PROPOSAL FOR THE ADDITION OF AMITRIPTYLINE TO THE WHO MODEL LIST OF ESSENTIAL MEDICINES FOR THE PROPHYLAXIS OF MIGRAINE

Proposed listing on the EML:

7. ANTIMIGRAINE TREATMENTS

7.2 Migraine prophylaxis

Amitriptyline tablet 25 mg

Applicant:
The applicants are, jointly, two international scientific societies (the International Headache Society [https://ihs-headache.org/en/] and the European Headache Federation [https://www.ehf-headache.com/]), and two charities (*Lifting The Burden* [https://www.l-t-b.org/], which is in Official Relations with WHO), and Disease Relief by Excellent and Advanced Means (DREAM [https://www.dream-health.org/a-new-public-health-model/?lang=en]).

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Section 1: Summary statement of the proposal

The global migraine prevalence is 14–15%, with minor variations across regions *(1)*. Reliable estimates show that migraine accounts for 4.9% of global population ill health quantified in years lived with disability (YLDs) *(2, 3)*. Migraine manifests with recurrent and unpredictable attacks of head pain, often severe, accompanied by other disabling symptoms such as nausea, vomiting, intolerance to sensory stimuli (photophobia and phonophobia), all of which impair function*(4, 5)*. Inadequately treated, it may increase in frequency and evolve into chronic migraine, with headache on more days than not, with commensurate increases in ill-health and disability burdens, and in direct and indirect costs*(5)*.

This submission calls for the addition of amitriptyline 25 mg as an individual medicine to the EML for the preventive treatment of episodic migraine in adults. Migraine preventative treatment is recommended in the presence of at least 4 migraine days per month and/or when migraine substantially impacts quality of life *(6)*. Effective migraine prevention can improve health, function, participation in daily activities and quality of life, and avert both acute medication overuse and progression into chronic migraine *(7)*.

Amitriptyline is recommended among the first- or second-line treatment options for migraine prevention in several guidelines (see Section 9 of this proposal).

The 23rd (2023) edition of the EML includes propranolol 20 mg and 40 mg tablets as the sole option for migraine prevention. Its efficacy, measured in randomised controlled trials (RCTs) as proportion of responders (those in whom attack frequency is reduced by at least half) is <50%. Other options are therefore needed. The mode of action of amitriptyline in migraine prevention is assumed to be different from that of propranolol, so that failure of propranolol does not predict failure of amitriptyline. Addition of amitriptyline to the EML will increase the proportion who benefit from preventative treatment among those needing it.

Amitriptyline is on the EML for other indications, and is readily available worldwide.

Section 2: Consultation with WHO technical departments

During the preparation of this application there have been multiple meetings with Drs Tarun Dua, Nicoline Schiess and Rodrigo Cataldi of the Brain Health Unit, Department of Mental Health, Brain health & Substance Use, World Health Organization (WHO).

They have provided guidance and suggestions, and critically assessed drafts of this application.

Section 3: Other organization(s) consulted and/or supporting the submission

In addition to the four joint applicants (IHS, EHF, LTB and DREAM), we have also consulted the European Migraine and Headache Association (Mrs Elena Ruiz de la Torre), https://www.emhalliance.org/, who is in full support of this applicaton (see last page of this document).

Section 4: Key information summary for the proposed medicine(s)

INN	Amitriptyline
ATC code	N06AA09
Indication	Migraine prophylaxis
ICD-11 code	**8A80 1-3** Migraine, migraine with aura, chronic migraine

Dosage form	**Strength**	**EML**	**EMLc**
Tablets	25 mg	Yes (for other indications)	No

Section 5: Listing as an individual medicine or representative of a pharmacological class / therapeutic group

In the 23rd (2023) edition of the EML, section 7 Antimigraine medicines lists only propranolol for the prophylaxis of migraine.

The submission proposes individual listing of amitriptyline as an alternative to propranolol, representing a different pharmacological class and acting of a completely different pathway.

Amitriptyline has a similar profile of efficacy as propranolol and requires the intake of one pill a day. It is recommended among the first- or second-line treatment options for migraine prevention in several guidelines (see section 9 of this application).

Amitriptyline is listed in the EML for the treatment of depression, it is a widely available and cheap drug.

Section 6: Information supporting the public health relevance

Indication

We propose the addition of amitriptyline for the prophylaxis of migraine with and without aura.

Epidemiology and burden of migraine

Migraine is a prevalent neurovascular disorder characterized by moderate to severe headache attacks, often accompanied by nausea, vomiting, and photophobia/phonophobia and sensitivity to external stimuli (light, noise, odours) *(4)*. All of these symptoms are disabling and impair participation in life activities. In about one quarter of those affected, episodes may be preceded by transient focal neurological symptoms (most commonly visual disturbances, less commonly paresthesias, rarely motor or language deficits). The global prevalence of migraine is estimated at 14-15% (more than one billion people worldwide), 2-3 times higher in women than men *(2, 8)*. The disorder is ubiquitous, despite regional variations *(9)*.

Migraine contributes significantly to the global disease burden*(2, 8, 9)*. In the Global Burden of Disease (GBD) study 2021 *(8)*, migraine was the fourth highest cause of years lived with disability (YLDs) at level 4. In the detailed analysis of GBD2016, migraine accounted for 45.1 million disability-adjusted life years (DALYs).

There is evidence that, every year, 2-3% of people with episodic migraine (headache on fewer than 15 days/month transition to the much more disabling chronic migraine (headache on ≥15 days/month of which a majority are with symptoms of migraine) *(10)*.

Therefore, the impact of migraine on population health is very substantial, and associated with major impairments in participation, quality of life and productivity *(11)*. However, all of these can be reduced by appropriate treatments to abort ongoing episodes (acute treatment) or to prevent new ones (prophylaxis).

Multiple drugs belonging to different pharmacological classes are used for migraine prophylaxis *(4)*. They can be subdivided into two general categories depending on their mechanisms of action: non-migraine specific and migraine-specific. Beta blockers and amitriptyline belong to the non-migraine specific group. Drugs for migraine prophylaxis reduce monthly migraine days by a percentage that varies from 30 to 75%. So far, it is not possible to predict which subject will respond to a drug, nor the extent of the response.

Alternative medicines currently included on the Model Lists for the proposed indication

Propranolol

The WHO Model List of Essential Medicines includes only propranolol for migraine prophylaxis. Propranolol is a non-selective beta-blocker that has been widely used for migraine prevention. Its mechanism of action in migraine prophylaxis is not fully understood, but it is believed to involve several pathways. Propranolol blocks both β1- and β2-adrenergic receptors, leading to

reduced sympathetic nervous system activity. This results in the stabilization of vascular tone, preventing the vasodilation and subsequent vasoconstriction believed to contribute to migraine headaches. Additionally, propranolol may inhibit cortical spreading depression, a wave of neuronal and glial depolarization associated with migraine aura. It may also reduce the sensitivity of the trigeminal nerve to pain stimuli, further decreasing the likelihood of migraine attacks. The cumulative effect of these actions makes propranolol an effective option for reducing the frequency and severity of migraines in many patients *(12)*.

Why the addition of amitriptyline is important for a large population of subjects with migraine?
The beneficial use of amitriptyline in migraine was first reported in the late 1960s by Friedman *(13)* and Mahloudji *(14)*. Studies of migraine preventive use in the USA show that tricyclic antidepressants are the second most prescribed medications for migraine prevention, after topiramate *(15)*. The exact mechanism of action of amitriptyline in migraine prophylaxis is not fully understood, but it definitely tackles different targets from propranolol. The neurotransmitter 5-hydroxytryptamine (5-HT, serotonin) is involved in migraine pathophysiology *(16)* and the acute antimigraine medication class of triptans targets the 5-HT receptor subtypes $5\text{-HT}_{1B/1D/(1F)}$ *(17)*. TCAs inhibit the uptake of 5-HT in the synaptic cleft *(18)*. Therefore, the antimigraine effect of amitriptyline is likely related to its effects on serotonergic transmission. Moreover, inhibition of reuptake of noradrenaline leads to increased concentrations of this neurotransmitter in the synaptic cleft, which could exert antinociceptive effects through activation of α_2-adrenoreceptors *(18, 19)*. In addition to 5-HT and noradrenaline reuptake inhibition, tricyclic antidepressants have multiple other targets, including anticholinergic and antihistaminergic effects, they affect sodium, calcium *(20)* and potassium channels *(21)*, and exert an effect on adrenergic α_1-adrenoreceptors, N-methyl-D-aspartate (NMDA) receptors and opioid receptors *(22)*. Moreover, in a rat model, amitriptyline was shown to suppress cortical spreading depression (CSD), which is thought to be the underlying mechanism of migraine aura *(23)*. Thus, many sites of action could potentially contribute to the antimigraine effect of amitriptyline *(24)*, therefore amitriptyline represents a valid alternative for the subjects who did not benefit or did not tolerate propranolol.

Section 7: Treatment details

Dosage Regimen and Duration of Treatment

Medicine Delivery:

- Route of Administration: Oral administration.

- Dosage Range: 10-75 mg once daily, at bedtime.

Amitriptyline should be given at the lowest effective dose. Dose modifications should be accurately personalized balancing efficacy and adverse events.

- Titration: The typical starting dose of amitriptyline for migraine prevention is 10 mg once daily, with weekly increments of 10-25 mg as tolerated. Higher doses (up to 150 mg per day) could be reached in patients with comorbid depression – taking into due consideration the poor efficacy-to-tolerability ratio of this drug.

- Duration of Treatment: Migraine prophylaxis with amitriptyline is typically long-term. Patients should be reassessed periodically (e.g., every 3 to 6 months) to evaluate the effectiveness of the therapy and determine whether to continue, adjust, or discontinue treatment. In cases where migraine attacks have been well-controlled for 6 to 12 months, a trial of tapering off the medication may be considered under medical supervision.

Requirements to Ensure Appropriate Use of Amitriptyline

Patient Eligibility Criteria:

- Age: Amitriptyline is generally recommended for adult patients. It is not typically used in children for migraine prevention due to limited evidence on safety and efficacy in this population.

- Comorbid Conditions: Patients with depression, which is frequently comorbid with migraine, may particularly benefit from amitriptyline as it can address both migraine and the psychiatric condition.

- Special conditions: Amitriptyline should be used with caution in patients with epilepsy, impaired liver function, pheochromocytoma, urinary retention, prostate enlargement, hyperthyroidism, and pyloric stenosis *(25)*.

In patients with the rare condition of shallow anterior chamber and narrow anterior chamber angle, amitriptyline may provoke attacks of acute glaucoma. CYP2D6 poor metabolizers may experience increased side effects and should avoid amitriptyline or reduce the dose.

Amitriptyline can be used with caution during pregnancy and lactation *(26)*.

Contraindications

- The known contraindications of amitriptyline are:
  - History of myocardial infarction or coronary artery disease.

- History of arrhythmias, particularly any degree of heart block
- Porphyria
- Severe liver disease
- Use of MAOIs concurrently or in the last 14 days

Diagnostic and Monitoring Test Requirements

Amitriptyline treatment does not require any baseline tests or specific monitoring, besides the routine assessment to verify efficacy, need for dose adjustment and tolerability.

A baseline ECG might be indicated in subjects starting the drug above 50 years of age.

Treatment Administration Requirements and Setting

- Administration: Amitriptyline is taken orally, once daily, at bedtime.

Setting: Amitriptyline administration for migraine prevention is typically managed in an outpatient setting, such as neurology clinics, primary care and, potentially, also via community pharmacy facilities.

- Preparation: No special compounding or preparation is required. Amitriptyline is available in tablet form and is easy to administer.

Required Skill Levels of Healthcare Providers and Availability

- Provider Expertise: Healthcare providers prescribing amitriptyline for migraine prevention should have basic expertise in managing migraine and be familiar with antidepressant use, including potential side effects and contraindications.

- Provider Availability: amitriptyline is a commonly prescribed medication and there are no special requirements. Regular follow-up can be managed through primary care or specialty clinics, depending on the patient's needs.

Section 8: Review of evidence for benefits and harms

Summary of available evidence for comparative effectiveness and comparative safety

The analyses in the current paragraph are based on a critical re-appraisal and meta-analysis of oral drugs in migraine prevention *(27)*, as well as a systematic review and network meta-analysis on comparative effectiveness of migraine preventive drugs *(28)* of the European Headache Federation.

Search strategy: In consultation with an experienced research librarian, we searched MEDLINE, EMBASE, Cochrane CENTRAL, and ClinicalTrials.gov from inception to August 13, 2022 for randomized trials of pharmacologic treatments for migraine prophylaxis, without language restrictions. We supplemented our search by retrieving references of similar systematic reviews and meta-analyses.

As described in Lampl et al. *(27)*, literature was screened and judged for its eligibility, data were extracted, the risk of bias was assessed, data were synthesized and analyzed, and the quality of evidence was assessed. This procedure led to the inclusion of only three clinical trials (see Figure 1 below for the flow chart).

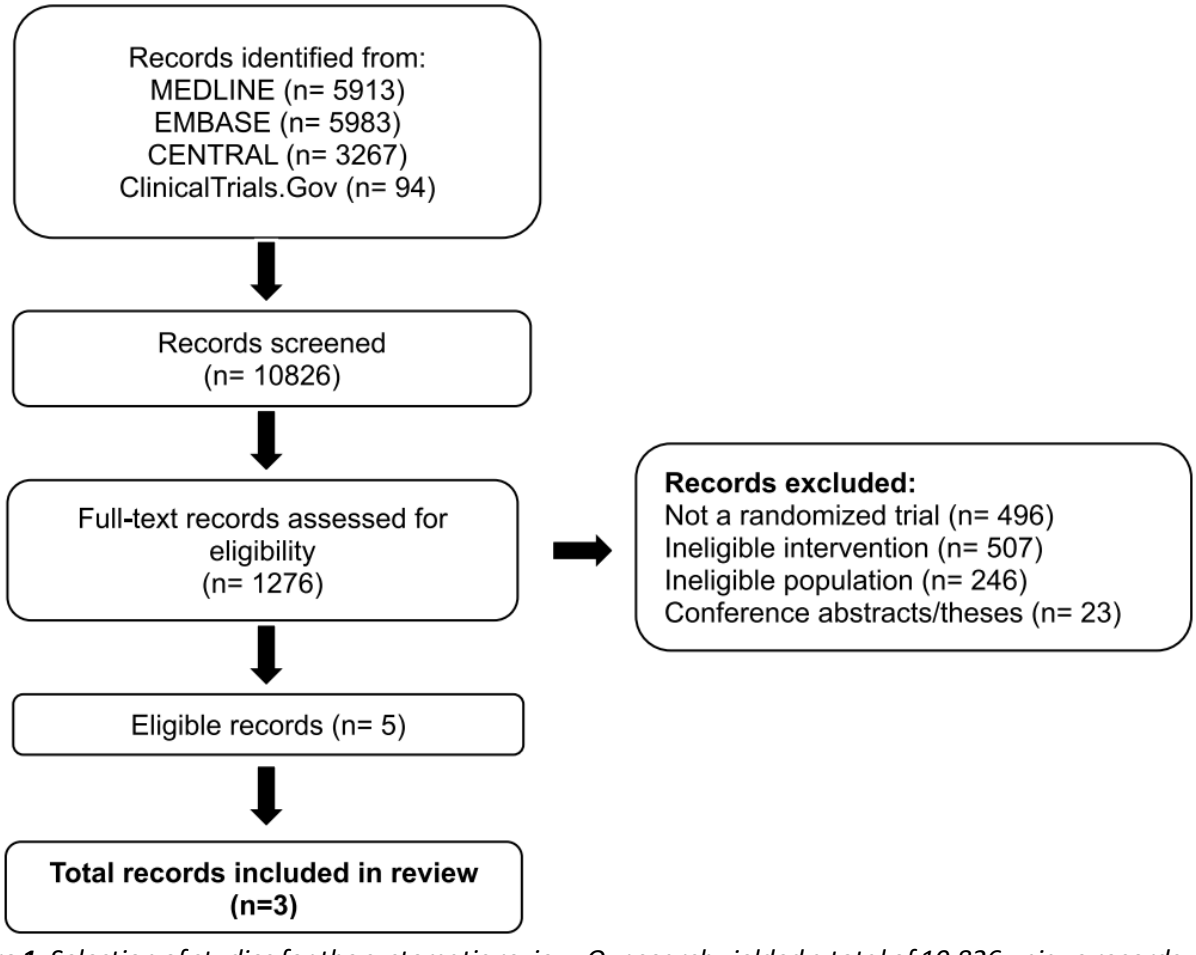


Figure 1. *Selection of studies for the systematic review. Our search yielded a total of 10,826 unique records. After title and abstract screening 1,276 records proved potentially eligible and after full-text review 5 records proved eligible. We excluded records if they did not describe full-text peer-reviewed reports of randomized trials that compared amitriptyline with placebo for prophylaxis of migraine in adult patients.*

Summary of the included studies: Among the three trials assessed, only one had a low risk of bias and assessed the efficacy of amitriptyline versus placebo and melatonin as active comparator *(29)* in 196 subjects. Amitriptyline 25 mg was superior to placebo ($p < 0.05$) for reducing migraine days per month after 12 weeks compared to baseline and as effective as melatonin. Amitriptyline has been preferred to melatonin because of its antidepressant effect, which is an added value when considering tha migraine is frequently comorbid with depression Couch and Hassanein used a specific migraine score including frequency, severity, and duration of attacks as the primary outcome parameter for efficacy *(30)*. This specific score was reduced by more than 50% in 55% of the amitriptyline-treated subjects (dose up to 100 mg per day), compared with 34% of the placebo-treated patients. The therapeutic gain in that particular study was 21%. Data on migraine frequency were not presented, and patients with comorbid depression were not excluded. Couch published an analysis of an amitriptyline trial that was performed between 1976 and 1979 later on in 2011 *(31)*. In this paper, 391 subjects with migraine and chronic daily headache were included. The drop-out rate was however 52% at week 20. There was a significant improvement in headache frequency for amitriptyline 25 mg over placebo at 8 weeks (p=0.018) but not at 12, 16, or 20 weeks. There were no significant differences in headache severity or duration between amitriptyline and placebo at any time point during the study.

Risk of bias assessment: this is illustrated in Figure 2 below.

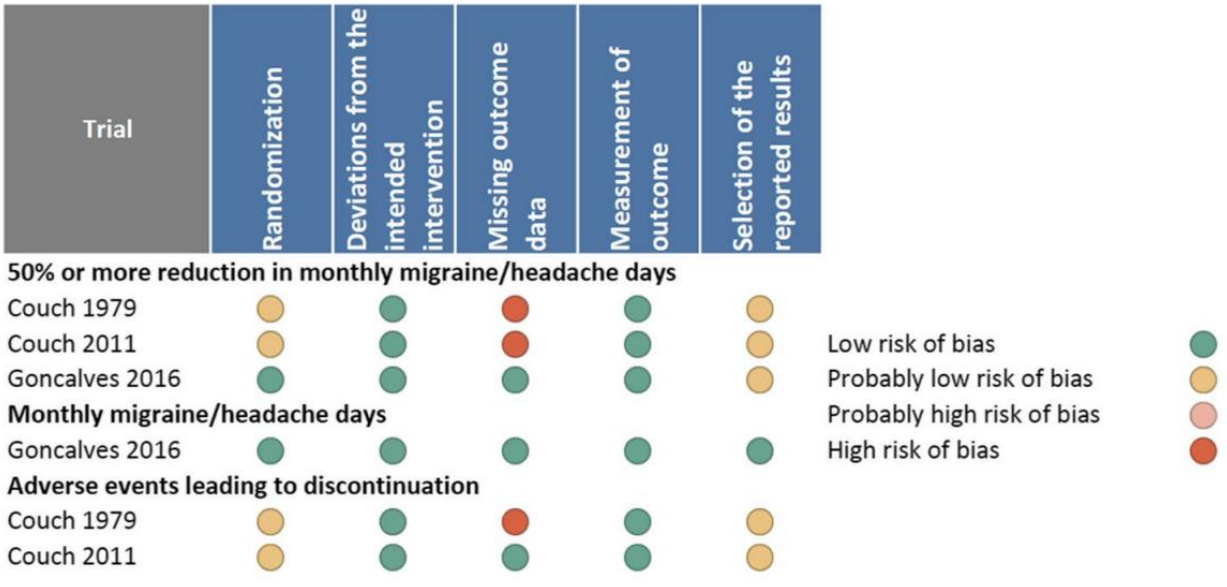


Figure 2. *Risk of bias ratings. Two out of three trials and one out of two trials were at high risk of bias due to missing outcome data for 50% or more reduction in monthly migraine days and adverse events leading to discontinuation, respectively. One trial, reporting on monthly migraine days, was at low risk of bias.*

50% responder rate

Two trials reported on 50% or more reduction in monthly migraine days in 289 patients and one trial reported on 50% responder rate in 100 patients. We performed a sensitivity analysis excluding the trial that reported responder rate. The sensitivity analysis produced results consistent with the main analysis (Fig. 3). Two out of three trials were rated at high risk of bias, due to missing outcome data. Two of the trials also failed to describe methods for allocation concealment. We were unable to make confdent judgements about potential for selective reporting due to lack of publicly accessible protocol or registration fles for two trials — likely since these trials were performed/published before trial registration practices became common. We found moderate certainty evidence that amitriptyline probably increases the proportion of patients who experience a 50% or more reduction in monthly migraine days, compared to placebo (Figures 4 and 5). The certainty of evidence was downgraded by one level due to concerns about risk of bias. We anticipated that the efects of amitriptyline may be diferent based on risk of bias (i.e., low vs. high risk of bias), mean monthly migraine days at baseline, and the proportion of patients who reported having previously used prophylactic drugs and had planned to perform subgroup analyses investigating the efects of these variables on results. Due to lack of reporting of mean monthly migraine days at baseline and the proportion of patients who had previously used prophylactic drugs, we were unable to perform subgroup analyses addressing these factors. The subgroup analysis based on risk of bias did not suggest that the trial at low risk of bias produced results that were diferent from the trial at high risk of bias (Fig. 5).

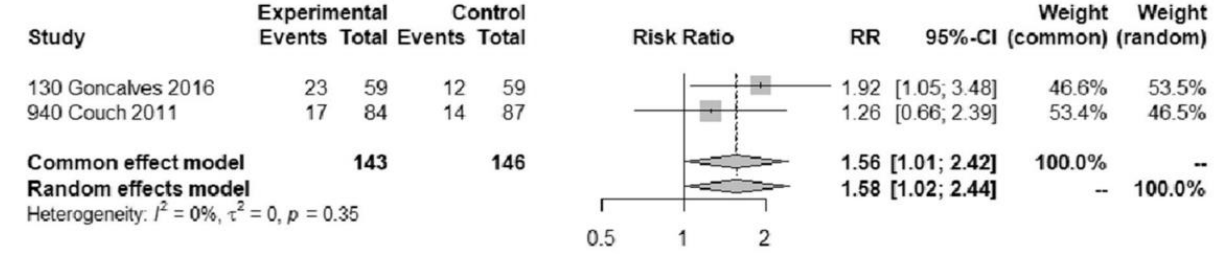


Figure 3. *Sensitivity analysis of analysis for 50% or more reduction in monthly migraine days excluding a trial that reported on a 50% reduction in a migraine score.*

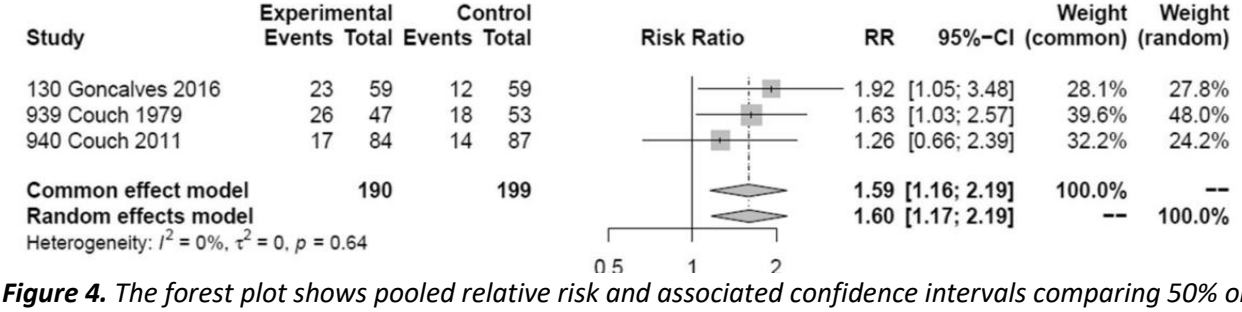


Figure 4. *The forest plot shows pooled relative risk and associated confidence intervals comparing 50% or more reduction in monthly migraine days for amitriptyline versus placebo.*

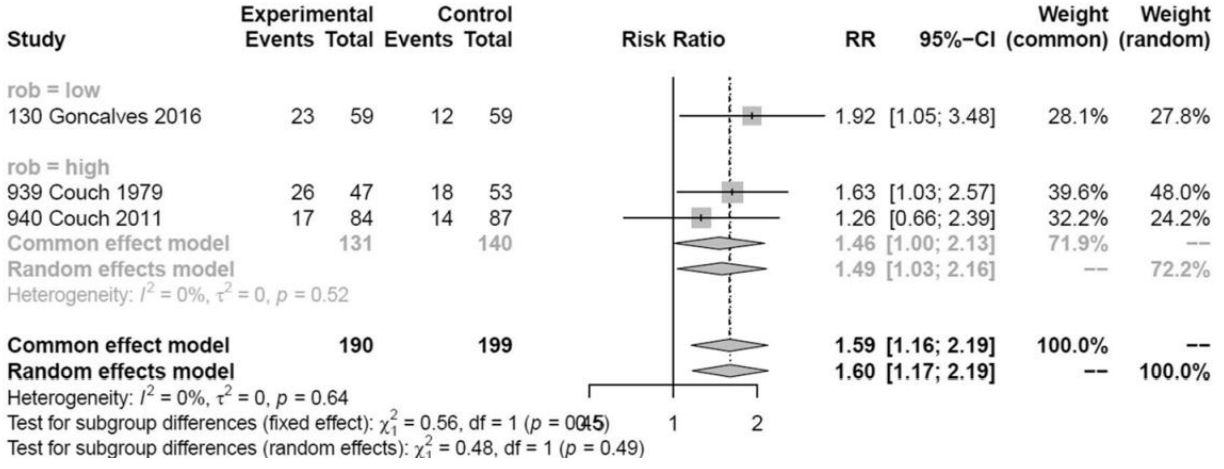


Figure 5. *Subgroup analysis comparing results of trials at low vs. high risk of bias for 50% responder rate.*

Evidence of Comparative Efficacy of Amitriptyline

In the literature there is only one randomized controlled trial that compared the efficacy of amitriptyline with propranolol and with placebo in a cross-over design. It was conducted on a small number of subjects (n. 30) and the outcome measure was the headache score obtained by multiplying the hours of headache by the intensity of pain *(32)*. Both drugs were superior to placebo, while there was no difference between the efficacy of the 2 drugs.
In another trial, amitriptyline proved as effective as melatonin.

Safety and tolerability of amitriptyline

Adverse events leading to discontinuation in clinical trials:
Two trials, including 507 patients, reported on adverse events leading to discontinuation (29,30). One of the two trials was rated at high risk of bias due to missing outcome data. We found moderate certainty evidence that amitriptyline probably increases the proportion of patients who discontinue due to adverse events compared to placebo *(27)*. The duration of treatment in the available studies was rather limited. In contrast, real-life treatment is required for a longer period thus making more compelling any issue related to tolerability more compelling. The most important adverse effects of amitriptyline are drowsiness and anticholinergic symptoms such as dry mouth, constipation, and tachycardia. Weight gain occurs in many patients together with elevated levels of leptin, insulin, and C peptide *(33)*, and can be a limiting factor leading to impaired compliance and discontinuation. Occasionally, amitriptyline may provoke glaucoma, PQ and QT interval prolongation on electrocardiogram (ECG), as well as benign prostate hypertrophy. Amitriptyline is metabolized by cytochrome P450 (CYP) isoenzymes, particularly CYP2D6, which is responsible for multiple interactions *(34)*. See for a graphical representation of the results Figure 6 below.

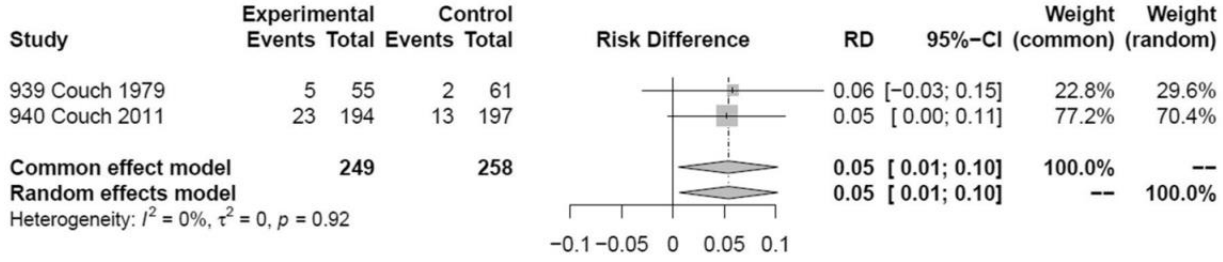


Figure 6*. Forest plot showing meta-analysis comparing amitriptyline with placebo for adverse events leading to discontinuation.*

In conclusion, though based on old, low quality trials, the efficacy of amitriptyline is similar to that of propranolol. Tolerability of the drug may be problematic, but this aspect can be managed by slow titration. Considering that migraine and depression are frequently comorbid (in 30% of subjects with episodic migraine and in 56% of subjects with chronic migraine) *(35)*, amitriptyline can be extremely useful in the presence of such comorbidity, while propranolol has been associated with an increased risk of depression *(36)*.

Section 9: Summary of recommendations in current clinical guidelines

Recommendations in existing WHO guidelines

N.A.

Recommendations in other current clinical guidelines

Summary of recent guidelines and recommendations including amitriptyline for the prophylaxis of migraine.

Guideline	Year	Recommendation
European Federation of Neurological Societies (EFNS) Guidelines *(37)*	2009	Amitriptyline 50-150 mg is classed as drug of second choice for migraine prophylaxis (evidence of efficacy, but less effective or more side effects than drugs of first choice)
TOP Primary care management of headache in adults *(38)*	2016	Amitriptyline can be considered for prophylaxis of chronic migraine
Scottish Headache Society Guidelines *(39)*	2018	Amitriptyline (25–150 mg at night) should be considered as a prophylactic treatment for patients with episodic or chronic migraine
British Association for the Study of Headache (BASH) Guidelines *(40)*	2019	Amitriptyline (25–150 mg at night) is recommended as first-line preventive treatment in episodic and chronic migraine
Japanese Headache Society Guidelines *(41)*	2019	Amitriptyline is effective for migraine prevention. […] A dose of 10-60 mg/day it is recommended.
European Headache Federation and Lifting the Burden aids to the management of headache disorders *(42)*	2019	Amitriptyline 10-100 mg at bedtime may be preferred when migraine coexists with tension-type headache, depression or sleep disturbance
Danish Headache Society Guidelines *(43)*	2021	Amitriptyline is particularly suitable if the patient also suffers from frequent tension-type headache or chronic migraine. Typical dosage is 10 mg × 1 increasing by 10 mg at one-week intervals to 10–100 mg daily.
American Headache Society Guidelines *(44)*	2021	Amitriptyline is classed as 'probably effective' in migraine prevention
French Headache Society Guidelines *(45)*	2021	Strong recommendation for amitriptyline (10-100 mg daily) for episodic migraine prevention; moderate recommendation for chronic migraine

German Headache Society Guidelines *(46)*	2022	Amitriptyline is effective in preventing migraine
Korean Headache Society Guidelines *(47)*	2023	We strongly recommend using amitriptyline for the preventive treatment of episodic migraine (Level of Evidence: II, Recommendation grade: Strong for).
Practice Recommendations of the International Headache Society *(48)*	2024	Amitriptyline is mentioned together with propranolol as an option when migraine- specific drugs (such monoclonal antibodies) are not accessible or topiramate is not effective or tolerated
International Headache Society Guidelines *(49)*	2024	Amitriptyline recommended for the prophylaxis of episodic migraine with a moderate strength of evidence,

Section 10: Summary of available data on comparative cost and cost-effectiveness

There are no published studies directly examining the cost-effectiveness of amitriptyline for migraine prevention, although the study by Linde, Steiner and Chisholm (50) in four low- and middle-income countries, using WHO-CHOICE, reported that "combining prophylaxis (with amitriptyline) and acute management (with ASA) presents a favourable ratio of cost to effect when compared to no treatment, particularly if accompanied by consumer education and provider training (below US$ 600 per HLY gained in Zambia, and below US$ 1,000 in China and India)".

In this modelling, we compared amitriptyline (25 mg daily for the first week, 50 mg daily for the second week and 75 mg daily thereafter) with propranolol (160 mg daily), the latter being already on the EML for this indication. The study by Linde et al.*(50)*, already referred to, provided a valuable cost-effectiveness modelling framework.

We assessed effectiveness in terms of healthy life years (HLYs) gained per treated individual. We estimated HLYs gained as the product of the reduction in mean time in the ictal state (rTIS) and the disability weight (DW) of 0.441 for the ictal state from the Global Burden of Disease (GBD) 2013 study. We used a treatment timeframe of 6 months, the typical duration of treatment in clinical practice.

To derive rTIS, we used mean reported reductions in monthly migraine days (rrMMD) in RCTs, assuming that effective treatment reduced the frequency of attacks without affecting their duration. For propranolol, 3 RCTs (28-30) (N=283) provided mean rrMMD = 1.5. For amitriptyline, a single trial (N=59) using a relatively low dose of 25 mg daily provided mean MMDs of 7.2 at baseline, 5.0 during month 3; from these data, rrMMD = 2.2.

We assumed conservatively that rrMMD was achieved by linear reduction over the first 3 months then maintained over months 4-6. Thus, actual reduction over a 6-month treatment period (arMMD) was given by the formula:

arMMD (per 6 months) = ([rrMMD/2*3]+[rrMMD*3]) = rrMMD*4.5.

To establish mean duration of headache (D) occurring on 1 MMD, we used data from population-based studies conducted by *Lifting The Burden* among N=8,363 in 14 countries (China, Mongolia, Nepal, India, Pakistan, Saudi Arabia, Morocco, Benin, Cameroon, Ethiopia, Zambia, Peru, Lithuania and Russian Federation, which represented a range of low- to high-income settings), considering only those reporting 4-14 days/month (the candidate population for prophylaxis). These sources provided D=21.5 hours. Therefore:

rTIS (per 6 months) = (arMMD*[21.5/24])/365 years

and

HLYs gained per treated patient (per 6 months) = rTIS*0.441.

Table 1. Medication acquisition costs reported from nine countries and in the UK NHS drug tariff (US$; 2024 terms)

		Propranolol 160 mg (4*40 mg)				Amitriptyline 25 mg			
Country	**Exchange local to US$**	**Cost local**	**Quantity**	**Cost local per 160 mg**	**Cost/160 mg US$**	**Cost local**	**Quantity**	**Cost local per 25 mg**	**Cost/25 mg US$**
Egypt	0.02064	55.00	12.5	4.400	0.091	21.00	30	0.700	0.014
Moldova	0.05643	19.00	12.5	1.520	0.086	37.00	50	0.740	0.042
Nepal	0.00737	40.50	2.5	16.200	0.119	3.63	1	3.630	0.027
India	0.01198	10.00	10	1.000	0.012	1.00	1	1.000	0.012
Georgia	0.3663	3.62	5	0.724	0.265	1.70	10	0.170	0.062
Indonesia	0.00006	488.00	0.25	1952.000	0.117	2500.00	1	2500.000	0.150
Mongolia	0.000296	7600.00	5	1520.000	0.450	11058.00	50	221.160	0.065
Argentina	0.00104	280.45	0.25	1121.800	1.167	373.02	1	373.020	0.388
Brazil	0.17961	0.11	0.25	0.428	0.077	0.43	1	0.430	0.077
UK (NHS drug tariff)	1.31205	0.71	7	0.101	0.133	0.68	28	0.024	0.032
Mean					**0.252**				**0.087**

In terms of costs, we included only medication acquisition costs, assuming other healthcare costs to remain constant across different treatment options. We assumed treatment was continued initially for 3 months, but from months 4 to 6 only in the proportion (Pr) who had responded (ie, those reporting a reduction in MMDs after 3 months of at least 50%). We used data from three RCTs (section 8, Figures 4, 6 and 7) to calculate Pr = 133/283 (47.0%) for propranolol, while a single RCT (28) provided Pr = 39.1% for amitriptyline 25 mg. We established dosage costs of amitriptyline 25 mg (US$ 0.087) and propranolol 160 mg (4*40 mg tablets: US$ 0.252) as the means of those reported for each by experts in nine countries (Moldova, Georgia, Egypt, Nepal, India, Indonesia, Mongolia, Argentina and Brazil) along with those provided by the UK NHS drug tariff (Table 1). We regarded the cost for propranolol 4*40 mg as the daily dosage cost throughout 6 months of usage; for amitriptyline, we calculated the daily dosage cost as US$ 0.087 for the first week, twice this (US$ 0.174) for the second week and three times this (US$ 0.261) thereafter.

Accordingly, the treatments costs per person for 6 months (180 days) were given by the formulae:

for propranolol:

6-month cost = US$ 0.252 * {(180*Pr)+(90*[1–Pr])};

for amitriptyline:

6-month cost = US$ [(0.087*7)+(0.174*7)+(0.261*76)] + (0.261*90*Pr);

reflecting that treatment was discontinued after 3 months (with no further costs) in non-responders.

Table 2 summarises the input data.

Table 2: Summary of input data

	Daily dosage cost (US$ 2024 values)	**Mean attack duration (D) (hours) from N=8,363 in 14 countries (F 4-14)**	**Proportion of those treated who report response (Pr) (reduction in F by ≥50% at 3 months)**	**Change in monthly migraine days (treated)**
Amitriptyline (25 mg daily for first week, 50 mg daily for second week, 75 mg daily thereafter)	0.087 daily for first week, 0.174 for second week, 0.261 thereafter	21.5 hours	39.1%	-2.2
Propranolol (160 mg daily)	0.252	21.5 hours	133/283 (47.0%)	-1.5

Cost/HLY gained

Accordingly, cost/HLY gained was given by:

cost over 180 days/{[(rrMMD*4.5)*(21.5/24)]/365}*0.441}

for propranolol:

cost/HLY gained = {0.252*[(180*0.47)+(90*0.53)]}/{[(1.5*4.5)*(21.5/24)]/365}*0.441 = US$ 887;

for amitriptyline:

cost/HLY gained = {[(0.087*7)+(0.174*7)+(0.261*76)]+(0.261*90*0.391)}/{[(2.2*4.5)*(21.5/24)]/365}*0.441 = US$ 560.

Both treatments are highly cost-effective, with amitriptyline more less so (same cost, more effective on this measure).

Importantly, modes of action differ, so amitriptyline may be effective in those in whom propranolol is not. It should be noted that the analysis of amitriptyline did not include probable better adherence to treatment (less wastage) because of its once-daily dosing, as opposed to the twice daily dosing of propranolol *(51)*.

Neither analysis included additional healthcare provider costs that might be associated with prescriptions and monitoring.

Incremental cost-effectiveness (ICER)

Table 3: ICER analysis

	Six-month treatment cost per person (US$ 2024 values)	**HLY gained per person**	**Diff 6-month costs per person**	**Diff HLY gained per person**	**ICER (extra US$ to be invested per HLY gained)**	**Comments**
Amitriptyline (25 mg daily for first week, 50 mg daily for second week, 75 mg daily thereafter)	30.84	1.07E-02	-2.50	3.40E-03	lower cost, more effective	**preferred option**
Propranolol (160 mg daily)	33.34	7.31E-03	comparator			**dominated**

In this modelling, again comparing amitriptyline (25 mg daily for the first week, 50 mg daily for the second week, 75 mg daily thereafter) with propranolol (160 mg daily), we applied the same assumptions and took data from the same sources. Among non-responders, MMDs were

considered to remain unchanged during the treatment period. In contrast, responders were assumed to experience a linear decline in MMDs during the first 3 months to their new value, maintaining this reduction for the remainder of the 6 months. The key findings are in Table 3.

Amitriptyline is the preferred option over propranolol (less expensive, more effective) (Table 3).

It should be noted that this analysis, and the preceding one, was sensitive to comparative costs. While mean cost of amitriptyline was lower than mean cost of propranolol, in some countries amitriptyline was more expensive (Table 1).

It should further be noted that both analyses are subject to substantial uncertainties because of the poor quality of the efficacy data (especially for amitriptyline, which applied to a lower dosage than recommended now).

Section 11: Regulatory status, market availability and pharmacopeial standards

Regulatory Approval
-United States: Amitriptyline is an FDA-approved medication to treat depression in adults. The non-FDA approved indications include migraine, anxiety, post-traumatic stress disorder, insomnia and several painful conditions (chronic pain, diabetic neuropathy, fibromyalgia, irritable bowel syndrome, interstitial cystitis and postherpetic neuralgia. Amitriptyline has been used for post-COVID headaches.

- Europe: Amitriptyline is approved for migraine prevention in Europe.

- UK: Amitriptyline is a prescription drug in the UK, where it is indicated for depression and migraine prevention by Medicines and Healthcare Products Regulatory Agency (MHRA)

- Japan: Amitriptyline is approved for off-label use for migraine prevention

It is produced by multiple international companies in both the branded version and the generic one. It is available in the majority of Countries as it is already on the EML for other indications.

Market Availability

- Brand Availability: Amitriptyline is available globally under several brand names (e.g. Elavil Endep, Vanatrip, Abamax, Amaril, Amiclozor etc.) (Appendix 1).

- Generics: Amitriptyline is available in generic form in many countries, contributing to its widespread availability and lower cost compared to branded versions.

- Patent Status: Amitriptyline original patents have expired, leading to a broad availability of generic versions. There are numerous generic manufacturers producing amitriptyline.

Supply Chain and Shortages
- Amitriptyline is generally well-supplied. There are typically few supply chain issues for amitriptyline, but regional distribution problems could impact availability.

Pharmacopoieal standards
https://pheur.edqm.eu/app/11-5/content/11-5/0464E.htm?highlight=on&terms=amitriptyline

Appendix 1

Availability of amitriptyline in the World (International Headache Society internal survey coordinated by Dr Francesca Puledda, 2024)

Amitriptyline				
Country	**Available**	**Prescription**	**Reimbursement**	**Within country differences**
Algeria	Yes	Prescription – GP	Full reimbursement	No
Argentina	Yes			No
Armenia	Yes	Pharmacy	No reimbursement	No
Australia	Yes	Prescription – GP	Partial reimbursement	No
Austria	Yes	Prescription – GP	Full reimbursement	No
Azerbaijan	Yes	Prescription – specialist only	No reimbursement	No
Belgium	Yes	Prescription – GP	No reimbursement	No
Bolivia (Plurinational State of)	Yes			No
Bosnia and Herzegovina	Yes	Prescription – specialist only	No reimbursement	No
Brazil	Yes	Pharmacy	Partial reimbursement	No
Brunei Darussalam	Yes	Prescription – GP		No
Bulgaria	Yes			No
Burkina Faso	Yes			No
Burundi	Yes			No
Cabo Verde	Yes	Prescription – GP	Partial reimbursement	No
Cameroon	Yes	Prescription – GP	No reimbursement	Yes
Canada	Yes	Prescription – GP	Partial reimbursement	No
Chad	Yes			No
Chile	Yes	Prescription – GP	Full reimbursement	No
China	Yes	Prescription – GP	Full reimbursement	Yes
Colombia	Yes	Prescription – GP	Full reimbursement	No
Côte D'Ivoire	Yes			Yes
Czech Republic	Yes	Prescription – GP	Full reimbursement	No
Denmark	Yes	Prescription – specialist only	Partial reimbursement	No
Djibouti	Yes	Prescription – specialist only	Partial reimbursement	Yes
Dominican Republic	Yes			Unknown
Ecuador	Yes	Prescription – specialist only	Full reimbursement	No
Egypt	Yes	Pharmacy	Full reimbursement	No
El Salvador	Yes	General sales list	Full reimbursement	No
Ethiopia				Unknown
Finland	Yes	Prescription – GP	Partial reimbursement	No
France	Yes	Prescription – GP	Full reimbursement	No
Gabon	Yes	Prescription – specialist only	Partial reimbursement	Yes
Georgia	Yes	Prescription – GP	Full reimbursement	No
Germany	Yes	Prescription – specialist only	Full reimbursement	No
Ghana	Yes	Prescription – GP	Full reimbursement	No

Greece	Yes	Prescription – specialist only	Partial reimbursement	No
Guinea				Unknown
India	Yes	Prescription – GP	No reimbursement	No
Iran (Islamic Republic of)	Yes			No
Italy	Yes	Prescription – GP	Full reimbursement	No
Latvia	Yes	Prescription – GP	No reimbursement	No
Libya	Yes			No
Lithuania	Yes	Prescription – GP	No reimbursement	No
Madagascar	Yes			No
Mali	Yes	Prescription – specialist only	Partial reimbursement	Yes
Mexico	Yes	Prescription – GP	No reimbursement	Yes
Mongolia	Yes	Prescription – specialist only		No
Nepal	Yes	Prescription – specialist only	No reimbursement	No
Netherlands	Yes	Prescription – GP	Full reimbursement	No
New Zealand	Yes	Prescription – GP	No reimbursement	No
Niger	Yes	Prescription – GP		Yes
Nigeria	Yes			No
Norway	Yes	Prescription – GP	Full reimbursement	No
Pakistan	Yes			Yes
Panama	Yes	Pharmacy		No
Peru	Yes	Prescription – GP	Partial reimbursement	Yes
Poland	Yes	Prescription – GP	No reimbursement	No
Portugal	Yes	Prescription – GP	Partial reimbursement	No
Republic of Korea	Yes	Prescription – GP	Full reimbursement	No
Republic of Moldova	Yes	Prescription – specialist only	No reimbursement	No
Romania	Yes	Prescription – GP	No reimbursement	No
Russian Federation	Yes	Prescription – GP	No reimbursement	Yes
Rwanda	Yes	Prescription – GP	Full reimbursement	No
Senegal	Yes	Prescription – GP		Unknown
Singapore				Unknown
Slovenia	Yes	Prescription – GP	Full reimbursement	No
South Africa				Unknown
Spain	Yes	Prescription – GP	Full reimbursement	No
Sudan	Yes	Pharmacy		No
Switzerland	Yes	Prescription – GP	Full reimbursement	No
Thailand	Yes	Prescription – GP	Full reimbursement	No
Togo	Yes			Yes
Tunisia	Yes	Prescription – GP	Full reimbursement	No
Turkey	Yes	Prescription – specialist only	Partial reimbursement	No
Uganda	Yes	Pharmacy	Full reimbursement	Yes
Ukraine	Yes			No
United Kingdom of Great Britain and Northern Ireland	Yes	Prescription – GP	Full reimbursement	No
United Republic of Tanzania	Yes			Yes
United States of America	Yes	Prescription – GP	Partial reimbursement	No
Uruguay	Yes	Prescription – GP	No reimbursement	Unknown

Vietnam	Yes	Prescription – specialist only	No reimbursement	Yes
Zambia	Yes	Prescription – GP		No
Zimbabwe	Yes	Prescription – GP	Full reimbursement	No

To whom it may concern

Re: Support and Endorsement for the application for the inclusion of additional drugs for the treatment of migraine in the WHO Essential Medicines List

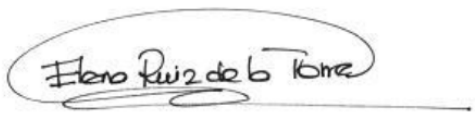
On behalf of EHMA, the leading non-profit umbrella organization of 34 patient associations for Migraine, Cluster Headache, Trigeminal Neuralgia and other headache diseases, dedicated to supporting individuals with migraine and other headache, I am writing to express our wholehearted support and endorsement for the joint application made by the International Headache Society, Lifting the Burden and European Headache Federation to include addition drugs for the acute and preventive treatment of migraine in the World Health Organization Essential Medicines List.

Migraine, characterized by their severe and debilitating nature, pose a significant challenge to those affected, impacting their quality of life and daily functioning. As a patient organization, we witness firsthand the profound suffering experienced by individuals with this condition. Despite the availability of effective treatments, many patients still face barriers to accessing these critical therapies, particularly in regions with limited healthcare resources.

The inclusion of additional treatment options, such as naproxen, eletriptan, amitriptyline, bisoprolol and fremanezumab in the WHO Essential Medicines List is a crucial step towards improving global access to these essential medications. It would ensure that effective and life-changing treatments are available to individuals regardless of their geographic or economic circumstances. This inclusion not only aligns with the WHO's mission to improve global health equity but also represents a significant advancement in the fight against a condition that affects millions worldwide.

Our organisation is committed to supporting this initiative and are available to provide any further information or assistance. We look forward to the positive impact this development will have on the global health landscape.

Sincerely,
EMHA – European Migraine and headache Alliance



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