FACULTEIT FARMACEUTISCHE WETENSCHAPPEN

FACULTEIT GENEESKUNDE EN GEZONDHEIDSWETENSCHAPPEN

UZ GENT

UNIVERSITEIT GENT

Migraine: van zelfzorg tot migraine-kliniek

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Apotheek

Apotheekstudie naar zelfzorg van hoofdpijn

Self-medication of regular headache: a community pharmacy-based survey

E. Mehuys[a], K. Paemeleire[b], T. Van Hees[c], T. Christiaens[d], L. M. Van Bortel[e], I. Van Tongelen[a], L. De Bolle[a], J.-P. Remon[a] and K. Boussery[a]

European Journal of Neurology 2012, **19:** 1093–1099

Observationele studie in 152 Belgische officina-apotheken

→ 1205 patiënten die min. 1x/maand hoofdpijn hebben én om OTC-pijnstiller voor hoofdpijn komen

Deze studie stelde vast:

1. Migraine is ondergediagnosticeerd

2. Migraine is onderbehandeld

3. Acute hoofdpijnmedicatie wordt vaak overgebruikt

1. Migraine is ondergediagnosticeerd

44% (n=528) had geen artsdiagnose hoofdpijn → 225 van hen (42,6%) positief op ID-Migraine Screener!

Photophobia

Inability to function

Nausea

Figuur 1 - ID-Migraine Screener

	Ja	Nee
1. Heb je last van het licht als je hoofdpijn hebt?		
2. Heeft de hoofdpijn je dagelijkse activiteiten ten minste één dag beperkt in de laatste drie maanden?		
3. Ben je misselijk of heb je maaglast wanneer je hoofdpijn hebt?		

Antwoordt de patiënt 'ja' op minstens twee van de drie vragen, dan is er 93% kans dat hij/zij aan migraine lijdt. De 3 vragen kunnen gememoriseerd worden a.d.h.v. het acroniem PIN (Photophobia, Inability to function, Nausea)

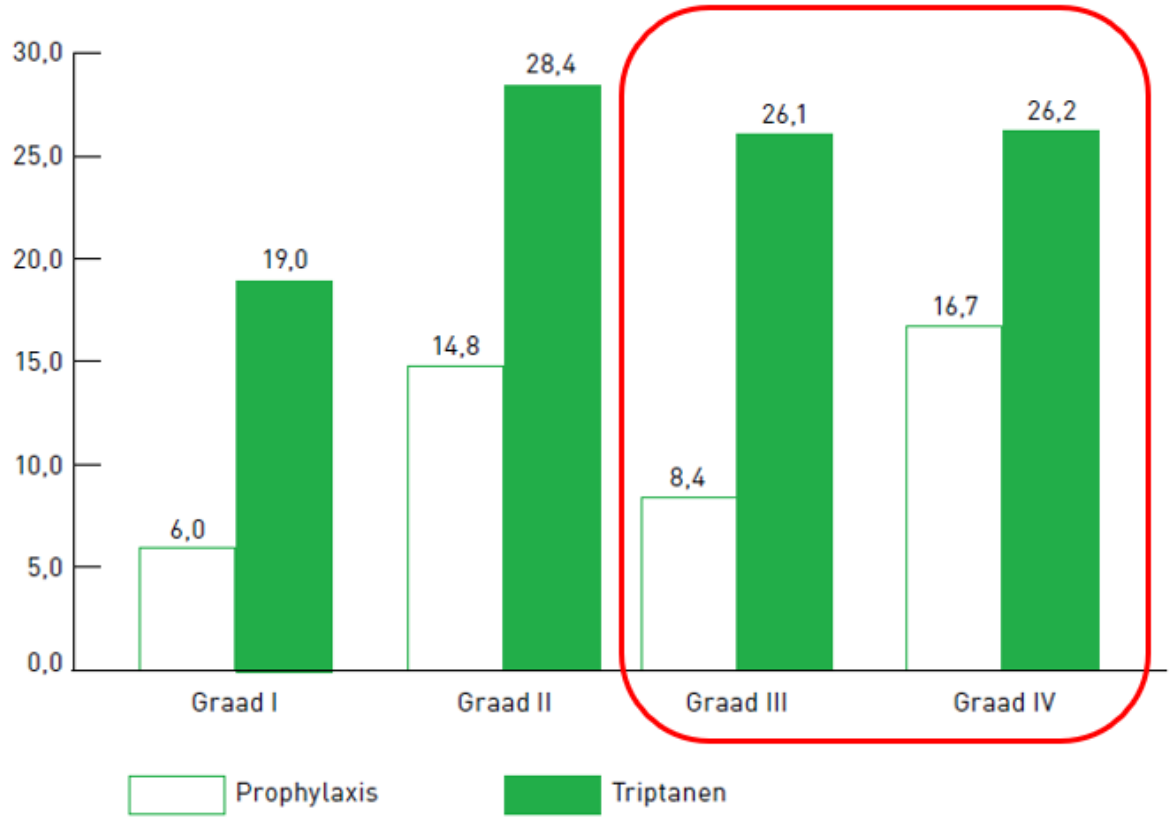
- ✓ Sensitiviteit: 81%
- ✓ Specificiteit: 75%
- ✓ PPV: 93%

NEUROLOGY 2003;61:375–382

2. Migraine is onderbehandeld

Van de patiënten met migraine-diagnose (n=426): slechts 25% gebruikt triptanen en 12% profylaxis

Figuur 2 - Profylaxis- en triptaangebruik door patiënten
met een arts-diagnose van migraine, in functie van hun MIDAS-graad



Rol apr:

- Zelfzorgbehandeling migraine:

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

The Journal of Headache and Pain (2019) 20:57

Table 7 Recommended drugs and doses for acute migraine therap, step one

Analgesics	Antiemetics
Adults	
Non-steroidal anti-inflammatory drugs: • Acetylsalicylic acid 900–1000 mg *or* • Ibuprofen 400–800 mg *or* • Diclofenac 50–100 mg	• Domperidone 10 mg (supportive evidence of efficacy is for 20 mg, but the European Medicines Agency recommends restriction to 10 mg orally [up to three times daily] or 30 mg by suppository [up to twice daily]), *or* • Metoclopramide 10 mg (the European Medicines Agency restricts dosing to 10 mg [up to three times daily])
Or (where these are contraindicated): • Paracetamol 1000 mg[a]	
Or (possibly benefiting from the different mechanisms of action): • Combinations of paracetamol with acetylsalicylic acid or ibuprofen	
Children (when needed)	
Ibuprofen 200–400 mg according to age and weight	• Domperidone (dosage according to age and weight)

[a]Paracetamol on its own has lower efficacy and is **not** first-line treatment

Self-medication of migraine and tension-type headache: summary of the evidence-based recommendations of the Deutsche Migräne und Kopfschmerzgesellschaft (DMKG), the Deutsche Gesellschaft für Neurologie (DGN), the Österreichische Kopfschmerzgesellschaft (ÖKSG) and the Schweizerische Kopfwehgesellschaft (SKG)

Drug or fixed-dose combination	Quality of scientific evidence	Scientific evidence of efficacy	Clinical impression of effectiveness	Clinical impression of tolerability	Comments	Recommendation for self-medication
Two tablets of the fixed combination: (250–265 mg) acetylsalicylic acid + (200–265 mg) paracetamol + (50–65 mg) caffeine	A	+++	++	+++	Highlighted recommendation on the basis of the analysed comparative studies	Drug of first choice
Acetylsalicylic acid (900–1,000 mg)	A	+++	++	++	As tablet and as effervescent tablet	Drug of first choice
Ibuprofen (400 mg)	A	+++	++	+++		Drug of first choice
Naratriptan (2.5 mg)	A	++	++	+++		Drug of first choice
Paracetamol (1,000 mg)	A	++	+	+++		Drug of first choice

J Headache Pain (2011) 12:201–217

In BEL niet OTC beschikbaar

<u>Rol apr</u>:

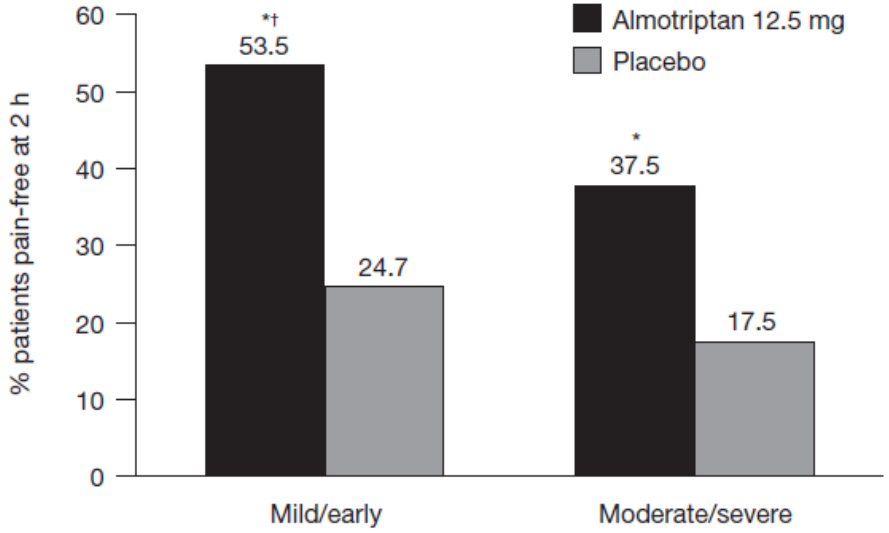
- **Doorverwijzen** bij:
  - migraine-screener positief (tenzij gewone pijnstiller voldoet bij normaal gebruik)
  - onvoldoende effect huidige behandeling (3 opeenvolgende aanvallen)
  - Hoofdpijnmedicatie nodig > 6 à 8 d/maand
    > 2d/week

<u>Rol apr</u>:

- Aandacht voor <u>goed gebruik</u> acute hoofdpijnmedicatie (zowel OTC als Rx !)
    - In adequate dosering
    - Juiste toedientechniek voor bv. nasale spray en SC triptanen (zie bijsluiter)
    - Vroeg in de aanval nemen (“Act when mild”)

The ‘Act when Mild’ (AwM) Study: a step forward in our understanding of early treatment in acute migraine

- RCT bij 491 migrainepatiënten
- Inname triptan wanneer pijn nog mild is en nog maar max. 1u aanwezig **(‘mild/early’ groep**) *versus* inname triptan wanneer pijn al matig of ernstig is (**‘moderate/severe’ groep**)



*$p \leq 0.001$ vs. placebo; †$p = 0.02$ vs. almotriptan moderate/severe

Cephalalgia, 2008, **28** (Suppl. 2), 36–41

3. Acute hoofdpijnmedicatie wordt vaak overgebruikt

- 24% overgebruikt acute hoofdpijnmedicatie (vooral combinatie-analgetica en 'eenvoudige analgetica')
- Slechts **14,5%** kreeg ooit het advies om inname-frequentie acute hoofdpijnmedicatie te beperken

→ risico op '**medication-overuse headache**' (MOH)!

Diagnostische criteria MOH (ICHD-3):

Description: Headache occurring on 15 or more days per month in a patient with a preexisting primary headache and developing as a consequence of regular overuse of acute or symptomatic headache medication (on 10 or more or 15 or more days per month, depending on the medication) for more than three months. It usually, but not invariably, resolves after the overuse is stopped.
A. Headache occurring on 15 or more days per month in a patient with a preexisting headache disorder. ⟶ vaak migraine!
B. Regular overuse for more than three months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache:
Regular intake for ≥10 days per month for >3 months of ergotamine, triptans, or opioids, or combination analgesics, **or** any combination of ergotamines, triptans, simple analgesics, NSAIDs and/or opioids without overuse of any single drug or drug class alone or when the pattern of overuse cannot be reliably established.
Regular intake for ≥15 days per month for >3 months of simple analgesics (ie, acetaminophen, aspirin, or NSAID).
C. Not better accounted for by another ICHD-3 diagnosis.

ICHD-3: International Classification of Headache Disorders 3rd edition; NSAID: nonsteroidal antiinflammatory drug.

***Rol apr**:*

- **PREVENTIE**: Adviseer gebruik acute hoofdpijnmedicatie te beperken tot max. 6 à 8 d/maand **en** max. 2d/week, en leg uit waarom

- I.g.v. vermoeden MOH: doorverwijzen of evt. zelf advies geven i.v.m. stop acute hoofdpijnmedicatie

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

The Journal of Headache and Pain (2019) 20:57

2.5.9.4 Principles of withdrawal

- **Worsening headache** for 1–2 weeks is almost inevitable:
  - accordingly, withdrawal should be **planned** to avoid unnecessary lifestyle disruption;
  - 1–2 weeks' **sick leave** may be needed;
  - **admission to hospital** during withdrawal is **rarely necessary** unless:
    - overused medication(s) include opioids;
    - for management of comorbidities.
- **Withdrawal** may be undertaken in **any of three ways**, the choice being made by the patient:
  - **abruptly**:
    - there is evidence that this is the most successful approach;
  - by **tapering** over a period of 2–4 weeks:
    - withdrawal symptoms are likely to be less intense but more prolonged;
  - by **replacing** the overused medication(s) with **naproxen 500 mg twice daily** for 3–4 weeks and no longer:
    - the purpose is to break the behavioural "have headache – take medication" link;
    - many patients become headache-free on this medication;
    - naproxen must be stopped after this period (never continued).
- Headache usually shows signs of **improvement** 1–2 weeks after stopping overused medication(s).
- **Recovery** continues slowly for up to 2 months.
- **Prophylaxis** against the antecedent headache (most often migraine) may be introduced on its return, or commenced in parallel with the withdrawal process.

+ patiënteducatie heel belangrijk!

Key points of information are:

- The "treatment" a patient is taking for headache is actually **the cause** of it.
- Effective treatment requires, in the first instance, **stopping use of the suspected medication(s)** (withdrawal):
  - there is **no other option**;
  - many patients recover from this alone.
- **Initial worsening** of symptoms for 1–2 weeks during and after withdrawal must be expected.
- The **outcome is usually very good**, with reversion in most cases, within 2 months, to the antecedent episodic headache disorder.

Hulpmiddel voor patiënteducatie: www.thuisarts.nl > ‘Ik heb hoofdpijn doordat ik vaak pijnstillers tegen hoofdpijn gebruik’

Brief intervention for medication-overuse headache in primary care. The BIMOH study: a double-blind pragmatic cluster randomised parallel controlled trial

Kristoffersen ES, *et al*. *J Neurol Neurosurg Psychiatry* 2015;**86**:505–512.

Brief intervention = - Korte gestructureerde info over MOH en de link tussen medicatie-overgebruik en chronische hoofdpijn

- Geïndividualiseerd advies over afbouw acute hoofdpijnmedicatie

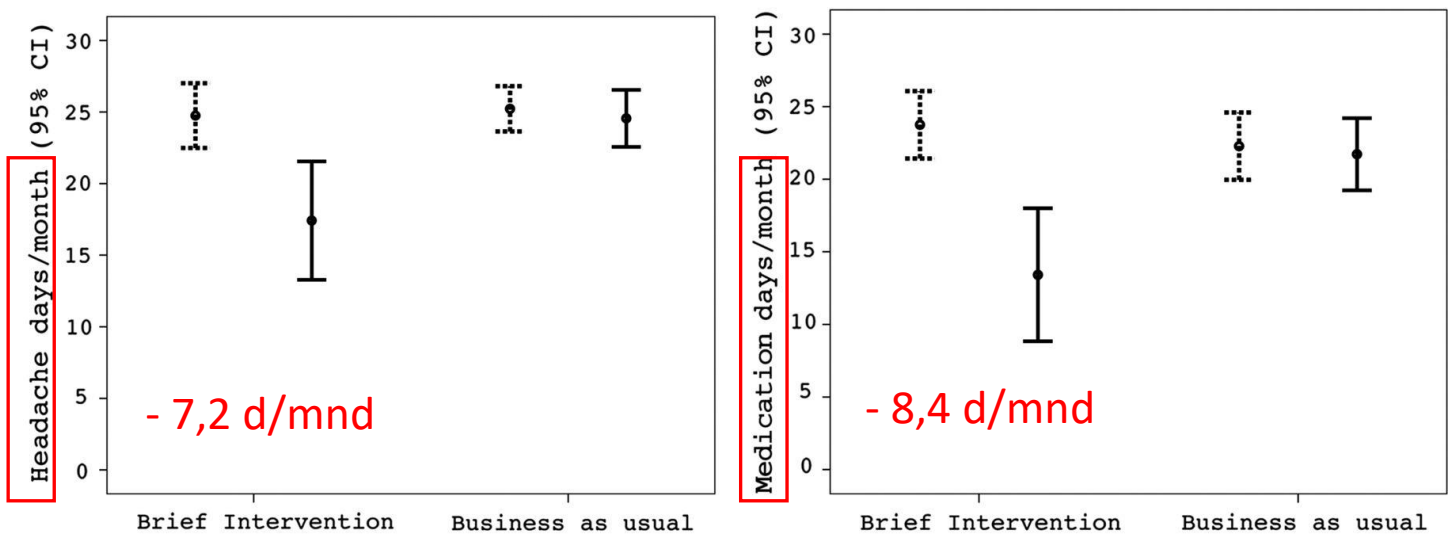


Figure 3

Crude headache and medication data at baseline (dotted) and at 3 months follow-up (solid) in the brief intervention and business as usual.

CONSENSUS STATEMENT

OPEN

Check for updates

Diagnosis and management of migraine in ten steps

Anna K. Eigenbrodt[1,36], Håkan Ashina[1,36], Sabrina Khan[1], Hans-Christoph Diener[2], Dimos D. Mitsikostas[3], Alexandra J. Sinclair[4,5,6,7], Patricia Pozo-Rosich[8,9], Paolo Martelletti[10,11], Anne Ducros[12], Michel Lantéri-Minet[13], Mark Braschinsky[14], Margarita Sanchez del Rio[15], Oved Daniel[16], Aynur Özge[17], Ayten Mammadbayli[18], Mihails Arons[19], Kirill Skorobogatykh[20], Vladimir Romanenko[21], Gisela M. Terwindt[22], Koen Paemeleire[23], Simona Sacco[24], Uwe Reuter[25], Christian Lampl[26,27], Henrik W. Schytz[1], Zaza Katsarava[28,29,30,31], Timothy J. Steiner[32,33] and Messoud Ashina[1,31,34,35]✉

Nat Rev Neurol 2021;17(8):501-514

4 Acute treatment

First-line medication

- NSAIDs (acetylsalicylic acid, ibuprofen or diclofenac potassium)

Second-line medication

- Triptans
- When triptans provide insufficient pain relief, combine with fast-acting NSAIDs

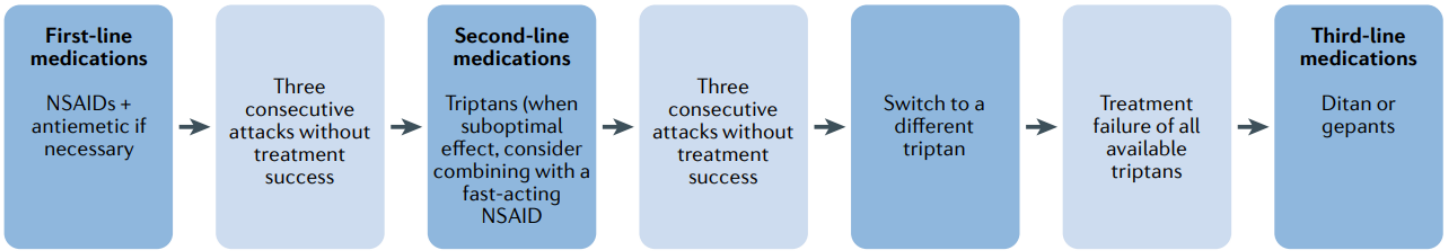
Third-line medication

- Ditans
- Gepants

Adjunct medications for nausea and/or vomiting

- Prokinetic antiemetics (domperidone or metoclopramide)

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



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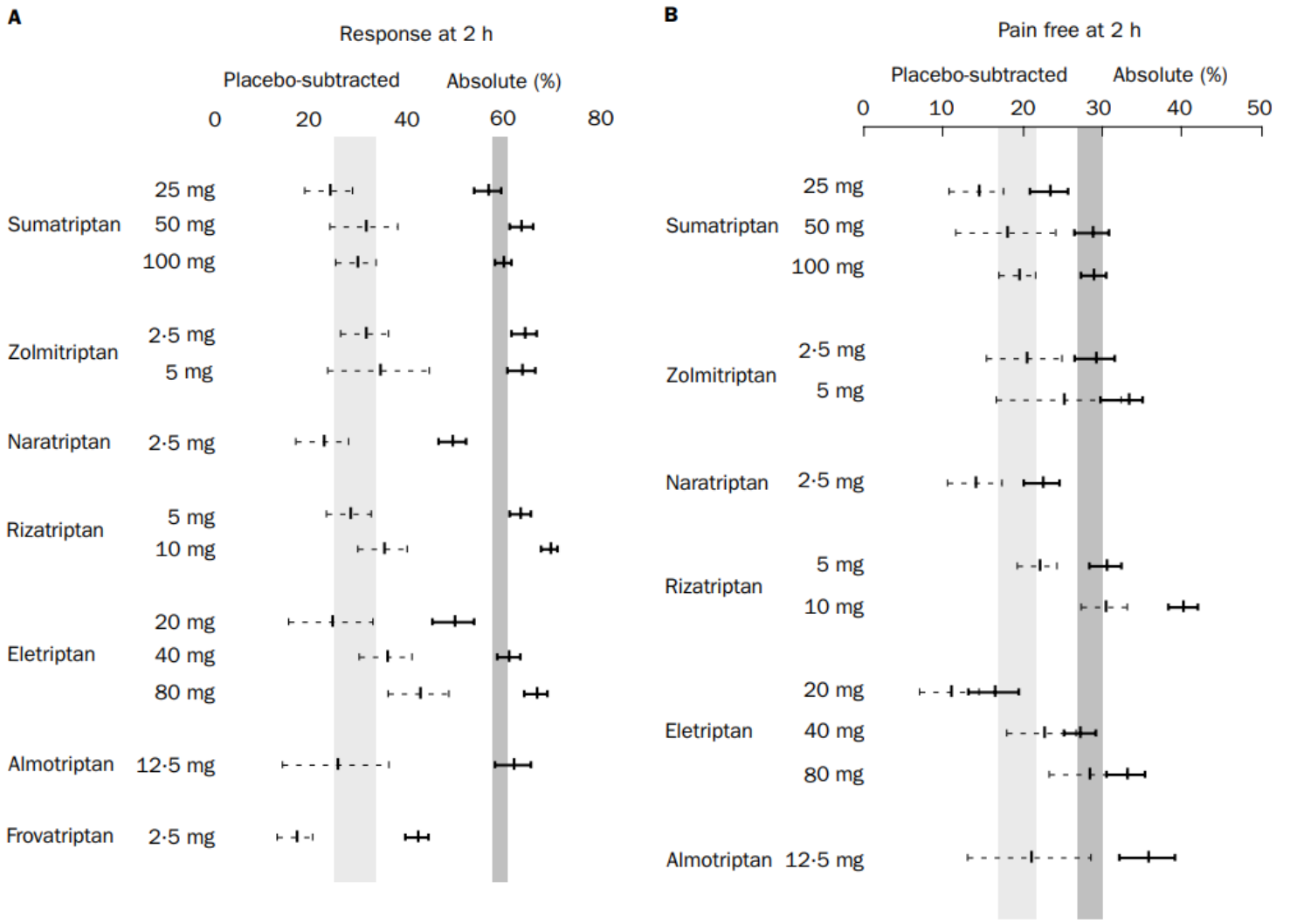
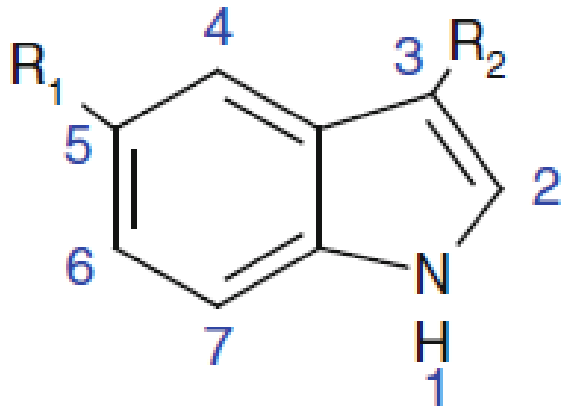


Figure 1: **Absolute and placebo subtracted efficacy results at 2 h**
A: rates of headache response; B: rates of pain-free. Mean and 95% CIs given for each triptan. Grey shaded regions are the 95% CIs for 100 mg sumatriptan.

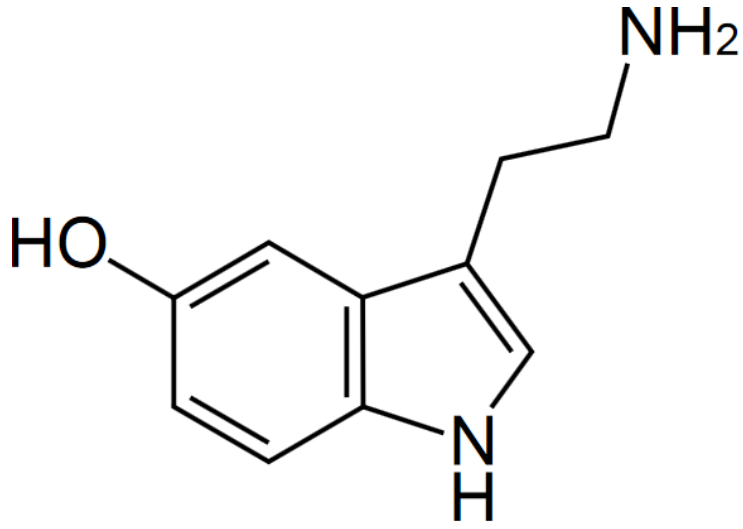
Nat Rev Neurol 2021;17(8):501-514
Lancet 2001; 358: 1668–75

MOA of triptans

- Specifically designed for acute migraine treatment
- 5-HT1B/1D/(1F) receptor agonists
- Trigeminovascular system

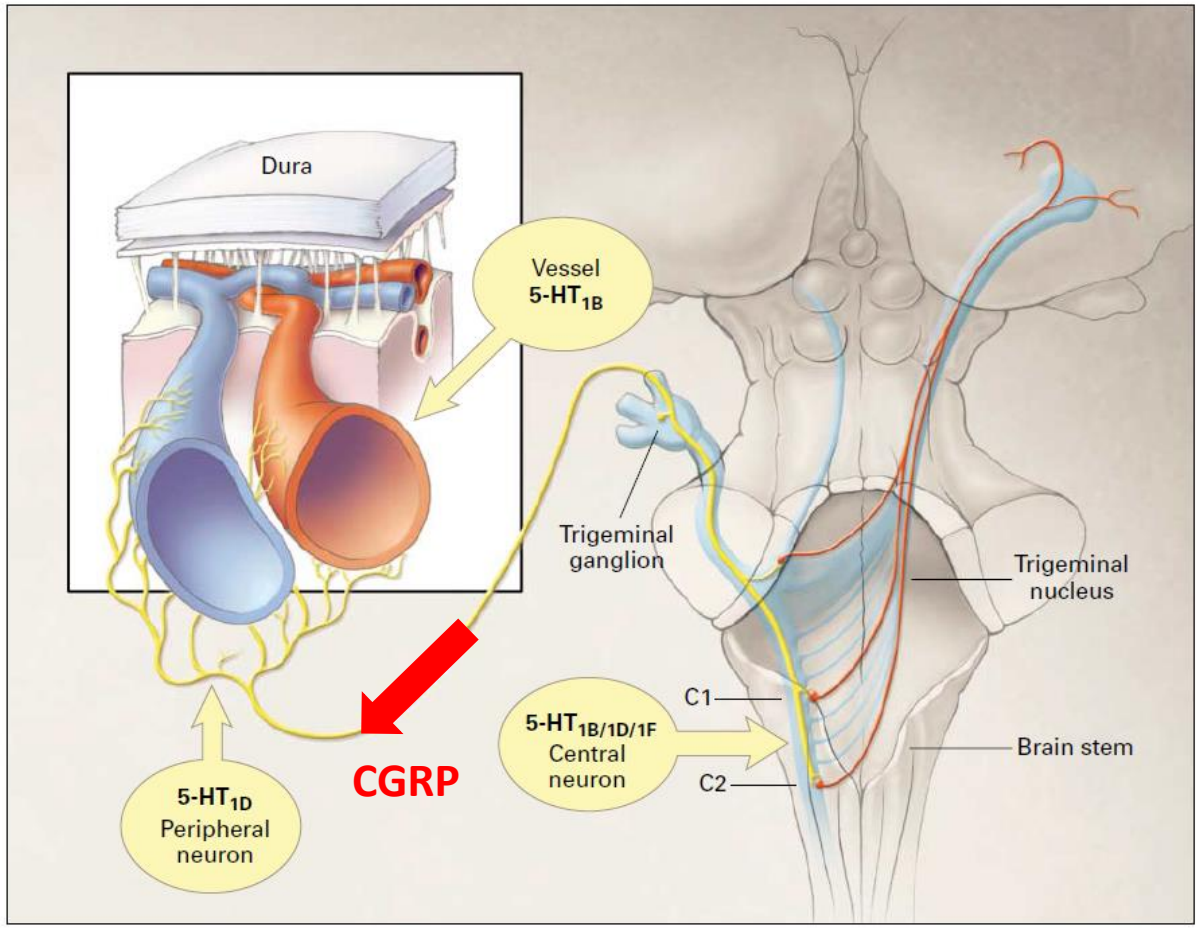


Indole structure



Serotonin

Trigeminovasculair systeem

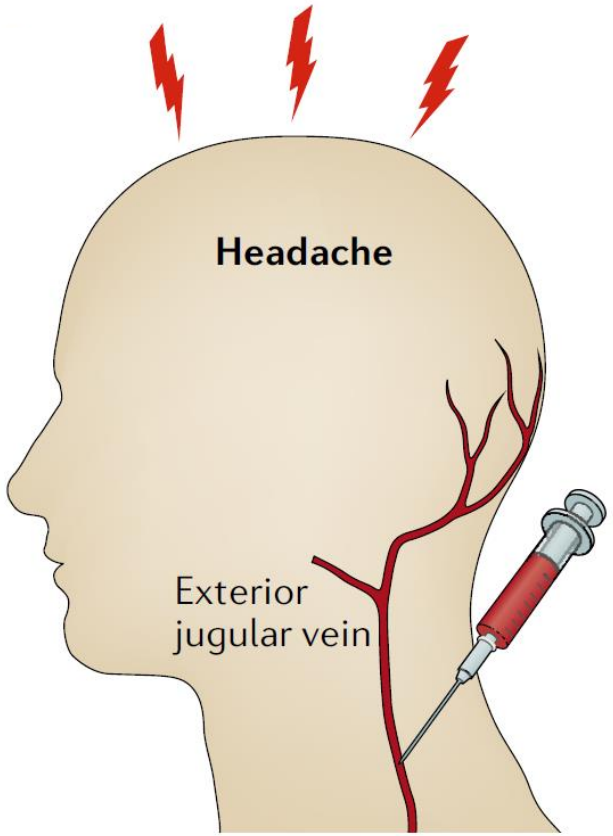


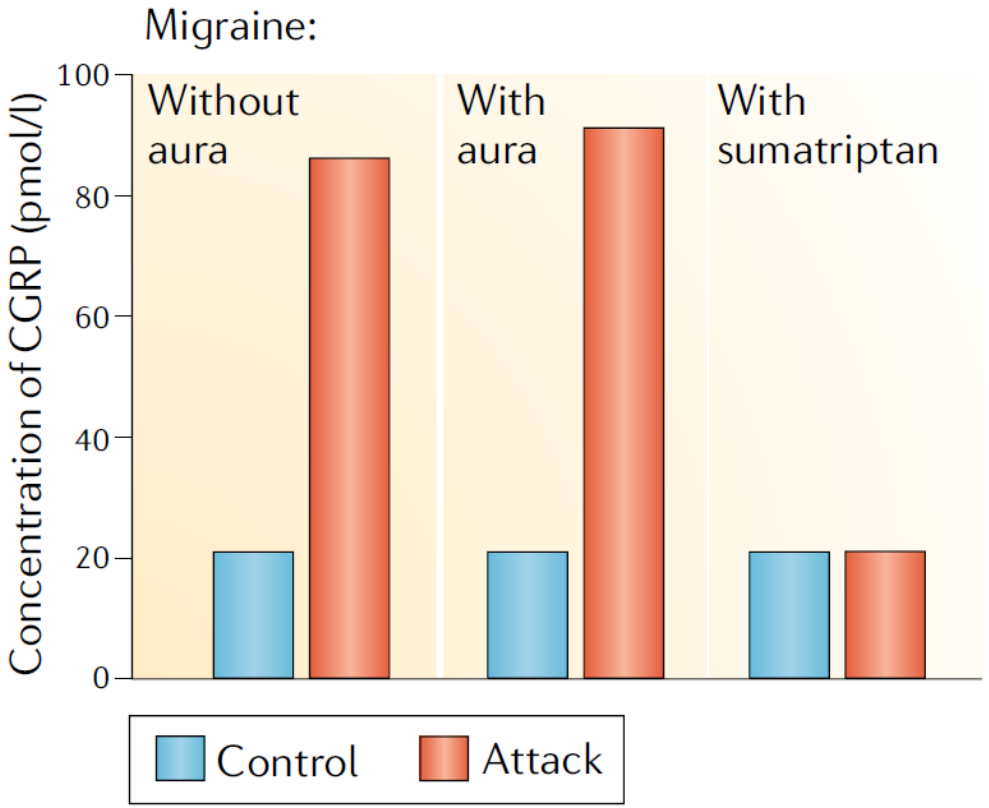
Triptans

(i) inhibition peripheral neuropeptide release
(ii) cranial vasoconstriction
(iii) inhibition second-order neurons TCC
(iv) other central effects

N Engl J Med 2002;346:257-270

Migraine: CGRP





Ann Neurol 1993;33:48-56
Nat Rev Neurol 2018;14(6):338-350

Triptans: formulations

Drug	Formulation	Remark
almotriptan	tablets	
eletriptan	tablets	
frovatriptan	tablets	
naratriptan	tablets	
rizatriptan	(oral disintegr.) tablets	
sumatriptan	tablets	
	nasal spray	limited nasal abs.
	SC	NNT 2hPF: 2.3
zolmitriptan	(oral disintegr.) tablets	
	nasal spray	30 % nasal abs.

Contraindications to triptans

Cardiovascular disease, including

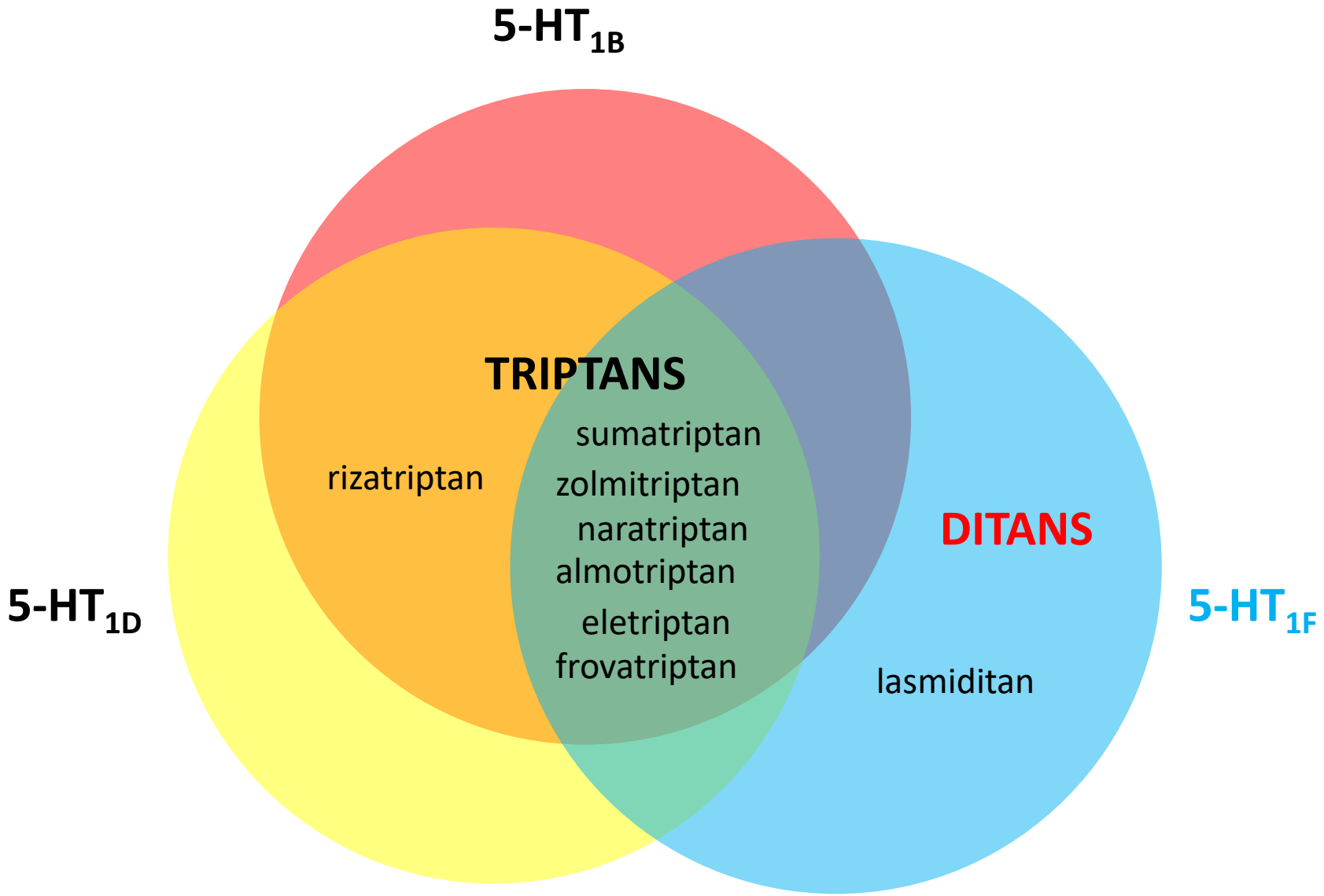
- Uncontrolled hypertension
- Cerebrovascular disease
- Coronary artery disease

> 65 years

Hemiplegic migraine

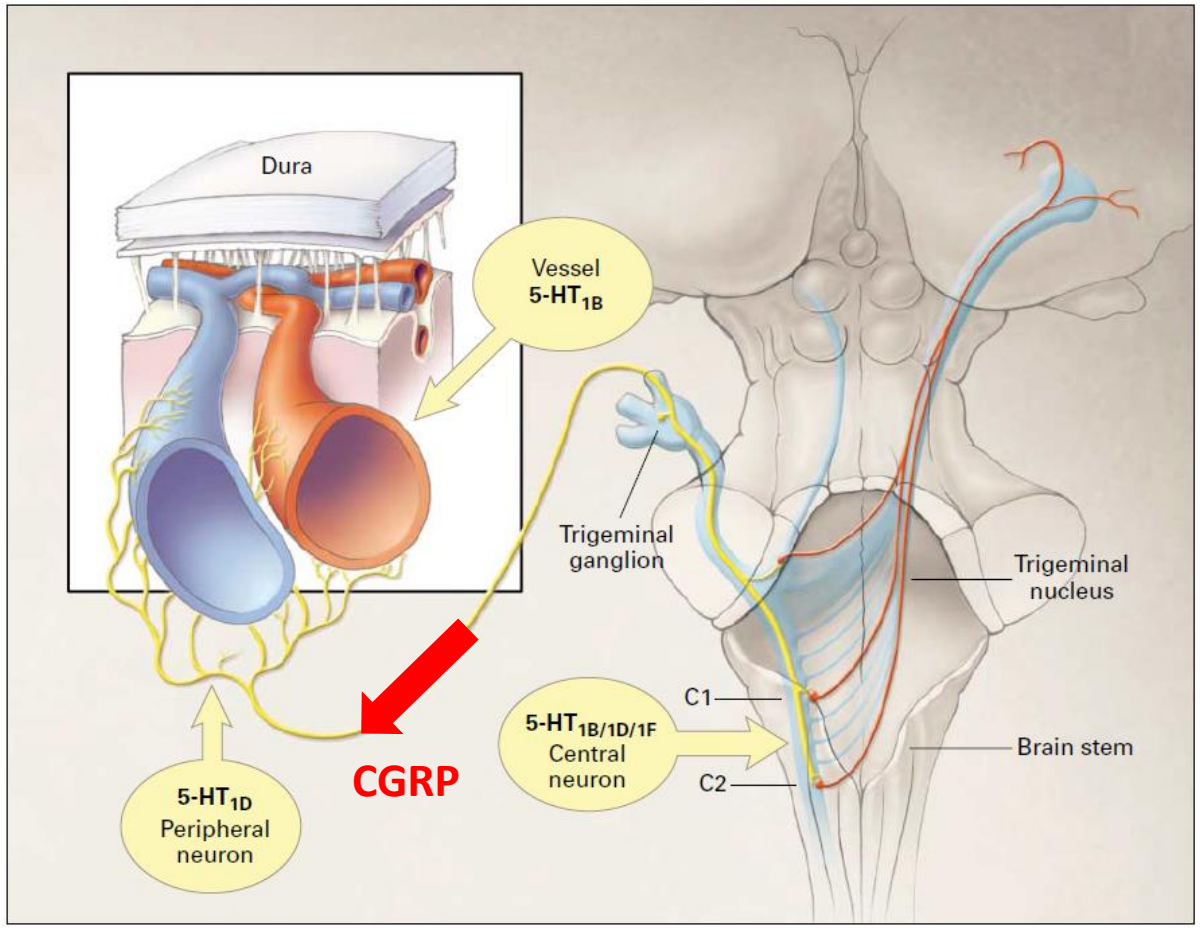
Migraine with brainstem aura

(At risk of) pregnancy; lactation



After Pharmacol Ther 2018;186:88-97

Trigeminovasculair systeem



Triptans

Ditans

Centrally acting 5-HT_{1F} agonist

Lacks vasoconstrictive activity

N Engl J Med 2002;346:257-270

Lasmiditan

- Centrally acting 5-HT_{1F} agonist
- Lacks vasoconstrictive activity
- Same efficacy range as triptans (no head-to-head comparison)
- Safe option for patients unable to use triptans
  due to vascular risk factors/cardiovascular disease
- Side effect profile
  dizziness, somnolence $\leftrightarrow$ operate machinery for $\geq$ 8 hrs

Clin Pharmacol Drug Dev 2020;9(3):292-296

5 Preventative treatment

- Recommended for patients adversely affected on ≥2 days per month despite optimized acute therapy

First-line medication

- Beta blockers (propranolol, metoprolol, atenolol, bisoprolol)
- Topiramate
- Candesartan

Second-line medication

- Flunarizine
- Amitriptyline
- Sodium valproate[a]

Third-line medication

- CGRP monoclonal antibodies[b]

8 Managing complications

- Use preventive treatment for chronic migraine: topiramate, onabotulinumtoxinA or CGRP monoclonal antibodies[b]

Assess efficacy for

- Oral preventive medication: after 2–**3** months
- Monoclonal antibody treatments that target CGRP/its receptor: after **3**–6 months
- OnabotulinumtoxinA: after **6**–9 months

Failure of one preventive treatment does not predict failure with other drug classes

Treatment adherence ↑ by simplified dosing schedules (once daily or less)

For most preventive medications, clinical experience suggests that pausing can be considered when treatment has been successful for 6–12 months

Nat Rev Neurol 2021;17(8):501-514

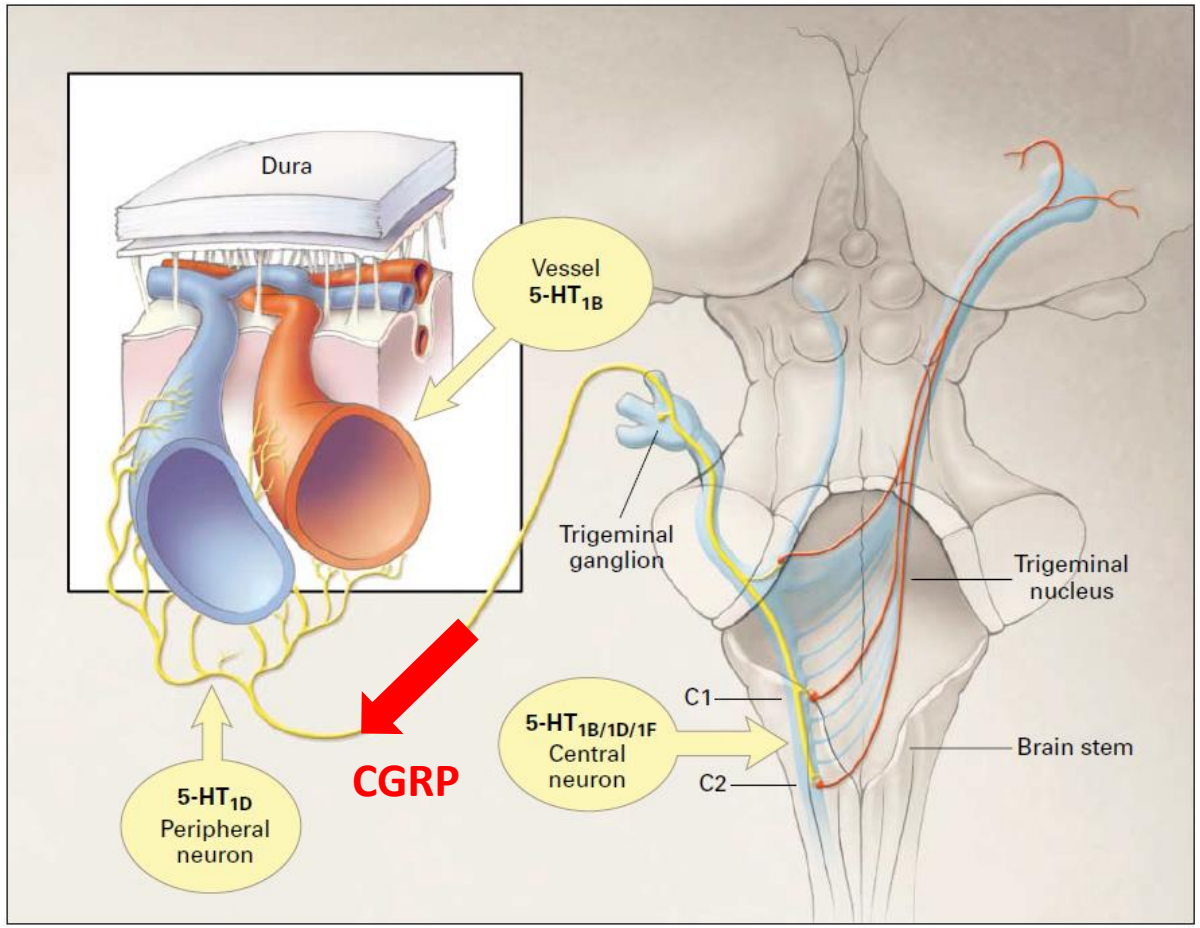
CONSENSUS ARTICLE Open Access

Latest clinical recommendations on valproate use for migraine prophylaxis in women of childbearing age: overview from European Medicines Agency and European Headache Federation

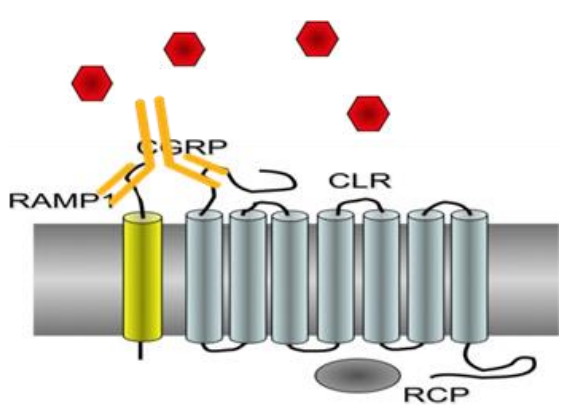
"In view of the risks for the unborn child when exposed to valproate in utero, valproate should only be used as last line medication for prophylaxis of migraine attacks in female children, adolescents and women of childbearing potential."

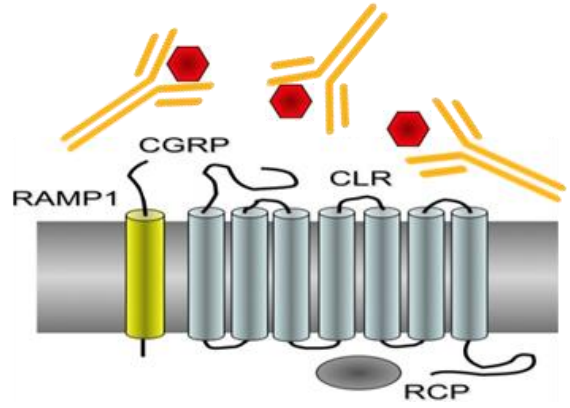
J Headache Pain 2018 ;19(1):68

Trigeminovasculair systeem



Triptans
Ditans
CGRP receptor and ligand mAbs





N Engl J Med 2002;346:257-270

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 /28 days	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, EMA

CGRP pathway mAbs

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

CGRP pathway mAbs

Contraindications

Hypersensitivity

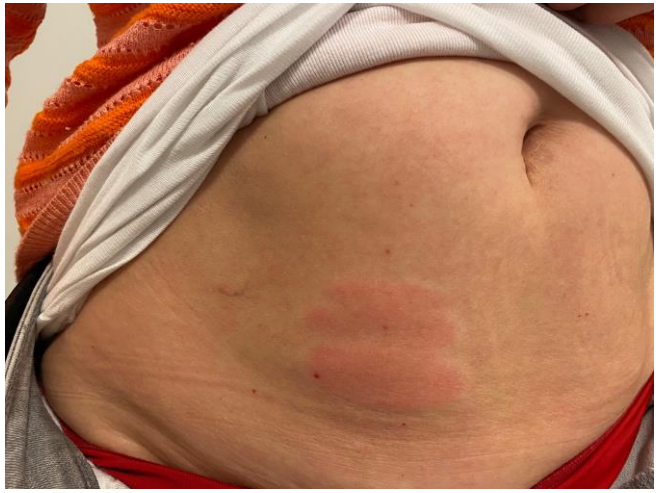
Not recommended in patients with a history of stroke, subarachnoid haemorrhage, coronary heart disease, inflammatory bowel disease, chronic obstructive pulmonary disease or impaired wound healing

Side effects

Injection site reaction

Constipation

Blood pressure ?



Nat Rev Neurol 2021;17(8):501-514

Neurology 2022;99(17):e1897-e1904

Terugbetaling CGRP mAbs België

Gefaalde profylactische behandelingen:

ten minste 1 bèta-blokker (propranolol, metoprolol, atenolol, bisoprolol, timolol) [of CI]

en

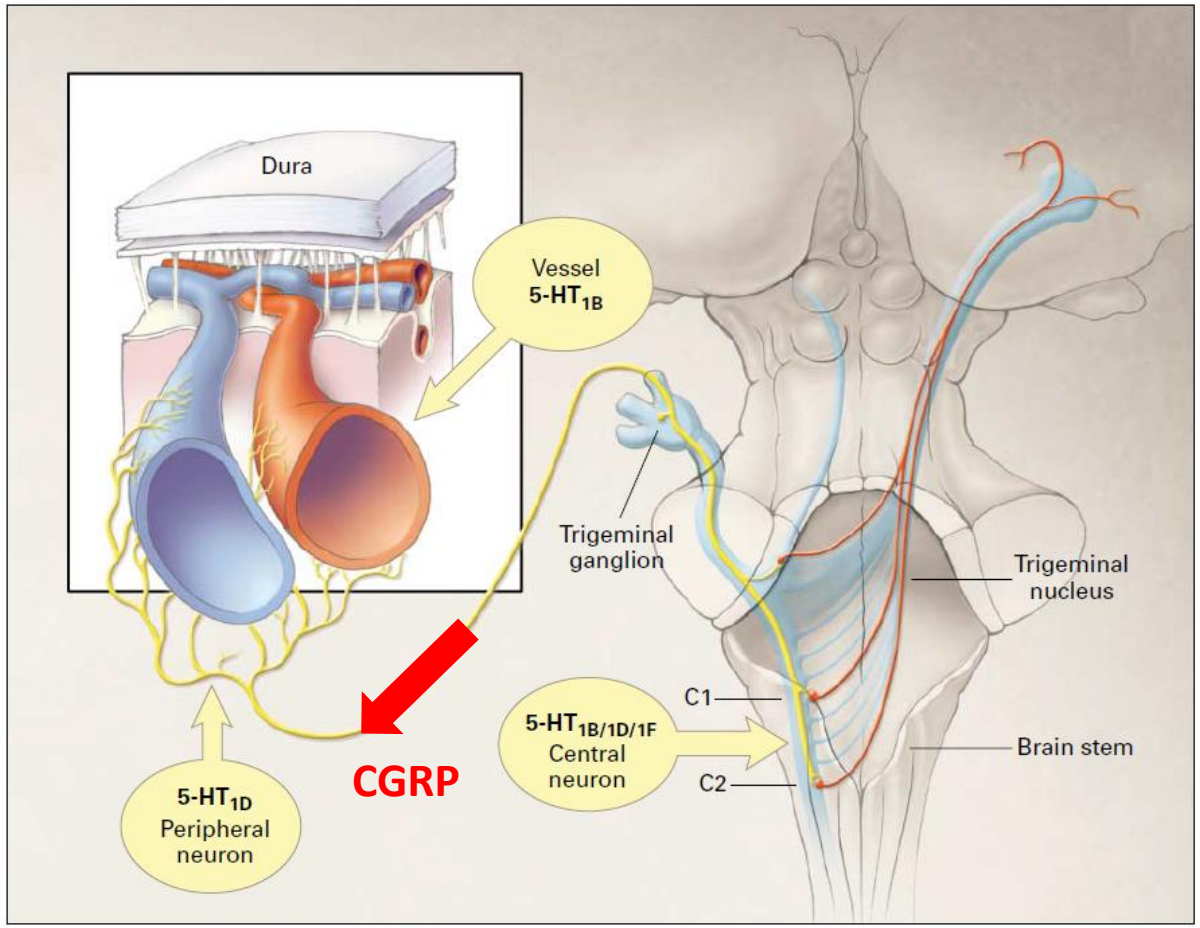
ten minste topiramaat [of CI]

en

ten minste één van volgende: valproïnezuur/valproaat, amitriptyline, venlafaxine, flunarizine, candesartan, onabotulinetoxine A (CM)

Gemiddeld ≥ 8 migrainedagen per maand (≥ 4 weken migrainedagboek)

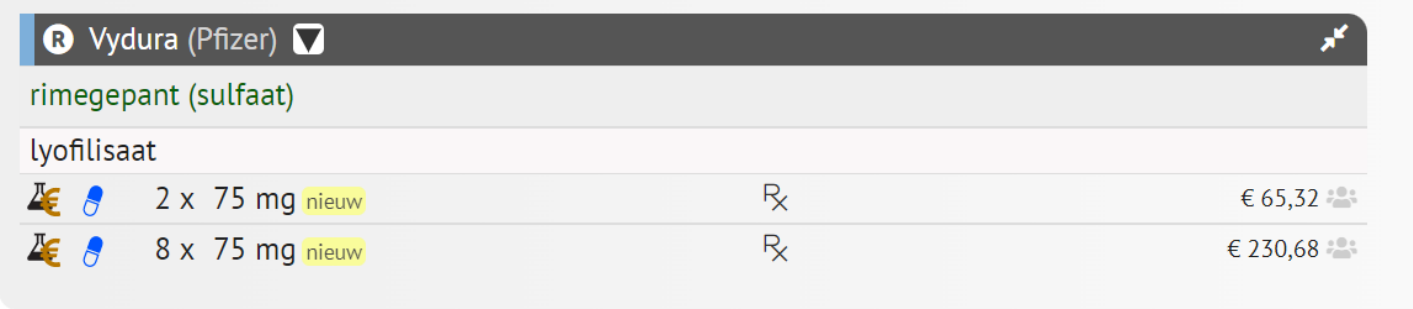
Trigeminovasculair systeem



Triptans
Ditans
CGRP receptor and ligand mAbs
Gepants = small molecule CGRP rec. antagonists

N Engl J Med 2002;346:257-270

Second generation gepants



Dual indication in adults:

- acute treatment of migraine +/- aura
- preventive treatment of episodic migraine (≥4 MMDs)

- Low TG
- No vasoconstrictor effect
- Most common SE: nausea (~2% rimegepant)

Curr Opin Neurol 2020;33:309-315
Lancet 2019;394(10200):737-745
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Consensusconferentie RIZIV

25/5/2023

‘Rationeel gebruik van geneesmiddelen bij behandeling van migraine’


The End