Place in therapy review

Topiramate: the evidence for its therapeutic value in the prevention of migraine

Carole Nadin

Core Medical Publishing, Knutsford, UK

Abstract

Introduction: Preventive therapy is recommended in patients with migraines frequent and/or severe enough to interfere with daily life, and/or with an inadequate response to acute therapy (26–43% of patients with migraine in a recent US survey). Preventive treatments include beta blockers, amitriptyline, and antiepileptics (sodium valproate, gabapentin), but these may have significant adverse effects and are contraindicated in some patients. Topiramate is an antiepileptic recently approved for prevention of migraine.

Aims: To assess the evidence on the therapeutic value of topiramate as preventive treatment for migraine in adults.

Evidence review: All identified outcomes were patient-oriented. Strong evidence shows that topiramate 100 or 200 mg/day is more effective than placebo in reducing mean monthly migraine frequency, and further evidence shows better effectiveness than placebo on responder rate, rescue medication use, migraine severity, and migraine duration. The 100 mg/day dose appears generally better tolerated than 200 mg/day. Evidence shows that topiramate is associated with weight loss rather than weight gain. Limited evidence suggests that topiramate can improve health-related quality of life and reduce days with disability. Uncontrolled studies indicate effectiveness in refractory migraine. Limited evidence indicates broadly similar efficacy and tolerability for topiramate 100 mg/day and propranolol 160 mg/day, though more comparative trials are required. There is insufficient economic evidence to assess the cost effectiveness of topiramate.

Place in therapy: Topiramate 100 mg/day is the dose with the best balance between efficacy and tolerability, and offers therapeutic value in patients in whom propranolol or other preventive migraine therapies are contraindicated, poorly tolerated, or ineffective.

Key words: migraine, prophylaxis, topiramate, evidence

Core evidence place in therapy summary for topiramate in migraine prevention in adults

Outcome measure	Evidence	Implications
Patient-oriented evidence		
Reduction in mean monthly migraine frequency and % of responders	Clear	Topiramate 100 or 200 mg/day is more effective than placebo
Reduction in mean monthly migraine days	Clear	Topiramate 100 or 200 mg/day is more effective than placebo
Reduction in need for acute migraine medication	Clear	Topiramate 100 or 200 mg/day is more effective than placebo
		May reduce risk of medication overuse headache
Side effects: weight loss, paresthesia	Clear	Higher incidence with topiramate than placebo
		Weight loss may be considered an advantage by some patients
Side effects: altered taste, anorexia, cognitive difficulties, fatigue, nausea	Substantial	Higher incidence with topiramate than placebo
Efficacy in refractory migraine	Moderate	Topiramate may be effective as add-on or monotherapy in some patients who have not responded to other preventive drugs
Improved HRQOL	Substantial	Topiramate improves HRQOL more than placebo
Reduction in disability	Moderate	Greater reduction in days with disability with topiramate than placebo
Reduction in migraine duration and severity	Moderate	Shorter migraine duration and lower severity with topiramate than placebo
Improved MIDAS score	Limited	Topiramate improves MIDAS score from baseline
continued overleaf…		

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Outcome measure	Evidence	Implications
Reduction in aura occurrence	Limited	Conflicting evidence on whether topiramate reduces the frequency of aura
Reduction in photophobia and phonophobia symptoms	Limited	Lower incidence with topiramate than placebo
Efficacy and tolerability compared with propranolol	Limited	Topiramate 100 mg/day similar to propranolol 160 mg/day
Patient acceptability and/or adherence compared with other preventive migraine medications	No evidence	
Economic evidence		
Cost effectiveness compared with gabapentin	Limited	Better or similar CEN for topiramate
Cost effectiveness compared with divalproex sodium and metoprolol	Limited	Poorer CEN for topiramate
Cost effectiveness compared with propranolol	No evidence	
Impact on indirect costs and use of healthcare resources	Limited	Additional costs of topiramate are partly offset by savings in indirect costs and the costs of acute treatment

CEN, cost-equivalent number (number of migraines per month required for the savings in acute medication costs to outweigh the costs of preventive migraine therapy); HRQOL, health-related quality of life; MIDAS, Migraine Disability Assessment questionnaire.

Scope, aims, and objectives

Topiramate (Topamax®) was first developed for the treatment of epilepsy, and in August 2004 was approved by the US Food and Drug Administration (FDA) for the prophylaxis of migraine in adults.

This article reviews the evidence for the clinical use of topiramate in the prevention of migraine in adults. Use in children and in the acute treatment of migraine is not considered, as these are not presently approved. Use in conditions other than migraine, such as epilepsy, is outside the scope of this review.

Methods

Literature searches were conducted on February 9–17, 2005 in the following databases, searching from the beginning of the database to date unless otherwise stated. The search strategy was "topiramate AND migraine" unless otherwise stated.

• Pub Med, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi, 1966 to date. Search strategy "(prevention OR prophylaxis OR preventive OR prophylactic) AND migraine AND (topamax OR topiramate)" limited to English-language results only, which was expanded by Automatic Term Mapping to "(('prevention and control'[Subheading] OR prevention[Text Word]) OR ('prevention and control'[Subheading] OR prophylaxis[Text Word]) OR preventive[All Fields] OR prophylactic[All Fields]) AND ('migraine'[MeSH Terms] OR migraine[Text Word]) AND (('topiramate'[Substance Name] OR topamax[Text Word]) OR ('topiramate'[Substance Name] OR topiramate[Text Word])) AND English[Lang]"

• EMBASE, http://www.datastarweb.com, 1974 to date. Search strategy: "(prevention OR prophylaxis OR preventive OR prophylactic) AND migraine AND (topamax OR topiramate)" limited to English-language results only

• Database of Abstracts of Reviews of Effectiveness (DARE), NHS Economic Evaluations Database (NHSEED), Health Technology Assessment (HTA), www.york.ac.uk/inst/crd/darehp.htm. All three databases were searched together. All fields searched

• NHS HTA, www.ncchta.org

• National Guideline Clearing House, www.guideline.gov

• National Institute for Health and Clinical Excellence (NICE), www.nice.org.uk

• Cochrane Database of Systematic Reviews (CDSR), www.cochrane.org/index0.htm. Entire site searched

• Clinical Evidence (BMJ), www.clinicalevidence.com

• www.clinicaltrials.gov

• www.clinicalstudyresults.org

Four sets of clinical guidelines were identified. After removal of duplicates, a total of 142 records, excluding guidelines, were identified from the search. Records were manually reviewed and 125 excluded for the following reasons: nonsystematic reviews (n=71), studies in children (n=15), letters, editorials, news items, comments and corrections (n=13), and articles that did not investigate the clinical use of topiramate in migraine prevention (n=26). A total of 17 remained and were included (Table 1). One additional case report was identified, bringing the total to 18.

Meeting abstracts from 2002 or later were identified by searching BIOSIS Previews, http://www.datastarweb.com, 1996 to date, using the search strategy "(prevention OR prophylaxis OR preventive OR prophylactic) AND migraine AND (topamax OR

Table 1 | Evidence base included in the review

Category	Number of records	
	Full papers	**Abstracts**
Initial search	142	21
records excluded	125	14
records included	17	7
Additional studies identified	1	n/a
Search update, new records	40	0
records excluded	38	0
records included	2	0
Publications not available on databases and supplied by manufacturer	0	9
Level 1 clinical evidence (systematic review, meta analysis)	1	0
Level 2 clinical evidence (RCT)	8	12
Level ≥3 clinical evidence	10	3
trials other than RCT	8	3
case reports	2	0
Economic evidence	1	1
Total records included	20	16

For definition of levels of evidence, see Editorial Information on inside back cover. RCT, randomized controlled trial.

Table 2 | Definition and classification of the main types of migraine (adapted from IHS 2004)

Migraine type	Characteristics
Migraine without aura	At least five attacks not attributed to another disorder and fulfilling the following criteria: • headache lasting 4–72 h if untreated or unsuccessfully treated • headache has at least two of the following features: unilateral location; pulsating quality; moderate or severe intensity; aggravation by, or causing avoidance of, routine physical activity (e.g. walking, climbing stairs) • during headache at least one of the following is also present: nausea and/or vomiting; photophobia and phonophobia
Migraine with typical aura	At least two attacks not attributed to another disorder and fulfilling the following criteria: • aura consisting of at least one of the following but without motor weakness: fully reversible visual symptoms (e.g. flickering lights, spots, or lines; loss of vision); fully reversible sensory symptoms (e.g. pins and needles, numbness); fully reversible dysphasic speech disturbance • at least two of the following: homonymous visual symptoms and/or unilateral sensory symptoms; at least one aura symptom develops gradually over at least 5 min and/or different aura symptoms occur in succession over at least 5 min; each symptom lasts between 5 and 60 min • headache fulfilling the criteria for "Migraine without aura" begins during the aura or follows the aura within 60 min

topiramate) AND LG=EN AND PT=MEETING$ AND (YEAR=2002 OR YEAR=2003 OR YEAR=2004 OR YEAR=2005)." A total of 21 abstracts were retrieved, of which 13 were excluded for the following reasons: studies in children (n=2), studies in animals (n=2), studies in subjects without migraine (n=1), and duplicate publications of data already presented in full papers (n=8). One further abstract presented very limited information and appeared to be probably an interim publication of a study published in full elsewhere, although the amount of information was insufficient to be certain, and this was also excluded. A total of seven were included in the review (Table 1).

The searches were updated on June 28, 2005. A total of 40 new records were identified, excluding duplicates. Of these, 38 were excluded because they were animal studies (n=1), studies in children (n=3), nonsystematic reviews (n=23), letters, notes or editorials (n=8), or studies that did not investigate the clinical use of topiramate in migraine prevention (n=3). The remaining two were included (see Table 1). In addition, a further nine abstracts not available on the databases searched were provided by the manufacturer, Ortho McNeil (see Table 1).

For each outcome, preference was given to higher-level evidence (level 1 and 2), with level 3 evidence also included where level 1 and/or 2 evidence was lacking or conflicting. Where outcomes from level 2 or 3 studies were included in level 1 evidence, data

on these outcomes from the original studies were not considered separately in this review.

Disease overview

Migraine is defined and classified according to criteria published by the International Headache Society (IHS 2004). Several subtypes are recognized, but the most common are migraine without aura (formerly called common migraine) and migraine with typical aura (formerly called classical migraine). The characteristics of these types are summarized in Table 2. Chronic migraine is defined as migraine occurring on at least 15 days per month for over 3 months, not attributable to medication overuse (IHS 2004). The term "transformed migraine" has been proposed to describe headaches that originally presented as episodic migraine and have changed over time into chronic daily headache (very frequent or continuous headaches) (Nappi et al. 1999).

Burden of disease

Migraine is more common in women than men, affecting 18.2% of women and 6.5% of men in a survey of over 29 000 people in the US in 1999 (Lipton et al. 2001b). The prevalence was higher in whites than in African-Americans and increased with declining household income. In both sexes, the prevalence increased from age 12 years (the youngest age group in the survey) to age 40 years and then declined in older age groups (Lipton et al. 2001b). These results mirrored those of an identical survey conducted in 1989,

indicating that migraine prevalence and distribution have remained stable over the period (Lipton et al. 2001b). Prevalence in other Western countries is similar to that in the USA (Silberstein 2004).

Migraine frequently causes disability; 53% of the 1999 US survey respondents reported that their headaches caused substantial impairment in their activities, and 31% had missed at least 1 day of work or school because of migraine in the last 3 months (Lipton et al. 2001b). Patients with chronic migraine missed significantly ($P<0.05$) more days of work, school, housework, leisure, or social activities than patients with episodic migraine, and had significantly ($P<0.001$) higher scores on the Migraine Disability Assessment (MIDAS) questionnaire (higher MIDAS score indicates greater impairment) (Bigal et al. 2003).

Surveys in the US have shown that average total healthcare costs were approximately 1.3 times higher for patients with self-reported (Edmeads & Mackell 2002) or interview-ascertained (Lafata et al. 2004) migraine than for people without migraine. Retrospective claims data analysis has shown that families in which one member has diagnosed migraine incur healthcare costs up to 70% higher than in matched families with no migraine (Stang et al. 2004). The total cost burden of migraine is substantial (Table 3). As migraine is concentrated in adults of working age and causes disability and/or impairment, the largest component of cost is indirect cost (the cost of lost productivity due to absence from work or reduced functional ability at work).

As well as the economic burden, migraine is also associated with intangible burdens to patients. In a survey of over 5000 adults in five countries, 34% of those with migraine considered that migraine interfered considerably with their daily lives (Brandes 2002). Health-related quality of life (HRQOL) is substantially impaired in patients with migraine. In a case–control study in 200 migraine patients and 200 matched controls in the UK, the migraine patients scored significantly lower than the controls in eight of nine domains on the Medical Outcomes Study Short Form 36 (SF-36), a well-established general instrument for measuring HRQOL (Lipton et al. 2003). Similar results were reported from a study in 84 migraine patients in Italy, where all domains of the SF-36 were statistically ($P<0.001$) and clinically (>5 points) worse in the migraine patients than in the general Italian population (Bussone et al. 2004).

Table 3	Cost burden of migraine			
Country	Cost of migraine per year			Reference
	Direct	**Indirect**	**Total**	
France	€1044 million	NR	NR	Pradalier et al. 2004
Spain	€344 million	€732 million	€1076 million	Badia et al. 2004
USA	$US1 billion	$US13 billion	$US14 billion	Hu et al. 1999

NR, not reported.
Costs are given in the original currency. The average exchange rate in 2004 was €1 = $US1.24 (source: www.fxtop.com)

Pathophysiology of migraine

The causes and pathophysiology of migraine are incompletely understood (Bussone 2004). Various factors may trigger migraine attacks in individual patients, including missing meals, bright lights and loud noise, changes in sleep patterns, unaccustomed strenuous exercise, estrogen levels (this may contribute to the higher prevalence of migraine in women between the ages of puberty and menopause, compared with older women and men), and dietary items such as certain alcoholic drinks and citrus fruits (BASH 2004). Overuse of medications for acute headache (ergots, triptans, and analgesics) may also cause chronic headaches (BASH 2004), and it is recommended that acute medication use should be restricted to 2–3 days per week to avoid this (Silberstein 2004).

Migraine was once thought to be a vascular disease because of the throbbing nature of the pain, with the aura caused by cerebral vasoconstriction and the headache caused by reactive vasodilation (Silberstein 2004). However, more recent data have shown that cerebral blood flow is often reduced when the headache begins (Olesen et al. 1990), and migraine is now thought to be caused by neuronal dysfunction (Bussone 2004; Silberstein 2004). The migraine aura is thought to be produced by a neurologic phenomenon called cortical spreading depression, a decrease in electrical activity that spreads across the cerebral cortex at a rate of 2–3 mm/min (Silberstein 2004). Magnetic resonance imaging studies of patients with migraine have shown that the migraine aura is accompanied by a spreading change in blood oxygenation in the visual cortex, consistent with a decrease in cortical blood flow resulting from fluctuations in neuronal activity (Hadjikhani et al. 2001). In animal models, blockade of calcium channel conduction (Richter et al. 2002) or N-methyl-D-aspartate glutamate receptors (Anderson & Andrew 2002) have been shown to inhibit cortical spreading depression. The release of potassium, nitric oxide, and other agents stimulates trigeminal sensory nerve endings on cortical blood vessels, which in turn activates the trigeminal nucleus in the brainstem. Neurons from the trigeminal nucleus release neuropeptides such as substance P and calcitonin-gene-related peptide (CGRP) in the meninges (the membranes surrounding the brain), producing meningeal vasodilation and neurogenic inflammation. The neurogenic inflammation sensitizes nerve endings, so that normal stimuli (such as blood vessel pulsations) now trigger nerve impulses, thus causing (in part) the pain of a migraine headache (Silberstein 2004).

Antimigraine drugs may interfere with these processes in a variety of ways, as reviewed by Silberstein (2004). For example, ergots and triptans act on 5-HT_{1B} and 5-HT_{1D} receptors to constrict extracerebral intracranial blood vessels, inhibit trigeminal neurons, and block transmission in the trigeminal nucleus (Silberstein 2004). The mechanism of action of topiramate in migraine is not well understood, but it has several actions that may be relevant. Topiramate inhibits sodium ion channels and may thus limit the repetitive firing ability of neurons (Taverna et al. 1999), it reduces the activity of L-type calcium channels (Zhang et al. 2000), it is a negative modulator

of glutamate transmission (Skradski & White 2000), and it enhances neurotransmission mediated by gamma-amino-butyric acid (GABA) (White et al. 2000). In animal models GABA agonists can suppress activity of neuronal pain pathways in the trigeminal nucleus (Storer et al. 2004). Topiramate is also a weak inhibitor of carbonic anhydrase, though it is not known whether this action contributes to its effects in migraine and epilepsy (Cutrer 2001).

Current therapy options

Treatment guidelines from the USA and Europe recommend broadly similar therapeutic options for migraine management (Silberstein 2000; Snow et al. 2002; BASH 2004; Géraud et al. 2004) (Table 4). Topiramate was approved by the FDA for prevention of migraine in adults in August 2004 (Anon. 2004),

and thus had not been approved when the two sets of US guidelines were published. As this review is concerned with the use of topiramate in migraine prevention, acute therapies are outside the scope of the article and are summarized only very briefly.

There is debate over the most effective treatment strategy in acute migraine. Some practitioners advocate stepped care, where patients are treated first with the safest and cheapest therapy known to have efficacy (simple oral analgesics with or without antiemetics), and if this fails to work treatment is stepped up to specific antimigraine therapy (triptans or ergots). Others suggest using a stratified care model, which categorizes patients into severity classes at the beginning of treatment and selects treatment accordingly. One study has reported that a stratified care strategy, in which patients with lower migraine severity

Table 4 | Current therapy options recommended in migraine treatment guidelines

	BASH 2004	Géraud et al. 2004	Silberstein 2000 (US Headache Consortium)[a]	Snow et al. 2002 (AAFP/ACP-ASIM)[b]
Acute treatment	Simple analgesics with or without antiemetics	NSAIDs alone or with metoclopramide	Triptans	NSAIDs
	Triptans	Triptans	Analgesics	Triptans
	Ergotamine	Ergotamine	Metoclopramide	Dihydroergotamine
			Ergotamine	
Criteria for preventive migraine treatment	Inadequate symptom control with acute therapy	Severe, frequent and/or disabling migraine	Frequent headaches that interfere with daily life	2 or more attacks per month producing 3 or more days of disability per month
	Over-frequent use of acute therapy	In patients taking 6–8 doses of acute medication per month for ≥3 months	Contraindication, failure, overuse or intolerance of acute treatments	Contraindication, failure or overuse of acute treatments
			Patient preference and cost	Uncommon types of migraine
			Uncommon types of migraine	
Preventive treatment				
First-line	Beta blockers without partial agonist activity (atenolol, metoprolol, propranolol)	Propranolol, metoprolol	Amitriptyline	Propranolol, timolol
		Oxeterone	Divalproex sodium[c]	Amitriptyline
	Amitriptyline	Amitriptyline	Propranolol, timolol	Divalproex sodium, sodium valproate
Second-line	Sodium valproate	Pizotifen	Atenolol, metoprolol, nadolol	Flunarizine
	Topiramate	Flunarizine	Calcium channel blockers (verapamil, nimodipine)	Lisuride
		Sodium valproate	NSAIDs	Pizotifen
		Gabapentin	Fluoxetine	Time-released dihydroergotamine
		Topiramate	Gabapentin	Methysergide
			Feverfew, magnesium, vitamin B_2	
Third-line	Gabapentin	Methysergide	Antidepressants	
	Methysergide		Cyproheptadine	
			Diltiazem	
			Ibuprofen	
			Topiramate	
			Phenelzine	
			Methysergide	

[a]These guidelines classified medication into Group 1 (proven high efficacy and mild–moderate adverse events), Group 2 (lower efficacy and mild–moderate adverse events), Group 3 (use based on opinion), and Group 4 (proven efficacy but frequent or severe adverse events). Group 1 is listed here as first-line, group 2 as second-line, and groups 3 and 4 as third-line.

[b]These guidelines classified medication into first-line agents and "other agents with proven efficacy but frequent or severe adverse events or limited published data on adverse events" (listed here as second-line).

[c]Divalproex sodium (also called valproate semisodium) is a complex of sodium valproate and valproic acid in a 1:1 ratio.

AAFP, American Academy of Family Physicians; ACP-ASIM, American College of Physicians–American Society of Internal Medicine; BASH, British Association for Study of Headache; NSAID, nonsteroidal antiinflammatory drug.

received nonsteroidal antiinflammatory drugs (NSAIDs) plus metoclopramide while patients with higher migraine severity received a triptan, was more effective and cost effective than stepped care (Von Seggern 2002). However, the BASH (2004) guidelines recommend a stepped care model for acute treatment, and other guidelines consider that it is not yet clear which is the most effective approach (Snow et al. 2002).

Treatment guidelines recommend broadly similar criteria for determining whether patients should be offered preventive treatment for migraine (Table 4). A questionnaire survey of 77 879 households in the USA found that 11.7% of respondents met clinical criteria for migraine, of whom 26–43% would be eligible for preventive treatment (Silberstein et al. 2005a). The US Headache Consortium guidelines (Silberstein 2000) recommended the following goals for preventive treatment of migraine:

• reduce attack frequency, severity, and duration

• improve responsiveness to treatment of acute attacks

• improve function and reduce disability.

Treatment guidelines have grouped preventive drugs into categories based on available evidence for their effectiveness and tolerability. The exact methods and definitions vary, but there is a considerable degree of agreement (see Table 4). In general, the preferred agents are amitriptyline, propranolol, and divalproex sodium (also called valproate semisodium). Table 5 presents summary information on the efficacy and tolerability of some migraine prophylactic drugs.

There is uncertainty over the optimal duration of migraine preventive therapy, although treatment guidelines generally recommend that an attempt should be made to taper or discontinue preventive treatment (Evans 2004). The BASH 2004 guidelines recommend that an attempt should be made to withdraw preventive therapy after 4–6 months of effectiveness to test continued need, and that uninterrupted treatment for very long periods is rarely appropriate (BASH 2004).

Treatment of migraine in special patient groups

Women with menstrual migraine can generally be managed in the same way as patients with nonmenstrual migraine (Landy 2004). Migraine improves during pregnancy in 50–80% of patients, possibly due to the increased level of estrogen, but attacks continue in some patients (Gladstone et al. 2004). First-line acute therapy in pregnant women is acetaminophen (paracetamol) and antiemetics if required, and other analgesics may be used with caution (Gladstone et al. 2004). Triptans are categorized as FDA category C (no risk in humans has been proved, but cannot be ruled out), while ergots are contraindicated (Landy 2004). Preventive therapy should be avoided in pregnant women, but some category C medications (propranolol, amitriptyline, verapamil, topiramate) may be used when the benefit outweighs the risk (Gladstone et al. 2004).

Treatment in elderly patients may be challenging due to the presence of concomitant medical conditions, polypharmacy, and age-related changes in drug distribution, elimination, and metabolism that increase the risk of adverse effects (Gladstone et al. 2004). First-line acute therapy options include acetaminophen and NSAIDs, but these should be used with caution because of the risks of gastrointestinal bleeding and renal or hepatic insufficiency. Triptans are contraindicated in patients with a history of, or risk factors for, cardiovascular, cerebrovascular, and peripheral vascular disease (Gladstone et al. 2004). Preventive options are limited because of contraindications (see Table 5) and side effects. Cognitive and sedative side effects may be particularly problematic in elderly patients and may occur with propranolol, tricyclic antidepressants (e.g. amitriptyline), valproic acid, gabapentin, and topiramate (Gladstone et al. 2004).

Unmet needs

Despite the availability of treatment guidelines, current treatment of migraine is not optimal. Migraine is underdiagnosed, as reported by a survey in 1999 of over 3000 patients in the US who met IHS criteria for migraine, only 48% of whom had received a physician diagnosis of migraine (Lipton et al. 2001a). This had improved since an identical survey carried out 10 years earlier, when the proportion was only 38%, but indicates that half of patients with migraine are still not diagnosed. One reason for the low diagnosis rate may be that many patients with migraine do not consult a doctor. In a survey of over 5000 adults in five countries, consultation rates for patients with headache varied from 41% in the USA to 63% in France (Brandes 2002).

Satisfaction with migraine treatment is poor. Among 516 patients with clinically diagnosed migraine in five countries, only 27% considered that their current medication was consistently effective, and only 36% were "very satisfied" with their therapy (Brandes 2002). In a survey of 22 patients with migraine requesting advice on treatment from a community pharmacy in Chicago, 46% of patients were dissatisfied with their current migraine therapy, and 91% wished they could prevent their headaches (Wenzel et al. 2004).

Current preventive migraine therapies have significant disadvantages. Only about half to two-thirds of patients respond to treatment (see Table 5). Some patients may fail to respond to numerous preventive treatments; one trial of 69 patients with refractory migraine reported that the median number of previously failed therapies was nine (Von Seggern et al. 2002). There is little information on the relative efficacy of migraine preventive therapies. Many of the established drugs in migraine prophylaxis have been in use for many years (e.g. propranolol, amitriptyline), and comparative trials conducted to modern methodologic standards are few. A recent systematic review of propranolol in migraine prevention found that "the methodological quality of the majority of trials was unsatisfactory" (Linde & Rossnagel 2004). This review concluded that propranolol was more effective than placebo and as effective as calcium channel blockers, other beta blockers and a variety of other drugs including amitriptyline, methysergide, and divalproex sodium, although the authors

Table 5	Current migraine preventive drugs (adapted from Chronicle & Mulleners 2004; Silberstein 2000, 2004)			
Drug	**Effectiveness**	**Adverse effects**	**Contraindications**	**Reference**
Divalproex sodium/sodium valproate[a]	Divalproex sodium responders to treatment[b] 148/352 (42%) Sodium valproate responders to treatment[b] 17/34 (50%) Clinical impression of effect[c] +++	Occasional to frequent	Liver disease, bleeding disorders	Chronicle & Mulleners 2004; Silberstein 2000, 2004
Gabapentin	Responders to treatment[b] 26/56 (46%) Clinical impression of effect[c] ++	Occasional to frequent	Liver disease, bleeding disorders	Chronicle & Mulleners 2004; Silberstein 2000, 2004
Carbamazepine	Responders to treatment[b] 26/45 (58%) Clinical impression of effect[c] 0	Occasional to frequent		Chronicle & Mulleners 2004; Silberstein 2000
Topiramate	Responders to treatment[b] 132/264 (50%) Clinical impression of effect[c] ++	Occasional to frequent	Kidney stones	Chronicle & Mulleners 2004; Silberstein 2000, 2004
Propranolol	Responders to treatment[d] 77/114 (68%) Clinical impression of effect[c] +++	Infrequent to occasional Dropout rate due to AEs[e] 9/193 (4.7%)	Asthma, depression, congestive heart failure, Raynaud's disease, diabetes	Linde & Rossnagel 2004; Silberstein 2000, 2004
Amitriptyline	Clinical impression of effect[c] +++	Frequent	Mania, urinary retention, heart block	Silberstein 2000, 2004
Naproxen/ naproxen sodium	Clinical impression of effect[c] +	Infrequent	Ulcer disease, gastritis	Silberstein 2000, 2004

[a]Divalproex sodium (also called valproate semisodium) is a complex of sodium valproate and valproic acid in a 1:1 ratio.

[b]Defined as patients with a 50% or greater reduction in migraine frequency compared with baseline. Number of events (patients who responded) and total number of patients presented in original source (Chronicle & Mulleners 2004).

[c]Definitions as follows: 0, most people get no improvement; +, few people get clinically significant improvement; ++, some people get clinically significant improvement; +++, most people get clinically significant improvement.

[d]Definition of response varied among the pooled trials. Data given here are for propranolol 160 mg/day. Number of events (patients who responded) and total number of patients presented in original source (Linde & Rossnagel 2004).

[e]Data given here are for propranolol 160 mg/day. Number of events (patients who dropped out due to AEs) and total number of patients presented in original source (Linde & Rossnagel 2004).

AE, adverse event.

commented that "sample size was insufficient in most trials to establish equivalence" (Linde & Rossnagel 2004). Treatment guidelines typically categorize preventive migraine drugs according to the amount of evidence supporting their efficacy and the frequency and severity of side effects (see Table 4), rather than on the basis of relative efficacy. This suggests that efficacy is considered to be broadly similar for current preventive migraine drugs, and that treatment choice among those agents with evidence of efficacy may be guided by adverse events, contraindications, and/or patient preference. Uptake of preventive migraine drugs is low. For example, in Sweden less than 10% of patients with migraine who consult a physician use preventive therapy, although more than 50% would be eligible (C. Dahlöf, personal communication). Similarly, in the US a survey of 77 789 households identified 19 018 individuals with migraine, and found that of those who would be eligible for preventive therapy only 20% were receiving it (Lipton et al. 2005). There is a need for improved therapies with better efficacy and, if possible, improved overall tolerability.

Some preventive agents are contraindicated in patients with certain comorbid conditions, limiting potential treatment options in these individuals (see Table 5; Silberstein 2004). Patients may also discontinue therapy because of side effects

they find distressing or intolerable. Weight gain has been reported as a particular issue in patient satisfaction with headache drugs (Young & Rozen 2004), and a cause of discontinuation of therapy with amitriptyline (Von Seggern 2002) and valproate (Young & Rozen 2004). This may reflect the preponderance of migraine in adult women, in whom weight gain may be an especially undesirable effect (Von Seggern 2002). Valproate is also associated with gastrointestinal side effects (e.g. nausea, vomiting, dyspepsia), asthenia, drowsiness, tremor, and hair loss, although it has little effect on cognitive function (Krymchantowski et al. 2002). Gabapentin is associated with asthenia, dizziness, and somnolence, but has advantages over valproate in that it is free from some disturbing adverse events such as weight gain, tremor, and hair loss (Krymchantowski et al. 2002).

The major areas where a new treatment could offer valuable improvements over current therapies are:

- improved effectiveness (particularly in patients with refractory migraine that does not respond to current therapies)

- reduced incidence of side effects that patients find distressing and that may provoke treatment discontinuation

Table 6 | Effects of topiramate on migraine frequency and number of patients responding to treatment (defined as a reduction of ≥50% in mean monthly migraine frequency)

Level of evidence	Design	Treatment and target dose [median dose]	Outcome Migraine frequency (mean no. of attacks/month)	% responders	Reference
1	Systematic review and meta analysis of 3 RCTs	Placebo T 50 mg/day T 100 mg/day T 200 mg/day	Lower with T 100 mg or 200 mg vs placebo (P<0.0001) Lower with T 100 mg or 200 mg vs T 50 mg (P<0.05) NSD T 50 mg vs placebo NSD T 100 mg vs 200 mg	More responders with T 50 mg, 100 mg or 200 mg vs placebo (P<0.001) More responders with T 100 mg or 200 mg vs T 50 mg (P<0.01) NSD T 100 mg vs 200 mg	Chronicle & Mulleners 2004[a]
2	Double-blind multicenter RCT, 12 weeks maintenance	Placebo (n=73) T 200 mg/day [135 mg/day[b]] (n=138)	NSD T vs placebo in ITT analysis In subgroup of patients with migraine with aura (approx. 1/3 of total), decrease from baseline with T (P=0.018)	NR	Freitag 2003
2	Pooled analysis of 2 double-blind single-center RCTs, 8–12 weeks maintenance	Placebo (n=36) T 200 mg/day (n=34)	Lower with T vs placebo (P=0.001)	More responders with T vs placebo (P=0.008)	Edwards et al. 2003
2	Multicenter RCT, 7 weeks double-blind followed by 11 weeks open-label	Placebo (n=115) T 50 mg/day (n=117) T 100 mg/day (n=125) T 200 mg/day (n=112)[c]	Greater decrease with T 100 mg or 200 mg vs placebo (P<0.001) NSD T 50 mg vs placebo	23% placebo 35% T 50 mg 54% T 100 mg 52% T 200 mg[d]	Silberstein 2003
2	Double-blind single-center RCT, 12 weeks maintenance	Placebo (n=37) T 100 mg/day (n=35)[e]	Greater decrease with T vs placebo (P<0.001)	More responders with T vs placebo (P<0.01)	Mei et al. 2004
2	Double-blind RCT, 20 weeks, followed by open-label extension, 56 weeks, n=29 total	T for 76 weeks of treatment Placebo for 20 weeks then T for 56 weeks Mean T dose during open-label phase, 127 mg/day	Significant reduction in both groups (P<0.01)	NR	Hart et al. 2002
2	Double-blind multicenter RCT, 18 weeks maintenance	Placebo (n=143) T 100 mg/day [87.9 mg/day] (n=139) T 200 mg/day [124.2 mg/day] (n=143) Propranolol 160 [129.6 mg/day] mg/day (n=143)	Greater decrease with T 100 mg vs placebo (P=0.011) NSD T 200 mg vs placebo Similar decrease for T 100 mg and propranolol[f]	More responders with T 100 mg or 200 mg vs placebo (P<0.05) Similar for T 100 mg or 200 mg and propranolol[f]	Diener et al. 2004

[a]The three trials included were Brandes et al. 2004, Silberstein et al. 2004, and Storey et al. 2001.
[b]Mean dose.
[c]Patient numbers unclear in the original as the numbers given in the figures (given here) do not match the numbers given in the text.
[d]No between-group comparison reported.
[e]Patients who completed the trial.
[f]No between-group P value reported, but 95% confidence intervals for the difference between topiramate and propranolol included zero, indicating comparable results.
ITT, intention-to-treat; NR, not reported; NSD, not statistically significantly different; RCT, randomized controlled trial; T, topiramate.

- fewer contraindications, allowing use in patients with common comorbid conditions (e.g. asthma, diabetes) in whom one or more of the current first-line preventive treatments are contraindicated.

Important outcome measures include the number of headache episodes per month, the number of headache days per month, HRQOL, and overall tolerability.

Clinical evidence with topiramate

As pain and aura are subjective symptoms, migraine outcomes rely on the patient's report and/or grading of symptoms. The most commonly measured outcomes in the published evidence are concerned specifically with migraine symptoms, e.g. recording the presence or absence of migraine in a diary (from which the frequency of migraine attacks in a given period may be calculated), recording the presence of aura symptoms, recording the duration of each migraine attack, or categorizing the severity of the migraine attack on a scale such as mild, moderate, or severe. Others, less commonly measured, estimate the broader effect of migraine on the patient's life by recording disability or HRQOL. Even the outcomes concerned specifically with migraine have an obvious benefit to the patient; for example, it is clearly better to have fewer migraine attacks in a month, or for the attacks to be shorter or less painful when they occur. Thus, all the outcomes covered by the evidence reviewed in this section can be considered patient-oriented outcomes.

Outcomes where individual symptoms are not specified, such as reduction in migraine frequency, responder rate, migraine duration, and migraine severity, refer to a migraine attack as classified by the patient's own judgment.

Most trials titrated the dose of study drug(s) over a period of several weeks aiming to reach a specified target dose, then continued at the dose reached for a maintenance period. The dose groups are normally referred to in the study publications by the target dosage, and the same convention is followed in this review. Where the original publication also gave the median or mean dose actually reached, this is noted in the data tables (Tables 6–10).

Reduction in migraine frequency

The reduction in mean number of migraine attacks per month was the primary efficacy endpoint in most trials, and therefore the measure on which they were powered. Strong evidence from a systematic review and meta analysis and three further randomized controlled trials (RCTs) indicated that topiramate was more effective than placebo in reducing mean monthly migraine frequency at target doses of either 100 mg/day or 200 mg/day (Table 6). One study failed to find a difference between topiramate 200 mg/day and placebo in the main intention-to-treat (ITT) analysis (Freitag 2003), but this study is difficult to evaluate as it was presented only in the form of conference proceedings and very little detail was given. Another study (Diener et al. 2004) failed to find a statistically significant difference between topiramate

200 mg/day and placebo, but as the same study found that topiramate 100 mg/day was significantly more effective than placebo this may represent an aberrant result. The study authors consider that it was probably due to a high early dropout rate (mainly due to adverse events) in the topiramate 200 mg/day group (Diener et al. 2004).

In the trials which included a 50-mg target dose, it was found to be not statistically significantly different from placebo in reducing mean monthly migraine frequency. The systematic review and meta analysis compared the topiramate doses and found that both 100 mg/day and 200 mg/day were significantly more effective than 50 mg/day, but there was no significant difference between 100 mg/day and 200 mg/day (see Table 6). Taken together, the evidence indicates that topiramate was equally effective at either 100 mg/day or 200 mg/day, but not at 50 mg/day.

Only one published trial included an active control, propranolol 160 mg/day (Diener et al. 2004). This trial was primarily designed and powered to compare topiramate with placebo rather than topiramate with propranolol, and no P values were presented for comparisons between topiramate and propranolol. However, 95% confidence intervals (CI) calculated for the difference in mean monthly migraine frequency between topiramate 100 mg/day and propranolol 160 mg/day indicated similar efficacy. More comparative trials are required to further assess the relative efficacy of the two agents.

Evidence from open-label extension periods following two double-blind clinical trials indicates that topiramate remained effective on this outcome measure in long-term treatment (up to 8 months) (Rapoport et al. 2005). After the end of the double-blind phase, a total of 567 patients entered the extension and received open-label topiramate, titrated according to clinical need up to a maximum of 1600 mg/day (mean dose 124.7 mg/day and 150.3 mg/day for patients who had received placebo or topiramate, respectively). After 8 months' open-label treatment, the mean monthly migraine frequency was 2.2 among patients who had previously received topiramate (compared with 3.4 at the end of the double-blind phase) and 3 among patients who had previously received placebo (compared with 4.9 at the end of the double-blind phase) (Rapoport et al. 2005).

Onset of action

In some trials, migraine frequency was recorded at several time points during the study period, allowing a time course to be plotted. The onset of drug action was considered to be the first time point at which there was a statistically significant difference from placebo.

Two large multicenter RCTs (Brandes et al. 2004; Silberstein et al. 2004) both reported that topiramate 100 mg/day and 200 mg/day reduced mean monthly migraine frequency significantly ($P<0.05$) more than placebo at the first time point, which was 1 month into the titration period, and maintained a statistically significant difference throughout the study. This was supported by results from a single-center RCT, which reported a statistically significant

Table 7	Effects of topiramate on number of monthly migraine days, rescue medication use, migraine severity, and migraine duration					

Level of evidence	Design	Treatment and target dose [median dose]	Outcome				Reference
			Migraine days/month	Rescue medication days	Migraine duration	Migraine severity	
2	Double-blind, multicenter RCT, 18 weeks maintenance	Placebo (n=114) T 50 mg/day [46.5 mg/day] (n=117) T 100 mg/day [85.6 mg/day] (n=120) T 200 mg/day [150.2 mg/day] (n=117)	Greater decrease from baseline with T 100 mg or 200 mg vs placebo ($P<0.01$) NSD T 50 mg vs placebo	Greater decrease from baseline with T 100 mg or 200 mg vs placebo ($P<0.05$) NSD T 50 mg vs placebo	Greater decrease from baseline with T 200 mg vs placebo ($P=0.007$) NSD T 50 mg or 100 mg vs placebo	Lower with T 100 mg vs placebo ($P=0.04$) NSD T 50 mg or 200 mg vs placebo	Brandes et al. 2004
2	Double-blind, multicenter RCT, 18 weeks maintenance	Placebo (n=115) T 50 mg/day [44.7 mg/day[a]] (n=117) T 100 mg/day [78.3 mg/day[a]] (n=125) T 200 mg/day [116.2 mg/day[a]] (n=112)	Greater decrease from baseline with T 100 mg or 200 mg vs placebo ($P<0.001$) NSD T 50 mg vs placebo	Greater decrease from baseline with T 100 mg or 200 mg vs placebo ($P<0.01$) NSD T 50 mg vs placebo	NR	NR	Silberstein et al. 2004
2	Double-blind multicenter RCT, 12 weeks maintenance	Placebo (n=73) T 200 mg/day [135 mg/day[a]] (n=138)	Decrease from baseline with T ($P=0.016$)[b]	NSD T vs placebo	Decrease 30% with T Increase 30% with placebo[b]	Decrease 7% with T Decrease 0.5% with placebo[b]	Freitag 2003
2	Multicenter RCT, 7 weeks double-blind followed by 11 weeks open-label	Placebo (n=115) T 50 mg/day (n=117) T 100 mg/day (n=125) T 200 mg/day (n=112)[c]	Greater decrease from baseline for T 100 mg or 200 mg vs placebo ($P<0.01$)	NR	NR	NR	Silberstein 2003
2	Double-blind single-center RCT, 12 weeks maintenance	Placebo (n=37) T 100 mg/day (n=35)[d]	NR	Greater decrease from baseline with T vs placebo ($P<0.001$)	NR	NR	Mei et al. 2004
2	Double-blind, single-center RCT, 8 weeks maintenance	Placebo (n=21) T 200 mg/day [125 mg/day[a]] (n=19)	NR	NR	NR	NSD T vs placebo	Storey et al. 2001
2	Double-blind multicenter RCT, 18 weeks maintenance	Placebo (n=143) T 100 mg/day [87.9 mg/day] (n=139) T 200 mg/day [124.2 mg/day] (n=143) Propranolol 160 [129.6 mg/day] mg/day (n=143)	Greater decrease with T 100 mg vs placebo ($P=0.026$) NSD T 200 mg vs placebo Similar decrease for T 100 mg or 200 mg and propranolol[e]	Greater decrease with T 100 mg vs placebo ($P=0.029$) NSD T 200 mg vs placebo Similar decrease for T 100 mg and propranolol[e]	Decrease from baseline 0.8 days for T 100 mg, 0.6 days for T 200 mg, 0.4 days for placebo[b] NR for propranolol	NR	Diener et al. 2004

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Level of evidence	Design	Treatment and target dose [median dose]	Outcome				Reference
			Migraine days/month	Rescue medication days	Migraine duration	Migraine severity	
3	Open survey, mean treatment duration 7 months	T up to 50 mg/day (n=102)	NR	NR	NR	Reduction in % of patients reporting intense headaches (from 88% to 18%)	Kowacs et al. 2003
3	Open longitudinal study, 6 months	T 100 mg/day (n=12) Results after 6 months T treatment compared vs baseline	NR	NR	62% patients reported shorter headache duration with T	Lower during T treatment (P<0.001)	Lampl et al. 2004
3	Retrospective case series, mean treatment duration 149 days	T mean dose 208 mg/day (n=74) Topiramate treatment period compared with previous treatment	Lower during T treatment (P<0.0001)	74% patients reported using less rescue medication during T treatment	45–58% patients reported shorter headache duration during T treatment	Lower during T treatment (P<0.001)	Young et al. 2002

...table continued

[a]Mean dose.

[b]No between-group statistical comparison presented.

[c]Patient numbers unclear in the original as the numbers given in the figures (given here) do not match the numbers given in the text.

[d]Patients who completed the trial.

[e]No between-group P value reported, but 95% confidence intervals for the difference between topiramate and propranolol included zero, indicating comparable results.

NR, not reported; NSD, not statistically significantly different; RCT, randomized controlled trial; T, topiramate.

difference in mean monthly migraine frequency between topiramate 100 mg/day and placebo at the end of the 4-week titration period (Mei et al. 2004).

A further large multicenter RCT with propranolol as an active control found that both topiramate 100 mg/day and propranolol 160 mg/day reduced mean monthly migraine frequency significantly more than placebo (P<0.05) at the first time point (1 month into the titration period) (Diener et al. 2004). Thus, the available evidence shows that topiramate has an onset of action of approximately 1 month, similar to that of propranolol.

Responder rate

The evidence also demonstrates a similar pattern for responder rate (the percentage of patients who experienced at least a 50% reduction in the mean frequency of migraine attacks). Topiramate 100 mg and 200 mg appear to be equally effective and more effective than either placebo or topiramate 50 mg, although on this outcome measure topiramate 50 mg was also more effective than placebo (see Table 6).

As with the data on reduction in migraine frequency, there were no comparative data on responder rates between different agents. One trial that included propranolol as an active control reported similar effects for propranolol 160 mg/day and topiramate 100 or 200 mg/day (Diener et al. 2004).

Although the 50% threshold is the most widely used definition of response, there is limited evidence (two level 3 studies) of topiramate's effects on response rate defined by more stringent criteria. In a telephone survey of 102 patients with migraine or transformed migraine who were using low-dose topiramate (up to 50 mg/day), 66% reported an improvement of at least 75% in headache frequency, and 11 patients became headache-free (Kowacs et al. 2003). An observational study in Spain in 115 patients with refractory migraine (no response to, or intolerant of, beta blockers, amitriptyline, flunarizine, and/or valproate) reported that 34 patients (29%) experienced a reduction in headache frequency of >75% after 3 months of treatment with topiramate (median dose 100 mg/day) (Pascual et al. 2003).

Number of migraine days/month

There is strong evidence from three RCTs that topiramate 100 mg/day and 200 mg/day reduced the mean number of migraine days per month statistically significantly more than placebo, although topiramate 50 mg/day was not significantly better than placebo (Table 7). One trial reported that topiramate 100 mg/day was superior to placebo but topiramate 200 mg was not, but this paradoxical result may reflect the high dropout rate in the topiramate 200 mg/day group in that study (Diener et al. 2004).

The effect of topiramate 100 mg or 200 mg on this outcome measure was similar to that of propranolol in the one study with an active control, although the study was not designed to compare the two agents (see Table 7; Diener et al. 2004).

Rescue medication use

Evidence from two large RCTs showed that topiramate 100 mg/day and 200 mg/day were both effective in reducing the use of rescue medication (medication used to treat acute migraine attacks) compared with placebo, while topiramate 50 mg/day was not (see Table 7). One study (Freitag 2003) reported no statistically significant difference between topiramate 200 mg/day and placebo, but this study reported results only in a small subgroup of patients who had migraine with aura and was published only as a conference proceedings paper with limited detail. The study of Diener et al. (2004) again found a paradoxical result that topiramate 100 mg/day was statistically significantly more effective than placebo but that topiramate 200 mg/day was not, which may have been due to a high rate of early withdrawals due to adverse events.

In the one study that used propranolol as an active control, the effects of topiramate 100 mg/day were reported to be similar to propranolol (see Table 7).

Migraine duration

There is evidence from one large RCT that topiramate 200 mg/day significantly reduced mean migraine duration compared with placebo, while topiramate 100 mg/day and 50 mg/day did not (see Table 7). Two other RCTs reported that headache duration was shorter in patients receiving topiramate than placebo, or that the mean duration decreased with topiramate but not with placebo, but neither presented a test of statistical significance (see Table 7). In addition, two single-group open-label studies found that around half the patients reported a reduction in headache duration during topiramate treatment compared with the period before topiramate treatment (see Table 7). This evidence suggests that topiramate can reduce mean migraine duration, particularly at higher doses.

Migraine severity

One large RCT reported that topiramate 100 mg/day was associated with a significant reduction in mean migraine severity score compared with placebo, but no statistically significant difference was found for topiramate 200 mg/day or 50 mg/day (see Table 7). A further RCT reported a greater percentage decrease in severity score for topiramate compared with placebo, but this was in a small subgroup of patients who had migraine with aura and no statistical test was reported (Freitag 2003). A small RCT found no statistically significant difference between topiramate and placebo, but this study involved only 40 patients (Storey et al. 2001). All three level 3 studies reported a decrease in mean migraine severity or in the percentage of patients with severe headaches after patients began topiramate treatment (see Table 7). Taken together, the evidence indicates that topiramate can improve migraine severity, but the dose–response relationship is not clear.

Number of days with disability

Topiramate 100 mg/day was associated with a statistically significant ($P<0.01$) reduction from baseline in the mean number of days with disability due to migraine after 8, 12, and 16 weeks of treatment in the one study reporting data on this outcome measure (Mei et al. 2004; level 2 evidence). In the month before the trial, the mean number of days with disability was 6.8 in the topiramate group, and after 16 weeks of treatment this had declined by around 4.2 days. The placebo group had a similar baseline number of days with disability (6.95 days/month), and after 16 weeks this had declined by approximately 1 day. No statistical comparison between the topiramate and placebo groups was reported (Mei et al. 2004).

MIDAS score

An open-label study (level 3 evidence) in 26 patients with migraine taking either topiramate 100 mg/day (n=23) or 200 mg/day (n=2) for prophylaxis with a 12-week maintenance phase reported that mean MIDAS score improved from 3.47 before treatment to 1.6 at the end of the treatment period (no statistical comparison reported) (Dolezil et al. 2003).

A retrospective chart study (level 3 evidence) reported data on MIDAS scores in 96 patients with transformed migraine treated with topiramate up to 200 mg/day as adjunctive therapy (Mathew et al. 2002). The mean MIDAS score was 90.2 before treatment and improved significantly to 24.9 after treatment ($P<0.0001$) (Mathew et al. 2002).

Frequency of aura

Topiramate did not statistically significantly reduce either the frequency or duration of migraine aura in an open-label study (level 3 evidence) of 12 patients with migraine with aura treated with topiramate 100 mg/day for 6 months (Lampl et al. 2004). A conference proceedings paper on a study of topiramate in 211 patients with migraine, of whom "almost one-third" had migraine with aura, commented that "patients with aura showed a marked reduction in the incidence of aura from baseline" (Freitag 2003), but no further details were provided. A post-hoc pooled analysis of patients with migraine with aura enrolled in three double-blind clinical trials reported that topiramate (target dose 100 mg/day) reduced the mean monthly frequency of aura significantly more than placebo ($P=0.020$) (Silberstein et al. 2005b).

Frequency of photophobia and phonophobia

A report of conference proceedings describing a subgroup of patients with migraine with aura enrolled in a double-blind placebo-controlled trial ("almost one-third" of 211 patients) (Freitag 2003) reported that topiramate treatment was associated with a significantly greater reduction in the occurrence of photophobia compared with placebo (41% reduction vs 15% reduction, $P=0.02$). Topiramate also reduced phonophobia symptoms by 40%, but the difference from placebo was not statistically significant (Freitag 2003).

Patient global evaluation

A retrospective chart study (level 3 evidence) reported data on 96 patients with transformed migraine taking topiramate up to 200 mg/day as adjunctive therapy and 70 patients with episodic

migraine taking topiramate as monotherapy (Mathew et al. 2002). Patients were asked to evaluate the overall effectiveness of their treatment at clinic visits. Among the patients with transformed migraine, 27% rated topiramate as having produced a marked improvement and a further 27% as moderate improvement. Among the patients with episodic migraine, the corresponding values were 61% and 17% (Mathew et al. 2002).

Health-related quality of life

A double-blind, placebo-controlled clinical trial (Brandes et al. 2004) measured HRQOL and these results were presented separately in abstract form (Diamond et al. 2003). HRQOL was measured with a widely used generic measure, the SF-36, and a disease-specific measure, the Migraine-Specific Quality-of-Life questionnaire (MSQ). Topiramate 50 mg, 100 mg, or 200 mg improved the MSQ Role-Restrictive and Role-Preventive subscales significantly more than placebo ($P \leq 0.019$). Topiramate 100 mg or 200 mg also improved the MSQ Emotional Function subscale ($P < 0.001$) and the SF-36 Role-Physical subscale ($P \leq 0.022$) significantly more than placebo (Diamond et al. 2003). A similar analysis of a second double-blind placebo-controlled trial (Silberstein et al. 2004) reported that topiramate 100 mg/day significantly improved HRQOL, though no quantitative data were presented in the abstract (Dahlöf et al. 2003).

Further evidence comes from pooled analyses of all three large double-blind topiramate studies (Brandes et al. 2004; Diener et al. 2004; Silberstein et al. 2004). In the intent-to-treat population, topiramate 100 mg (n=372) improved all three of the MSQ subscale scores significantly ($P < 0.001$) more than placebo (n=362) (Dahlöf et al. 2005). Similar results were reported in another analysis with slightly fewer patients included (topiramate 100 mg, n=358; placebo, n=347) (Diamond et al. 2005a).

Another pooled analysis of data from the same three studies, also in the intent-to-treat population but with 384 patients in the topiramate 100 mg group and 372 in the placebo group, investigated the effect on SF-36 score. This analysis found that topiramate 100 mg improved the SF-36 Physical Component Score significantly more than placebo ($P < 0.001$) (Diamond et al. 2005b). Subgroup analysis showed that patients who responded to treatment with topiramate 100 mg (defined as a reduction of at least 50% in mean monthly migraine frequency at end of treatment compared with baseline) had significantly greater improvements on all three MSQ subscale scores ($P < 0.001$) and on the SF-36 Physical Component Score ($P < 0.001$) and the SF-36 Mental Component Score ($P = 0.026$) compared with patients who did not respond to treatment (Diamond et al. 2005c).

Tolerability

Evidence on the reported incidence of adverse events is presented in Table 8. Paresthesia appears clearly linked to topiramate use; the systematic review reported number-needed-to-harm (NNH)[1] values of 2.3 and 2.4 for the topiramate 200 mg/day and 100 mg/day doses, respectively, and the incidence in the topiramate groups in the other trials ranged up to 65%, compared with 6–22% in the placebo groups and 12% for propranolol in the one trial using this drug. As with the other adverse events, statistical tests of the difference in incidence between groups were not presented. There appeared to be little difference in incidence between topiramate 100 mg and 200 mg in trials containing both doses. Altered taste also seems clearly linked to topiramate, although fewer trials reported data. The NNH values were 6.7–11.8, and the incidence was noticeably higher than for placebo or propranolol where comparative data were presented.

Cognitive problems and anorexia appeared to be more common at the 200 mg/day dose than at the 100 mg/day dose, though both doses appeared to show a higher incidence than placebo or propranolol. Anorexia is likely to be linked to topiramate's effects on weight loss (see separate section below). Fatigue appeared to occur somewhat more commonly with topiramate than placebo, perhaps especially at the 200 mg dose, and also occurred at a similar rate with propranolol. Few trials reported data on nausea, although the limited evidence suggests that its incidence was higher at the 200 mg dose than the 100 mg dose, both were higher than placebo, and the 100 mg dose was similar to propranolol (see Table 8).

Withdrawal rates due to adverse events also appeared to show a dose-related pattern, with withdrawal rates for 100 mg and 200 mg topiramate higher than for placebo, 200 mg higher than 100 mg, and 100 mg similar to propranolol (see Table 8). A pooled analysis of data from patients in four double-blind placebo-controlled trials (topiramate 100 mg, n=386; placebo, n=445) reported that the most common topiramate-associated adverse events of paresthesia, fatigue, and anorexia all occurred more frequently during the titration period than during the maintenance period (Freitag et al. 2005).

In summary, the evidence indicates that paresthesia, altered taste, anorexia, and cognitive problems may be associated with topiramate. The 100 mg/day dose appears better tolerated than the 200 mg/day dose overall. The authors of the trial using propranolol as an active control concluded that the tolerability profile of topiramate 100 mg/day was comparable to that of propranolol 160 mg/day (Diener et al. 2004), although as the trial was not powered to compare topiramate and propranolol more evidence is needed to confirm this.

A case of psychosis, manifested as auditory hallucinations, after 2 days of treatment with topiramate 25 mg twice daily for migraine prophylaxis has been reported in a 28-year-old woman with a history of bipolar-type schizoaffective disorder and migraine without aura, with no history of seizures (Matthews & Miller 2001). Two days after discontinuing topiramate, the

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[1]The reciprocal of the absolute difference in risk between the active treatment group and the placebo group. The smaller the NNH, the higher the risk of the adverse event in the active treatment group relative to the placebo group.

Table 8 | Adverse events reported with topiramate

Level of evidence	Design	Treatment and target dose [median dose]	Outcome							Reference
			Paresthesia	Anorexia	Fatigue	Nausea	Altered taste	Cognitive difficulty[a]	Withdrawals due to AEs	
1	Systematic review and meta analysis of 3 RCTs	Placebo T 50 mg/day T 100 mg/day T 200 mg/day	NNH: T 50 mg: 3.4 T 100 mg: 2.4 T 200 mg: 2.3	NNH: T 50 mg: 30.5 T 100 mg: 14.4 T 200 mg: 11.3	NNH: T 50 mg: 22.3 T 100 mg: 32.9 T 200 mg: 12.1	NNH: T 50 mg: undefined T 100 mg: 29 T 200 mg: 19.2	NNH: T 50 mg: 6.9 T 100 mg: 11.8 T 200 mg: 6.7	NNH: T 50 mg: 19.7 T 100 mg: 14.1 T 200 mg: 7.7	T 50 mg: 17% T 100 mg: 19–26% T 200 mg: 11–32%	Chronicle & Mulleners 2004[b]
2	Double-blind multicenter RCT, 12 weeks maintenance	Placebo (n=73) T 200 mg/day [135 mg/day[c]] (n=138)[d]	T: 43% Placebo: NR	NR	T: 24% Placebo: NR	NR	NR	NR	4 patients (total number of patients NR)	Freitag 2003
2	Pooled analysis of 2 double-blind single center RCTs, 8–12 weeks maintenance	Placebo (n=36) T 200 mg/day (n=34)	T: 65% Placebo: 22%	T: 12% Placebo: 6%	NR	NR	T: 32% Placebo: 3%	T: 18% Placebo: 6%	T: 6/34 Placebo: 0/36	Edwards et al. 2003
2	Multicenter RCT, 7 weeks double-blind followed by 11 weeks open-label	Placebo (n=115) T 50 mg/day (n=117) T 100 mg/day (n=125) T 200 mg/day (n=112)[e]	NR 5% of patients with paresthesia stopped treatment as a result	NR	NR	NR	NR	Withdrawal: T 100: 2% T 200: 2%	NR	Silberstein 2003
2	Double-blind single-center RCT, 12 weeks maintenance	Placebo (n=37) T 100 mg/day (n=35)[f]	T: 23% Placebo: 6%	NR	T: 11% Placebo: 0	NR	T: 6% Placebo: 0	T: 8% Placebo: 0	T: 17/58 P: 2/57	Mei et al. 2004
2	Double-blind multicenter RCT, 18 weeks maintenance	Placebo (n=143) T 100 mg/day [87.9 mg/day] (n=139) T 200 mg/day [124.2 mg/day] (n=143) Propranolol 160 [129.6 mg/day] mg/day (n=143)	T 100: 55% T 200: 56% Propranolol: 12% Placebo: 6%	T 100: 17% T 200: 14% Propranolol: 3% Placebo: 6%	T 100: 19% T 200: 24% Propranolol: 22% Placebo: 15%	T 100: 13% T 200: 17% Propranolol: 13% Placebo: 8%	T 100: 5% T 200: 14% Propranolol: 0 Placebo: 1%	T 100: 9% T 200: 15% Propranolol: 5% Placebo: 4%	T 100: 37/141 T 200: 63/144 Propranolol: 29/144 Placebo: 15/146	Diener et al. 2004

continued opposite…

Level of evidence	Design	Treatment and target dose [median dose]	Outcome							Reference
			Paresthesia	Anorexia	Fatigue	Nausea	Altered taste	Cognitive difficulty[a]	Withdrawals due to AEs	
2	Pooled analysis of 2 RCTs[g]	Placebo T 50 mg/day T 100 mg/day T 200 mg/day	T 100: 48% Placebo: 6%	T 100: 13% Placebo: 6%	T 100: 13% Placebo: 10%	NR	NR	NR	T 50: 17% T 100: 23% T 200: 27% Placebo: 11%	Hart et al. 2003
2	Pooled analysis of 4 RCTs	Placebo T 50 mg/day T 100 mg/day T 200 mg/day n=1580 total	Withdrawal: T: 7%	NR	Withdrawal: T: 4%	Withdrawal: T: 4%	NR	Withdrawal: T: 3%	NR	Lainez et al. 2003

...table continued

[a]Definitions varied; terms included "language problems," "memory impairment," "difficulty with concentration."
[b]The three trials included were Brandes et al. (2004), Silberstein et al. (2004), and Storey et al. (2001).
[c]Mean dose.
[d]Results refer to a subgroup of patients with migraine with aura, approximately 1/3 of the total.
[e]Patient numbers unclear in the original as the numbers given in the figures (given here) do not match the numbers given in the text.
[f]Number of patients completing the trial. The dropout rate results are given for the number of patients randomized.
[g]The two trials were Brandes et al. (2004) and Silberstein et al. (2004).
AE, adverse events; NNH, number needed to harm; NR, not reported; RCT, randomized controlled trial; T, topiramate.

patient's mental state returned to baseline. The authors comment that an association between psychosis and epilepsy is well established, and suggest that topiramate may be associated with development of psychotic symptoms via poorly understood effects on neurotransmitter systems (Matthews & Miller 2001). However, this appears to be an isolated case.

A case report from India described the occurrence of acute myopia and elevated intra-ocular pressure leading to temporary loss of vision in a 40-year old woman with migraine, 4 days after beginning treatment with topiramate 25 mg/day and flunarizine 5 mg/day (Bhattacharyya & Basu 2005). Topiramate was immediately withdrawn and diuretics begun to reduce the intra-ocular pressure, and the patient's visual acuity returned to normal on the 5th day (Bhattacharyya & Basu 2005). Other cases of acute glaucoma with topiramate have been reported (Fraunfelder et al. 2004), and the potential occurrence of this adverse reaction is noted in the prescribing information (Anon 2005a) and on the manufacturer's website (http://www.topamax.com/utilities/safety_info.jsp).

Weight loss

Strong evidence shows that topiramate is associated with weight loss (Table 9). Typically, mean weight loss in the groups taking topiramate 100 mg/day or 200 mg/day was around 2–3 kg or 3–4% of body weight at baseline. The reported percentage of patients with weight loss varied considerably between the studies. However, this may reflect differences in the definition of weight loss between the studies; there was insufficient information presented to assess this point further.

Economic evidence

One study published as a full paper has investigated the cost effectiveness of topiramate (Adelman et al. 2002). This study used data on reduction in mean monthly migraine frequency from published clinical trials combined with US drug prices to estimate the monthly costs of preventive therapy with topiramate 200 mg/day, gabapentin, divalproex sodium, and metoprolol, and the number of migraines per month required for the savings in acute medication costs to offset preventive medication costs. The efficacy data for topiramate 200 mg/day were taken from the study of Edwards et al. (2003).

For each preventive treatment, the authors calculated the cost of 1 month of therapy and divided this by the reduction in mean monthly migraine frequency to estimate the cost of treatment per headache prevented. They also estimated the cost-equivalent number (CEN)—the number of migraines per month at which the savings in the cost of acute medications would outweigh the cost of preventive therapy (i.e. the number of migraines per month at which the preventive therapy would "pay for itself" in reduced acute treatment costs). This was calculated from the cost of preventive therapy per month, the percentage reduction in migraine frequency, and the cost of acute sumatriptan treatment. The lower the CEN, the more cost effective the preventive treatment.

For topiramate 200 mg/day, the CEN was 13.7 or 22.5, depending on whether the cost was based on one 200 mg tablet or two 100 mg tablets. This compared favorably with gabapentin 2400 mg/day (CEN 24.1), but unfavorably with divalproex sodium

			Outcome		
Level of evidence	**Design**	**Treatment and target dose [median dose]**	**Patients reporting weight loss (%)**	**Mean weight change**	**Reference**
2	Double-blind, multicenter RCT, 18 weeks maintenance	Placebo (n=114) T 50 mg/day [46.5 mg/day] (n=117) T 100 mg/day [85.6 mg/day] (n=120) T 200 mg/day [150.2 mg/day] (n=117)	Placebo: 3% T 50: 6% T 100: 11% T 200: 9%	Placebo: increase 0.2% T 50: decrease 2.2% T 100: decrease 3.3% T 200: decrease 4.6% All T *P*<0.001 vs placebo	Brandes et al. 2004
2	Double-blind, multicenter RCT, 18 weeks maintenance	Placebo (n=115) T 50 mg/day [44.7 mg/day[a]] (n=117) T 100 mg/day [78.3 mg/day[a]] (n=125) T 200 mg/day [116.2 mg/day[a]] (n=112)	Placebo: 1% T 50: 5% T 100: 10% T 200: 12%	Placebo: increase 0.3% T 50: decrease 2.4% T 100: decrease 3.8% T 200: decrease 3.9% All T *P*<0.01 vs placebo	Silberstein et al. 2004
2	Pooled analysis of 2 double-blind single-center RCTs, 8–12 weeks maintenance	Placebo (n=36) T 200 mg/day (n=34)	NR	Placebo: No change T: decrease 5.5 lb *P*=0.0005 T vs placebo	Edwards et al. 2003
2	Multicenter RCT, 7 weeks double-blind followed by 11 weeks open-label	Placebo (n=115) T 50 mg/day (n=117) T 100 mg/day (n=125) T 200 mg/day (n=112)[b]	NR	Placebo: increase 0.3% T 50: decrease 2.4% T 100 or T 200: decrease 3.8%[c]	Silberstein 2003
2	Double-blind single-center RCT, 12 weeks maintenance	Placebo (n=37) T 100 mg/day (n=35)[d]	Placebo: 0 T: 23%	NR	Mei et al. 2004
2	Double-blind, single-center RCT, 8 weeks maintenance	Placebo (n=21) T 200 mg/day [125 mg/day[a]] (n=19)	Placebo: 29% T: 53%	Placebo: increase 0.55 lb T: decrease 4.88 lb *P*=0.015 T vs placebo	Storey et al. 2001
2	Double-blind multicenter RCT, 18 weeks maintenance	Placebo (n=143) T 100 mg/day [87.9 mg/day] (n=139) T 200 mg/day [124.2 mg/day] (n=143) Propranolol 160 [129.6 mg/day] mg/day (n=143)	Placebo: 1% T 100: 7% T 200: 9% Propranolol: 0%	Placebo: increase 0.6% T 100: decrease 2.7% (*P*≤0.001 vs placebo) T 200: decrease 3.4% (*P*≤0.001 vs placebo) Propranolol: increase 2.3% (*P*=0.025 vs placebo)	Diener et al. 2004
2	Pooled analysis of 4 RCTs	Placebo T 50 mg/day T 100 mg/day T 200 mg/day (n=1580 total)	NR	Placebo: NR T 50: decrease 1.8 kg T 100: decrease 2.5 kg T 200: decrease 2.8 kg[c]	Lainez et al. 2003
3	Open survey, mean treatment duration 7 months	T up to 50 mg/day (n=102)	33%	3–20 kg in 90 days (no mean given)	Kowacs et al. 2003

Table 9 | Effects of topiramate on weight in patients treated for migraine prophylaxis

continued opposite…

Level of evidence	Design	Treatment and target dose [median dose]	Outcome		Reference
			Patients reporting weight loss (%)	**Mean weight change**	
3	Retrospective case series, mean treatment duration 149 days	T mean dose 208 mg/day (n=74) Topiramate treatment period compared with previous treatment	NR	Decrease 3.1 kg (3.8%)	Young et al. 2002
3	Open-label longitudinal single-center study, 134 patients assessed after 3 months of topiramate treatment	T titrated up to 100 mg/day target dose	78%	Decrease 3.44 kg	Krymchantowski & Tavares 2004

…table continued

aMean dose.
bPatient numbers unclear in the original as the numbers given in the figures (given here) do not match the numbers given in the text.
cNo between-group comparison reported.
dPatients who completed the trial.
ITT, intention-to-treat; NR, not reported; NSD, not statistically significantly different; RCT, randomized controlled trial; T, topiramate.

1000 mg/day (CEN 9.4) and metoprolol 200 mg/day (CEN 1.2). The cost per headache prevented showed a similar pattern ($US138 for gabapentin, $US115 or $US67 for topiramate, $US48 for divalproex sodium, and $US8 for metoprolol) (Adelman et al. 2002).

However, this study has a number of limitations. First, it included only the costs of acute and preventive migraine medication, and did not take account of any other healthcare costs (e.g. visits to physicians or emergency rooms). There is some evidence that preventive migraine treatment can reduce such costs (Silberstein et al. 2003). Second, no account was taken of adverse events, which vary between the different preventive medications available and may influence costs. Third, the study did not include indirect costs, although the authors consider that indirect costs would be minimal or nonexistent, as their study applies only to patients demonstrating an excellent response to acute care. Fourth, no account was taken of rebound headaches. The authors state that these do not seem to occur with triptan usage limited to no more than 10 days per month, a value also cited by the BASH guidelines (BASH 2004), and suggest that for patients experiencing migraines at higher frequency than this, avoidance of rebound headache could be an additional benefit of preventive therapy (Adelman et al. 2002).

Furthermore, the study pre-dates the publication of three large RCTs of topiramate in migraine (Brandes et al. 2004; Diener et al. 2004; Silberstein et al. 2004) and a systematic review (Chronicle & Mulleners 2004). These studies indicated that topiramate 100 mg/day and 200 mg/day appear to have equivalent effectiveness, which may indicate that the dose of 200 mg/day used by Adelman et al. (2002) may not be the most appropriate. Reanalyzing the data using the efficacy results from the large recent trials and at the 100 mg/dose would provide important evidence.

A more recent cost-effectiveness model using the efficacy data from the three large randomized placebo-controlled trials and

comparing topiramate 100 mg/day with placebo has been published in abstract form (Brown et al. 2004). This study included the cost of preventive therapy, cost of acute treatment, and indirect costs (time lost from work) for a base-case population of people who experience a mean of 6 migraine attacks per month in the absence of preventive therapy. Topiramate treatment was associated with a mean reduction of 1.68 migraines per month and approximately 5 fewer hours lost from work per month, compared with placebo treatment. The monthly cost of preventive treatment with topiramate 100 mg/day was $US113, which was partially offset by savings in the cost of acute treatment ($US25) and in the cost of time off work ($US46). Thus, the net cost of preventive treatment with topiramate 100 mg/day was estimated at approximately $US42 per month, and the net cost per migraine avoided was $US26 (Brown et al. 2004). For populations with a higher baseline migraine frequency the cost effectiveness improved, and in patients with 10 migraines per month the model predicted that topiramate 100 mg would be cost saving (Brown et al. 2004). These findings need to be confirmed by results from direct observation.

Resource utilization

The acquisition price of topiramate is higher than some alternative migraine preventive therapies; for example, in the USA the cost of 30 days' treatment with topiramate 100 mg/day has been estimated at $US203, compared with $US31 for generic propranolol, $US73 for divalproex sodium (Depakote®), and $US4 for generic amitriptyline (Anon. 2005b). Widespread use of topiramate for migraine prevention may therefore be expected to increase medication costs.

Successful migraine prophylaxis could have the potential to reduce usage of other healthcare resources. This has been investigated in a claims data analysis of the health insurance records of 366 US patients receiving acute and preventive treatment for migraine (Silberstein et al. 2003). Physician visits for migraine decreased by

Table 10	Effects of topiramate in refractory and/or transformed migraine (all level 3 evidence)		
Design and patients	**Treatment**	**Results**	**Reference**
Observational study in patients with >1 migraine/week, who had not responded to or tolerated beta blockers, amitriptyline, flunarizine, and/or valproate (n=115)	Topiramate (most common dose 100 mg/day) for 3 months	56% responded (reduction in migraine frequency >50%)	Pascual et al. 2003
Retrospective chart review of patients with transformed migraine (n=96)	Add-on topiramate (mean dose 87.5 mg/day), mean follow-up 8.4 months[a]	Reduction in mean migraine frequency, mean severity, mean headache days/month, mean MIDAS score and rescue medication use vs baseline ($P<0.01$)	Mathew et al. 2002
Retrospective chart review of patients who had not responded to a median of 9 preventive migraine medications (n=69)	Topiramate (median dose 100 mg/day), median follow-up 12 weeks 49 of 69 patients took additional preventive therapy	Reduction in mean 28-day frequency of moderate/severe migraines vs baseline ($P=0.0004$). NSD vs baseline for frequency of mild headaches	Von Seggern et al. 2002
Uncontrolled trial in patients with >3 migraines/month, 80% were taking propranolol and/or flunarizine (n=36)	Add-on topiramate (up to 100 mg/day) for 3 months	Reduction in mean migraine frequency, duration and intensity vs baseline ($P<0.001$)	Martinéz et al. 2003
Uncontrolled trial in patients with high frequency migraine refractory to other prophylactic drugs (n=7)	Topiramate 100 mg/day for 12 weeks maintenance	Reduction in mean number of days with migraine vs baseline ($P=0.0036$)	Tonini et al. 2003

[a]For all patients in the study, including patients with episodic migraine (n=70) and cluster headache (n=12).

51% and emergency room visits for migraine decreased by 82% in the second 6 months after the migraine preventive medication was first prescribed compared with the 6 months before (Silberstein et al. 2003). However, there has been some debate about the methods used by this study and its conclusions (Adelman et al. 2003). No specific evidence relating to the potential effect of topiramate on healthcare resources was identified.

As indirect costs are a major component of the total cost of migraine (see Disease overview section), successful migraine prevention could theoretically reduce the number of days on which patients are partly or entirely disabled by migraine. Evidence from one double-blind placebo-controlled trial reported that topiramate 100 mg/day reduced the mean monthly number of days with disability by approximately 4.2 after 16 weeks of treatment, compared with a reduction of approximately 1 with placebo (Mei et al. 2004). Furthermore, a cost-effectiveness modeling study estimated that topiramate 100 mg/day was associated with a saving of US$46 per patient per month in the cost of lost work time in a population with a baseline migraine frequency of 6 migraines/month, partly offsetting the additional cost of topiramate (Brown et al. 2004). This evidence indicates that topiramate has the potential to reduce time away from work or normal activities due to migraine, thereby reducing indirect costs, but direct evidence is needed to assess this possibility. No evidence was identified comparing topiramate with other preventive migraine treatments on this issue.

Topiramate has been shown to improve HRQOL relative to placebo, especially at doses of 100 or 200 mg/day (Diamond et al. 2003). However, there was no evidence comparing the effects of topiramate on HRQOL with that of other migraine prophylactic treatments. No cost–utility study has been published estimating the potential effect of topiramate on quality-adjusted life-years (QALYs).

Weight gain may be an important cause of treatment discontinuation (Von Seggern 2002). Several preventive migraine treatments are typically associated with weight gain, such as propranolol, amitriptyline, and divalproex sodium. In contrast, topiramate may be associated with weight loss rather than weight gain, which some patients may prefer. This in turn may help to encourage better adherence to therapy and consequently better effectiveness. However, no evidence is available on this point.

Further economic studies comparing topiramate with other widely used migraine preventive treatments (e.g. propranolol) and including a wider range of costs and outcomes are required for a full evaluation of the cost effectiveness of topiramate in migraine prevention.

Patient group/population

Treatment guidelines recommend that preventive therapy should be considered in patients with migraine that is severe and/or frequent enough to interfere with daily life, patients with overuse of acute therapy, and patients with an inadequate response to acute therapy (see Table 4). A treatment trial period of at least 2–3 months is generally recommended for preventive therapy (Silberstein 2000; Snow et al. 2002), though the optimum duration of treatment is uncertain (Evans 2004).

As reviewed in the Clinical evidence section, topiramate has demonstrated greater effectiveness than placebo in reducing migraine frequency in several RCTs. Patients recruited to these trials typically had a diagnosis of migraine by IHS criteria, had experienced migraine attacks for at least 6 months or at least 1

year, and had a frequency of migraine attacks of at least two per month (Storey et al. 2001; Edwards et al. 2003), 2–6 per month (Mei et al. 2004), or 3–12 per month (Brandes et al. 2004; Diener et al. 2004; Silberstein et al. 2004), but no more than 15 migraine days per month (Brandes et al. 2004; Diener et al. 2004). The frequency of migraines in the population in the RCTs corresponds broadly to the frequency considered an indication for preventive treatment in the US guidelines (Snow et al. 2002; see Table 4). Thus, the evidence on effectiveness and tolerability of topiramate reviewed above can be considered relevant to the general population of patients eligible for preventive migraine treatment. Further evidence relating to specific population groups is reviewed below.

Refractory and transformed migraine

Topiramate has been shown to be effective, either as monotherapy or as add-on therapy, in patients with transformed migraine and/or migraine refractory to previous preventive therapy in several retrospective, uncontrolled, and observational studies (Table 10). Evidence from RCTs is required to confirm the effects of topiramate in this patient group.

Migraine with vertigo

Carmona and Settecase (2005) reported an open trial of topiramate (average dose 100 mg/day) in 10 patients with migraine and vertigo. At the time of publication, the authors reported that only two of 10 patients had experienced a migraine crisis during the treatment period (range 6–16 months, mean 9 months).

Cost effectiveness in different patient populations

It has been suggested that antiepileptic drugs (including topiramate) are likely to demonstrate greater clinical and economic value in patients who experience >10 migraines/month than in patients with less frequent migraine (Adelman et al. 2002). The recommendation appears to be derived in part from the authors' calculations of cost-equivalent number (see Economic evidence section) and partly because headache rebound "does not seem to occur with [triptan] use limited to 10 days/month or less" (Adelman et al. 2002). However, it is consistent with results from a cost-effectiveness model utilizing efficacy data from three large randomized double-blind studies and US unit costs (Brown et al. 2004). This model indicated that topiramate 100 mg/day would be cost saving in patients who experience 10 migraines/month in the absence of preventive therapy (Brown et al. 2004). Further direct evidence is needed to evaluate the frequency threshold at which topiramate and other preventive therapies become cost effective.

Dosage, administration, and formulations

Topiramate (Topamax®) is indicated for the prophylaxis of migraine in adults (Anon. 2005a). It is available as coated tablets containing 25 mg, 50 mg, 100 mg, or 200 mg topiramate, and as sprinkle capsules containing 15 mg or 25 mg topiramate. The sprinkle capsules may be taken as whole capsules or opened and the granular contents sprinkled onto a teaspoon of soft food which should then be eaten immediately (Anon. 2005a).

The recommended total daily dose for topiramate in migraine prevention is 100 mg/day administered in two divided doses. The dose should be titrated gradually as follows: week 1, 25 mg in the evening; week 2, 25 mg morning and evening; week 3, 50 mg in the evening and 25 mg in the morning; and week 4, 50 mg morning and evening. In patients with renal impairment (creatinine clearance <70 mL/min/1.73 m^2) the dose should be adjusted to half the normal adult dose. Topiramate is cleared by hemodialysis 4–6 times faster than its clearance in a healthy individual, so in patients undergoing hemodialysis a supplemental dose of topiramate may be required to maintain a steady-state topiramate plasma concentration. The dose adjustment depends on the duration and clearance rate of the dialysis and the effective renal clearance of topiramate in the patient being dialyzed (Anon. 2005a).

Place in therapy

The evidence summary table at the beginning of this article summarizes the evidence published on topiramate in the preventive treatment of migraine. All the outcome measures reported were considered to be patient-oriented rather than disease-oriented, as they measured endpoints such as a reduction in migraine frequency or severity that are of clear benefit to the patient. Most evidence concentrated on measures specific to migraine (e.g. attack frequency), though a few studies attempted to assess the broader impact of migraine on patients' lives by measuring disability or HRQOL.

All the comparative trials were placebo-controlled and powered only for the comparison of topiramate with placebo. One (Diener et al. 2004) included a propranolol group as an active control. Although not powered to compare the two active treatments, this trial is at present the only evidence of the efficacy and tolerability of topiramate in relation to existing preventive migraine treatment. Since it is probably unlikely that a patient requesting preventive therapy for frequent and/or disabling migraine would be sent away with no treatment, the placebo-controlled trials do not represent a treatment choice (topiramate or no treatment) that is likely to be widespread in current practice. Comparative trials against current first-line preventive therapies will be required to change practice in the general population of patients needing preventive migraine treatment. In the population of patients with migraine refractory to existing therapies, the limited evidence available suggests that topiramate may be effective in some patients where existing treatments have failed or have not been tolerated. Although limited, this evidence may guide practice to consider a trial of topiramate in such patients.

Substantial evidence from pooled analyses of RCTs suggests a positive effect for topiramate on HRQOL compared with placebo.

Limited evidence indicates that topiramate may have the potential to reduce disability due to migraine, but this needs to be confirmed by further trials.

Clear evidence from randomized controlled trials powered on this endpoint has demonstrated that topiramate 100 mg/day or 200 mg/day is more effective than placebo in reducing the mean monthly frequency of migraines. A systematic review and meta analysis compared the doses and found that 100 mg/day and 200 mg/day were not significantly different in efficacy, and that both were significantly superior to 50 mg/day.

This pattern is supported by evidence from secondary efficacy endpoints in RCTs (responder rate, mean number of migraine days/month, rescue medication use, migraine severity, and migraine duration). One RCT reported that 200 mg/day was less effective than 100 mg/day (Diener et al. 2004), but the authors consider that this paradoxical result may reflect the high rate of early dropouts due to adverse events observed in the 200 mg/day group. Some evidence from uncontrolled studies indicates that topiramate (either alone or as add-on therapy) may be effective in patients who have previously failed to respond to, or have not tolerated, other preventive migraine therapies. This observation requires confirmation by RCTs in this patient population.

There have been no trials published that were powered to compare topiramate with alternative treatments for prevention of migraine. One large RCT used propranolol 160 mg/day as an active control, but this trial was powered only to compare between active treatment and placebo and the authors stress that comparing between topiramate and propranolol as well would have required a larger sample size (Diener et al. 2004). Nevertheless, this trial found that topiramate 100 mg/day and propranolol 160 mg/day appeared to have broadly comparable efficacy and tolerability. As the two agents have different adverse event profiles and contraindications, the authors concluded that either drug could be used in cases where the other is contraindicated or not tolerated (Diener et al. 2004). This seems a fair conclusion from the current limited evidence base. Further evidence from true comparative trials is required to assess the therapeutic value of topiramate relative to other agents.

The main adverse events associated with topiramate appear to be central nervous system effects such as paresthesia, altered taste, and cognitive problems. These have been consistently reported at a higher rate than with placebo in RCTs, and appear to occur more frequently at the 200 mg/day dose than the 100 mg/day dose. Since it has been reported that the 100 mg/day and 200 mg/day doses have similar efficacy, the overall evidence suggests that 100 mg/day may provide the best balance between efficacy and tolerability. This was the conclusion drawn by Diener et al. (2004). However, the optimum dose will vary between individual patients, and an uncontrolled survey has reported efficacy at doses of 50 mg/day and below (Kowacs et al. 2003).

Strong evidence from several trials, with no published contradictory evidence, shows that topiramate is associated with weight loss. The mean weight loss reported has typically been around 2–3 kg or 3–4% of baseline body weight over observation periods typically of a few months. As weight gain is common with other preventive migraine therapies, and has been suggested as a major reason for discontinuation of treatment, the occurrence of weight loss with topiramate may be considered advantageous by some patients. It may help to encourage adherence to therapy, although published evidence is lacking on this point. However, it is not clear from the current evidence base whether weight loss continues during long-term treatment or whether it reaches a plateau. Information is needed on this issue to determine whether topiramate-associated weight loss is likely to be a benefit or a drawback.

Very little economic evidence has been published on topiramate in migraine prevention. The sole fully published study compared topiramate, gabapentin, divalproex sodium, and metoprolol in terms of their cost per headache avoided and the number of migraines required per month for each drug to pay for itself in reduced expenditure on acute medication (Adelman et al. 2002). However, this study considered only a limited range of costs, used data from a small study that pre-dated the recent large randomized trials, and used a relatively high topiramate dose of 200 mg/day. Updating the study with more recent data and investigating the 100 mg/day dose (which, as discussed above, seems to be emerging as the likely preferred dose on the current evidence base) could be valuable. This has been addressed by a modeling study using data on topiramate 100 mg/day from three randomized controlled trials, which found that savings in time lost from work and the cost of acute treatment partially offset the cost of topiramate treatment (Brown et al. 2004). In patients who experience 10 migraines per month in the absence of preventive treatment, this study suggested that topiramate 100 mg/day would be cost saving. However, further economic studies on a wider range of costs and outcomes and in comparison with other widely-used agents are required to evaluate the cost effectiveness of topiramate in migraine prophylaxis.

In summary, the current evidence base suggests that topiramate is more effective than placebo in migraine prevention and that a dose of 100 mg/day is likely to offer the best balance between efficacy and tolerability (though the optimum dose will vary between individual patients). The limited evidence available indicates that topiramate 100 mg/day may be broadly comparable to propranolol 160 mg/day. Weight loss may be expected to occur with topiramate treatment, rather than weight gain, and this may be an important consideration for some patients. As generic propranolol has a considerably lower acquisition cost than topiramate, propranolol is likely to remain first-line therapy in patients in whom it is well tolerated, effective, and not contraindicated. For patients in whom propranolol or other preventive migraine therapies are contraindicated, poorly tolerated, or have been found ineffective, topiramate is a valuable therapeutic option.

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Correspondence: Carole Nadin, Core Medical Publishing, Mere House, Brook Street, Knutsford, Cheshire WA16 8GP, UK or at editor@coreevidence.com