CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Prodrome & Interictal Burden

David Dodick, MD, FAAN
Professor Emeritus, Department of Neurology, Mayo Clinic; C
hief Science Officer, Atria Academy of Science and Medicine;
Adjunct Professor, University of Copenhagen, Norwegian University of
Science and Technology USA

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Canadian Headache Society

National Neurology Resident Headache Course 2024

Prodrome and Interictal Burden (Symptoms)

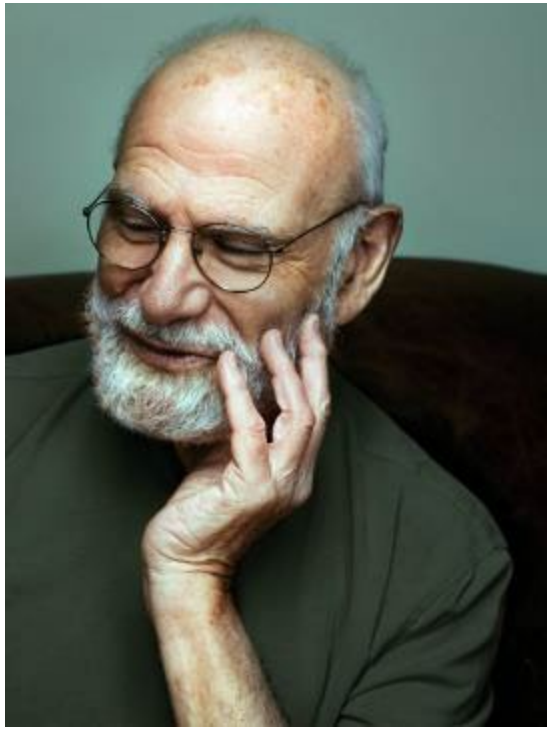
David W. Dodick, MD

Disclosure (12 months)

	No, nothing to disclose
x	Yes, please specify:

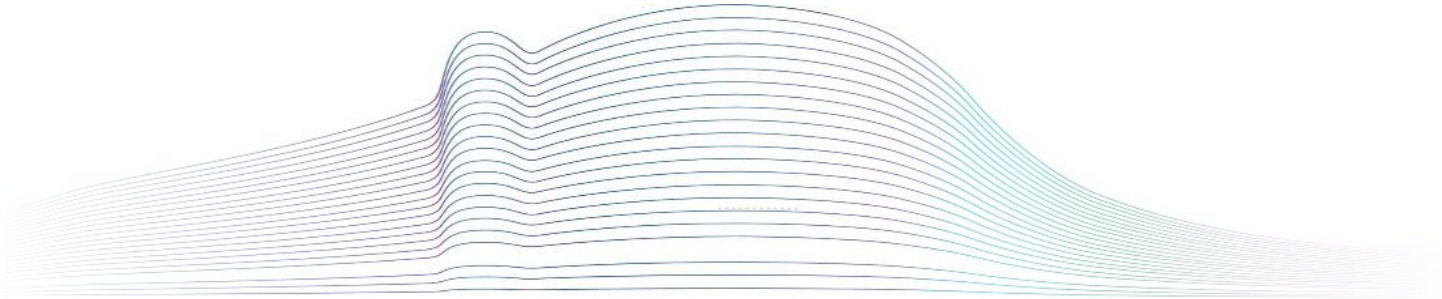
Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*
Genentech	x	X (consulting)						
Amgen (Japan)	x							
Abbvie		X (consulting)						
Axon					x	x		
Palion								
Healint								x (shares)
Man and Science								x (shares)
Theranica								x (shares)
Nocira								x (shares)
King-Devick Technologies								x (shares)
Cephalgia						x		x (shares)
Oxford Univ Press				x				
Cambridge Univ Press				x				
Wolters Kluwer				x				

“… glimpsing your destination from far off, in a plane, having it get clearer and clearer as you descend through the clouds … the migraine looms, but it’s just a change of scale—everything is already there from the start.”



MAYO CLINIC

PRODROME AND INTERICTAL PERIOD



The Phases of Migraine

1 2 3 4 5

PRODROME

Fatigue
Food cravings
Nausea
Cognitive symptoms
Neck discomfort
Photophobia, phonophobia

AURA

Aura symptoms

HEADACHE (ICTAL)

Moderate-to-severe head pain
Photophobia, phonophobia
Nausea, vomiting
Allodynia
Neck discomfort
Cranial autonomic symptoms
Cognitive symptoms

POSTDROME

Photophobia, phonophobia
Nausea
Fatigue
Cognitive symptoms
Neck discomfort

INTERICTAL

Photophobia, phonophobia
Cognitive symptoms
Nausea
Fatigue
Allodynia
Neck discomfort

DODICK DW. THE LANCET 2018;10127:P1315-1330

Eigenbrodt *et al.*
The Journal of Headache and Pain (2022) 23:140
https://doi.org/10.1186/s10194-022-01510-z

The Journal of Headache and Pain

RESEARCH Open Access

Premonitory symptoms in migraine: a systematic review and meta-analysis of observational studies reporting prevalence or relative frequency

Anna K. Eigenbrodt[1], Rune Häckert Christensen[1], Håkan Ashina[1,2,3], Afrim Iljazi[1], Casper Emil Christensen[1], Timothy J. Steiner[4,5], Richard B. Lipton[6] and Messoud Ashina[1*]

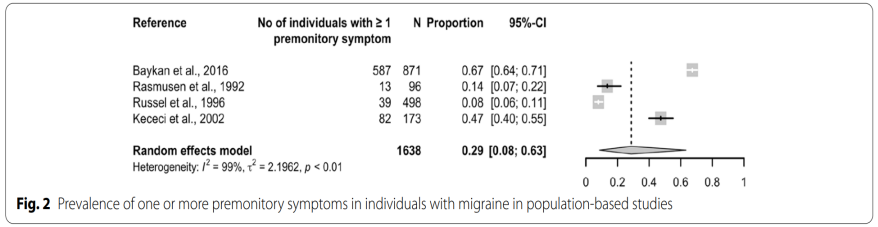


Fig. 2 Prevalence of one or more premonitory symptoms in individuals with migraine in population-based studies

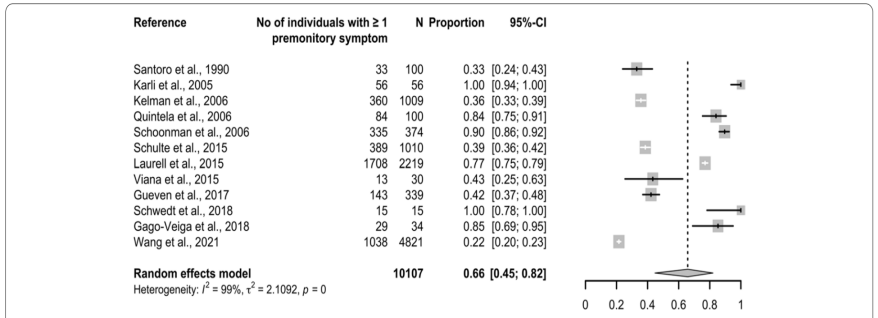


Fig. 3 Relative frequency of one or more premonitory symptoms in individuals with migraine in clinic-based studies.

- Clinic-based studies: **66%**
- Population-based studies: **29%**
- Clinic sample of 461 patients with migraine who were questioned about the presence of 12 predefined prodromal symptoms, **87% reported at least one prodromal symptom.**
- Fatigue (49%), neck stiffness (46%), mood change (37%).
- Substantial between-study heterogeneity

Original Article

Cephalalgia
An International Journal of Headache

International Headache Society

Cephalalgia
44(2) 1–11

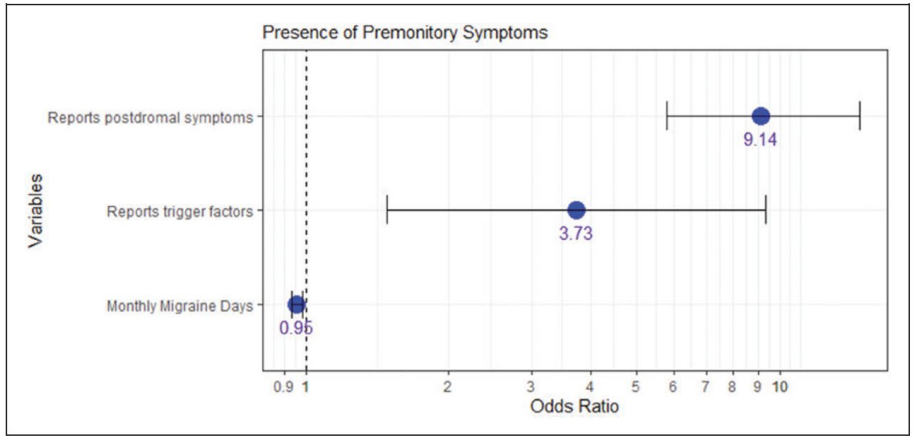
DOI: 10.1177/03331024231223979
journals.sagepub.com/home/cep

Sage

Premonitory symptoms in migraine: A REFORM Study

Janu Thuraiaiyah[1,2], Håkan Ashina[1,2,3,4,5], Rune H Christensen[1,2,4,5], Haidar M Al-Khazali[1,2,4,5], Astrid Wiggers[1], Faisal Mohammad Amin[1,2,3], Timothy J Steiner[2,6,7] and Messoud Ashina[1,2,8]

Prompted enquiry resulted in a greater proportion reporting premonitory symptoms than unprompted (69.9% vs. 43.0%; p<0.001) and with higher symptom counts.



Clinical implications

- The estimated proportion of patients reporting premonitory symptoms depends on the assessment method, and therefore standardized methods are needed.
- The impact of premonitory symptoms on migraine-attributed burden has previously been overlooked, although our findings suggest it is of less importance, relative to the impact of headache, both in clinical practice and to public health.

Prodrome Symptoms Checklist

Do you have **warning signs** that tell you that a headache is about to start?

YES	NO
☐	☐

Is this symptom routinely experienced before headache onset?

Appetite	YES	NO
Excessive energy	☐	☐
Food craving	☐	☐
Loss of appetite	☐	☐
Thirst	☐	☐

Autonomic	YES	NO
Nausea	☐	☐
Changes in bowel movement	☐	☐
Frequent urination	☐	☐
Pale or flushed face	☐	☐
Temperature change	☐	☐
Vomiting	☐	☐

Cognitive	YES	NO
Difficulty concentrating	☐	☐
Difficulty reading or writing	☐	☐
Difficulty speaking	☐	☐
Difficulty thinking	☐	☐

Cranial Parasympathetic	YES	NO
Stuffy nose	☐	☐
Teary / red eyes	☐	☐

Emotional	YES	NO
Emotional	☐	☐
Irritability	☐	☐

Is this symptom routinely experienced before headache onset?

General	YES	NO
Fatigue	☐	☐
Yawning	☐	☐

Pain	YES	NO
Muscle pain	☐	☐
Neck pain	☐	☐

Sensory hypersensitivity	YES	NO
Sensitive skin	☐	☐
Sensitivity to light	☐	☐
Sensitivity to smell	☐	☐
Sensitivity to sound	☐	☐

Vestibular	YES	NO
Dizziness	☐	☐

Visual	YES	NO
Blurred vision	☐	☐

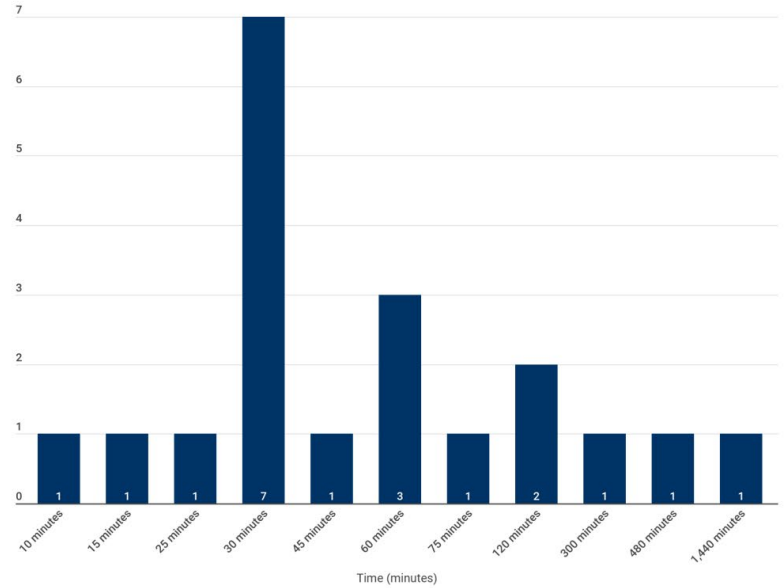
Other	YES	NO
Feeling difficult to describe	☐	☐
Other	☐	☐

References 1. Blau, J. N. 1980. Br Med J 281.6241: 658-660 **2.** Drummond & Lance. 1984 Clinical and experimental neurology **3.** Waelkens, J. Cephalalgia 5.4 (1985): 223-228. **4.** Giffin, N. J., et al. 2003. Neurology 60.6 (2003): 935-940. **5.** Karsan & Goadsby. 2018. Nature Reviews Neurology 14.12 (2018): 699-710.

Characterizing the Patient Experience During the Prodrome Phase of Migraine: A Qualitative Study of Symptoms and their Timing

N=20 participants

Estimate time until headache onset from the first prodromal symptom



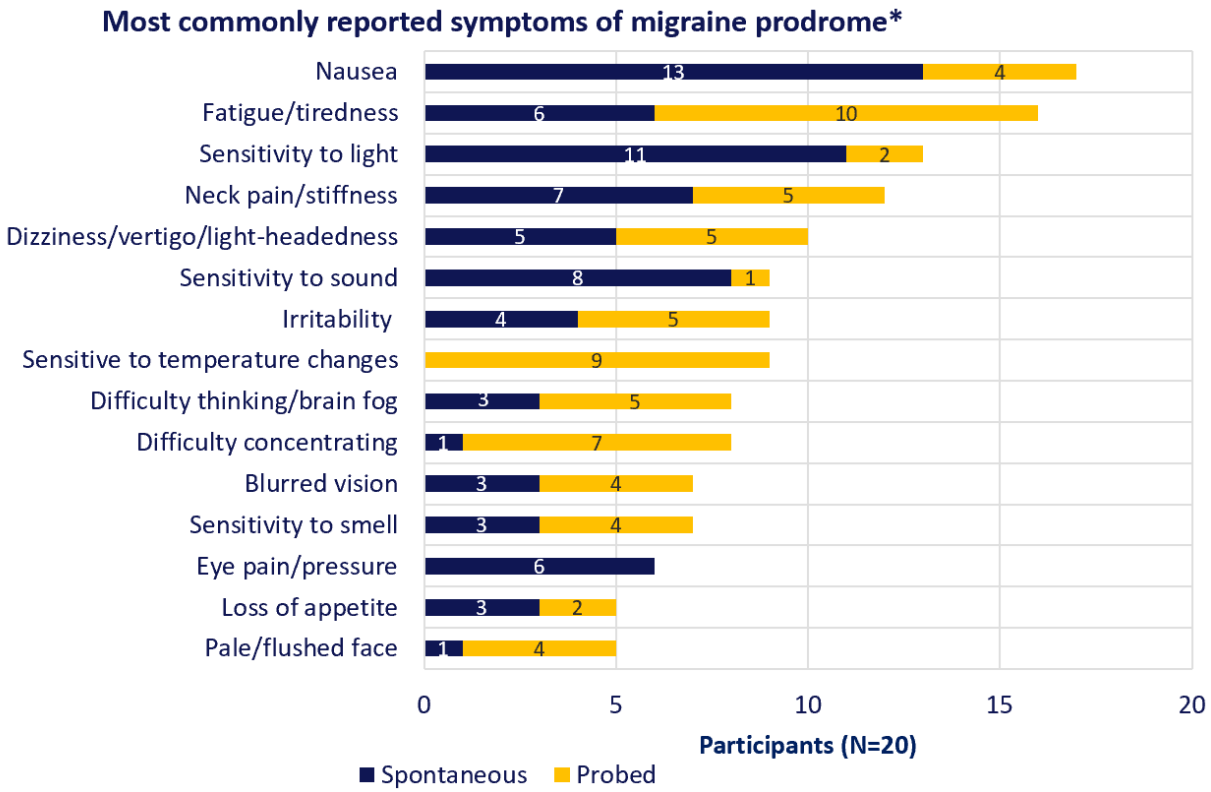
Mean: 151 minutes

Median: 37.5 minutes

Mode: 30 minutes

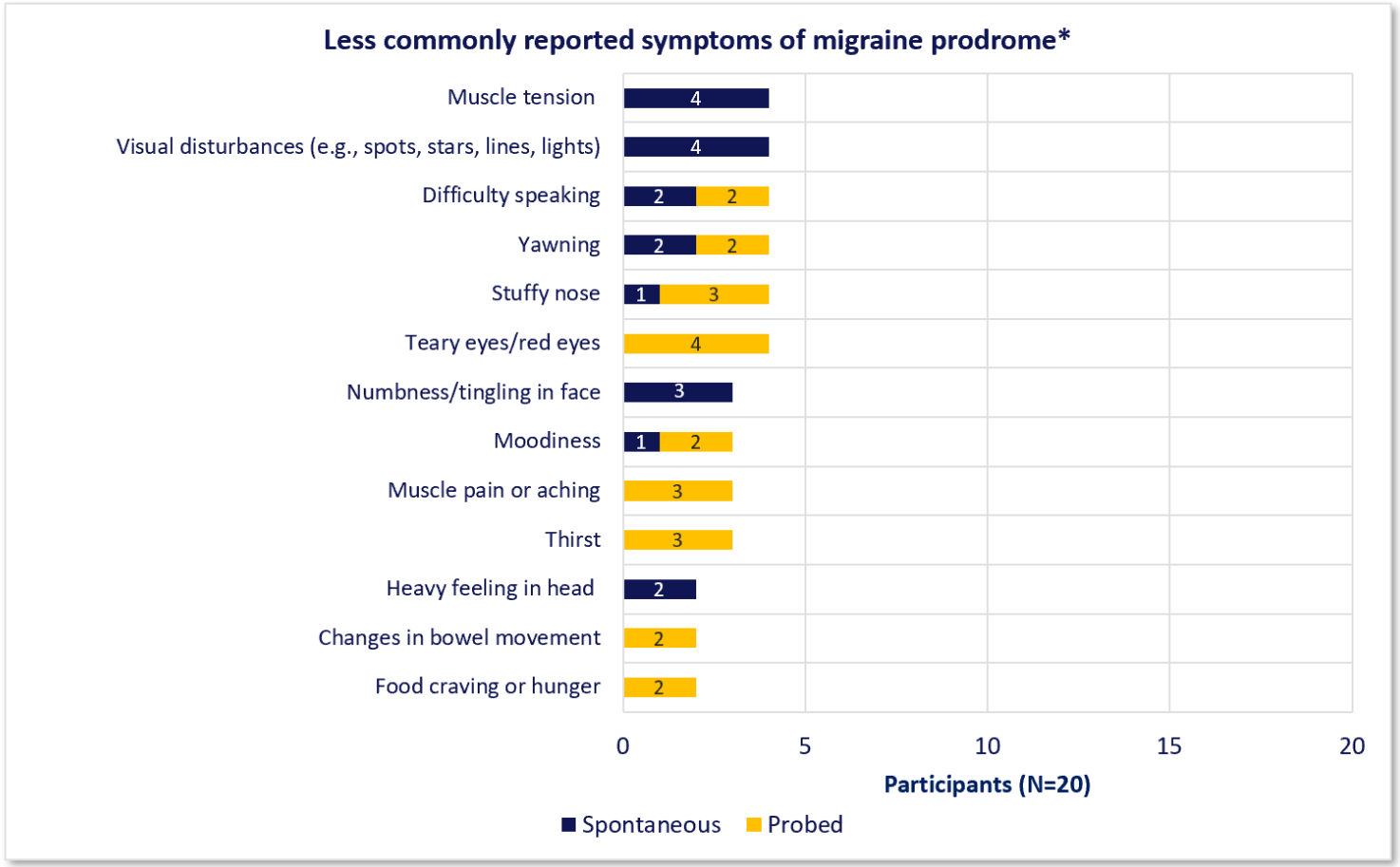
Stokes et al. Neurology 2023; issue 100 (17_supplement_2)

Characterizing the Patient Experience During the Prodrome Phase of Migraine: A Qualitative Study of Symptoms and their Timing



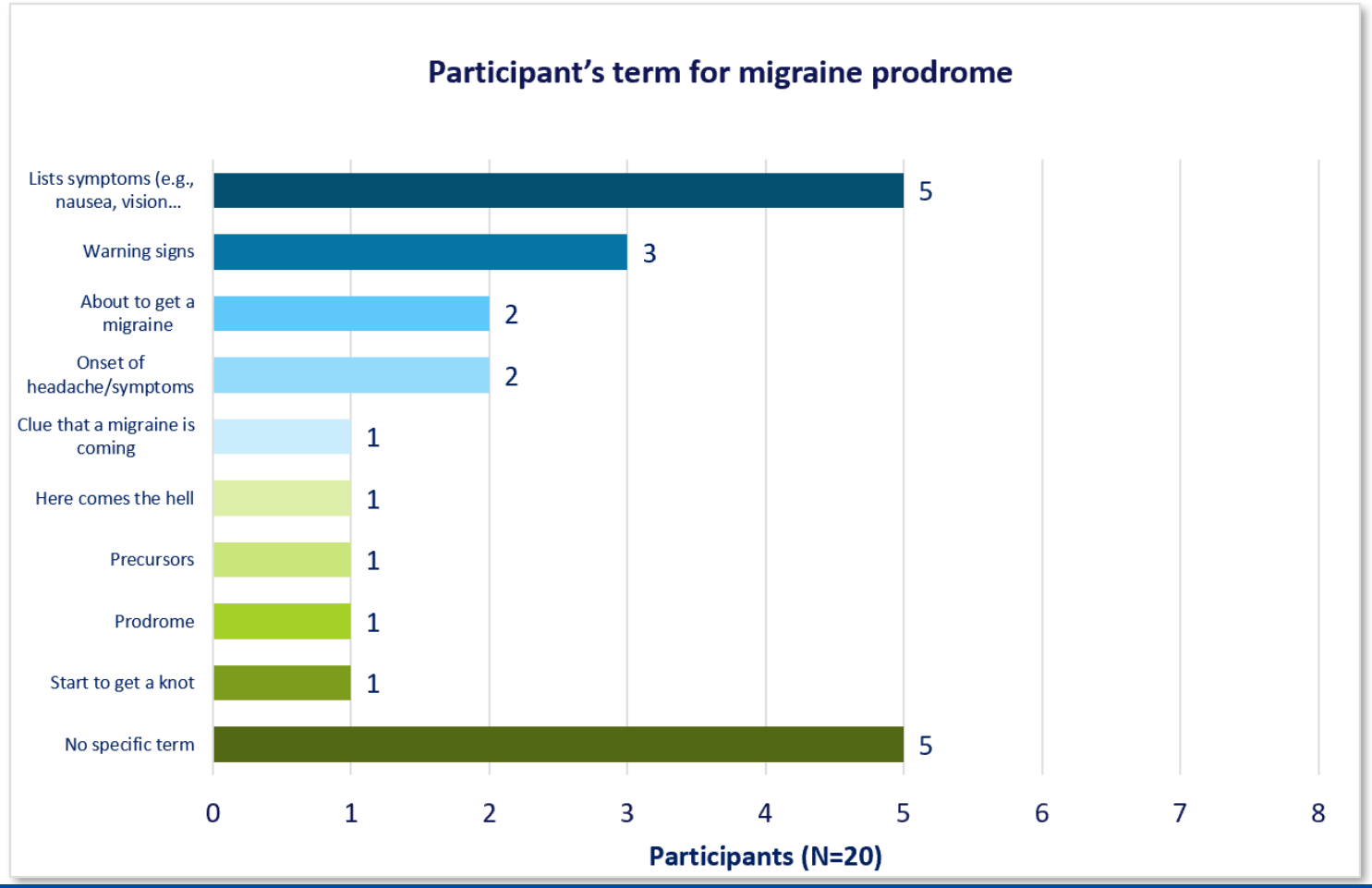
Stokes et al. Neurology 2023; issue 100 (17_supplement_2)

Characterizing the Patient Experience During the Prodrome Phase of Migraine: A Qualitative Study of Symptoms and their Timing



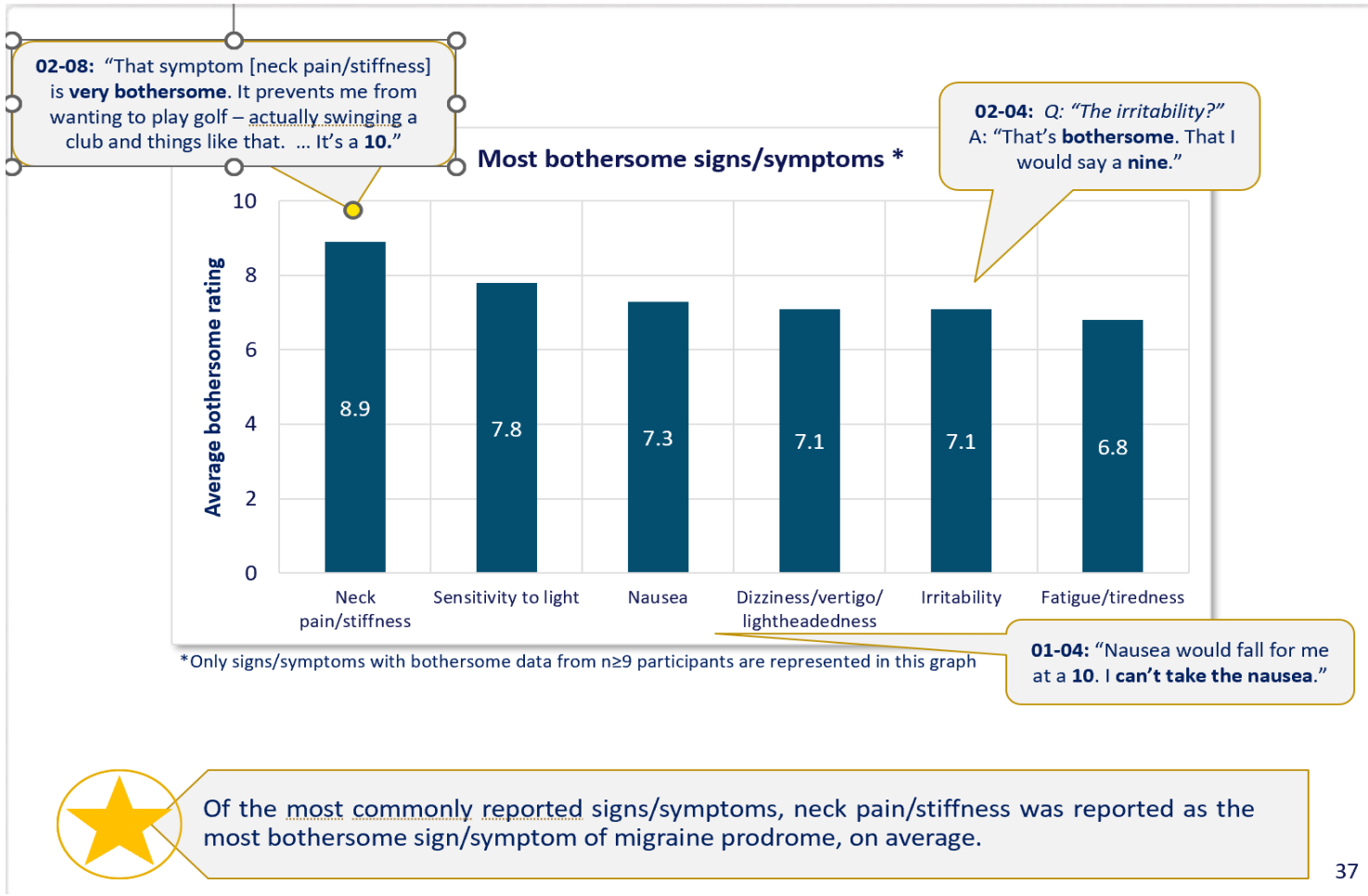
Stokes et al. Neurology 2023; issue 100 (17_supplement_2)

Characterizing the Patient Experience During the Prodrome Phase of Migraine: A Qualitative Study of Symptoms and their Timing



Stokes et al. Neurology 2023; issue 100 (17_supplement_2)

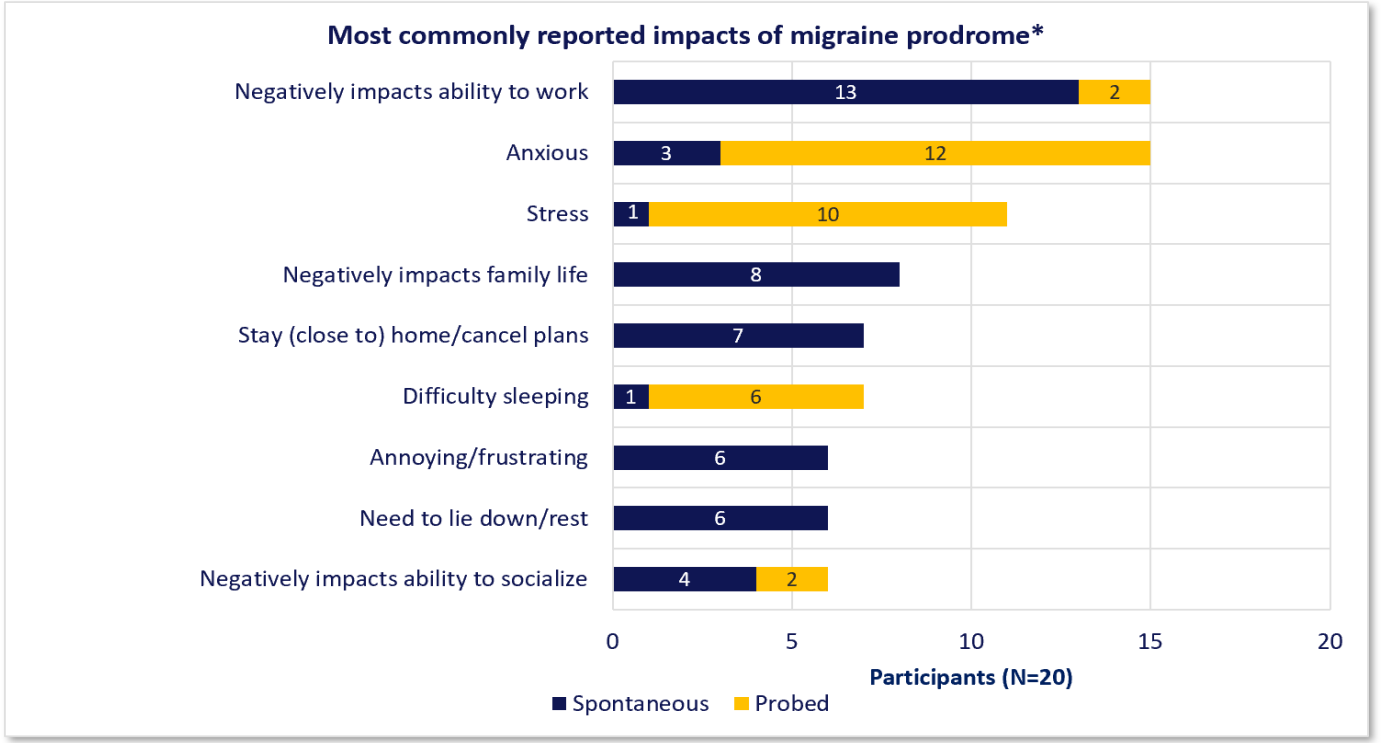
Characterizing the Patient Experience During the Prodrome Phase of Migraine: A Qualitative Study of Symptoms and their Timing



Of the most commonly reported signs/symptoms, neck pain/stiffness was reported as the most bothersome sign/symptom of migraine prodrome, on average.

Stokes et al. Neurology 2023; issue 100 (17_supplement_2)

Characterizing the Patient Experience During the Prodrome Phase of Migraine: A Qualitative Study of Symptoms and their Timing

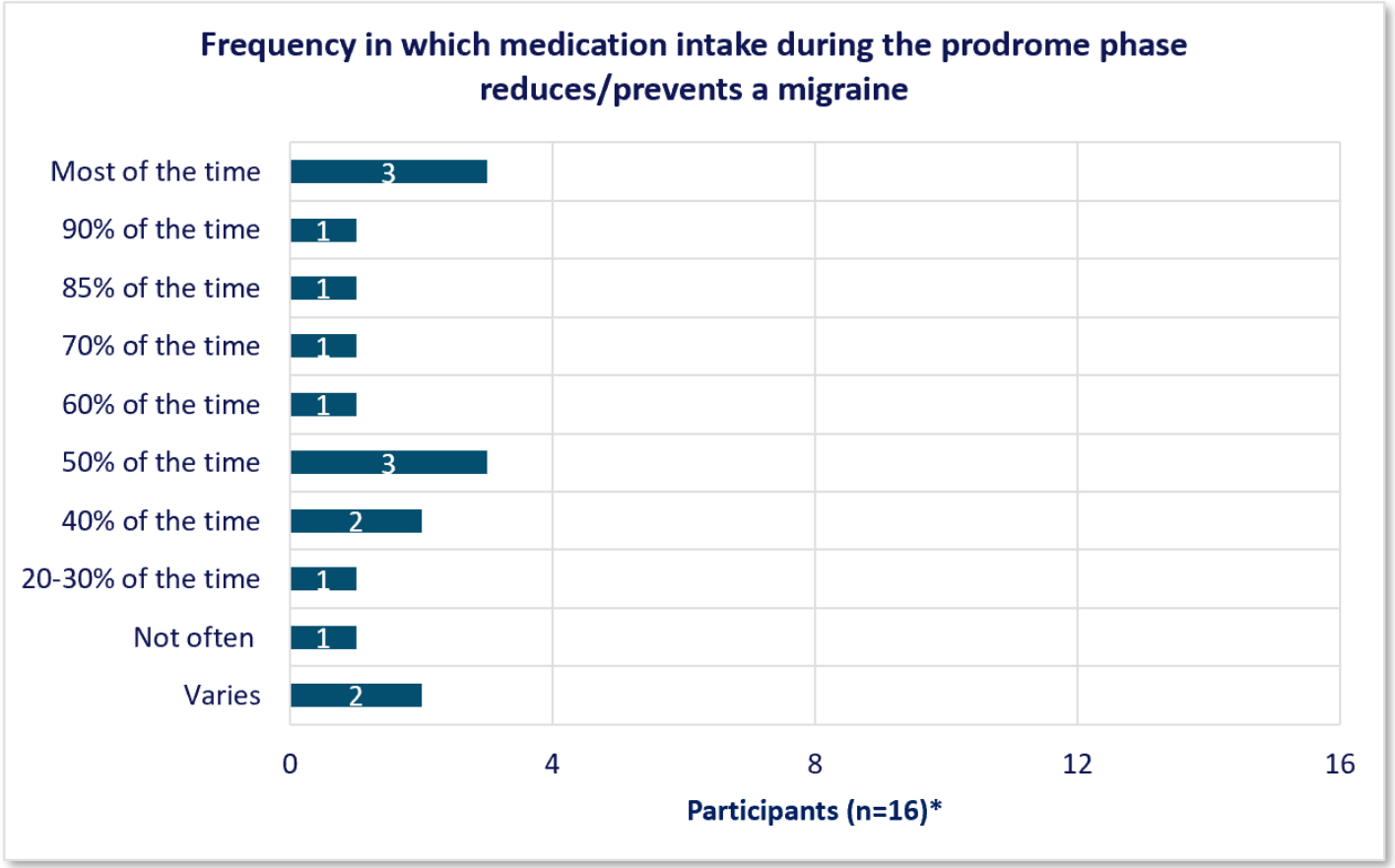


*Impacts reported by n≥5 participants are represented in this graph

More than half of the participants reported negative impacts to their ability to work (75.0%). Additionally, emotional impacts such as feeling anxious and stressed due to their prodrome symptoms were reported by more than half of participants (≥50.0%).

Stokes et al. Neurology 2023; issue 100 (17_supplement_2)

Characterizing the Patient Experience During the Prodrome Phase of Migraine: A Qualitative Study of Symptoms and their Timing



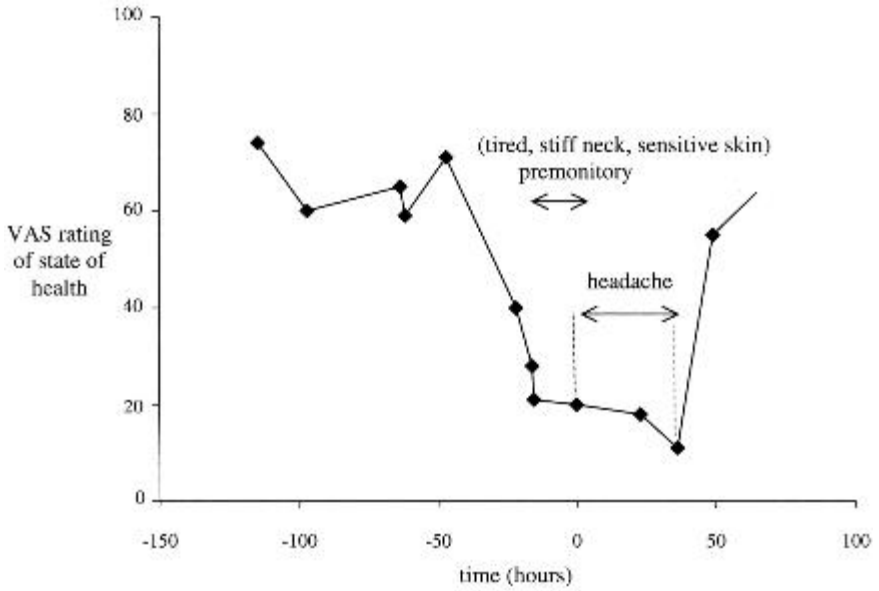
*Of n=16 participants who reported that they take medication during the prodrome phase

Stokes et al. Neurology 2023; issue 100 (17_supplement_2)

Premonitory symptoms in migraine

An electronic diary study

N.J. Giffin, MRCP; L. Ruggiero, BSc; R.B. Lipton, MD; S.D. Silberstein, MD; J.F. Tvedskov, MD; J. Olesen, MD; J. Altman, CStat; P.J. Goadsby, DSc; and A. Macrae, MRCP



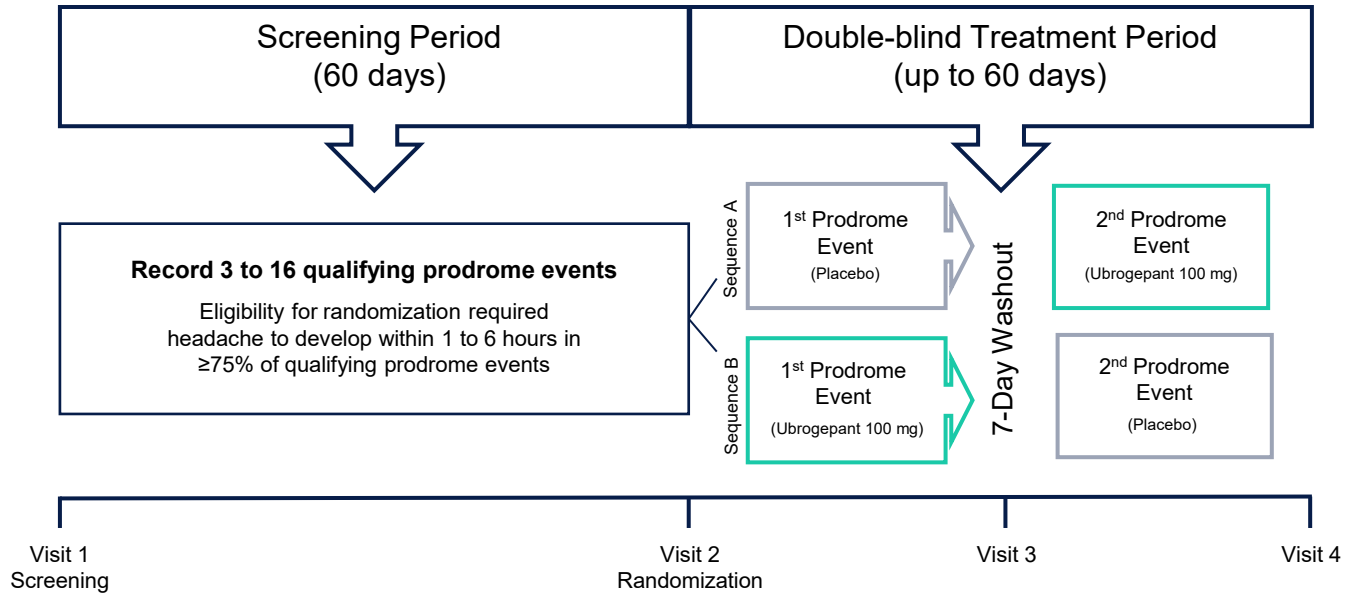
- Patients correctly predicted migraine headaches from **72%** of diary entries with premonitory symptoms.
- **Tired** and weary (72%), difficulty **concentrating** (51%), **stiff neck** (50%).
- Subjects who functioned poorly in the premonitory phase were the most likely to correctly predict headache.

NEUROLOGY 2003;60:935–940

Ubrogepant for the treatment of migraine attacks during the prodrome: a phase 3, multicentre, randomised, double-blind, placebo-controlled, crossover trial in the USA

David W Dodick, Peter J Goadsby, Todd J Schwedt, Richard B Lipton, Chengcheng Liu, Kaifeng Lu, Sung Yun Yu, Lawrence Severt, Michelle Finnegan, Joel M Trugman

- PRODROME was a multicenter, randomized, double-blind, placebo-controlled, crossover trial
- Patients recruited if they had identifiable prodrome symptoms that were followed by headache at least 75% of the time
- A “qualifying prodrome event” was defined as a migraine attack with prodromal symptoms in which headache was not present at the time, the participant had not had a headache in the previous 48 hours, treatments for acute headache had not been taken in the previous 48 hours, and the participant was confident a headache would follow within 1 to 6 hours



EMERGENT SCIENCES AND TOP HEADACHE RESEARCH | April 28, 2023 |

Characterizing Prodrome (Premonitory Phase) in Migraine: Results From the PRODROME Trial Screening Period (S41.009)

Todd J. Schwedt, Richard B. Lipton, Peter J. Goadsby, Chia-Chun Chiang, Brad Klein, Chengcheng Liu, Sung Yun Yu, Lawrence Severt, Michelle Finnegan, and Joel M. Trugman | AUTHORS INFO & AFFILIATIONS

Participants: 920

Qualifying prodrome events: 4802

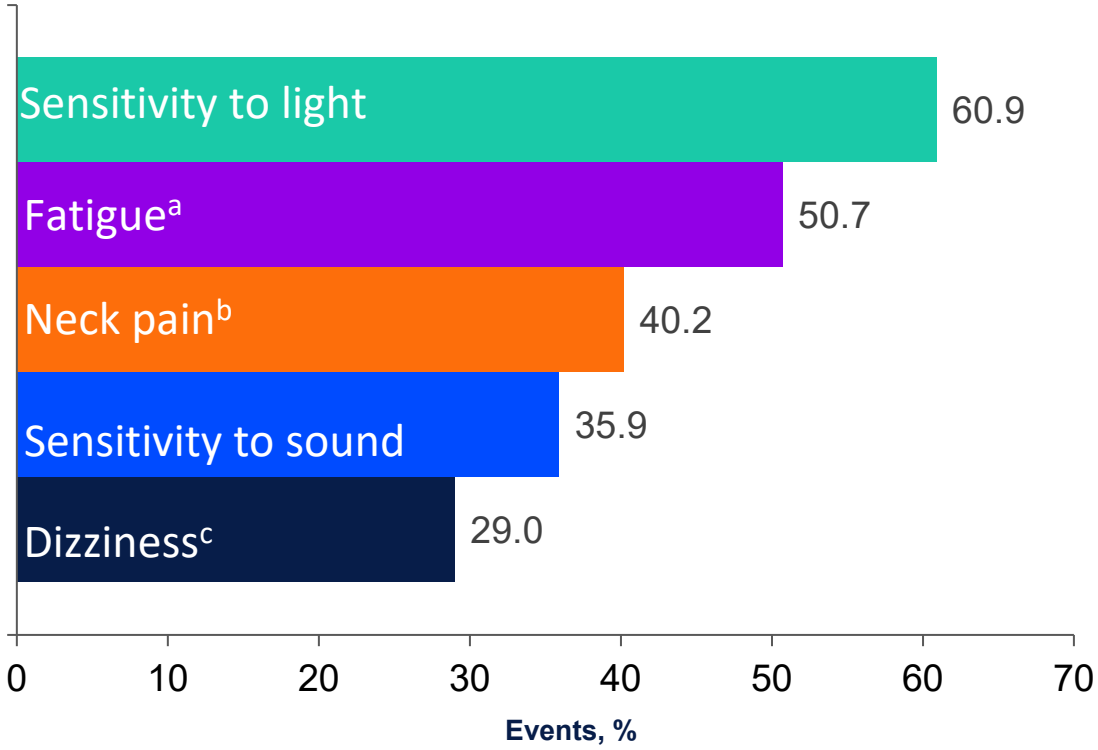
Mean 5.2 qualifying prodrome events per participant.

For each participant, a mean (median) of 84.4% (100%) of their qualifying prodrome events followed by a headache **<1–6 hours**.

Ubrogepant for the treatment of migraine attacks during the prodrome: a phase 3, multicentre, randomised, double-blind, placebo-controlled, crossover trial in the USA

David W Dodick, Peter J Goadsby, Todd J Schwedt, Richard B Lipton, Chengcheng Liu, Kaifeng Lu, Sung Yun Yu, Lawrence Severt, Michelle Finnegan, Joel M Trugman

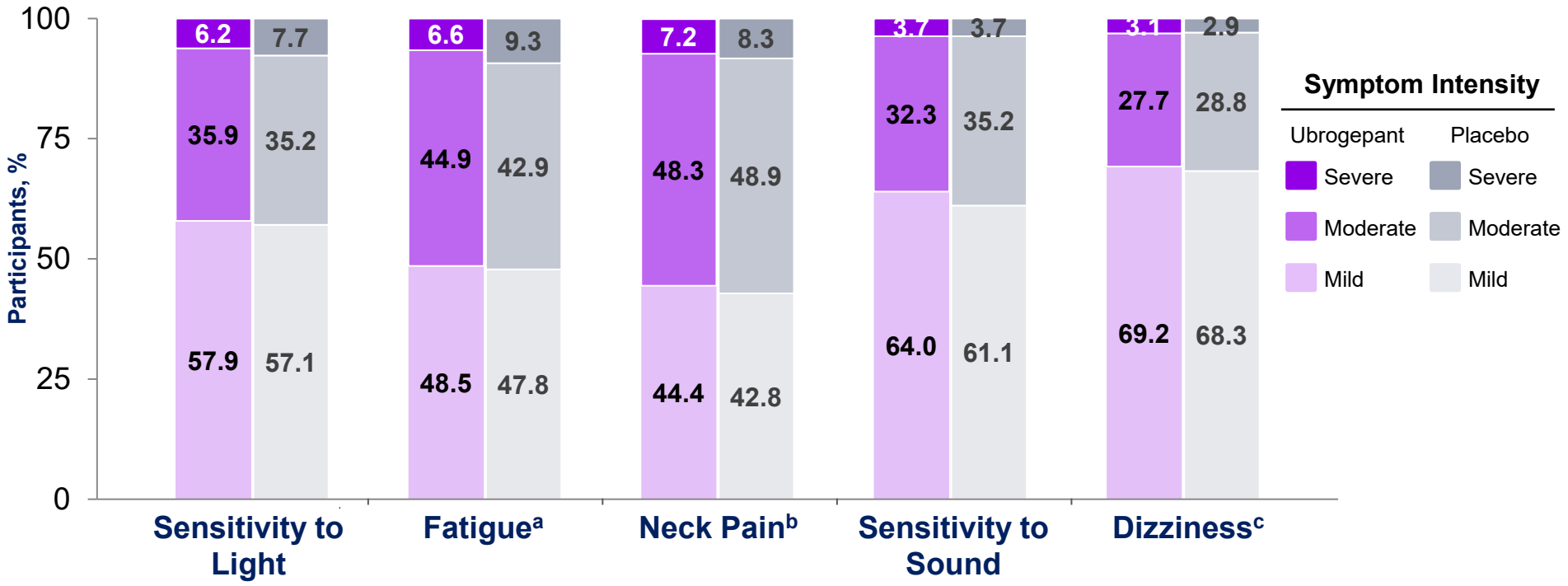
- The 5 most common symptoms identified pre-dose for ubrogepant-treated (N=448) and placebo-treated (N=449), respectively, qualifying prodrome events were:
  - Sensitivity to light (60.9% and 60.8%)
  - Fatigue (50.7% and 50.3%)
  - Neck pain (40.2% and 40.1%)
  - Sensitivity to sound (35.9% and 36.1%)
  - Dizziness (29.0% and 31.0%).



[a]Represents tired/sleepy/fatigue category in the eDiary.
[b]Represents neck pain/stiff neck category in the eDiary.
[c]Represents dizziness/lightheaded/vertigo/imbalance category in the eDiary.

Severity of the 5 Most Common Prodromal Symptoms

The 5 most common prodromal symptoms rated moderate or severe in intensity in 31%-57% of participants



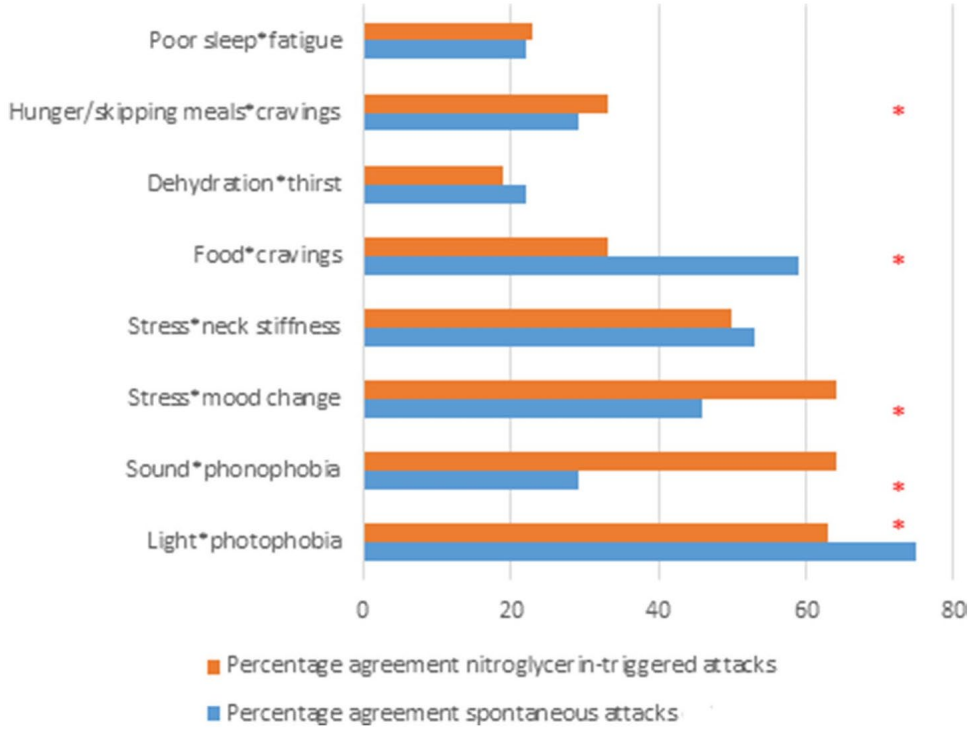
Journal of Neurology (2021) 268:1885–1893
https://doi.org/10.1007/s00415-020-10344-1

ORIGINAL COMMUNICATION

Are some patient-perceived migraine triggers simply early manifestations of the attack?

Nazia Karsan[1,2] · Pyari Bose[3] · Jayde Newman[1,2] · Peter J. Goadsby[1,2]

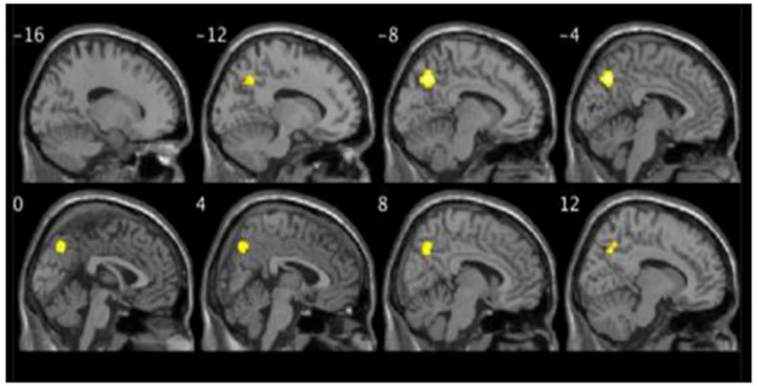
There was statistically significant agreement between perception of light as a migraine trigger and spontaneous premonitory photophobia; perception of sound as a trigger and triggered premonitory phonophobia; skipping meals as a trigger and spontaneous premonitory food cravings; and food triggers and spontaneous premonitory food cravings. There was good agreement between stress and premonitory triggered mood change.

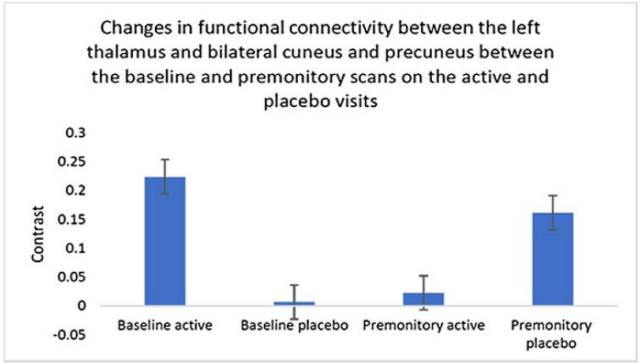


At least some patient-reported triggers, such as light, sound, foods and skipping meals, may represent early brain manifestations of the premonitory phase of the migraine attack.

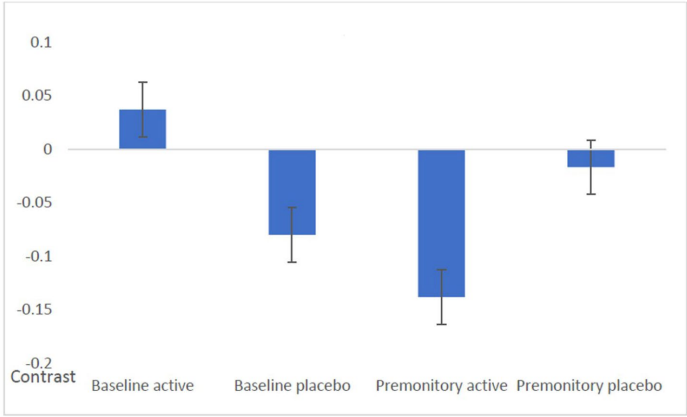
Alterations in Functional Connectivity During Prodrome

Alterations in FC between sensory thalamus and the precuneus/cuneus (involved in **multisensory integration** and cognitive processing) during premonitory symptoms





Negative coupling between limbic/frontal/cingulate and brainstem regions (pons) = **altered control of cortical modulation of brainstem regions** involved in sensory, autonomic, sleep and pain symptoms of migraine



Karzan N, et al. Headache 2020;60:1244-1258

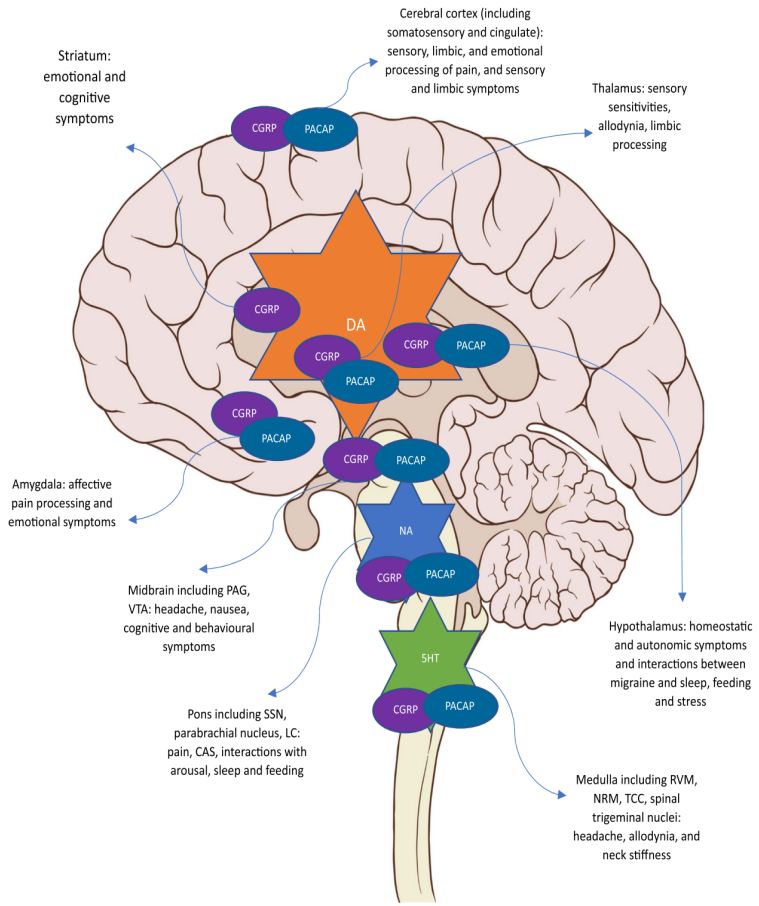
Karsan and Goadsby
The Journal of Headache and Pain (2023) 24:106
https://doi.org/10.1186/s10194-023-01617-x

The Journal of Headache and Pain

REVIEW Open Access

Neuroimaging in the pre-ictal or premonitory phase of migraine: a narrative review

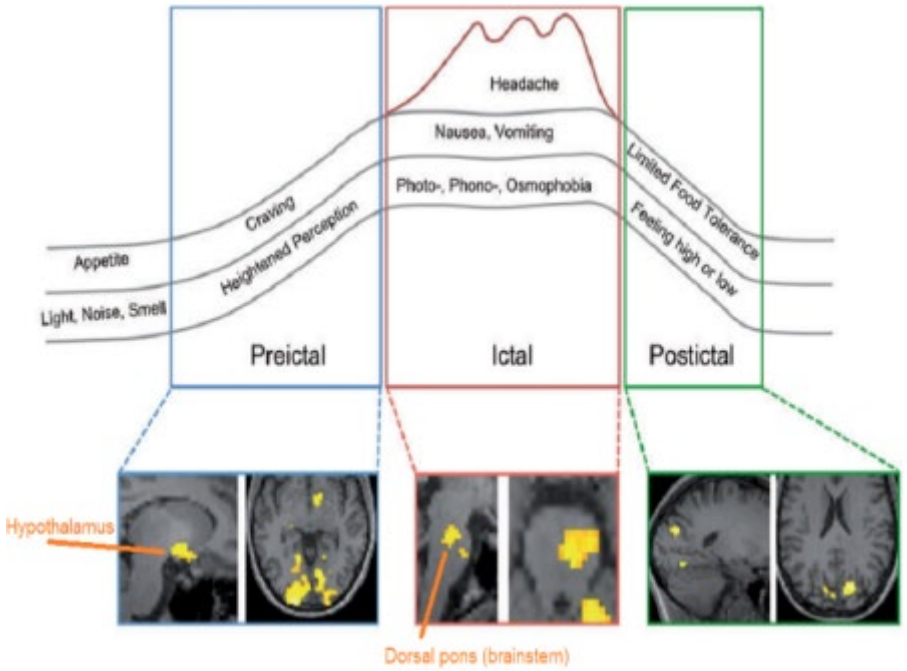
Nazia Karsan[1*] and Peter J. Goadsby[1,2]



- Various imaging modalities have contributed to a theory of disordered brain function early in the attack, involving areas involved in pain, sensory, limbic and homeostatic regulation.
- These areas are structurally and functionally connected via pathways involving dopamine, serotonin and noradrenaline, CGRP and PACAP.
- Combination of monoaminergic and peptidergic brain dysfunction in areas shared between pain processing and other physiological systems is likely to contribute to the heterogeneous migraine phenotype, the association between symptoms and triggers, and the links to other symptoms and disorders such as those involving mood, sleep and cognition

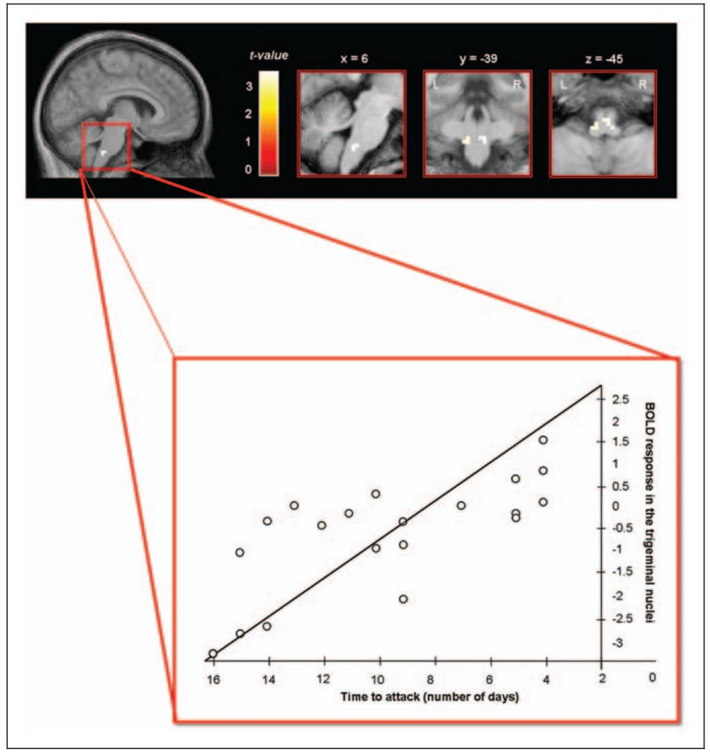
Prodromal Phase: The new ‘migraine generator’

In the early premonitory phase activation posterior/lateral hypothalamus/midbrain ventral tegmentum followed by activation of occipital cortex.



Significant functional coupling with trigeminal nucleus in the 24 hours before headache pain

Schulte and May, *Brain. 2016;*139:1987

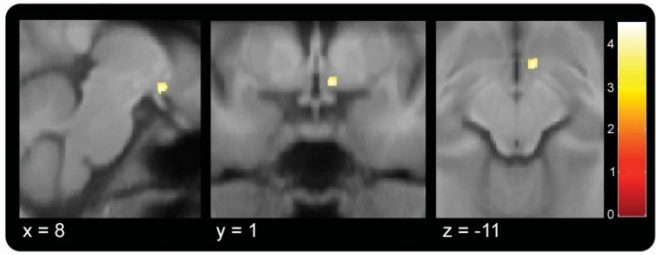


Progressive increase in activity of trigeminal nucleus caudalis in the days leading up to headache attack.

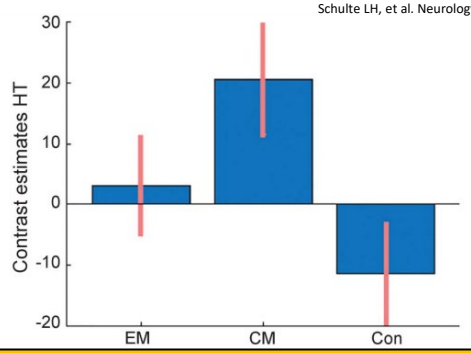
May A. Cephalalgia 2012; 33(8)554–565

Hypothalamus as central generator of migraine attacks, disease progression, and a target for treatment

Hypothalamus as generator of migraine and mediator of chronic migraine

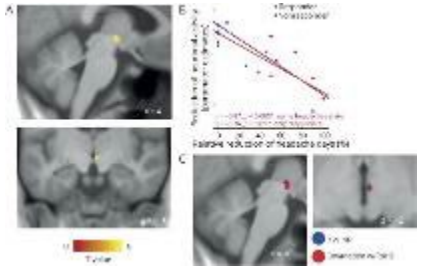


Schulte LH, et al. Neurology® 2017;88:2011–2016

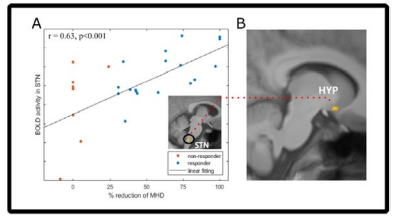


Increased anterior hypothalamic activation in CMs compared to HCs

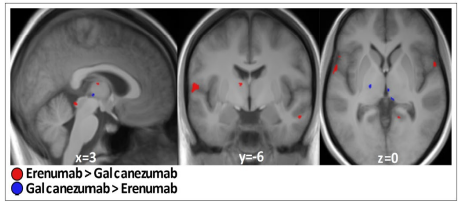
Hypothalamus as target and biomarker of response to treatment



Ziegeler et al. Neurology 2020



Basedau *et al*. eLife 2022;11:e77146



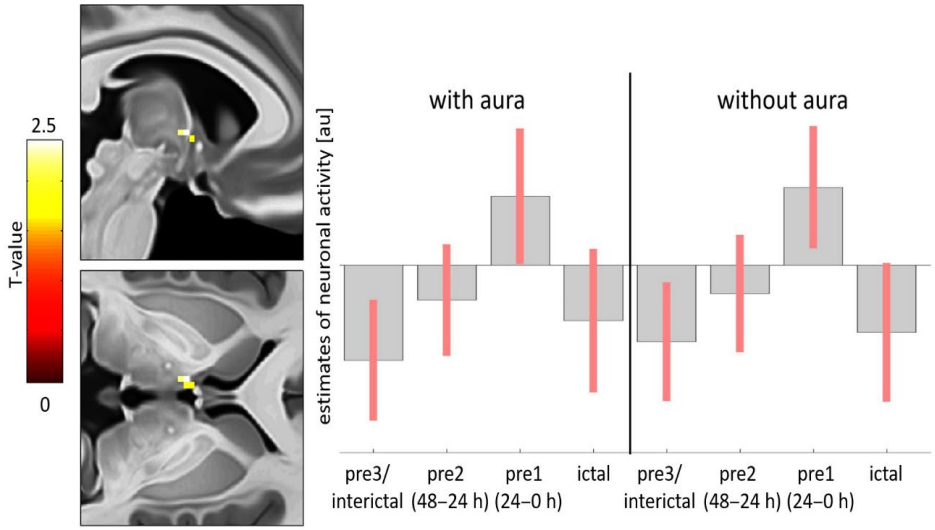
Erenumab and galcanezumab reduces hypothalamic activity in responders compared to non-responders

Received: 11 April 2023 | Accepted: 23 June 2023
DOI: 10.1111/head.14597

RESEARCH SUBMISSIONS

Aura phenomena do not initiate migraine attacks—Findings from neuroimaging

Jan Mehnert PhD[1] | Laura Fischer-Schulte MD, PhD[1,2] | Arne May MD, PhD[1]



Comparing the preictal phases between both attack types revealed a common hyperactivation of the hypothalamus ($p < 0.01$), which was already present 2 days before the actual attack.

Aura is an epiphenomenon and does not initiate headache attacks

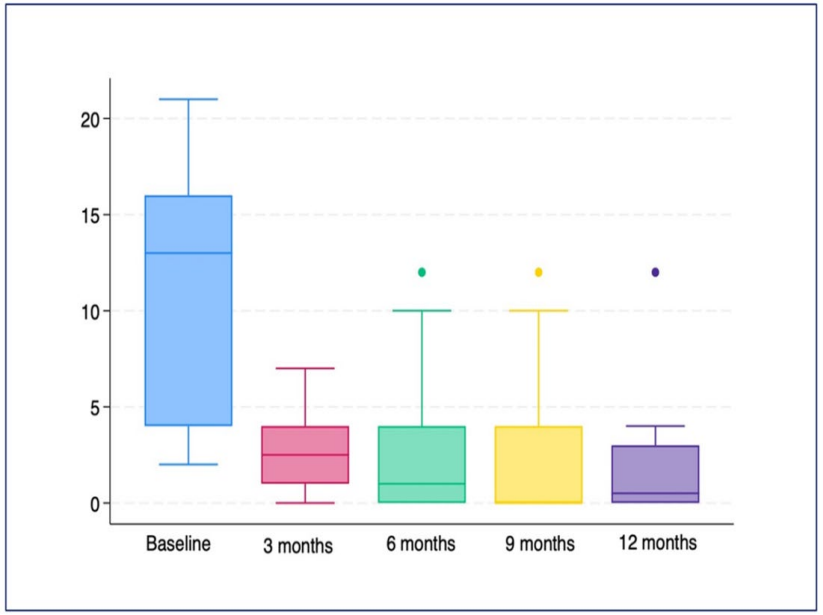
Home › Neurological Sciences › Article

Are anti-calcitonin gene-related peptide monoclonal antibodies effective in treating migraine aura? A pilot prospective observational cohort study

Original Article | Published: 13 December 2023

Volume 45, pages 1655–1660, (2024) Cite this article

Neurological Sciences



A significant decrease in mean monthly aura days was observed throughout the observation period (median baseline: **13**, interquartile range: 4-16; after 12 months: **1**, interquartile range: 0-3, $p < 0.001$).

Braca S, Miele A, Stornaiuolo A, et al. Neurol Sci. 2024 Apr;45(4):1655-1660

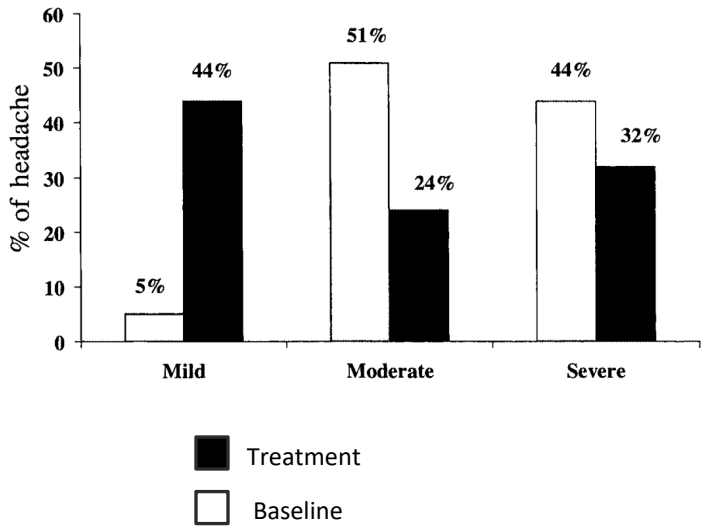
Prevention of migraine during prodrome with naratriptan

R Luciani[1], D Carter[2], L Mannix[3], M Hemphill[4], M Diamond[5] & R Cady[2]

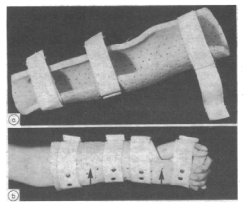
[1]Albuquerque Clinic for Pain, Stress and Health Rehabilitation, Albuquerque, New Mexico, [2]Headache Care Center, Springfield, Missouri, [3]Headache Wellness Center, Greensboro, North Carolina, [4]Georgia Neurological Institute, Savannah, Georgia, [5]Diamond Headache Clinic, Chicago, Illinois, USA

Cephalalgia

Luciani R, Carter D, Mannix L, Hemphill M, Diamond M & Cady R. Prevention of migraine during prodrome with naratriptan. Cephalalgia 2000; 20:122–126. London. ISSN 0333-1024



60% prodromes not followed by headache



A: Elbow splint. B: Left wrist splint with reinforcing plastic strip arrowed.

The cannula puncture site was covered with a small dressing and the drip tubing held in place with the usual Elastoplast strips.

The splints were used by 100 consecutive patients recruited for a trial to investigate infusion thrombophlebitis.[1] They were enthusiastically accepted by the patients and nurses. The absence of an all-embracing bandage permitted easy inspection of the drip site.

Four splints were made for the investigation. No complications attributable to the splint were encountered, and none of the splints wore out. They were cleaned with a cloth moistened with cetrimide.

Comment

Moulded Plastazote splints are a comfortable and cheap alternative to the traditional board in intravenous infusions.

[1] Woodhouse CRJ. Movelat in the prophylaxis of infusion thrombophlebitis. *Br Med J* 1979;i:454-5.

(Accepted 24 December 1981)

North Middlesex Hospital, London N18

C R J WOODHOUSE, MB, FRCS, surgical registrar (present appointment: consultant urologist, Royal Marsden Hospital, London SW3, and senior lecturer, Institute of Urology, London WC2)

Domperidone in the prevention of complete classical migraine

Clinically, migraine is usually associated with a disturbance of various autonomic functions. Objective measurements have suggested that gastric emptying is delayed during migraine attacks.[1 2] Although studies of the autonomic nervous system during the prodromal period have not been performed an autonomic malfunction could possibly precipitate the migraine. Furthermore, since manifold interactions occur within the autonomic nervous system, correcting one defective function could possibly restore the autonomic balance and thus perhaps prevent an attack. In patients with complete migraine physical or psychic changes or both are experienced some 24 hours before an attack.[3] In an open pilot study I found that the attack was prevented when patients were given a high dose (30 mg) of domperidone immediately the warning signals occurred. Domperidone is a peripheral dopamine-receptor antagonist with antiemetic and gastrokinetic properties.[4] The present double-blind study was undertaken to confirm this observation.

Patients, methods, and results

I studied 19 patients with classical migraine, all of whom experienced warning phenomena (primarily sensory or psychic intolerance) which occurred from seven to 48 (median, 24) hours before a severe to incapacitating headache. Each patient was studied during four consecutive (imminent) attacks, two of which were treated prophylactically with domperidone and two with a placebo under double-blind randomised conditions. The patients were given either three 10 mg domperidone tablets or three matching placebo tablets as soon as they became aware of the warning symptoms.

No aura or headache was experienced in 25 out of the 38 (66%) attacks when domperidone was taken and in only two out of the 38 (5%) after the placebo (table). Ten patients, in whom the placebo failed twice to prevent an attack, had no attack on two occasions when treated with domperidone. In all but one patient the attacks were as severe as usual when treated prophylactically with the placebo. The effects of domperidone were not related to either the type of warning symptoms or to the time lag before the actual attack. There were no side effects.

Number of patients with complete classical migraine experiencing attacks after prophylactic treatment with domperidone 30 mg and placebo (n=19)

No of attacks after administration of: Placebo	Domperidone 0	Domperidone 1	Domperidone 2
0	1	0	0
1	0	0	0
2	10	3	5

Statistically significant difference between drug and placebo, $p<0.001$ (Wilcoxon's matched-pairs signed ranks test).

Comment

I know of no investigators who have tried to prevent migraine attacks in patients with early warning phenomena. The present findings show, however, that this can be achieved in most cases with a relatively high dose of domperidone. How domperidone acts in this condition is nevertheless not known. Since it does not cross the blood-brain barrier[4] its effects are unlikely to be mediated by the central nervous system, unless patients with migraine have a defective barrier.[5] As it is a potent dopamine-antagonist domperidone would, however, provoke extrapyramidal symptoms if the blood-brain barrier was defective; no such problems have been reported in patients with migraine. Thus, domperidone probably does not act on the central nervous system, which is often thought to play a part in the pathogenesis of migraine. Whatever the mechanism domperidone, paradoxically, prevents migraine attacks when it is taken up to 48 hours before the attack even though its duration of action is about six hours. Thus, thorough investigation of patients with complete migraine during the day before an attack should give more information on the pathogenesis of the disease.

[1] Volans GN. The effect of metoclopramide on the absorption of effervescent aspirin in migraine. *Br J Clin Pharmacol* 1975;2:57-63.
[2] Wilkinson M. The treatment of acute migraine attacks. *Headache* 1976; 15:291-2.
[3] Blau JN. Migraine prodromes separated from the aura: complete migraine. *Br Med J* 1980;281:658-60.
[4] Van Nueten JM, Schuurkes JAJ. Animal pharmacology of domperidone, anti-emetic and gastrokinetic properties. In: Towse G, ed. *Progress with domperidone, a gastrokinetic and anti-emetic agent*. London: Royal Society of Medicine, 1981:21-7.
[5] Harper AM, McCulloch J, MacKenzie ET, Pickard JD. Migraine and the blood-brain barrier. *Lancet* 1977;i:1034-6.

(Accepted 23 December 1981)

Populierenlaan 1, B-3620 Lanaken, Belgium

J WAELKENS, MD, general practitioner

66% prodromes not followed by headache after domperidone 30mg compared to 5% placebo

20, 30, 40mg prevented 30%, 58%, and 63% of headaches in another study of domperidone

Cephalalgia 1984; 4:85–90.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Original Article

Cephalalgia
An International Journal of Headache
International Headache Society

The migraine postdrome: Spontaneous and triggered phenotypes

Nazia Karsan[1,2], Abigail Peréz-Rodríguez[1,2,3], Karthik Nagaraj[1,2,4], Pyari R Bose[1,2,5] and Peter J Goadsby[1,2]

Cephalalgia
0(0) 1–10

DOI: 10.1177/0333102420975401
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The prodrome and postdrome represents a symptom continuum

- Phenotype of the postdrome less heterogeneous than the prodromal phase, but there is a similarity in brain systems involved (arousal, cognition and homeostasis)
- Phenotype of prodrome and postdrome is similar within individuals, suggesting that **prodromal symptoms** begin prior to headache and perhaps **persist throughout pain and postdrome** as a symptom continuum.

Interictal Phase

- Interictal period associated with a range of disease-related symptoms including cutaneous allodynia, cognitive impairment, photophobia, depression, anxiety, anxiety or anticipatory anxiety, and decreased health-related quality of life.
- Interictal burden may also disrupt education, career/work, relationships, social life, and family life.
- Eurolight[2] project indicated 26% of people with migraine have interictal symptoms; including anxiety, avoidance behavior, non-headache symptoms, social isolation, and cumulative burden attributed to hampered education, career, and family life.
- About 15% of patients with migraine reported interictal anxiety and avoidance behaviors (compromise of daily-life).
- **Most studies have looked at hardship or burden, but not a rigorous characterization of the symptoms patients may experience that are related to migraine**

1. Vinent et al. Front. Neurol. 13:1032103
2. Lampl et al. The Journal of Headache and Pain (2016) 17:9

Assessing and Managing All Aspects of Migraine: Migraine Attacks, Migraine-Related Functional Impairment, Common Comorbidities, and Quality of Life

DAWN C. BUSE, PHD; MARCIA F. T. RUPNOW, PHD; AND RICHARD B. LIPTON, MD

Please answer each of the following statements about the effect of your headaches in the past 4 weeks on days when you are not having an attack. **(X one box for each statement)**

Between headache attacks or at times when I do not have a headache

	Don't know/NA	Never	Rarely	Some of the time	Much of the time	Most or all of the time
1. My headaches affect my work or school at times when I do not have a headache	☐	☐	☐	☐	☐	☐
2. I worry about planning social or leisure activities because I might have a headache	☐	☐	☐	☐	☐	☐
3. My headaches impact my life at times when I do not have a headache	☐	☐	☐	☐	☐	☐
4. At times when I do not have a headache, I feel helpless because of my headaches	☐	☐	☐	☐	☐	☐
Total number of checks in column						
Multiply number of checks by value = total score per column	×0	×0	×1	×2	×3	×3
Total score per column						
Total score		+	+	+	+	+ =

MIBS-4 scoring key

Score	Level of interictal burden	Treatment recommendations
0	None	• No action needed
1-2	Mild	• Offer non-pharmacological strategies for reducing interictal burden • Offer/optimize acute pharmacological treatment
3-4	Moderate	• Offer non-pharmacological strategies for reducing interictal burden • Offer/optimize acute pharmacological treatment • Consider preventive pharmacological treatment
5+	Severe	• Offer non-pharmacological strategies for reducing interictal burden • Offer/optimize acute pharmacological treatment • Offer preventive pharmacological treatment

Hubig *et al. The Journal of Headache and Pain* (2022) 23:97
https://doi.org/10.1186/s10194-022-01467-z

The Journal of Headache and Pain

RESEARCH Open Access

Measuring interictal burden among people affected by migraine: a descriptive survey study

Lena T. Hubig[1*], Timothy Smith[2], Emma Williams[1], Lauren Powell[3], Karissa Johnston[3], Linda Harris[4], Gilbert L'Italien[4], Vladimir Coric[4], Andrew J. Lloyd[1] and Siu Hing Lo[1]

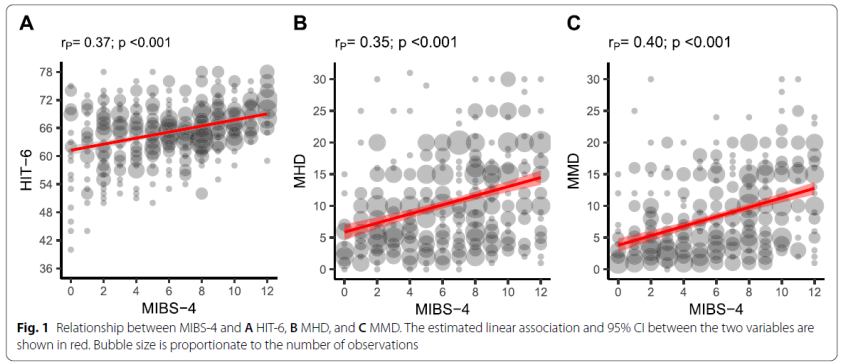

Fig. 1 Relationship between MIBS-4 and **A** HIT-6, **B** MHD, and **C** MMD. The estimated linear association and 95% CI between the two variables are shown in red. Bubble size is proportionate to the number of observations

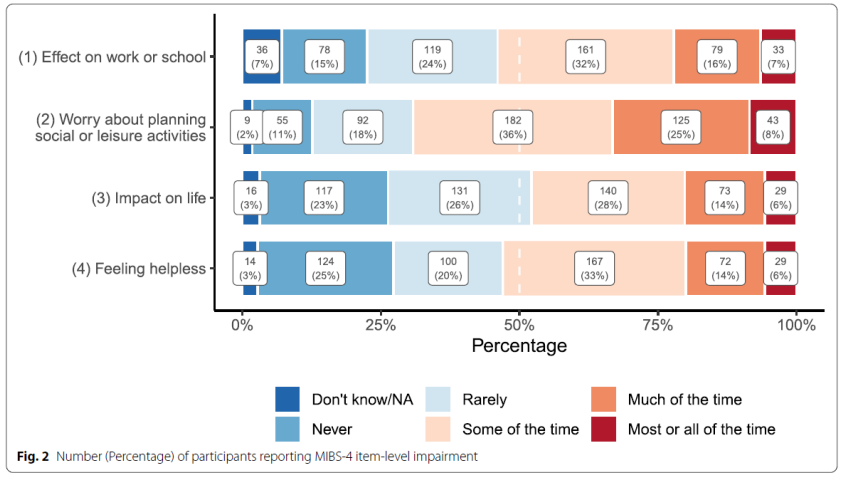

Fig. 2 Number (Percentage) of participants reporting MIBS-4 item-level impairment

- Severe interictal burden category (67%)
- Only 4% had no interictal burden
- Interictal burden associated with migraine frequency, impact, depression, and CGRP mAb experience.

Original Article

Cephalalgia
An International Journal of Headache
International Headache Society

Physical impairment during and between migraine attacks: A daily diary study of patients with chronic migraine

Cephalalgia
2024, Vol. 44(4) 1–10

DOI: 10.1177/03331024241249747
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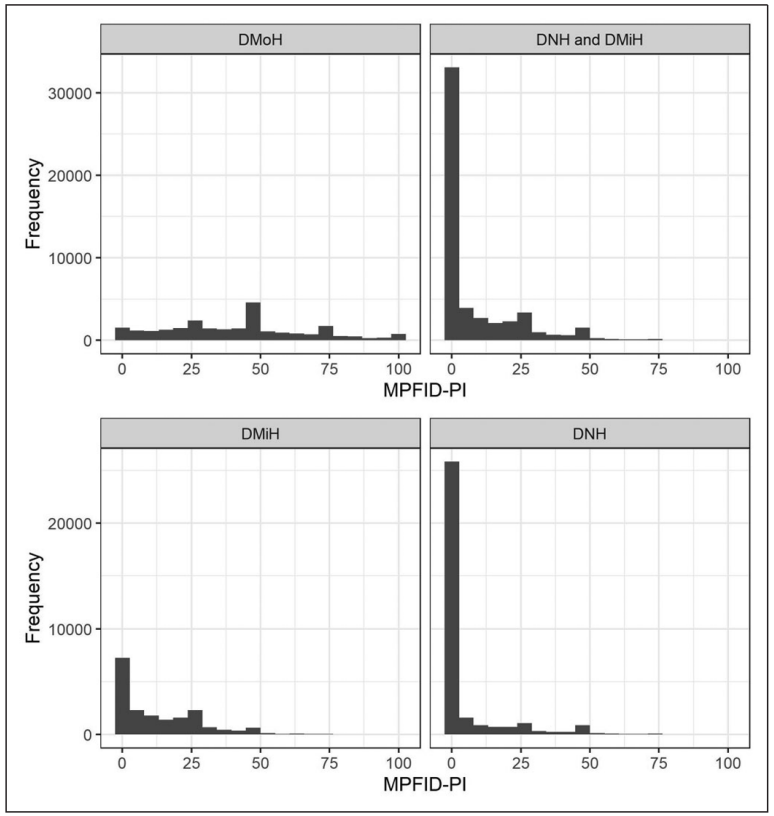
David J Whitaker[1], Gina M Dumkrieger[1], Joseph G Hentz[2], David W Dodick[1,3] and Todd J Schwedt[1]



Key findings

- People living with chronic migraine experience physical impairment on days with headache and days without headache.
- Physical impairment on days with mild or no headache is associated with days since last moderate to severe headache, physical impairment on the last day with moderate to severe headache, currently having a mild headache (rather than no headache), depression, hypersensitivities, and cranial autonomic symptoms.

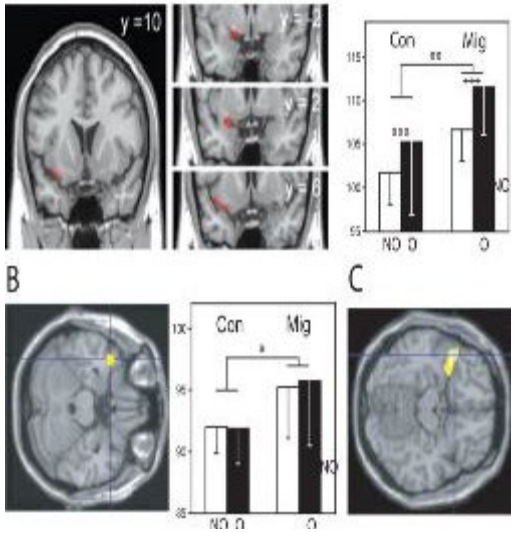
Migraine: disorder of sensory processing

Increased activation anterior TP which also exhibited increased functional connectivity in structures related to pain processing in interictal migraine patients relative to controls. (Temporal pole (TP): associative multisensory area that processes visual, odor, and auditory information In interictal migraine patients)

Further increased activation in fMRI BOLD signal in the TP during the ictal period.

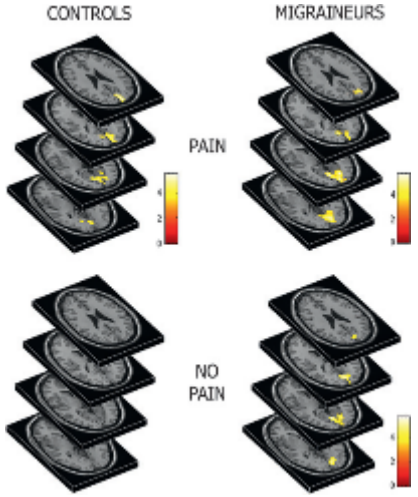
Accounts for interictal symptoms, sensory stimuli as trigger due to functional connectivity to pain processing areas, and why sensory hypersensitivity increases during attacks.

Olfaction



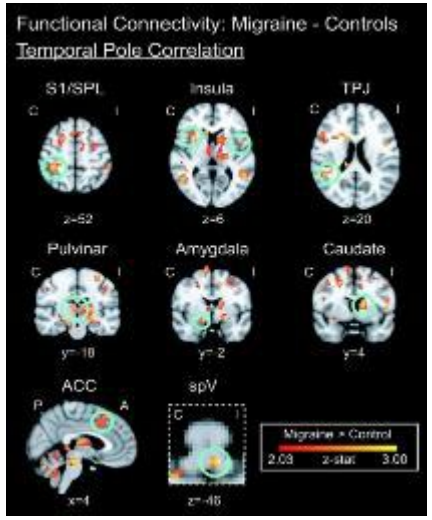
Demarquay, et al. Cephalalgia 2008

Light



Boulloche N, et al. JNNP 2010;81:978e984.

Pain

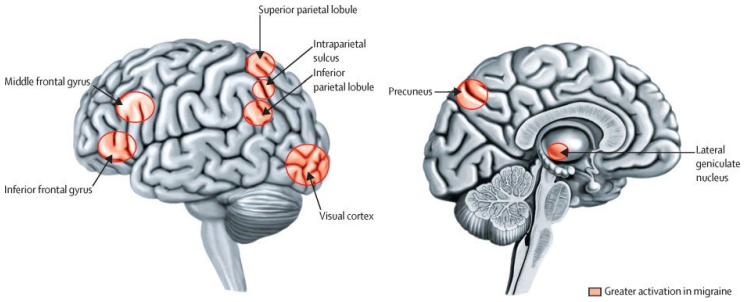


Moulton, et al. Cerebral Cortex 2011

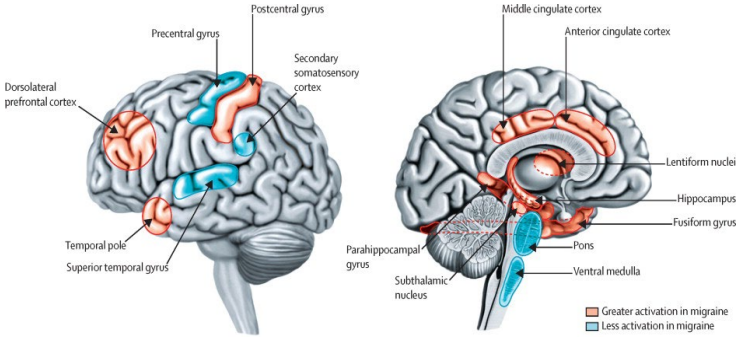
Atypical Activation Patterns in the Migraine Brain

Functional MRI of migraine

Todd J Schwedt, Chia-Chun Chiang, Catherine D Chong, David W Dodick



Visual stimuli-induced brain activations that differ in migraineurs versus controls



Pain-induced brain activations that differ in migraineurs versus controls

- atypical brain responses to sensory stimuli
- absence of the normal habituating response between attacks
- atypical functional connectivity of sensory processing regions.

Lancet Neurol 2015;14:81-91

ARTICLE OPEN ACCESS CLASS OF EVIDENCE

Fremanezumab for preventive treatment of migraine

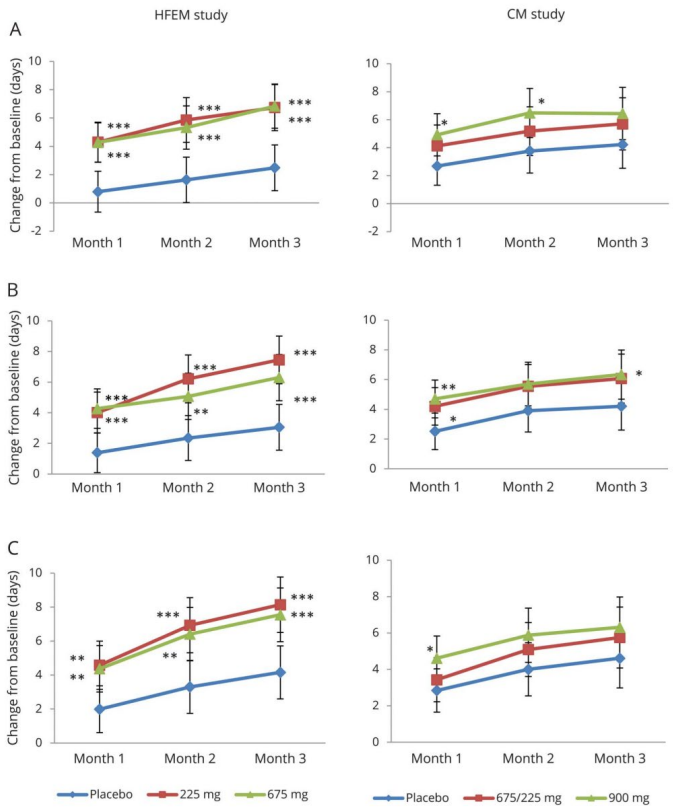
Functional status on headache-free days

Juliana VanderPluym, MD, David W. Dodick, MD, Richard B. Lipton, MD, Yuju Ma, MA, Pippa S. Loupe, PhD, and Marcelo E. Bigal, MD

Correspondence
Dr. VanderPluym
VanderPluym.Juliana@mayo.edu

Neurology® 2018;91:e1152-e1165. doi:10.1212/01.wnl.0000544321.19316.40

Figure 2 Patient responses to questions on having difficulty in concentration and mental fatigue



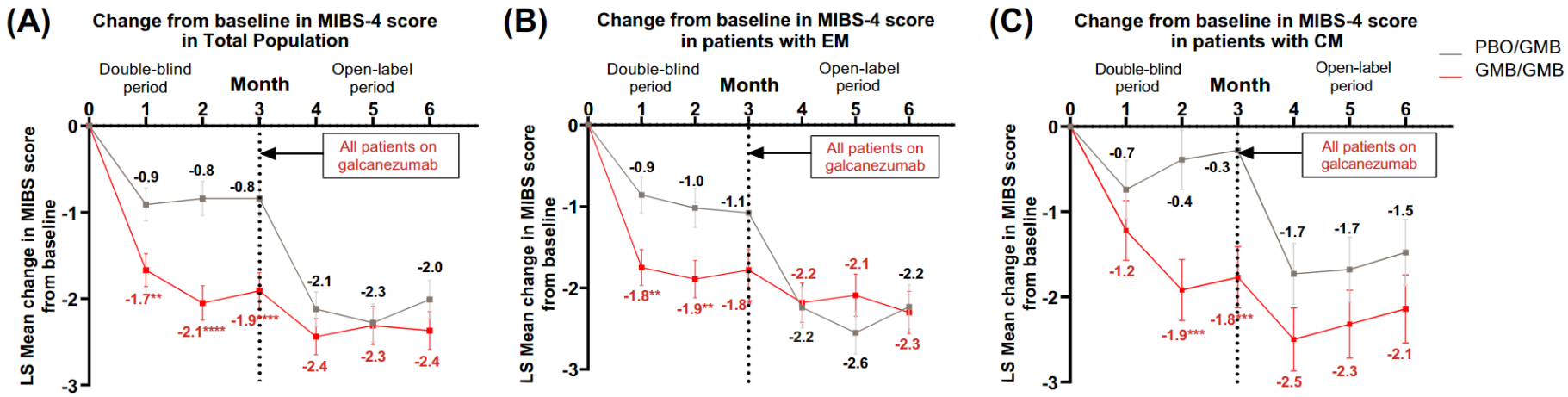
- Fremanezumab increased number of headache-free days with normal function in work/school/household chore performance and concentration/mental fatigue measures compared to placebo and compared to their baseline over the entire treatment period (all $p < 0.005$).
- An increased number of headache-free days with normal functional performance for some measures was also found in the CM group in those treated with fremanezumab.

Received: 21 March 2022 | Accepted: 4 August 2022
DOI: 10.1111/head.14460

RESEARCH SUBMISSIONS

Changes in migraine interictal burden following treatment with galcanezumab: Results from a phase III randomized, placebo-controlled study

Richard B. Lipton MD[1] | Dawn C. Buse PhD[1] | Claire H. Sandoe MD, MSc[2] | Janet H. Ford PhD[3] | Austin L. Hand PhD[4] | Jakub P. Jedynak PhD[3] | Martha D. Port PhD[3] | Holland C. Detke PhD[3]



The percentage of patients with severe interictal burden decreased substantially for the galcanezumab-treated patients, from 59% at baseline to 27% at Month 6 (EM from 51% to 23%; CM from 71% to 33%).

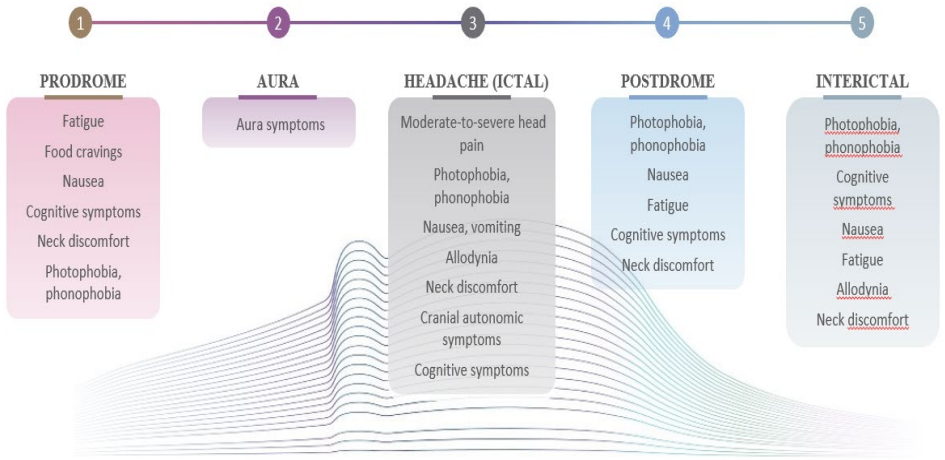
Migraine: A polygenic trait disorder of sensory processing with enduring symptoms and discrete exacerbations

Prodrome and Interictal Phase

Unique biology

New targets for treatment

New outcome measures



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