Traditional headache preventatives in migraine

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Traditional oral preventative

- All older drugs used in migraine prevention were developed for other indications and later found to be effective in migraine
- Trials for modern headache therapeutics have been on patients who have previously been treated with 2-3 of the traditional treatments
- NICE approval for Botox and CGRP antagonists on basis that patient has not responded to three traditional treatments
- Any positive effect takes weeks to establish
- Three months treatment regarded as adequate trial

General principles

- All drugs from the main classes regarded as roughly equivalent with few head-to-head trials of efficacy
- Most data is from EM or patients of mixed headache types
- Fewer trials specifically on chronic migraine populations
- Start with low dose and increase incrementally
- Choice of treatment based on
  - Possibilities of multitarget action: eg co-existing depression may prompt use of antidepressant migraine preventative
  - Avoidance of possible adverse effects: eg betablocker and asthma

Amitriptyline

- Benefits in migraine first reported in 1960s
- One of commonest drugs used in migraine and headache prophylaxis
- Multiple potential mechanisms proposed
- TCAs have multiple target sites of action including 5-HT reuptake inhibition, noradrenaline reuptake inhibition, plus action on sodium, potassium and calcium channels

Amitriptyline: mechanism of action?

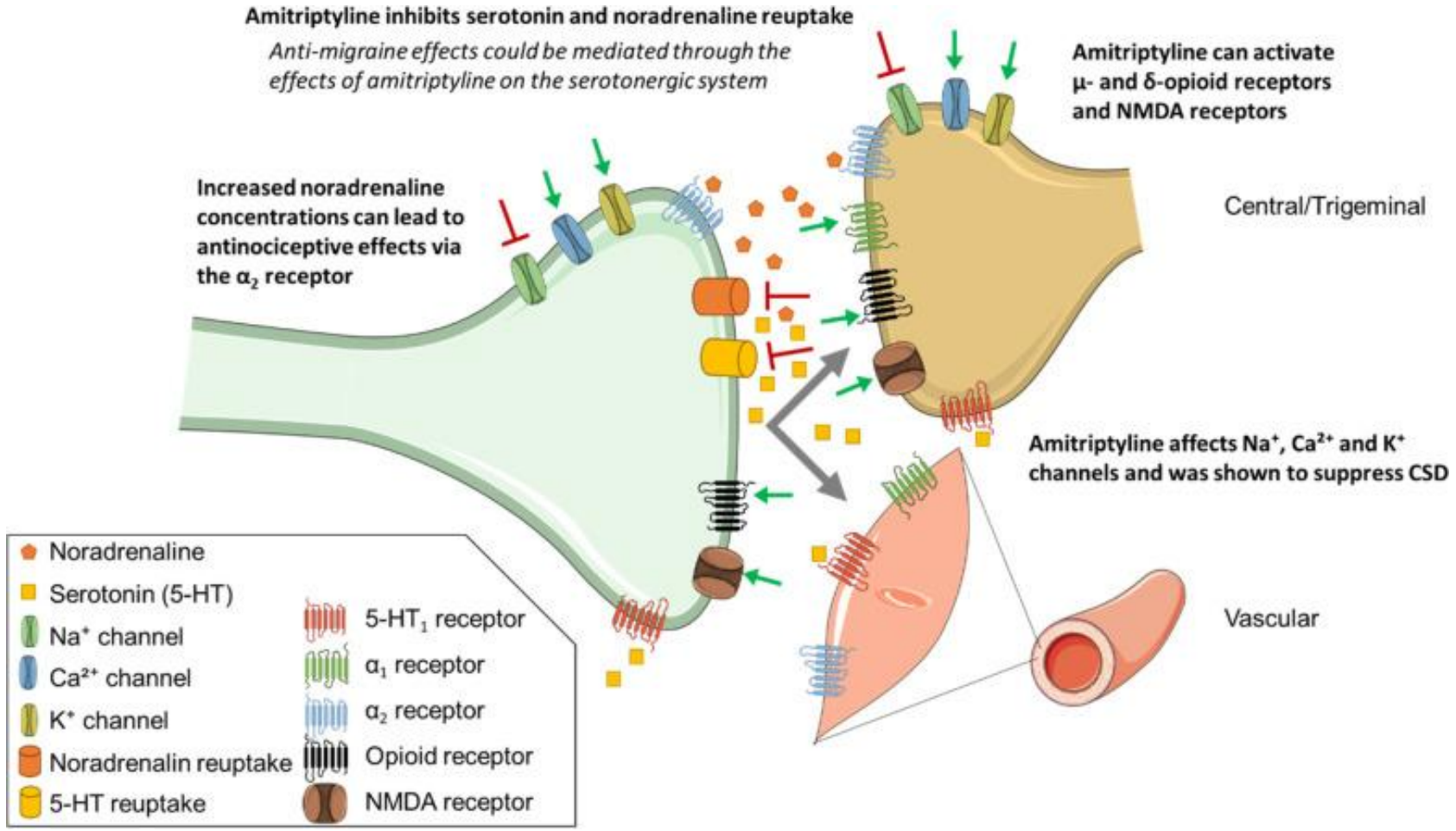
Multiple potential sites of action of tricyclic agents in migraine prevention

Synaptic cleft
- Serotonin uptake
- Noradrenergic uptake

Ion channels
- Sodium
- Potassium
- Calcium

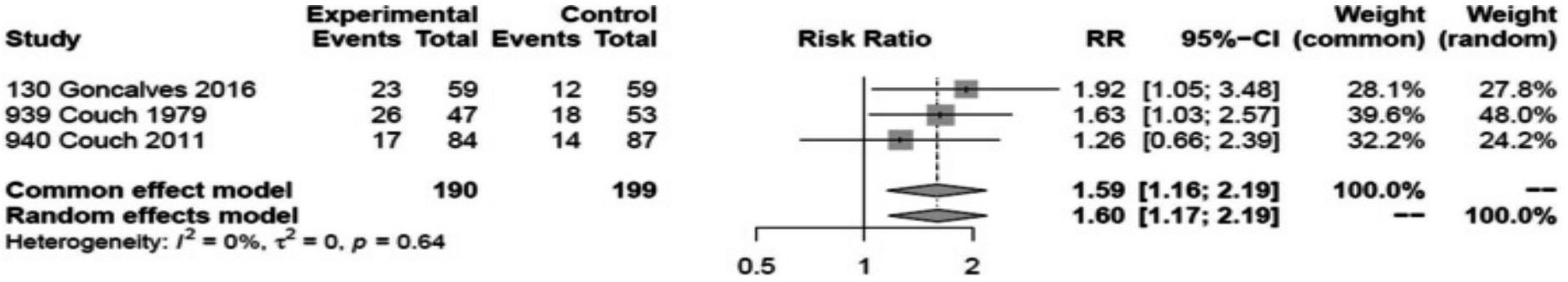
Other receptor targets
- NMDA receptors
- Opioid receptors

Suppression of cortical spreading depression



Amitriptyline efficacy

- Meta analysis of placebo controlled randomised trials for migraine prophylaxis
- Of >10,000 migraine prevention trials (all migraine drugs) 3 were suitable for analysis with total 622 patients
- Moderate certainty evidence that amitriptyline increased the proportion of patients who experience 50% or more reduction in monthly migraine days (RR 1.60 (CI 1.17-2.19))



Lampl C et al J Headache Pain. 2023 Apr 11;24(1):39

Amitriptyline

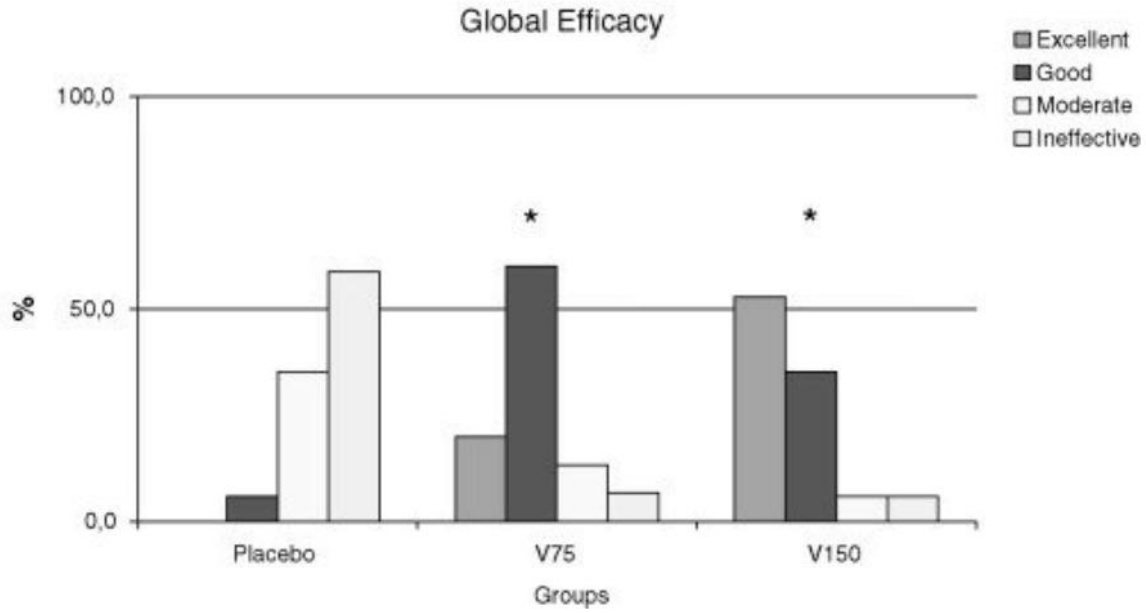
- Initiate 10mg at night and increase gradually on 2-4 week cycle
- Dose escalation up to around 1mg/kg,, sometimes beyond
- Side effects may limit initiation or dose
  - anticholinergic: dry mouth, constipation
  - caution in elderly and bladder outflow obstruction
- Uses
  - Patients with co-existing depression, neuropathic pain
  - Patients who may benefit from sleep-promoting effect

Other antidepressants

- Fewer trial and less data on other antidepressants in comparison with amitriptyline
  - Nortriptyline: active metabolite of amitriptyline, may have fewer side effects, especially sedation and weight gain
  - Often used as amitriptyline alternative if sedation a concern
  - Little trial data on nortriptyline as a migraine preventative and no trials vs placebo
- Other antidepressants used in migraine
  - Tricyclics: Duloxetine, Dosulepin
  - Tetracyclic: Mirtazapine

Venlafaxine

- Serotonin and noradrenaline reuptake inhibitor
- Effective in prospective double-blind randomized trial vs placebo. N=60, venlafaxine 75mg, 150mg in patients with migraine without aura
- Non-inferior to amitriptyline in randomized double-blind crossover study
  - N=52, 12 weeks on each treatment
  - Similar benefit on attacks in patients with migraine without aura
  - Fewer side effects than amitriptyline
- Similar study showing non-inferiority to nortriptyline
- Use in migraine
  - Migraine with co-existing depression
  - Side-effects with other agents



Venlafaxine 75mg or 150mg vs placebo

Ozyalcin SN Headache. 2005 Feb;45(2):144-152.
Bulut S Clin Neurol and neurosurg. 2004 Dec 1;107(1):44-8
Mehrdad Roghani Clin Neurol and Neurosurg 243,2024,

Betablockers

- Betablockers licensed in the UK for migraine
  - Propranolol: Usually initiated at 40mg daily and increase
  - Metoprolol: 100mg daily
  - Timolol: 10-20mg daily, up to 60mg. Eyedrops can be used acutely
  - Nadolol: 40mg daily increased in 40mg increments to 80-160mg

Propranolol is used most commonly

Of the other licensed drugs metoprolol used most commonly.

Unlicensed use common for atenolol and bisoprolol, especially for therapeutic synergy with cardiovascular indications

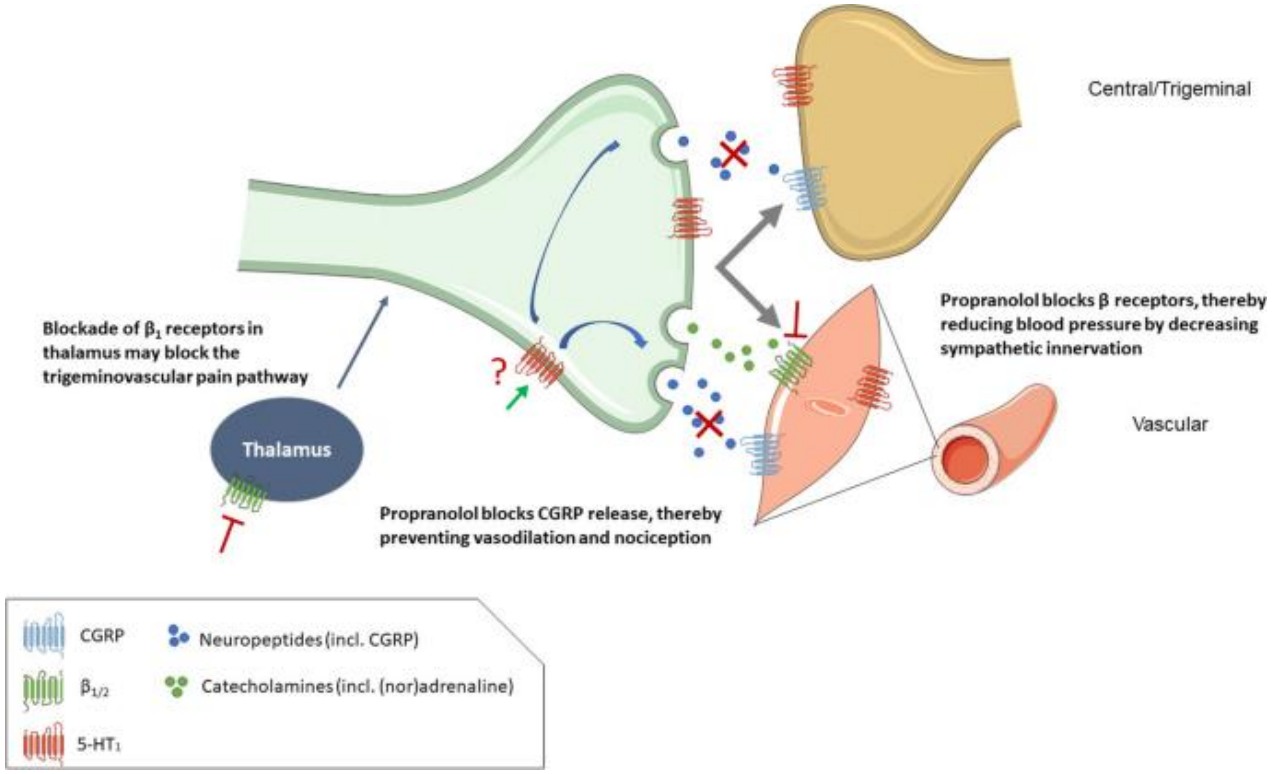
Propranolol

- Action on migraine discovered incidentally in 1960s during treatment of patients with angina
- Clinical trials in 1970s
- Subsequent widespread use and remain first line agents for migraine prophylaxis
- Antagonists of beta-1 and beta-2 adrenoreceptors

- Use in migraine
  - Multi-target action: hypertension, heart disease
  - Avoid in asthma or hypotension

Propranolol: mechanism of action

- Unknown mechanism of action
- Potential mechanisms
  - Reduction of blood pressure
  - Blockade of thalamic trigeminovascular pain pathway
  - Possible action on pre-synaptic 5-HT2 receptors to block CGRP release



Versijpt, J et al *J Headache Pain* **25**, 119 (2024

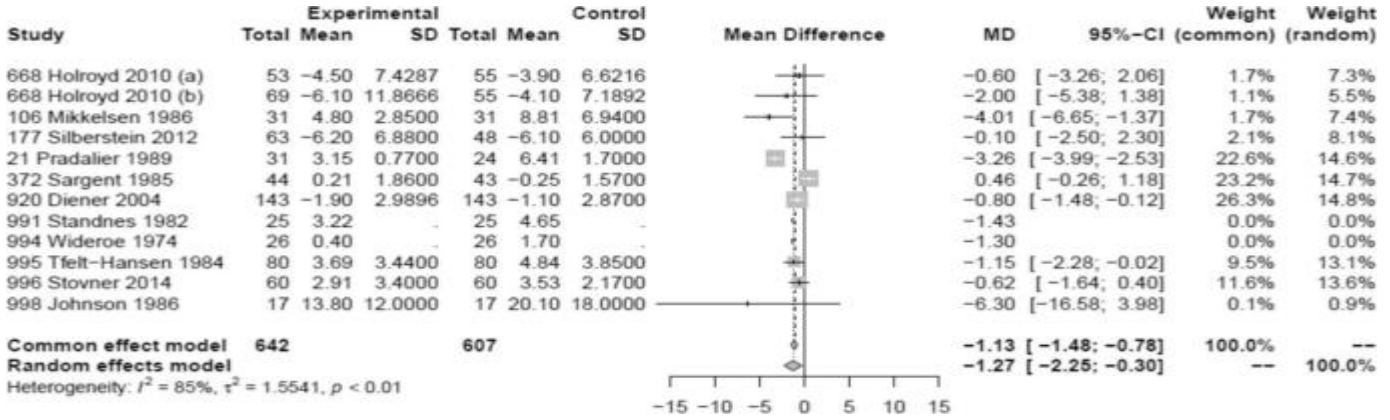
Propranolol: Efficacy

Meta-analyses

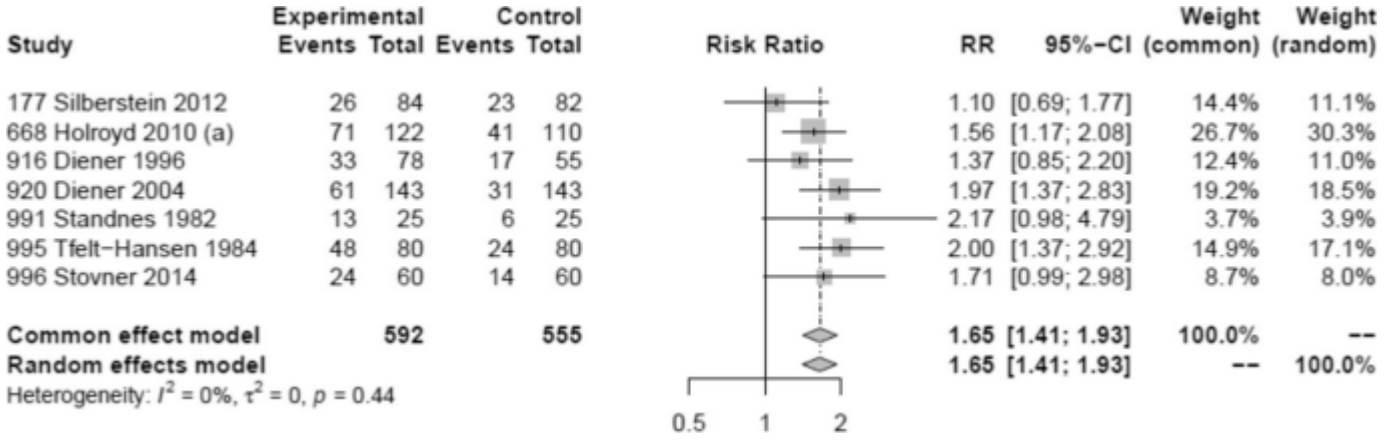
Reduction in MMDs

- 12 trials, n=642
- Moderate certainty of mean reduction 1.27 (0.3-2.25)

- 50% reduction in MMDs
- 7 trials, n=592
- Moderate certainty that increases proportion of 50% responders
- RR 1.65 (1.41-1.93)



Forest plot: 50% reduction in headache days

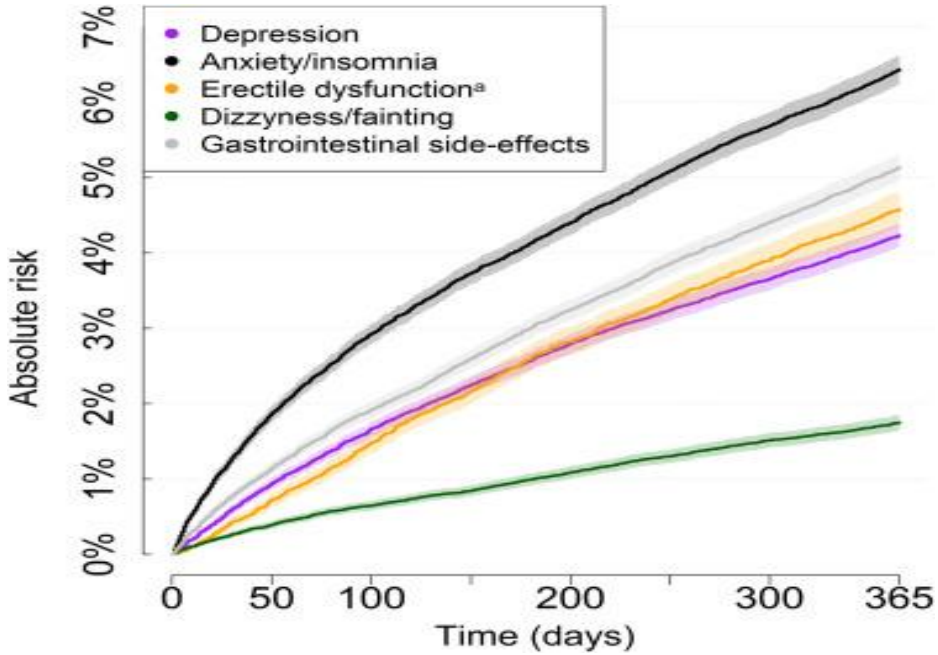


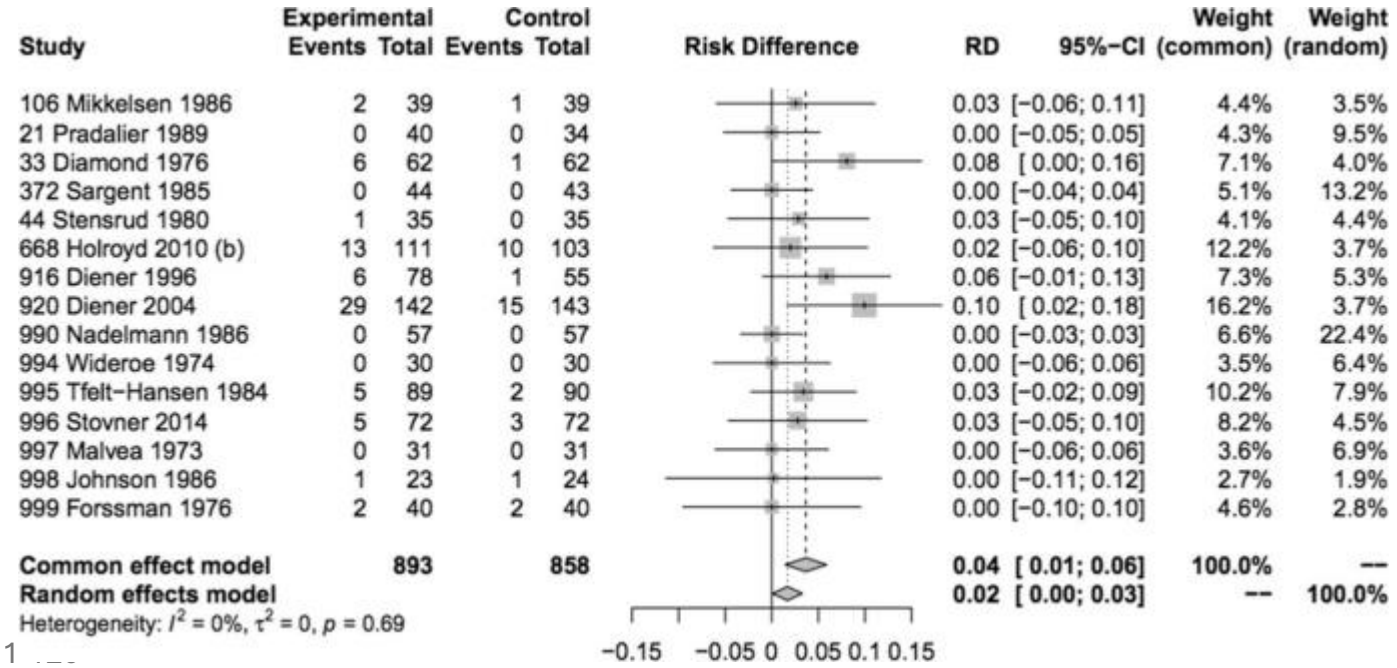
Forest plot: 50% reduction in MMDs

Betablocker side effects

Common side effects of betablockers include

- fatigue
- reduced exercise capacity
- depression
- Insomnia
- erectile dysfunction
  hypotension
- gastrointestinal
  exacerbation of asthma,
  nightmares (propranolol)





Rasmussen PV et al American Heart Journal, Volume 291, 2026,Pages 111
Versijpt, J et al *J Headache Pain* **25**, 119 (2024

Betablocker side effects

- Systematic review of betablockers in trials of use in heart failure
- 28 of the 33 classically described side effects were not significantly more common with beta-blocker vs placebo
- Depression and insomnia were less common on beta-blocker treatment
- Side effects similar between all types of betablockers except for oedema more common in selective betablockers

- Consider nocebo effect

Barron AJ et al Int J Cardiol. 2013 Oct 9;168(4):3572-9.

Side-effect	Effect size and 95% interval			Test of null (2-Tail)		Number of patients (from 100 presenting with a symptom) where Beta-blockers are NOT causative
	Point estimate	Lower limit	Upper limit	Z-value	P-value	
Tachycardia	0.518281	0.413645	0.649386	−5.7122	0.000	
Palpitations	0.712785	0.553098	0.918577	−2.6162	0.009	
Depression	0.72055	0.561046	0.9254	−2.5673	0.010	
Insomnia	0.758349	0.608176	0.945603	−2.4567	0.014	
Cardiac failure	0.694798	0.556296	0.867782	−3.2102	0.001	
Chest pain	0.800591	0.693194	0.924628	−3.0263	0.002	
Nausea	1.414402	0.660837	3.027273	0.8930	0.372	
Unstable angina	0.67559	0.424112	1.076182	−1.6509	0.099	
Pneumonia	0.69845	0.406139	1.201145	−1.2974	0.194	
Bronchitis	0.671762	0.202397	2.229595	−0.6500	0.516	
Vomiting	0.900001	0.729547	1.110281	−0.9835	0.325	
Hypertension	0.875701	0.60281	1.27213	−0.6967	0.486	
Renal impairment	0.806366	0.412185	1.57751	−0.6286	0.530	
Syncope	0.992266	0.787619	1.250086	−0.0659	0.947	
Headache	1.112715	0.754139	1.641784	0.5381	0.590	
Abdominal pain	1.022958	0.839855	1.24598	0.2256	0.822	
Anaemia	0.967067	0.609964	1.533235	−0.1424	0.887	
Impotence	0.975447	0.630081	1.510119	−0.1115	0.911	
Oedema	1.54966	0.728607	3.295941	1.1376	0.255	>99
Anorexia	1.017501	0.824116	1.256265	0.1613	0.872	99
Weight increase	1.212673	0.918669	1.600768	1.3612	0.173	94
Fatigue	1.07301	0.945909	1.217188	1.0955	0.273	94
TIA	1.09255	0.609594	1.958131	0.2973	0.766	92
Hypotension	1.226011	0.916276	1.640448	1.3715	0.170	92
Postural hypotension	1.131948	0.879632	1.456639	0.9632	0.335	89
Dyspnoea	0.848755	0.689807	1.044329	−1.5450	0.121	89
Nasopharyngitis	1.268411	0.802288	2.005348	1.0174	0.309	80
Asthenia	1.75	0.583236	5.250876	0.9982	0.318	59
Hyperglycaemia	1.313181	1.082524	1.592986	2.7646	0.006	83
Diarrhoea	1.400816	1.176932	1.667287	3.7935	0.000	82
Dizziness	1.454969	1.171747	1.806648	3.3945	0.001	81
Claudication	2.465368	1.316957	4.615216	2.8206	0.005	41
Bradycardia	3.449837	2.194331	5.423692	5.3643	0.000	33

Topiramate

- Licensed in adults for use in migraine prophylaxis
- Developed in 1970s as an anticonvulsant
- First case series in migraine in 1990s

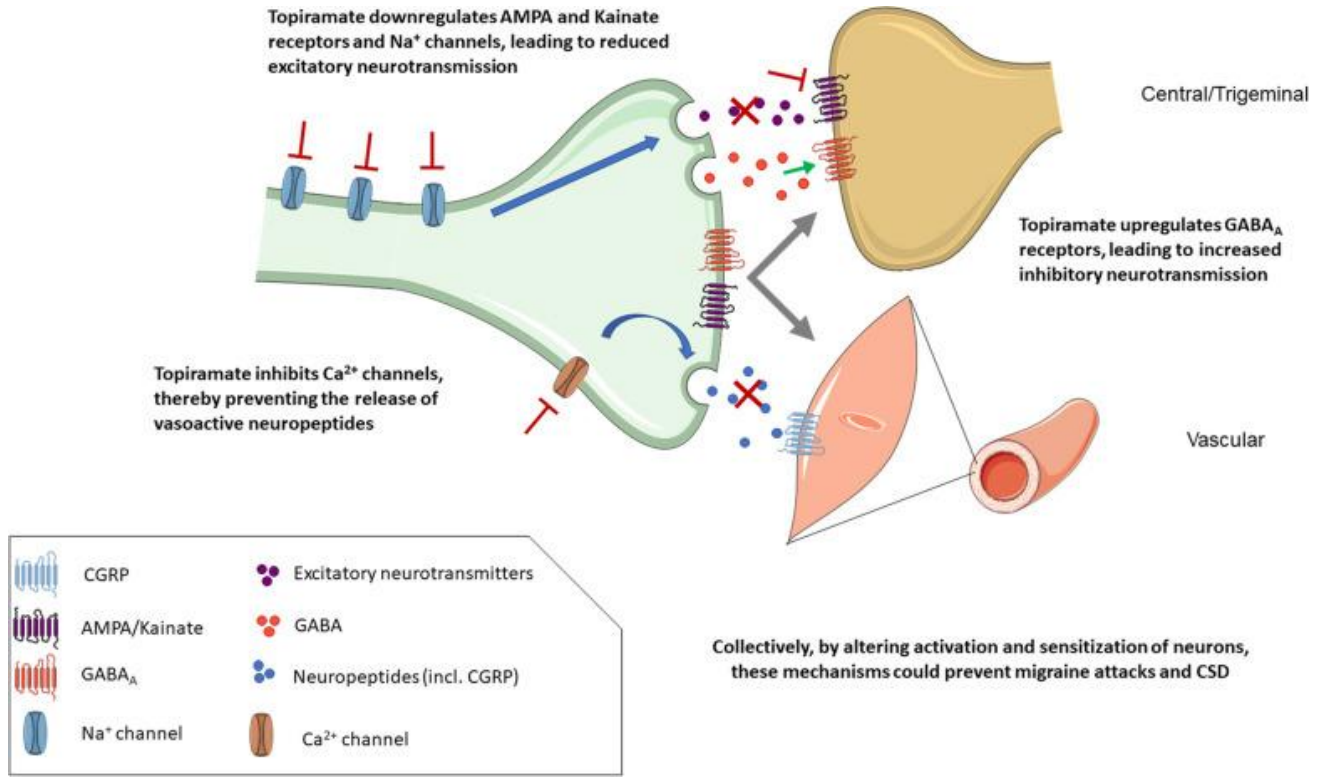
- Randomized trials:

  - 40 patients vs placebo: increasing dose to tolerance, mean dose 125mg daily
    - MMDs in treatment group reduced by 36% vs 16% reduction in placebo
    - 50% reduction in MMDs 25% vs 9.6%
  -
  - 306 patients with chronic migraine randomized to topiramate 25mg daily increasing dose to 100mg daily vs placebo
    - Topiramate resulted in reduced MMDs -6.4 vs -4.7, p=.01
    - High incidence of adverse effects in both study arms: topiramate 82.5% and placebo 70%

Storey JR et al Headache. 2001 Nov-Dec;41(10):968-75
Silberstein SD et al. Headache. 2007 Feb;47(2):170-80

Topiramate: mechanism of action

- Mechanism of action not understood
- ? Inhibition of nociceptive transmission in trigeminocervical complex

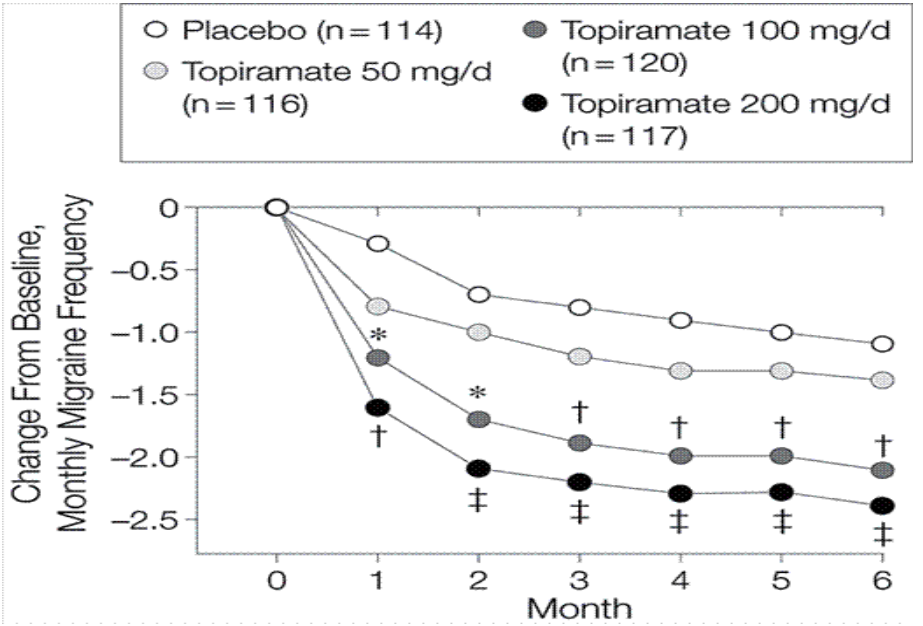


Raffaelli B et al Headache Pain. 2023 Oct 10;24(1):134

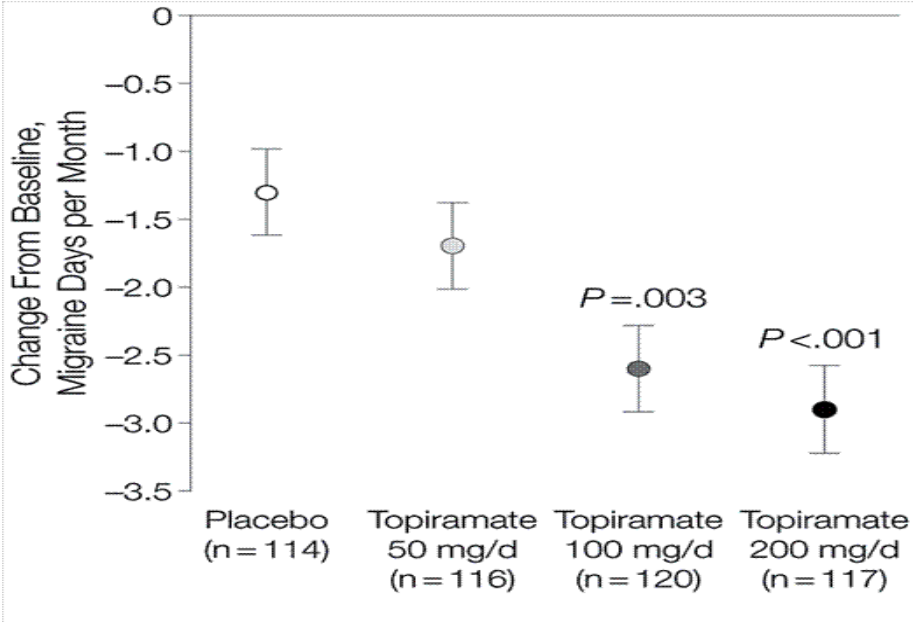
Topiramate

- 483 patients with episodic migraine randomized vs placebo over 26 weeks

- Monthly migraine frequency
  - 50mg 39% p= 0.01
  - 100mg 49% p<0.001
  - 200mg 47% p<0.001
- Reduction in MMDs
  - 100mg p= 0.003
  - 200mg p<0.001



Change From Baseline in Cumulative Monthly Migraine Frequency

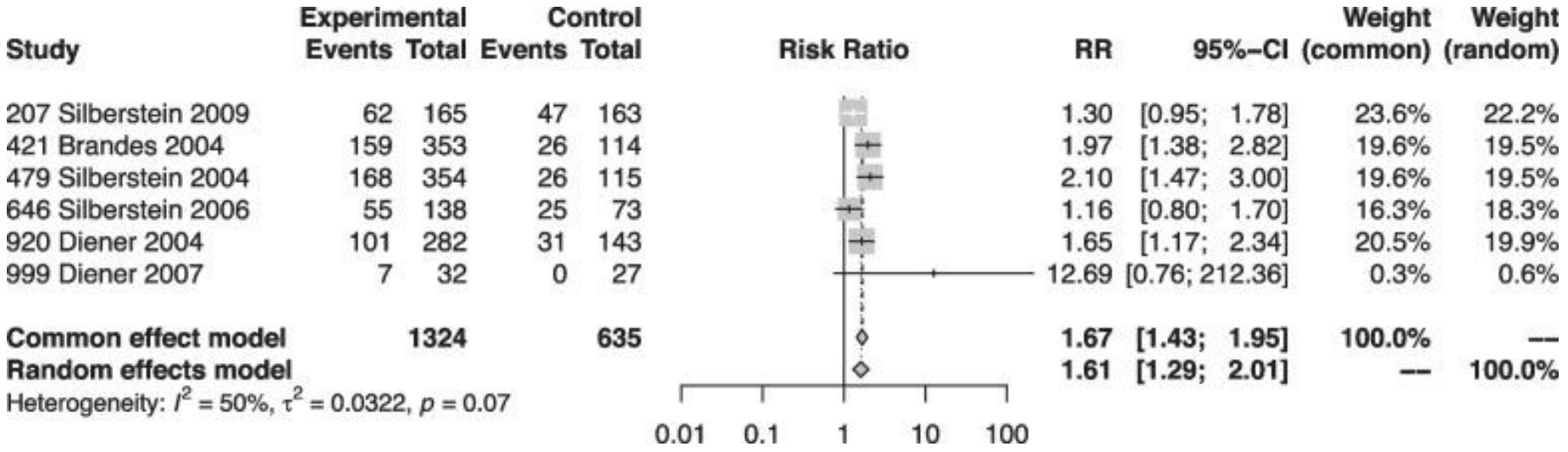


Change From Baseline in migraine days per month

Brandes JL et al JAMA. 2004 Feb 25;291(8):965-73

Topiramate: efficacy

- Meta-analysis of 8 identified randomized placebo-controlled studies comprising 2610 randomized patients, 6 studies of EM and 2 of CM
- Only drug of traditional treatments with RCT evidence in chronic migraine
- High certainty that topiramate
  - Increased proportion of patients with 50% reduction in MMDs RR 1.61 (1.29-2.01)
  - Associated with 0.99 fewer migraine days than placebo
  - Higher proportion of patients with adverse effects leading to treatment discontinuation: absolute difference 80/1000 patients



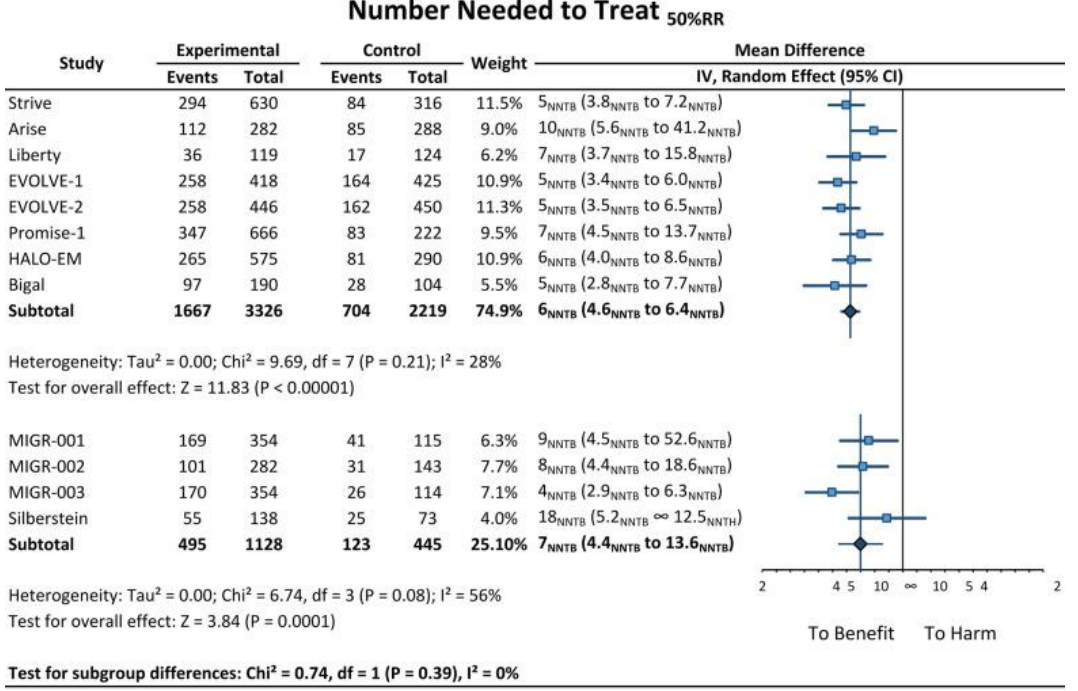
Raffaelli B et al Headache Pain. 2023 Oct 10;24(1):134

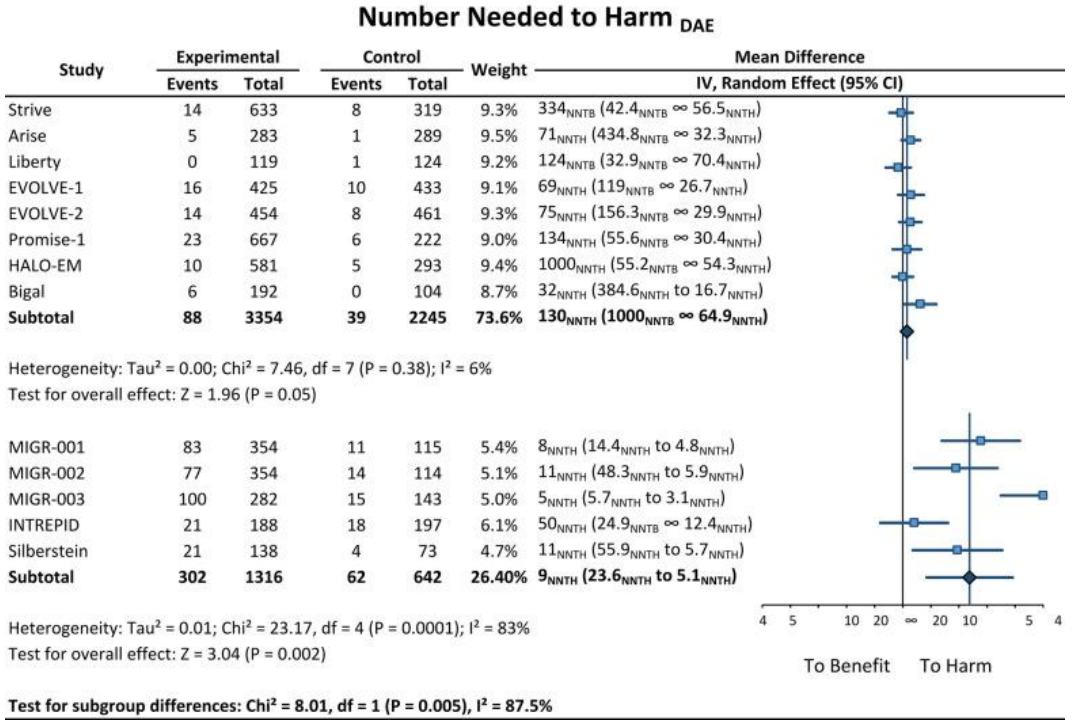
Topiramate: adverse effects

- Parasthesia, fatigue, cognitive impairment and cognitive slowing, and word-finding difficulties, dizziness, nausea and GI disturbance, anorexia, weight loss, agitation
- Severe adverse effects
  - Drug induced choroidal effusion – acute glaucoma
  - Renal calculi
  - Suicidal ideation and behaviour

Long term study of topiramate treatment for epilepsy (higher doses that in migraine): 50% stopped at 1 year, 70% at 4 years. Main reason for stopping was adverse events

Bootsma HRR et al Epilepsy & Behavior, Volume 5, Issue 3, 2004
Overeem LH et al CNS Drugs. 2021 Aug;35(8):805-820.





Topiramate: MHRA guidance

- MHRA guidance
- Topiramate should not be used:
  - in pregnancy for prophylaxis of migraine
  - in pregnancy for epilepsy unless there is no other suitable treatment
- Topiramate should not be used in women of childbearing potential unless the conditions of the Pregnancy Prevention Programme are fulfilled. This aims to ensure that all women of childbearing potential:
  - are using highly effective contraception
  - have a pregnancy test to exclude pregnancy before starting topiramate
  - are aware of the risks from use of topiramate

MHRA drug safety update: UK MHRA 20.6.24

Sodium Valproate

- Not licensed in UK for migraine
- Infrequently initiated now due to safety concerns

- Mechanism of action unknown
- Broad range of chemical effects
  - Voltage dependent sodium channels
  - Suppression of CSD
  - Increases brain GABA levels
  - May suppress neurogenic inflammation
  - May directly suppress nociceptive neurotransmission

- Multiple trials showing efficacy in treating episodic migraine
- Can be used as a migraine abortive

Cutrer FM Cephalalgia. 1997 Apr;17(2):93-100
Damore V et al 2024 Neurology 102 7 supplement 1

Sodium Valproate: adverse effects

- Mild effects
  - Gastrointestinal disturbance
  - Ataxia, tremor

- Serious adverse effects
  - Hepatic toxicity
  - Pancreatitis
  - Encephalopathy
  - Parkinsonism
  - Foetal toxicity, congenital malformation and neurodevelopmental abnormalities incl autism

- Requires monitoring of LFTs and FBC
- Multiple drug interactions
  - P450 enzyme inhibition, protein binding,
- Initiation at 200mg BD and gradual increase up to limit of tolerance

Valproate: MHRA guidance

- 11% major congenital malformation
  - Spina bifida, facial and skull malformation, limb and organ malformation, hearing
- 30% neurodevelopmental malformation
  - Delayed motor and language milestones
  - Intellectual disability
  - Autism or autism spectrum disorder and possibly ADHD
- Valproate should not be used:
  - In women of childbearing potential
  - In men of childbearing potential unless they are using effective contraception

MHRA drug safety update: UK MHRA 20.6.24

Flunarizine

- First used in 1980s
- Widely used worldwide for prophylaxis of migraine, including Ireland

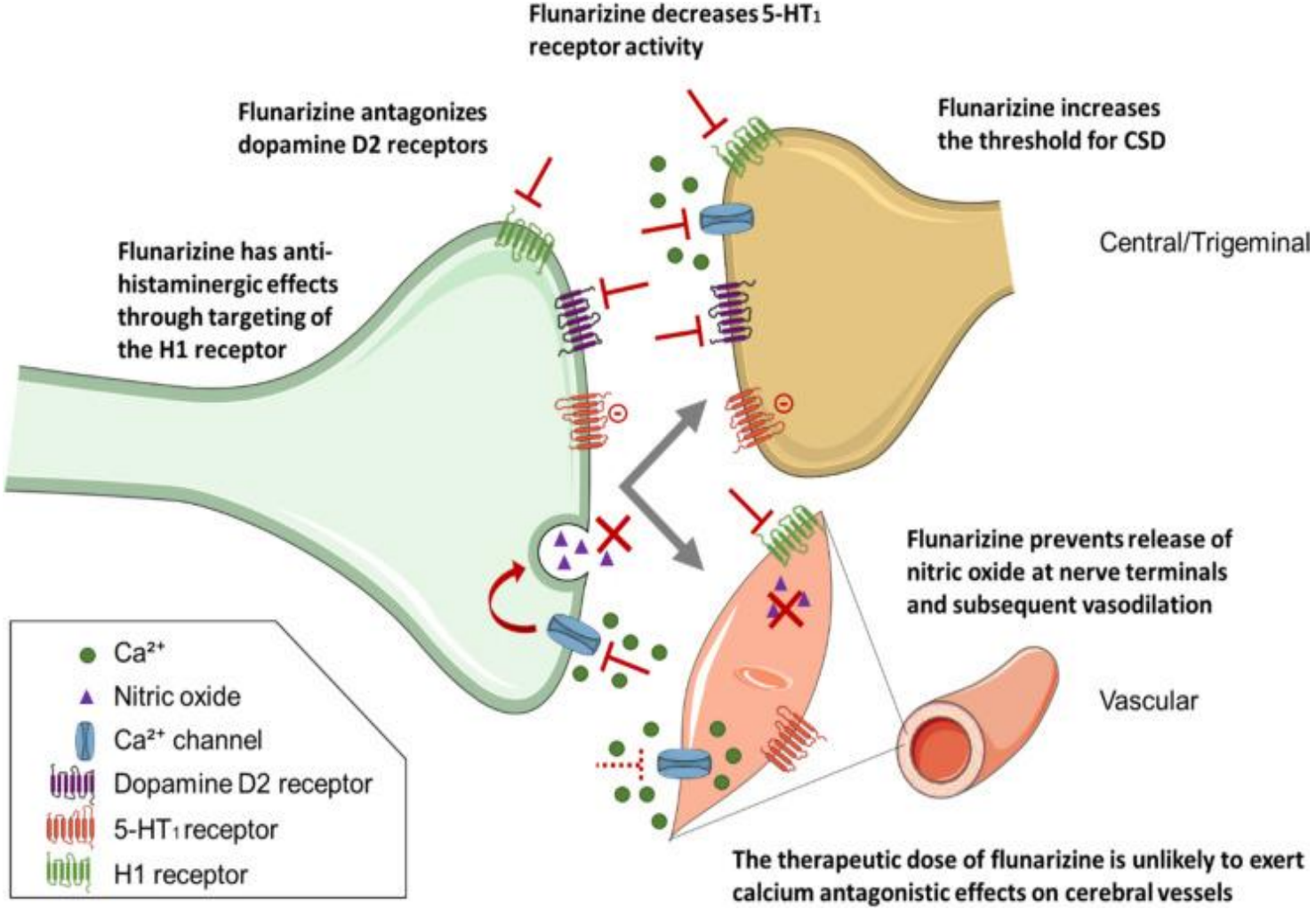
- Not licensed for any indication in the UK
- Available on a named patient basis through hospital pharmacies at headache centres
- Can be prescribed by GP on FP10
- Initiate 5mg daily and increase to 10mg daily

- Mixed sodium and calcium channel blocking agent

- Blocks P/Q channel: presynaptic calcium channel contributing to vesicle release at synaptic terminals
- Flunarizine is also a dopamine D2 receptors and histamine H2 receptor antagonist
- Therapeutic mechanism is not understood

Flunarizine: mechanism of action

- Blocks P/Q channel: presynaptic calcium channel involved in vesicle release at synaptic terminals – though to raise the threshold for CSD
- Also a dopamine D2 receptors and histamine H2 receptor antagonist
- Therapeutic mechanism is not understood

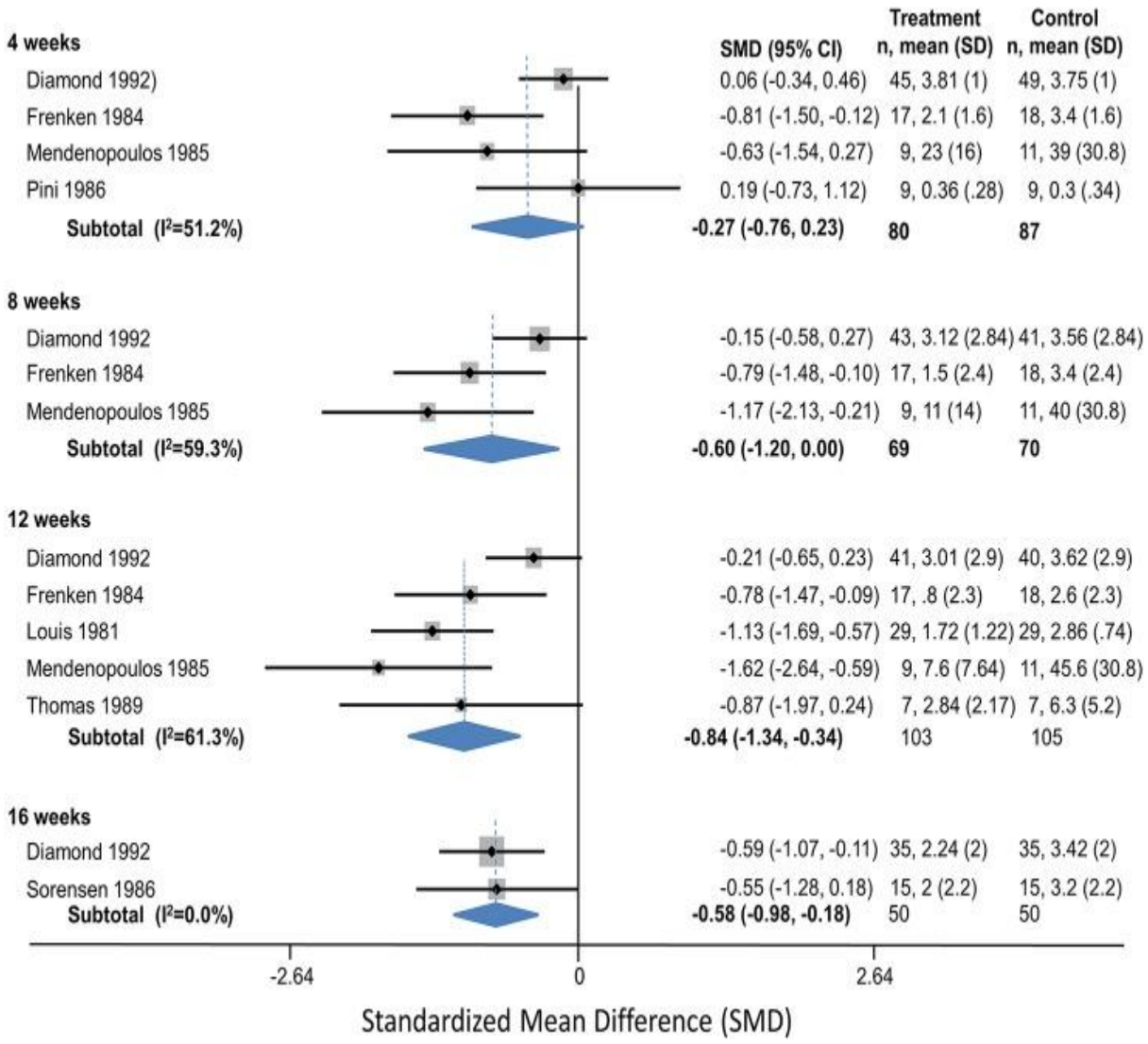


Deligianni CI J Headache Pain. 2023 Sep 19;24(1):128

Flunarizine: Efficacy

- RCT vs propranolol n=783: equally effective. MMA reduced from 3 to 2 over 16 week study period
- RCT n=150: flunarizine vs topiramate vs combination: no difference in those with 50% reduction in MMAs at 1 year

- Meta-analysis of published trials included 5 randomized trials after screening. No reported data of outcomes of 50% reduction in MMDs, change in MMDs or AEs leading to discontinuation.
- All trials reported reduction in migraine attacks vs placebo



Deligianni, C.I *J Headache Pain* **24**, 128 (2023).
Diener HC et al Cephalalgia. 2002 Apr;22(3):209-21.
Luo N et al Pain Med. 2012 Jan;13(1):80-6.
Jackson JL et al Plos One. 2015 Jul 14;10(7)

Flunarizine: Use and adverse effects

- Weight gain: 10%
- Parkinsonian syndrome
- Depression
- Does not tend to cause hypotension
- Contraindicated
  - Depression or history of recurrent depression
  - Extrapyramidal disease
- Uses in migraine
  - Patients with resistant migraine where other treatments ineffective
  - Patients with severe aura, migrainous vertigo
  - Chronic migraine or medication overuse headache

Diener HC et al Cephalalgia. 2002 Apr;22(3):209-21
Gracia-Naya M, J Headache Pain. 2013;14(Suppl 1):P202
Visvanathan N eta l Neurology 2017 88(167_supplement)
Wouters L et al J Laryngol Otol. 1983 Aug;97(8):697-704.

Candesartan

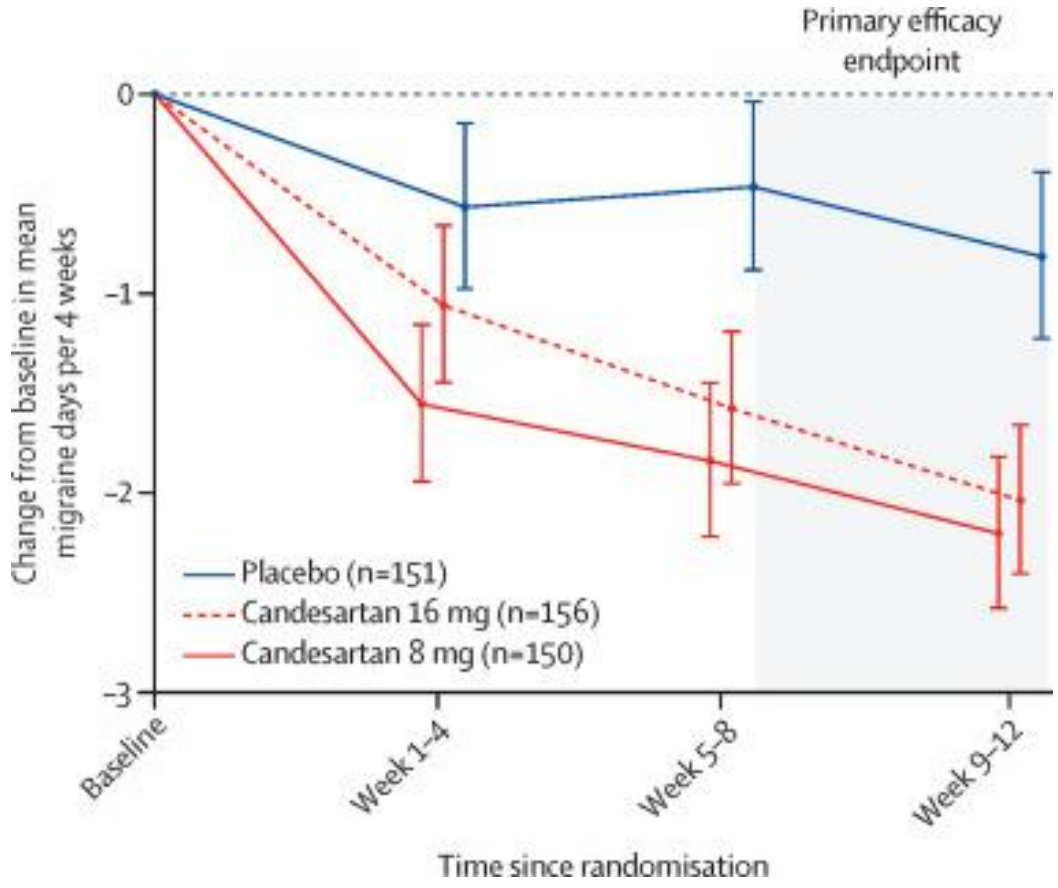
- Angiotensin II receptor antagonist: 16mg daily for migraine
- Not licensed for this indication in the UK

- Mechanism of action not understood
  - ACE inhibitors and ARBs have shown migraine reducing action in multiple studies
  - Candesartan investigated as more lipophilic than other agents

Asghar T el al 2025 SN Comprehensive Clinical Medicine. 7. 10.1007/s42399-025-01877-5
Naoe E at al Clinical Therapeutics,Volume 47, Issue 9,2025,

Candesartan: Efficacy

- Randomised triple blind placebo controlled trial of candesartan 8mg and 16mg for treatment of episodic migraine
- 457 patients with EM: Rx with candesartan 8mg, 16mg or placebo over 12 week treatment period



Changes from baseline in migraine days per 4 weeks

Oie et al Lancet Neurology, Volume 24, Issue 10,2025, 817-827,

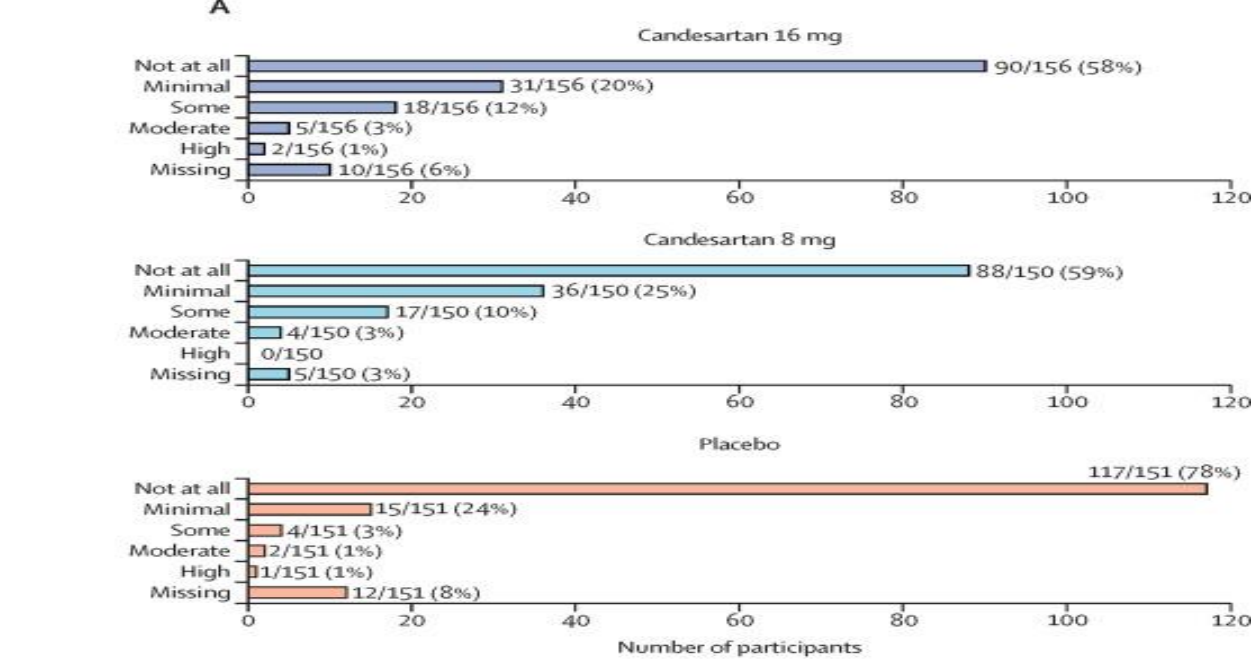
Candesartan adverse effects

- Good tolerability
- Low incidence of side effects

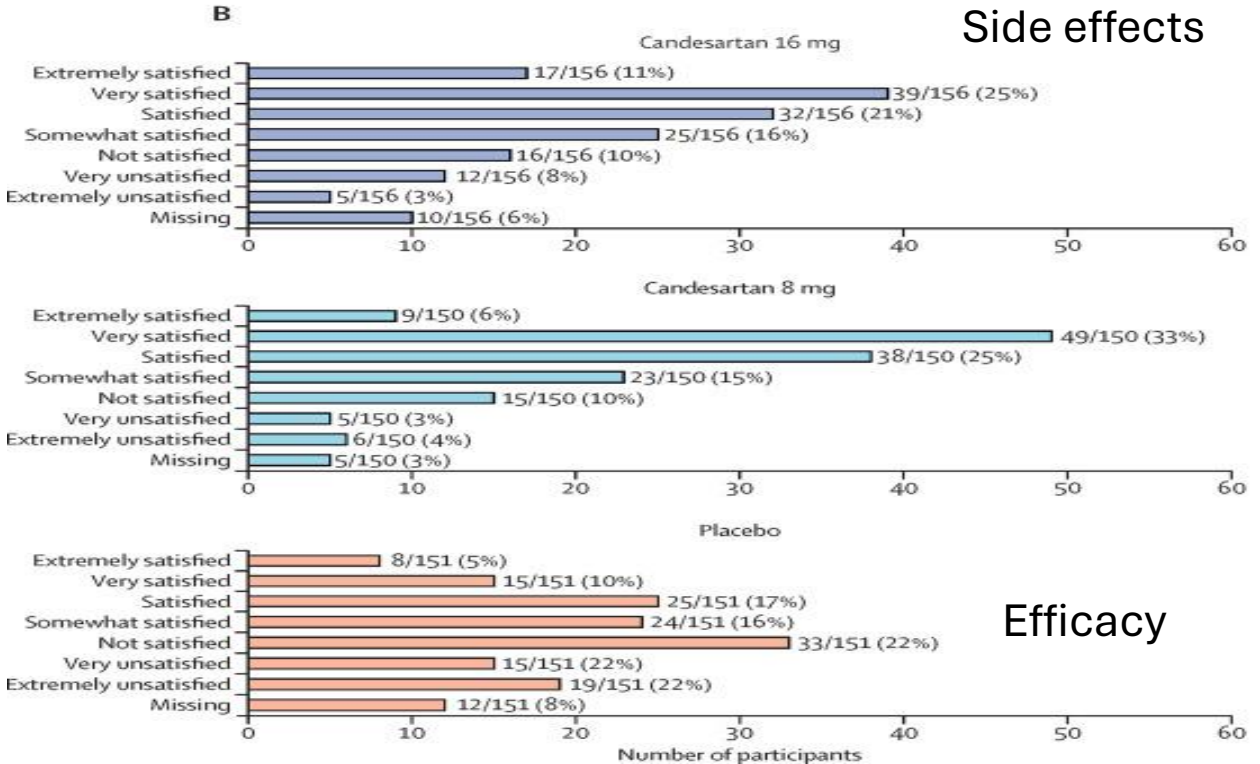
- Adverse effects
  - Upper respiratory tract infections
  - Hypotension
  - Renal impairment
  - Vertigo
  - Hyperkalaemia

Avoid in pregnancy

Use: well tolerated in majority though caution in renal disease



Side effects



Efficacy

Oie et al Lancet Neurology, Volume 24, Issue 10,2025, 817-827,

Pizotifen

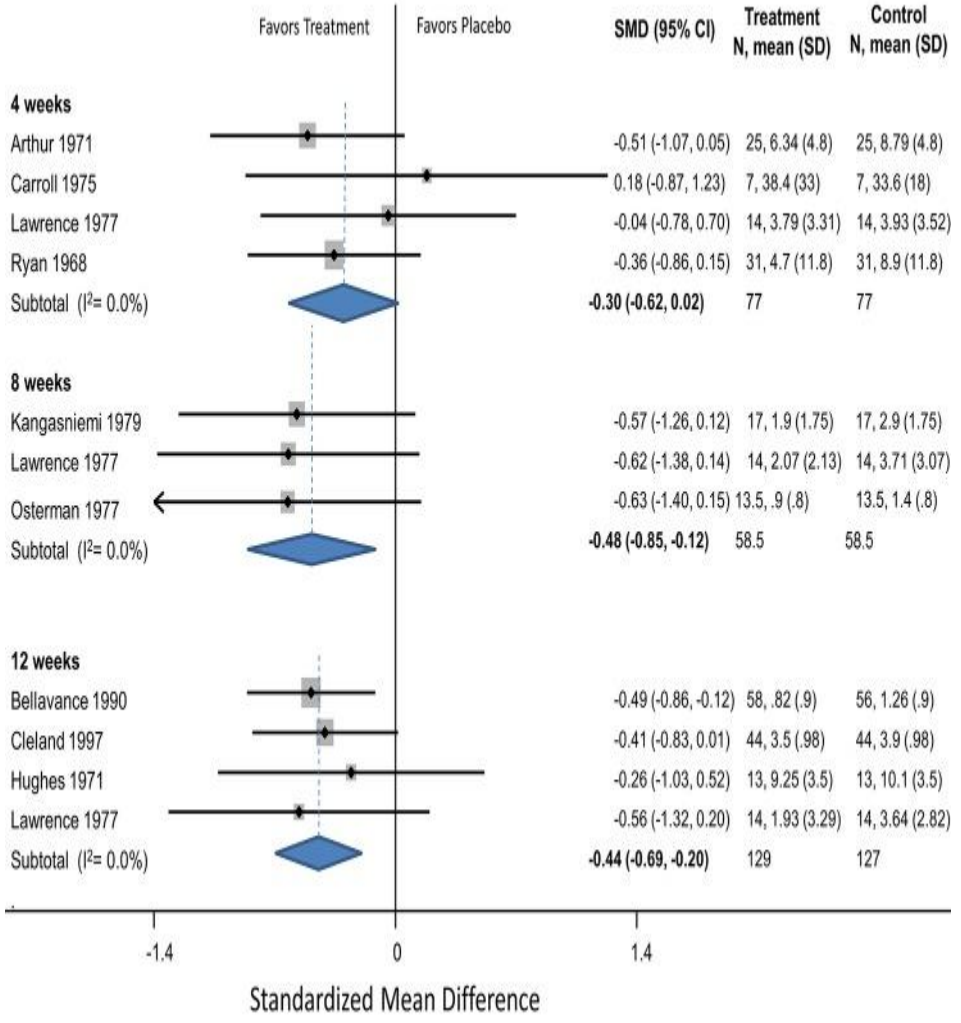
- Tricyclic Serotonin antagonist plus histamine and cholinergic antagonist
- Mechanism of action in migraine not fully understood
- Placebo controlled RCTs in EM

Use in migraine: any form of migraine. More commonly used in children

Adverse effects: weight gain, increased appetite, anticholinergic

Avoid in pregnancy

Initiate 0.5mg at night and increase eg to 3mg. Higher doses commonly used in other countries.

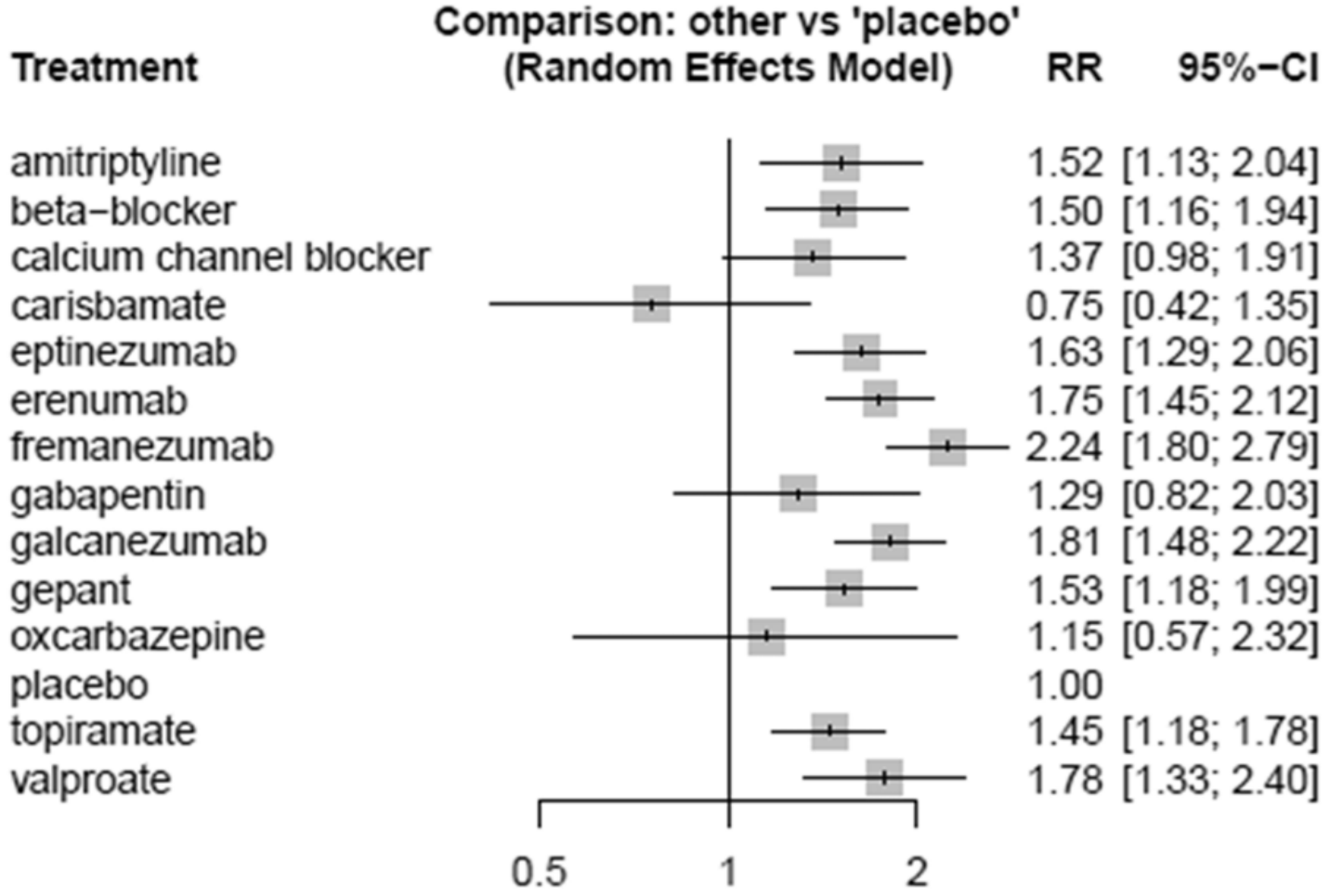


Jackson JL et al Plos One. 2015 Jul 14;10(7)

Comparative Efficacy of traditional drugs

- Meta-analysis: 74 randomized trials, 32,990 patients

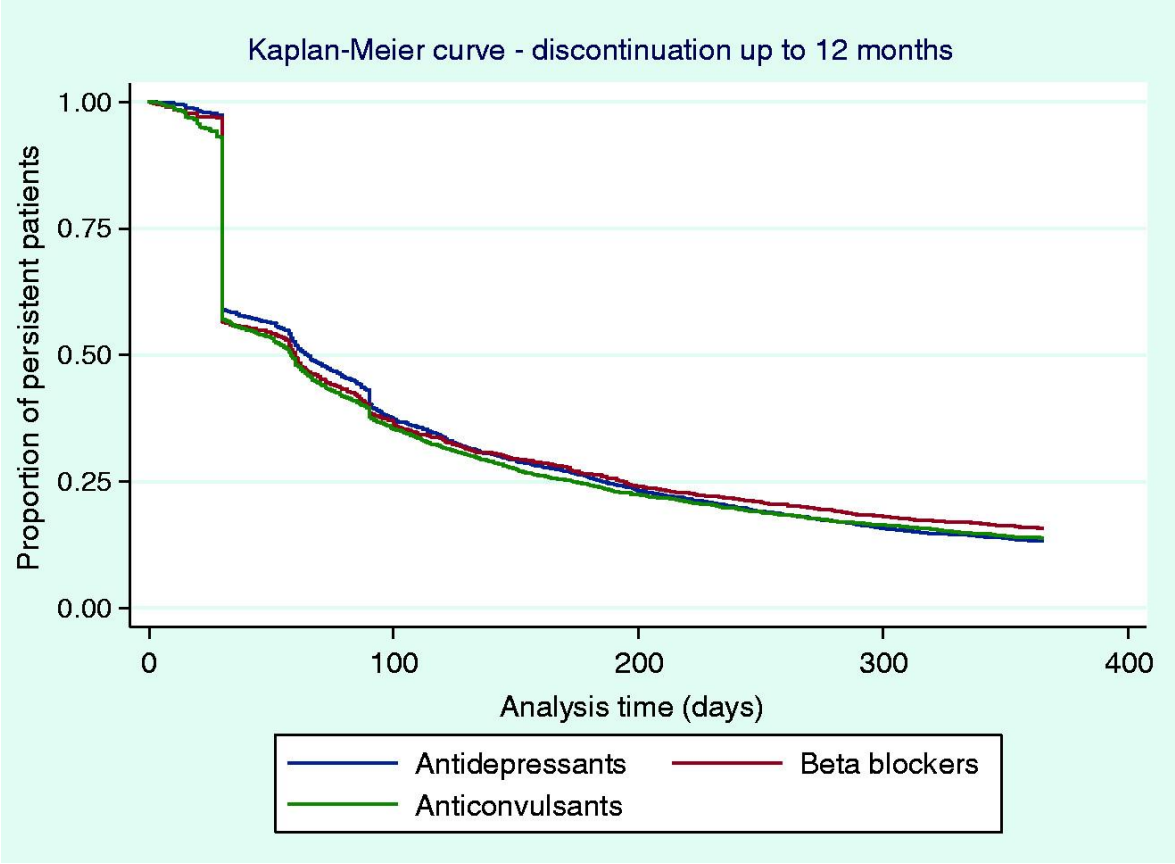
- 50% reduction in monthly migraine days
- Traditional agents generally display similar efficacy
- High certainty evidence for topiramate
- Moderate certainty evidence for amitriptyline, beta-blockers and valproate.
- Lower certainty evidence than gepants and MAbs



Lampl, C., MaassenVanDenBrink, A., Deligianni, C.I. *et al. J Headache Pain* **24**, 56 (2023).

Oral migraine drugs: Persistence and Switching

- Likely measure of efficacy and tolerability
- Examination of drug reimbursement claims in US patients with CM
- High rate of drug discontinuation and switching to alternative treatment



Time to discontinuation over 12 months

Hepp Z et al Cephalalgia. 2017 Apr;37(5):470-485

Persistence and Switching

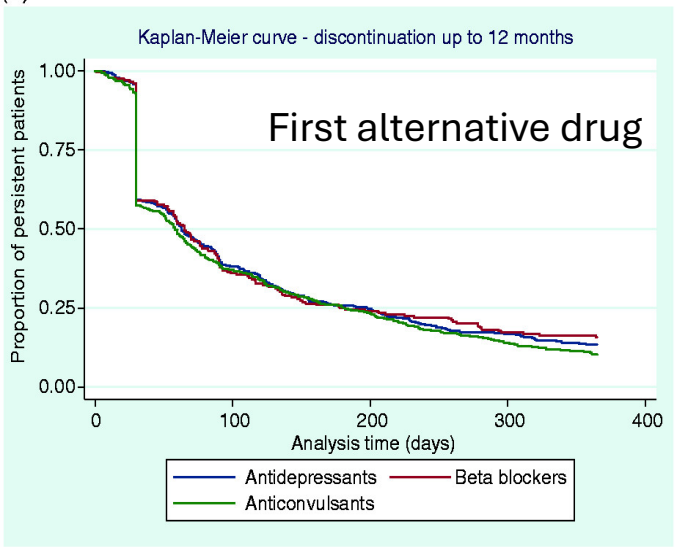
Many patients stop the first prophylactic treatment

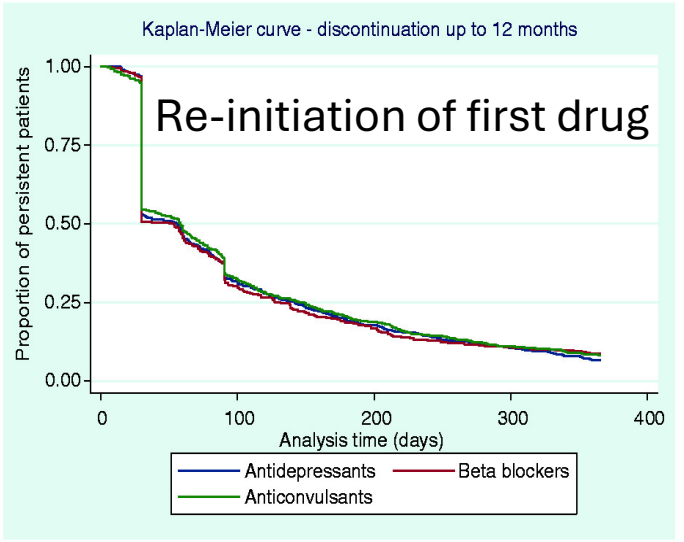
- Often by 30 days
- 50% by 60 days

Similar rates of persistence with second and third drugs

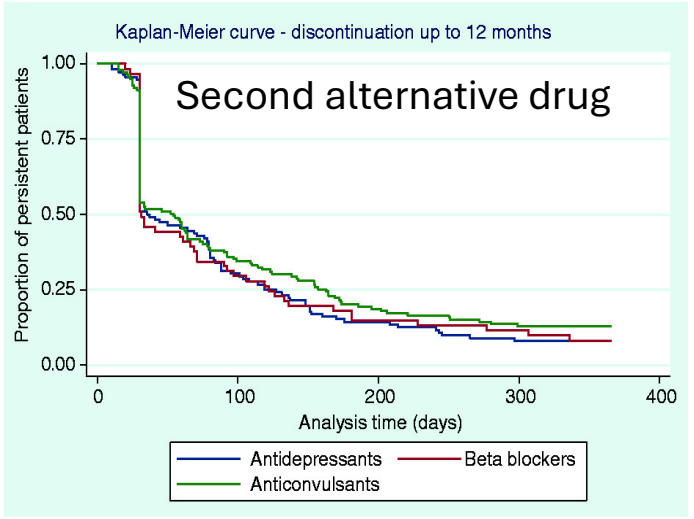
Similar rates with all drug classes

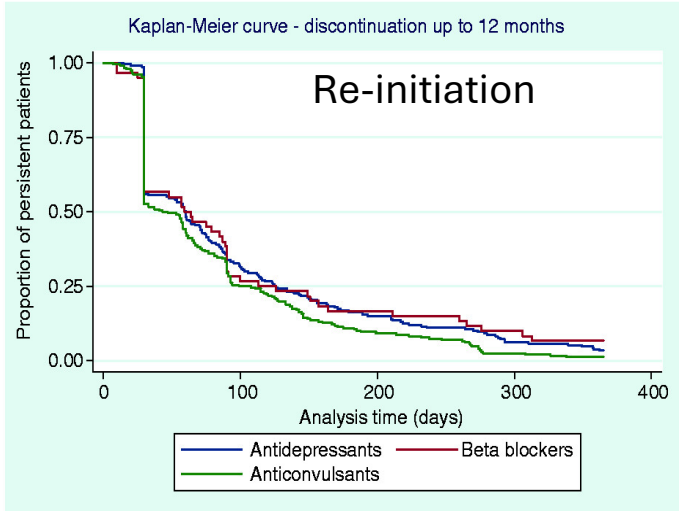
(a)



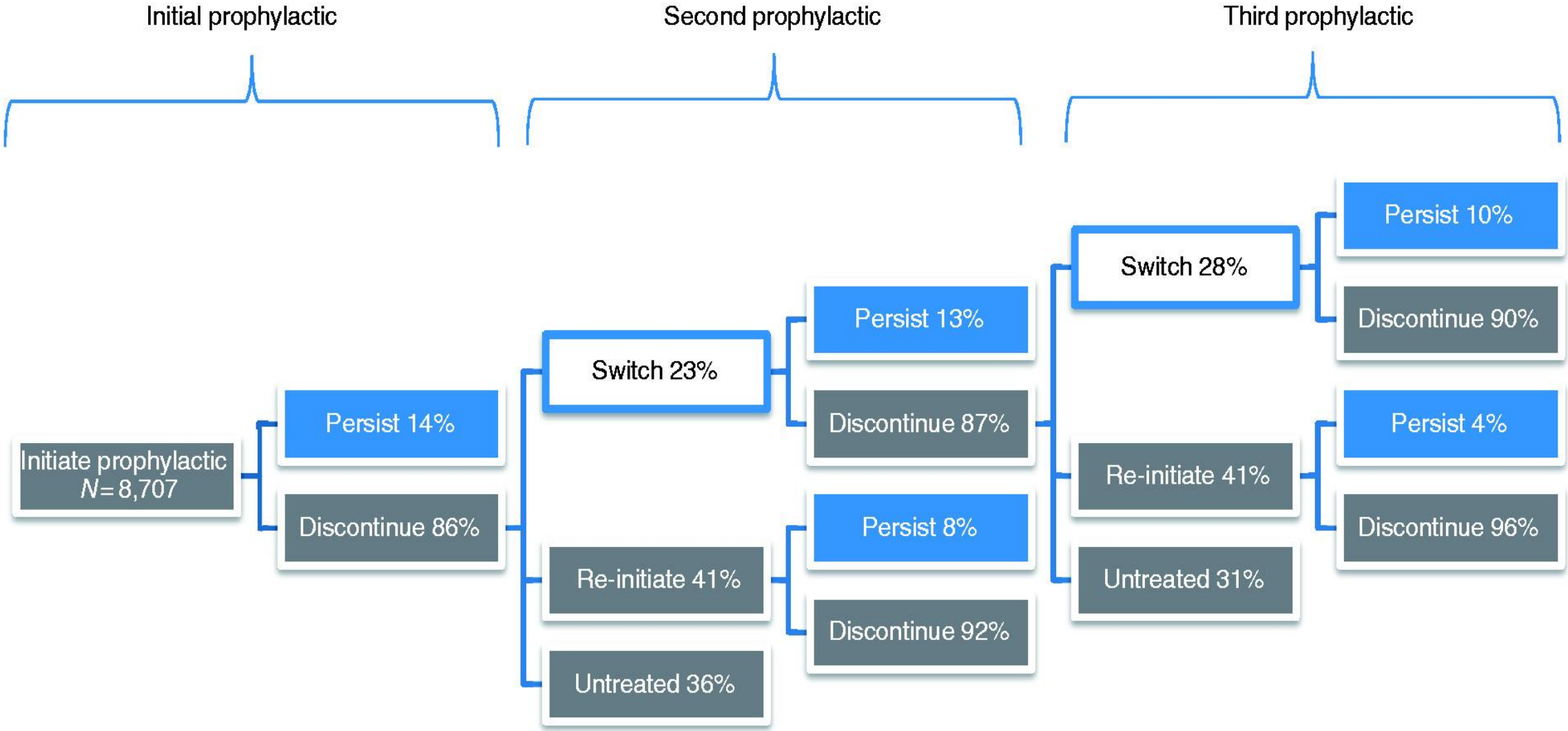


(b)





Hepp Z et al Cephalalgia. 2017 Apr;37(5):470-485

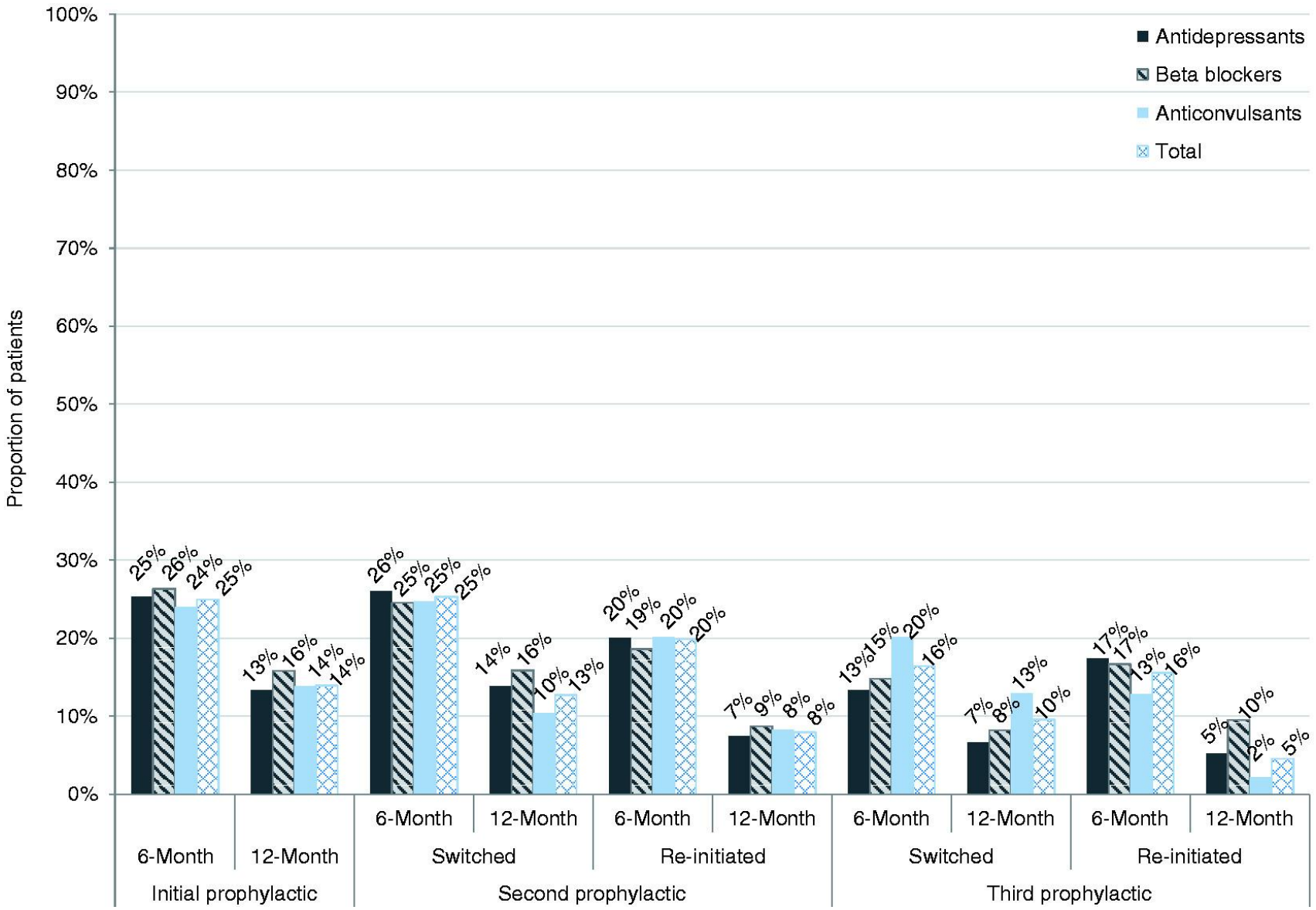


Proportion of patients who continued, discontinued, switched or re-initiated
Data over 12 months

Hepp Z et al Cephalalgia. 2017 Apr;37(5):470-485

Persistence at 6 and 12 months' follow-up on the first three cycles treatment

Proportion of persistent patients declined over successive treatments



Hepp Z et al Cephalalgia. 2017 Apr;37(5):470-485

	Use in migraine	Avoid in migraine
Amitriptyline/antidepressants	Co-existing depression Neuropathic pain	Elderly, risk of constipation, weight gain, sedation, bladder obstruction, arrhythmia
Beta-blockers	Hypertension, heart disease, anxiety (some patients)	Hypotension, asthma, bradycardia, heart block, heart failure, caution in diabetes, peripheral vascular disease, Raynaud's
Candesartan	Hypertension, diabetes, heart failure, renal protection in hypertension and diabetes	Cholestasis, aortic or mitral stenosis, HOCM, angioedema, high aldosterone state, renal artery stenosis, hypotension, renal disease, conception and pregnancy
Flunarizine	Resistant migraine, chronic migraine, severe aura, migrainous vertigo	Depression, risk of weight gain, Parkinson's disease, extrapyramidal features, cardiac failure. Not hypotension
Topiramate	Chronic migraine, analgesic overuse, co-morbid epilepsy (some patients)	Conception, pregnancy, weight loss, cognitive risks, renal calculi

Conclusions

- Traditional oral preventative drugs have shown efficacy in reducing migraine attacks in episodic migraine
- Topiramate and flunarizine may be effective in chronic migraine
- Start at low dose and increase over 3 month trial
- Selection of drugs based as much on adverse event profile, perceived side effect risk as on efficacy
- Some opportunities to also treat co-morbid conditions with same drug
- Patient persistence and adherence to oral treatments is low, likely reflecting the efficacy and tolerability of these treatments
- Current UK guidelines and prescription policies require patients to have been treated with three oral headache drugs prior to treatment with CGRP-antagonists or Botox