Migraine

klinische gegevens
pathofysiologie
behandeling
/ontwikkelingen

Paul Bouma

Blaricum, 5 april 2018

Disclaimer / disclosures

Contacten met, onderzoek gedaan voor of vergoedingen ontvangen van

- Astra Zeneca
- Bayer Schering
- Biogen Idec
- Celgene
- GSK
- MerckSerono

MSD
Novartis
Pfizer
Roche
Sanofi Genzyme
TEVA Aventis

In het kader van Migraine onderwijs, presentaties en advies gegeven via NVHP en OOR Utrecht

Lid van de NHV, NVHC, Fellow IHS

Geen aandelen of opties Farma.

http://transparantieregister.nl/nl-NL/Zoeken-in-het-register/2016/99020213101

Deze presentatie

Klinische gegevens

- Epidemologie
- Classificatie

Pathofysiologie

- Hoofdpijn
- Migraine

Farmacologie / ontwikkelingen

- Huidig arsenaal
- “The next big thing”

Klinische gegevens

Hoofdpijn & Migraine en werk

VS: totale kosten hoofdpijn 12 mrd USD, waarvan de helft door arbeidsongeschiktheid

Prevalentie voor hoofdpijn bedraagt 46%, waarvan een kwart voor migraine. Spanningshoofdpijn tot 78%

Meeste migraine tussen 25 en 55 jaar, meeste spanningshoofdpijn tussen 30 en 40 jaar

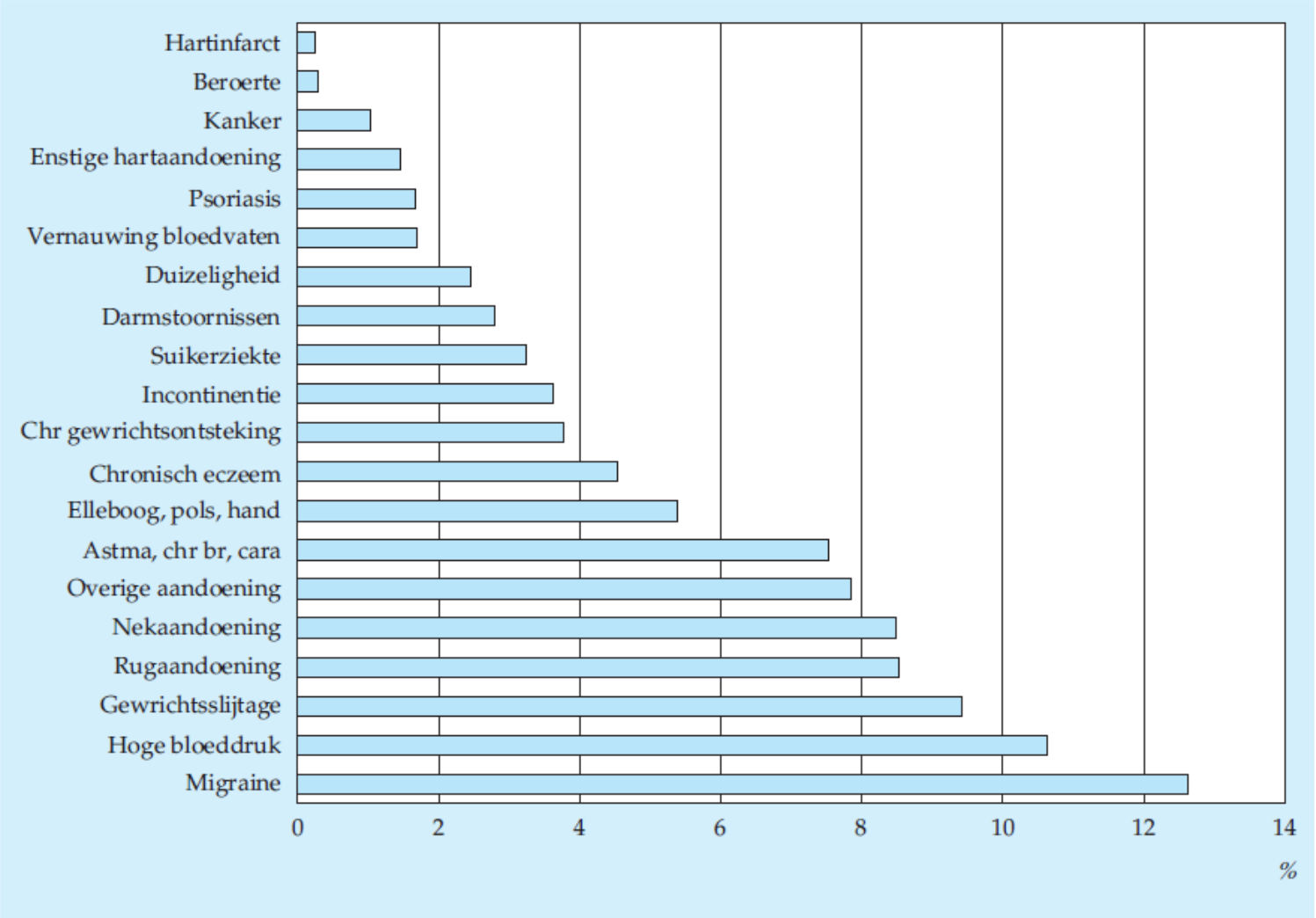
Arbeidsverlies bedraagt meer dan tien dagen, terwijl 29% migaineurs met hoofdpijn doorwerkt (in NL)

Doorwerken met migraine vermindert effectiviteit en productiviteit met 50%

Hawkins K, et al. J Occup Environ Med 2007; 49: 368–374
Pop PH, Gierveld CM, Karis HA, et al. Eur J Neurol 2002; 9: 171–174
Lardon A, et al. Cephalalgia 2017, Vol. 37(1) 64–73

Wat is het probleem?

5.1 Prevalenties chronische ziektes, 2001/2008



Bron: CBS.

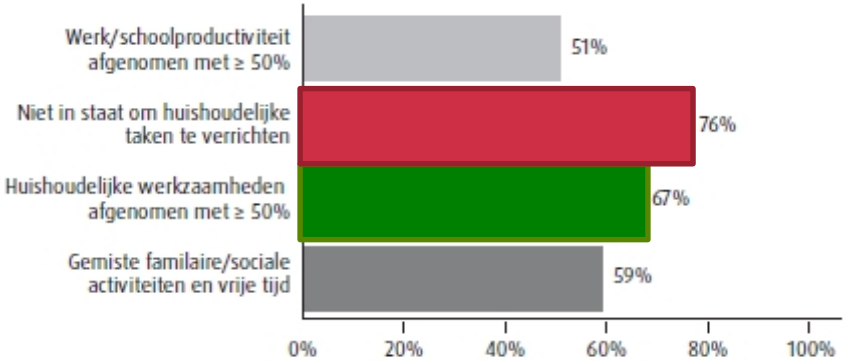
Migraine in Nederland

De nederlandse situatie:

Voorkomen: vrouwen 17%, mannen 8%

Behandeling

- 1/3 is nooit door arts gezien
- 1/3 gaat niet meer naar arts
- 1/3 wordt behandeld door arts



"Treatment gap"

- Ongeveer 50% gebruikt adequate aanvalsbehandeling
- Ongeveer 50% heeft indicatie voor onderhoudsbehandeling
- Hiervan krijgt 13% daadwerkelijk medicatie

Dus: meer dan voldoende ruimte voor verbetering!

Dekker J, ea; Cephalalgia 2013;33:1070

Hoofdpijnclassificatie

Headache Classification Committee of the International Headache Society (IHS)
The International Classification of Headache Disorders, 3rd edition (beta version)

2. Tension-type headache (TTH)
2.1 Infrequent episodic tension-type headache
2.1.1 Infrequent episodic tension-type headache associated with pericranial tenderness
2.1.2 Infrequent episodic tension-type headache not associated with pericranial tenderness
2.2 Frequent episodic tension-type headache
2.2.1 Frequent episodic tension-type headache associated with pericranial tenderness
2.2.2 Frequent episodic tension-type headache not associated with pericranial tenderness
2.3 Chronic tension-type headache
2.3.1 Chronic tension-type headache associated with pericranial tenderness
2.3.2 Chronic tension-type headache not associated with pericranial tenderness
2.4 Probable tension-type headache
2.4.1 Probable infrequent episodic tension-type headache
2.4.2 Probable frequent episodic tension-type headache
2.4.3 Probable chronic tension-type headache

3. Trigeminal autonomic cephalalgias (TACs)
3.1 Cluster headache
3.1.1 Episodic cluster headache
3.1.2 Chronic cluster headache
3.2 Paroxysmal hemicrania
3.2.1 Episodic paroxysmal hemicrania
3.2.2 Chronic paroxysmal hemicrania
3.3 Short-lasting unilateral neuralgiform headache attacks
3.3.1 Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)
3.3.1.1 Episodic SUNCT
3.3.1.2 Chronic SUNCT
3.3.2 Short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA)
3.3.2.1 Episodic SUNA
3.3.2.2 Chronic SUNA
3.4 Hemicrania continua
3.5 Probable trigeminal autonomic cephalalgia
3.5.1 Probable cluster headache
3.5.2 Probable paroxysmal hemicrania
3.5.3 Probable short-lasting unilateral neuralgiform headache attacks
3.5.4 Probable hemicrania continua

Headache Classification Committee of the International Headache Society (IHS)
The International Classification of Headache Disorders,
3rd edition (beta version). Cephalalgia 33(9) 629–808

Hoofdpijnclassificatie

Headache Classification Committee of the International Headache Society (IHS)
The International Classification of Headache Disorders, 3rd edition (beta version)

1. Migraine
1.1 Migraine without aura
1.2 Migraine with aura
- 1.2.1 Migraine with typical aura
  - 1.2.1.1 Typical aura with headache
  - 1.2.1.2 Typical aura without headache
- 1.2.2 Migraine with brainstem aura
- 1.2.3 Hemiplegic migraine
  - 1.2.3.1 Familial hemiplegic migraine (FHM)
    - 1.2.3.1.1 Familial hemiplegic migraine type 1
    - 1.2.3.1.2 Familial hemiplegic migraine type 2
    - 1.2.3.1.3 Familial hemiplegic migraine type 3
    - 1.2.3.1.4 Familial hemiplegic migraine, other loci
  - 1.2.3.2 Sporadic hemiplegic migraine

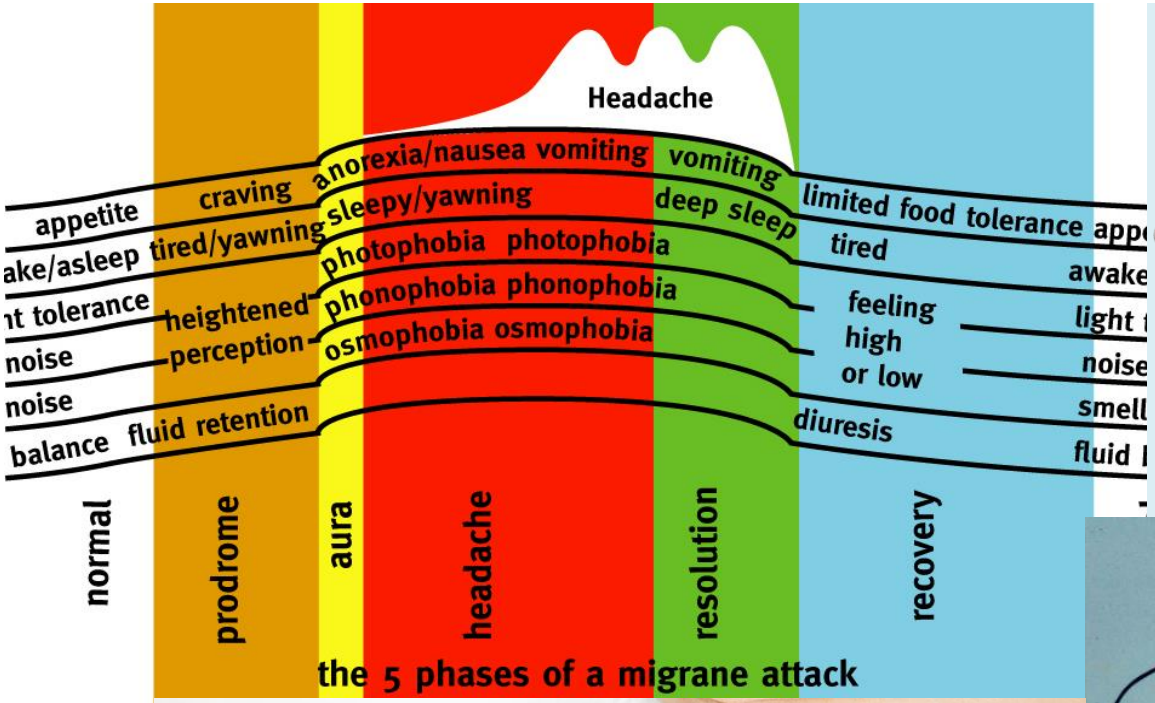
1.2.4 Retinal migraine
1.3 Chronic migraine
1.4 Complications of migraine
- 1.4.1 Status migrainosus
- 1.4.2 Persistent aura without infarction
- 1.4.3 Migrainous infarction
- 1.4.4 Migraine aura-triggered seizure

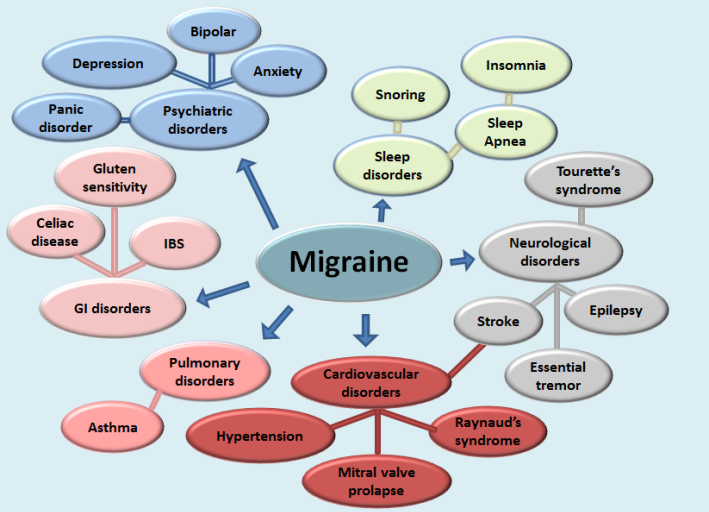
1.5 Probable migraine
- 1.5.1 Probable migraine without aura
- 1.5.2 Probable migraine with aura

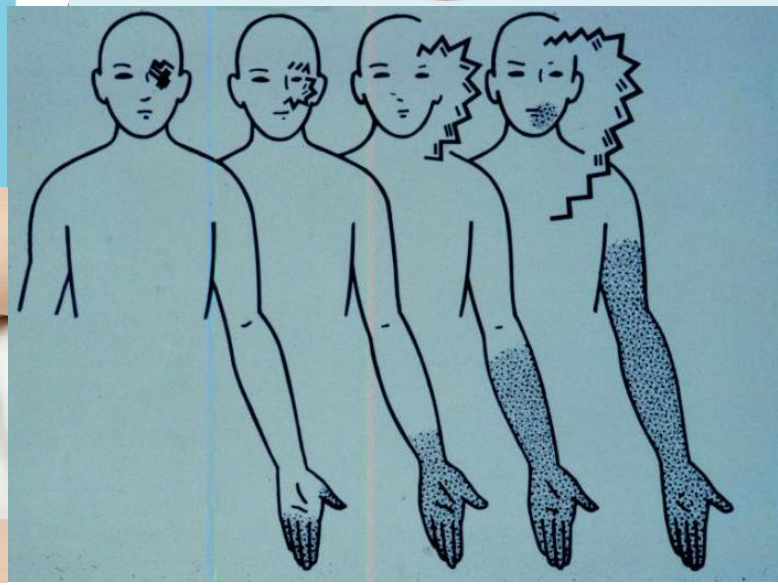
1.6 Episodic syndromes that may be associated with migraine
- 1.6.1 Recurrent gastrointestinal disturbance
  - 1.6.1.1 Cyclical vomiting syndrome
  - 1.6.1.2 Abdominal migraine
- 1.6.2 Benign paroxysmal vertigo
- 1.6.3 Benign paroxysmal torticollis

Headache Classification Committee of the International Headache Society (IHS)
The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 33(9) 629–808

Migraine is geen hoofdpijn!



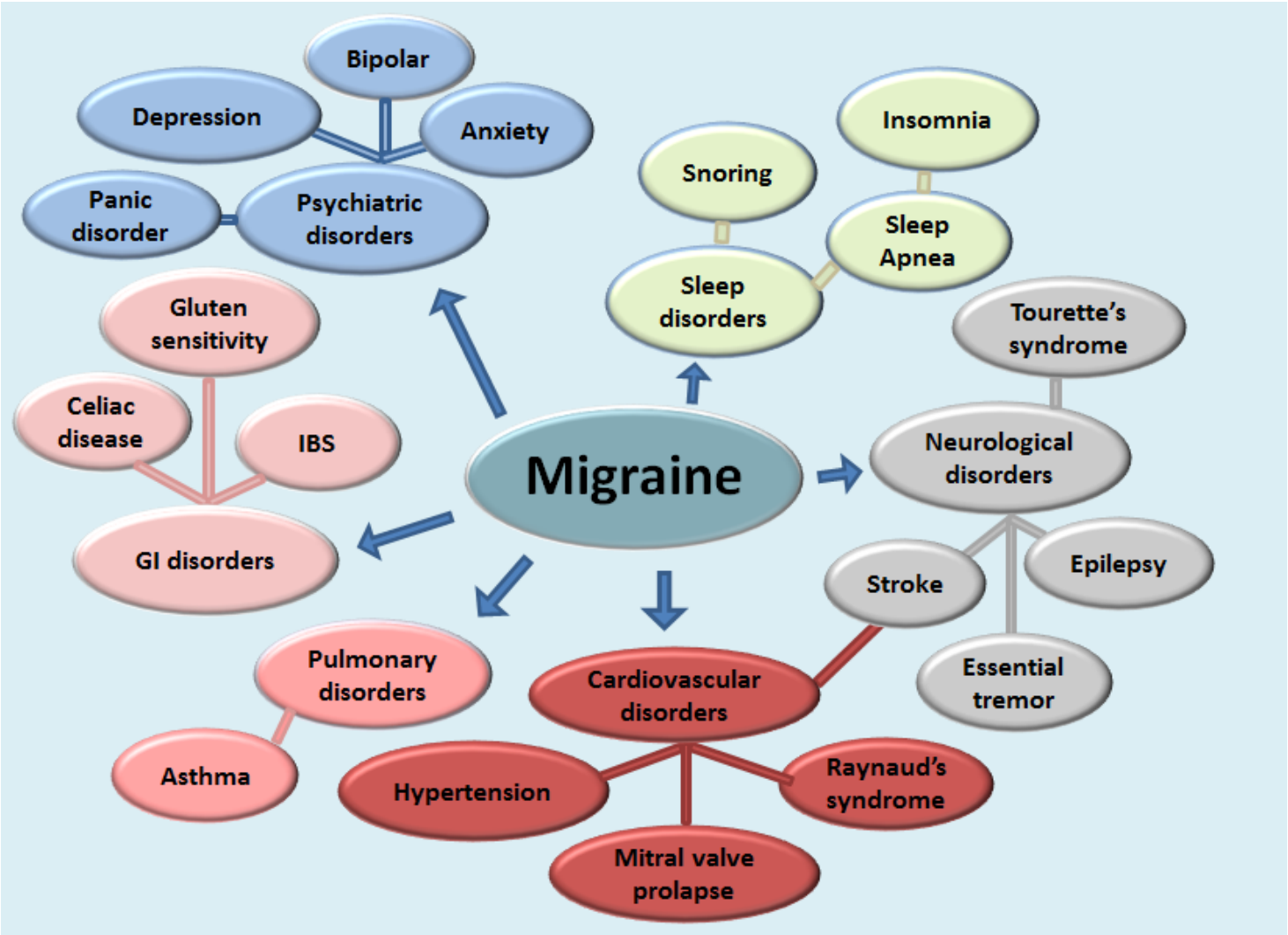




Tergooi zorgt vooruit.

Kenmerken van migraine
auraverschijnselen

Migraine is geen hoofdpijn!



Hoofdpijnbehandelcentrum

Hoofdpijncentra in Nederland

Overzicht hoofdpijncentra

- Alkmaar: DC Alkmaar
- Amersfoort: Meander Medisch Centrum
- Amsterdam: Medisch Centrum Boerhave
- Assen: Wilhelmina Ziekenhuis
- Blaricum: Tergooiziekenhuizen locatie Blaricum
- Breda: Amphia Ziekenhuis
- Delden: ZBC rugpoli
- Den Bosch: Jeroen Bosch Ziekenhuis
- Den Haag: Hagaziekenhuis
- Dordrecht: Albert Schweitzer Ziekenhuis
- Ede: Ziekenhuis Gelderse Vallei
- Enschede: Medisch Spectrum Twente
- Gouda: Groene Hart Ziekenhuis
- Groningen: Martini Ziekenhuis
- Haarlem: Kennemer Gasthuis, locatie Zuid
- Heerlen: Atrium Medisch Centrum
- Hengelo: ZGT hoofdpijncentrum
- Hilversum: Tergooiziekenhuizen locatie Hilversum
- Leiden: Leids Universitair Medisch Centrum
- Leiderdorp: Rijnland Ziekenhuis
- Nijmegen: Canisius-Wilhelmina Ziekenhuis
- Roermond: Laurentius Ziekenhuis
- Roosendaal: Franciscus Ziekenhuis
- Rotterdam: Maasstadziekenhuis
- Schiedam: Vlietland Ziekenhuis
- Sittard-Geleen: Orbis Medisch Centrum
- Sneek: Antonius Ziekenhuis
- Utrecht: PraktijkVoorNeurologie
- Terneuzen: Zorgzaam Zeeuws-Vlaanderen, loc de Honte
- Velp: Rugpoli Veluwe
- Venray: Viecuri Medisch Centrum
- Waalwijk: TweeSteden Ziekenhuis, locatie Waalwijk
- Zutphen: Gelre ziekenhuizen, locatie Zutphen
- Zwolle: Isala Klinieken locatie Weezenlanden

Home | Online vragenuur | Nieuwsbrief | Centra | Links | Contact

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Tergooi zorgt vooruit.

Pathofysiologie

Drietal vormen van hoofdpijn

Cluster

korte aanval
rondom oog
is wanhopig

Spierspanning

vanuit de nek naar
voren of boven de
ogen (band-gevoel)

Migraine

Aanvallen
Misselijkheid
Foto & fonofobie
bed/rust

Drietal vormen van hoofdpijn

Gedachtebepaling

- Pijn in het hoofd
  - TTH, chronisch dagelijkse hoofdpijn
- Trigeminovasculaire hoofdpijn
  - Clusterhoofdpijn, TACs
- Neurovasculaire hoofdpijn
  - Migraine met/zonder aura
- (Trigeminus pijn)
  - Trigeminusneuralgie, secundaire hoofdpijnen

“Ieder hoofd zijn eigen hoofdpijn”

Wilder Penfield: hersenen pijnloos tijdens ingrepen (1935)

Pijn gevoelige structuren:

- Basale dura, veneuze sinus, arterien, cirkel van Willis
- Nn. Glossopharyngeus, trigeminus, bovenste cervicale spinale zenuwen (ansa cervicalis)

Trigeminovasculaire systeem

- Primaire afferente neuronen van de cervicale ganglia
- C-vezels, A delta nociceptieve vezels, “silent nociceptors” vanuit perivasculair naar TNC

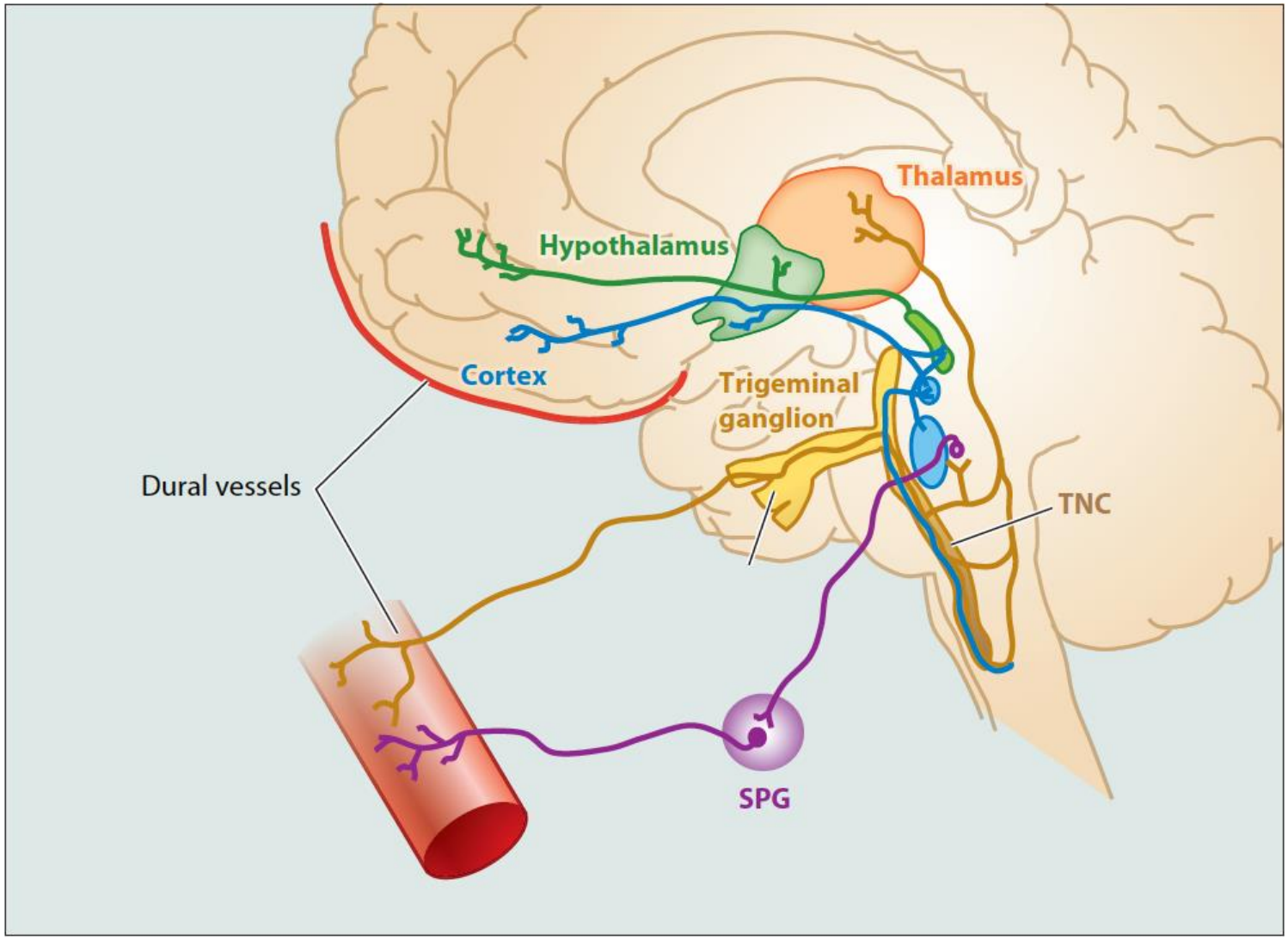
Pijntransmissie

- C-vezels: glutamaat, substance-P, CGRP, neurokinine-A, andere transmitters en modulators
- Glutamaatreceptors: ionotroop: Ca- en Na-kanalen: postsynaptische excitatie (NMDA, kainaat)
- Glutamaatreceptors: metabotroop: glutamaat en substance-P: proteine kinase C activatie

- Projecties ventrobasale thalamus-cortex: aard en localisatie van pijn
- Projecties mediale thalamus-cingulum-cortex: affectieve pijncomponent

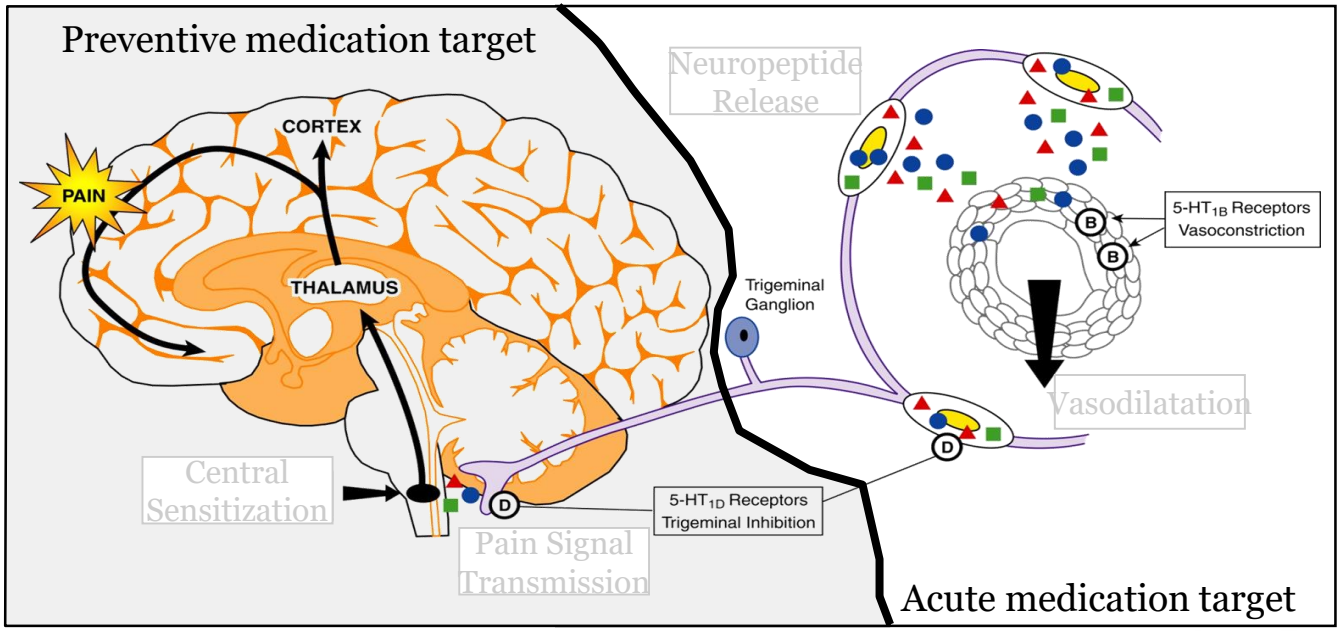
Trad.: Arabisch spreekwoord

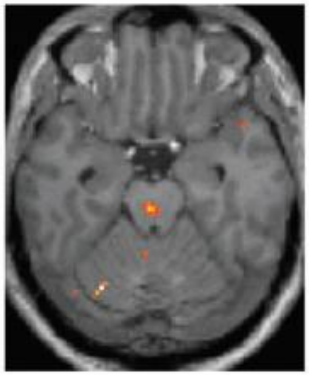
Trigeminovasculaire systeem

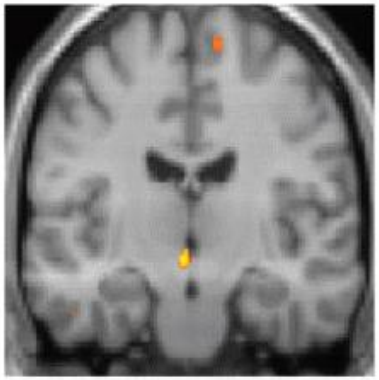


Annu Rev Pharmacol Toxicol 2015. 55:533–52

Neurovasculaire hoofdpijn
vasculaire hypothese **obsoleet**





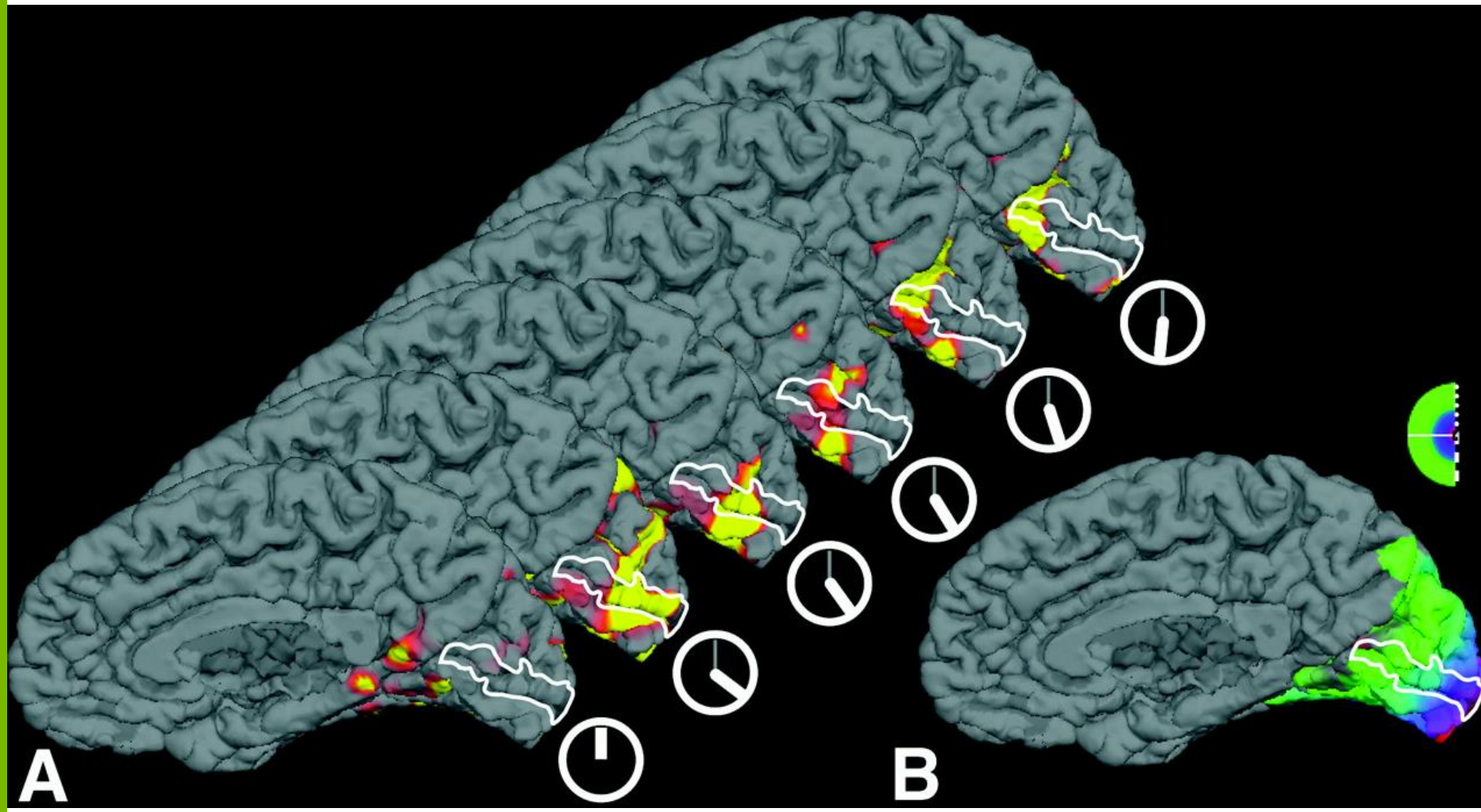


Tergooi zorgt vooruit.

Hargreaves RJ, Shepheard SL. Can J Neurol Sci. 1999;26(suppl 3):S12-S19.

The vascular theory of migraine- a great story wrecked by the facts. Goadsby PJ, Brain 2008;132:6

Kenmerken van migraine
auraverschijnselen



doi:10.1093/brain/awn321 Brain 2009: 132; 6–7 | 6

BRAIN
A JOURNAL OF NEUROLOGY

Scientific Commentary

The vascular theory of migraine—a great story wrecked by the facts

doi:10.1093/brain/awn094 *Brain* (2008), **131**, 2192–2200

Migraine headache is not associated with cerebral or meningeal vasodilatation—a 3T magnetic resonance angiography study

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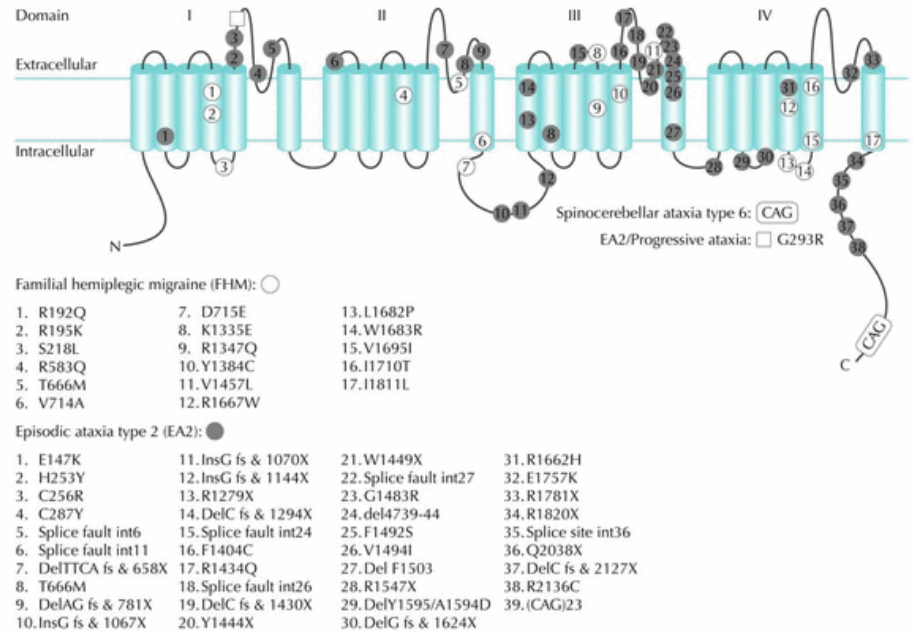
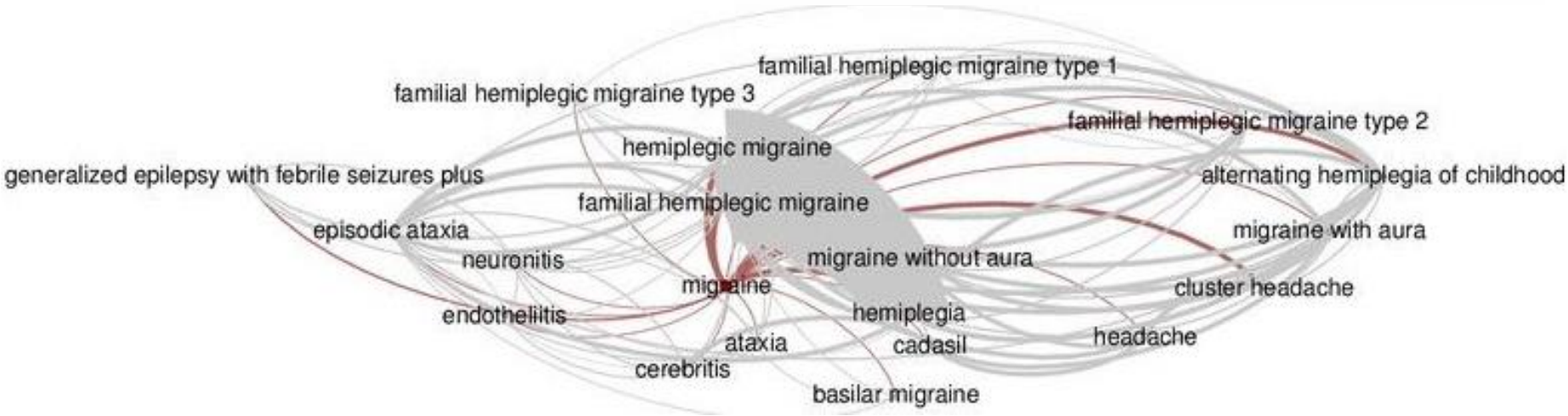
Kenmerken van migraine

genetica

Drietal genen:

- CACNA1A
- ATP1A2
- SCN1A





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Haan J, ea, Curr Pain headache Reports 2005;9:213

Pathofysiologie van migraine
genetica

Gene	Cases (n)[a] Migraine (MA/MO)	Controls (n)	Associated allele with phenotype (p value)[b]	Reference
MTHFR	652 (465/187)	320	677T: NS ($p=0.017/-$)	Lea et al. 2004 (18)
	413 (187/226)	1212	677T: – ($p<0.006$/NS)	Scher et al. 2006 (19)
	2961 (2170/791)	3844	677T: NS ($p=0.0005$/NS)	Rubino et al. 2009 (20)
	477 (124/353)	1402	677T: NS ($p=0.02/-$)	Samaan et al. 2011 (21)
DBH	830 (588/242)	500	−1021T: $p=0.004$ ($p=0.011$/NS)	Fernandez et al. 2009 (22)
	650 (650/–)	650	rs2097629: – ($p=0.01/-$)	Todt et al. 2009 (23)
DRD1	543 (318/225)	561	rs251937: $p=0.0261$ (–/–)	Corominas et al. 2009 (24)
DRD2	650 (650/–)	650	rs7131056: – ($p=0.006/-$)	Todt et al. 2009 (23)
	543 (318/225)	561	rs2283265: $p=0.0030$ ($p=0.037/p=0.0081$)	Corominas et al. 2009 (24)
DRD3	543 (318/225)	561	rs3732790: $p=0.0033$ (–/–)	Corominas et al. 2009 (24)
SLC6A3	543 (318/225)	561	rs40184: – ($p=0.03/-$)	Todt et al. 2009 (23)
TH	543 (318/225)	561	rs2070762: $p=0.0035$ (NS/$P=0.036$)	Corominas et al. 2009 (24)
EDNRA	850 (850/–)	890	rs2048894: – ($p=0.015$/–) rs5334: – ($p=0.046$/–)	Tikka-Kleemola et al. 2009 (25)
EDNRB	850 (850/–)	890	rs2329047: – (0.035/–)	Tikka-Kleemola et al. 2009 (25)
STX1A	569 (407/129)	720	rs941298: $p=0.004$(NS/$p=0.008$)	Tropeano et al. 2012 (26)
TRPV1	1040 (490/650)	1037	rs222741: $p=0.03$ (NS/NS)	Carreno et al. 2012 (27)
TRPV3	1040 (490/650)	1037	rs7217270: NS ($p=0.02$/NS)	Carreno et al. 2012 (27)
FSHR	356 (198/158)	374	Rs6166: NS ($p=0.03$/NS)	
ESR1	484 (360/124)	484	594A: $p=0.003$ ($p=0.01/p=0.02$)	
	898 (898/–)	900	rs6557170, rs2347867, rs6557171, rs4870062 and rs1801132 (p values 0.007–0.034)	
	356 (198/158)	374	rs1801132: $p=0.03$ ($p=0.045$/NS)	
ESR2	356 (198/158)	374	2039G: NS ($p=0.01$/NS)	
PGR	509 (371/138)	454	PROGINS ins: $p=0.02$ (NS/$p=0.008$)	
TNFA	299 (38/261)	306	308G: $p<0.001$ (NS/$p<0.001$)	
SLC6A4	546 (257/289)	770	STin2: $p=0.002$ (NS/NS)	
TPH2	503 (214/289)	515	Haplotype block with five SNPs: $p=0.04$ ($p=0.4/p=0.006$)	
LTA	439 (65/327)	382	−294C: $p=0.0002$ ($p=0.0006/p=0.0008$)	
INSR	827 (377/450)	765	c.2946-713A: NS ($p=0.002$/NS) c.2842+1451A: NS ($p=0.007$/NS) c.3255T: NS ($p=0.008$/NS)	
	1278 (1278/–)	1337	c.2842+1451T: – ($p=0.005/-$)	

MA: migraine with aura; MO: migraine without migraine; NS: not significant; –: not tested/not available; SNP: Ins: insertion; Del: deletion; VNTR: variable number of tandem repeats. [a]Number of cases and [b]p values are giv when specified between brackets, for migraine with aura cases only and/or migraine without aura cases only.

Genetische associaties

Migraine en depressie

Migraine en hart- en vaatziekten

Migraine en medicatie gevoeligheid

Gene	Relation to migraine	Reference
CACNA1A (FHM1)	A linkage study identified *CACNA1A* as the first FHM gene. *CACNA1A* encodes the α1 pore-forming subunit of $Ca_V2.1$ calcium channels.	Ophoff et al. 1996 (12)
ATP1A2 (FHM2)	A linkage study identified *ATP1A2* as the second FHM gene. *ATP1A2* encodes the α2 subunit of sodium-potassium pumps.	De Fusco et al. 2003 (13)
SCN1A (FHM3)	A linkage study identified *SCN1A* as the third FHM gene. *SCN1A* encodes the α1 subunit of neuronal $Na_V1.1$ sodium channels.	Dichgans et al. 2005 (14)
SLC1A3/EAAT1	A mutation in a single case with SHM that was identified through sequencing of the coding exons of *SLC1A3* and presented first evidence for *SLC1A3* as an SHM gene. *SLC1A3* encodes the EAAT1 glutamate transporter.	Freilinger et al. 2010 (15)
SLC4A4/NBCe1	Homozygous mutations in *SLC4A4* were reported in two sisters with reported hemiplegic migraine, in addition to proximal renal tubular acidosis and ocular abnormalities, and presented first evidence for *SLC4A4* as a migraine gene. *SLC4A4* encodes the Na^+–NCO_3^- cotransporter NBCe1.	Suzuki et al. 2010 (16)
KCNK18/TRESK	A mutation in *KCNK18* in a single family with familiar migraine was identified in a candidate gene sequencing approach and presented first evidence for *KCNK18* as a migraine gene. *KCNK18* encodes for the ion channel TRESK.	Lafrenière et al. 2010 (17)

FHM: familial hemiplegic migraine; SHM: sporadic hemiplegic migraine; MA: migraine with aura.

De Vries B, et al. On behalf of the International Headache Genetics consortium. Cephalalgia 2016, Vol. 36(7) 604–614

Genetic Models of Migraine

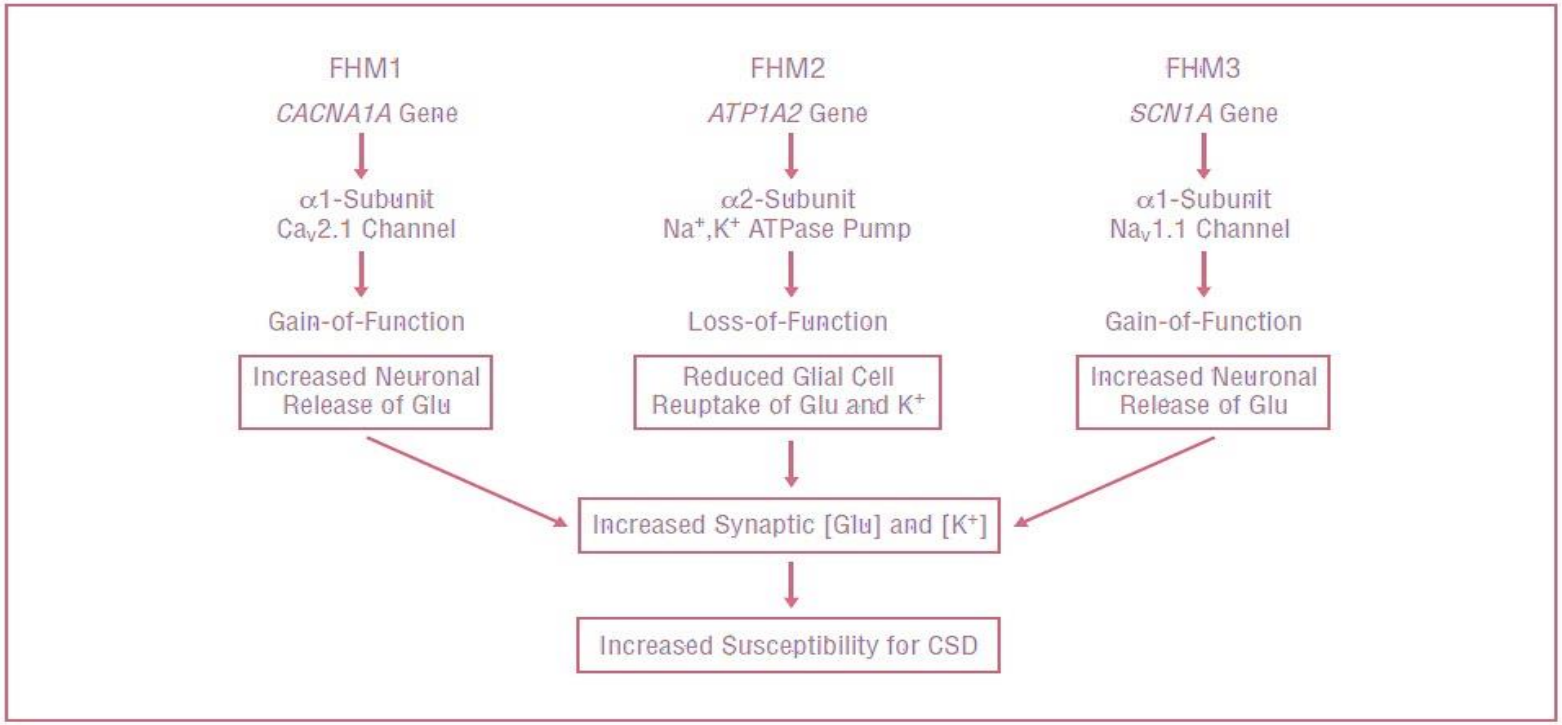


Figure 2. Schematic representation of the mechanism by which familial hemiplegic migraine (FHM) genes can cause increased neuronal excitability and susceptibility to cortical spreading depression (CSD). All 3 genes are implicated in ion transport and consequences of the mutations can result in increased extracellular glutamate (Glu) and potassium (K^+) levels. The FHM1 mutation causes increased calcium influx through presynaptic channels and enhanced neurotransmitter release; the FHM2 mutation predicts reduced removal of Glu and K^+ from the synaptic cleft; and the FHM3 mutation leads to enhanced recovery from inactivation, thereby facilitating a high rate of neuronal firing. Na^+,K^+ ATPase indicates sodium-potassium pump. Adapted from *Curr Opin Neurol*. 2006;19:294-298.

Arch Neurol. 2007;64:643-646

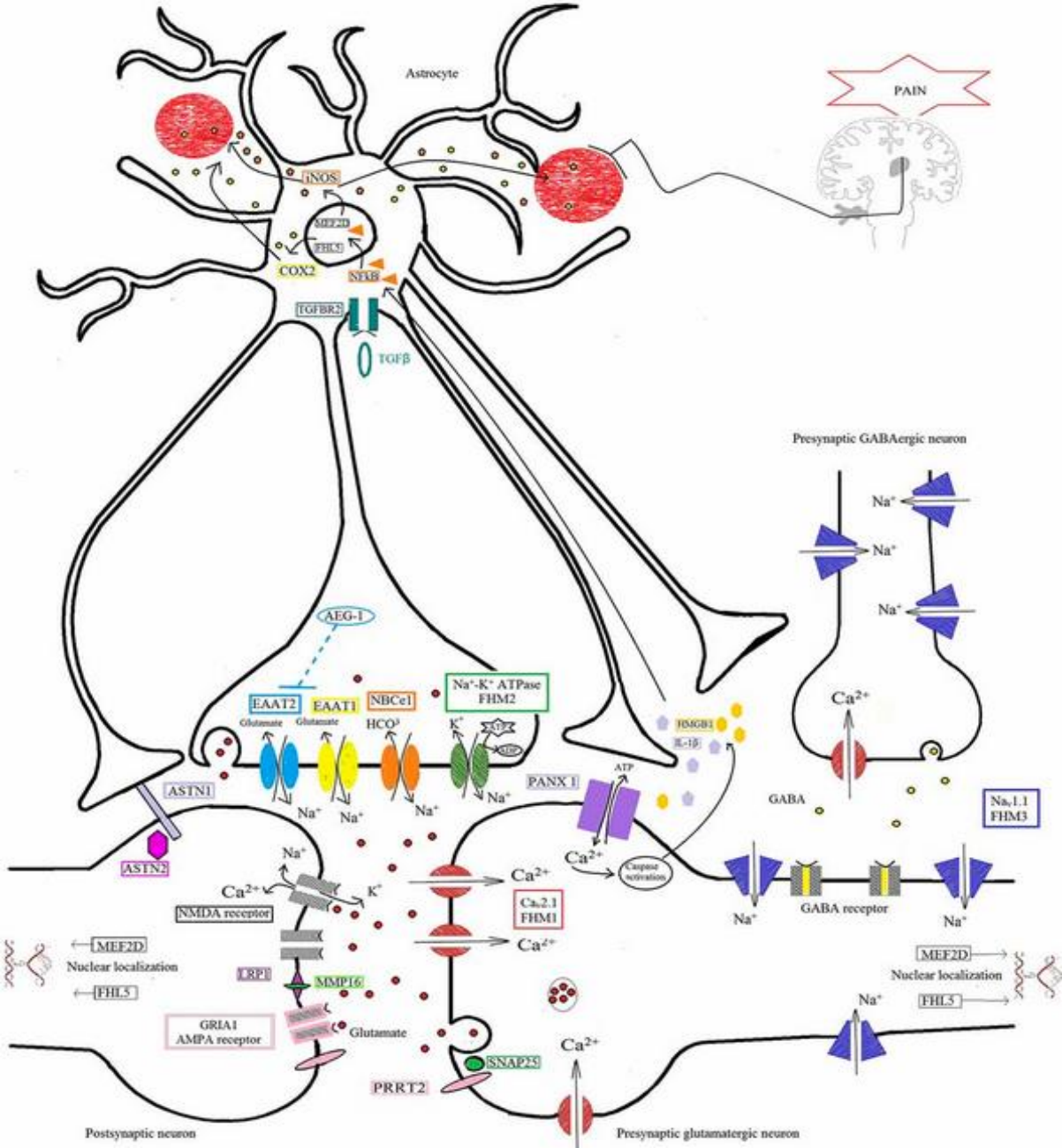
Moleculaire hoofdpijnproductie

Centrale sensitisatie

- TNC en C-vezels
- Verhoogde respons ook voor niet nociceptieve stimuli
- Drempel durale nociceptie verlaagd
- Verhoogde gevoeligheid voor mechanische- en chemische stimuli

Centrale inhibitie

- GABA erge projecties
- Thalamus – cortex
- Thalamus- achterhoorn en peri-aquaductale grijze stof
- Afname glutamaat, substance P, 5-HT afgifte



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Migraine Strikes as Neuronal Excitability Reaches a Tipping Point

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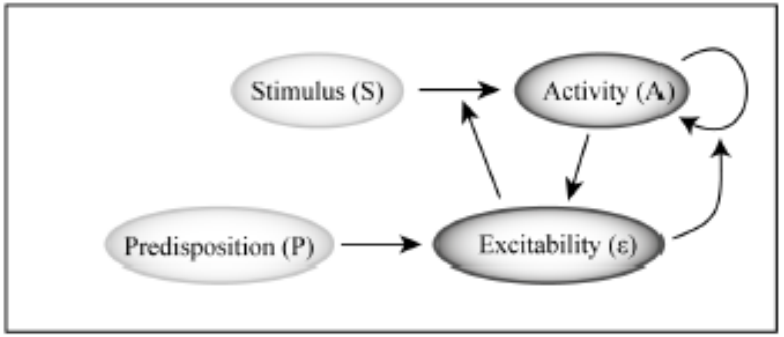
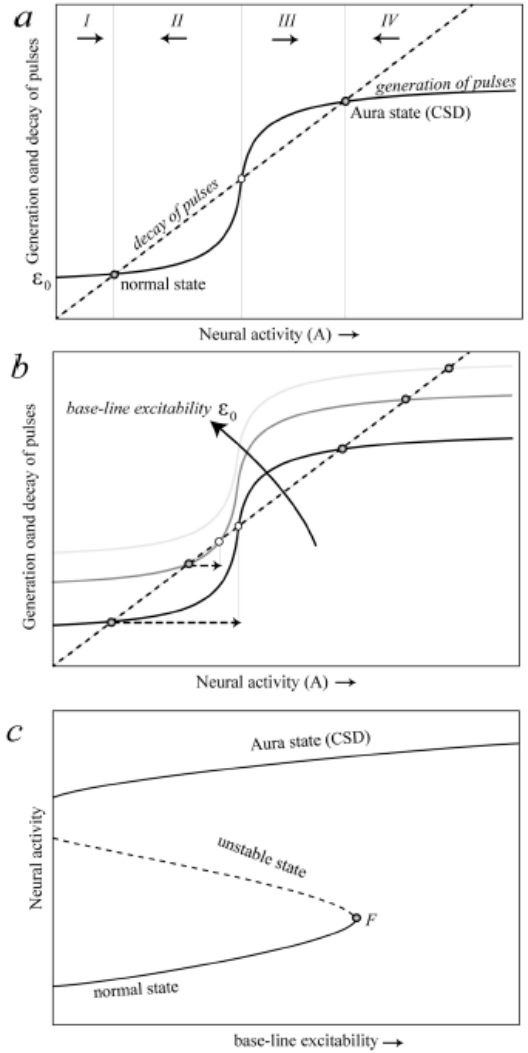
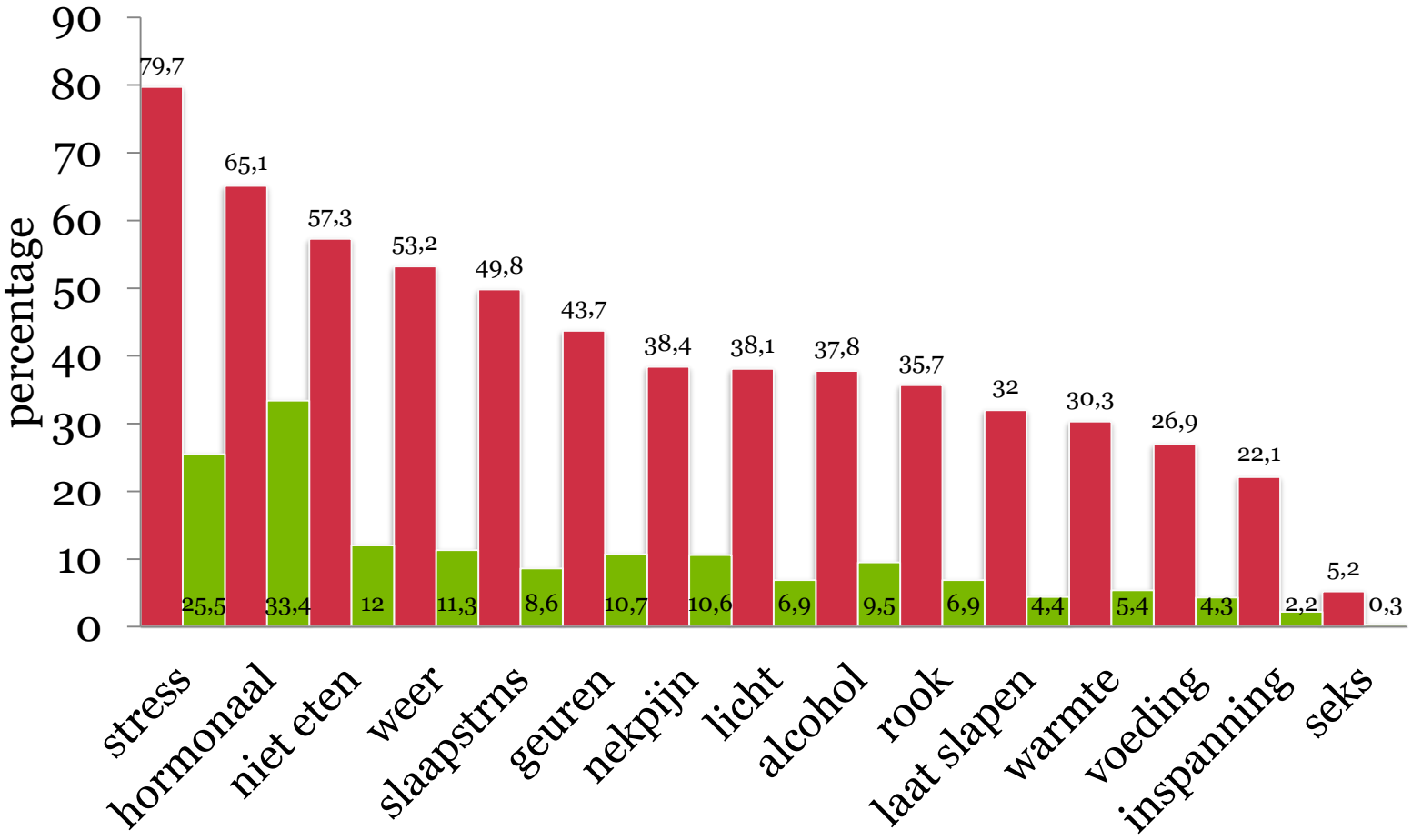


Figure 1. Causal structure that may lead to a tipping point for autonomous firing, as illustrated by the minimal model.



PLOS one 2013;8(8):e72514

Kenmerken van migraine: triggers



Triggers: gemeld; gemeten

Kelman L Cephalalgia 2007;27:394-402

Farmacologie / ontwikkelingen

Behandeling van migraine

Aanvalsbehandeling

couperen

- Aspirine, ibuprofen
- Diclofenac, naproxen
- Metoclopramide, domperidon

Triptanen

- Almotriptan
- Eletriptan
- Sumatriptan
- Frovatriptan
- Naratriptan
- Rizatriptan
- Zolmitriptan

- Ergotamines

Combinaties:

- NSAID + triptan
- Kort + lang triptan

Onderhoudsbehandeling

Profylaxe

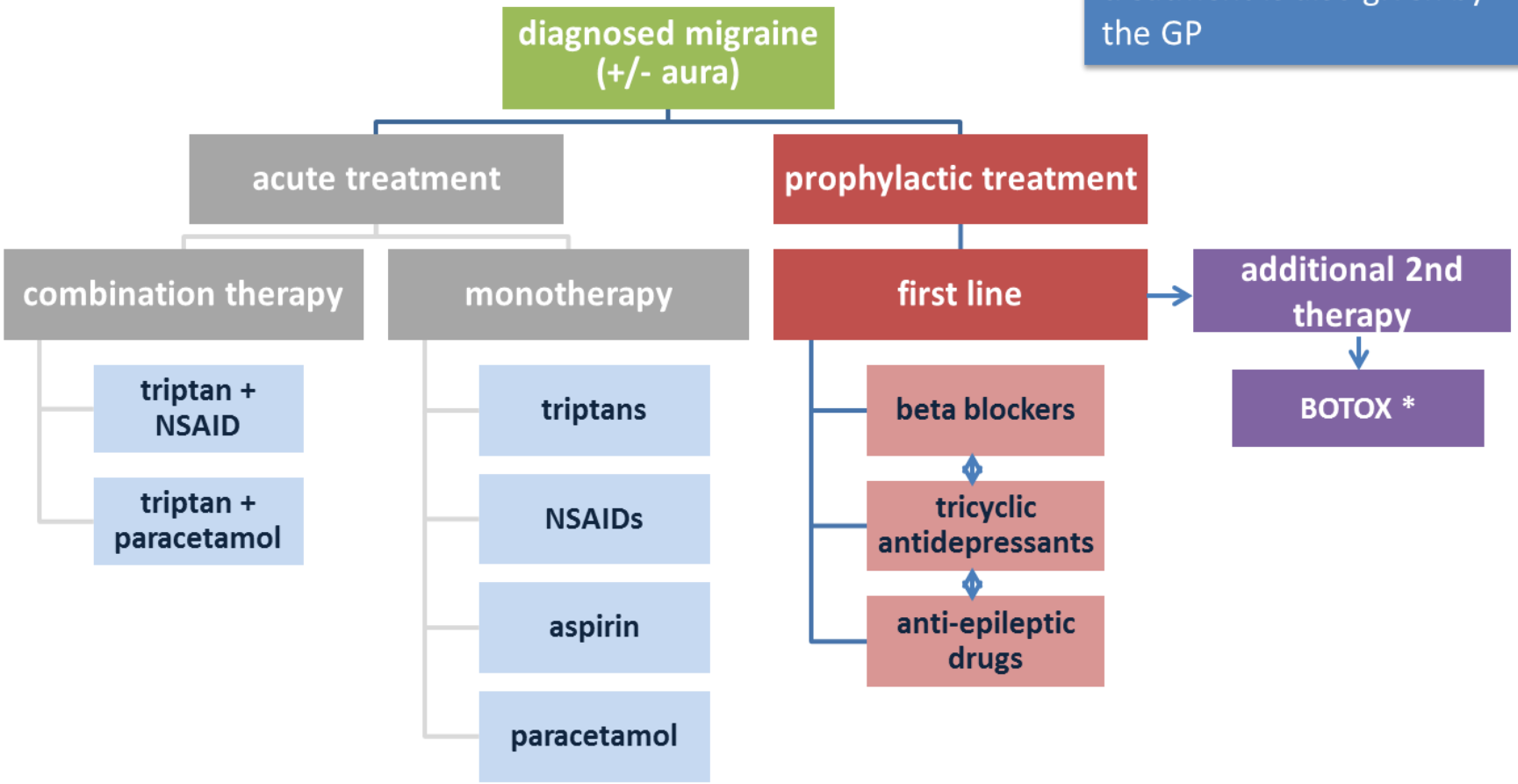
	Alternatieven
Beta blokkers	
Atenolol	valproaat infuus
Metoprolol	fenytoine
Propranolol	lamotrigine
	verapamil
Anti epileptica	lithium
Topiramaat	steroiden
Valproaat	
Gabapentine	
Overige:	riboflavine (vitamine B2)
Flunarizine	magnesium
Pizotifeen	groot hoefblad
Methysergide	Teunisbloem
Lisinopril	frovatriptan
candesartan	

Richtlijn hoofdpijn NVN 2017

Tergooi zorgt vooruit.

Behandeling in de klinische praktijk

According to NHG standard acute and prophylactic treatment is also given by the GP



Source: NICE migraine pathway 2013; AAN/AHS 2012 Guidelines; EFNS 2009

Effectiviteit triptanen NNT =3; NNH =17

Volwassenen: 133 RCTs	
Pijnvrij binnen 2 uur	42 tot 76%
Blijvend pijnvrij	18 tot 50%
Blijvende pijnafname 24 uur:	29 tot 50%
Blijvend pijnvrij na 24 uur:	18 tot 33%
Triptan plus NSAID	62 tot 80%
NSAIDs, ASA, PCM	46 tot 52%
Ergotaminepreparaten	38%
“rescue medications”	20 tot 34%
Kinderen: 27 RCTs	
sumatriptan plus naproxen	50%
sumatriptan alleen	28%
Placebo	18%

PLACEBO
18 – 32 %

Cochrane Database Syst Rev:,2016 Apr 19;4:CD005220, 2016 Apr 20;4:CD008541
Headache 2015 Jul-Aug;55 Suppl 4:221-35

Effectiviteit profylaxe

Optreden van bijwerkingen

Stoppen met medicatie: na 6 mnd

- 73.4% - antidepressiva
- 70.2% - anti-epileptica
- 67.6% - beta-blokkers

Farmacofobie: angst voor medicatie

Nocebo: een negatief verwachtingseffect: reden staken

Dus: meer dan voldoende ruimte voor verbetering!

Gracia-Naya M Rev Neurol. 2011
Berger a. Pain Pract 2012,
Mitsikostas DD. Curr Neurol Neurosci Rep. 2012

Hoofdpijntherapieen in ontwikkeling

Mechanism/indication	Treatment	Stage
CGRP mechanism antagonist		
Acute attack treatment		
CGRP receptor antagonist (*gepant*)	Olcegepant (Olesen *et al.*, 2004)	Phase II
	Telcagepant- acute (Ho *et al.*, 2008)	Phase II[a]
	Telcagepant- preventive (Ho *et al.*, 2014)	Phase II
	Rimagepant (Marcus *et al.*, 2013)	Phase II
Preventive attack treatment		
CGRP antibody		
Episodic migraine		
Chronic migraine		
CGRP receptor antibody		
CGRP receptor antagonis		
Serotonin-related		
Serotonin 5-HT$_{1F}$ receptor		
Nitric oxide synthase (N		
Pan NOS		
Inducible NOS		
Neuronal NOS plus triptan		
Glutamatergic targets		
NMDA receptor migraine v		
AMPA/kainate		
iGluR5 (kainate) receptor		
mGluR5 (glurants)		
AMPA receptor antagonist		
Neuroinflammatory targ		
TRPV1		
Substance P/neurokinin-1		
Neurogenic plasma protein ext		
Other targets		
Orexin 1 and 2 receptors (*rex*		
Angiotensin receptor	Candesartan (Tronvik *et al.*, 2003; Stovner *et al.*, 2014)	Off-license use
	Telmisartan (Diener *et al.*, 2009)	Phase II (F)
Prevention of aura not headache	Tonabersat (Goadsby *et al.*, 2009; Hauge *et al.*, 2009)	Phase II (F)
Phosphodiesterase inhibition	Ibudilast (Johnson *et al.*, 2015)	Phase II (F)
Emerging targets		
Acid sensing ion channel (ASICs)	Amiloride (Holland *et al.*, 2012)	
Pituitary adenylate cyclase activating peptide (PACAP)	PACAP receptor antagonists (Amin *et al.*, 2014; Zagami *et al.*, 2014; Akerman and Goadsby, 2015)	
Neuronal NOS	Neuronal NOS inhibition (Akerman *et al.*, 2002)	
Neuromodulation strategies		
Transcranial magnetic stimulation (TMS)	Single pulse TMS (Lipton *et al.*, 2010; Bhola *et al.*, 2015)	Marketed
Occipital nerve stimulation (ONS)	Chronic migraine (Lipton *et al.*, 2009; Saper *et al.*, 2011; Silberstein *et al.*, 2012)	Phase II (F)
Transcutaneous vagal nerve stimulation	Gammacore device (Goadsby *et al.*, 2014; Silberstein *et al.*, 2016)	Phase II (F)
Supraorbital nerve stimulation	Cefaly (Schoenen *et al.*, 2013)	Marketed
Sphenopalatine ganglion stimulation	ATI device (NCT01540799)	Phase II

CGRP mechanism antagonist

Acute attack treatment

CGRP receptor antagonist (*gepant*)

- Olcegepant (Olesen *et al.*, 2004)
- Telcagepant- acute (Ho *et al.*, 2008)
- Telcagepant- preventive (Ho *et al.*, 2014)
- Rimagepant (Marcus *et al.*, 2013)
- BI44370TA (Diener *et al.*, 2011)
- MK-3207 (Hewitt *et al.*, 2011)
- Ubrogepant (NCT02867709) (Voss *et al.*, 2016)

Preventive attack treatment

CGRP antibody

Episodic migraine

- ALD-403 (Dodick *et al.*, 2014a)
- Galcanezumab (Dodick *et al.*, 2014b; Oakes *et al.*, 2016)
- TEV-48125 (Bigal *et al.*, 2015a)

Chronic migraine

- TEV-48125 (Bigal *et al.*, 2015b)
- ALD-403 (Smith *et al.*, 2016)

CGRP receptor antibody

- Erenumab (Sun *et al.*, 2016)

CGRP receptor antagonist

- Atogepant (AGN-241689; NCT02848326)

Goadsby PJ. BRAIN 2016: 139; 2571–2577

Tergooi zorgt vooruit.

CGRP: oligopeptide en receptor

a

Ala-Cys-Asp-Thr-Ala-Thr-Cys-Val-Thr-His-
Arg-Leu-Ala-Gly-Leu-Leu-Ser-Arg-Ser-Gly-
Gly-Val-Val-Lys-Asn-Asn-Phe-Val-Pro-Thr-
Asn-Val-Gly-Ser-Lys-Ala-Phe-NH_2

b

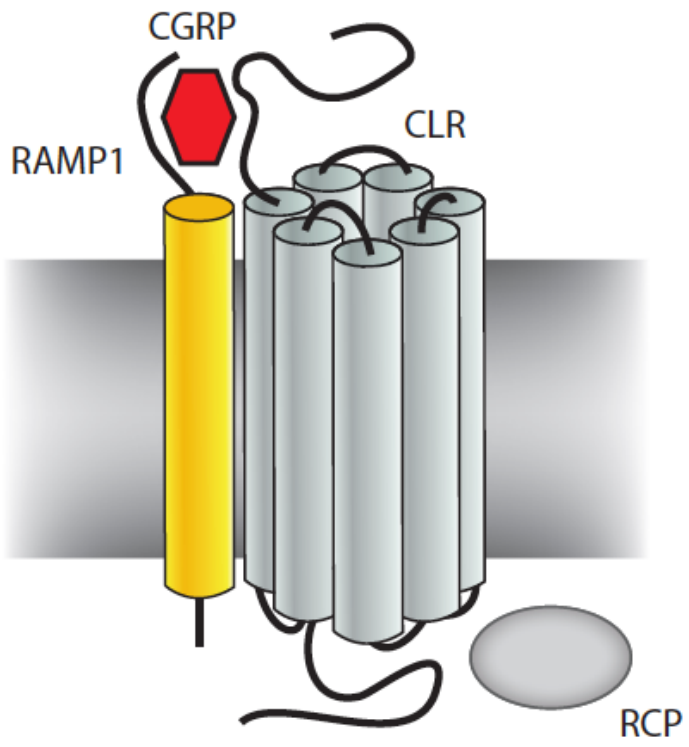


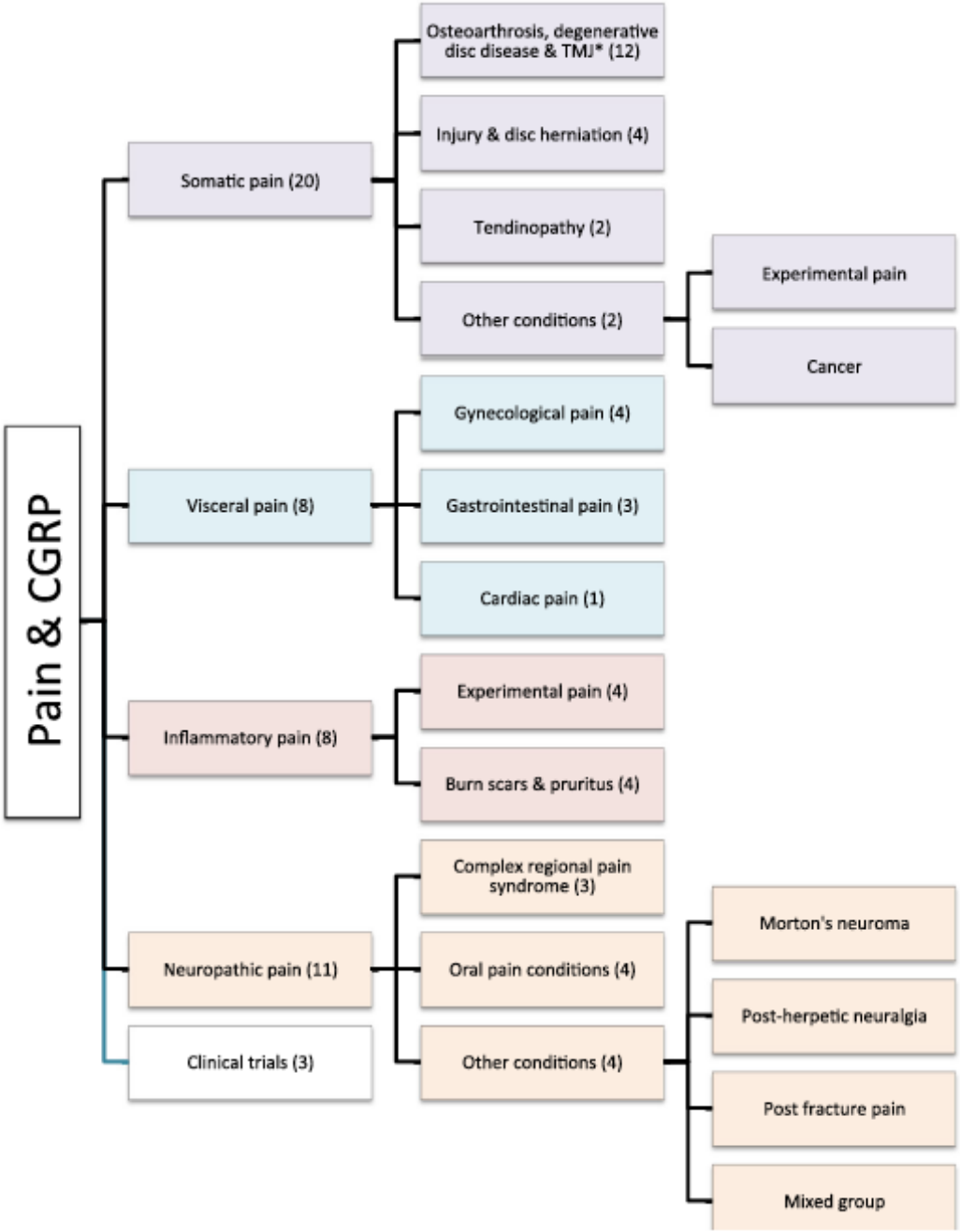
Figure 2

CGRP and its receptor. (*a*) Human α-CGRP sequence with an amidated C terminus and N-terminal disulfide bond, indicated by the bracket. (*b*) The CGRP receptor complex, which contains three subunits: CLR, RAMP1, and RCP. Abbreviations: CGRP, calcitonin gene-related peptide; CLR, calcitonin-like receptor; RAMP1, receptor activity-modifying protein 1; RCP, receptor component protein.

Russo AF. Annu Rev Pharmacol Toxicol 2015. 55:533–52

Tergooi zorgt vooruit.

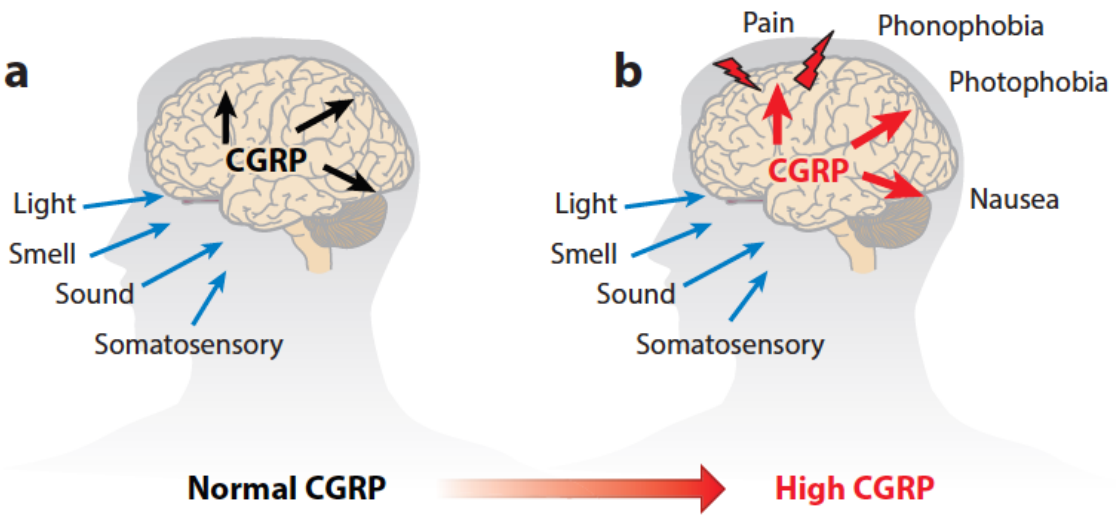
CGRP:



Schou WS, et al. The Journal of Headache and Pain (2017) 18:34

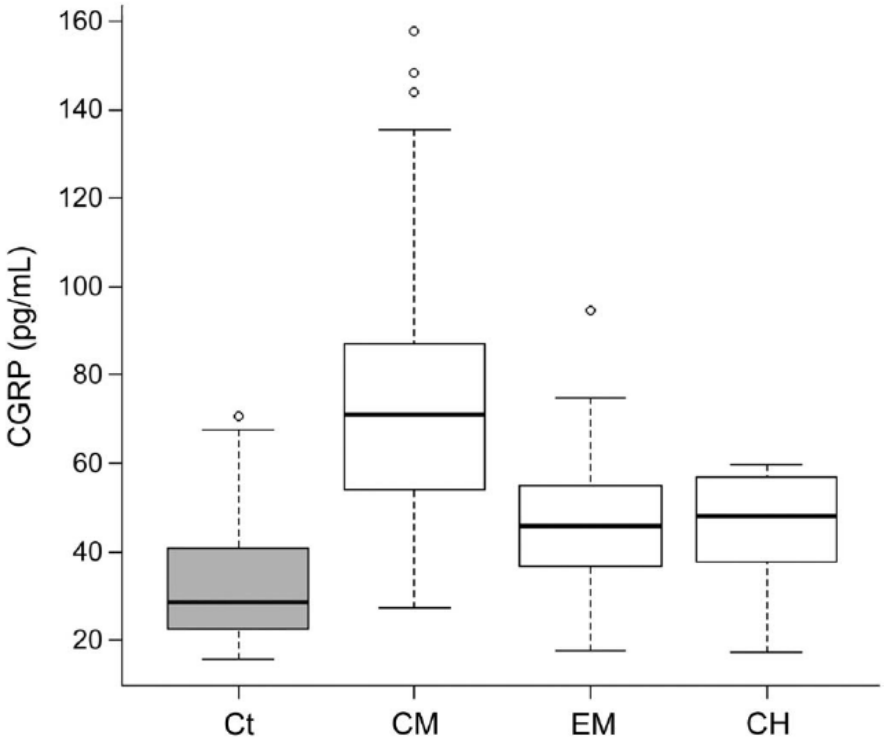
CGRP veroorzaakt overgevoeligheid voor sensorische stimuli bij migraine

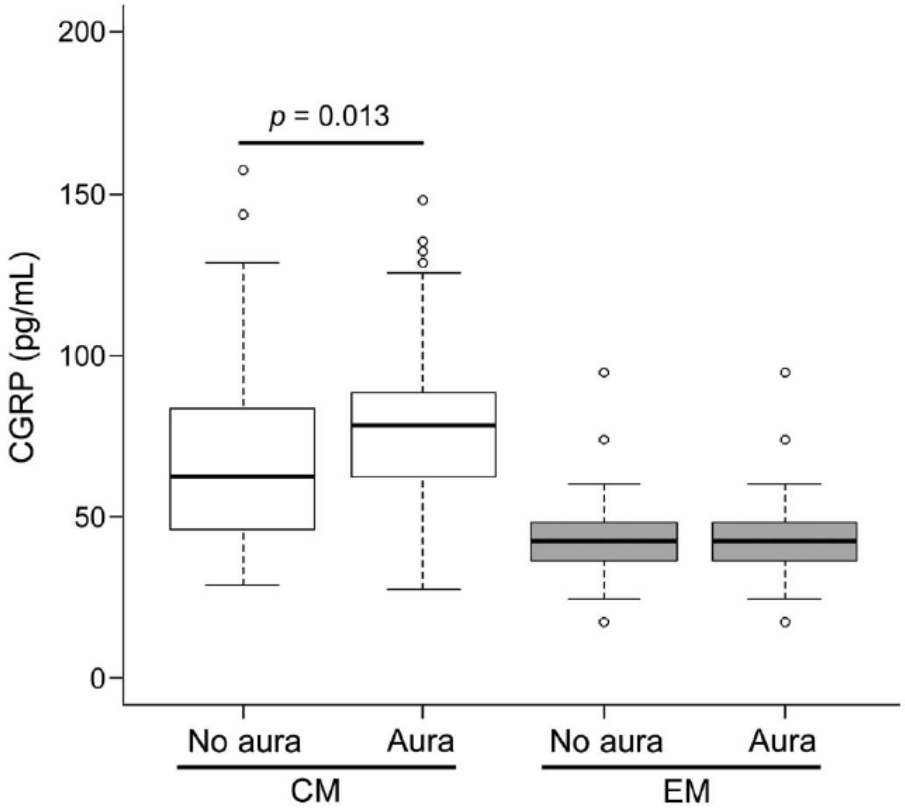
(Lars Edvinsson, Lund, 1990)



Annu Rev Pharmacol Toxicol 2015. 55:533–52

CGRP in bloed verhoogd bij hoofdpijn





Neurology 2013;81(14):1191-6

Tergooi zorgt vooruit.

Ontwikkeling gepant compounds (2004-2011)

Table 1. Note all data in this table, comparing verum to placebo, were statistically significant ($P < 0.05$) in the individual trials

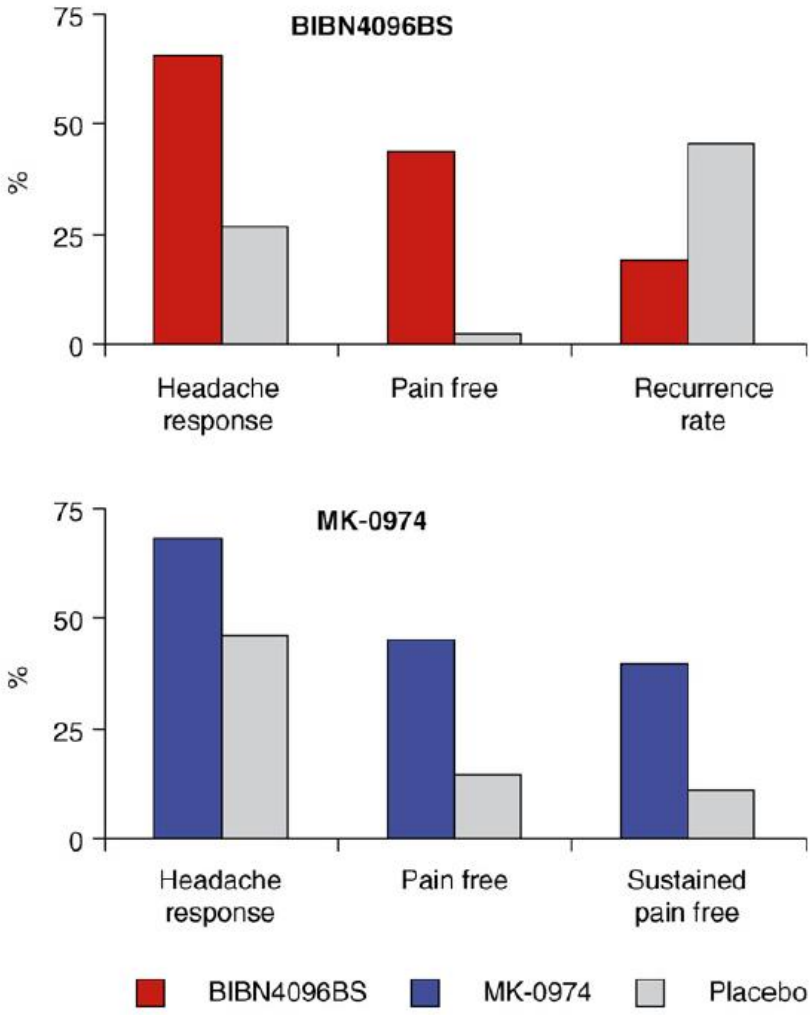
Drug	Pain free at 2 h (%)		Side-effects reported	Status in pharmacological trials	Reference
	Verum	Placebo			
Olcegepant	44; 2.5 mg	2	20% Reported adverse effects	Discontinued development – poor oral bioavailability	[45]
Telcegepant	27; 300 mg	10	Transaminitis	Discontinued – hepatotoxic concerns	[46–52]
MK3207	69; 200 mg	39.1	Transaminitis	Discontinued – hepatotoxic concerns	[53]
BI44370	27.4; 400 mg	8.6	1.4–9.4% Reported adverse effects, dose dependant	Phase IIa complete	[54]
BMS-927711	32.9; 150 mg	15.3	1–8% Reported adverse effects, dose dependant	Phase IIa complete	[55]

Summary of the gepants class of calcitonin gene-related peptide antagonists that have demonstrated clinical efficacy and the recent literature from pharmacological studies regarding their effects and status in drug trials.

Curr Opin Neurol 2015;28(3):250-4

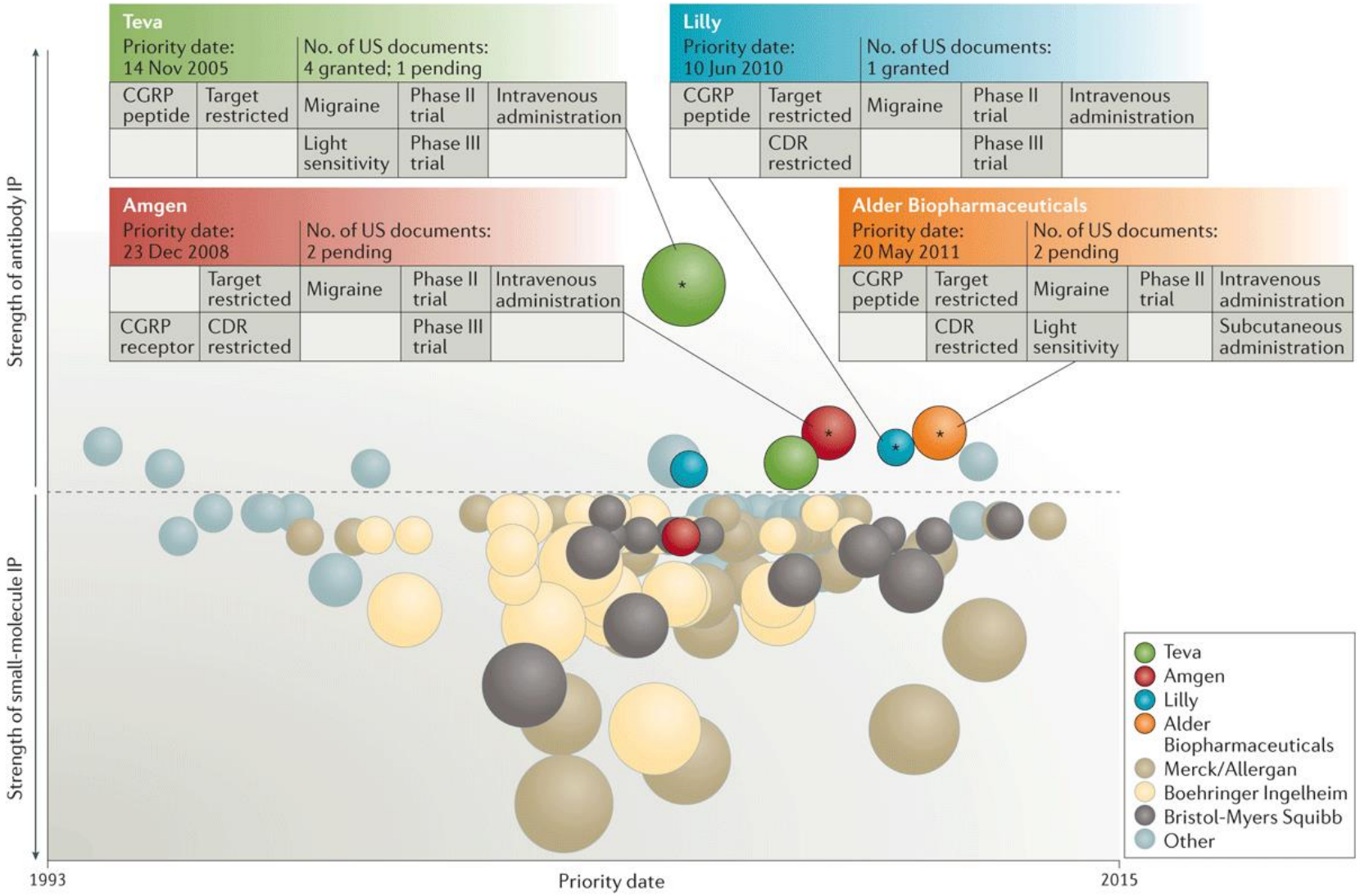
Tergooi zorgt vooruit.

Effectiviteit gepants



Doods H, et al. TIPS 2007;28:580-7

Biobusiness: intellectual property landscape



Nature Reviews | Drug Discovery

Tergooi zorgt vooruit.

Nat Rev Drug Discov 2016;15:8-9

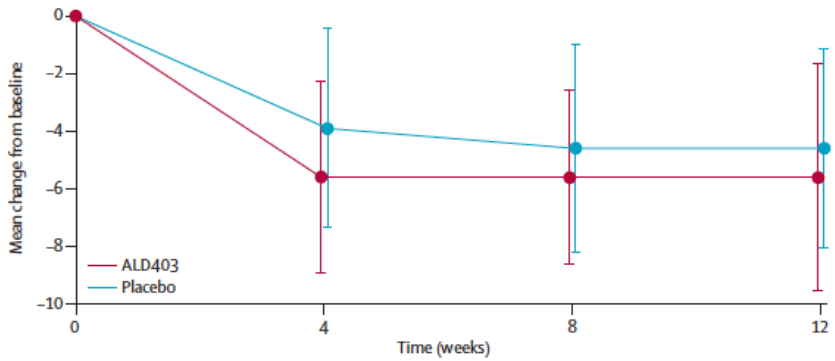
4 compounds in klinische trials

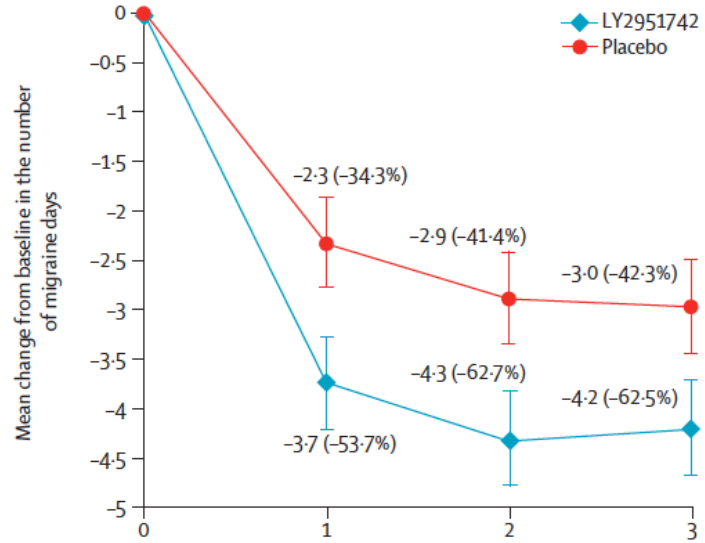
	ALD403	LY2951742	AMG 334	TEV-48125
Target	CGRP with a humanized antibody	CGRP with a humanized antibody	CGRP **receptor** with a human antibody	CGRP with a fully humanized antibody
$t_{1/2}$	Around 32 days	25–30 days	Not disclosed	Around 45 days
Migraine state	Episodic and chronic	Episodic and chronic	Episodic and chronic	Episodic and chronic
Current development phase	Finalized positive POC study with a single dose level administered once (Phase 2a) Currently conducting dose-ranging (Phase 2b).	Finalized positive POC study with single dose level Currently conducting dose-ranging (Phase 2b).	Dose-ranging (Phase 2b)	Dose-ranging (Phase 2b)
Form of administration in phase 2	i.v.*	s.c.	s.c.	s.c.
Phase 2 dosing frequency	Monthly for s.c. and every 3 months for i.v.†	Twice per month (2a) and once per month (2b)	Once per month	Once per month

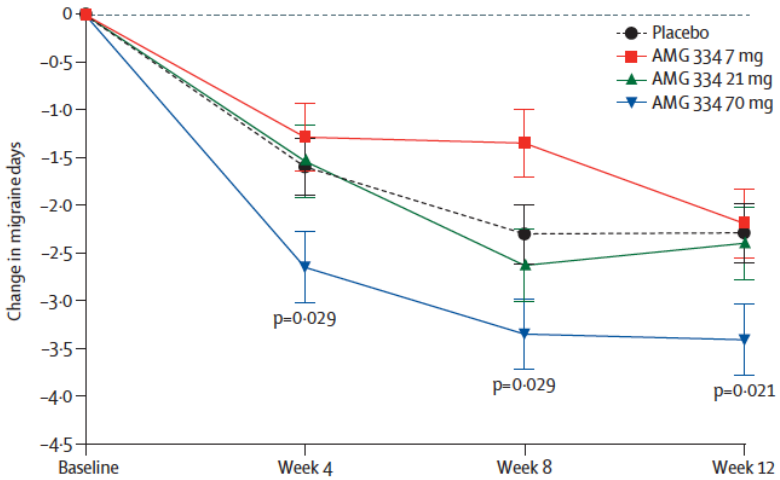
TEV-48125 (formerly known as LBR-101, RN-307)

Br J Clin Pharmacol 2015;79(6):886-895

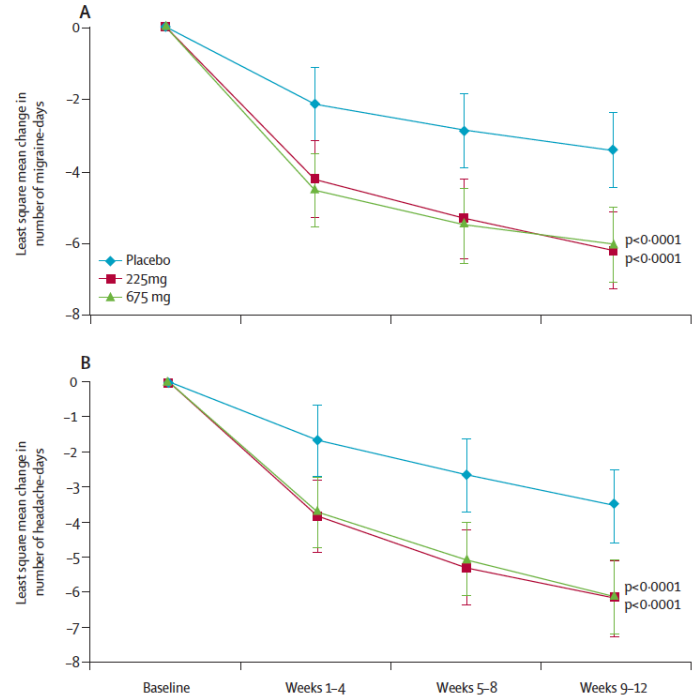
Resultaten fase IIB trials





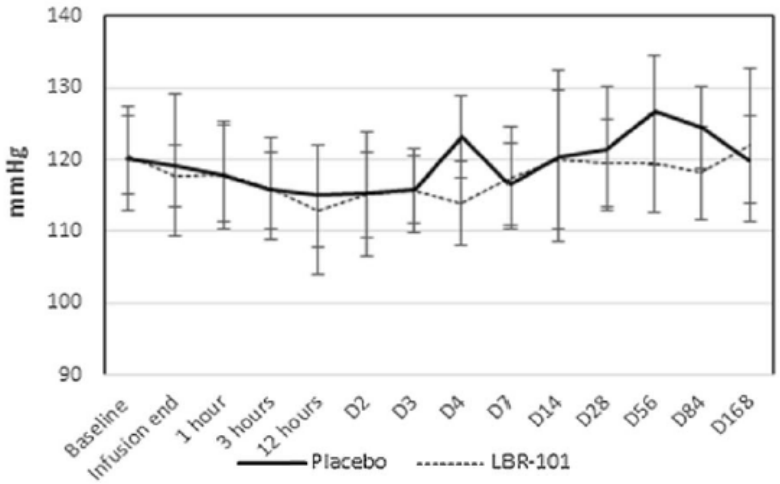


Number of patients				
Placebo	153	151	144	144
AMG 334 7 mg	107	107	106	104
AMG 334 21 mg	102	99	97	93
AMG 334 70 mg	104	103	103	99

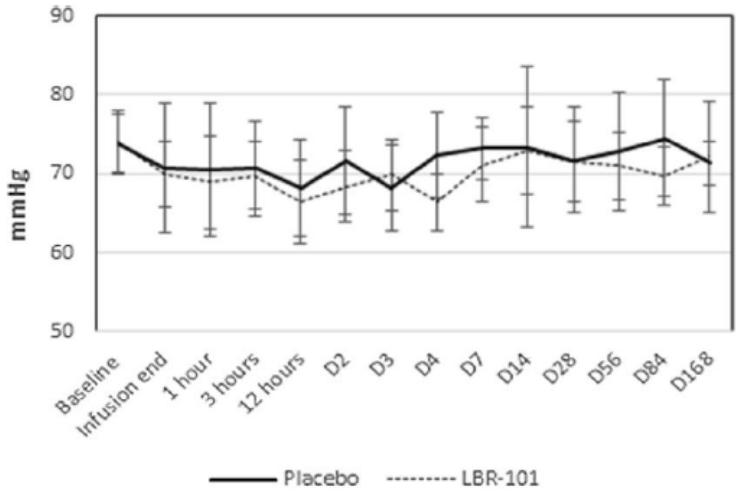


Dodick DW, et al. Lancet Neurol 2014; 13: 1100–07
Sun H, et al. Lancet Neurol 2016; 15: 382–90
Dodick DW, et al. Lancet Neurol 2014; 13: 885–92
Bigal ME, et al. Lancet Neurol 2015; 14: 1081–90

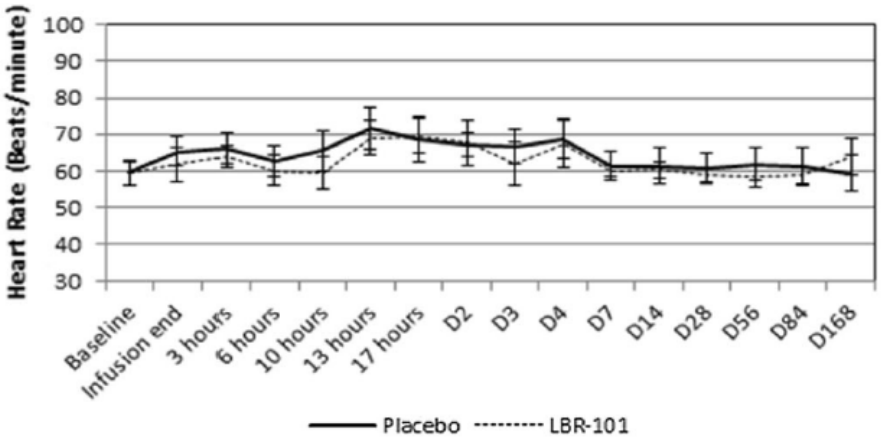
Cardiovasculaire effecten (?)



Systolic Blood Pressure



Diastolic Blood Pressure



Heart Rate

CNS Drugs (2014) 28:389–399

Table 1. Phase 2 RCTs of calcitonin gene-related peptide mAbs for migraine prevention

Antibody target	Effective dose (mg)	Route and frequency of administration	Study size population (total active vs. placebo)	Key inclusion criteria	Key exclusion criteria	Mean baseline MHD/28 days (active vs. placebo)	Primary endpoint (decrease from baseline)
ALD403 (eptinezumab) CGRP ligand	1000	i.v., once	163 (81 vs. 82)	5–14 MHD/28 days	Preventive treatments and analgesic overuse	6.7 vs. 7.0	MHD/28 days at 5–8 weeks
AMG 344 (erenumab) CGRP receptor	70	s.c., monthly for 3 months	483 (4 arms) (107 vs. 160)	4–14 MHD/28 days	Preventive treatments and analgesic overuse	8.6 vs. 8.8	MHD/28 days at 9–12 weeks
LY2951742 (galcanezumab) CGRP ligand	150	s.c., every 2 weeks for 3 months	218 (108 vs. 110)	4–14 MHD/28 days	Preventive treatments	6.7 vs. 7.0	MHD/28 days at 9–12 weeks
TEV-48125 CGRP ligand (fremanezumab)	225 (675)	s.c., monthly for 3 months	297 (96 vs. 104)	8–14 MHD/28 days triptan overuse allowed preventive treatment allowed	Use of opioids or barbiturates for >4 days/months	11.5 vs. 11.5	MHD/28 days at 9–12 weeks
	900 (675/225)	s.c., monthly for 3 months	264 (87 vs. 89 at 900-mg arm)	Chronic migraine preventive treatment allowed	Use of opioids or barbiturates for >4 days/months	16.4 vs. 16.8 (900 mg)	Headache hours at 9–12 weeks

Antibody target	Active vs. placebo primary endpoint	50% responder ratio (NNT)	Dropout ratio	Patients (%) with any AE (active vs. placebo)	Common AEs	Antidrug antibodies (neutralizing)	Reference
ALD403 (eptinezumab) CGRP ligand	5.6 vs. 4.6	75 vs. 54% (4.7)	12%	57 vs. 52	Dizziness; EGG changes; dry month	14%	Dodick *et al.* [22]
	1 day difference						
	$P=0.03$						
AMG 344 (erenumab) CGRP receptor	3.4 vs. 2.3	46 vs. 30% (6.2)	7%	54 (70 mg) vs. 54	Fatigue; headache	10% (3%)	Sun *et al.* [24]
	1.1 days difference						
	$P=0.021$						
LY2951742 (galcanezumab) CGRP ligand	4.2 vs. 3.0	70 vs. 45% (4.0)	12%	72 vs. 67	Erythema; site pain; infection; abdominal pain	18.7%	Dodick *et al.* [21]
	1.2 days difference						
	$P=0.003$						
TEV-48125 CGRP ligand (fremanezumab)	6.27 vs. 3.46	53 vs. 28% (4.0)	0.3%	27 (225 mg) vs. 23[a]	Injection pain; erythema	1%	Bigal *et al.* [23]
	2.18 days difference						
	$P=0.0001$ (225 mg)	(225 mg)					
	30.41 h difference from placebo $P=0.0057$	NA	1.1%	28 (900 mg) vs. 17[a]	Injection pain; pruritus	1%	Bigal *et al.* [25]
	2.0 MHD difference from placebo ($P=0.041$) (900 mg)						

AE, adverse event; CGRP, calcitonin gene-related peptide; MHD, migraine headache days; NNT, number needed to treat.
[a]Drug-related adverse events.

Mitsikostas DD, Reuter U. Calcitonin gene-related peptide monoclonal antibodies for migraine prevention: comparisons across randomized controlled studies. Curr Op Neurol 2017;30:272-280

Tergooi zorgt vooruit.

Table 2. Phase 3 RCTs of calcitonin gene-related peptide mAbs for migraine prevention

Antibody	Study name	ClinicalTrials.gov identifier	Optimum dose (mg)	Route and frequency of administration	Study size population (active vs. placebo)	Inclusion criteria	Mean baseline MHD/28 days (active vs. placebo)	Primary endpoint	Active vs. placebo primary endpoint	Common AEs	Estimated study completion
ALD403 (eptinezumab)	PROMISE 1	NCT02559895	1 dose	i.v., once	800	Frequent episodic migraine	NA	Responder rate at weeks 1–12	NA	NA	June 2017
	PROMISE 2	NCT02974153	2 doses	i.v., once	1050	Chronic migraine	NA	Decrease of MHD/28 days at 1–12 weeks	NA	NA	June 2018
AMG 344 (erenumab)	ARISE	NCT02483585	70	s.c., monthly for 3 months	577	4–14 MHD/28 days	8	MHD/28 days at 9–12 weeks	2.9 vs. 1.8	Nasopharyngitis; respiratory infection; injection site pain	Completed
	[34]								1.1 days difference		
	STRIVE	NCT02456740	70 and 140	s.c., monthly for 6 months	955	4–14 MHD/28 days	8.3	Decrease of MHD/28 days at 12–24 weeks	(70 mg) 3.7 vs. 1.8	Nasopharyngitis; respiratory infection; sinusitis	Completed
	[35]								1.9 days difference		
LY2951742 (galcanezumab)	EVOLVE 1	NCT02614183	2 doses	s.c., monthly for 6 months	825	Episodic migraine	NA	Decrease of MHD/28 days at week 24	NA	NA	June 2017
	EVOLVE 2	NCT02614196	2 doses	s.c., monthly for 6 months	825	Episodic migraine	NA	Decrease of MHD/28 days at week 24	NA	NA	July 2017
	REGAIN	NCT02614261	1 dose	s.c., monthly for 3 months	825	Chronic migraine	NA	Decrease of MHD/28 days at week 12	NA	NA	May 2018
TEV-48125 (fremanezumab)		NCT02638103	2 doses	s.c., monthly for 18 months	1842	Episodic or chronic migraine	NA	% of Participants with AEs	NA	NA	October 2018
		NCT02629861	2 doses	s.c., monthly for 3 months	786	Episodic migraine	NA	Decrease of MHD/28 days at week 12 and % of participants with AEs	NA	NA	October 2017
		NCT02621931	2 doses	s.c., monthly for 3 months	1020	Chronic migraine	NA	Decrease of MHD/28 days at week 12 and % of participants with AEs	NA	NA	October 2017

AE, adverse event; MHD, migraine headache days; NA, not available.

Mitsikostas DD, Reuter U. Calcitonin gene-related peptide monoclonal antibodies for migraine prevention: comparisons across randomized controlled studies. Curr Op Neurol 2017;30:272-280

Tergooi zorgt vooruit.

CGRP en MIGRAINE

- Migraine is een primair neurale hoofdpijn
- Etiologie: kanalopathieen (Na, Ca, K): genetisch
- Behandeling tot dusverre incompleet (treatment gap)
- Effectiviteit huidige arsenaal beperkt (triptanen)
- Calcitonin Gene Related Peptide is biomarker voor pijn
- CGRP is aangrijpingspunt voor hoofdpijnbehandeling
- Nieuwe klasse CGRP antagonisten veelbelovend

- CAVE: P x Q ! (“half a billion people are waiting”)

Binnenkort in dit theater!

Study Number TV48125-CNS-30068

A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study with an Open-Label Period to Evaluate the Efficacy and Safety of Fremanezumab for the Prophylactic Treatment of Migraine in Patients with Inadequate Response to Prior Preventive Treatments

A Randomized, Double-Blind, Placebo-Controlled Study with an Open-Label Period on Efficacy and Safety of Fremanezumab in Adults with Migraine

A Study to Test if Fremanezumab is Effective in Preventing Migraine in Patients Who Did Not Respond to Prior Preventive Migraine Treatments

Efficacy and Safety Study (Phase 3)

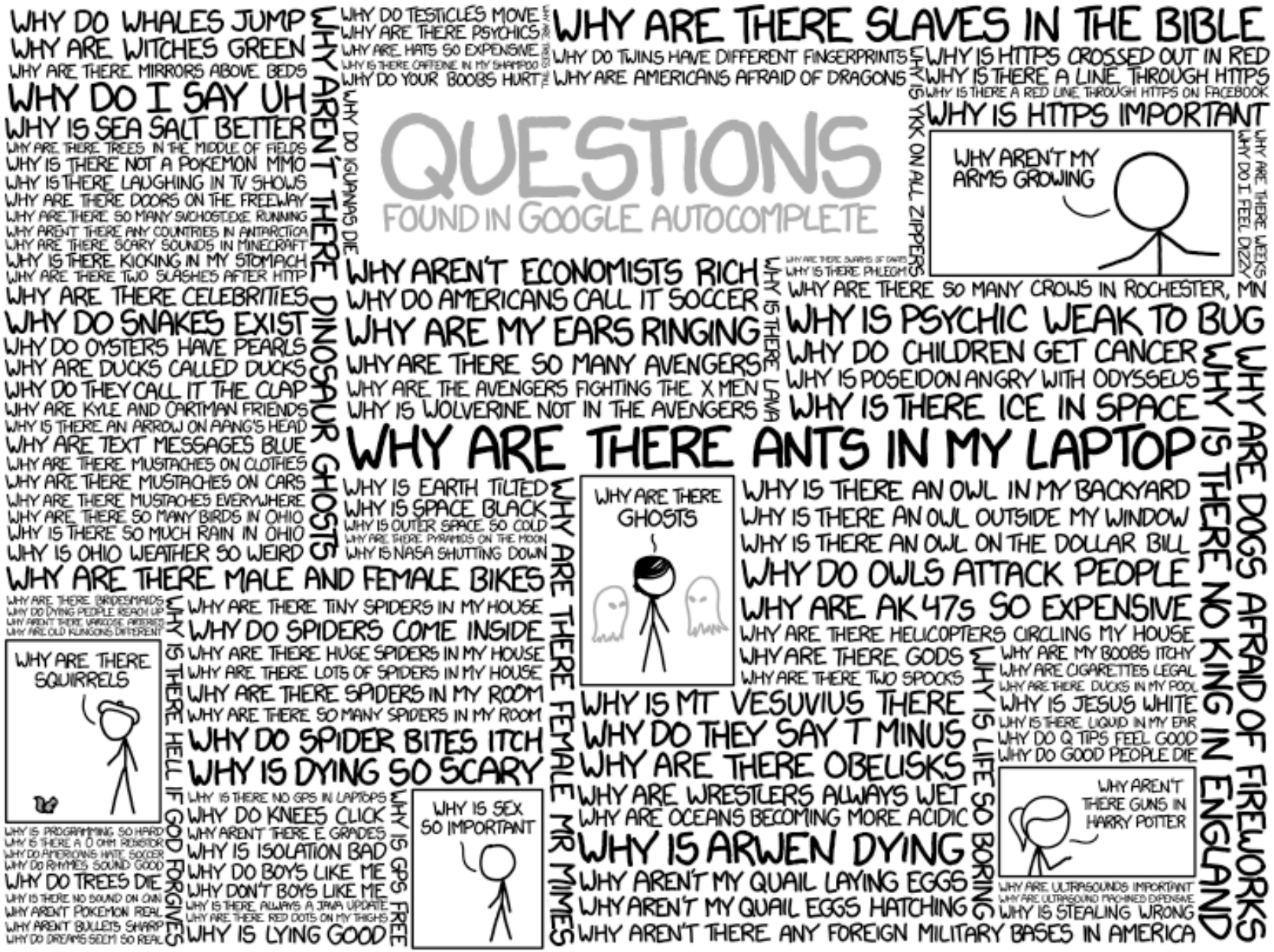
IND number: 106,533; NDA number: Not applicable; BLA number: Not applicable;

EudraCT number: 2017-002441-30

EMA Decision number of Pediatric Investigation Plan: Not applicable

Article 45 or 46 of 1901/2006 does not apply

Zo, klaar. Vragen?

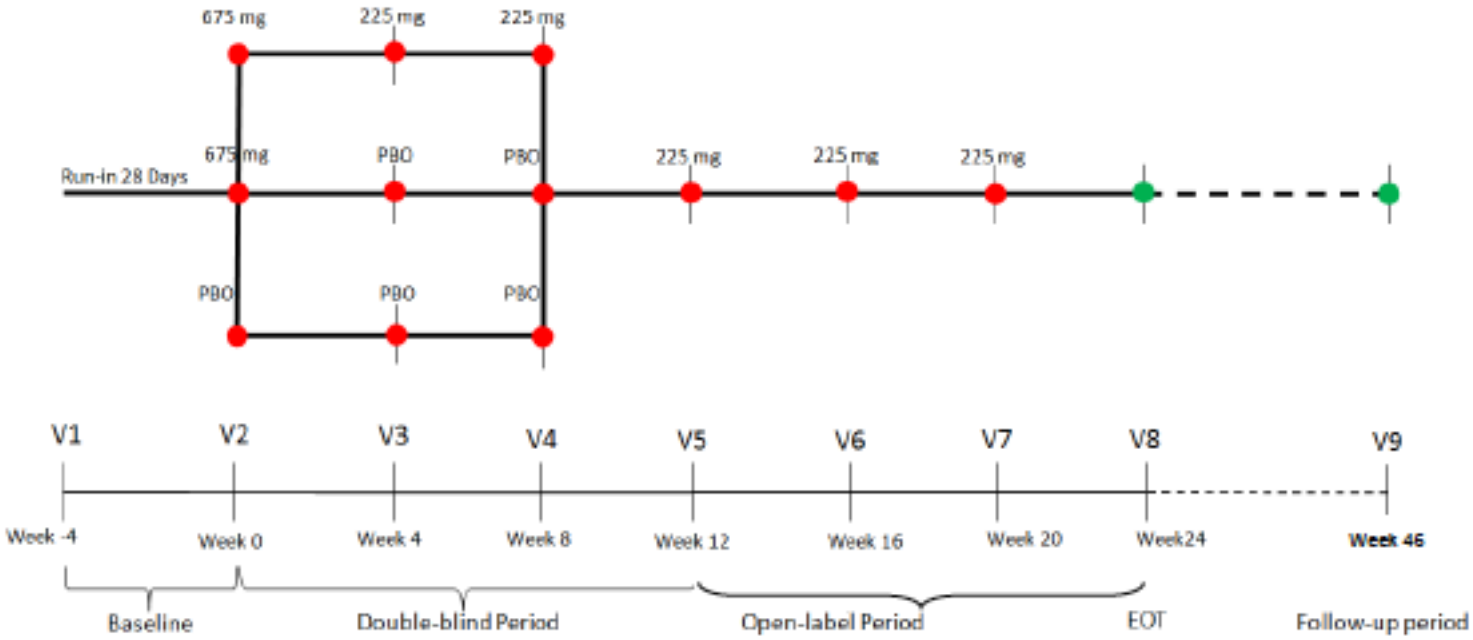


Pablo Diego José
Francisco de Paula
Juan Nepomuceno
María de os Remedios
Cipriano de la Santísima Trinidad
Ruiz y Picasso
1881-1973

Les demoiselles d'Avignon
1907

MOMA, New York, NY
Olie op doek,
244 X 234

TV 48125-CNS-30068, site 37128



EOT=end of treatment; PBO=placebo; V=visit.