MIGRAINE PATHOPHYSIOLOGY AND NEW TARGETS FOR HEADACHE TREATMENT

Andrew Charles, M.D.
Professor
Director, UCLA Goldberg Migraine Program
Meyer and Renee Luskin Chair in Migraine and Headache Studies
David Geffen School of Medicine at UCLA

UCLA Goldberg Migraine Program

1

DISCLOSURES

Consultant for:

- Amgen
- Biohaven
- Eli Lilly
- Lundbeck
- Satsuma

President elect – American Headache Society

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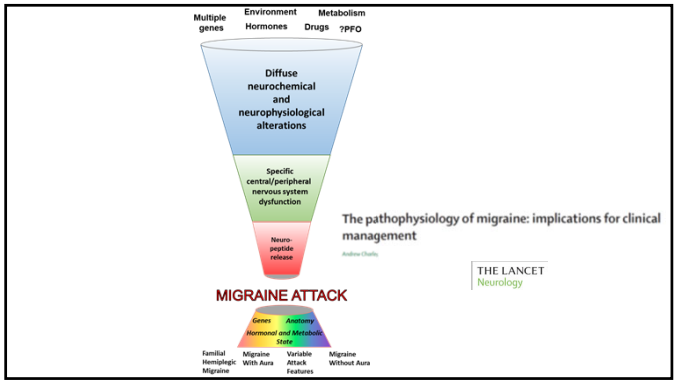

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Identification of New Therapeutic Targets

- Modifications of therapies with known efficacy
- Anatomy
- Human models (triggered migraine)
- Genetics
- Serum levels of potential targets.
- Animal models

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New Targets for Treatment Based on Migraine Pathophysiology

- Hypothalamus
- Upper cervical nerves
- Patent foramen ovale
- Adenosine receptors
- Potassium channel modulators
- Sodium channel modulators
- Peptide targets
  - PACAP
  - Amylin
- Delta opioid receptors
- Glutamate receptors

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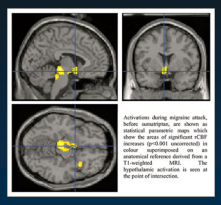
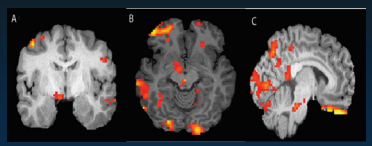
PET Studies -Imaging Evidence for a Role of the Hypothalamus in Migraine



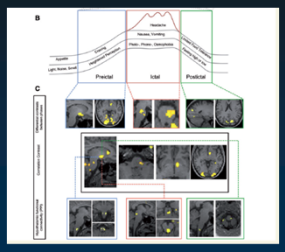
Denuelle et al., Headache, 2007



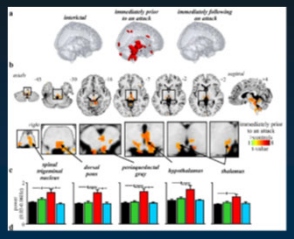
Maniyar et al., Brain, 2013

6

fMRI studies – activation and increased connectivity of hypothalamus



Schulte and May, Brain, 2016



Meylakh, et al. Human Brain Mapping, 2018

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The Hypothalamus as a Therapeutic Target

- Hypothalamus has neurons that respond activity to gluccocorticoids
- Hypothalamic neurons release:
  - Somatostatin
  - Oxytocin
  - Orexins
  - Dopamine
  - Other substances potentially involved in migraine

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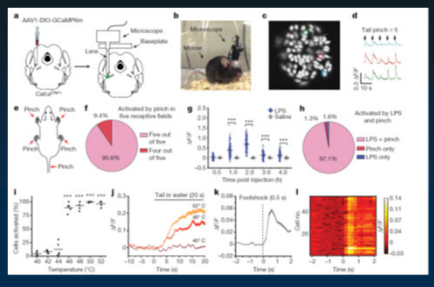
Encoding of danger by parabrachial CGRP neurons



- CGRP neurons in the brainstem are activated by a variety of environmental and physiological "danger" signals
- Migraine triggers??

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Localization of CGRP Receptor Components and Receptor Binding Sites in Rhesus Monkey Brainstem: A Detailed Study Using In Situ Hybridization, Immunofluorescence, and Autoradiography

Sajedeh Eftekhari,[1]* Renee C. Caspar,[2] Rhonda Roberts,[3] Tsing-Bau Chen,[4] Zhizhen Zeng,[4] Stephanie Villarreal,[1] Lars Edvinsson,[1] and Christopher A. Salvatore[3]
[1]Department of Clinical Sciences, Division of Experimental Vascular Research, Lund University, SE-22184 Lund, Sweden
[2]Department of Pain and Migraine Research, Merck Research Laboratories, West Point, Pennsylvania 19486
[3]Department of Neuroscience, Merck Research Laboratories, West Point, Pennsylvania 19486
[4]Department of Imaging, Merck Research Laboratories, West Point, Pennsylvania 19486

The Journal of Comparative Neurology | Research in Systems Neuroscience 524:90–118 (2016)

" Interestingly, we found receptor expression and antagonist binding in some areas that are not protected by the blood–brain barrier (hypothalamus, pineal, area postrema), which suggests that drugs inhibiting CGRP signaling may be able to penetrate the central nervous system to antagonize receptors in these brain regions."

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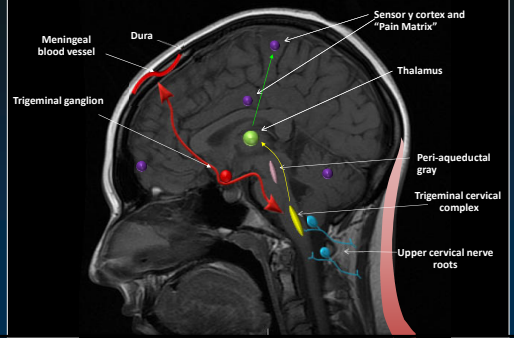
PAIN PATHWAYS IN MIGRAINE



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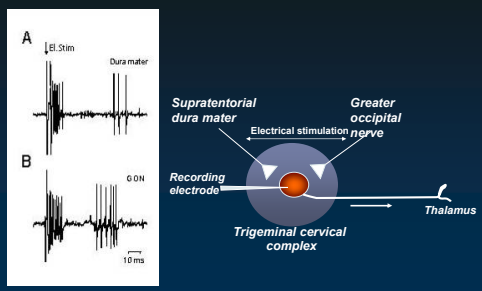
Upper Neck and Head Pain are Referred to the Same Neurons in the Lower Brainstem



Bartsch T, Goadsby PJ. Cur Pain Headache Rep 2003;7:371-376

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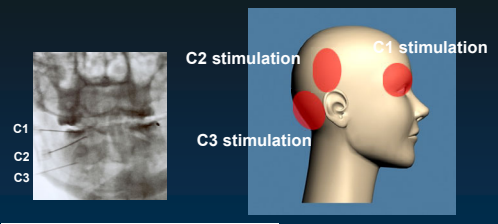
Cervical Nerve Roots in Migraine?



Pain Referral Patterns of the C1 to C3 Nerves: Implications for Headache Disorders

Mollie M. Johnston, Sheldon E. Jordan, and Andrew C. Charles

ANN NEUROL 2013;00:000–000

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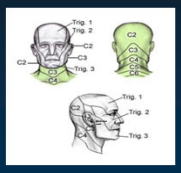
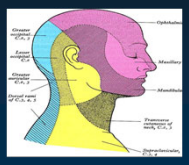
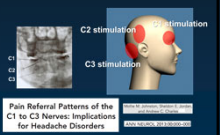
MIGRAINE IS A TRIGEMINOVASCULAR DISORDER

IF THIS IS TRUE, WHY DOES A MIGRAINE ATTACK COMMONLY START WITH NECK PAIN?







Pain Referral Patterns of the C1 to C3 Nerves: Implications for Headache Disorders

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If migraine is a trigeminal nerve disorder, why is there no overlap with trigeminal neuralgia?

- Different location of pain
- Different quality of pain
- Completely different response to therapies

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Migraine and Right-to-left Shunt

- Migraine with aura associated with patent foramen ovale
- Migraine with aura associated with pulmonary right to left shunt in hereditary hemorrhagic telangiectasia
- Multiple negative studies of PFO closure for migraine with and without aura

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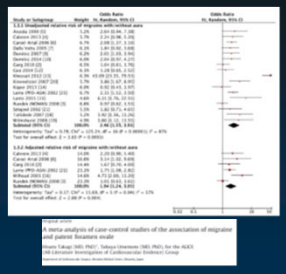
PFO and Migraine



Journal of Cardiology 67 (2016) 493–501

PFO-Migraine Odds Ratios

Migraine with aura- 3.4
(p<.00001)

Migraine with or without aura – 2.5
(p=.0001)

Migraine without aura – 1.3
(no statistical significance)

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The "Premium Trial" OF PFO Closure For Migraine

- 230 Patients Enrolled
- 119 Device implanted
- 107 Sham Control – medical management
- F/U at 12 months
- Primary Endpoint:
  - Responder rate

Percutaneous Closure of Patent Foramen Ovale in Patients With Migraine

The PREMIUM Trial

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

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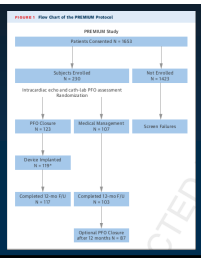
Jonathan Tobis, Andrew Charles, Stephen Silberstein, et al.



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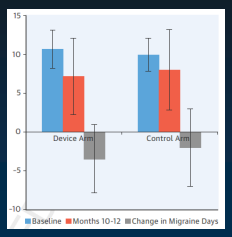
Premium Study Did Not Reach Primary Endpoint

TABLE 3 Average Number of Migraine Attacks at Baseline and at Months 10 to 12

	Device (n = 117)	Control (n = 103)	p Value
Responder rate	38.5 (45/117)	32.0 (33/103)	0.32
Baseline phase	4.8 ± 1.3 (117)	4.6 ± 1.4 (103)	0.14
Months 10-12	2.9 ± 1.8 (116)	3.2 ± 1.7 (103)	0.67

Responder Rate



Migraine Days

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Secondary Analysis

- Statistically significant reduction in migraine days
- Subjects in whom majority of migraine attacks included aura had significantly better response
- Overall 8 % of PFO closure patients had complete remission of migraine after 1 year, compared with 1% of controls.
- Of those with aura with the majority of their attacks, 6 of 39 (15.4%) had complete remission of migraine attacks in the PFO closure group vs. 1 of 40 (2.5%) in the control group

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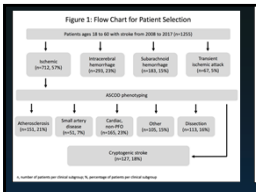

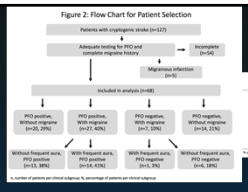

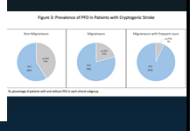

West, et al. The frequency of patent foramen ovale and migraine in patients with cryptogenic stroke. Stroke In Press, 2018

UCLA Stroke Database Review

- **PFO and migraine with frequent aura overrepresented in cryptogenic stroke**
- **Migrainous infarction very uncommon**

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Ongoing Questions

- Does PFO play a causative or exacerbating role in migraine patients (particularly those with frequent aura?)
- Could association of migraine with aura with PFO explain the association of migraine with stroke?
- Should PFO closure be a treatment for migraine with aura with stroke risk?

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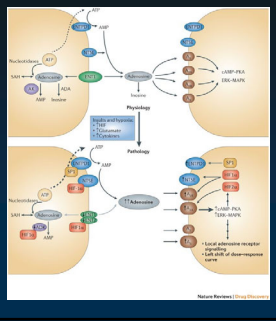
ADENOSINE RECEPTORS



- Adenosine is a product of energy metabolism (breakdown of ATP)
- Adenosine is a potent, primarily inhibitory transmitter
- Accumulation of adenosine is thought to play an important role in the metabolic drive to sleep
- Caffeine is a non-selective adenosine receptor antagonist
- Multiple adenosine receptor subtypes with differential expression on different cell types
- The only receptor subtype modulator that is in current clinical use is the A2A receptor antagonist istradefylline, which is approved for use in Asia for the treatment of Parkinson's disease.

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Adenosine receptor *agonists* inhibit peripheral pain in animal models

- Multiple adenosine receptor agonists have been shown to inhibit nociceptive signaling in different peripheral pain models, including trigeminal pain models
- None have been brought forward successfully as therapeutics

Borghi, V., Przewlocka, B., Labuz, D., Maj, M., Ilona, O., & Pavone, F. (2002). Formalin-induced pain and mu-opioid receptor density in brain and spinal cord ar modulated by A1 and A2a adenosine agonists in mice. *Brain Res, 956(2), 339-348.*
Goadsby, P. J., Hoskin, K. L., Storer, R. J., Edvinsson, L., & Connor, H. E. (2002). Adenosine A1 receptor agonists inhibit trigeminovascular nociceptive transmission. *Brain, 125(Pt 6), 1392-1401.*
Macedo-Junior, S. J., Nascimento, F. P., Luiz-Cerutti, M., & Santos, A. R. S. (2021). The role of peripheral adenosine receptors in glutamate-induced pain nociceptive behavior. *Purinergic Signal.*
Terayama, R., Tabata, M., Maruhama, K., & Iida, S. (2018). A3 adenosine receptor agonist attenuates neuropathic pain by suppressing activation of microglia and convergence of nociceptive inputs in the spinal dorsal horn. *Exp Brain Res, 236(12), 3203-3213.*

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Caffeine

- Known to have benefit as an acute therapy
- Withdrawal from regular caffeine use can trigger migraine

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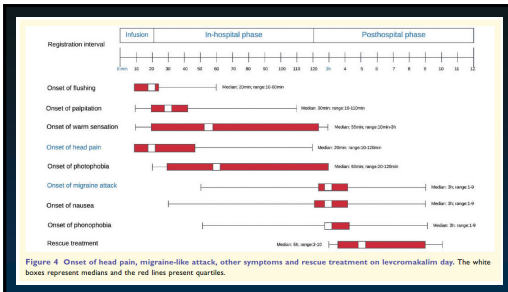

Figure 4 Onset of head pain, migraine-like attack, other symptoms and rescue treatment on levcromakalim day. The white boxes represent medians and the red lines present quartiles.

Opening of ATP-sensitive potassium channels causes migraine attacks: a new target for the treatment of migraine

Mohammad Al-Mahdi Al-Karagholi, Jakob Møller Hansen, Song Guo, Jes Olesen and Messoud Ashina

BRAIN
A JOURNAL OF NEUROLOGY
BRAIN 2019: 142; 2644–2654

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Caffeine effects on migraine mechanisms

- Increases threshold for CSD and reduces amplitude of vasoconstriction response to CSD
- Dilates cortical surface blood vessels
- Effects are mimicked by selective adenosine receptor subtype antagonists, especially A1
- Opposite effects are observed with adenosine receptor subtype *agonists*

Dimitri Yousef-Yengeh, Kimiya Aframian

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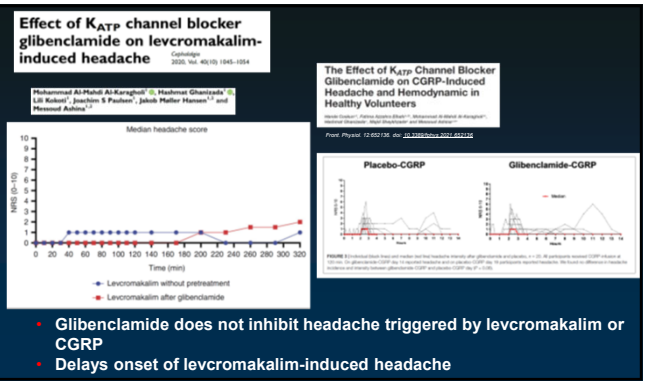

- **Glibenclamide does not inhibit headache triggered by levcromakalim or CGRP**
- **Delays onset of levcromakalim-induced headache**

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Could a more selective adenosine receptor antagonist reproduce therapeutic benefit of caffeine but with less withdrawal effect?

- Potentially different effects of selective A1, A2a/b, A3 antagonists
- Multiple naturally occurring substances may have antagonist action on adenosine receptors
  - Flavonoids
  - Other xanthines

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Evidence for Na+ channels in headache disorders and facial pain

- Multiple sodium channel blockers may have therapeutic benefit (e.g. lidocaine, multiple anti-convulsants)
- Mutations in a sodium channel (SCN1A) responsible for FHM type 3
- Humans with mutations of Nav1.7 sodium channel have persistent analgesia

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Table 1 | Selected Nav1.7 inhibitors

Drug candidate	Sponsor	Modality	Development status
PF-05089771	Pfizer	Small-molecule inhibitor	Discontinued in 2015 after failed phase II trial in painful diabetic peripheral neuropathy
TV-45070	Teva/Xenon	Small-molecule inhibitor	Discontinued in 2017 after failed phase II trial in post-herpetic neuralgia
RG-6029/GDC-0310	Roche/ Genentech/Xenon	Small-molecule inhibitor	Discontinued in 2018 prior to phase II initiation
Vixotrigine	Biogen	Small-molecule inhibitor	Discontinued in painful lumbosacral radiculopathy after phase II failure in 2018; phase III trial planned in trigeminal neuralgia; phase II trial ongoing in small fibre neuropathy
BIIB-095	Biogen	Small-molecule inhibitor	Phase I trial for neuropathic pain ongoing
ST-2427	SiteOne	Small-molecule inhibitor	IND for post-operative pain
AM-6120, AM-8145 and AM-0422	Amgen	Peptide derived from tarantula venom	Discovery
Nav1.7-targeted mAb	Shionogi	mAb	Discovery
VY-NAV-01	Voyager Therapeutics	Gene therapy Nav1.7 knockdown	Discovery

IND, investigational new drug; mAb, monoclonal antibody.

Nav1.7 withholds its pain potential

NATURE REVIEWS | DRUG DISCOVERY

- Multiple small molecule, antibody, and molecular approaches targeting Nav1.7 channels have been brought forward as pain treatments
- Thus far none have shown clinical benefit or been brought forward as therapeutic agents

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Other types of sodium channels as therapeutic targets

- One example: persistent sodium channel
- PRAX-562 (Praxis) being investigated as potential for SUNCT-SUNA and trigeminal neuralgia

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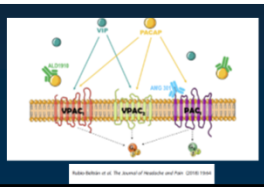
PACAP

ANNALS of Clinical and Translational Neurology

BRIEF COMMUNICATION

Pituitary adenylate cyclase activating polypeptide and migraine

Alessandro S. Zagami[1], Lars Edvinsson[2] & Peter J. Goadsby[1]



A phase 2, randomized, double-blind, placebo-controlled trial of AMG 301, a pituitary adenylate cyclase-activating polypeptide PAC1 receptor monoclonal antibody for migraine prevention

Messoud Ashina[1], David Dolezil[2], Jo H Bonner[3], Lifen Zhou[4], Jan Klatt[4], Hernan Picard[4] and Daniel D Mikol[4]

Cephalalgia 2021, Vol. 41(1) 33–44

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AMYLIN/AMYLIN RECEPTORS?

A second trigeminal CGRP receptor: function and expression of the AMY$_1$ receptor

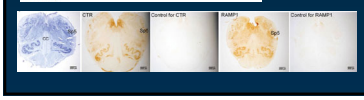
Christopher S. Walker[1,2], Sajedeh Eftekhari[1], Rebekah L. Bower[1,2], Andrea Wilderman[1], Paul A. Insel[3], Lars Edvinsson[4], Henry J. Waldvogel[5,6], Muhammad A. Jamaluddin[1], Andrew F. Russo[1,7] & Debbie L. Hay[1,2]

ANNALS of Clinical and Translational Neurology

Annals of Clinical and Translational Neurology 2015; 2(6): 599–608

Amylin Analog Pramlintide Induces Migraine-like Attacks in Patients

ANN NEUROL 2021;89:1157–1171



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OPIOID RECEPTORS

MU RECEPTORS

- Primary target for most opioid analgesics in current clinical use
- Mu agonists cause tolerance, dependence, and addiction
- Cause hyperalgesia
- Contribute to contribute to worsening of migraine over time

DELTA RECEPTORS

- Expressed on different cells than mu receptors
- Delta agonists have reduced potential for tolerance and dependence
- Do not cause hyperalgesia
- Have anti-anxiety an antidepressant properties
- ? Potentially useful for migraine

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Delta Opioid Receptor Agonists Inhibit Migraine-Related Hyperalgesia, Aversive State, and Cortical Spreading Depression

Amynah A Pradhan[1,2,3,*]
Monique L Smith[1,2,3]
Jekaterina Zyuzin[2] and
Andrew Charles[2,3]

BJP

- ***Multiple delta agonists inhibit nitroglycerin-evoked hyperalgesia***
- ***The delta agonist SNC80 inhibit NTG-evoked conditioned place aversion***
- ***SNC80 inhibits cortical spreading depression***

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THE Na+/K+ pump as a therapeutic target in migraine

- Mutation of pump causes FHM
- Inhibition of pump with ouabain causes CSD
- Function of the pump is not static: endogenous ouabain-like substances are released in response to changes in barometric pressure, hormonal changes
- Multiple medications may target the ouabain binding site – e.g. spironolactone

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Glutamate Receptors Memantine

- Multiple lines of evidence implicate glutamate and its receptors as mediators of migraine
- Memantine is an activity-dependent glutamate receptor antagonist
- Memantine inhibits cortical spreading depression in animal models
- Memantine is known to be well tolerated based upon extensive use for Alzheimer's disease

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Memantine for migraine?

Role of memantine in the prophylactic treatment of episodic migraine: A systematic review

Vinita M. Mistry PharmD | Paige L. Morizio PharmD, BCPS | Marc J. Pepin PharmD, BCPS, BCGP | William E. Bryan PharmD, BCPS | Jamie N. Brown PharmD, FCCP, BCPS, BCACP

Headache. 2021;61:1207-1213.

GUEST EDITORIAL

Memantine for migraine—Big promise but little evidence

Andrew Charles MD

Headache. 2021;61:1151-1152.

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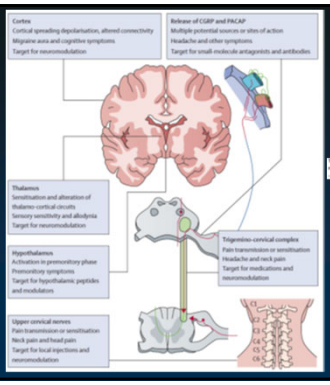

THE LANCET Neurology

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Mammoth Lakes, California

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