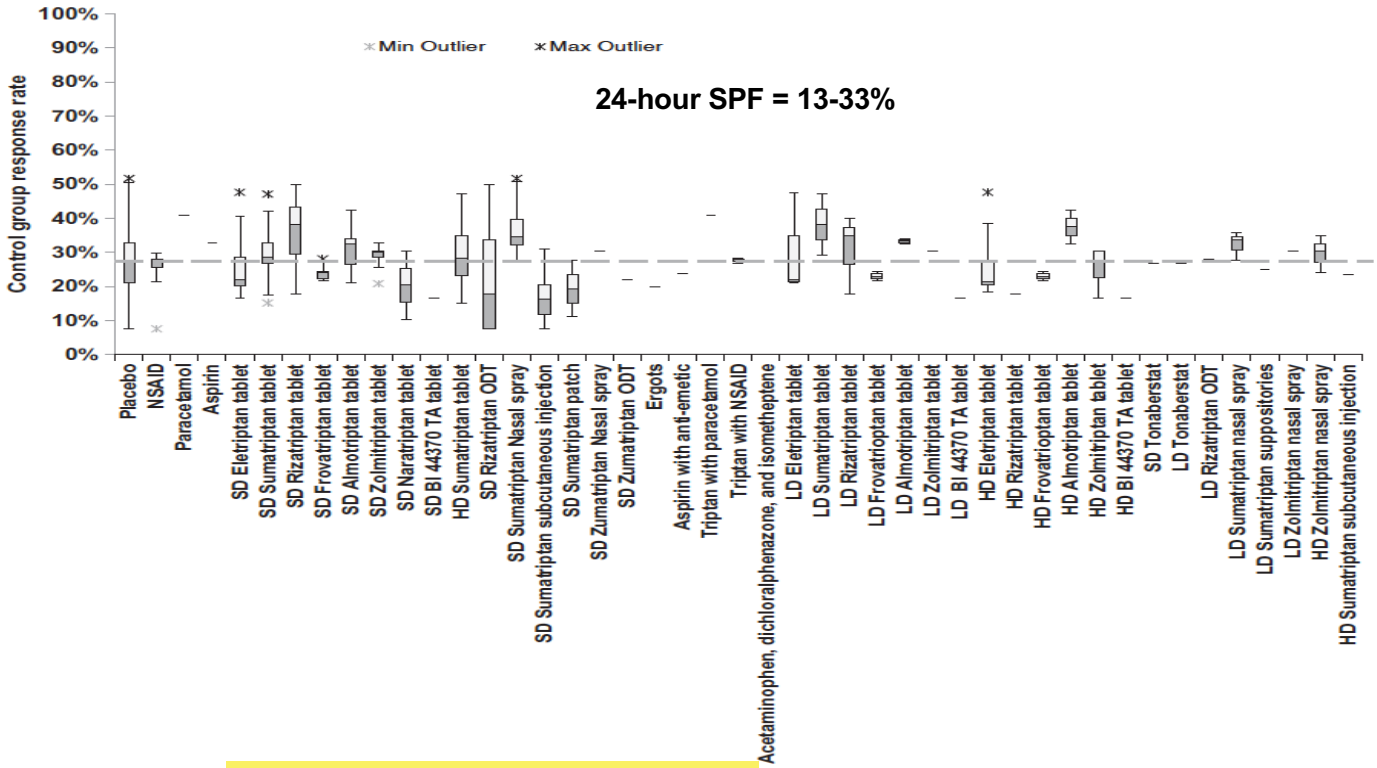
Table 2 | **Top transformative drugs or drug classes identified via modified Delphi protocol**

Clinical field	Consensus top selection*	Consensus second-place selection	Notes on results
Anaesthesiology	Propofol (11)	Remifentanil (2)	Propofol was a clear consensus choice
Cardiology	Lovastatin (7)	ACE inhibitors (0)	Alteplase (recombinant tPA) came in a close third, receiving fewer second-place mentions than ACE inhibitors
Dermatology	TNF blockers (7)	OnabotulinumtoxinA (3)	Participants selected multiple TNF blockers, so the drugs were considered as a single class; some participants mentioned the transformative role of isotretinoin, which fell outside our date range for inclusion
Endocrinology	Bisphosphonates (6)	Metformin (3)	Most participants picked out multiple bisphosphonates, so the individual drugs were collated into a group
Gastroenterology	Omeprazole (6)	TNF blockers	Omeprazole was the runaway choice
Infectious diseases	HIV protease inhibitors (4)	Zidovudine (2)	Participants were inclined to include all of the initial group of HIV protease inhibitors (saquinavir, ritonavir and indinavir)
Genetics	Alglucerase (4)	Nitisinone (1)	Many participants also chose sodium phenylacetate and sodium benzoate but noted that the use of sodium benzoate pre-dated the time period of this study
Nephrology	ACE inhibitors (10)	Epoetin alfa (2)	Captopril was selected by the majority of participants, even though it was outside the date range of our study, so the group of ACE inhibitors was collated into one class
Neurology	Sumatriptan (4)	Interferon beta-1b, interferon beta-1a (4)	Opinion was closely divided between sumatriptan and the interferons
Oncology	Imatinib (5)	Rituximab (3)	Trastuzumab (3) had fewer second-place mentions than rituximab
Ophthalmology	Anti-VEGF agents (7)	Latanoprost (3)	Anti-VEGF agents were collated into a class at the suggestion of several participants
Psychiatry	Fluoxetine (6)	Clozapine (4)	Opinion was closely divided among these choices, but no other product classes received even a marginal consideration
Pulmonary medicine	Epoprostenol (3)	Combination fluticasone and salmeterol (2)	Opinion was closely divided among all choices (including synthetic surfactants, receiving two first-place mentions), with the combination of fluticasone and salmeterol selected for its substantial patient impact rather than its novelty of drug design
Rheumatology	TNF blockers (11)	Bisphosphonates (1)	Rituximab came in a close third
Urology	Sildenafil (5)	Tamsulosin (3)	Finasteride (a 5-alpha reductase inhibitor) came in a close third (and received one first-place mention)

Kesselheim AS, Avorn J. *Nat Rev Drug Discovery*. 2013;12:425-431. Goadsby PJ, et al. *N Engl J Med* 2002; 346:257-270.

The Dilemma of Triptans



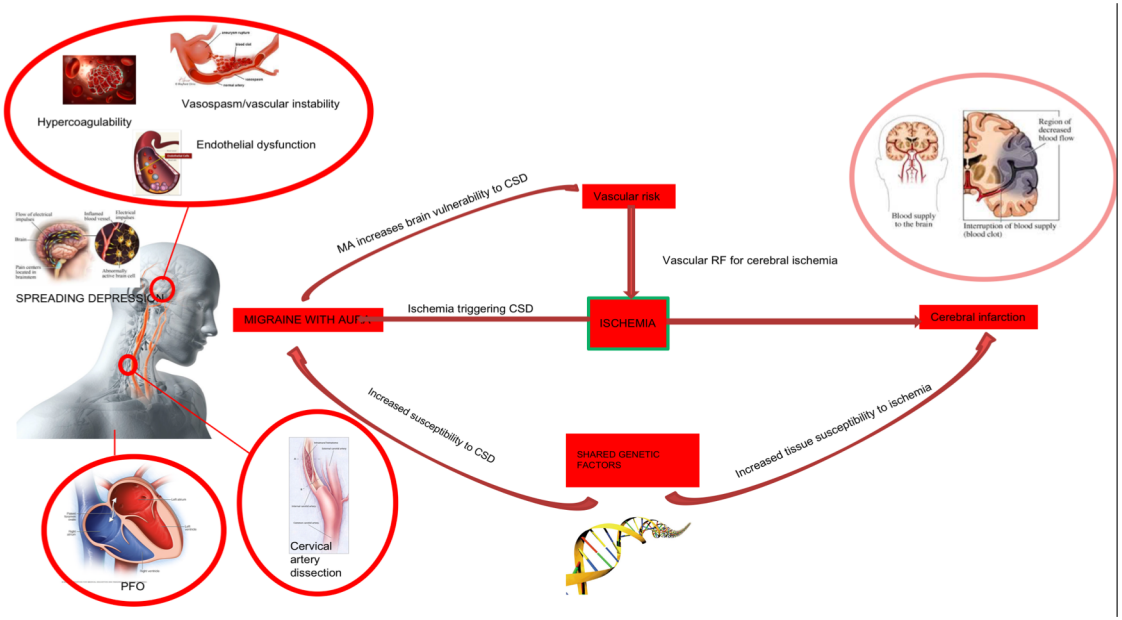


MAST 2017 Study

96% of current triptan users have ≥1 unmet treatment

Cameron C, et al. *Headache*. 2015(Suppl 4):221-s35. Lipton RB, et al. AHS. 2018. Abstract OR02.

The Dilemma of Triptans



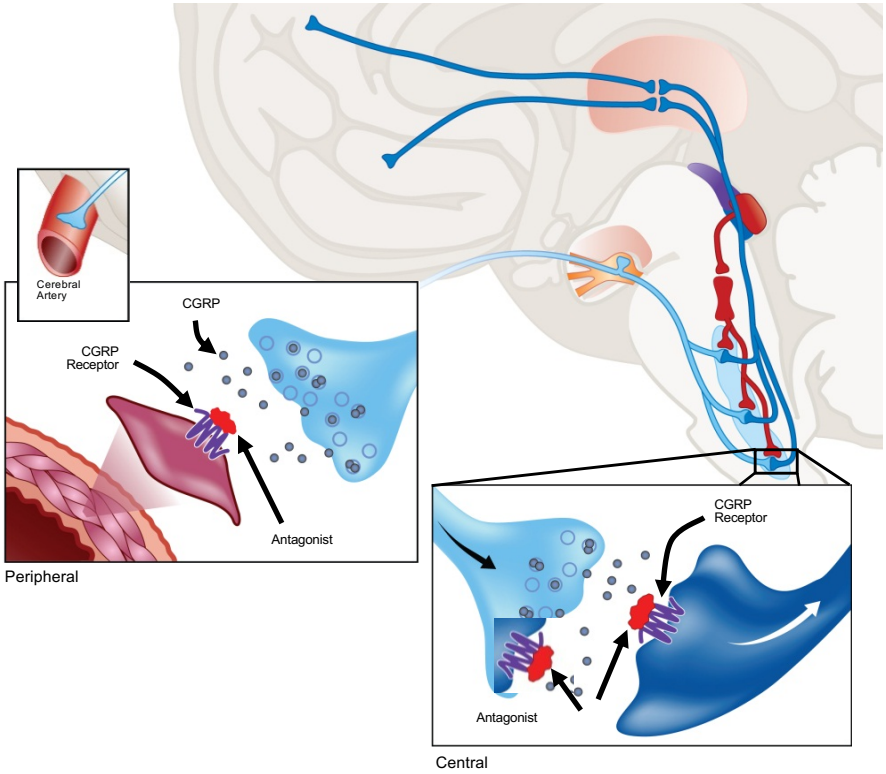
Migraine is associated with increased risk of:

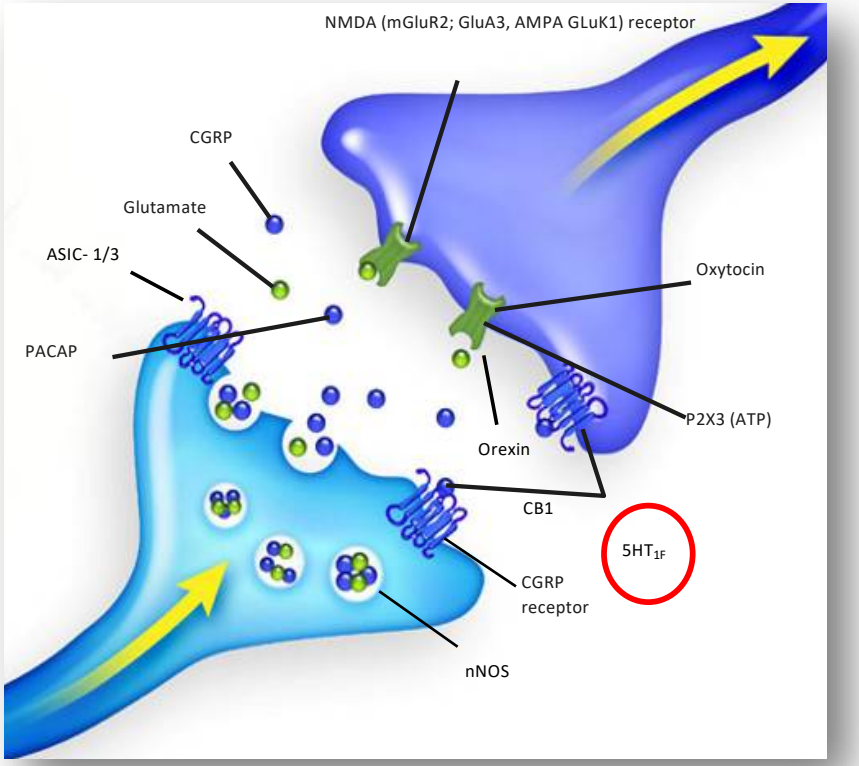
- Major cardiovascular disease (CVD)
- Myocardial infarction
- Stroke
- Angina/coronary revascularisation procedures
- Significant increased risk for CVD mortality

2.64 million Americans with migraine and CV contraindications to triptans

Kato Y, et al. *Neurol Clin Neurosci*. 2016;4:203-208. Kurth, et al. *BMJ*. 2016;353:i2610. Pavlovic JM, et al. AHS. 2018. Abstract PF74.

Trigeminal Sensory Targets



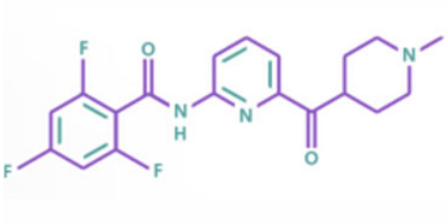


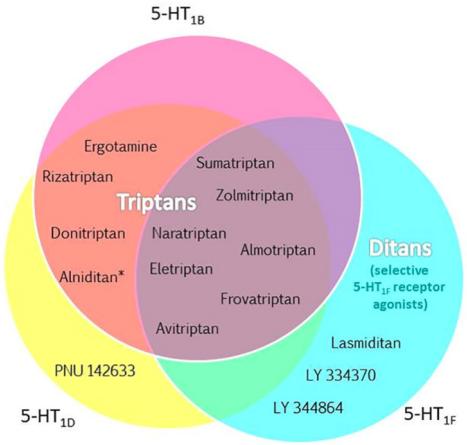
CGRP = calcitonin gene-related peptide

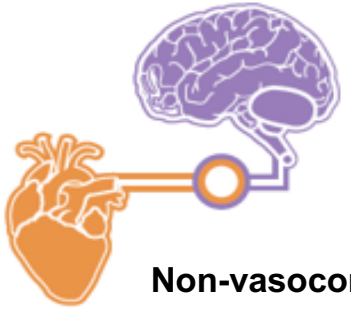
Dodick DW. *Lancet* 2018; 391: 1315–30.

Lasmiditan: Selective 5-HT1F Receptor Agonist

5-HT$_{1F}$ receptor agonist

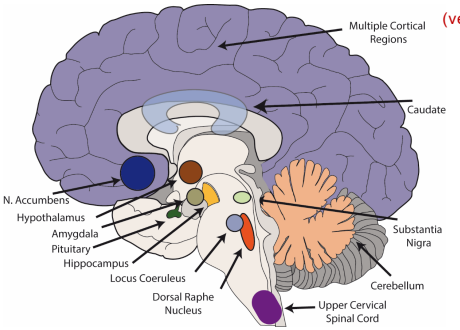


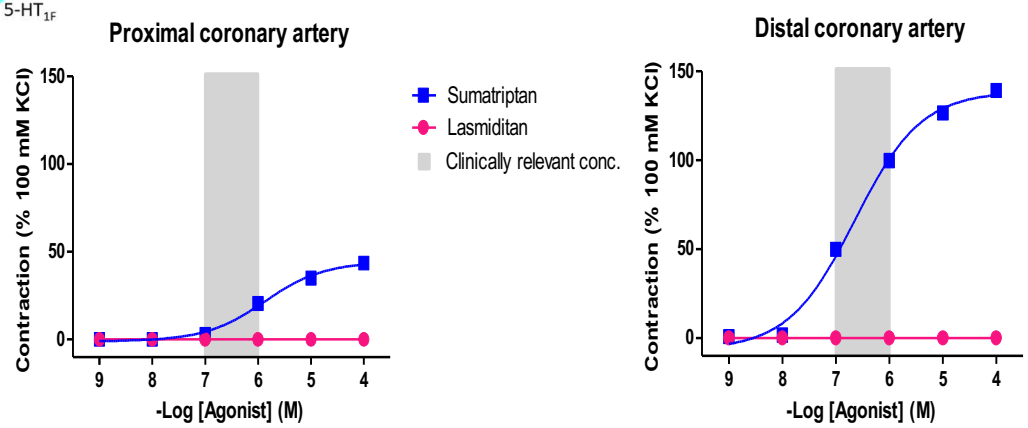




Non-vasoconstrictive mechanism of action

5-HT$_{1F}$ receptor distribution

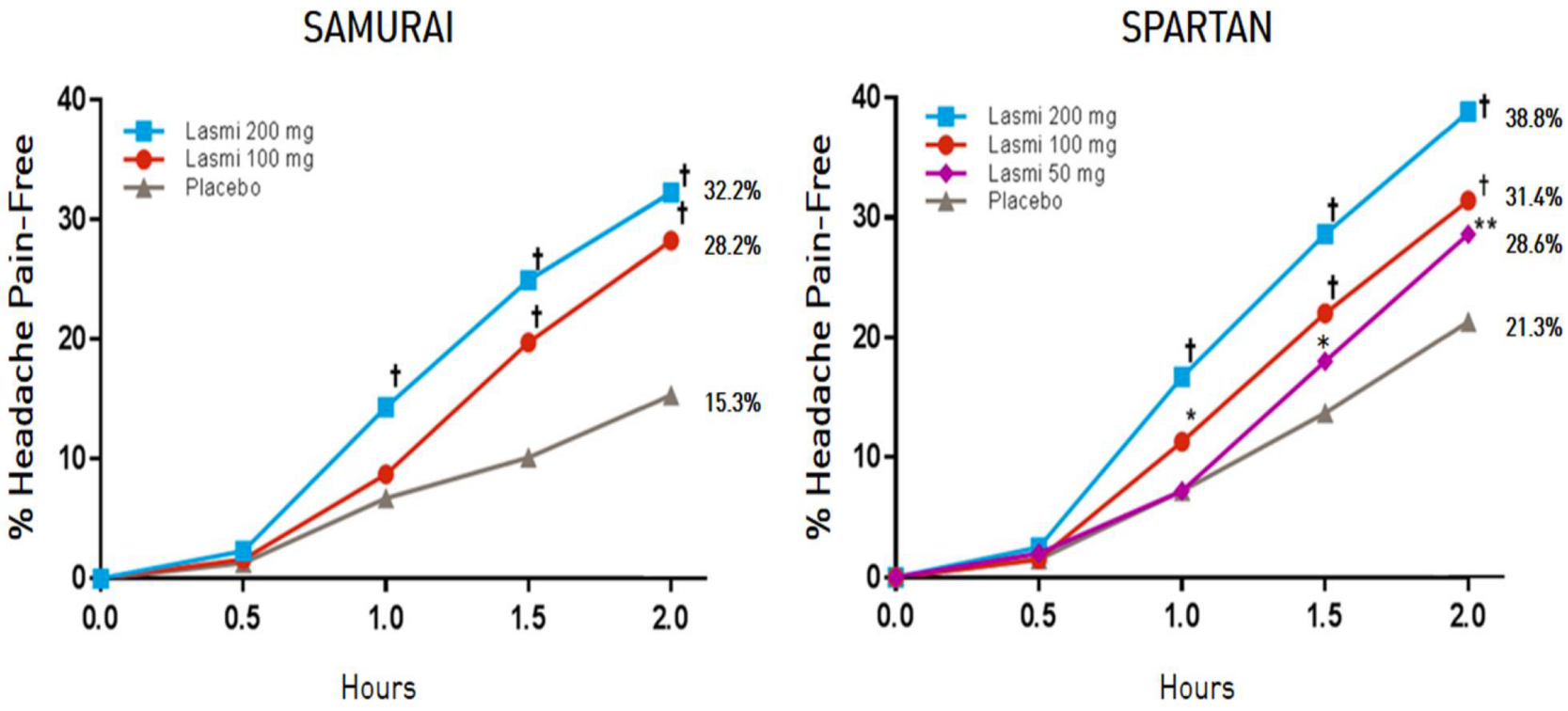




Vila-Pueyo, M. *Neurotherapeutics*. 2018;15:291-303. Rubio-Beltrán E, et al. *Pharmacol Ther.* 2018;186:88-97.

SAMURAI and SPARTAN: Efficacy of Lasmiditan

Pain-Free



†$p < .001$, **$p < .01$, *$p < .05$ versus placebo.

Kuca B, et al. Neurology 2018;91:e2222-e2232.

SAMURAI and SPARTAN: Tolerability of Lasmiditan

	SAMURAI (First Dose)			SPARTAN (First Dose)			
TEAEs[a]	L 200 mg (n=609)	L 100 mg (n=630)	PBO (n=617)	L 200 mg (n=649)	L 100 mg (n=635)	L 50 mg (n=654)	PBO (n=645)
≥1 TEAEs	42.2%	36.3%	16.0%	39.0%	36.1%	25.4%	11.6%
Dizziness	16.3%	12.5%	3.4%	18.0%	18.1%	8.6%	2.5%
Paresthesia	7.9%	5.7%	2.1%	6.6%	5.8%	2.4%	0.9%
Somnolence	5.4%	5.7%	2.3%	6.5%	4.6%	5.4%	2.0%
Fatigue	3.1%	4.1%	0.3%	4.8%	4.1%	2.8%	0.9%
Nausea	5.3%	3.0%	1.9%	2.6%	3.3%	2.8%	1.2%
Lethargy	2.5%	1.9%	0.3%	2.2%	1.3%	1.2%	0.2%

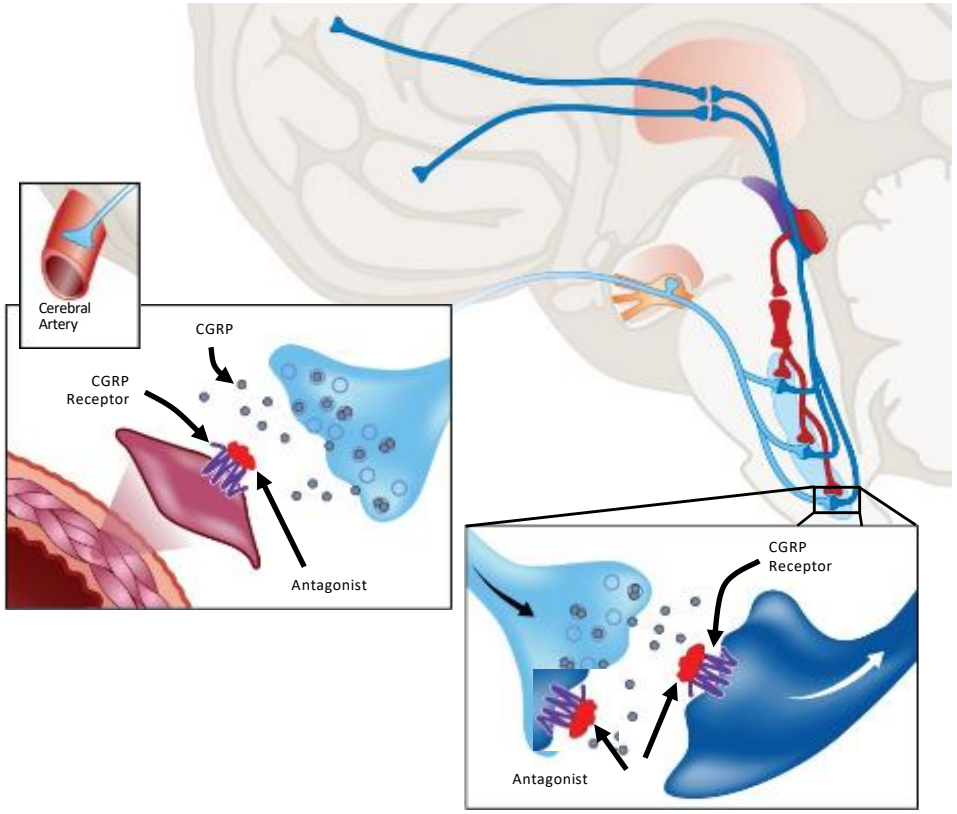
[a]TEAEs were events that occurred or worsened 0-48 hours after taking study drug. During this Phase 3 study, people were asked if they felt anything unusual since taking the study medication that they had not felt with a migraine before, and if so, a follow-up phone call from the site was made. If the symptom was new or different, or was a usual symptom but worsened in severity, it was recorded as a TEAE

TEAEs = treatment-emergent adverse events.

Kuca B, et al. *Neurology* 2018;91:e2222-e2232.

Calcitonin Gene-Related Peptide

- Main sensory peptide released by activated trigeminal neurons
- Released during migraine
- Triggers migraine attack
- Normalized with sumatriptan



Edvinsson L, et al. *Nat Rev Neurol* 2018;14:338-350. Dodick DW. *Lancet* 2018; 391: 1315–30.

CGRP mAbs for Migraine Prevention

	Eptinezumab	Erenumab	Fremanezumab	Galcanezumab
Type[a]	Humanized	Human	Humanized	Humanized
Target[a]	CGRP	CLR/RAMP1	CGRP	CGRP
$T_{1/2}$ (days)[a]	31	28	31	28
Route/frequency of administration[a]	iv (quarterly)	sc (monthly)	sc (monthly/**quarterly**)	sc (monthly)
Status	Completed phase III in EM; ongoing phase III in CM[b]	FDA approved May 17, 2018[c]	FDA approved Sept 17, 2018[d]	FDA approved Sept 27, 2018[e]

CGRP Receptor Antagonists for Acute/Preventive Treatment

	Ubrogepant	Rimegepant	Atogepant
Indication	Acute	Acute and preventive	Preventive
Status	2 phase III RCTs completed	2 phase III RCTs completed (acute)	1 phase III RCT completed

RCT = randomized clinical trial.

a. Edvinsson L. *Headache*. 2018;58(Suppl 1):33-47. b. Alder Press Release, 2018. c. FDA website. d. Teva Press Release, 2017. e. Lilly Press Release.

Patient Selection for CGRP mAbs

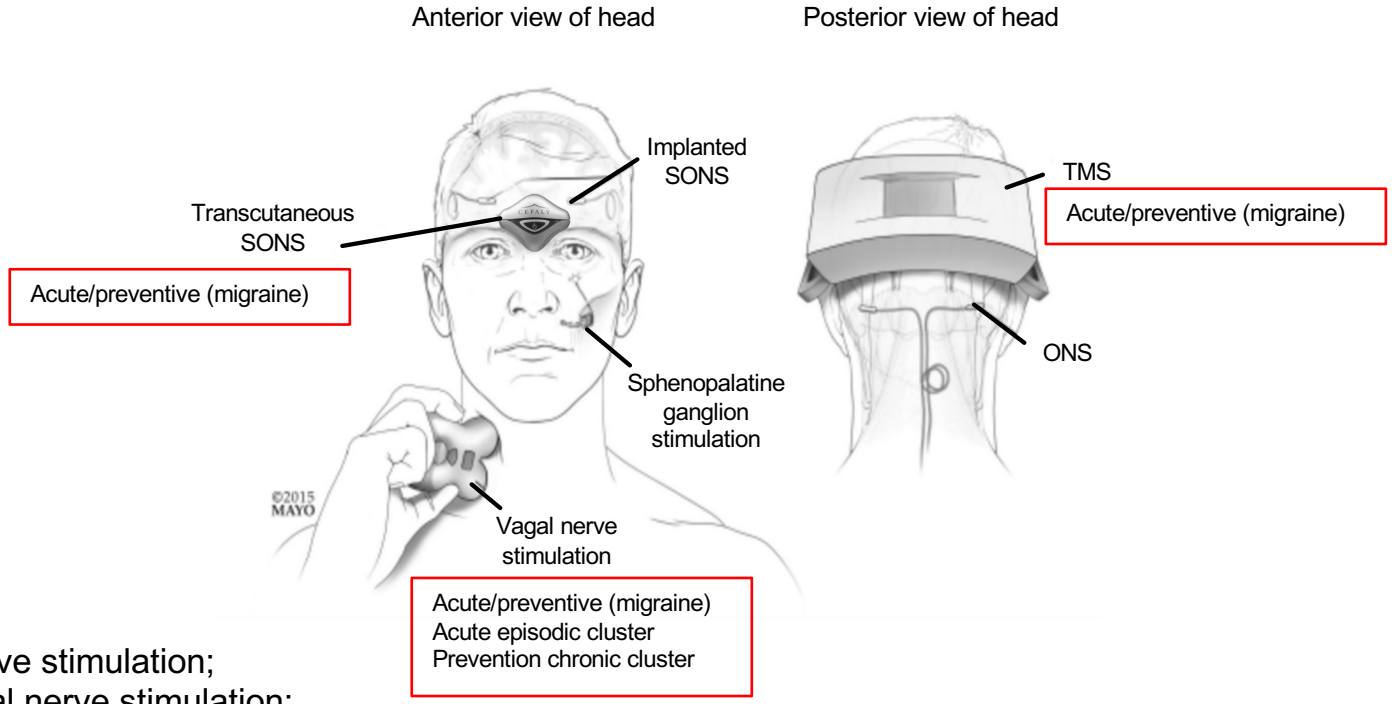
- No contraindications
- Potential for rapid onset of effect
- Very favorable side effect profile: patients with previous drug intolerance or compliance/adherence issues
- No drug interactions: patients with "polypharmacy" for headache or other diseases
- No effect on CHC (erenumab): women of child-bearing potential
- For patients with certain comorbid/coexisting disease
  - Obesity and related diseases (diabetes, hypertension, obstructive sleep apnea)
  - Asthma
  - Depression
  - Mild/moderate renal impairment (erenumab, galcanezumab)

Caveats

- No safety data in pregnant women (no adverse effects on embryofetal development in rats [galcanezumab 38x human 120 mg dose]), monkey (erenumab 20x human 140 mg dose), rats/rabbits (fremanezumab 2x 675 mg dose)
- No safety data in women who are lactating

AHS Consensus Statement. *Headache*. 2019;59:1-18. [Package Inserts]. Drugs@FDA Website.

Neurostimulation Methods for Treatment of Migraine and/or Cluster Headache



ONS = occipital nerve stimulation;
SONS = supraorbital nerve stimulation;
TMS = transcranial magnetic stimulation.

Schwedt TJ, Vargas B. *Pain Med*. 2015;16(9):1827-1834.

Learning Objective 3

Implement essential components of shared decision-making from the National Quality Forum (NQF) Playbook to develop individualized treatment strategies to mitigate the burden of migraine.

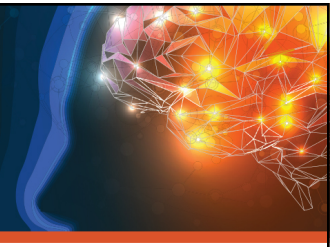
Shared Decision-Making

- Clear, accurate, and unbiased medical evidence about reasonable alternatives—including no intervention—and the risks and benefits of each
- Clinician expertise in communicating and tailoring that evidence for individual patients
- Patient values, goals, informed preferences, and concerns, which may include treatment burdens

National Quality Forum Shared Decision Making: A Standard of Care for All Patients. https://ohiohospitals.org/OHA/media/Images/Patient%20Safety%20and%20Quality/Documents/Patient%20Safety%20Awareness%20Week/shared_decision_making_action_brief-(002).pdf.

SMART Goals

Specific, **M**easurable, **A**ttainable, **R**elevant, **T**imely



- Shift from a “one-size-fits-all approach” toward individualized patient-centered care utilizing novel therapies for prevention and acute treatment of migraine

Questions & Answers

Don’t forget to fill out your evaluations to collect your credit.