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## Anti-epileptic drugs in the preventive treatment of migraine headache: a brief review

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**Abstract** Anti-epileptic drugs are employed for the prophylactic treatment of migraine. Valproic acid and its sodium salt (divalproex) have been shown to be effective in preventing migraine in double-blind placebo-controlled studies. Gabapentin and lamotrigine have also been proposed for migraine prophylaxis, but more extensive studies are needed to confirm their efficacies. The main mechanism of action of anti-epileptic drugs is the inhibition of the sodium channel to induce a depolarization, preventing the high, frequent action potentials typically excited by convulsive attacks. Moreover, valproate and gabapentin increase brain concentrations of GABA and, probably, inhibit the

degradation of GABA. Other proposed mechanisms of action for valproate are a direct effect on neuronal membranes and a reduction of excitatory transmission by aspartate. Valproate, at the recommended dose of 500 mg twice daily, is well tolerated. The more frequent unwanted effects associated with almost all drugs of this class are weight gain, drowsiness, dizziness and tremor. Topiramate has recently been proposed for the treatment of unresponsive, high frequency migraine, taking into account both the GABA and glutamatergic mechanisms of action.

**Key words** Antiepileptic drugs • Prophylactic treatment • Migraine • Headache

### Introduction

The pharmacological treatment of migraine may be acute or preventive, and patients who experience frequent severe headaches often require both approaches. The preventive treatment for migraine includes beta-blockers, antidepressants, calcium channel antagonists, serotonin antagonists, non-steroid anti-inflammatory drugs (NSAIDs), riboflavin at high doses and anticonvulsant drugs. The large variety of mechanisms of action of these drugs suggests that there are a number of key points where drugs can reduce or prevent the beginning of migraine attacks. Circumstances that warrant preventive treatment include: two or more attacks per month that produce disability that lasts two or more days,

and contraindication to or inefficacy of symptomatic medication [1]. On the other hand, prophylactic therapy should be provided when abortive medications are assumed more than twice per week, and in special circumstances such as hemiplegic migraine or rare headache attacks producing profound disruption or risk of permanent neurological injury [2].

Preventive medications should be started at low dosages and increased slowly until therapeutic effects develop or until the ceiling dosage for other indications is reached. For example, tricyclic anti-depressants are used for depression at dosages of 100–200 mg/day, while 20–30 mg/day may be effective for migraine. Sodium valproate at 500–750 mg/day can reduce migraine frequency, while higher dosages may be necessary to effectively treat epilepsy and mania [2].

A full therapeutic trial, to evaluate the efficacy in pre-

**Table 1** Mechanisms of action of sodium valproate and new anti-epileptic drugs

Anti-epileptic drug	Mechanism of action
Gabapentin	Stimulation of GABA turnover GABA mimetic
Lamotrigine	Inhibition of glutamate release Blockade of voltage-sensitive channels
Tiagabine	Reversible inhibition of GABA uptake
Topiramate	Potentialiation of GABA Antagonism of AMPA receptors Inhibition of carbonic anhydrase
Sodium valproate	Inhibition of GABA uptake and GABA aminotransferase Stimulation of brain GABA synthesis Inhibition of voltage-sensitive channels

GABA, gaba-aminobutyric acid

venting migraine attacks, may take 3–6 months. In controlled clinical trials, efficacy is often first noted after four weeks and continues to increase for three months. It is not uncommon for patients to be treated with a new preventive medication for 1–2 weeks without effect and for the treatment to be prematurely discontinued with both patient and physician believing it was not effective [2].

To obtain maximal benefit from preventive medication, the patient should not overuse analgesics or ergot derivatives. In addition, oral contraceptives, hormonal replacement therapy or vasodilating drugs such as nifedipine or nitroglycerin may interfere with preventive drugs [2].

Recently, sodium valproate and other anticonvulsive drugs have been more widely employed in preventive treatment of migraine with good results. These drugs reduce the firing response of neurons by acting on membrane ion channels or by acting on the GABA system. We do not know the mode of action of these drug in preventing migraine. Therefore, clinical evidence precedes the pharmacological explanation. This implies that the evaluation of prophylactic treatments for migraine needs to be carried out with care, and that results should be analyzed taking into account the lack of pharmacological basis for this therapy (Table 1).

In this review, we discuss the use of anti-epileptic drugs in the preventive treatment of migraine attacks.

### Sodium valproate

Sodium valproate is a classic anti-epileptic drug used since 1978. Its chemical structure is a simple branched-chain carboxylic acid. At therapeutic concentrations, valproate inhibits sustained repetitive firing induced by depolarization of mouse cortical or spinal cord neurons. The action is sim-

ilar to that of both phenytoin and carbamazepine, and appears to be mediated by a prolonged recovery of voltage-activated Na<sup>+</sup> channels from inactivation [3].

Another probable mechanism that may contribute to valproate's antiseizure action involves metabolism of gamma-aminobutyric acid (GABA). The increase of brain GABA concentrations depends on inhibition of both GABA aminotransferase and succinic dehydrogenase, enzymes involved in the synthesis and degradation of GABA. Selective increases of GABA have been reported to occur in synaptosomes, primarily in areas of high GABA activity after valproate administration. On the other hand, valproate inhibits GABA re-uptake and reduces glutamate by activating glutamic acid decarboxylase.

The enhancement of GABA activity in the brain, from increased GABA synthesis and decreased GABA degradation, has been assumed to be the mechanism of action in preventing migraine attacks [4]. Moreover, divalproex sodium acts on the brain serotonin system by enhancing the GABA-mediated inhibition of serotonin neurons of the dorsal raphe area and raising the threshold of the onset of migraine [5].

Finally, this drug prevents vasodilatation during migraine attacks [4].

Oral absorption is rapid, and occurs within 1–4 h. Peak serum concentrations range from 50 to 100 µg/ml and the volume of distribution is 0.130–0.23 l/kg. Protein binding is 91% and cerebrospinal fluid levels reach 10% of plasma concentrations. Elimination half-life ranges from 8 to 17 hours, and extensive hepatic metabolism is followed by renal excretion. Approximately 1.8%–3.2% of the administered dose is excreted without modification, while 7% is excreted in the bile within 7 h of administration.

Well-recognized adverse effects are thrombocytopenia, hemorrhage, red cell aplasia, tremor, ataxia, fatigue, sedation, abdominal cramps, dizziness, sedation, confusion,

**Table 2** Clinical studies with valproic acid for migraine treatment

Reference	Dosage (mg/day)	IHS	n	Efficacy
Mathew '95	500–1000	1.1	200	48%
Ghose '98	500–1000	1.2	36	50%–71%
Robbins '00	500	1.1	32	62%
Klapper '97	500, 1000, 1500	1.1	176	45%

IHS, International Headache Society classification; 1.1, migraine without aura; 1.2, migraine with aura

headache, nausea, diarrhea, alopecia and weight gain. In a long-term study of sodium valproate therapy (48–60 months), almost all patients gained weight whereas only 14% experienced tremors [6, 7].

Concurrent use of primidone and valproic acid may result in severe central nervous system depression. Aspirin, erythromycin or felbamate may increase valproic acid toxicity (CNS depression). Fosphenytoin, acyclovir, imipenem, isoniazid, phenobarbital and rifampicin may result in altered valproate levels.

For migraine headache prophylaxis, 500–1000 mg/kg day in divided doses was used by Klapper in a dose-response study that showed no improvement in activity up doses of 1000 mg/day (Table 2) [8].

### Clinical studies

In a series of 200 patients, divalproex sodium decreased migraine frequency and severity in 80% of cases [5]. In a series of 163 cases, Ghose found that in a 3-year follow-up divalproex sodium was well tolerated, and retention rate for tolerability was similar between placebo and treatment [6].

To assess the efficacy of sodium valproate as a prophylactic agent in migraine headache, a prospective randomized study was conducted in adult patients who previously derived no significant benefit from most conventional prophylactic therapy for migraine [9]. Twenty-seven patients with a diagnosis of migraine with aura or migraine without aura from a headache clinic received low dose sodium valproate for 3 months. Therapy response was defined as 50% or greater reduction in the frequency of headache, and 71% patients improved within 4–6 weeks. Plasma drug level monitoring helped to identify four noncompliers. Clinical improvement (percentage reduction in the frequency of migraine attacks) was inversely correlated with plasma drug levels at 13–24 months and daily dose of valproate. Patients who did not respond to low dosage valproate were unlikely to benefit from further increases in dosage [6, 9].

In a recently study, sodium valproate was used intravenously for the acute treatment of migraine attacks. A group of 32 female patients with a history of refractory severe headache received 500 mg sodium valproate. Valproate was well tolerated with minimal side effects. After one hour, complete relief was recorded in 8 patients, and at 24 hours 12 patients referred complete pain relief. Only one patient referred transient somnolence [10].

In another study the efficacy and tolerability of repetitive intravenous sodium valproate and intravenous dihydroergotamine (DHE) in intractable migraine were examined [11]. Intravenous sodium valproate was as effective as intravenous DHE in breaking intractable migraine attacks, but it was associated with less adverse events. In conclusion, these studies suggest that valproate may be used along with other migraine abortives.

### Gabapentin

Gabapentin is amino acid structurally related to GABA and possesses GABA-mimetic properties.

Gabapentin increases the release of GABA by a not completely known mechanism. Gabapentin inhibits the neural synthesis of L-glutamate, a mechanism that may be useful in chronic migraine treatment. In fact, the mechanism that transforms episodic migraine into chronic migraine may be linked to hyperalgesia and related neuroplastic changes, by the action of excitatory amino acids, chiefly the ones acting at *N*-methyl D-aspartate (NMDA) receptors [12].

Gabapentin is absorbed from the gastrointestinal tract and has a bioavailability of 50%–60%, depending on dose. Bioavailability is not influenced by food. Peak serum levels occur 1–3 h after oral administration. The drug is not bound by plasma proteins and does not appear to be metabolized. All absorbed dose is excreted unchanged in the urine. The terminal elimination half-life of gabapentin ranges between 5 and 7 hours.

The most frequent adverse effects of gabapentin are somnolence, dizziness, ataxia, nystagmus, skin rash, nausea, vomiting, tremor, blurred vision and slurred speech.

The dosage for migraine treatment is 1550–2700 mg/day with 65% improvement [12].

Anti-epileptic dosage of gabapentin is 900–1800 mg/day in three administrations.

No interactions with other anticonvulsants have been reported. Concurrent use of gabapentin and antacids may result in decreased gabapentin effectiveness.

In a study 63 patients, with migraine with or without aura, gabapentin (1200 mg/day) was well tolerated and reduced the use of symptomatic drugs and the frequency of headache. The authors concluded that gabapentin has a therapeutic action in the prophylactic treatment of migraine [13].

### Lamotrigine

Lamotrigine is a phenyltriazine derivative that blocks voltage-sensitive sodium channels and stabilizes neuronal membranes, leading to the inhibition of neuronal release of the excitatory neurotransmitter glutamate. Lamotrigine is well absorbed after oral administration. Its oral bioavailability is approximately 98%. Peak plasma levels are reached in 1–4 h after dosing. Lamotrigine is approximately 55% protein-bound. The volume of distribution ranges from 0.9 to 1.4 l/kg. The drug is primarily excreted in the urine as an *N*-glucuronide conjugate. Only 2% is excreted in the feces. The most frequent adverse effects of lamotrigine are fatigue, ataxia, dizziness, headache, diplopia and the rare, but severe, Stevens-Johnson syndrome or toxic epidermal necrolysis.

Oral doses of 200–500 mg/day are effective and well tolerated; 150–200 mg/day is used in concomitant valproic acid therapy for anticonvulsive treatment, while 100 mg/day is recommended for the prophylaxis of migraine headache.

Concurrent use of lamotrigine and valproic acid or sertraline may result in lamotrigine toxicity and increased risk of epidermal necrolysis. Primidone, methosuximide, oxcarbamazepine, phenytoin, carbamazepine, phenobarbital, phenytoin and acetaminophen may result in reduced lamotrigine effectiveness.

### Clinical studies

The efficacy of lamotrigine (100 mg/day) was evaluated in a controlled clinical trial for the prevention of migraine with aura in 24 patients affected by high frequency migraine. The patients took lamotrigine for 3 months. In the 21 patients who completed the study, the attacks were completely abolished at the third month of treatment [14].

In another controlled clinical trial, 13 patients suffering from migraine with aura and 2 patients with aura but without migraine were treated with lamotrigine. The dosage was gradually increased in steps of 25 mg/day to 100 mg/day, depending on the patient's aura symptoms and tolerability. The study concluded that lamotrigine is effective in preventing migraine aura symptoms and in influencing migraine headache frequency [15].

In a randomized, double-blind study, lamotrigine was shown to be superior to placebo in reducing migraine attacks in 110 patients. Lamotrigine therapy was started at the full dosage of 200 mg/day but, because of the high incidence of skin rashes, a slow dose-escalation was introduced: 25 mg/day for 2 weeks, 50 mg/day for 2 weeks, and finally 200 mg/day. Attack rates were reduced from baseline means of 3.6 per month on lamotrigine and 4.4 on placebo to 3.2 and 3.0, respectively, during the last month of treatment. Improvements were greater on placebo. These changes, not statistically significant, indicated that lamotrigine is ineffective for migraine prophylaxis (Table 3) [16].

These studies outline that lamotrigine is a first-choice drug for the treatment of migraine with aura with high frequency of attacks. Additionally, studies regarding SUNCT (short-lasting, unilateral, neuralgiform headache attacks with conjunctival injection and tearing) treatment suggest that the pathogenetic mechanism of migraine with aura likely involves the excitatory aminoacids [15–17]. Lamotrigine was effective in four cases with SUNCT syndrome [17, 18]. Lamotrigine was the first effective attempt to treat the SUNCT syndrome. Given the infrequency of this syndrome, it is difficult to organize a large clinical trial on this disease, and authors should be encouraged to refer to the treatments for this syndrome.

In conclusion, the efficacy of lamotrigine for migraine prophylaxis has not yet been completely demonstrated and results are summarized in Table 3.

**Table 3** Clinical studies with lamotrigine for migraine treatment

Reference	Dose (mg/day)	IHS	n	Efficacy
D'Andrea '99	100	1.2	24	100%
Lampl, '99	100	1.2	15	+++
Steiner, '97	25–200	1.1	110	Equivalent to placebo
D'Andrea '00	100–150	SUNCT	2	100%

IHS, International Headache Society; 1.1, migraine without aura; 1.2, migraine with aura

## Tiagabine

Tiagabine, a bis(3-methyl-2 thienyl) derivative of nipecotic acid, is a GABA inhibitor used for the treatment of partial epilepsy. Tiagabine induces a significant elevation of extracellular brain GABA levels in studies involving awake rats.

Peak serum concentrations of tiagabine usually occur within 40 min after oral administration and are conditioned by enterohepatic circulation. The drug is 98% protein-bound and is metabolized in the liver. The elimination half-life range from 4 to 7 h.

Tiagabine appears to be well tolerated. Predominant adverse reactions include sedation, dizziness, memory impairment, emotional lability, asthenia and tremor.

Concurrent use of tiagabine and carbamazepine, phenytoin and phenobarbital decreased tiagabine efficacy because of the induction of tiagabine metabolism, whereas the steady state pharmacokinetics of digoxin or the mean daily serum levels are not affected.

### Clinical studies

In a clinical trial, 36 patients were treated with tiagabine [19]. All patients suffered from migraine with or without aura, according to IHS diagnostic criteria. Tiagabine therapy was initiated at 4 mg/day for 1 week, then increased to 4 mg twice daily. Patients were re-evaluated after 1 month of therapy, and the doses were adjusted. Adverse events were experienced in 12 patients, resulting in the discontinuation of therapy in 9 of them. This study suggested that tiagabine is an effective medication for migraine prophylaxis [19].

## Topiramate

Topiramate is a sulfamate-substituted monosaccharide with anti-epileptic activity. Recently, it has been shown to be effective in neuropathic pain refractory to conventional medical treatment. The mechanism of action includes membrane-potential stabilization, increased GABA activity, decreased glutamate activity and carbonic acid anhydrase inhibition.

Topiramate is readily absorbed following oral administration with peak plasma concentration achieved about 2 h after a dose; a relevant enterohepatic circulation is also present. Bioavailability is not affected by the presence of food. The volume of distribution is 0.6–0.8 l/kg and in women is half that in men. The drug is metabolized in the liver and eliminated chiefly in urine, both unmodified and as metabolites. Plasma half-life is about 21 h. Steady state levels are

reached within 4–8 days, and drug elimination is impaired by liver and renal insufficiency. The recommended doses for seizure range between 200 and 400 mg/day. Topiramate plasma concentrations were closely related to dosage, and there were no significant interactions between topiramate and other anti-epileptics. The following adverse events are related to topiramate in 5% or more of patients: ataxia, impaired concentration, confusion, dizziness, fatigue, paresthesia, somnolence and abnormal thinking. Topiramate may also cause agitation and emotional lability (which may manifest as abnormal behavior) and depression. Less common adverse effects include amnesia, anorexia, aphasia, diplopia, nausea, nystagmus, speech disorder, alteration of the sense of taste, abnormal vision and weight loss. Topiramate increases the risk of nephrolithiasis, especially in people with a predisposition.

### Clinical studies

Thirty patients aged 18–65 years with an IHS diagnosis of migraine with or without aura were randomized to topiramate (n=5) or placebo (n=15) after completing a 4-week baseline phase [20]. Patients were treated over 6 weeks with 25 mg/day. Then, the dose was increased to a maximum of 100 mg, followed by a 12-week maintenance phase. The 50% responder rate was significantly higher in the topiramate vs. placebo group (46.7% vs. 6.7%,  $p=0.035$ ). The most common adverse events reported in the topiramate group were paresthesia, diarrhea, altered taste, and somnolence.

Wheeler and Carrazzana studied 15 consecutive cluster-headache patients (3 unremitting from onset, one cluster-tic, 11 episodic) [21]. Six women and 9 men, with a median age of 44.8 years, participated. The duration of headache ranged from 1 week to 36 months. Topiramate appeared to be effective for cluster headache. The mean time to remission induction was 1.8 weeks in 11 patients. One patient even achieved a steroid taper that had not been achieved before. Only one patient was non-compliant and lost to follow-up. Two patients dropped out of the study due to drowsiness. The researchers concluded that topiramate was safe, well-tolerated and efficacious in the treatment of cluster headache [21].

In a double-blind, randomized, placebo-controlled study, 138 patients were treated with topiramate, which was found to be efficacious in the prophylaxis of episodic migraine [22]. Di Trapani et al. [23] evaluated a 3-month treatment with topiramate as prophylaxis for migraine in 20 patients. The preliminary results revealed a significant reduction in the frequency and intensity of attacks, and no patients withdrew because of side effects [23]. Similar results were reported by Randall et al. in a retrospective study [24]. It was also studied the effect of topiramate on weight in

migraine and chronic daily headache with dosages ranging from 50 to 800 mg/day. Treatment of headache with topiramate was associated with loss of weight [25].

In conclusion, these results suggest that topiramate is effective in the prophylactic treatment of migraine.

## Conclusions

The goals of preventive treatment are to optimize the quality of life for patients. The medications used to prevent migraine fall into two major categories. First-line drugs have high efficacy and include  $\beta$ -blockers, tricyclic antidepressants, calcium-channel blockers such as flunarizine, and divalproex sodium. This category also includes drugs with lower demonstrated efficacy such as selective serotonin reuptake inhibitors (SSRIs), verapamil, nimodipine and NSAIDs. Second-line, high efficacy drugs include pizotifen, monoamino-oxidase inhibitors and drugs with unproved or low efficacy, including cyproheptadine, lithium and phenytoin. This category also includes new anti-epileptic drugs.

The choice of a preventive drug must involve the accurate evaluation of the clinical characteristics of the patients, with attention to their age, sex, life style and co-morbidity. In fact, only a complete evaluation of these parameters can allow a correct evaluation of the best risk-to-benefit ratio for the individual patient and take advantage of the side-effect profile of the drug (Table 4).

A woman of childbearing potential should be on adequate contraception before starting migraine medication. However, some women who are pregnant or who are

attempting to become pregnant may still require preventive medication. In these cases, the preventive treatment should take into account the potential teratogenic risk compared to the therapeutic benefit.

An underweight patient is a candidate for medication that increases appetite, such as cyproheptadine, flunarizine or tricyclic antidepressants (TCA) [25, 26]. In contrast, a young woman with dietary problems should avoid these drugs. Moreover, the type of employment should be evaluated, because TCA, flunarizine and pizotifen can impair attention and create dangerous situations for those who drive or use machines.

Comorbidity and coexisting diseases can provide therapeutic opportunities in the choice of a drug, but in the same way they impose therapeutic limitations. In the case of coexisting hypertension or angina,  $\beta$ -blockers and verapamil may be considered effective for the treatment of both diseases. Patients with depression should be treated successfully with TCA or SSRIs, and migraneurs suffering from seizures can be treated with divalproex sodium or other anti-epileptic drugs.

On the other hand, patients may have diseases that contraindicate some drugs. For example,  $\beta$ -blockers such as flunarizine should be used carefully in patients with depression. TCA and neuroleptics, used in acute treatment in emergency wards, can lower seizure threshold and should be used with caution in epileptic migraneurs [2, 26].

Preventive medications are considered to be effective when the reduction of the number of headaches is over 50% [2]. The anti-epileptic drugs that we have reported in this paper have been studied to detect this goal, and results are often encouraging, even if not conclusive. Some of these drugs, such as valproate and flunarizine, are certainly of

**Table 4** Preventive therapy and comorbidity

Drug	Efficacy	Side effects	Relative contraindications	Recognised clinical indications
Beta-blockers	4+	2+	Asthma, depression, CHF, Raynaud's disease, diabetes	Hypertension, angina
Verapamil	2+	1+	Constipation hypotension	Migraine with aura, hypertension, angina, asthma
Tricyclic antidepressants	4+	2+	Mania, urinary retention, heart block	Other pain, depression, anxiety, insomnia
Selective serotonin reuptake inhibitors	2+	1+	Mania	Depression, OCD
MAO-I	4+	4+	Unreliable patients	Refractory depression
Divalproex sodium and valproate	4+	2+	Liver disease, bleeding disorders	Mania, epilepsy, anxiety disorders

*MAO-I*, monoamino-oxidase I; *CHF*, chronic heart failure; *OCD*, obsessive compulsive disorders

first-choice in the prevention of migraine attacks, whereas other drugs such as lamotrigine, gabapentin and topiramate are useful in resistant headaches or in neuropathic pain syndromes.

The main goal we have is the improvement of the quality of life of our patients, and these newer drugs or these new indications can enlarge our possibility to find the best drug for the single patient.

## References

- Silberstein SD, Lipton RB (1994) Overview of diagnosis and treatment of migraine. *Neurology* 44:6
- Silberstein SD, Lipton BR, Goadsby PJ (1998) Headache in clinical practice. ISIS Medical Media, Oxford, pp 59–90
- McLean MJ, Macdonald RL (1986) Sodium valproate, but not ethosuximide, produces use and voltage-dependent limitation of high frequency repetitive firing of action potentials of mouse central neurons in cell culture. *J Pharmacol Exp* 237:1001–1011
- Silberstein SD (1996) Divalproex sodium in headache: literature review and clinical guidelines. *Headache* 36(9):547–555
- Mathew NT, Saper JR, Silberstein SD et al (1995) Migraine prophylaxis with divalproex. *Arch Neurol* 52:281–286
- Ghose K (1999) Long term efficacy and safety of sodium valproate in patients with drug resistant migraine. *Headache Quarterly* 10(2):127–113
- Dreifuss FE, Langer DH (1998) Side effects of valproate. *Am J Med* 84[Suppl 1A]:34–41
- Klapper J (1997) Divalproex sodium in migraine prophylaxis: a dose-controlled study. *Cephalalgia* 17(2):103–108
- Ghose K, Niven B (1998) Prophylactic sodium valproate therapy in patients with drug-resistant migraine. *Methods Find Exp Clin Pharmacol* 20:353–359
- Robins L (2000) Intravenous valproate for prolonged migraine headache. *Cephalalgia* 20:333
- Mathew NT, Kailasam J (2000) Repetitive intravenous administration of valproate sodium in intractable migraine: comparison with intravenous dihydroergotamine. *Neurology* 54[Suppl 3]:A22
- Nicolodi M, Sicuteri F (1998) Negative modulators of excitatory amino acid in episodic and chronic migraine: preventing and reverting chronic migraine. *Int J Clin Pharmacol Res* 18(2):93–100
- Di Trapani G, Mei D, Marra C, Mazza S, Capuano A (2000) Gabapentin in the prophylaxis of migraine: a double-blind, randomized, placebo-controlled study. *Cephalalgia* 20:338–357
- D'Andrea G, Granella F, Cadaldini M, Manzoni GC (1999) Effectiveness of lamotrigine in the prophylaxis of migraine with aura: an open pilot study. *Cephalalgia* 19:64–66
- Lampl C, Buzath A, Klinger D, Neuman K (1999) Lamotrigine in the prophylactic treatment of migraine aura: a pilot a study. *Cephalalgia* 19(1):58–63
- Steiner TJ, Findley LJ, Yuen AW (1997) Lamotrigine versus placebo in the prophylaxis of migraine with and without aura. *Cephalalgia* 17:109–112
- D'Andrea G, Bussone G, Granella F, Leone M, Rigamonti A, Nappi G (2000) Treatment of SUNCT syndrome with lamotrigine. *Cephalalgia* 20:377–384
- D'Andrea G, Granella F, Cadaldini M (1999) Possible usefulness of lamotrigine in the treatment of SUNCT syndrome. *Neurology* 22:53(7):1609
- Freitag GF, Diamond S, Diamond ML (1999) Tiagabine in the prophylaxis of migraine. *Neurology* 52[Suppl 2]:A208
- Edwards KR, Glantz MJ, Norton A, Cross N (2000) Prophylactic treatment of episodic migraine with topiramate: a double-blind, placebo-controlled trial in 30 patients. *Cephalalgia* 20:316
- Wheeler SD, Carrazzana EJ (2000) Topiramate-responsive cluster headache. *Cephalalgia* 20:325–331
- Potter DL, Hart DE, Calder CS, Storey JR (2000) A double-blind, randomized, placebo controlled, parallel study to determine the efficacy of Topamax (Topiramate) in the prophylactic of migraine. *Neurology* 54[Suppl 3]:A14
- Di Trapani G, Mei D, Marra C, Mazza S, Capuano A (2000) Use of Topiramate as prophylactic treatment in migraine: result of a pilot study. *Cephalalgia* 20:338–357
- Randal L, Von Seggern, Mannix Lisa K, James U (2000) Efficacy of Topiramate in migraine prophylaxis: a retrospective chart analysis. *Neurology* 54[Suppl 3]:A267
- Young WB, Hopkins MM, Sanchez Del Rio M, Shechter AL (2000) The effect of Topiramate on weight in chronic daily headache and episodic migraine patients. *Cephalalgia* 20:338–357
- Silberstein SD (1997) Preventive headache treatment. *Cephalalgia* 17:67–72