

Migraine anno 2020



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Neurologie

Universitair Ziekenhuis Gent



Oudenaarde | 15 december 2020



Disclosures

<i>Company Name</i>	<i>Honoraria/ Expenses</i>	<i>Consulting/ Advisory Board</i>	<i>Funded Research</i>	<i>Royalties/ Patent</i>	<i>Stock Options</i>	<i>Ownership/ Equity Position</i>	<i>Employee</i>
Allergan	x	x					
Almirall	x						
Amgen/Novartis	x	x					
Autonomic Technologies Inc.	x		x				
Coherex		x					
Janssen-Cilag	x						
Lilly	x	x					
Lundbeck	x						
Medtronic	x						
Pfizer		x					
Sandoz	x						
Sanofi	x						
St Jude Medical	x						
TEVA	x	x					

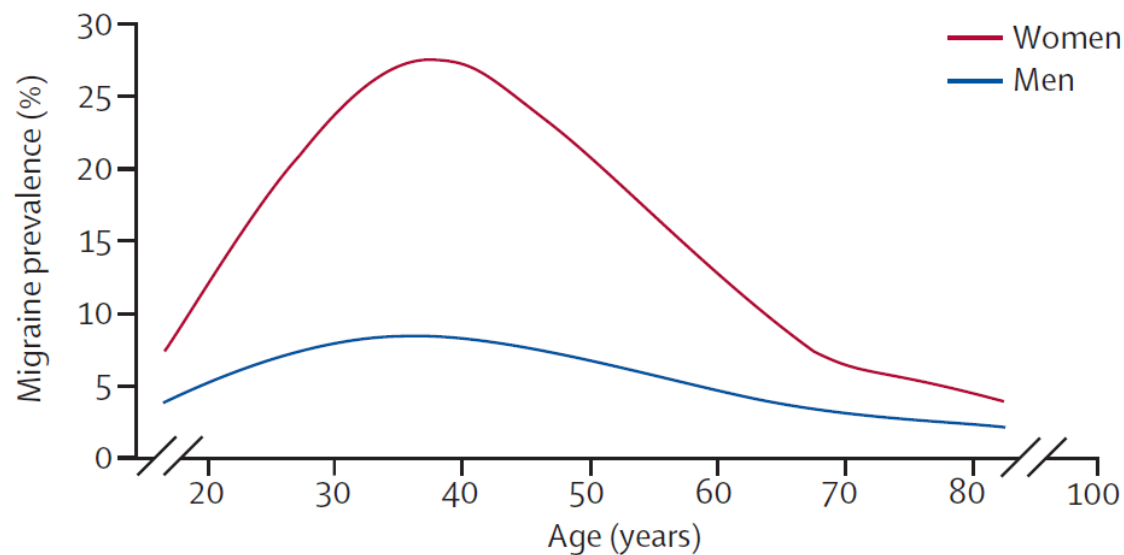
Impact
§
(Onder)diagnose
§
Fysiopathologie
§
Management
§
Q&A



DEEL 1: IMPACT



Migraine



20 % migraine patients ≥ 1 disabling headache day/week

EDITORIAL

Open Access



Migraine is *first* cause of disability in under 50s: will health politicians now take notice?

Leading causes 2016	Mean % change in number of YLDs (2006-16)	Mean % change in all-age YLD rate (2006-16)	Mean % change in age-standardised YLD rate (2006-16)
1 Low back pain	18.0	5.0	-2.0
2 Migraine	14.3	1.6	0.1
3 Age-related hearing loss	22.3	8.8	-1.7
4 Iron-deficiency anaemia	7.5	-4.4	-1.8
5 Major depression	11.2	-1.1	-4.9
6 Neck pain	21.9	8.4	0.1
7 Other musculoskeletal disorders	14.4	1.7	-3.5
8 Diabetes	23.6	10.0	-1.2
9 Anxiety disorders	13.1	0.6	-0.7
10 Falls	26.7	12.7	3.4
11 COPD	28.8	14.5	1.4
12 Osteoarthritis	31.5	16.9	2.4
13 Acne vulgaris	5.1	-6.5	2.1
14 Refraction and accommodation	14.9	2.2	-4.9
15 Schizophrenia	16.7	3.8	-0.9
16 Asthma	17.2	4.2	3.6
17 Ischaemic stroke	35.2	20.3	3.7
18 Dermatitis	11.6	-0.7	1.1
19 Opioid use disorders	18.0	4.9	2.7
20 Other mental and substance	17.8	4.8	0.1

Lancet Neurol 2008;7:354-361
 Neurology 2007;68:343-9
 Lancet 2017;390:1211-1259
 J Headache Pain 2018;19(1):17

Cost of brain disorders

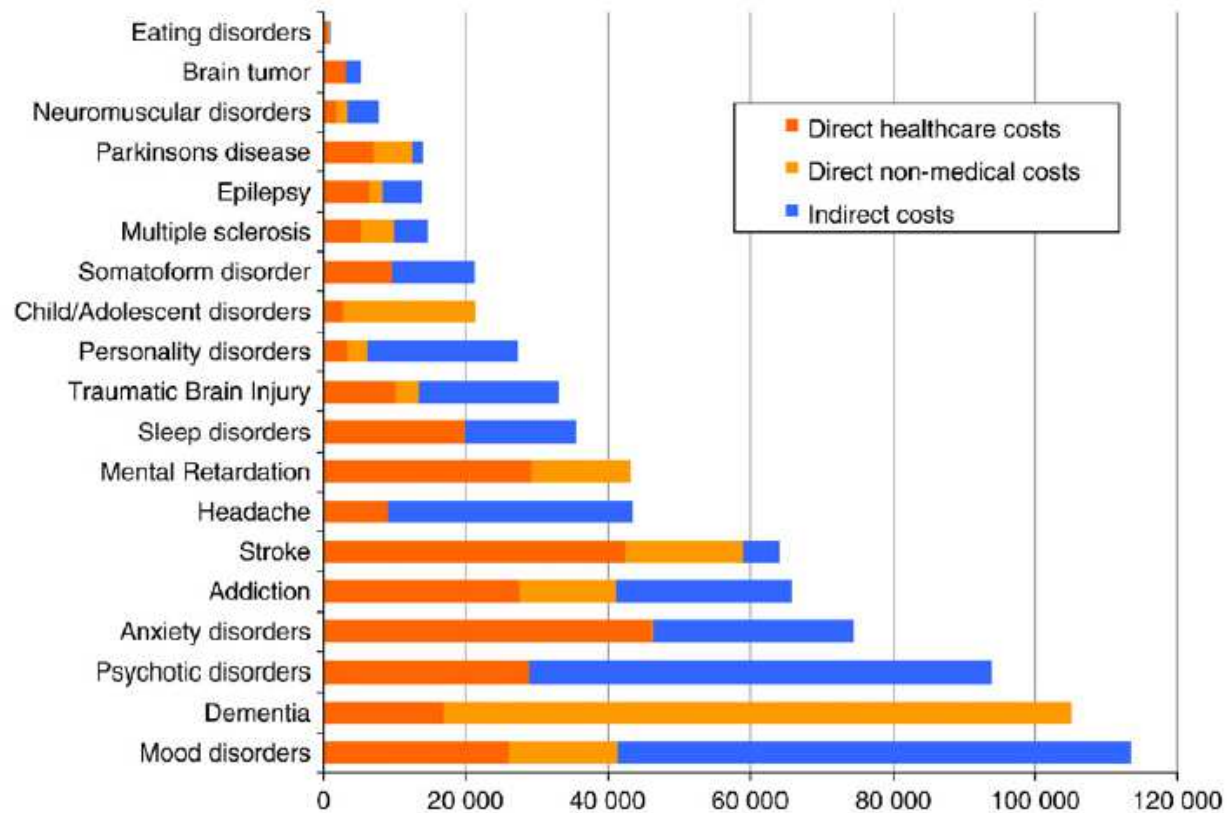
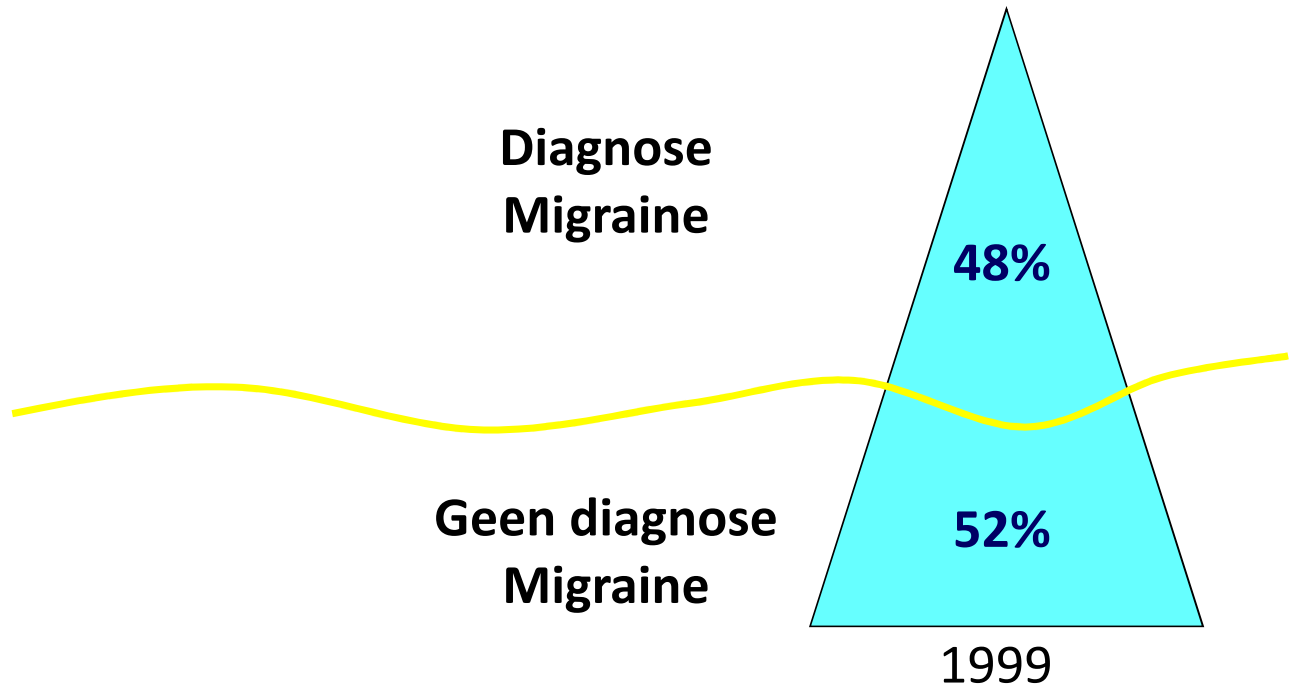
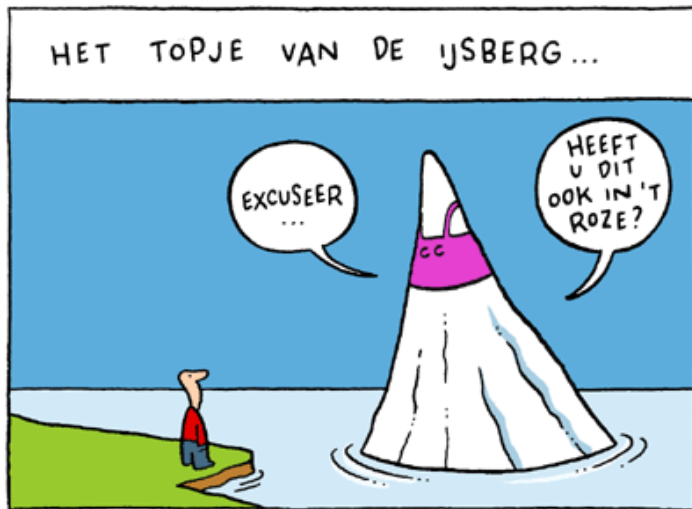


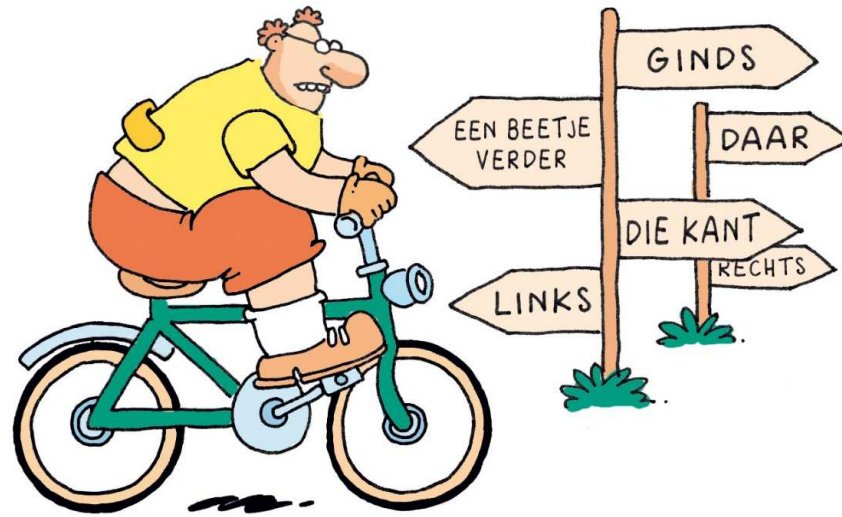
Figure 3 Total cost by disorder and type of cost (€PPP million, 2010), all disorders.

DEEL 2: (ONDER)DIAGNOSE

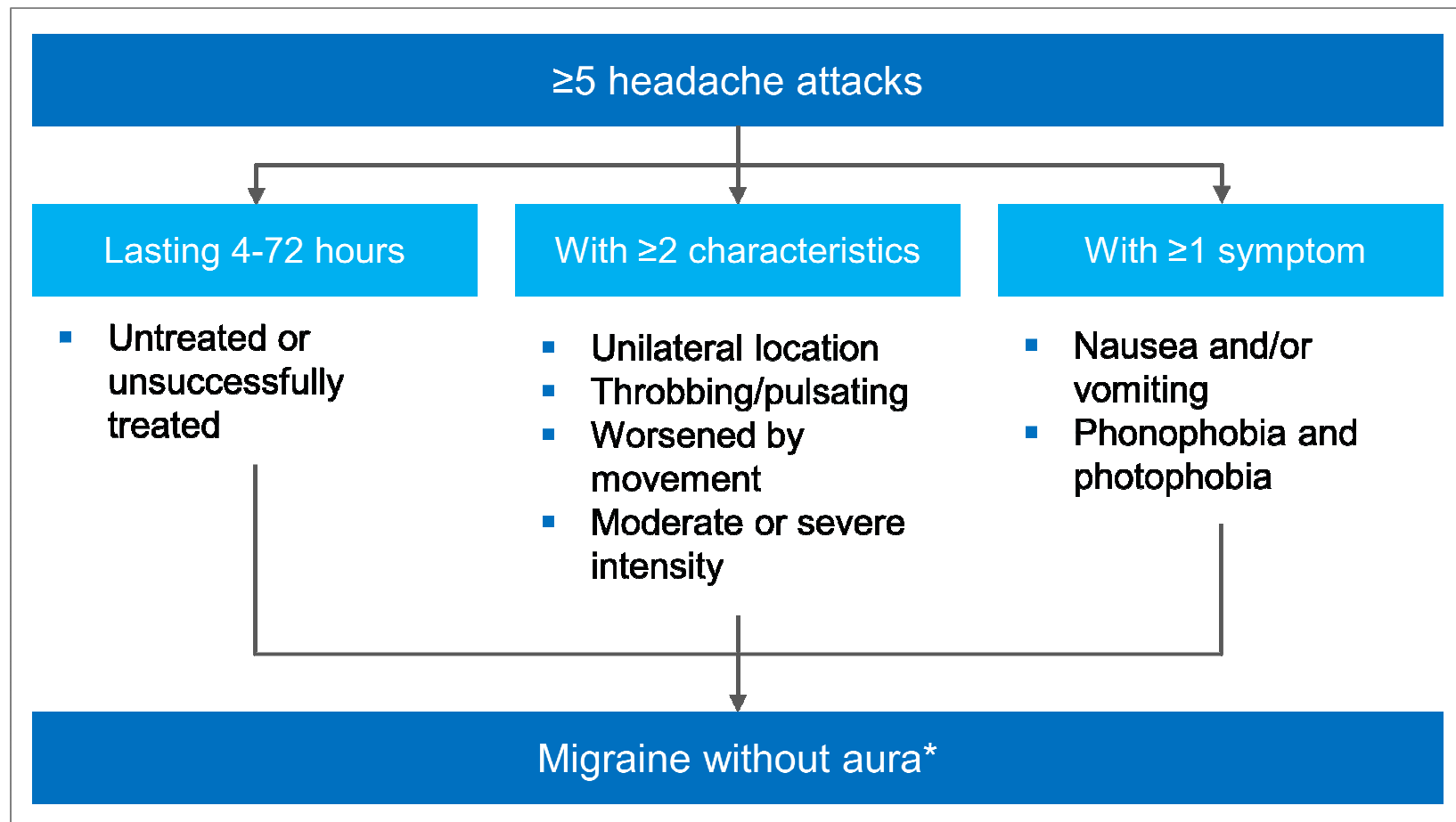


Headache 2001;41:646-657

Hoge prevalentie/disability
+
Onderdiagnose
+
Mythes
=



Diagnosis of migraine without aura

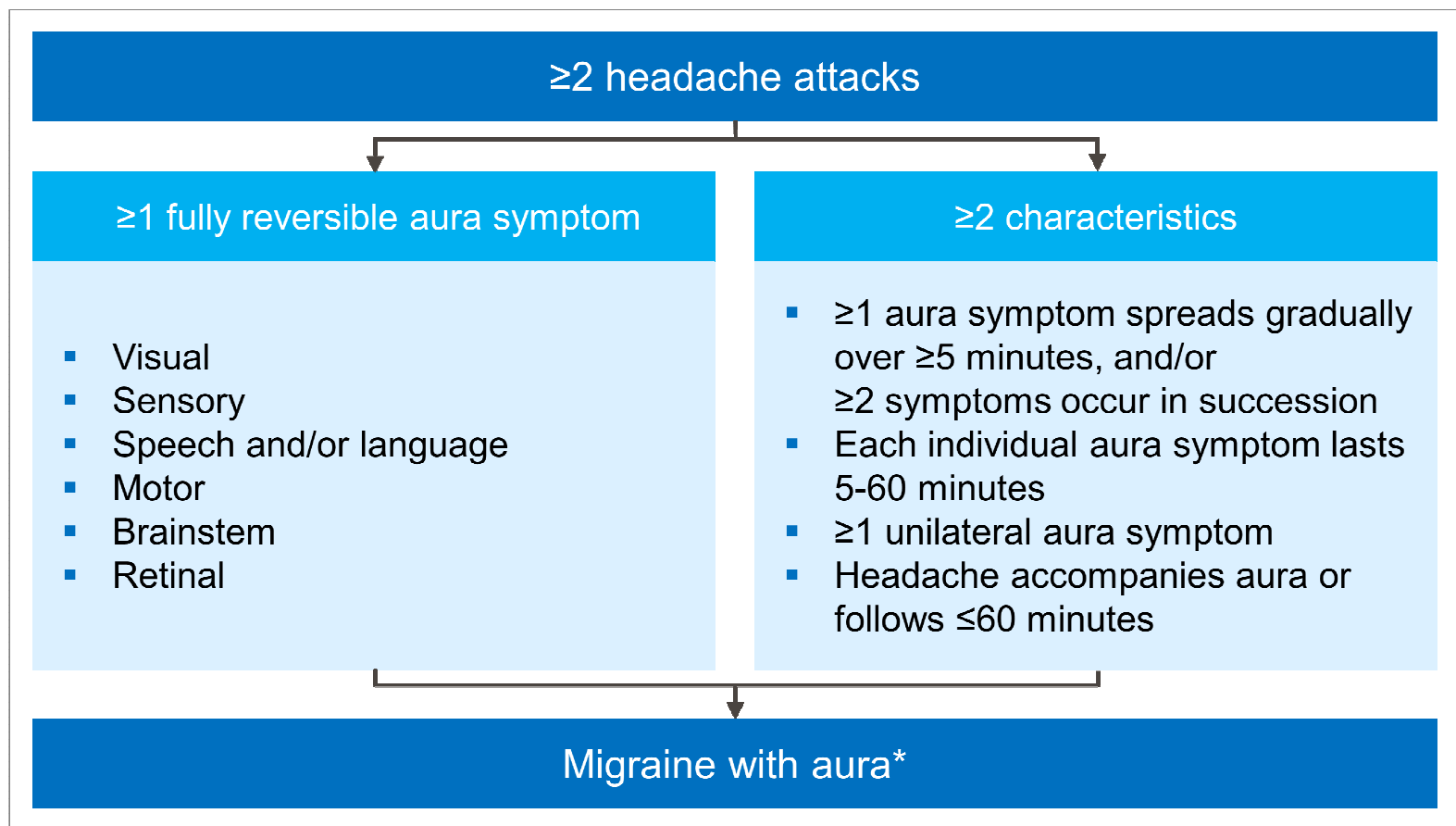
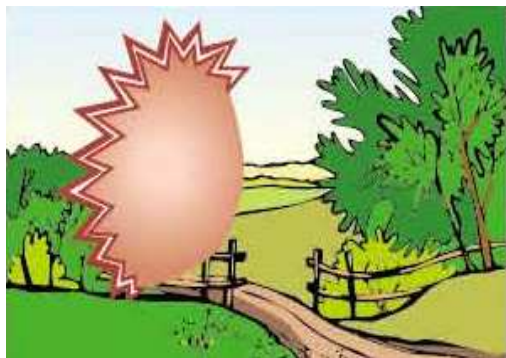


* Not better accounted for by another ICHD-3 diagnosis.

ICHD-3 = International Classification of Headache Disorders, 3rd edition.

Headache Classification Committee of the International Headache Society (IHS). *Cephalalgia*. 2018;38 (1):1-211.

Diagnosis of migraine with aura



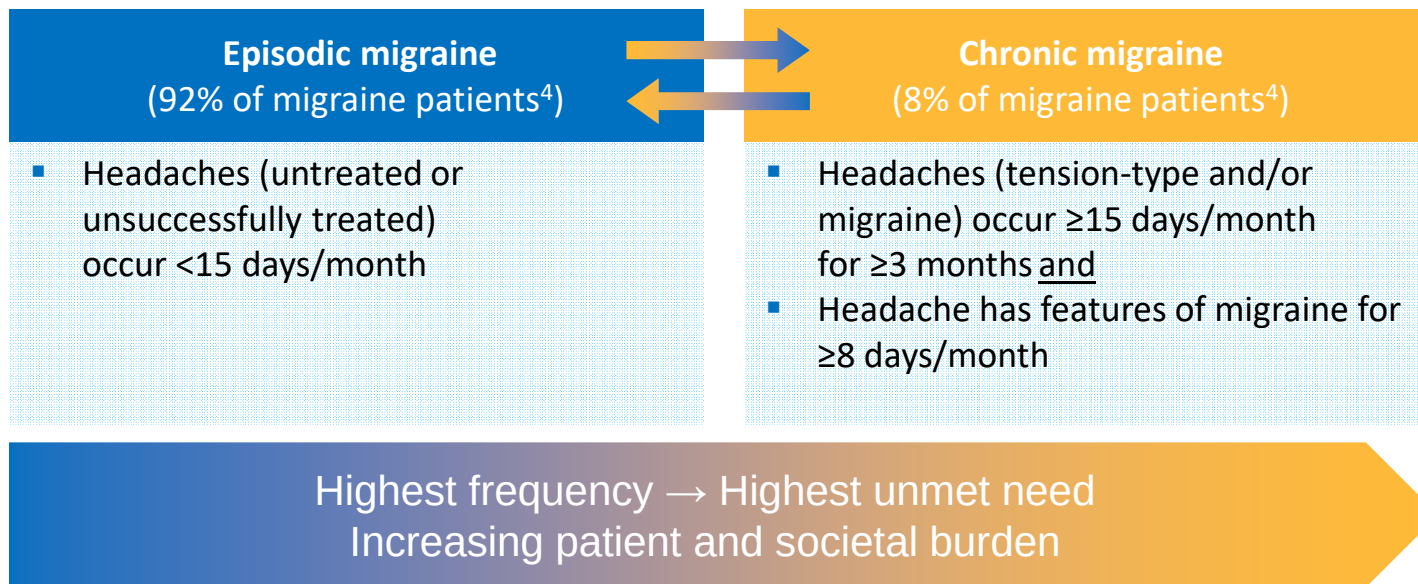
* Not better accounted for by another ICHD-3 diagnosis.

ICHD-3 = International Classification of Headache Disorders, 3rd edition.

Headache Classification Committee of the International Headache Society (IHS). *Cephalalgia*. 2018;38 (1):1-211.

Migraine: episodic or chronic

- An arbitrary frequency score of ≥ 15 days/month is often used to differentiate between EM and CM



- EM may transform to CM* at the rate of 2.5% per year
- CM often remits to EM (2-year transition rate of 26%)

Chronische migraine: risicofactoren

Painkiller overuse

Other chronic pain syndrome

Caffeine overuse

Stressful life events

Snoring, OSAS, obesity

Comorbidities (depression,...)

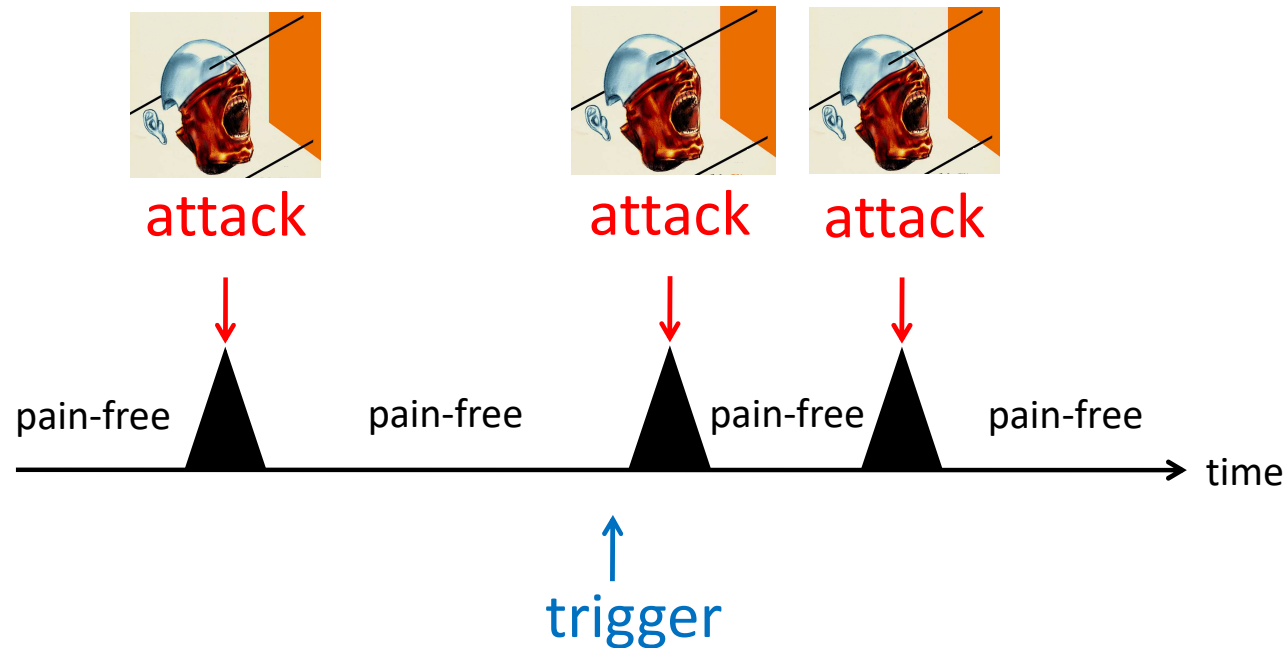
Curr Opin Neurol 2009;22:269-276

Nat Rev Neurol 2016;12(8):455-64

Nat Rev Neurol 2016;12(10):575-83

DEEL 3: FYSIOPATHOLOGIE

multifactorial brain disorder
neurovascular headaches



Migraine: aanval versus aandoening

Aanval

Voorboden (tot 80%)

Aura (tot 30 %)

Hoofdpijn

Misselijkheid-braken

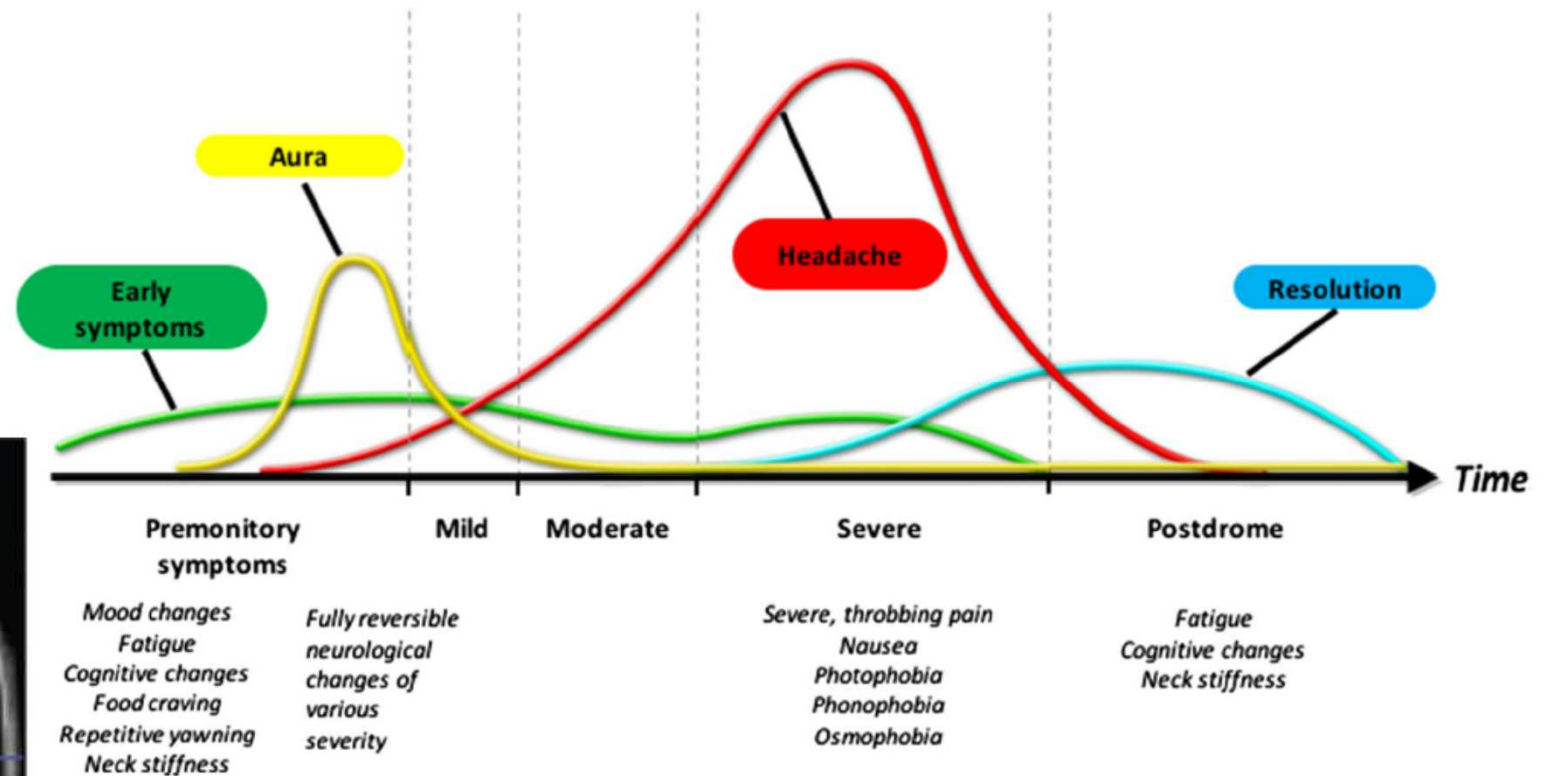
Overgevoeligheid

Craniale aut. sympt.

...

Postdrome

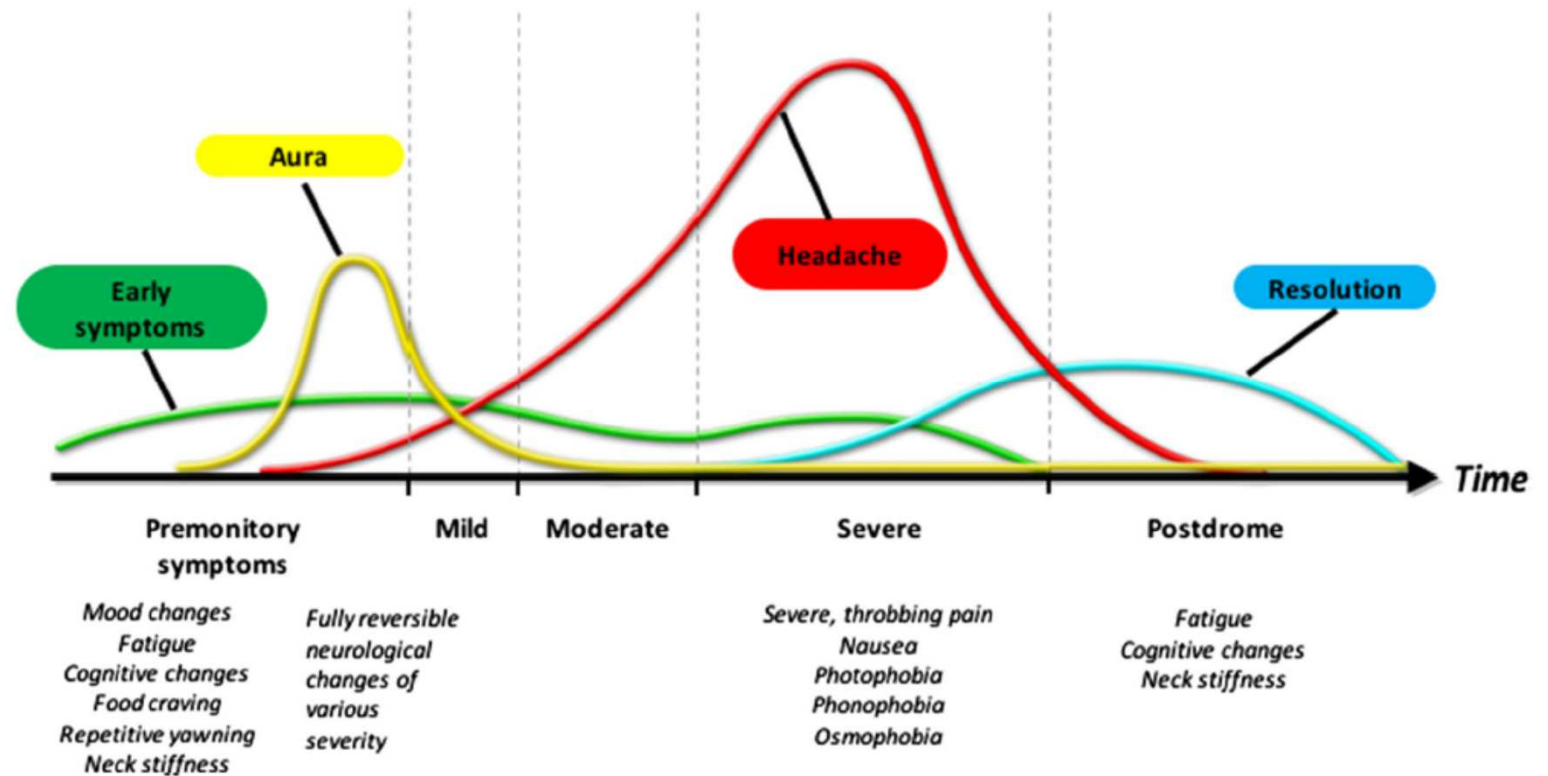
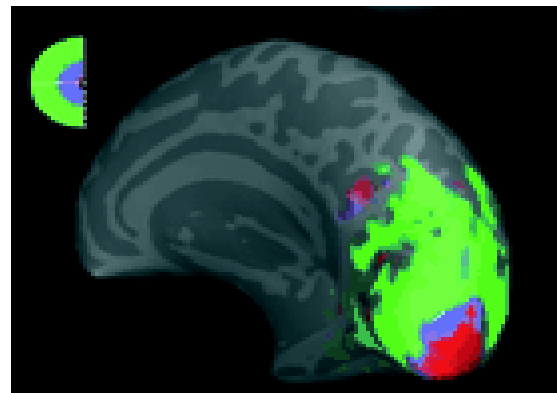
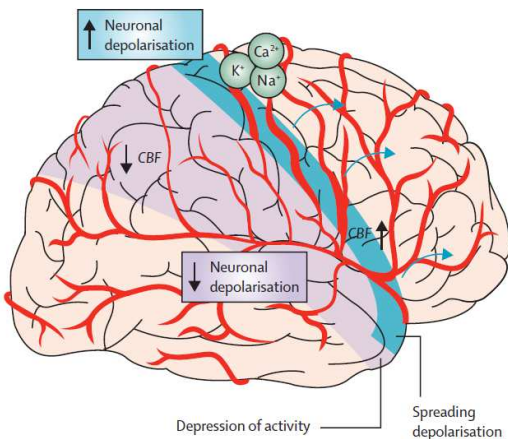
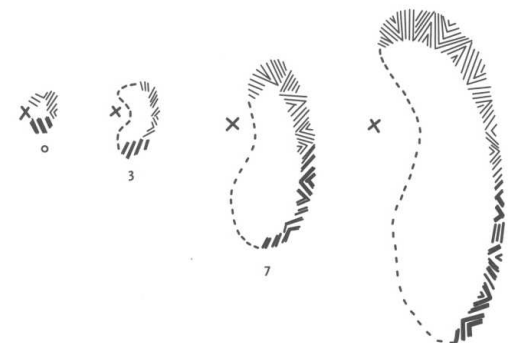
Migraine phases



Neurotherapeutics 2018;15(2):274-290
Headache 2007;47(10):1418-26

		Sessions where each nonheadache feature was reported, %		
Nonheadache feature		Premonitory (n = 803)	Headache (n = 559)	Postdrome (n = 425)
	Tired/weary	72.5	84.3	88.2
	Dizziness	22.9	31.1	19.3
	Lots of energy/hyperactivity	5.2	2.7	2.4
	Yawning	27.8	25.4	13.9
	Pale face	17.6	32.2	21.4
	Stiff neck	49.7	62.8	41.9
	Light sensitive	48.8	*	36.0
	Noise sensitive	38.4	*	31.8
	Blurred vision	28.0	34.7	17.4
	Sensitive skin	5.7	9.3	5.2
	Constipation	5.6	6.6	6.8
	Frequent urination	16.2	24.3	21.2
	Nausea/vomiting	23.5	*	14.8
	Hunger/food craving	18.2	18.1	15.1
	Thirst	26.0	32.2	32.2
	Intolerant/irritable	38.6	41.0	28.5
	Emotional	24.3	29.9	23.5
	Difficulty with thoughts	34.6	50.5	33.4
	Difficulty reading or writing	20.2	39.2	16.9
	Difficulty with speech	9.0	19.9	8.5
	Difficulty with concentration	51.1	72.6	55.5
	Other	53.8	34.5	43.8

Migraine phases



Neurotherapeutics 2018;15(2):274-290

Headache 2007;47(10):1418-26

Migraine: aanval versus aandoening

Aanval

Voorboden (tot 80%)

Aura (tot 30 %)

Hoofdpijn

Misselijkheid-braken

Overgevoeligheid

Craniale aut. sympt.

...

Postdrome

Aandoening (disorder)

Uitlokkende factoren

Familiaal

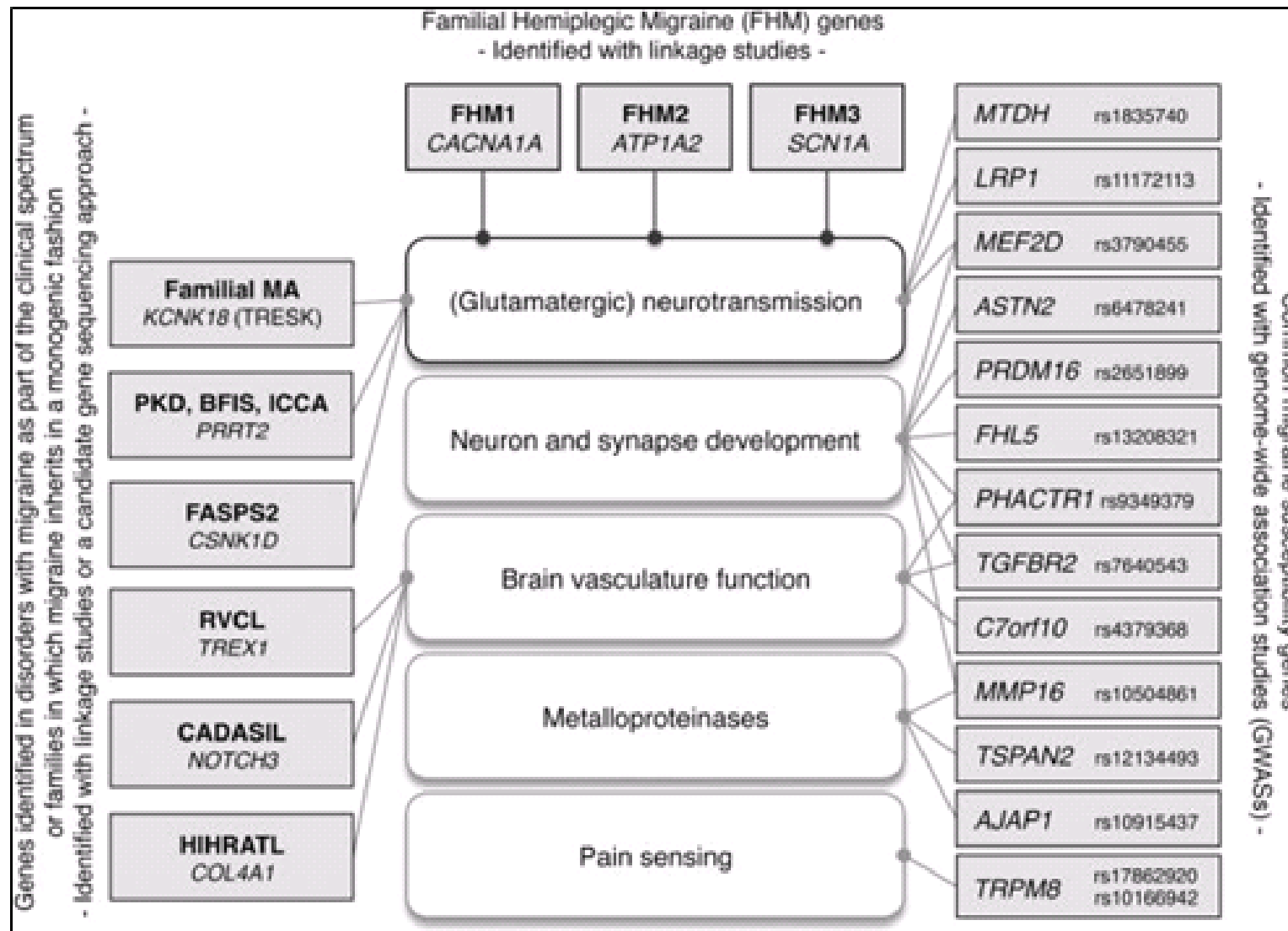
Neurobiologie

Migraine triggers

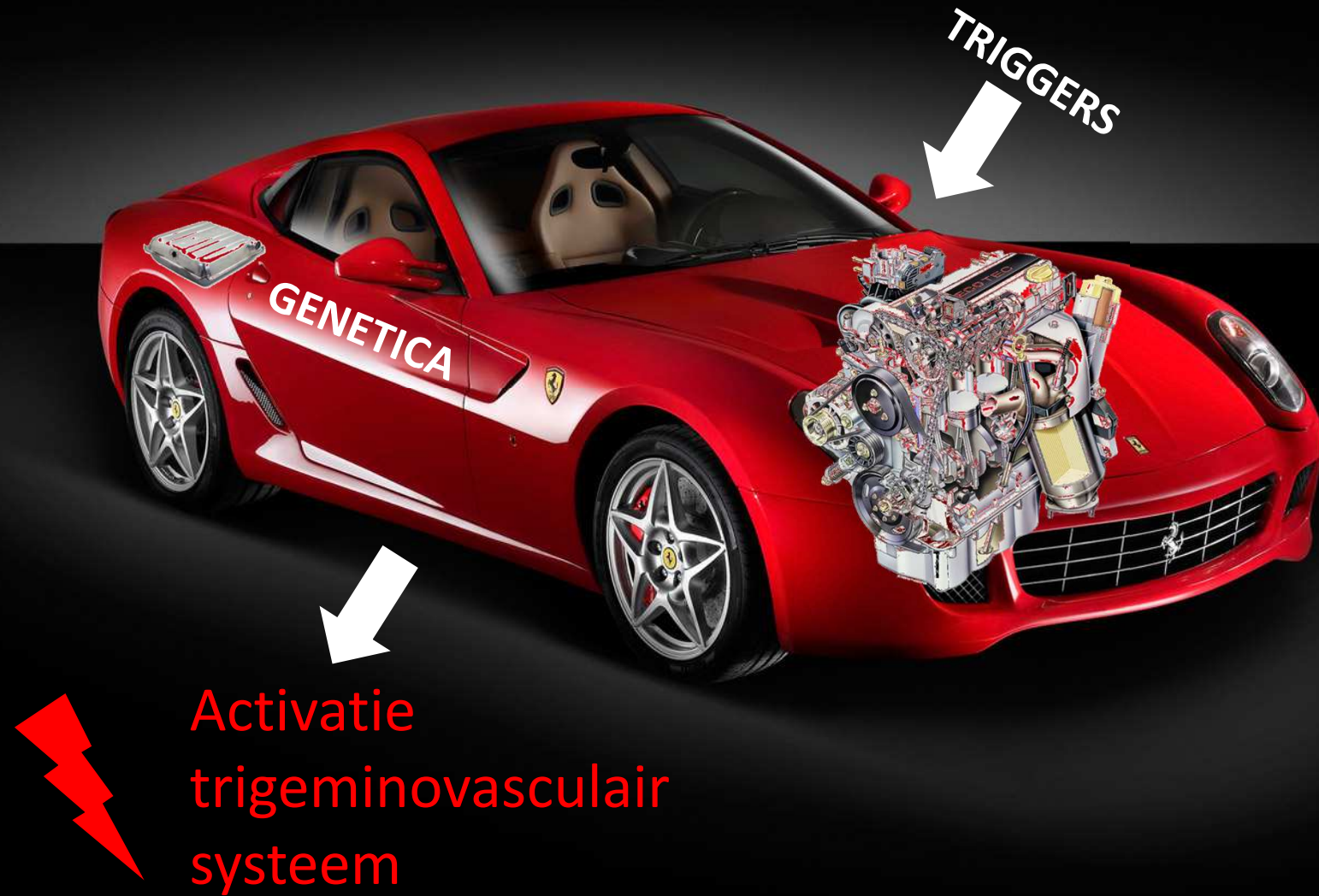


Diet	Certain foods in some people and alcohol, but more commonly delayed, missed or inadequate meals, caffeine withdrawal and/or dehydration	
Sleep	Changes in sleep patterns including lack of sleep or excessive sleep	
Other lifestyle	Intense exercise or long distance travel across time zones	
Environmental	Bright or flickering lights, strong smells and marked weather changes	
Psychological	Emotional distress or relaxation after a stressful period	
Hormonal changes (in women)	Changes in female hormones that cause menstruation as well as breaks in hormonal contraception or hormone-replacement therapy	

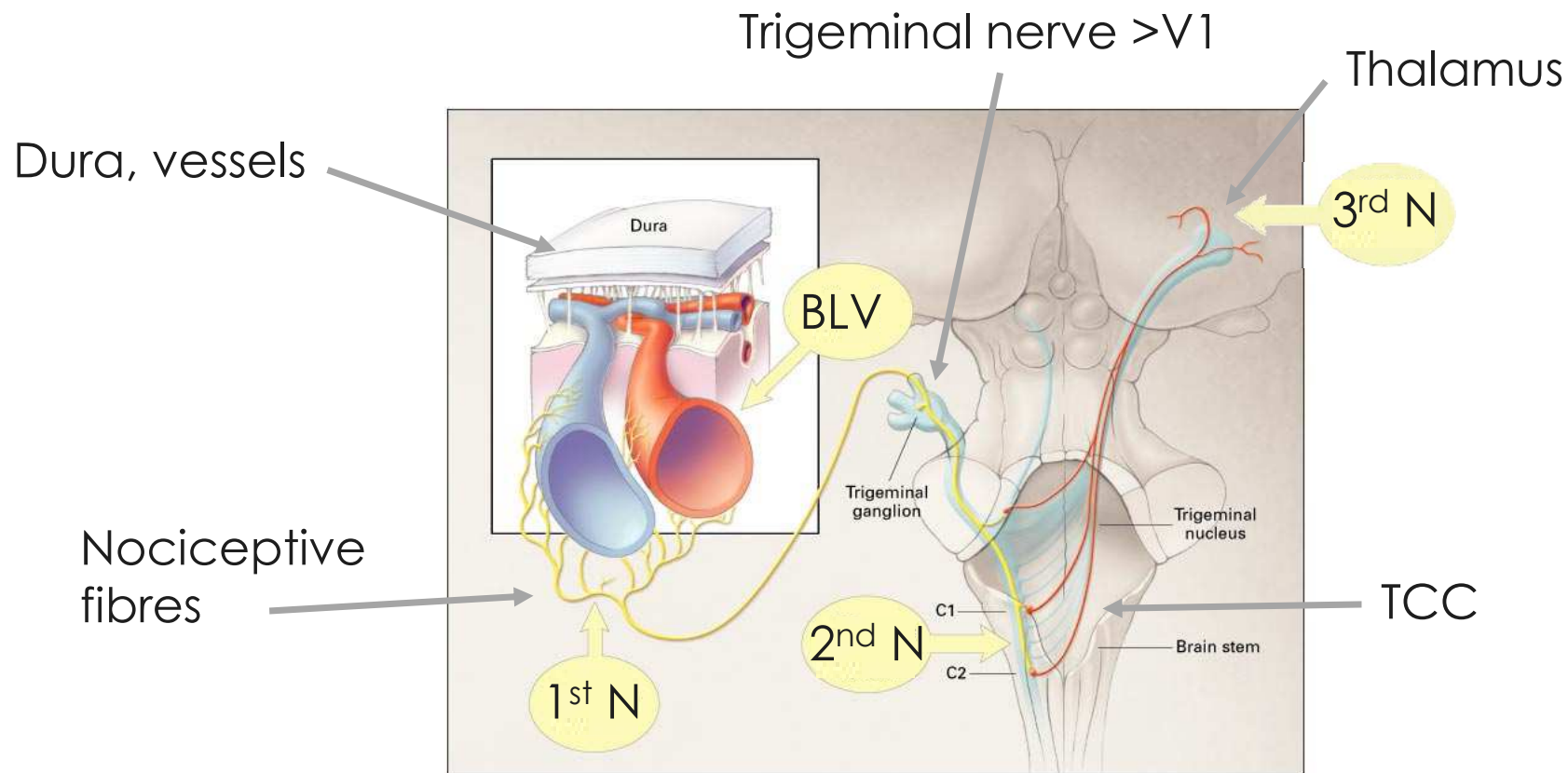
Belangrijk: individueel !



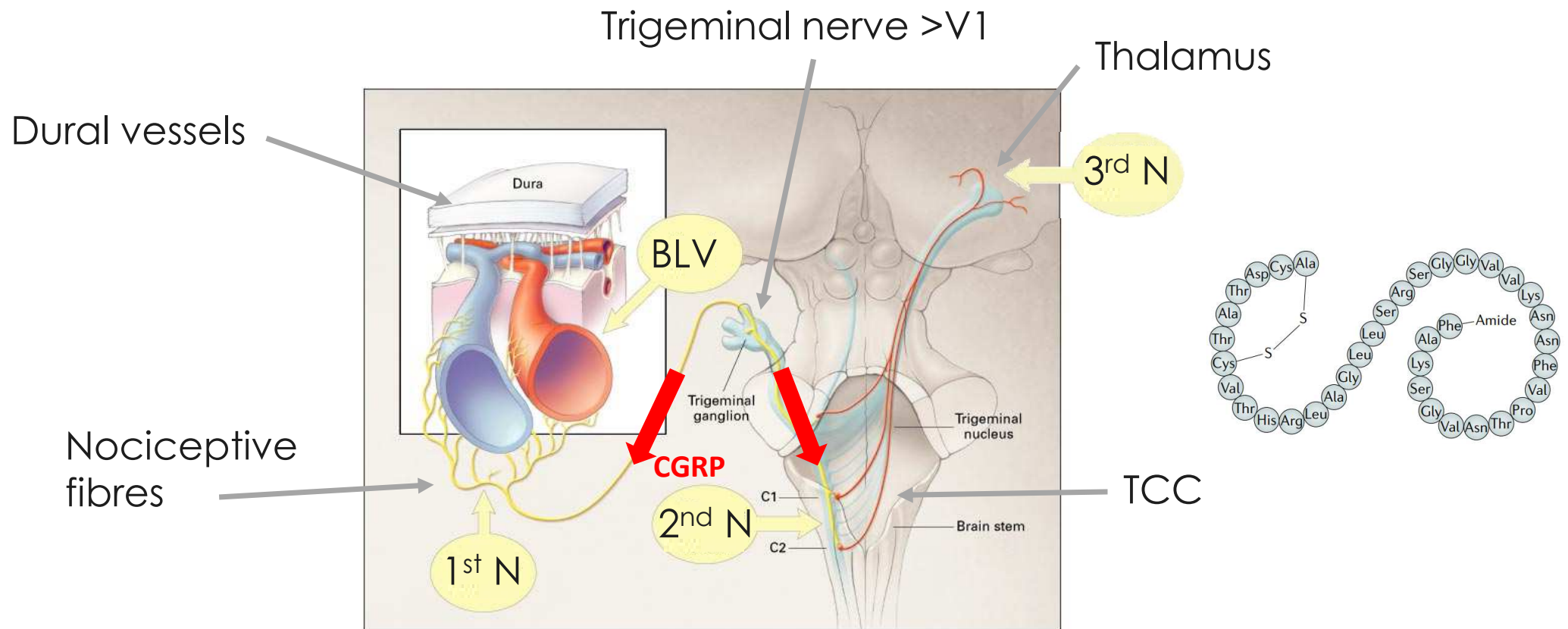
Migraine neurobiologie



Trigeminovascular system

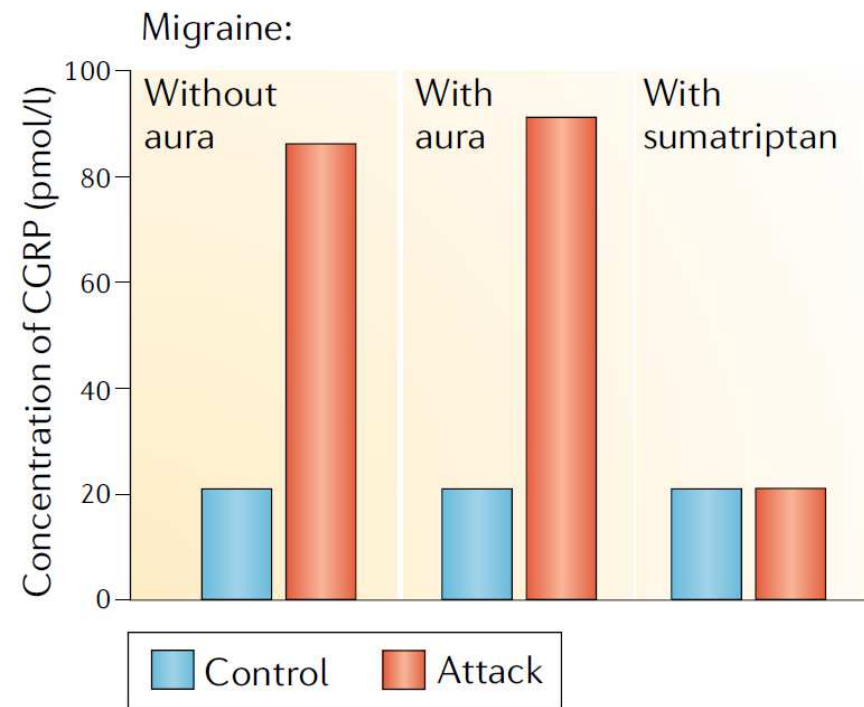
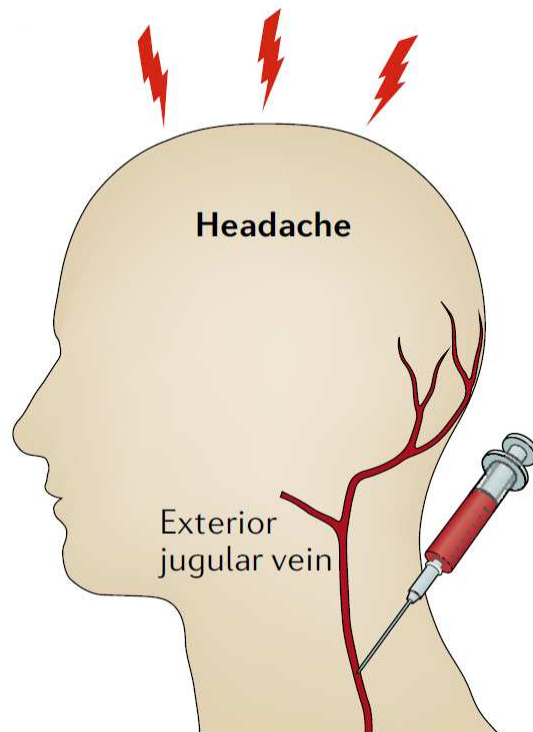


Calcitonin gene-related peptide



Nature 1982;298:240-244, Ann Neurol 1990;28(2):183-187

Migraine: TVS activation, CGRP



DEEL 4: MANAGEMENT

Steiner et al. *The Journal of Headache and Pain*
<https://doi.org/10.1186/s10194-018-0899-2>

(2019) 20:57

The Journal of Headache
and Pain

CONSENSUS ARTICLE

Open Access

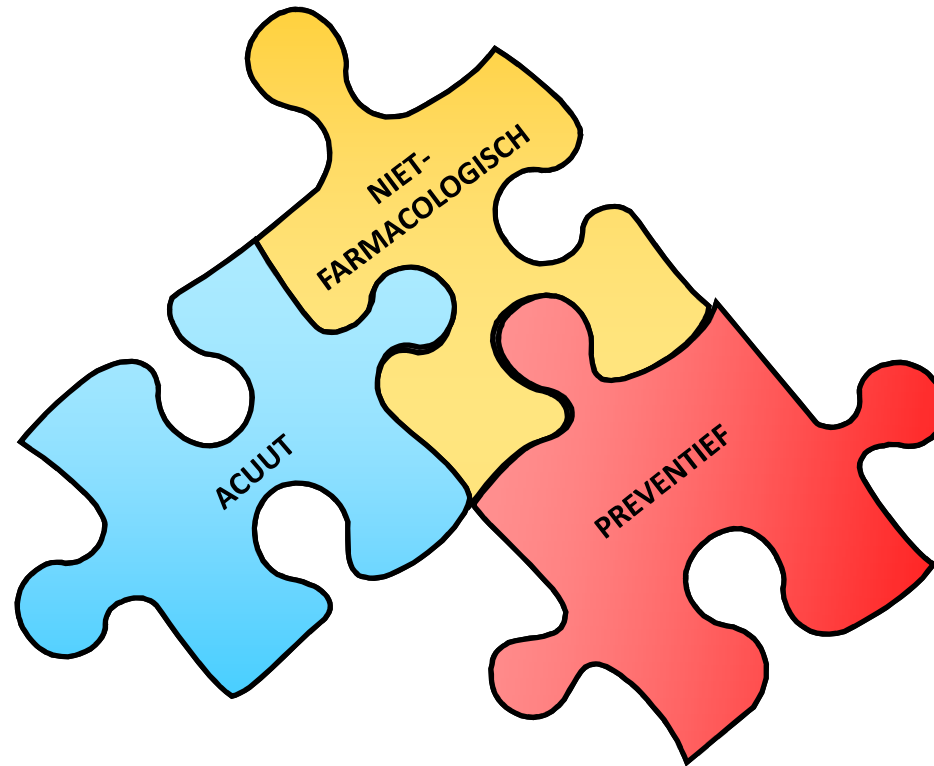
Aids to management of headache disorders in primary care (2nd edition)



on behalf of the European Headache Federation and *Lifting
The Burden: the Global Campaign against Headache*

T. J. Steiner^{1,2*}, R. Jensen³, Z. Katsarava^{4,5}, M. Linde^{1,6}, E. A. MacGregor⁷, V. Osipova^{8,9}, K. Paemeleire¹⁰, J. Olesen³,
M. Peters¹¹ and P. Martelletti^{12,13}

Migraine management



Agenda



**Migraine
dagboek**




Voorbeeld

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Migraine (M) Hoofdpijn (H)				H	H					H	M	M	H					H	M	H					M	H					
HP-Score				3	2					3	7	6	2					4	8	3					6	2					
Menstruatie																											0	0	0	0	0
Acute medicatie				X						X	T	X						X	T	X					X						

Naam :
Maand :

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Migraine (M) Hoofdpijn (H)																															
HP-Score																															
Menstruatie																															
Acute medicatie																															



Legende

M = Migraine

H = Hoofdpijn (buiten migraine-aanval)

HP = Hoofdpijnscore (0-10)
0 = geen pijn
10 = ondraaglijke pijn

0 = Ongesteld

X = Medicatie ingenomen

T = Triptanen

Trigger management

Regelmatige maaltijden, geen dieet

Alcohol

Deshydratatie vermijden

Lichaamsbeweging

Regelmatig slaappatroon

Caffeine overgebruik

Stress management

Rookstop

Chronische migraine: risicofactoren

Painkiller overuse

Other chronic pain syndrome

Caffeine overuse

Stressful life events

Snoring, OSAS, obesity

Comorbidities (depression,...)

Withdrawal

Treat and avoid excess analgesics

Decaf

Stress management

CPAP, weight loss, aerobic exercise

Manage comorbidities

Curr Opin Neurol 2009;22:269-276

Nat Rev Neurol 2016;12(8):455-64

Nat Rev Neurol 2016;12(10):575-83

Outcome of acute therapy trials

Guidelines for controlled trials of drugs in migraine: Third edition. A guide for investigators

- Pain-free at 2h (versus pain relief at 2h)
- Sustained pain-free
- Adverse events

AHS evidence assessment: level A

Paracetamol 1000 mg (for non-incapacitating attacks)

(DHE nasal spray)

NSAIDs: ASA, diclofenac, ibuprofen, naproxen

(Opioids: Butorphanol nasal spray 1 mg)

Triptans

Combinations:

paracetamol/ASA/caffeine

sumatriptan/naproxen

Properties of NSAIDs/paracetamol

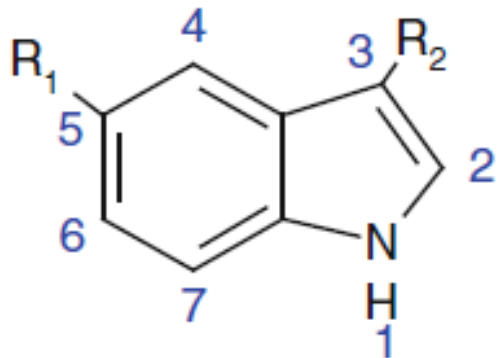
Medication	Formulation	T _{max} (h)	Elimination half-life (h)	Usual Dose (mg)	Dosage interval	Maximum daily dose (mg/day)	NNT: 2 hour headache relief	NNT: 2 hour pain free
Acetaminophen	Oral tablets	0.5-1	2	1000	4 h	4000	5.0	12
Ibuprofen	Oral tablets	1-2	2	400	4 h	2400	3.2	7.2
	Solubilised (liquid) tablets	<1	2	400	4 h	2400		
Naproxen sodium (absorbed more quickly than Naproxen)	Tablets	2	14	500-550mg (up to 852mg)	Twice a day	1375	6.0	11
Acetylsalicylic acid (ASA)	Tablets	1-2	ASA: 0.25 Salicylate (active): 5-6 (after 1g dose)	975-1000	4-6 h	5400	4.9	8.1
	Effervescent	~20 mins		975-1000	4 h	2600		
Diclofenac potassium	Tablets	<1	2	50	3-4 times a day	150	6.2	8.9
	Powder for oral solution	15 min	2	50	Single dose	50 (once per day)	5.1	7.4

Triptans: formulations

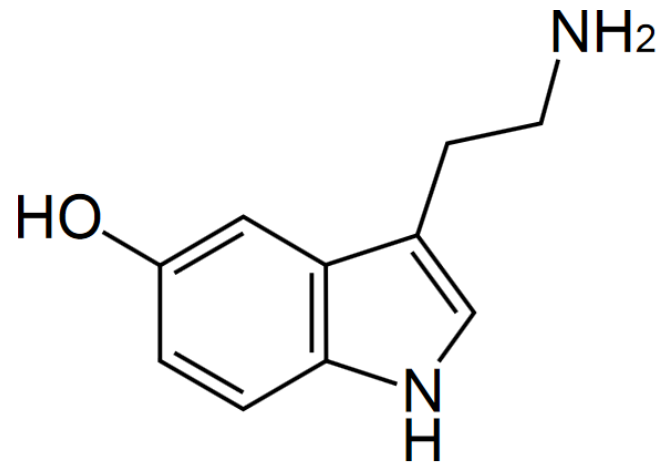
<u>Drug</u>	<u>Formulation</u>	<u>Remark</u>
almotriptan	tablets	
eletriptan	tablets	
frovatriptan	tablets	
naratriptan	tablets	
rizatriptan	tablets	propranolol: 5 mg
sumatriptan	tablets	
	nasal spray	limited nasal abs.
	SC	NNT 2hPF: 2.3
zolmitriptan	tablets	
	nasal spray	30 % nasal abs.

MOA of triptans

- Specifically designed for acute migraine treatment
- 5-HT_{1B}/1D/(1F) receptor agonists
- Trigeminovascular system



Indole structure



Serotonin

Contraindications to triptans

Cardiovascular disease, including

uncontrolled hypertension

cerebrovascular disease

coronary artery disease

> 65 years

Hemiplegic migraine

Migraine with brainstem aura

(At risk of) pregnancy; lactation

Ergotamine/DHE < 24 hours

MAOI < 2 weeks

Medication-overuse headache

Overgebruik van pijnstillers kan leiden tot frequenter hoofdpijn!

Ergotamine of triptanen	≥ 10 dagen/maand
Opiaten of combinatie-analgetica	≥ 10 dagen/maand
NSAID of ASA of paracetamol	≥ 15 dagen/maand

Opiaten, benzodiazepines en barbituraten hebben in de regel
GEEN PLAATS in de behandeling van migraine

Risico op: verslaving, toename pijn en ongewenste nevenwerkingen



Research Methodology

Ipsos Healthcare

SAMPLE DESCRIPTION



General practitioners
with at least 3 years
of experience &
having seen at least 5
patients with
migraine in the past 3
months

SAMPLE SIZE



n=80
general
practitioners

QUOTA



Language:
50/50
Dutch/French

AVG. INTERVIEW DURATION



30
minutes

DATA-COLLECTION METHOD



CAWI

FIELDWORK PERIOD

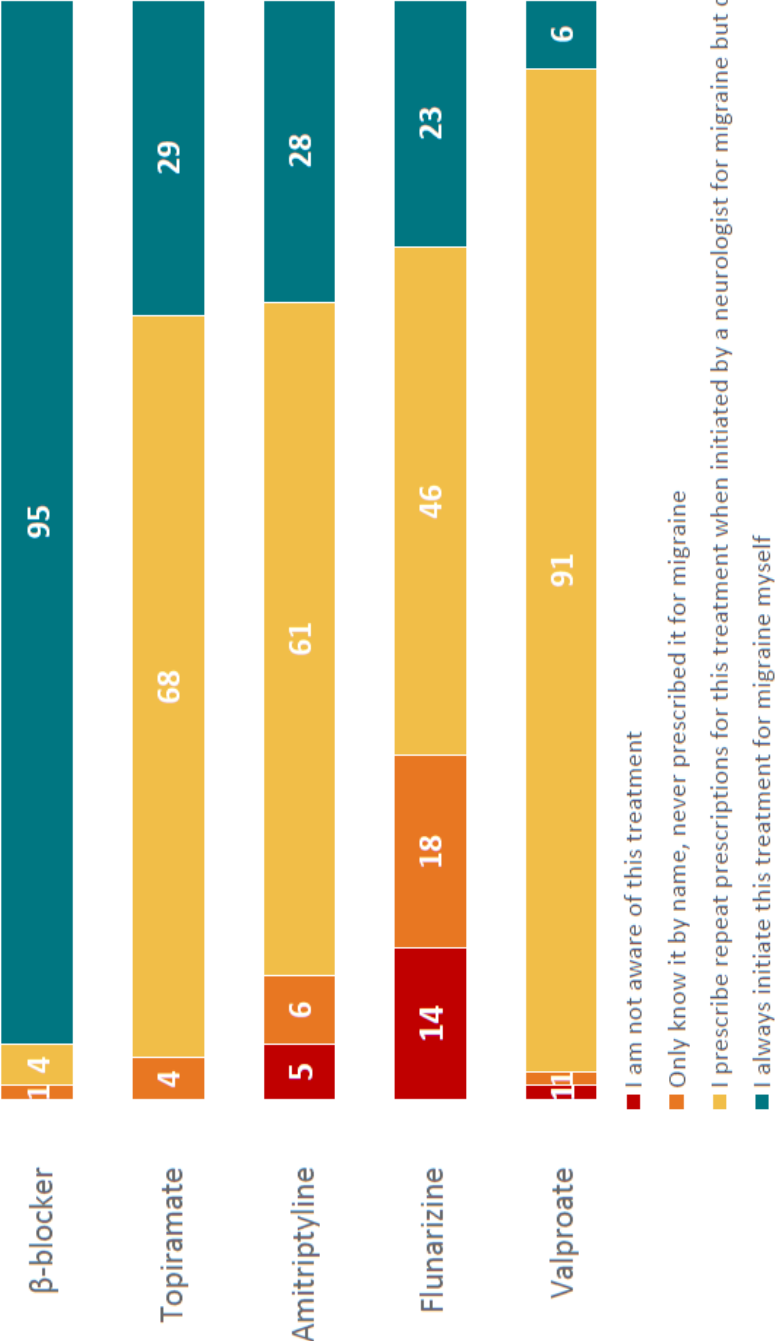


FROM:
27/07/2018
TO:
31/08/2018

GAME CHANGERS



The β -blocker is the most initiated by the GP himself as a prophylactic treatment for migraine. The other prophylactic treatments are often repeat prescriptions, of which Flunarizine is less well known compared to the other treatments. Experience with prophylactic treatments



More experienced GPs (40%) more often initiate treatment with Flunarizine for migraine themselves than less experienced GPs (5%). Less experienced GPs (68%) more often prescribe repeat prescriptions for Flunarizine than more experienced GPs (25%).

Base: Total sample (n=80)
Question: Q2.6 Which of the following statements describes best your experience with each of the following prophylactic treatments for migraine?

Migraine: preventive treatment

Prophylactic therapy should be added when migraine impairs quality of life,

And attacks cause disability on two or more days per month

And acute therapy has been optimised but does not prevent this, or is poorly tolerated

Or there is a risk of over-frequent use of acute therapy, even when it is effective

And the patient is willing to take daily medication

Migraine: preventive treatment

Migraine calendar	Should be kept by every patient to assess efficacy and promote adherence
Adherence	Poor adherence impairs efficacy of migraine prophylactics; once-daily dosing is associated with better adherence
Dosing	Start at a low dose and increase in the absence of troublesome side-effects
Therapeutic trial of adequate length	Do not discontinue drugs that appear to be ineffective too soon; 2-3 months may be needed to achieve efficacy
Withdrawal	Tapered withdrawal may be considered after 6 months of good control, No later than after 1 year
Contraindications	Take the contraindications and specific precautions associated with the available drugs into account

Table 9 Migraine prophylactic drugs with evidence of efficacy in adults (drugs are listed in a suggested order of use; within classes [beta blockers and CGRP monoclonal antibodies], they are listed alphabetically)

Beta-adrenergic blockers without partial agonism:		• observe general contraindications, including comorbid depression • propranolol has best evidence of efficacy, but not evidence of best efficacy • cardioselective and non-lipophilic drugs (bisoprolol, atenolol, metoprolol) are likely to be better tolerated
• atenolol 25-100 mg twice daily • bisoprolol 5-10 mg once daily • metoprolol 50-100 mg twice daily or modified-release 200 mg once daily • propranolol LA 80-160 mg once to twice daily		
Amitriptyline 10-100 mg at night		• may be preferred when migraine coexists with tension-type headache, depression or sleep disturbance
Topiramate 50 mg twice daily		• titrate over 4 weeks from 25 mg once daily • contraindicated in pregnancy
Candesartan 16 mg once daily		• start at 8 mg once daily and titrate weekly • contraindicated in pregnancy
Sodium valproate 600-1500 mg daily		• titrate upwards • avoid altogether in women of child-bearing potential (even on contraception); absolutely contraindicated in pregnancy
Flunarizine 5-10 mg once daily		• observe general contraindications, including comorbid depression
CGRP monoclonal antibodies (to the peptide or its receptor):		• newly licensed, not yet universally available or reimbursed, usually restricted to specialist care and reserved for those failing (or not tolerating) other prophylactics • all self-administered by auto-injector • high relative cost
• erenumab 70 or 140 mg s/c once monthly • fremanezumab 225 mg s/c once monthly or 675 mg s/c once quarterly • galcanezumab 240 mg s/c, then 120 mg s/c once monthly		

Aanvraag tot terugbetaling van
TOPAMAX® (Topiramaat, Janssen-Cilag N.V.)
in het kader van **MIGRAINE**

Ondergetekende Dokter in de Geneeskunde vraagt
aan de Adviserend Geneesheer van de verzekeringsinstelling
ten voordele van

— **Patiënt** —

Naam en voornaam:
Adres:
Gemeente: Postcode:
Titularis / echtgeno(o)t(e) / kind / ascendent (onnodige doorhalen)
Verzekeringsinstelling:
Nr Inschrijving:

— of kleeftrookje van de mutualiteit —

voor TOPAMAX®

60 tabletten/capsules à 25 mg topiramaat
60 tabletten/capsules à 50 mg topiramaat

- ☐ Terugbetaling voor maanden (max. 6 maanden)
☐ Aanvraag tot verlenging van terugbetaling voor maanden
(periodes van max. 60 maanden)

Voor de profylactische behandeling van migraine bij rechthebben-
den die voldoen aan de IHS-diagnosecriteria van migraine, bij wie
een profylaxisbehandeling aangewezen is wegens de frequentie
en/of de intensiteit van de migraineaanvallen en bij deze die een
onvoldoende respons hebben op propranolol, of die het niet ver-
dragen, of die een contra-indicatie zoals opgenomen in de officiële
wetenschappelijke bijsluiter van propranolol, vertonen.

De maximale dagelijkse vergoedbare dosering bedraagt: 2 x 50 mg
per dag, die, na de titratieperiode, zal bekomen worden met een
maximum van 2 tabletten per behandelingsdag.

— **Behandelend geneesheer** —

STEMPEL



A comparative study of candesartan versus propranolol for migraine prophylaxis: A randomised, triple-blind, placebo-controlled, double cross-over study

Cephalalgia

0(0) 1–10

© International Headache Society 2013

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DOI: 10.1177/0333102413515348

cep.sagepub.com

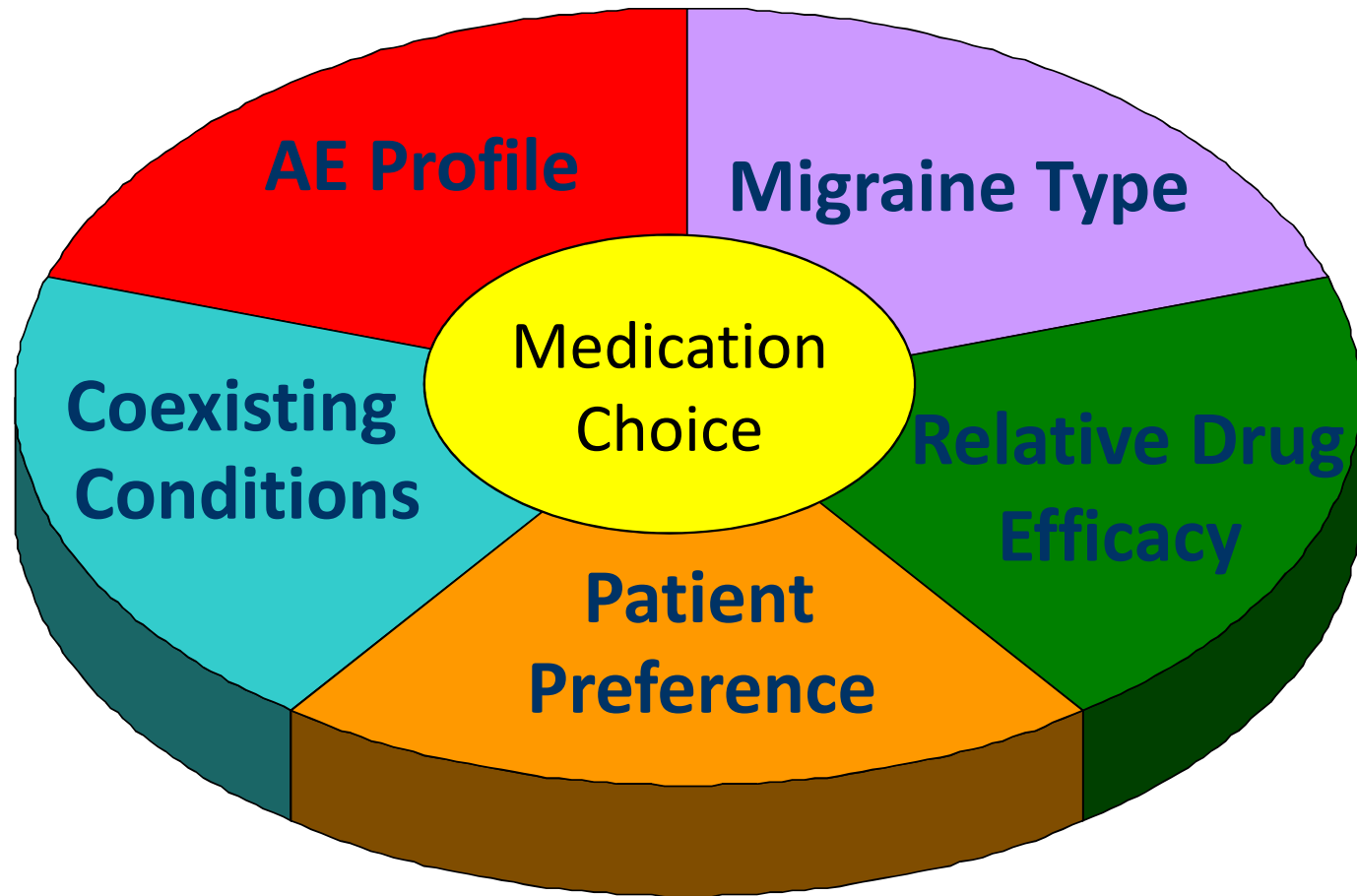


Conclusion: It is confirmed that candesartan 16 mg is effective for migraine prevention, with an effect size similar to propranolol 160 mg, and with somewhat different adverse events.

Table 10 Drugs used by specialists in chronic migraine prophylaxis

Topiramate, 50 mg or more twice daily	
Onabotulinum toxin A, 155-195 units by multisite injection	• not licensed for chronic migraine in some countries, <i>or</i> • not reimbursed, <i>and/or</i> • regulators require prior failure of two or more of the drugs used in prophylaxis of episodic migraine
CGRP monoclonal antibodies (to the peptide or its receptor):	• newly licensed, not yet universally available or reimbursed, usually restricted to specialist care and reserved for those failing (or not tolerating) other prophylactics • all self-administered by auto-injector • high relative cost
• erenumab 70 or 140 mg s/c once monthly • fremanezumab 225 mg s/c once monthly or 675 mg s/c once quarterly • galcanezumab 240 mg s/c, then 120 mg s/c once monthly	

Migraine: preventive treatment



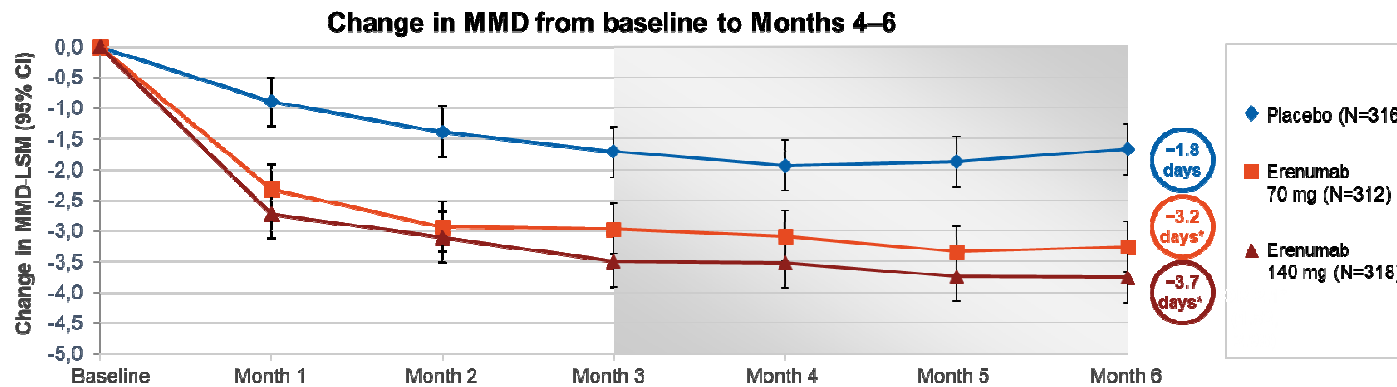
CGRP pathway mAbs

	Erenumab	Fremanezumab	Galcanezumab	Eptinezumab
Condition	EM, CM	EM, CM	EM, CM	EM, CM
Type	Human	Humanized	Humanized	Humanized
Target	CGRP receptor	CGRP	CGRP	CGRP
Route, dosing	70 mg or 140 mg SC monthly	Quarterly 675 mg SC or monthly 225 mg SC	Loading dose 240 mg SC followed by 120 mg SC monthly	Quarterly 100 to 300 mg IV
Regulatory	FDA, EMA	FDA, EMA	FDA, EMA	FDA

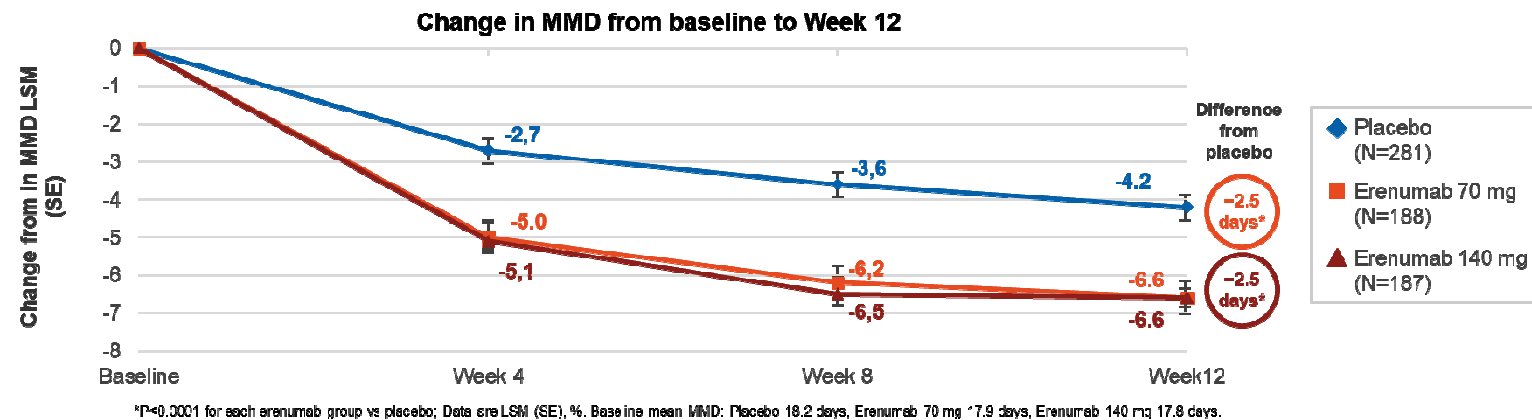


Erenumab significant efficacy in EM and CM

EM¹



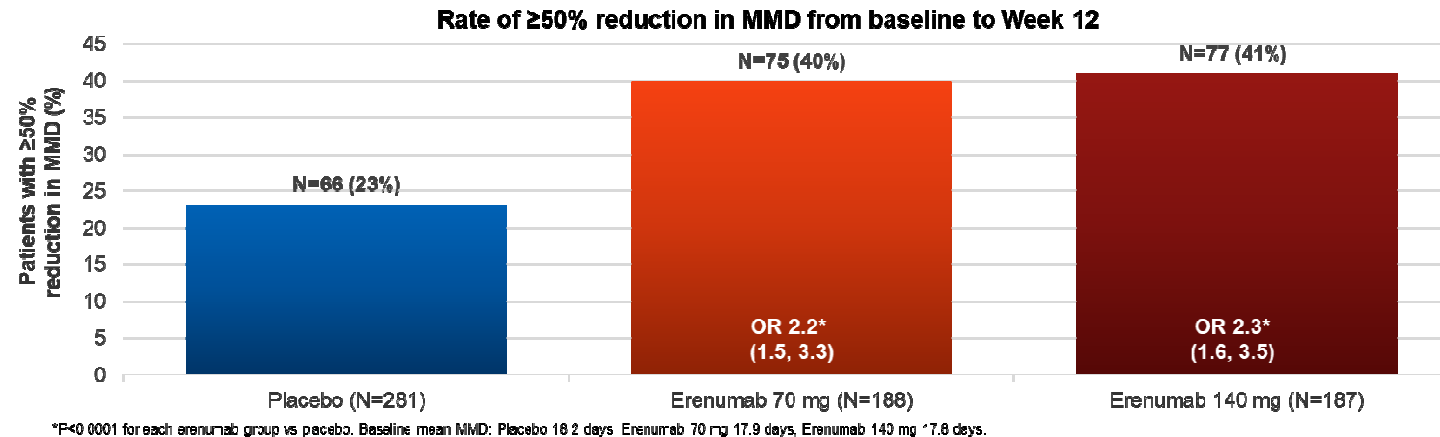
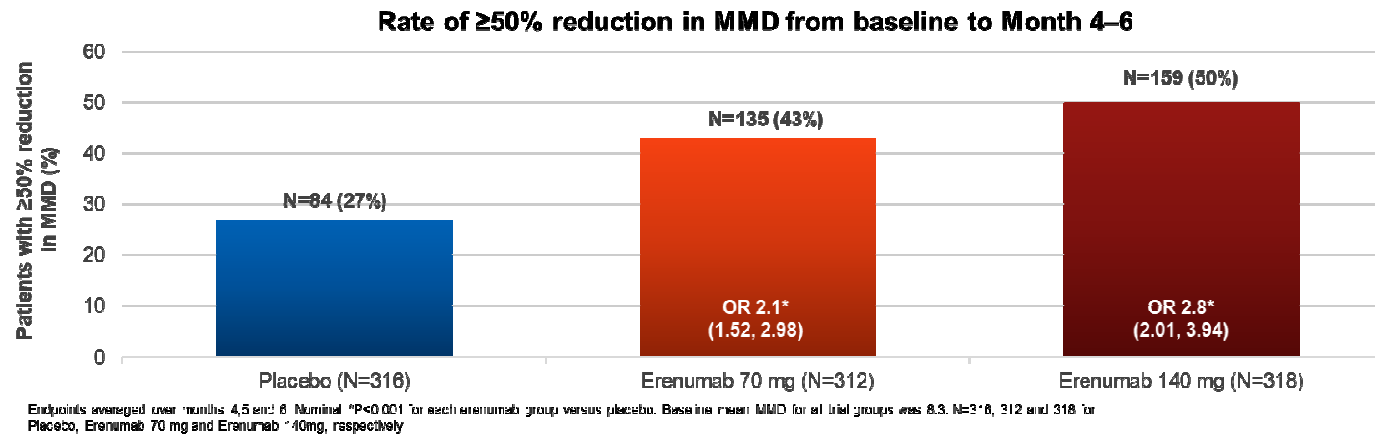
CM²



CI, confidence interval; EM, episodic migraine; CM, chronic migraine; LSM, least-square mean; SE, standard error; MMD, monthly migraine days.
 Episodic migraine defined as patients with at least 4 and fewer than 15 migraine / headache days per month; Chronic migraine defined as ≥15 headache days / month, 8 of which are migraine and in the absence of medication overuse.

1. Goadsby PJ et al. N Engl J Med.2017;377:2123–32; 2. Tepper S et al. Lancet Neurol 2017;16:425–34

Erenumab significant efficacy in EM and CM



Data are OR ± 95% CI. CI, confidence interval; EM, episodic migraine; CM, chronic migraine; MMD, monthly migraine days; OR, odds ratio. Episodic migraine defined as patients with at least 4 and fewer than 15 migraine / headache days per month. Chronic migraine defined as ≥15 headache days / month, 8 of which are migraine and in the absence of medication overuse.

1. Goadsby PJ et al. N Engl J Med.2017;377:2123–32; 2. Tepper S et al. Lancet Neurol 2017;16:425–34

CGRP PATHWAY mAbs

- mAbs do not cross the BBB
peripheral MOA sufficient to block migraine
- mAbs are eliminated by the RES
- Range EM, CM±MOH
- Quick onset (<1 week)
- Clinically meaningful response by 1 month
- Highly selective: ↓ off-target effects and interactions
- Safety and tolerability similar to placebo in RCT's

Take home messages

Tweede belangrijkste oorzaak YLD

Ijsberg

Criteria: spectrum

Multifactoriële hersenaandoening

Trigeminovasculair systeem (CGRP)

Triggers → lifestyle

Acuut: pain-free at 2 hrs, NSAID/triptan

Preventief: multipele, individualiseer, CGRP pathway mAbs