Amitriptyline

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 5. Medicines for neurological disorders > 5.1. Medicines for central nervous system disorders > 5.1.5. Medicines for headache disorders > 5.1.5.2. Medicines for migraine prophylaxis

ATC codes: N06AA09

Indication	Migraine ICD11 code: 8A80.Z
INN	Amitriptyline
Medicine type	Chemical agent
List type	Core
Formulations	Oral > Solid > tablet: 25 mg
EML status history	Application rejected in 2025 (TRS 1064)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Amitriptyline
DrugBank	Amitriptyline

Expert Committee recommendation

The Expert Committee noted that migraine is a common primary headache disorder characterized by recurrent moderate to severe pain and acknowledged the public health relevance of effective treatments. Migraine is a cause of considerable disability and results in a substantial socioeconomic burden, which is greater for women than for men. Migraine prophylaxis is generally recommended in the presence of at least four migraine days per month and/or when migraine substantially affects quality of life. The Expert Committee noted that several classes of medication are commonly used for migraine prophylaxis, including antidepressants, anticonvulsants, antihypertensives and calcitonin gene-related peptide (receptor) monoclonal antibodies. Currently, the Model Lists include only propranolol for migraine prophylaxis. The Committee noted that there is moderate-certainty evidence that amitriptyline increases the proportion of people who experience a 50% or greater reduction in monthly migraine days. However, amitriptyline was also associated with a greater proportion of patients who discontinued treatment due to adverse events compared with placebo. Furthermore, the Committee noted that very few data exist comparing the efficacy and safety of amitriptyline versus active comparators, e.g. propranolol, other beta-blockers or other prophylaxis interventions. Based on these considerations, the Expert Committee did not recommend the inclusion of amitriptyline on the EML for use in migraine prophylaxis. In the absence of adequate evidence for comparative benefit and safety versus currently listed propranolol, the Expert Committee was unable to determine if amitriptyline has a favourable and meaningful balance of benefits to harms.

Background

Amitriptyline has not previously been evaluated for inclusion on the EML for migraine prophylaxis. It is currently listed for use in the treatment of depression and other common symptoms in palliative care. Propranolol is currently included in the EML for

migraine prophylaxis.

Public health relevance

Migraine is a prevalent neurovascular disorder characterized by moderate to severe headache attacks, often accompanied by nausea, vomiting, photophobia/phonophobia and sensitivity to external stimuli (light, noise, odours). Symptoms are disabling and affect participation in life activities, quality of life and productivity (1). In around 25% of people 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 1 billion people worldwide), and it is two to three times higher in women than men (2). According to the Global Burden of Disease study 2021, migraine was the fourth highest cause of years lived with disability at level 4 (3). In an analysis of the Global Burden of Disease study 2016, migraine accounted for 45.1 million disability-adjusted life years (4). Around 2–3% of people with episodic migraine (headache on < 15 days/month) transition to more disabling chronic migraine (headache on ≥ 15 days/month of which a majority are with symptoms of migraine) (5). One of the main risk factors for the transition to chronic migraine is poorly managed acute treatment and the overuse of acute medications (6).

Benefits

The application presented the results of a critical re-appraisal and meta-analysis of amitriptyline for migraine prophylaxis (7). Three studies were included that compared amitriptyline and placebo for migraine prophylaxis (8–10). For efficacy outcome, two trials reported a ≥ 50% reduction in monthly migraine and one trial reported 50% responder rates. Two of the three trials were rated at high risk of bias, due to missing data on outcomes and failure to describe the methods for allocation concealment. In a pooled analysis, there was moderate-certainty evidence that amitriptyline probably increases the proportion of patients who experience ≥ 50% reduction in monthly migraine days (risk ratio 1.60, 95% confidence interval (CI) 1.17 to 2.19; three randomized controlled trials, 389 participants). A subgroup analysis based on risk of bias of the included trials did not indicate a difference between the trials at low and high risk of bias. One cross-over randomized controlled trial compared the efficacy of amitriptyline with propranolol and placebo for migraine prophylaxis in 30 patients over 40 weeks (11). The reported outcome measure was a headache score calculated by multiplying headache hours by pain severity. The arithmetic mean of weekly scores was calculated. Both amitriptyline and propranolol were significantly superior to placebo. No significant difference was observed between amitriptyline and propranolol. Of note, the superiority of amitriptyline over placebo did not correlate with significantly reduced test scores for depression.

Harms

Adverse effects of amitriptyline are well known and include drowsiness and anticholinergic symptoms (e.g. dry mouth, urinary retention, constipation, tachycardia, blurred vision), weight gain, glaucoma, benign prostatic hypertrophy, and PQ and QT interval prolongation. In the pooled analysis presented in the application, there was moderate-certainty evidence that amitriptyline probably increases the proportion of patients who discontinue treatment due to adverse events compared to placebo (risk difference 0.05, 95% CI 0.01 to 0.10; two randomized controlled trials, 507 participants) (7). The cross-over trial comparing amitriptyline and propranolol did not report safety outcomes (11).

Cost / cost effectiveness

A 2015 cost–effectiveness analysis investigated interventions for migraine in four low- and middle-income countries including prophylaxis with amitriptyline (12). A population model was run for two scenarios over a lifetime horizon. Scenario 1 reflected the natural history of migraine and scenario 2 represented the population-level impact of each intervention implemented for 10 years. The population included was aged between 18 and 65 years. It was assumed that prophylaxis was only offered to people with three or more migraine attacks per month. Amitriptyline was cheaper than topiramate and more cost-effective than propranolol. The combination of amitriptyline prophylaxis and acute management with acetylsalicylic acid was associated with costs per healthy life year gained of 1649 United States dollars (US$), US$ 1795, US$ 5264 and US$ 773 in China, India, Russian Federation and Zambia, respectively. Costs were lower when treatment was accompanied by consumer education and prescriber training: US$ 959, US$ 957, US$ 3059 and US$ 573 per healthy life year gained, respectively. Using the same modelling framework as the above study, the applicants conducted a cost–effectiveness analysis of amitriptyline versus propranolol. The model assumed an

amitriptyline dose of 25 mg daily for the first week, 50 mg daily for the second week and 75 mg daily thereafter, and a propranolol dose of 160 mg daily. Costs per healthy life year gained were US$ 560 for amitriptyline and US$ 887 for propranolol. In this analysis, amitriptyline dominated propranolol (i.e. lower cost and more effective). However, the results are considered highly uncertain due to the poor quality of the efficacy data.

WHO guidelines

WHO guidelines for migraine are not currently available. The application provided a brief summary of recommendations on amitriptyline for migraine prophylaxis from various current national and international clinical guidelines.

Availability

Amitriptyline has wide globally. Availability in branded and generic forms. In some jurisdictions, its use in migraine prophylaxis is an off-label indication.

Other considerations

The Department of Mental Health, Brain Health and Substance Use provided comments on the application. The technical department did not support the inclusion of amitriptyline on the EML for migraine prophylaxis, suggesting that more evidence with clearer outcomes and specific indications for use in particular populations should be required to be considered for inclusion on the EML.

1. Steiner TJ, Stovner LJ. Global epidemiology of migraine and its implications for public health and health policy. Nat Rev Neurol. 2023;19(2):109–17 (https://doi.org/10.1038/s41582-022-00763-1).
2. Stovner LJ, Hagen K, Linde M, Steiner TJ. The global prevalence of headache: an update, with analysis of the influences of methodological factors on prevalence estimates. J Headache Pain. 2022;23(1):34 (https://doi.org/10.1186/s10194-022-01402-2).
3. Global, regional, and national burden of disorders affecting the nervous system, 1990–-2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet Neurol. 2024;23(4):344–81 (https://doi.org/10.1016/s1474-4422(24)00038-3).
4. Global, regional, and national burden of migraine and tension-type headache, 1990–-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2018;17(11):954–76 (https://doi.org/10.1016/s1474-4422(18)30322-3).
5. Katsarava Z, Schneeweiss S, Kurth T, Kroener U, Fritsche G, Eikermann A et al. Incidence and predictors for chronicity of headache in patients with episodic migraine. Neurology. 2004;62(5):788–90 (https://doi.org/10.1212/01.wnl.0000113747.18760.d2).
6. Lipton RB, Buse DC, Nahas SJ, Tietjen GE, Martin VT, Löf E et al. Risk factors for migraine disease progression: a narrative review for a patient-centered approach. J Neurol. 2023;270(12):5692–710 (https://doi.org/10.1007/s00415-023-11880-2).
7. Lampl C, Versijpt J, Amin FM, Deligianni CI, Gil-Gouveia R, Jassal T et al. European Headache Federation (EHF) critical re-appraisal and meta-analysis of oral drugs in migraine prevention—part 1: amitriptyline. J Headache Pain. 2023;24(1):39 (https://doi.org/10.1186/s10194-023-01573-6).
8. Couch JR, Hassanein RS. Amitriptyline in migraine prophylaxis. Arch Neurol. 1979;36(11):695–9 (https://doi.org/10.1001/archneur.1979.00500470065013).
9. Couch JR, Group ftAVPS. Amitriptyline in the prophylactic treatment of migraine and chronic daily headache. Headache: 2011;51(1):33–51 (https://doi.org/https://doi.org/10.1111/j.1526-4610.2010.01800.x).
10. Gonçalves AL, Martini Ferreira A, Ribeiro RT, Zukerman E, Cipolla-Neto J, Peres MFP. Randomised clinical trial comparing melatonin 3 mg, amitriptyline 25 mg and placebo for migraine prevention. J Neurol Neurosurg Psychiatry. 2016;87(10):1127–32 (https://doi.org/10.1136/jnnp-2016-313458).
11. Ziegler DK, Hurwitz A, Hassanein RS, Kodanaz HA, Preskorn SH, Mason J. Migraine prophylaxis: a comparison of propranolol and amitriptyline. Arch Neurol. 1987;44(5):486–9 (https://doi.org/10.1001/archneur.1987.00520170016015).
12. Linde M, Steiner TJ, Chisholm D. Cost–effectiveness analysis of interventions for migraine in four low- and middle-income countries. J Headache Pain. 2015;16(1):15 (https://doi.org/10.1186/s10194-015-0496-6).