Topiramate (Topamax) for migraine prevention

(Toe-PEER-a-mate)

Summary

- The PBS listing of topiramate provides an alternative migraine-prevention option for adults unable to take beta blockers or pizotifen. It does not cover patients who have tolerated beta blockers or pizotifen but had an inadequate response.
- Establish a contraindication or intolerance to beta blockers or pizotifen before initiating topiramate.
- The recommended dosage of topiramate for migraine prevention is 100 mg/day (50 mg twice daily), which is less than the target anti-epileptic dose. Some patients benefit from a lower dose (for example, 50 mg/day).
- In clinical trials, around 50% of patients using topiramate experienced paraesthesia. Cognitive effects, including cognitive slowing, language difficulties and difficulties with memory and concentration, were common (6% to 7%) and led to treatment withdrawal in up to 3% of patients.
- Unlike most other migraine-prevention drugs, topiramate is more likely to be associated with weight loss than weight gain.
- In the absence of adequate head-to-head comparison trials, there is no evidence that topiramate is more effective than other migraine-prevention drugs. It may be as effective as propranolol.

PBS listing

Authority required

Initial treatment

For migraine prevention in patients who have experienced an average of 3 or more migraines per month over a period of at least 6 months and who:

- have a contraindication to beta blockers, as described in the relevant TGA-approved product information, OR
- have experienced intolerance of a severity necessitating permanent withdrawal during treatment with a beta blocker

AND

- have a contraindication to pizotifen because the weight gain associated with this drug poses an unacceptable risk, OR
- have experienced intolerance of a severity necessitating permanent withdrawal during treatment with pizotifen.

Details of the contraindication and/or intolerance(s) must be provided at the time of application.

Continuing treatment

For patients who have previously received PBS-subsidised topiramate for migraine prevention.

Reason for PBS listing

The Pharmaceutical Benefits Advisory Committee (PBAC) recommended listing on the basis of acceptable cost-effectiveness compared with placebo for migraine prevention in patients unable to take a beta blocker and/or pizotifen.[1] The PBAC noted that there was insufficient evidence that topiramate was effective in prior treatment failure and limited the listing to patients with contraindications or poor tolerance to longer-established migraine-prevention drugs.[2]

Place in therapy

Topiramate is more effective than placebo and may be as effective as propranolol in reducing the frequency of migraine.[3–5] There is no clear evidence that topiramate is more effective than longer-established therapies for migraine prevention. Its efficacy and adverse-effect profile mean that it is best reserved for migraine prevention in patients unable to tolerate beta blockers or pizotifen, or when a contraindication to these drugs exists. Failure to achieve an adequate response with propranolol or pizotifen is not an indication for topiramate use under the current PBS listing.

An accurate diagnosis is essential.[6] Criteria for diagnosing migraine can be found in the 2nd edition of the *International Classification of Headache Disorders (ICHD-II)*.[7] See *NPS News 38: Headache and migraine* for more information about the diagnosis and management of migraine.

When to consider migraine prevention therapy

Most people who experience migraine (62%) report one or more severe headaches per month, and more than 1 in 10 report one severe headache per week.[8] Consider migraine-prevention treatment in the following situations[6,9]:

- recurring migraines that produce disability lasting 3 or more days
- contraindication to, or ineffectiveness of, acute treatments
- use of acute treatments more than twice a week
- presence of uncommon migraine conditions, including hemiplegic migraine, migraine with prolonged aura, or migrainous infarction.

Patient preference and the cost of treatments for both acute migraine management and migraine prevention will influence treatment choice.[6,9]

When considering migraine-prevention therapy be aware of the possibility of medication-overuse headache (MOH), a disorder characterised by frequent migraine-like headaches (≥ 15 days per month) during regular acute medication overuse (on 2 or more days each week for > 3 months).[10] Treatment of MOH involves careful withdrawal of the overused agent. In patients with underlying migraine, initiate migraine-prevention therapy in parallel with MOH management.[11,12] Consider referring a patient with MOH to a specialist.

Unless contraindicated, beta blockers remain first-line migraine-prevention drugs[13]

There is consistent evidence for the efficacy of propranolol[14] as a first-line migraine-prevention drug. Other beta blockers such as metoprolol and atenolol have also shown efficacy.[14] There is also evidence for the efficacy of valproate and amitriptyline[6,9] although these drugs are not TGA approved for migraine prevention in Australia. The serotonin antagonist pizotifen is also used despite little trial data showing efficacy.[15,16] Pizotifen use may be limited by adverse effects, particularly weight gain.[17] Because of the potential for serious adverse effects, reserve methysergide for patients who do not respond to other migraine-prevention drugs.[12] Other migraine-prevention drugs have limited evidence of efficacy.

There is little evidence for the superior efficacy of one migraine-prevention drug over another

Effective migraine-prevention drugs can be expected to achieve at least 50% reduction in headache frequency.[18] There is no convincing evidence that one drug is superior to others. All migraine-preventive therapies have significant adverse effects that may limit effectiveness and patient adherence.[12,19] Clinical trials report a large placebo effect[18], suggesting that the nature of migraine may change over time.

Choose a drug with the highest level of evidence-based efficacy and the lowest potential for adverse effects in an individual patient.[9] Take contraindications (including pregnancy and planned pregnancy) into account, and the likelihood of patient adherence with a particular drug.[15] When possible, choose a drug that also treats a coexisting disease (for example beta blockers in patients with angina or hypertension). Discuss choice of therapy with patients so that expectations of success are realistic.[6,9,15]

Topiramate 100 mg/day has efficacy in migraine prevention

The goals of migraine prevention therapy are to:

- reduce the frequency, severity and duration of attacks
- improve responsiveness to treatment of acute attacks
- improve function and reduce disability.[6,9]

Compared with placebo, topiramate has reduced the frequency of monthly migraine attacks, the number of migraine days per month and use of rescue medication in trials of up to 6 months' duration.[3,4,20] In a pooled analysis, around half the patients with recurring migraine (3–12 attacks per month) achieved a 50% reduction in the number of monthly migraine attacks with topiramate, compared with only 23% using placebo ($p < 0.001$).[20] For patients who benefited from topiramate, positive effects were observed within the first month, and improvement continued over the 6-month period.[20]

The effectiveness of topiramate in refractory migraine remains unclear

The key trials of topiramate excluded patients who failed to respond to more than 2 previous migraine-prevention drugs.[3,4] While a trial of topiramate may be reasonable in patients with severe migraine not responding to adequate trials of established prevention therapies, such use is not subsidised under the current PBS listing.

Re-evaluate migraine prevention therapy at 4–6 months

Guidelines recommend an adequate trial for each migraine-prevention drug; clinical benefits may take 2–3 months to appear.[6,9] Avoid any other headache medications that may modify response (such as a different prevention drug or overuse of acute medications) during this time and monitor response using a patient headache diary. If treatment is effective (reduction in migraine frequency of 50% or more) and well tolerated, continue treatment for 4–6 months, then re-evaluate therapy and consider discontinuation. Gradually withdraw topiramate, tapering the dose over 2–3 weeks.[6,9,15]

Non-drug therapies have a role in migraine prevention

Advise patients to identify migraine trigger factors and avoid them if possible.[9,15,21] Consider non-drug therapies, especially in patients who have poor response, poor tolerance, or contraindications to drug therapies (e.g. pregnant or breastfeeding women), patients who have a preference for non-drug therapies and those with significant stress, anxiety or reduced coping strategies.[9] There is some evidence for the effectiveness of specific non-drug therapies such as relaxation training and cognitive behavioural therapy in migraine prevention.[22] Additional benefit may be seen when non-drug therapies are used in conjunction with preventive drug therapies.[9,12]

Safety issues

In clinical trials about 50% of patients who received topiramate experienced paraesthesia, which was usually transient and resolved over time or on discontinuation of the drug.[3,4] Cognitive effects may make this drug unsuitable for some patients, especially when a reasonable level of cognitive functioning is required. Adverse effects (in up to 7% of trial participants) included difficulties with memory and concentration/attention, word-finding difficulties and somnolence.[20] Unlike other drugs used for migraine prevention, topiramate is more likely to be associated with weight loss than weight gain. In clinical trials topiramate was associated with a mean weight loss of 3.2%.[23]

Topiramate use has been associated with a range of adverse events

In clinical trials almost 25% of patients using topiramate for migraine prevention withdrew because of adverse events, compared with 11% of patients using placebo ($p < 0.001$).[20]

Other adverse events reported more frequently with topiramate than with placebo include fatigue (15% with topiramate versus 12% with placebo), anorexia (14% vs 6%), nausea (13% vs 9%), diarrhoea (11% vs 4%), taste perversion (8% vs 1%), hypo-aesthesia (7% vs 1%), insomnia (7% vs 5%) and mood problems (6% vs 2%).[20]

Be aware of the following safety issues (see Topamax product information for a complete list of adverse effects, interactions and precautions).[23]

- Adequate hydration is important to reduce the risk of renal stone formation, oligohydrosis and hyperthermia (when exposed to warm temperatures).
- Topiramate can cause metabolic acidosis, especially in susceptible patients. Evaluate baseline and periodic serum sodium bicarbonate concentrations during treatment.
- Acute myopia associated with secondary angle-closure glaucoma has been reported with low-dose topiramate.[23,24] This is rare but can lead to permanent loss of eyesight if untreated. Alert patients to report symptoms which typically begin within 1 month of starting therapy.
- Topiramate at doses of 200 mg/day or higher may reduce the effectiveness of oral contraceptives. Advise women using oral contraceptives to report any changes in their bleeding patterns, such as breakthrough bleeding, while using topiramate.
- Increased incidence of mood problems and depression has been reported in patients treated with topiramate.[23] Monitor patients for signs of depression and refer for appropriate treatment when necessary.
- The safety and efficacy of topiramate in migraine prevention in children and pregnant or breastfeeding women has not been established. Topiramate is teratogenic in animals (Category B3)[25] and extensively excreted in breast milk.[23]

Report suspected adverse reactions to the Adverse Drug Reactions Advisory Committee (ADRAC) online (www.tgasime.health.gov.au) or by using the 'Blue Card' distributed with *Australian Prescriber.* For information about reporting adverse reactions, see the Therapeutic Goods Administration website (www.tga.gov.au).

Dosing issues

- The recommended dosage of topiramate for migraine prevention is 100 mg/day in divided doses of 50 mg twice daily. Some patients benefit from a lower dose (for example 50 mg/day). Start with 25 mg nightly for 1 week. When necessary, increase weekly by increments of 25 mg/day. Tolerability may be better with slower titration using longer intervals between dose adjustment.[23]
- Topiramate is mainly excreted by the kidneys, so elderly patients and those with renal dysfunction may take longer to reach stable steady-state plasma concentration at each dose titration. Clearance may be reduced in hepatic dysfunction[23] and may require dose reduction in some patients.
- Withdraw gradually over 2–3 weeks to minimise the potential for seizures. Rapid withdrawal requires appropriate monitoring.[23]
- Topiramate is available as tablets and sprinkle capsules, although sprinkle capsules are not covered by current PBS listing for migraine prevention.

Information for patients

Advise patients of the following[23]:

- paraesthesia (tingling or numbness in the fingers or toes) is a very common side effect of topiramate. This is usually transient and resolves over time. Some people experience other side effects, including fatique, anorexia, nausea, diarrhoea, altered sense of taste, altered sense of touch or sensation, insomnia, mood problems and memory loss
- report any side effects to their doctor because of the potential seriousness of some side effects of topiramate use
- tell their doctor immediately if they experience any changes in their eye sight (blurred vision or loss of vision) or if their eyes become red or sore
- check with their doctor or pharmacist before using any other prescription drugs or over-the-counter medicines while taking topiramate, including pain or sleep medications or the oral contraceptive pill
- make sure they are well hydrated (drink plenty of water), especially before and during exercise or when exposed to warm temperatures
- avoid drinking alcohol or using any other central nervous system depressants such as benzodiazepines or sleeping tablets while using topiramate
- do not drive or operate machinery if topiramate causes drowsiness or blurred vision
- advise their doctor if they are pregnant, trying to conceive or breastfeeding
- not to stop taking topiramate suddenly unless told to do so by their doctor
- keep a diary* recording the frequency, severity and duration of headaches while taking topiramate to help assess the effectiveness of therapy.

Suggest or provide the topiramate consumer medicine information (CMI) leaflet.

* The NSW Therapeutic Advisory Group migraine patient information brochure (www.clininfo.health.nsw.gov.au/nswtag/publications/guidelines/migraine_patient.pdf) includes a pain diary for monitoring migraine triggers, frequency and severity.

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence.
Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.

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