HEADACHE

Neurologist Ville Artto, MD, PhD
Department of Neurology
Helsinki University Central Hospital
16.4.2019

- Secondary or Primary Headache
- Migraine
- Tension Type Headache
- Cluster Headache

Headache patient

- Common – 0.4-3.6% of all patients in ER
- Emotional – Do I have a brain tumor?
- Benign (usually) – But it is important to recognize those who might have severe illness behind their headache symptoms

- Almost everybody suffers headaches at least sometimes (70-95%)
- Common cause to visit GP or other doctors
- Most common in young adults
- Major economic consequences:

Not only is headache painful, but it is also disabling. In the Global Burden of Disease Study, updated in 2013, migraine on its own was found to be the sixth highest cause worldwide of years lost due to disability (YLD). Headache disorders collectively were third highest.

In the United Kingdom, for example, some 25 millio
or school-days are lost every year because of migraine alone

World Health Organization

Main Menu

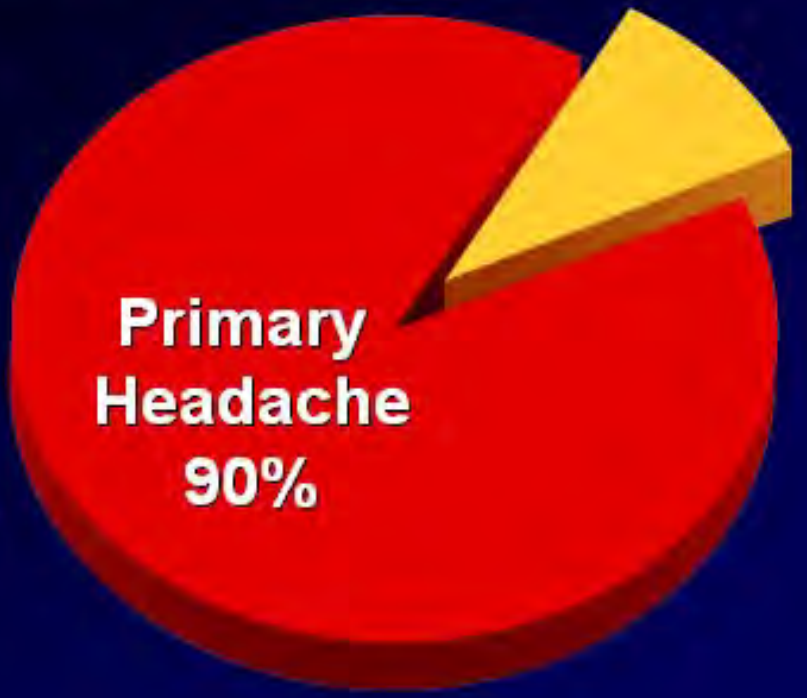
Headache Classification and Diagnosis

Primary Headaches

- Migraine
- Tension-type
- Cluster headache

Secondary Headaches

- Tumor
- Meningitis
- Giant cell arteritis



Adapted from Headache Classification Committee of the IHS. *Cephalalgia*. 1988

Secundary causes of headache

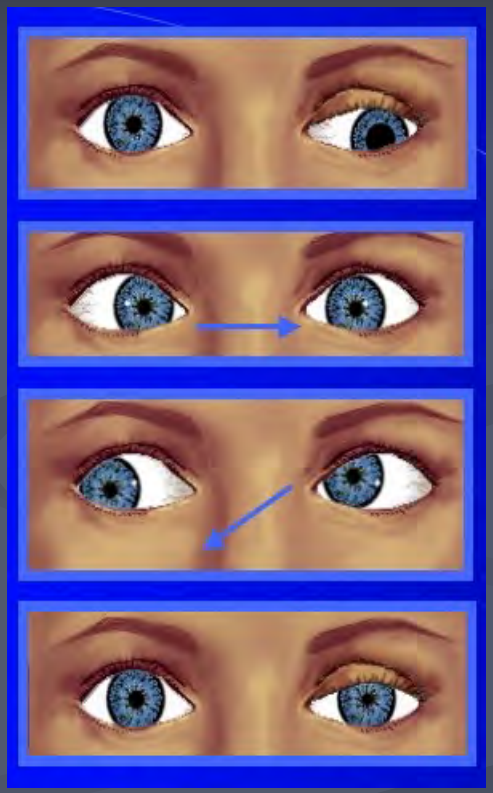
- Subarachnoid Haemorrhage (SAH)
- Sinusthrombosis
- Expansion or thrombosis of aneurysm
- Pituitary apoplexy
- Dissection (cervical or cerebral)
- Hypertensive crisis
- PRES
- Sympatomimetic-induced vasospasm
- Vasculitis
- Vasoconstrictive angiopathies
- SIH
- Meningoencephalitis
- Sphenoid sinusitis
- etc.

History

- Are the features of the headache novel?
- Or has the headache features changed recently?
- Diagnostic evaluations before?
- What kind of medications for headache normally?
- What kind of medications for headache this time and how much?
- Other health problems and medications?

Clinical examination

- General condition
- Body temperature, blood pressure, heart rate
- Signs of a trauma
- Menignism
- Neuro-oftalmological examination
- General neurological examination



red flags

American Headache Society
Headache Curriculum

Worrisome Headache Red Flags—"SNOOP"

- **S**YSTEMIC SYMPTOMS (fever, weight loss) or SECONDARY RISK FACTORS (HIV, systemic cancer)
- **N**EUROLOGIC SYMPTOMS or abnormal signs (confusion, impaired alertness or consciousness)
- **O**NSET: sudden, abrupt, or split-second
- **O**LDER: new onset and progressive headache, especially in middle age >50 yr (giant cell arteritis)
- **P**REVIOUS HEADACHE HISTORY: first headache or different (change in attack frequency, severity, or clinical features)

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- Migraine

1. Epidemiology
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3. Pathaphysiology
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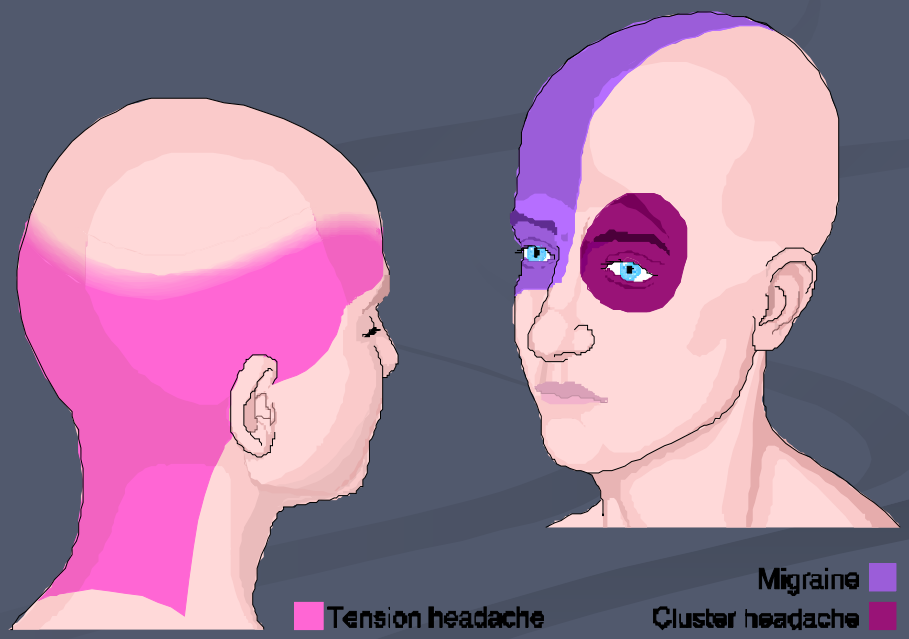
- Cluster headache



Migraine epidemiology

- Prevalence of migraine
1. 18% in women
2. 6% in men
3. 4% in children
- Migraine with aura (MA)
- Migraine without aura (MO)
- Familial (FHM) and sporadic hemiplegic migraine (SHM) 0.01%

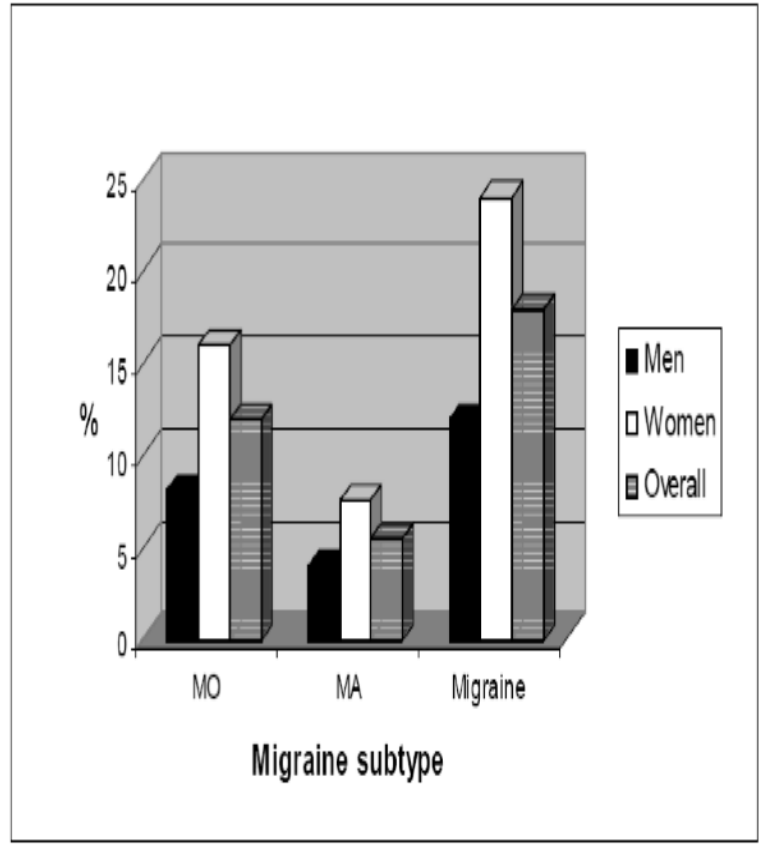
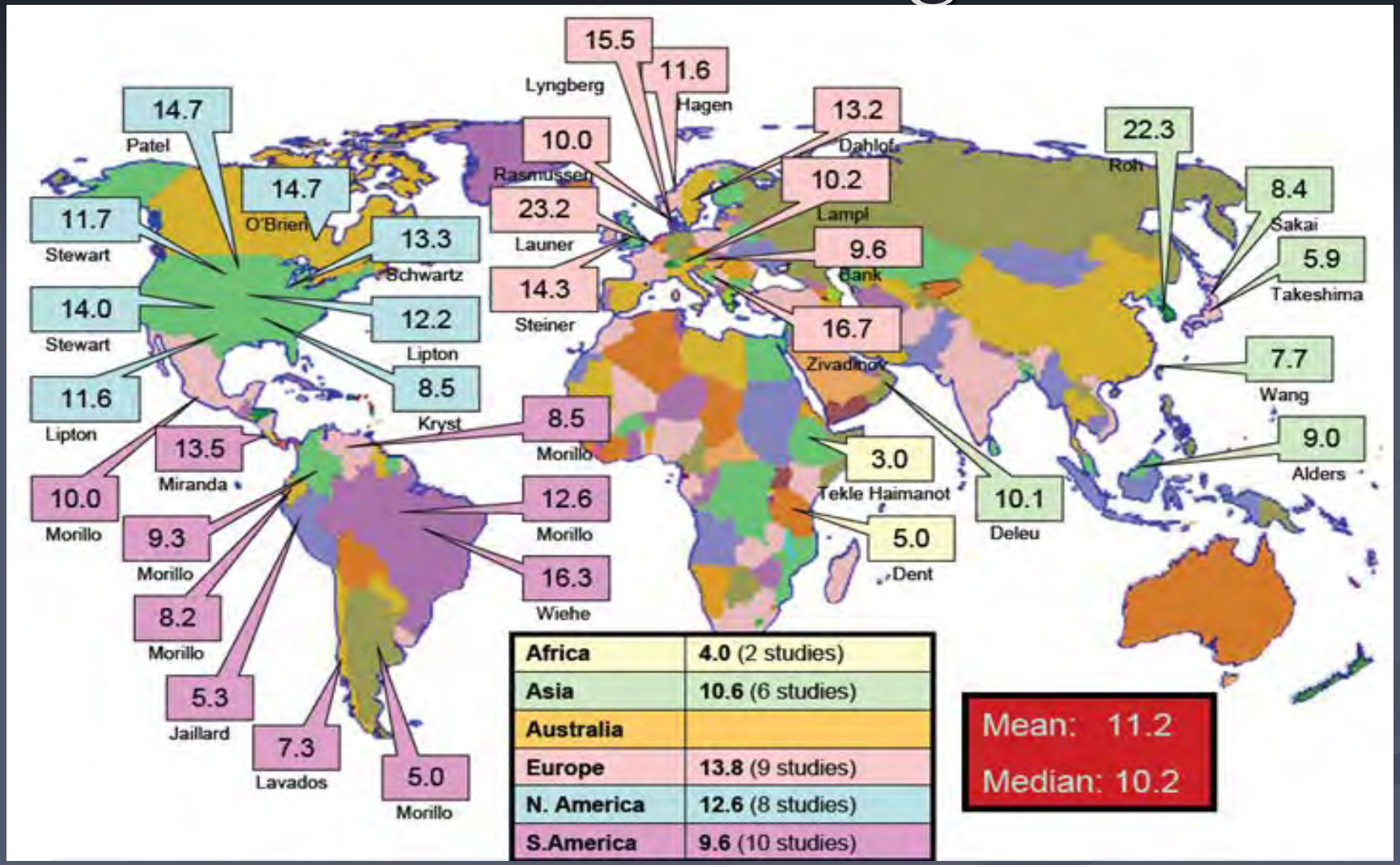


Figure 1. Lifetime prevalences of migraine with and without aura (Russell *et al.* 1995a).

Prevalence of Migraine



Common Disease

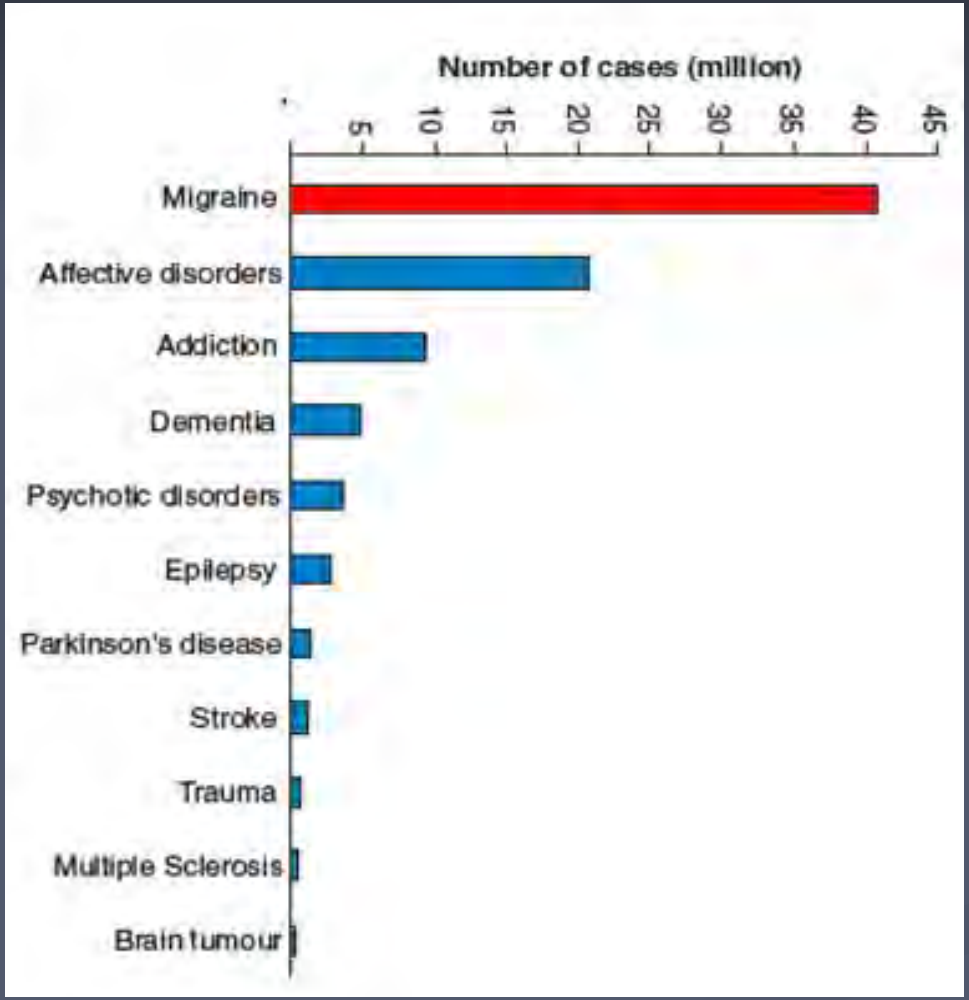
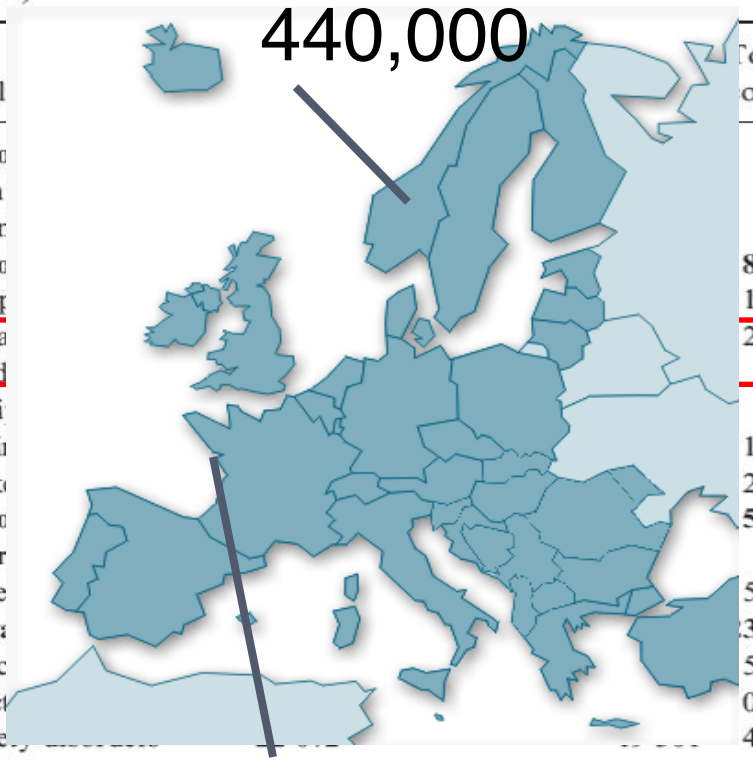


Table 8 Cost of brain disorders in Europe by disease area (€PPP million)

€ mill			Total cost
Neuro			7523
Brain			4586
Traur			2937
Neuro			**83 934**
Epilep			15 546
Migra			27 002
head			
Multi			8769
Parki			10 722
Stroke			21 895
Neuro			**55 176**
disor			
Deme			55 176
Menta			**39 542**
Addic			57 274
Affect			05 666
Anxie			41 373
Psychotic disorders	29 855	5374	35 229
All brain disorders			386 175



Important migraine comorbidities

- episodic neurological disorders - epilepsy
- vascular disorders - ischemic stroke, patent foramen ovale
- neuropsychiatric disorders – depression, anxiety

Famous Migraneurs

Julius Caesar
Saint Paul
John Calvin
Queen Mary Tudor
Blaise Pascal
Carolus Linnaeus
Lewis Carroll
Thomas Jefferson
Friedrich Nietzsche
Immanuel Kant
Edgar Allan Poe

Frédéric Chopin
Charles Darwin
Karl Marx
Ulysses S. Grant
Peter Tchaikovsky
Alfred Nobel
Leo Tolstoy
Sigmund Freud
Virginia Woolf
Princess Margaret
Ben Zyskowicz

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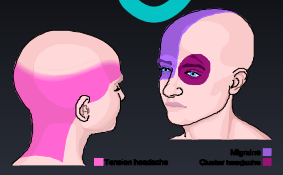
Prodromal symptoms

Yawning, graving for food, tiredness, irritability, etc



Vascular headache

Moderate or severe, unilateral, pulsating, made worse by physical activity, associated with nausea, vomiting, sensitivity to light and sound

Neurological aura symptoms

Visual, sensory, speech disturbance, hemiparetic, vertigo

Postdromal symptoms

“Hangover”, tiredness, lethargy, burst of energy

VISUAL AURA

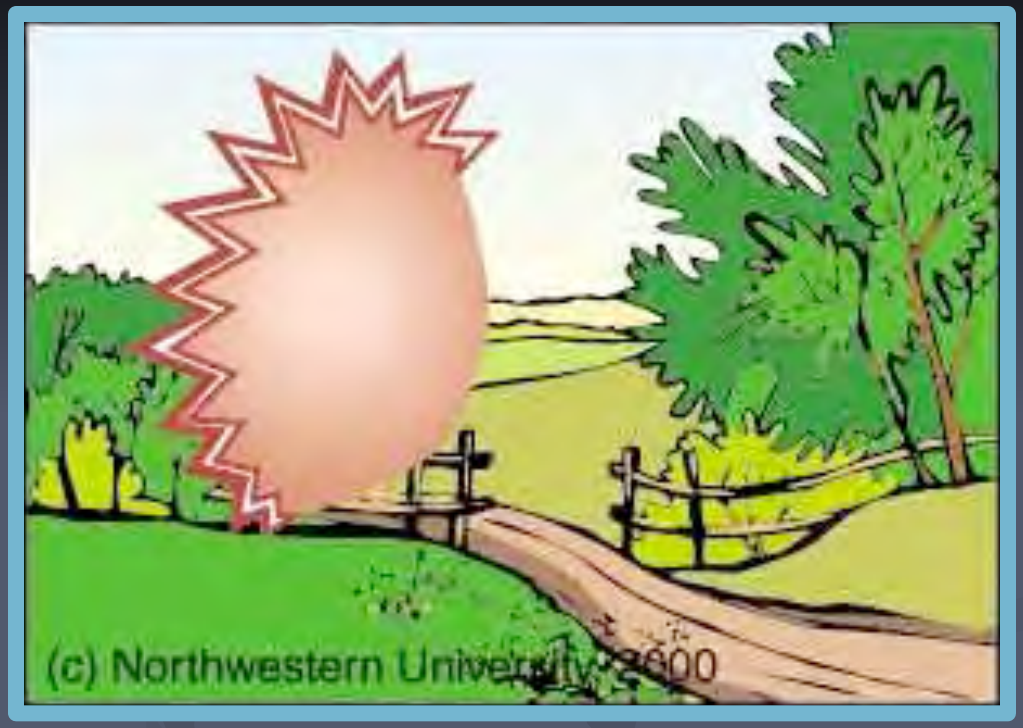

SCOTOMA
MIGRAINES CAUSE LOSS
OF VI
CENTE
WHICH IN ROVES AS THE
SCINTILLATING SCOTOMA
MOVES TO THE SIDE

selves through the usual round of work and play, a degree
ness and a desire for rest are characteristic
mi[illegible]. A vascular h[illegible] exquisitely use[illegible]
head r[illegible] itself enforce[illegible] ally, bu[illegible]
only, or even the chief, mec[illegible]sm at work. M[illegible]
during an attack and exhibit diminished tone of skeletal
[illegible] are dejected and [illegible]
drowsy.

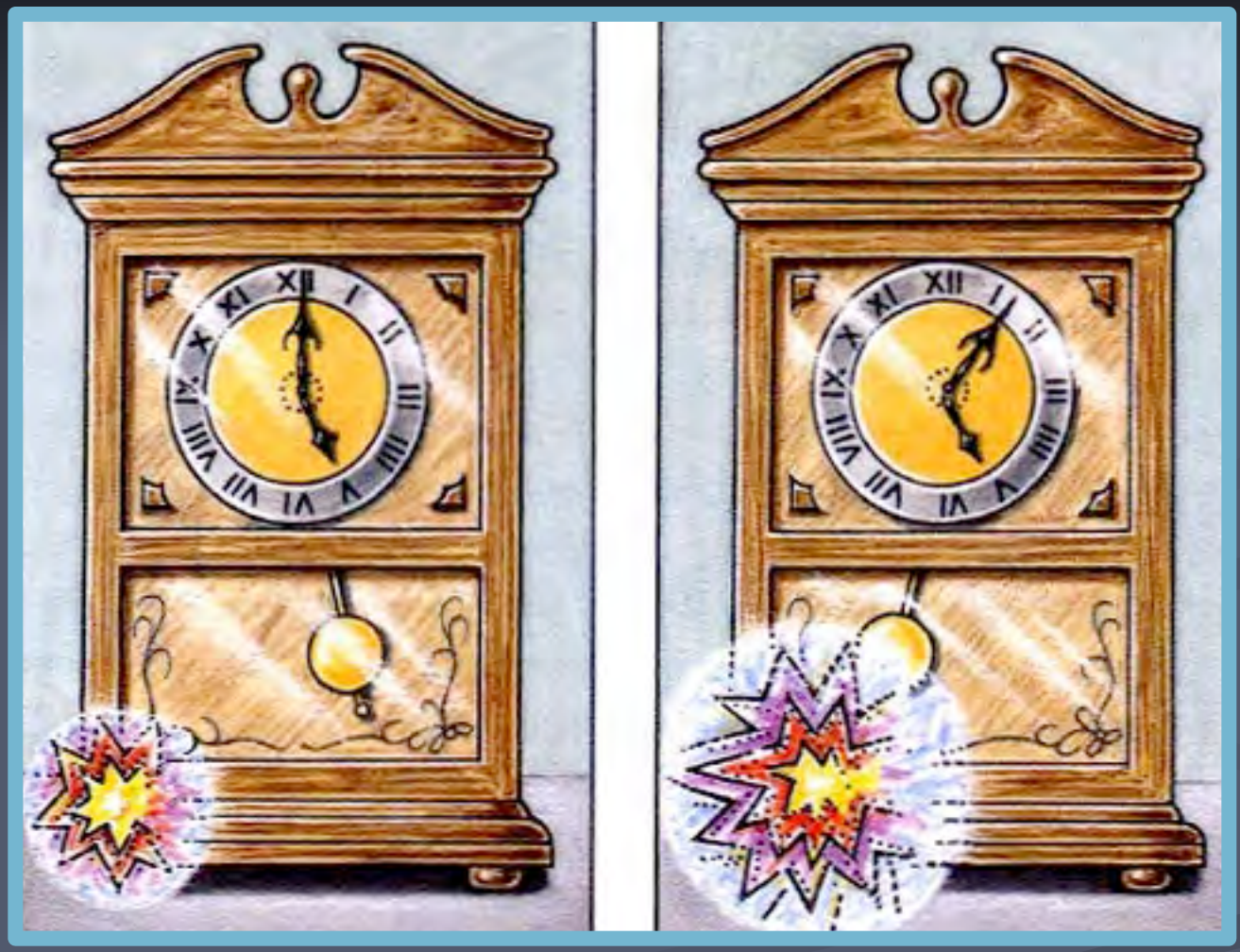
The relation of sle[illegible] plex an[illegible]
one, and we will h[illegible] touch upon it in many
contexts: the in[illegible]oye and stupor in the acutest
migraine (migr[illegible] classical migraine), the tend
migraines o[illegible] occur during sleep, and their
relation to [illegible] state. At this point we
attention to t[illegible] ship: the oc
of intense dr[illegible] a common
the occasional ab[illegible] sleep of unusua
and the typical prefaced [illegible] which many attacks
natural termination.

Nowhere in the literature can we find more vivid and
descriptions of migrainous stupor than in Liveing's monogr

Zig-zag patterns generated during a migraine headache



http://www.tchain.com/otoneurology/disorders/central/migraine/mav.html



http://www.familydoctor.co.uk/htdocs/MIGRAINE/MIGRAINE_specimen.html

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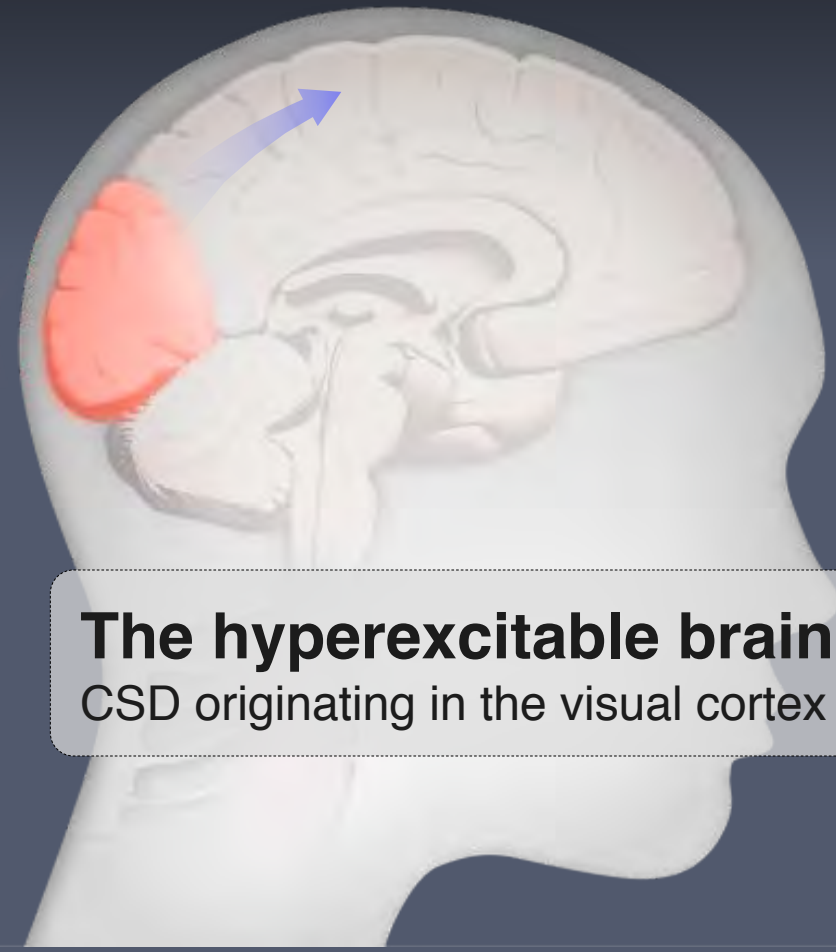
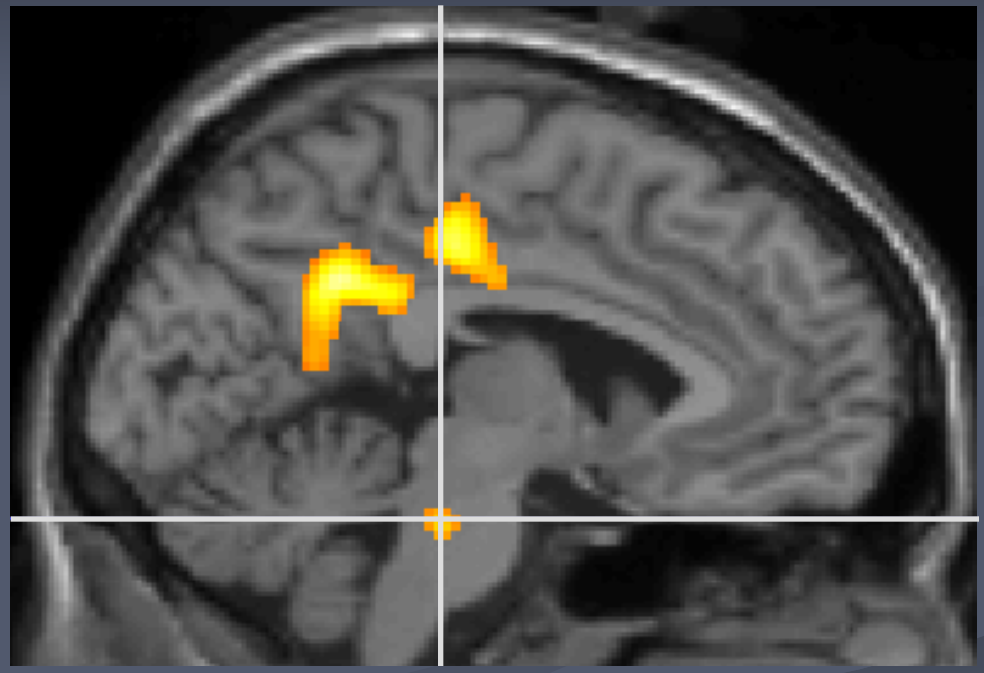
The Primary Cause of the Migraine Headache Lies in the Brain



The hyperexcitable brain?
CSD originating in the visual cortex

Both?

The dysmodulated brain?
Activation in the dorsal pons

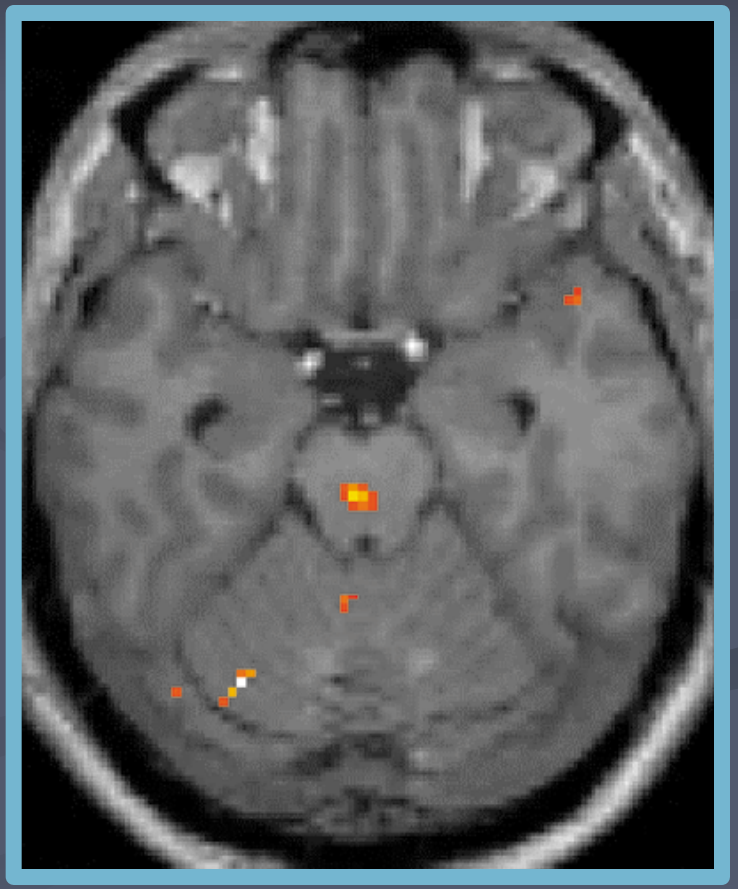


Brainstem activation specific to migraine headache

A Bahra, M S Matharu, C Buchel, R S J Frackowiak, P J Goadsby

The Lancet, Volume 357, Number 9261 31 March 2001

Brainstem activation during acute migraine

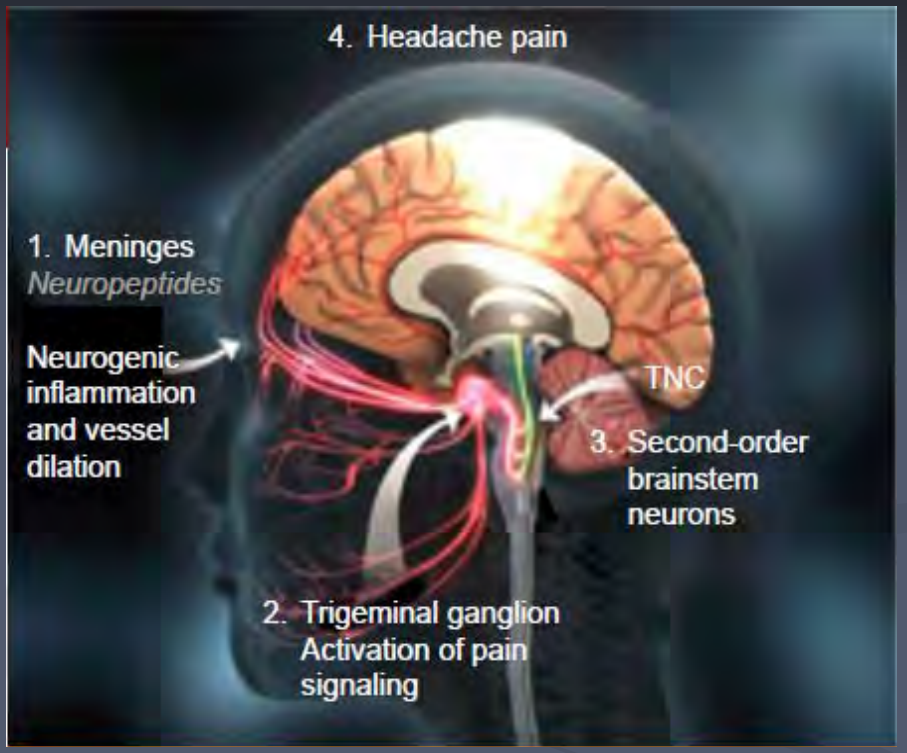


fMRI = functional Magnetic Resonance Imaging

Migraine and trigeminovascular system

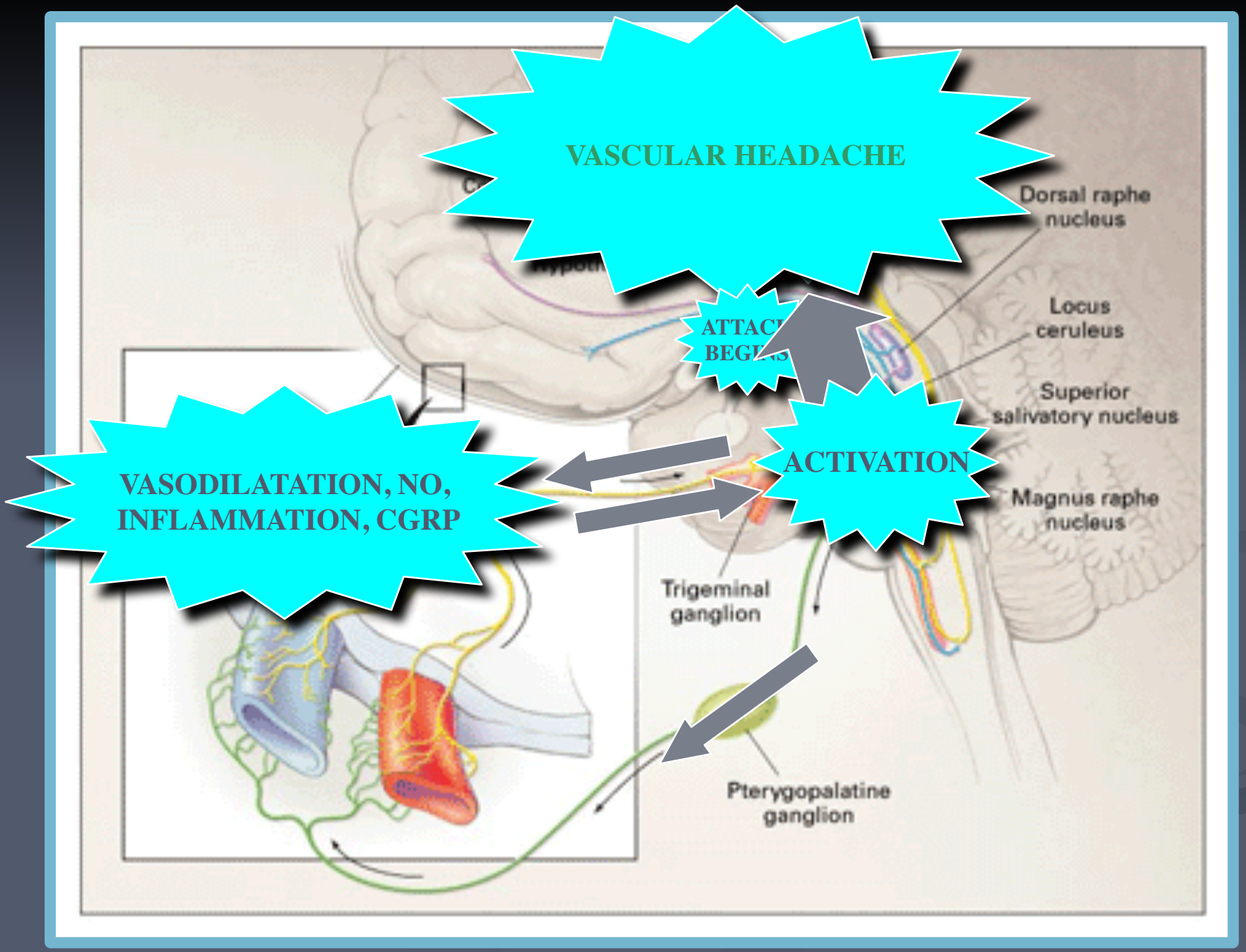
Pathophysiology includes:

Trigeminal-vascular activation
- Peripheral vasodilation and neurogenic inflammation
- Peripheral afferent signals to trigeminal ganglion
- CNS pain signals relay to higher order structures (i.e. TNC and cortex)



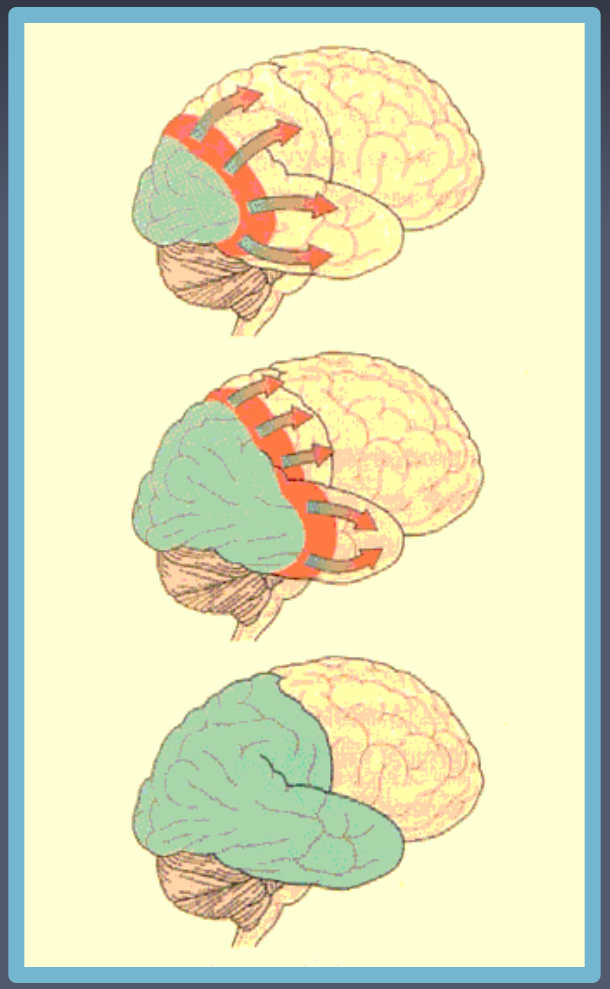
The key pathway for pain in migraine
Trigeminovascular input from meningeal vessels is relayed to second-order neurons in the brainstem via the trigeminal ganglion. This input to the brainstem is then relayed to the sensory cortex

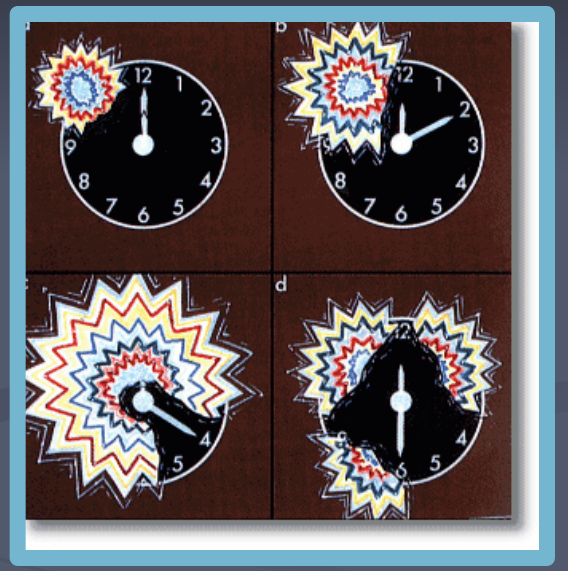
CGRP, calcitonin gene-related peptide; CNS, central nervous system; TNC, trigeminal nucleus caudalis. Russo AF. *Annu Rev Pharmacol Toxicol*. 2015;55:533-552; Bigal ME, et al. *Arq Neuropsiquiatr*. 2009;67(2-B):559-569.

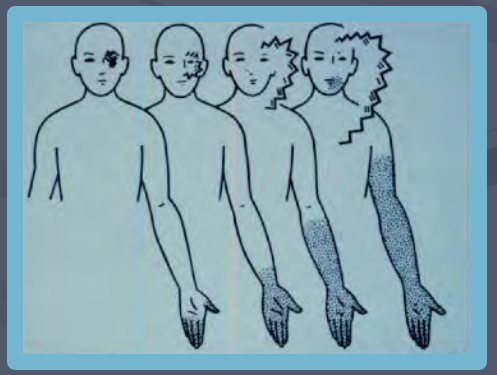

VASCULAR HEADACHE
Dorsal raphe nucleus
Locus ceruleus
Superior salivatory nucleus
Magnus raphe nucleus
ACTIVATION
VASODILATATION, NO, INFLAMMATION, CGRP
Trigeminal ganglion
Pterygopalatine ganglion

Aura

”Cortical spreading depression”

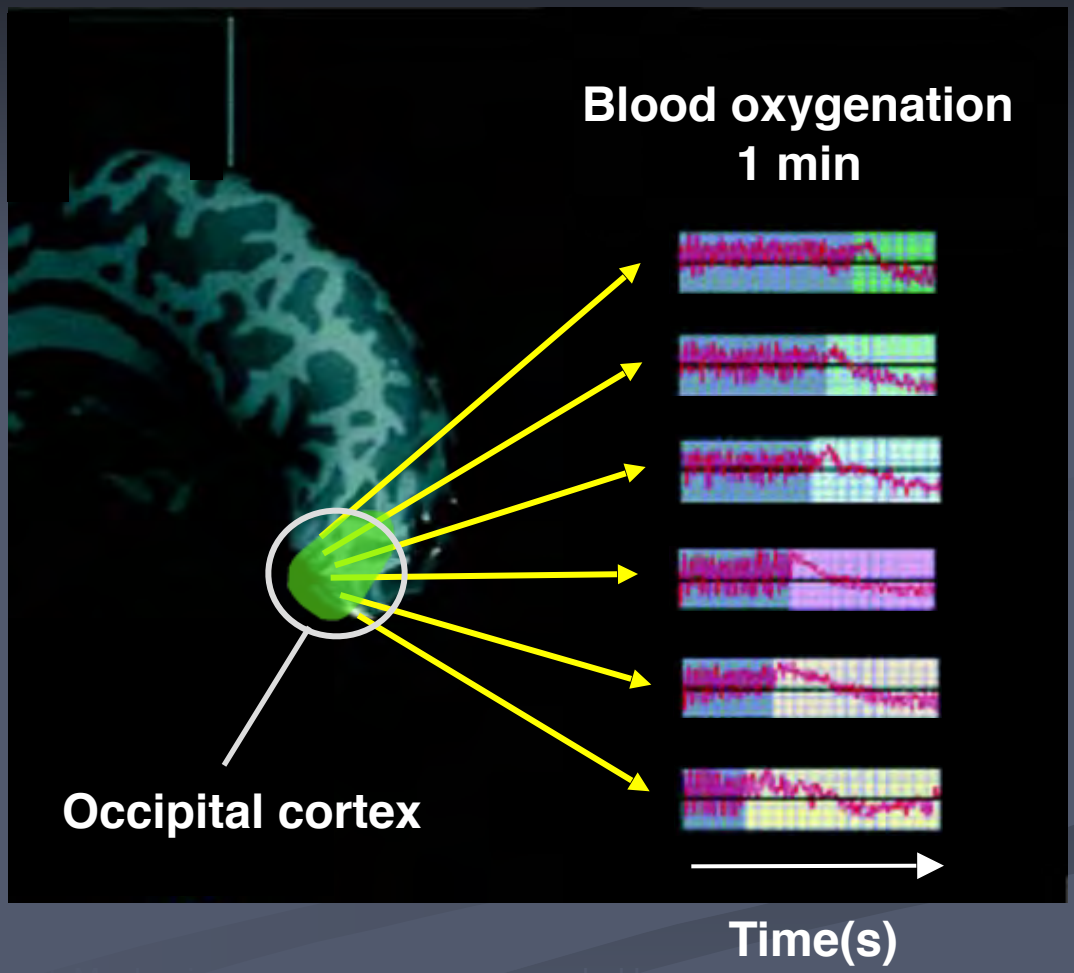






Cortical Spreading Depression

- Wave of intense cortical neuron activity
  - ↑ rCBF
- Followed by neuronal suppression
  - ↓ rCBF
  - Often coincides with headache onset
- Velocity: 2-3 mm/min
- Possibly underlies visual aura
- Occurs in clinically silent areas of the cortex?
  - Migraine without aura



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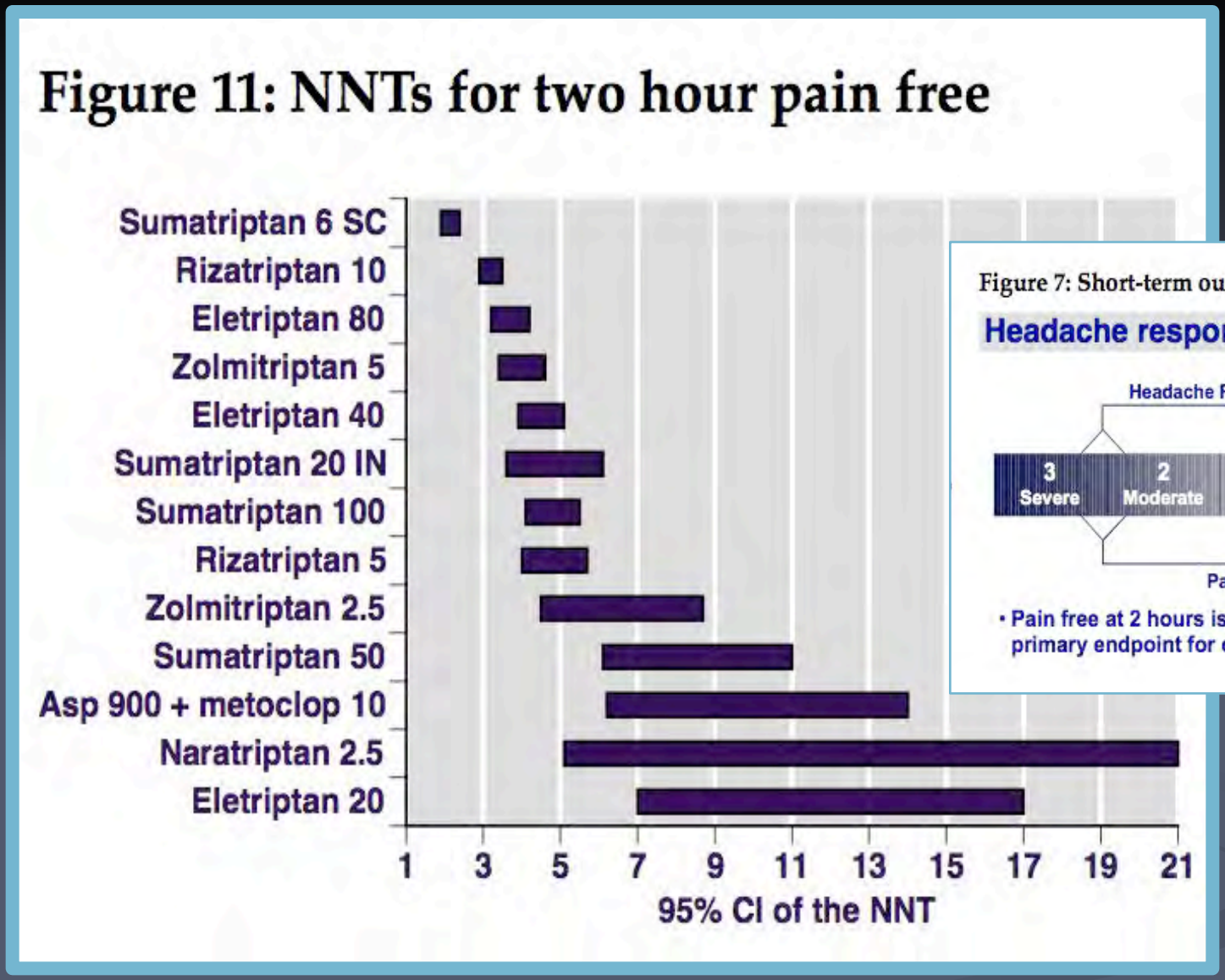
Treatment of migraine

- avoidance of triggering factors (alcohol, lack of sleep, stress etc.)
- acute medications (NSAIDs, triptans, anti-emetics etc.)
- preventive medications (antihypertensives, tricyclic antidepressants, antiepileptics etc.)
- non-pharmaceutical treatments (acupuncture etc.)
- CGRP antibodies



Bandolier: Evidence-based health care, January 2002
www.ebandolier.com

Combinations

- Antiemetics such as metoclopramide releave nausea but also help absorption of other acute medications
- Sumatriptan + Metoclopramide is more efficient than Sumatriptan alone

Table 3. Summary of 2- and 4-Hour Efficacy Data

	Participants, No. (%)				*P* Value	
	Sumatriptan–Naproxen Sodium	Sumatriptan	Naproxen Sodium	Placebo	Sumatriptan–Naproxen Sodium vs Placebo	Sumatriptan–Naproxen Sodium vs Sumatriptan
Efficacy population, No.						
Study 1	364	361	356	360		
Study 2	362	362	364	362		
Pain free at 2 h						
Study 1	125 (34)	90 (25)	53 (15)	33 (9)	<.001	.009*
Study 2	107 (30)	82 (23)	57 (16)	37 (10)	<.001	.02*
Headache relief at 2 h						
Study 1	237 (65)	200 (55)	157 (44)	102 (28)	<.001	.009
Study 2	207 (57)	182 (50)	156 (43)	103 (29)	<.001	.03
Headache relief at 2 h						
Study 1						
Moderate	170 (75)	148 (64)	109 (48)	73 (32)	<.001*	.02*
Severe	67 (49)	52 (40)	48 (38)	29 (22)	<.001*	.18*
Study 2						
Moderate	139 (66)	127 (58)	110 (52)	74 (32)	<.001*	.05*
Severe	68 (45)	55 (38)	48 (32)	35 (23)	<.001*	.20*
Absence of nausea at 2 h						
Study 1	260 (71)	238 (66)	248 (70)	233 (65)	.007	.07
Study 2	237 (65)	233 (64)	249 (68)	244 (64)	.71	.56
Absence of photophobia at 2 h						
Study 1	211 (58)	173 (48)	166 (47)	131 (36)	<.001	.007
Study 2	180 (50)	166 (46)	148 (41)	122 (32)	<.001	.22
Absence of phonophobia at 2 h						
Study 1	223 (61)	180 (50)	181 (51)	138 (38)	<.001	.002
Study 2	204 (56)	188 (52)	159 (44)	126 (34)	<.001	.14
Headache relief at 4 h						
Study 1	285 (78)	240 (66)	195 (55)	133 (37)	<.001	<.001
Study 2	259 (72)	222 (61)	195 (54)	141 (37)	<.001	.002
Absence of nausea at 4 h						
Study 1	295 (81)	257 (71)	240 (67)	199 (55)	<.001	.002
Study 2	266 (73)	250 (69)	247 (68)	213 (56)	<.001	.14
Absence of photophobia at 4 h						
Study 1	271 (74)	221 (61)	202 (57)	137 (38)	<.001	<.001
Study 2	248 (69)	213 (59)	185 (51)	144 (38)	<.001	.004
Absence of phonophobia at 4 h						
Study 1	274 (75)	226 (63)	215 (60)	148 (41)	<.001	<.001
Study 2	259 (72)	224 (62)	193 (53)	146 (38)	<.001	.003

*Statistical comparison was not part of the original planned analyses. Analysis was performed post hoc without adjustments for multiple comparisons.

Candesartan for migraine prevention

Table 1. Intention-to-Treat Analysis of Efficacy Outcomes in 57 Migraine Patients During 12-Week Treatment Periods

	Outcome, Mean (SD)		Reduction With Candesartan		*P* Value*
	Candesartan	Placebo	Mean (SD)	Percentage	
Headache days (primary efficacy measure)	13.6 (10.7)	18.5 (12.5)	4.9 (10.6)	26	.001
Secondary efficacy measures					
Headache hours	95.0 (118)	139 (146)	43.9 (105)	31	<.001
Migraine days	9.0 (8.6)	12.6 (8.2)	3.5 (6.4)	28	<.001
Migraine hours	59.4 (66.6)	92.2 (76.8)	32.8 (61.7)	36	<.001
Headache severity index†	191 (249)	293 (290)	102 (210)	35	<.001
Triptan doses	6.9 (10.3)	9.5 (14)	2.6 (10.0)	27	.03
Analgesic doses	12.7 (18.3)	18.9 (30.6)	6.2 (22.0)	33	.02
Disability level	14.1 (15.4)	20.6 (14.3)	6.5 (10.8)	32	<.001
Sick leave days	1.4 (5.2)	3.9 (12.0)	2.5 (8.9)	64	.01

*Calculated by the Wilcoxon signed rank test.
†See "Methods" section of text for explanation of headache severity index.

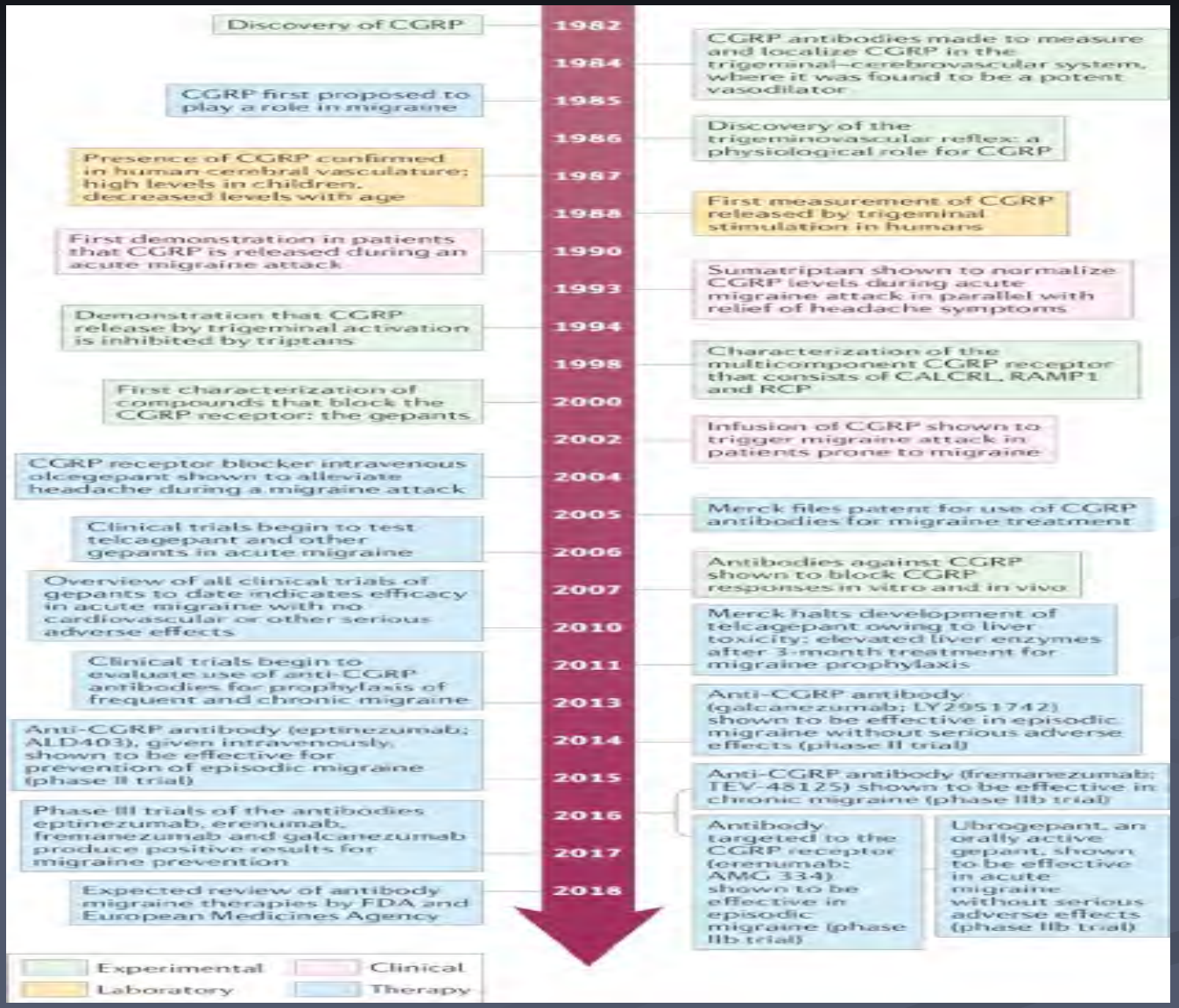
Tronvik 2003 JAMA

CGRP
Calcitonin Gene Related Peptide

- Lars Edvinsson, Lund University

REVIEWS

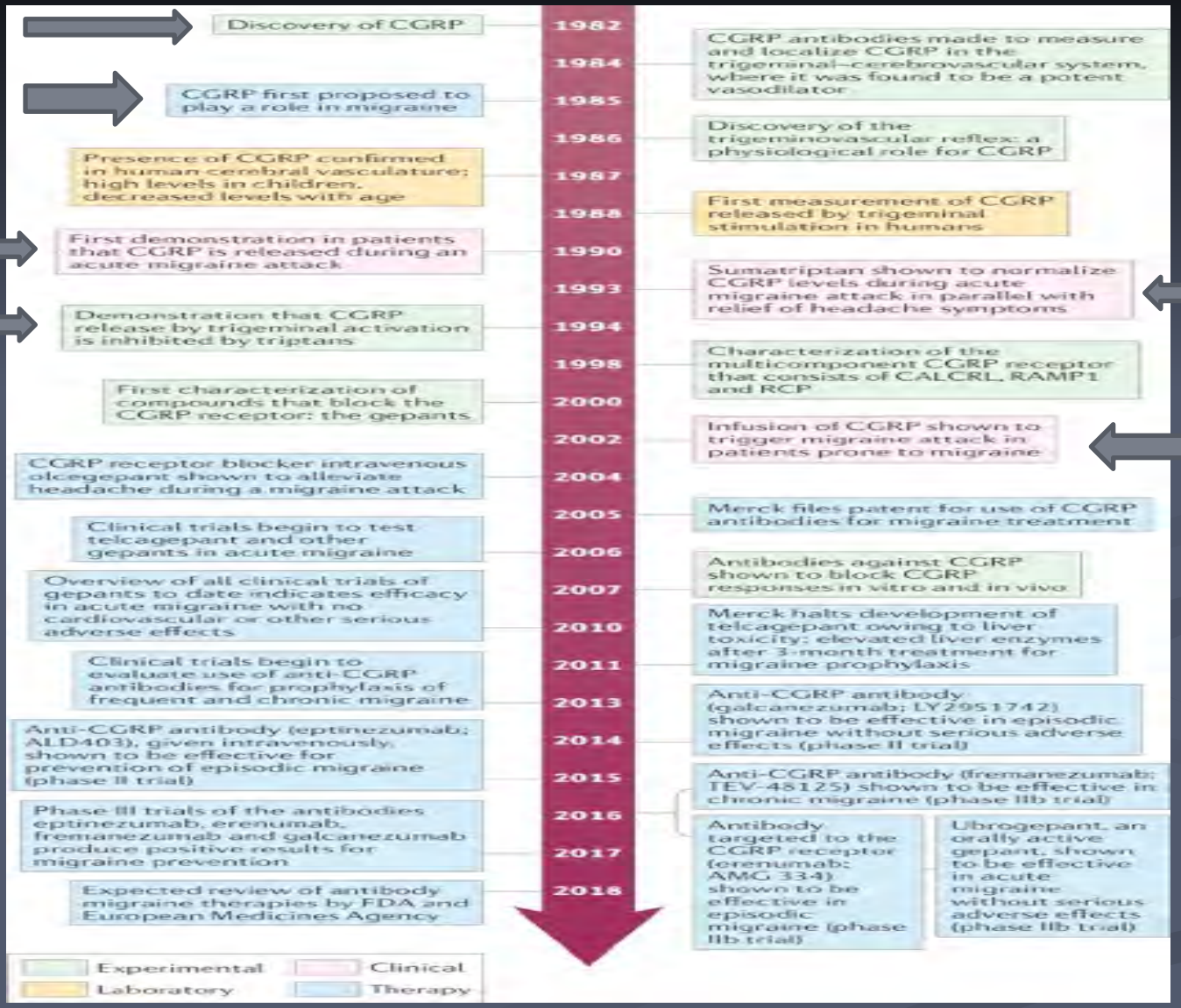
CGRP as the target of new migraine therapies — successful translation from bench to clinic



REVIEWS

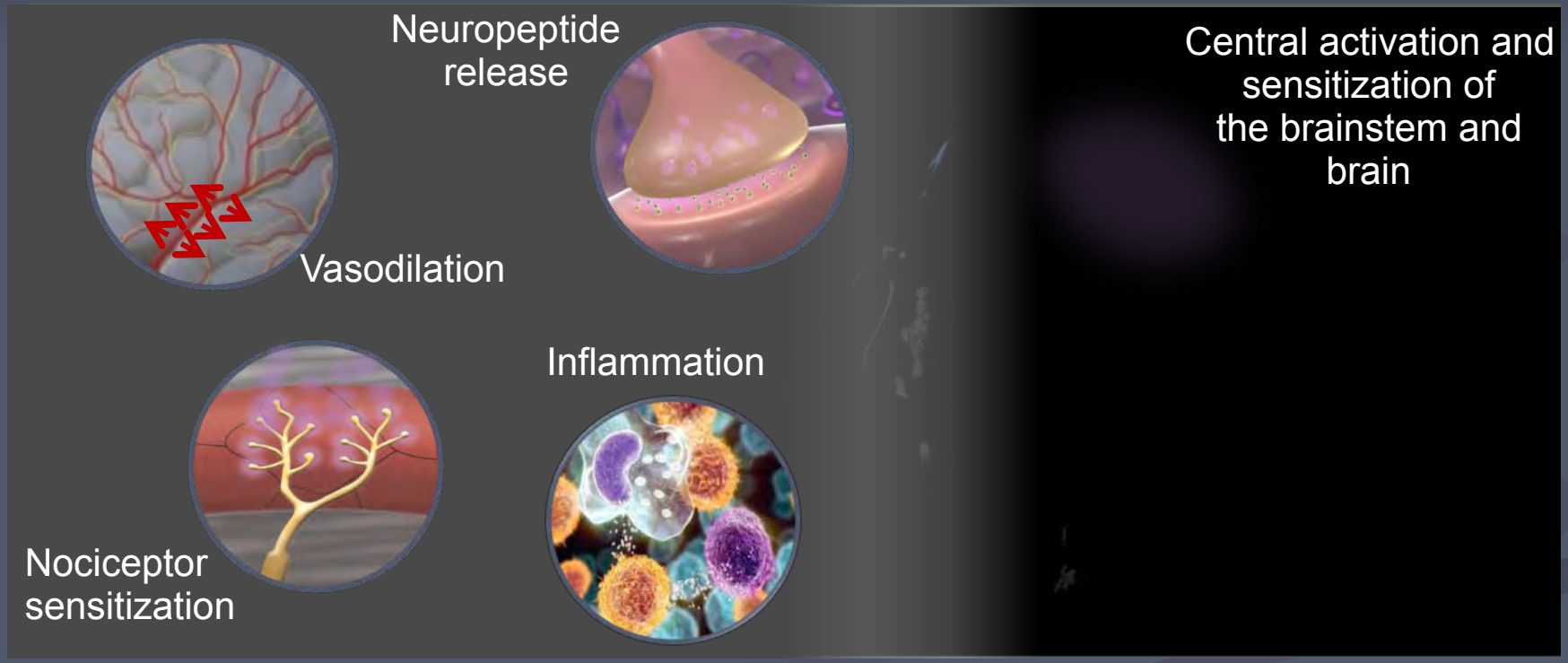
CGRP as the target of new migraine therapies — successful translation from bench to clinic

Edvinsson 2018



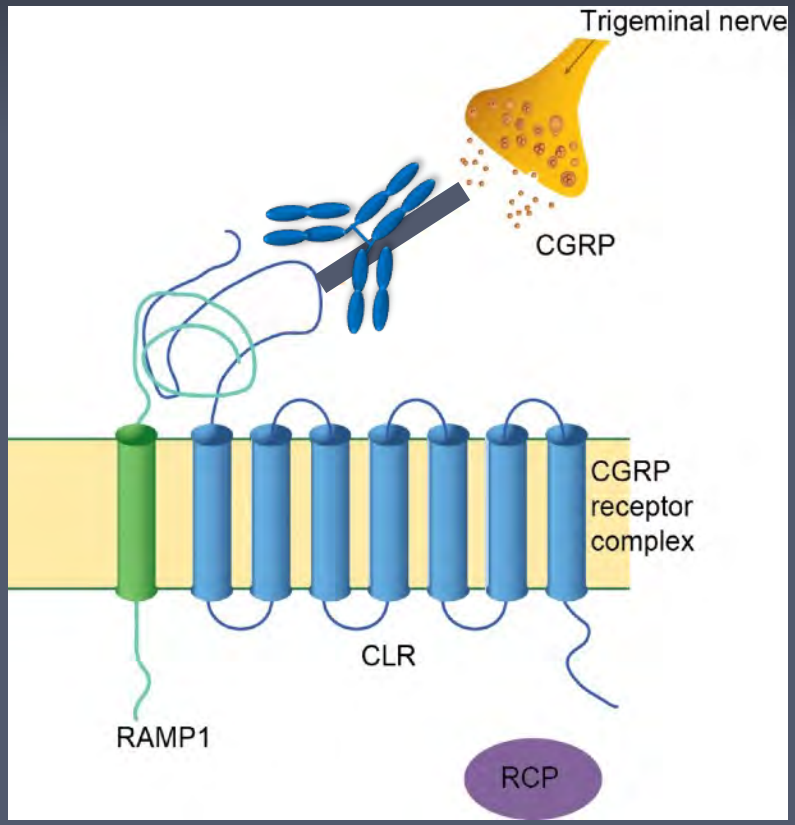
• The role of CGRP

The complex role of CGRP in migraine pathophysiology may involve multiple processes in both the CNS and in the periphery, including:

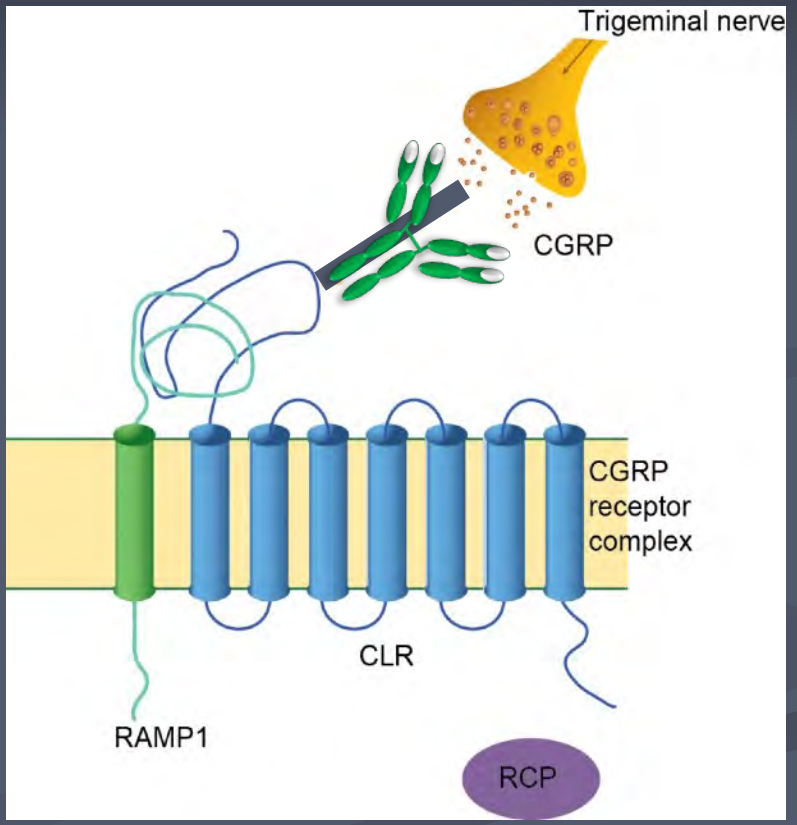


Edvinsson L. *Brit J Clin Pharmacol.* 2015;80:193-199; Raddant AC, Russo AF. *Expert Rev Mol Med.* 2011;13:e36; Russo AF. *Annu Rev Pharmacol Toxicol.* 2015;55:533-552.

a) Binding to the CGRP receptor

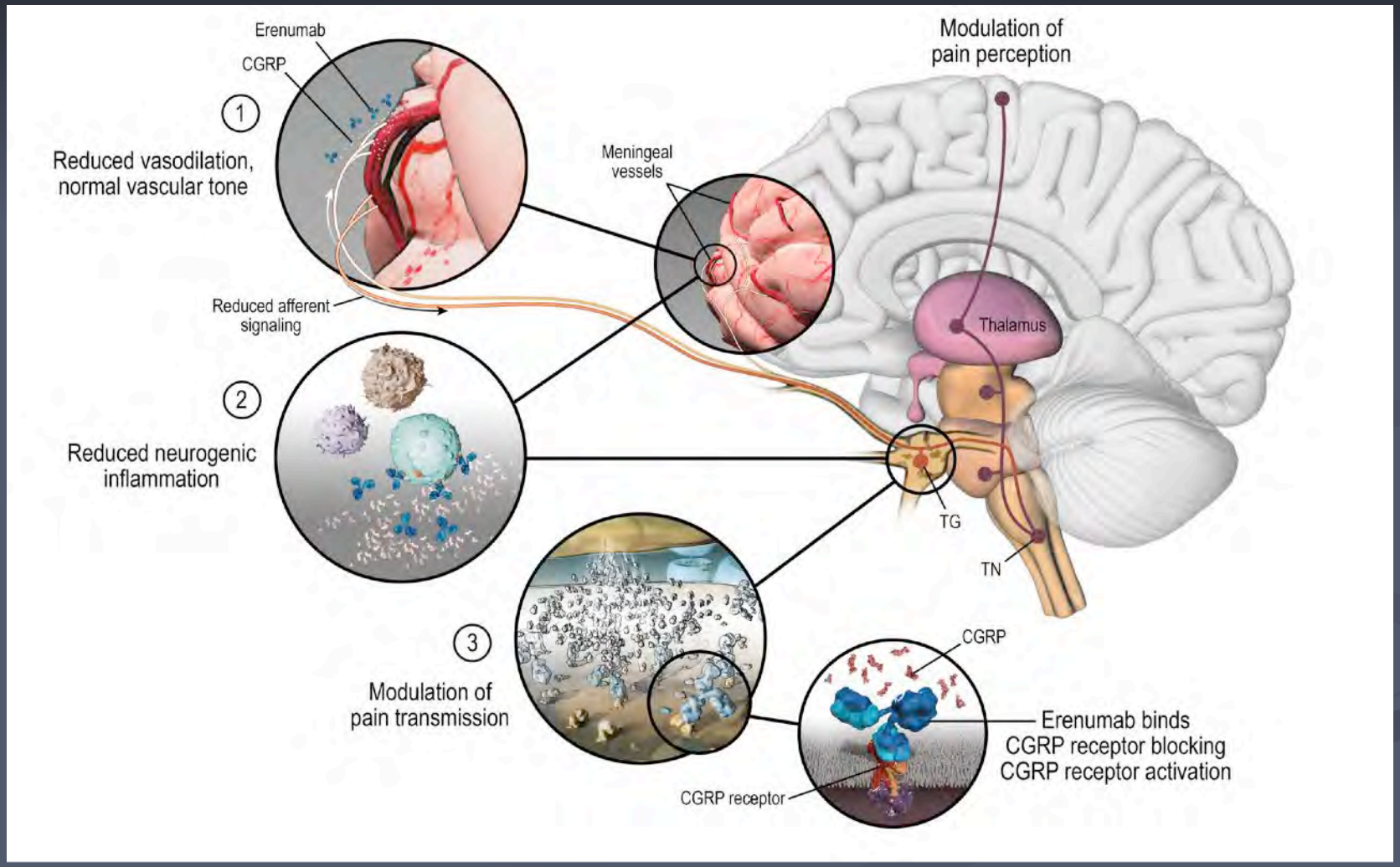


b) Binding to the CGRP



Edvinsson, Headache 2018;58:33-47

• Potential effects of Erenumab



CGRP, calcitonin-gene related peptide; CGRP-R, CGRP receptor; TN, trigeminal nerves. Tepper S, et al. Lance Neurol. 2017;16:425-434.; Sun H, et al. Lancet Neurol. 2016;15:382-390.; Russo AF. Annu Rev Pharmacol Toxicol. 2015;55:533–552.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Controlled Trial of Erenumab for Episodic Migraine

Peter J. Goadsby, M.D., Ph.D., Uwe Reuter, M.D., Yngve Hallström, M.D., Gregor Broessner, M.D., Jo H. Bonner, M.D., Feng Zhang, M.S., Sandhya Sapra, Ph.D., Hernan Picard, M.D., Ph.D., Daniel D. Mikol, M.D., Ph.D., and Robert A. Lenz, M.D., Ph.D.

ABSTRACT

BACKGROUND

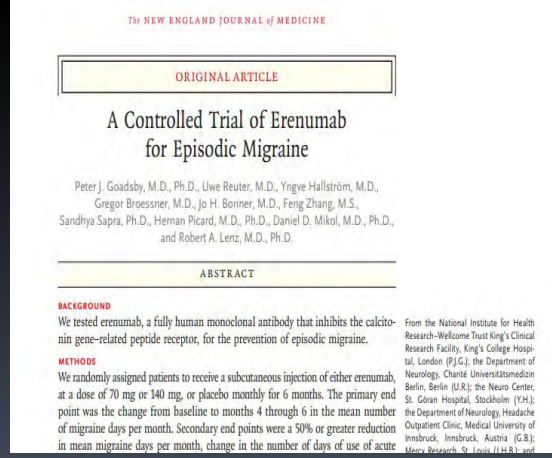
We tested erenumab, a fully human monoclonal antibody that inhibits the calcitonin gene–related peptide receptor, for the prevention of episodic migraine.

METHODS

We randomly assigned patients to receive a subcutaneous injection of either erenumab, at a dose of 70 mg or 140 mg, or placebo monthly for 6 months. The primary end point was the change from baseline to months 4 through 6 in the mean number of migraine days per month. Secondary end points were a 50% or greater reduction in mean migraine days per month, change in the number of days of use of acute

From the National Institute for Health Research–Wellcome Trust King's Clinical Research Facility, King's College Hospital, London (P.J.G.); the Department of Neurology, Charité Universitätsmedizin Berlin, Berlin (U.R.); the Neuro Center, St. Göran Hospital, Stockholm (Y.H.); the Department of Neurology, Headache Outpatient Clinic, Medical University of Innsbruck, Innsbruck, Austria (G.B.); Mercy Research, St. Louis (J.H.B.); and

Results – Monthly migraine days



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Controlled Trial of Erenumab for Episodic Migraine

Peter J. Goadsby, M.D., Ph.D., Uwe Reuter, M.D., Yngve Hallström, M.D., Gregor Broessner, M.D., Jo H. Bonner, M.D., Feng Zhang, M.S., Sandhya Sapra, Ph.D., Hernan Picard, M.D., Ph.D., Daniel D. Mikol, M.D., Ph.D., and Robert A. Lenz, M.D., Ph.D.

ABSTRACT

BACKGROUND

We tested erenumab, a fully human monoclonal antibody that inhibits the calcitonin gene–related peptide receptor, for the prevention of episodic migraine.

METHODS

We randomly assigned patients to receive a subcutaneous injection of either erenumab, at a dose of 70 mg or 140 mg, or placebo monthly for 6 months. The primary end point was the change from baseline to months 4 through 6 in the mean number of migraine days per month. Secondary end points were a 50% or greater reduction in mean migraine days per month, change in the number of days of use of acute

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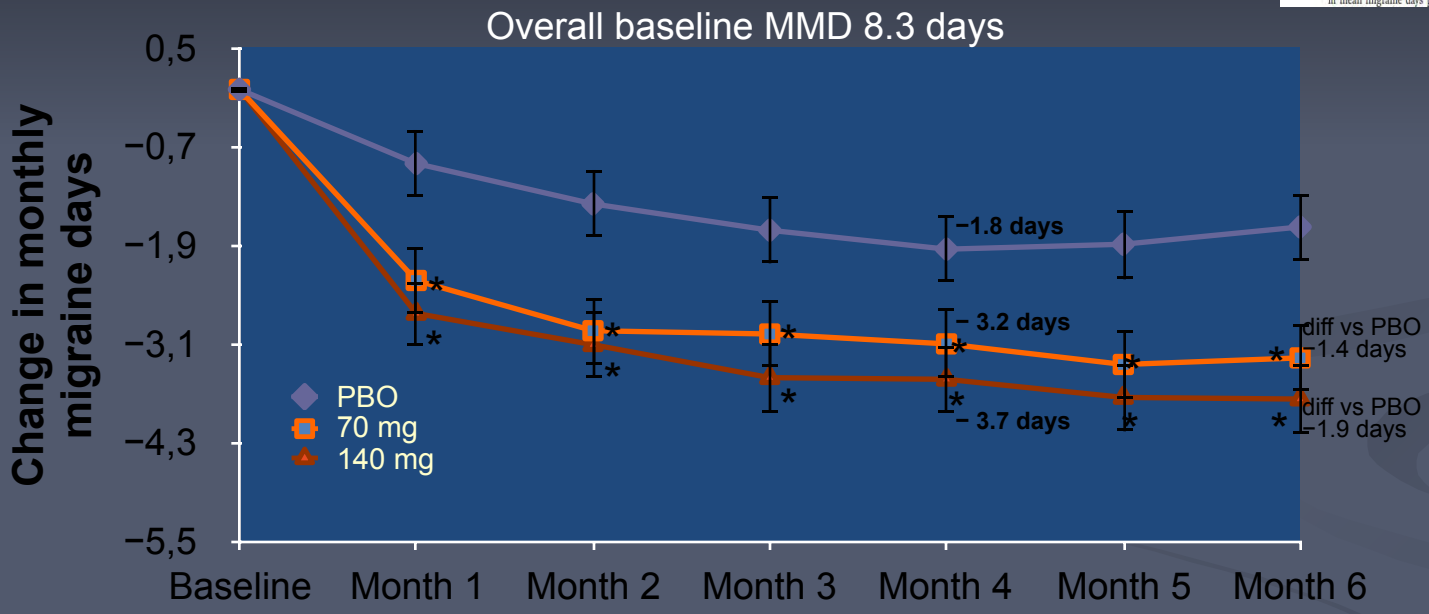

Data presented are least squares mean and 95% CI; *p<0.001 for each group vs placebo, not adjusted for multiplicity; Endpoint averaged over months 4, 5, and 6. MMD, monthly migraine days; PBO, placebo.

Goadsby et al. NEJM, 2017;377:2123-2132

Erenumab (AMG 334) in episodic migraine

Interim analysis of an ongoing open-label study

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David Dodick, MD
Peter J. Goadsby, MD, PhD
Uwe Reuter, MD
Stephen Silberstein, MD
Feng Zhang, MS
Julia R. Gage, PhD
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Correspondence to Dr. Ashina: ashina@dadlnet.dk

ABSTRACT

Objective: To assess long-term safety and efficacy of anti-calcitonin gene-related peptide receptor erenumab in patients with episodic migraine (EM).

Methods: Patients enrolled in a 12-week, double-blind, placebo-controlled clinical trial (NCT01952574) who continued in an open-label extension (OLE) study will receive erenumab 70 mg every 4 weeks for up to 5 years. This preplanned interim analysis, conducted after all participants had completed the 1-year open-label follow-up, evaluated changes in monthly migraine days (MMD), achievement of ≥50%, ≥75%, and 100% reductions, Headache Impact Test (HIT-6) score, Migraine-Specific Quality of Life (MSQ), Migraine Disability Assessment (MIDAS), and safety. Data reported as observed without imputation for missing data.

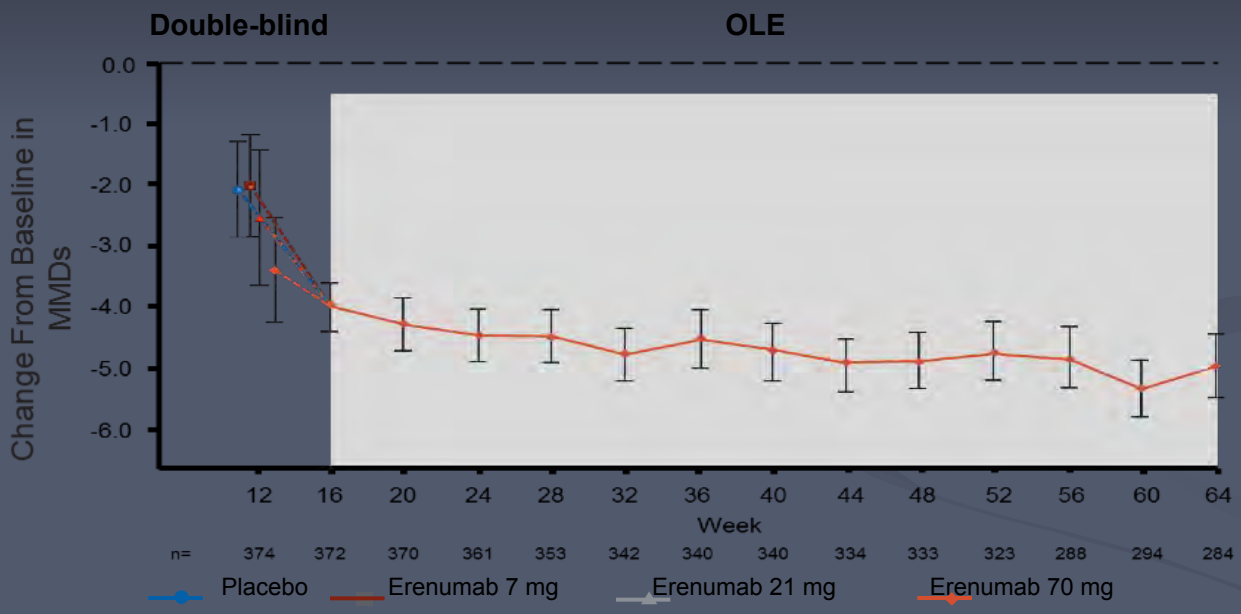
Results: Of 472 patients enrolled in the parent study, 383 continued in the OLE with a median exposure to erenumab of 575 days (range 28–822 days). Mean (SD) MMD were 8.8 (2.6) at parent study baseline, 6.3 (4.2) at week 12 (beginning of OLE), and 3.7 (4.0) at week 64 (mean change from baseline [reduction] of 5.0 days). At week 64, 65%, 42%, and 26% achieved ≥50%, ≥75%, and 100% reduction in MMD, respectively. Mean HIT-6 scores were 60.2 (6.3) at baseline and 51.7 (9.2) at week 64. MSQ and MIDAS improvements from baseline were maintained through week 64. Safety profiles during the OLE were similar to those in the double-blind phase, which overall were similar to placebo.

Conclusions: One-year efficacy, supported by functional improvements and favorable safety and tolerability profiles, supports further investigation of erenumab as a preventive treatment in patients with EM.

Clinicaltrials.gov identifier: NCT01952574.

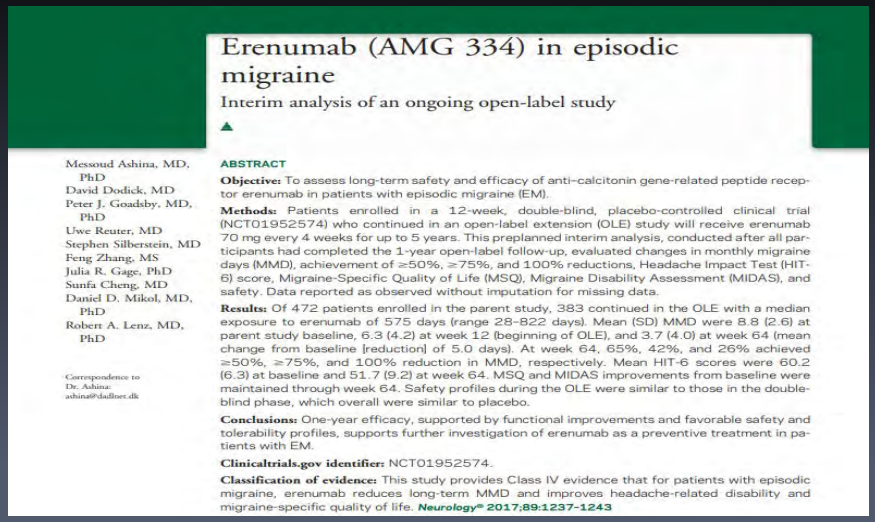
Classification of evidence: This study provides Class IV evidence that for patients with episodic migraine, erenumab reduces long-term MMD and improves headache-related disability and migraine-specific quality of life. *Neurology*® 2017;89:1237–1243

Results – Monthly migraine days



Data are mean (95% CI). n = total number of patients with observed MMDs at each visit.. CI = confidence interval; EM = episodic migraine; MMD = monthly migraine day; OLE = open-label extension.

Ashina et al. Neurology, 2017;89:1237-1243



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- A total of 307 patients (80%) completed 1 year of open-label treatment.
- For patients enrolled in the OLE, mean monthly migraine days were 8.8 days at baseline, 6.3 at week 12, and 3.7 at week 64.
- At week 64

a) 184 (65%) patients had achieved ≥50% reduction
b) 119 (42%) had achieved ≥75% reduction
c) 73 (26%) had achieved 100% reduction in monthly migraine days.

- *Secondary or primary headache*
- Migraine

1. Epidemiology
2. Migraine symptoms
3. Pathaphysiology
4. Migraine treatment
5. Chronic Migraine

- Tension type headache
- Cluster headache

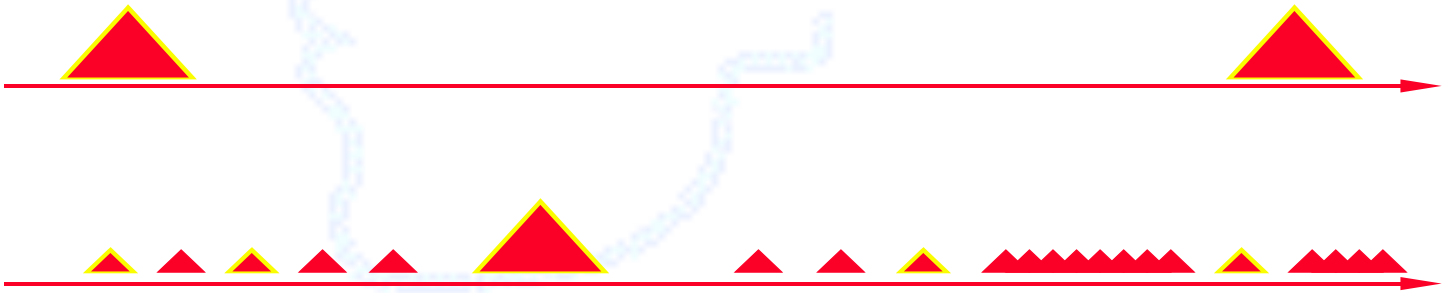
1.5.1 Chronic migraine

New entrant to classification

A. Headache fulfilling criteria C and D for

1.1 *Migraine without aura* on ≥15 d/mo for >3 mo

B. Not attributed to another disorder



ICHD-II. *Cephalalgia* 2004; **24** (Suppl 1)

Chronic migraine

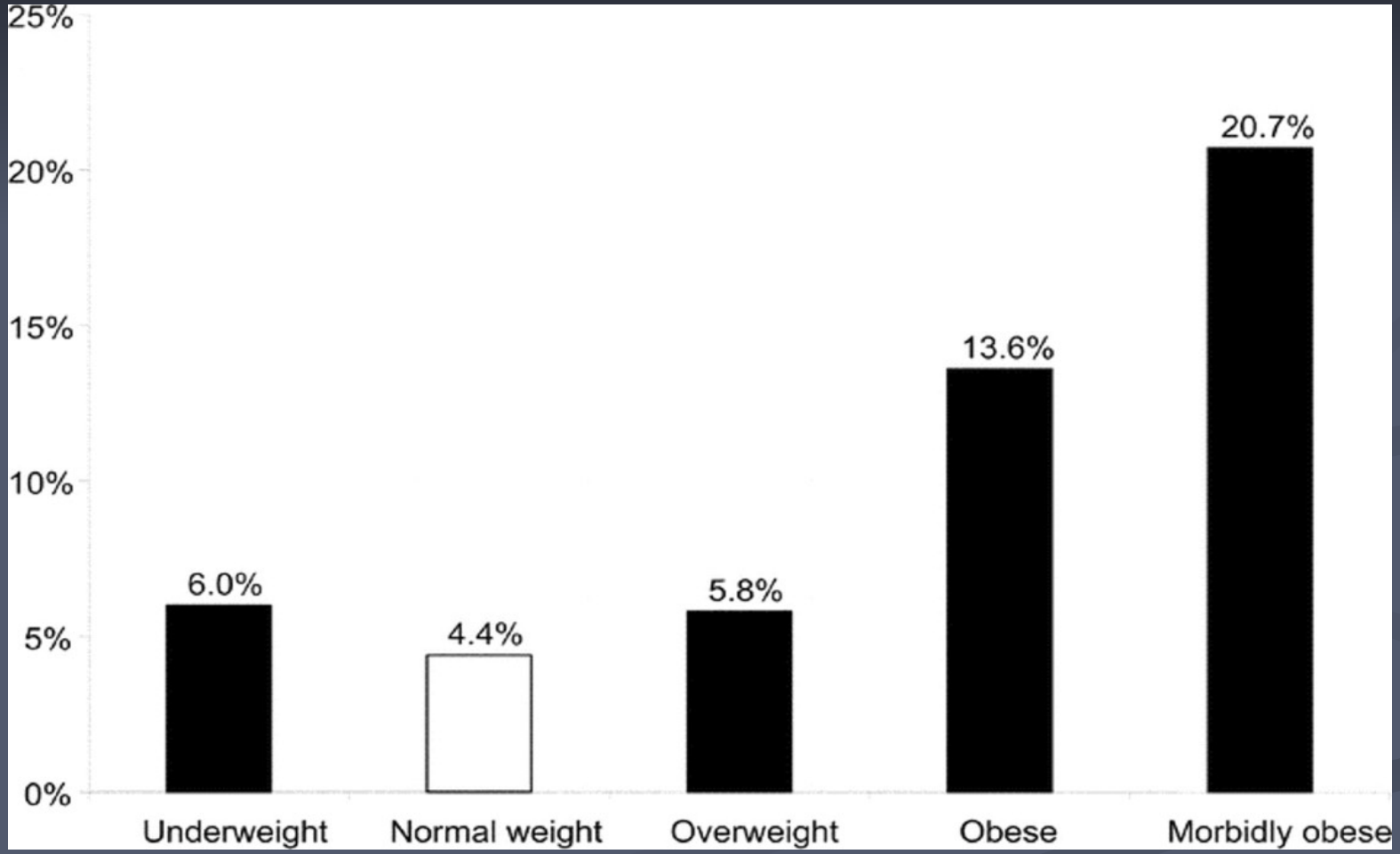
- Difficult version of migraine
- Headache more than 15 days per month and 8 migraine headache days (for at least three months)
- Prevalence 1,4-2,2%
- 3 years follow up 26% in remission (less than 10 headache days per month)
- Quality of life and working order lower than other migraine patients. Higher usage of health care system.
- Etiology unknown. Most likely complex
- Sensititation of sentral pain pathways?
- Treatment: Topiramate, Botulinumtoxin, detoxification if medication overuse, CGRP antibodies

Riskfactors for chronification of migraine

- Obesity
- Low education
- Female
- Diabetes
- Arthritis
- Allodynia
- High frequency of migraine attacks (> 10 headache days per month)
- Too much pain medications, especially opioids

Migraine and BMI

Proportion of migraine subjects with 10 or more headache days per month



Bigal, M. E. et al. Neurology 2006;66:545-550

Erenumab in the treatment of chronic migraine

Baseline 18 monthly migraine days

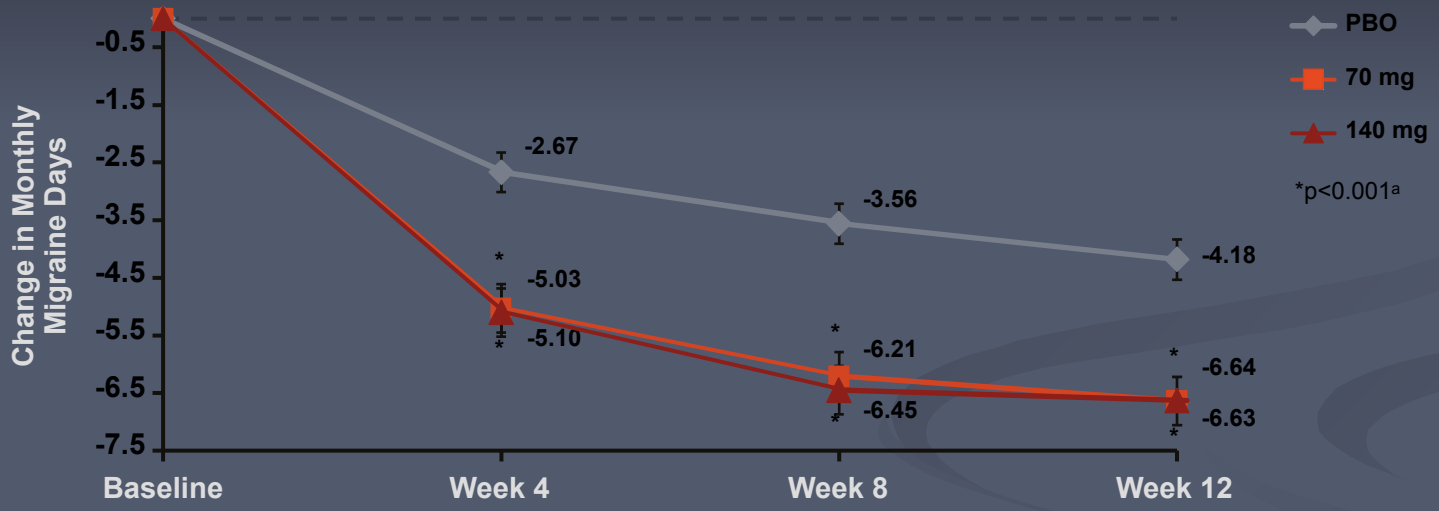

Articles

Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial

Summary

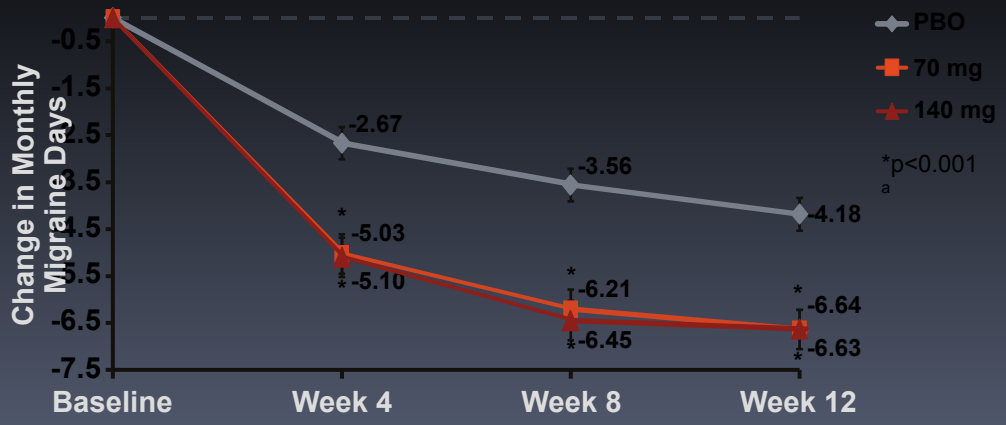
Background The calcitonin gene-related peptide (CGRP) pathway is important in migraine pathophysiology. We assessed the efficacy and safety of erenumab, a fully human monoclonal antibody against the CGRP receptor, in patients with chronic migraine.

Methods This was a phase 2, randomised, double-blind, placebo-controlled, multicentre study of erenumab for adults aged 18–65 years with chronic migraine, enrolled from 69 headache and clinical research centres in North America and Europe. Chronic migraine was defined as 15 or more headache days per month, of which eight or more were migraine days. Patients were randomly assigned (1:2:2) to subcutaneous placebo, erenumab 70 mg, or erenumab 140 mg, given every 4 weeks for 12 weeks. Randomisation was centrally executed using an interactive voice or web response system. Patients, study investigators, and study sponsor personnel were masked to treatment assignment.

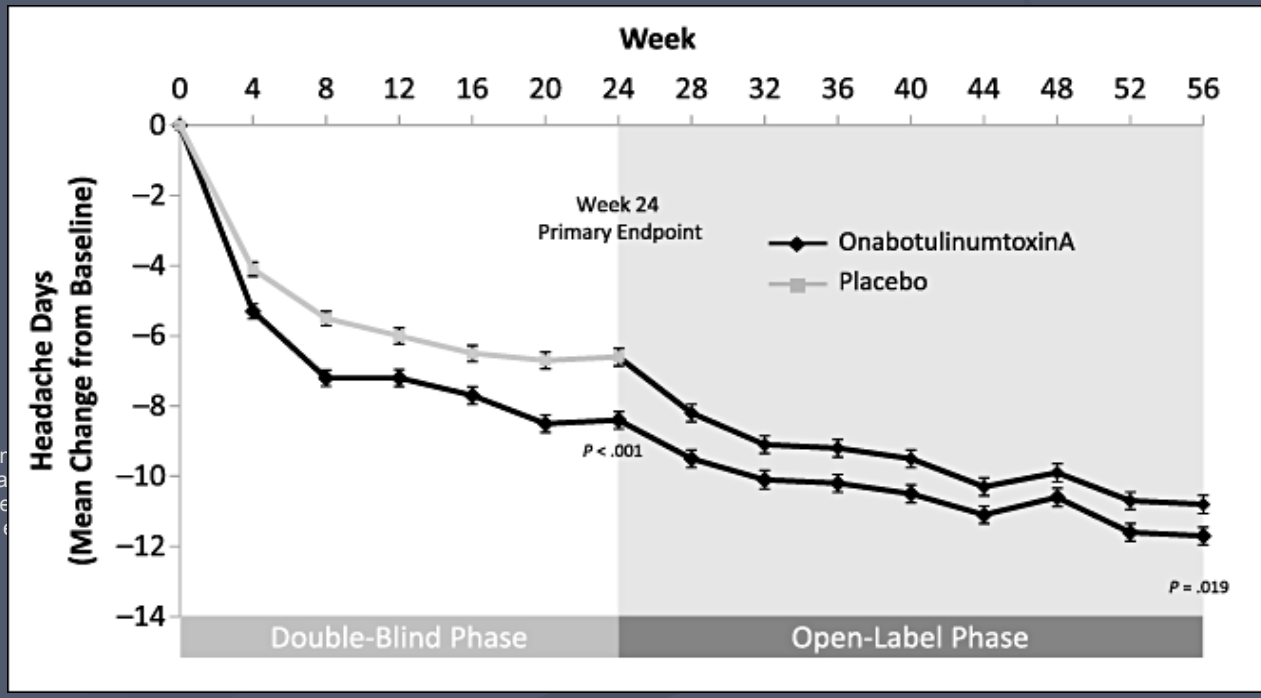


PBO n=281, erenumab 70 mg n=188, and erenumab 140 mg n=187. Baseline monthly migraine days, mean (SD): PBO 18.2 (4.7), erenumab 70 mg 17.9 (4.4), erenumab 140 mg 17.8 (4.7). Data are LSM (SE) change from baseline. Efficacy analysis set.; [a] Using a prespecified method for controlling for multiple comparisons, the p-values are considered statistically significant for the primary endpoint. LSM, least squares mean; PBO, placebo; SD, standard deviation; SE, standard error;

Tepper et al. Lancet Neurology, 2017;16:425-434



Botulinumtoxin



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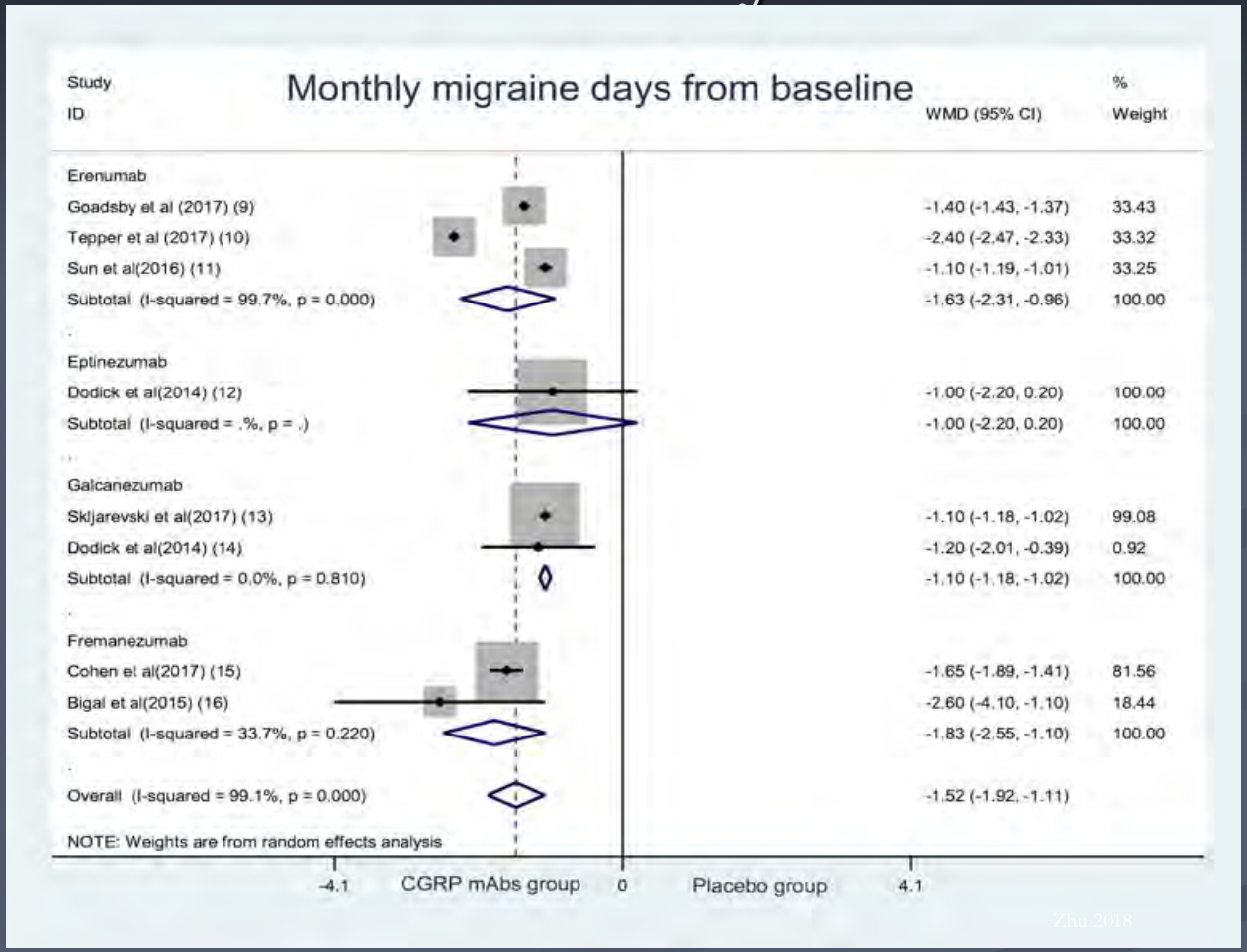
Meta-analysis



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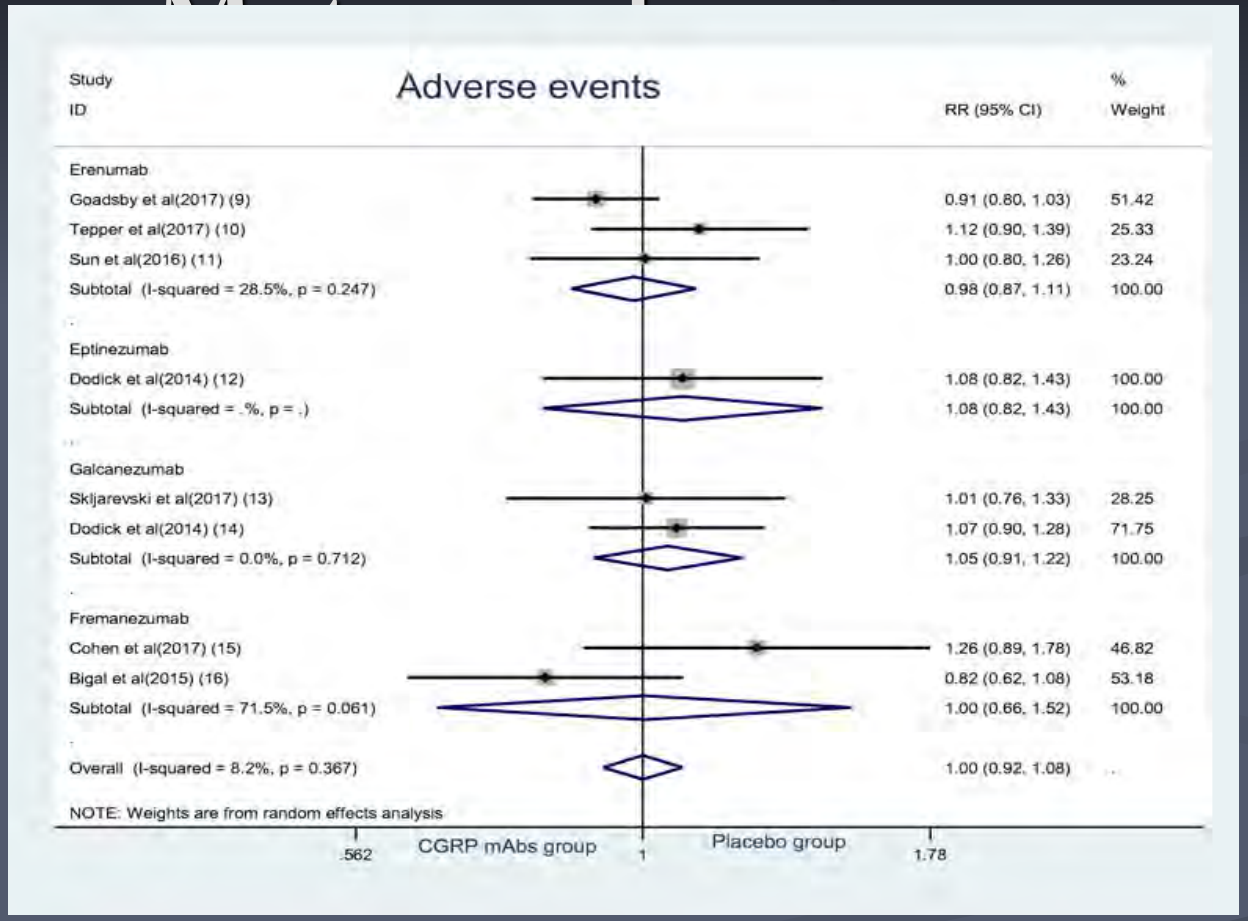
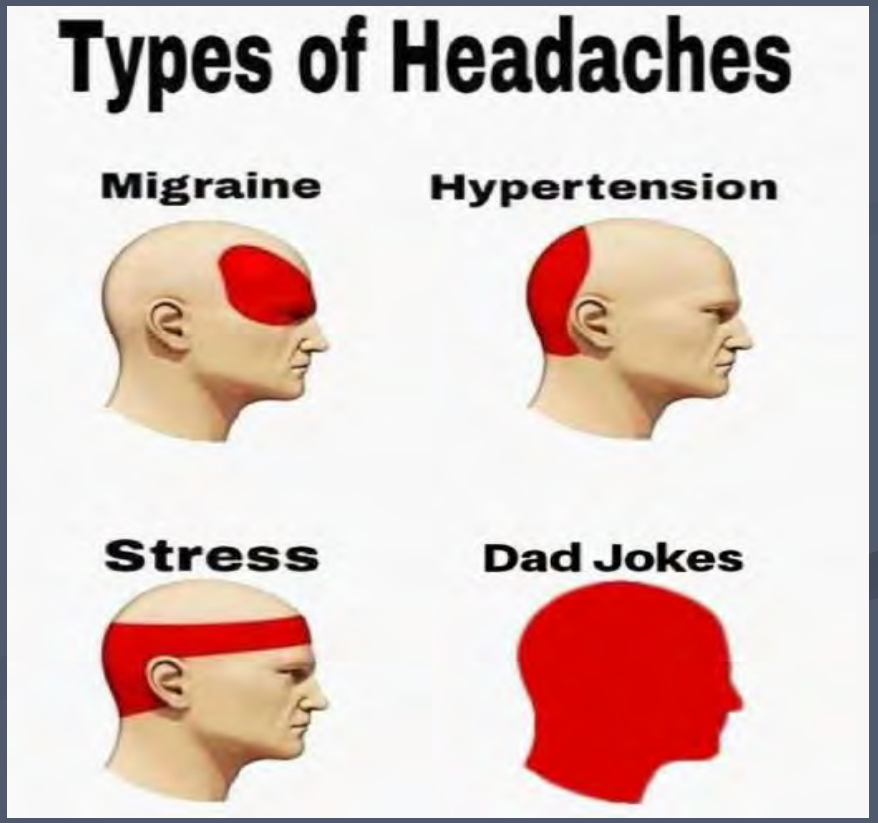
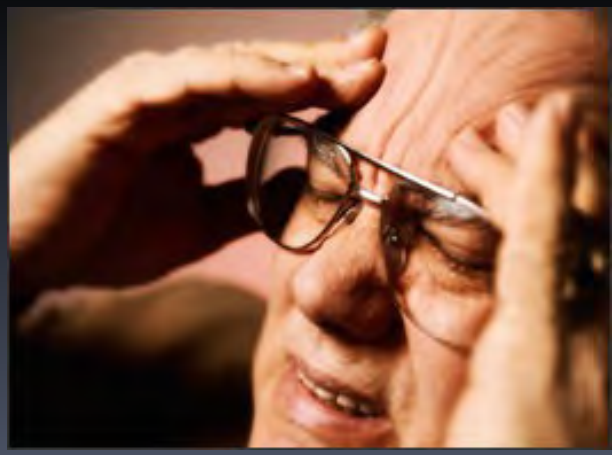


- *Secondary or primary headache*
- *Migraine*
- Tension type headache
- Cluster headache



Tension Type Headache

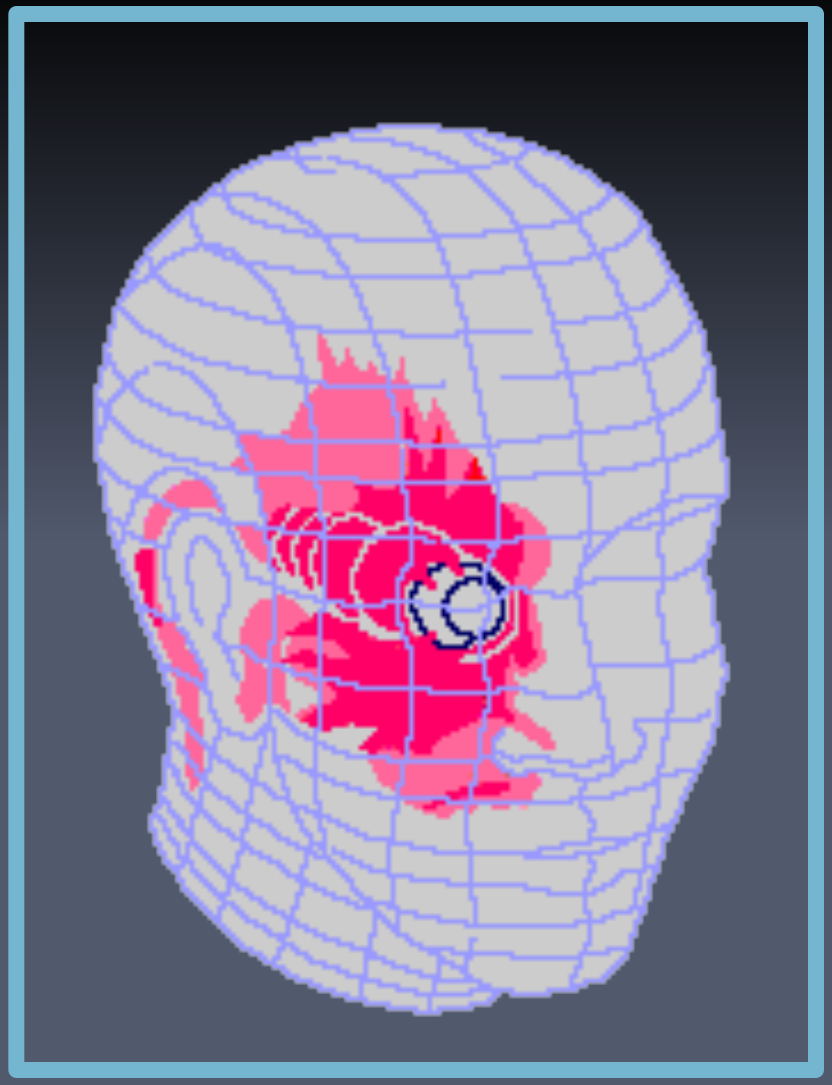


- Probably the most common cause of headache
- Continous headache instead of attacks
- Gets worse typically during the day
- Mild or moderate intensity
- Bilateral pain
- ”A band around a head”
- Tenderness of the pericranial (head and neck) muscles

Tension Type Headache

- Diagnosis is based on a patient history and normal examination
- Treatment
  - Exercise
  - Physiotherapy
  - Occupational ergonomics
  - NSAID (+BZD in evenings)
  - Amitriptyline
  - Nortriptyline

- *Secondary or primary headache*
- *Migraine*
- *Tension type headache*
- Cluster headache

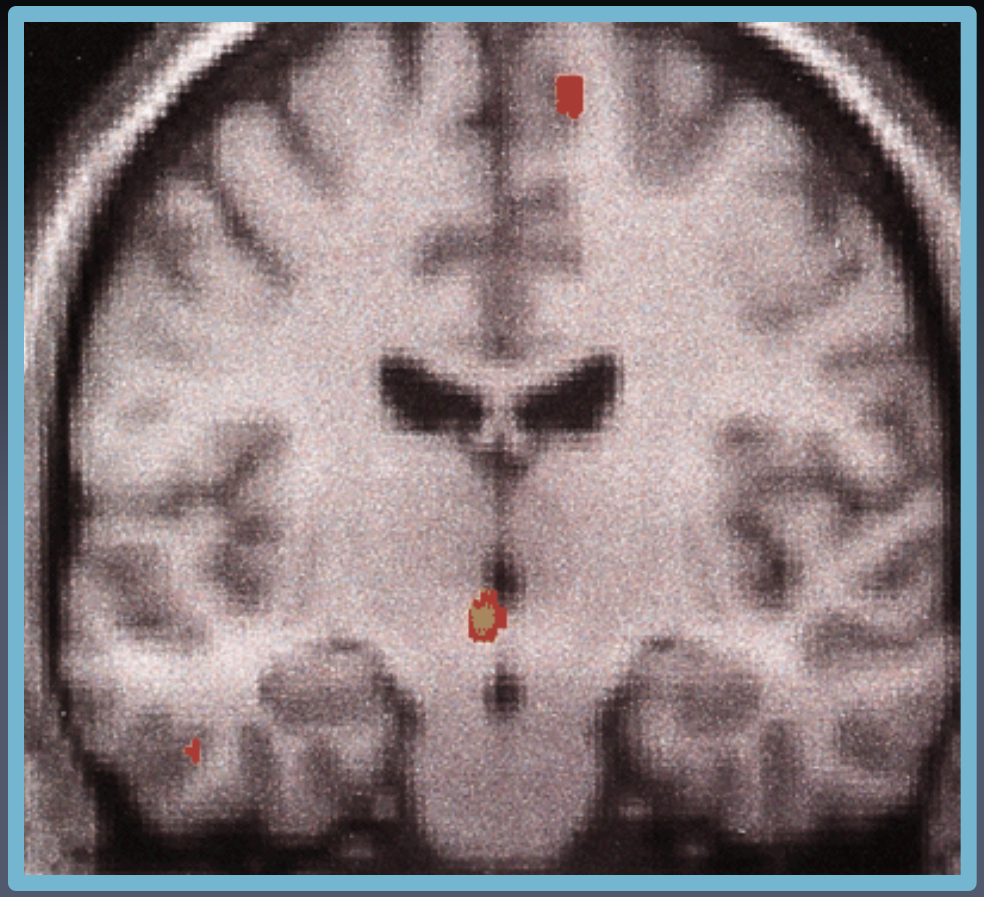


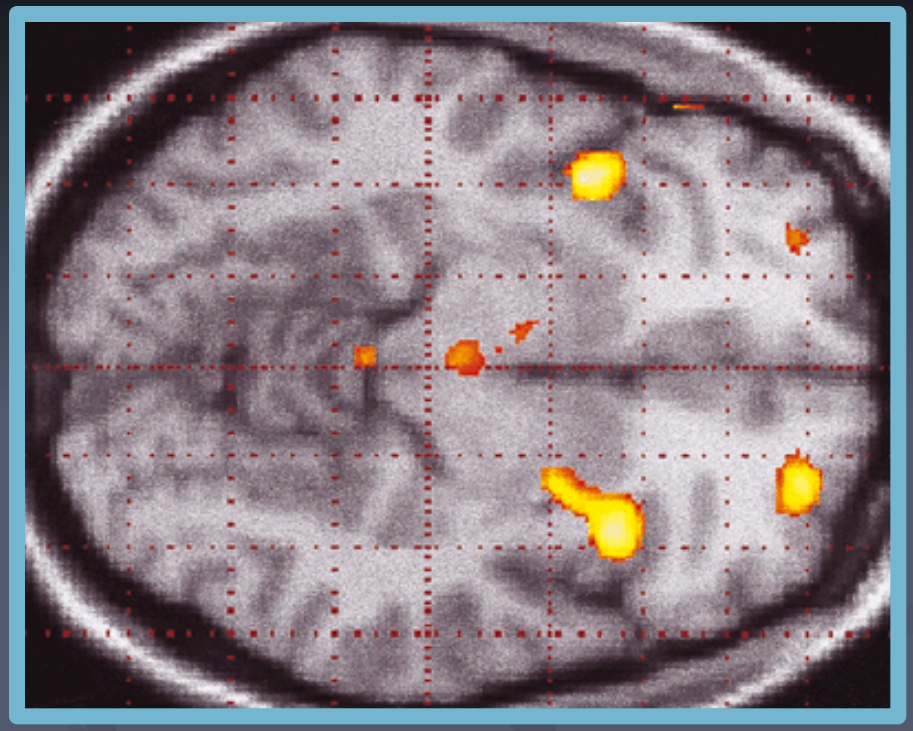
”The Cluster-triad”

1. **pain attacks in clusters**
   - **Attack: 15-180 min**
   - **1-8 attacks per days**
   - **Duration of a cluster: from 7 days to 1 year**
2. **pain around the eye (trigeminal distribution)**
3. **symptoms of the autonomic neurvous system**

http://www.clusterkopf.de/

http://medlineplus.gov/





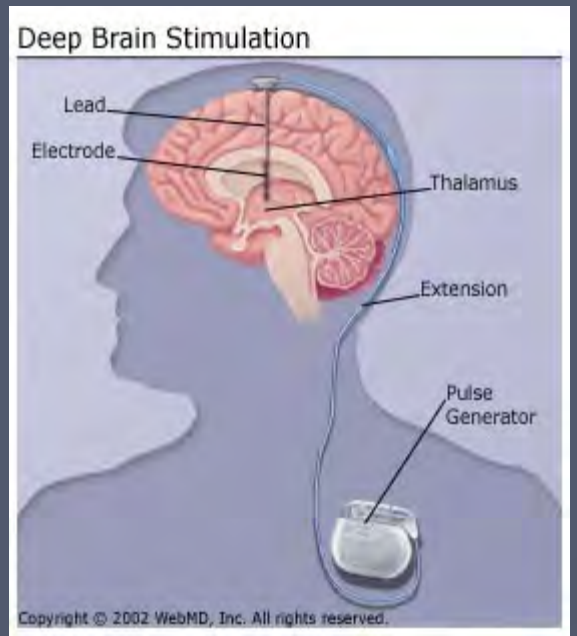
Hypothalamic activation in cluster headache attacks

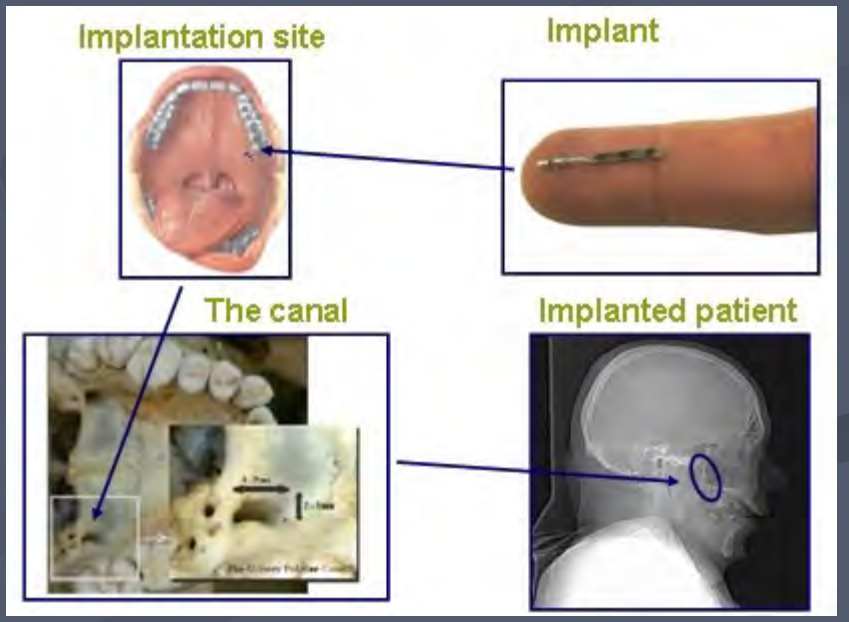
Arne May, Anish Bahra, Christian Büchel, Richard S J Frackowiak, Peter J Goadsby

fMRI = functional Magnetic Resonance Imaging

Treatment of Cluster Headache

- Preventive medications: Calcium channel blocker – Verapamil, Topiramate, Valproic acid, Melatonin, Lithium, Corticosteroids
- Acute treatments: Oxygen, triptans
- Deep brain stimulation, Occipital nerve stimulation and Sphenopalatine ganglion stimulation





Summary

- Mostly headache is caused by migraine, tensiontype headache or some other primary headache
- Migraine might have major impact on quality of life
- Migraine might even act as a risk factor for ischemic stroke
- Migraine causes major economical burden
- Headache is mostly benign, but however it might be extremely devastating