

Antiepileptic drugs: indications other than epilepsy

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ABSTRACT – Antiepileptic drugs (AEDs) are increasingly used for the treatment of several non-epileptic neurological conditions and psychiatric disorders. Most of the information available on the use of these agents in clinical disorders outside epilepsy is from case series, uncontrolled studies or small randomised clinical trials, and their apparent efficacy requires confirmation through well designed, large, phase III trials.

With regard to neurological conditions other than epilepsy, experimental evidence for the efficacy of AEDs is only available for the treatment of patients with trigeminal neuralgia, neuropathic pain syndromes, migraine and essential tremor. Carbamazepine is commonly prescribed as first-line therapy for patients with trigeminal neuralgia. Gabapentin has been recently marketed for the management of neuropathic pain syndromes, particularly diabetic neuropathy and postherpetic neuralgia. Valproic acid (sodium valproate), in the form of divalproex sodium, is approved for migraine prophylaxis. Primidone can be considered a valuable option for the treatment of essential tremor.

AEDs are also used to treat psychiatric conditions, in particular bipolar disorder. So far, the most commonly utilized AEDs in the treatment of this disorder have been carbamazepine and valproic acid, which have showed an antimanic effect and a probable long-term, mood-stabilizing effect in many bipolar patients, including those refractory or intolerant to lithium. The availability of a new generation of AEDs has broadened the therapeutic options in bipolar disorder. Lamotrigine, oxcarbazepine, gabapentin and topiramate appear to be promising in the treatment of refractory bipolar disorder, as a monotherapy as well as in combination with traditional mood stabilizers. In addition, newer AEDs appear to have a more favourable tolerability and drug interaction profile as compared to older compounds, so thus improving compliance to treatment.

KEY WORDS: antiepileptic drugs, trigeminal neuralgia, neuropathic pain, migraine, essential tremor, bipolar disorder

Antiepileptic drugs (AEDs) are widely used for the treatment of a variety of nonepileptic neurological conditions and psychiatric disorders. This presumably reflects their complex mechanism of action involving a wide range of pharmacological effects on different neurotransmitter systems and ion channels. Information from the utilization of both traditional and newer AEDs in some clinical disorders other than epi-

lepsy has been mostly based on case reports, uncontrolled studies or small randomised clinical trials and thus can not be used to determine the efficacy and safety of these medications. In other cases, evidence for efficacy has been supported by well designed, large, phase III trials and some AEDs are approved for selected indications.

The present article reviews the available evidence for the efficacy and

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safety of AEDs for the treatment of neurological conditions outside epilepsy and psychiatric disorders. For each clinical indication, an attempt has been made to identify the rationale for using AEDs, to describe the main results of randomized clinical trials or, if not available, of relevant open-label studies, and to examine the role played by AEDs in the overall treatment of that condition.

Use of antiepileptic drugs in neurological conditions other than epilepsy

Older and newer AEDs are increasingly used for the treatment of various neurological disorders other than epilepsy. Evidence from randomized clinical trials indicates that trigeminal neuralgia, neuropathic pain, migraine and essential tremor are the clinical conditions for which some AEDs may represent the treatment of choice or a valuable alternative to standard treatments [1].

Trigeminal neuralgia

Trigeminal neuralgia, also known as *tic douloureux*, is a paroxysmal form of facial pain usually affecting the second and third division of the trigeminal nerve. The abrupt nature of the painful attacks (with a temporal profile similar to that of seizures), led to the discovery that some anticonvulsant drugs are effective against this condition. Carbamazepine is commonly prescribed as first-line therapy for trigeminal neuralgia [2, 3]. Other traditional and newer anticonvulsants including valproic acid (sodium valproate), lamotrigine, gabapentin and topiramate have been used for the treatment of trigeminal neuralgia. With the exception of valproic acid and lamotrigine, evidence of their efficacy is based on uncontrolled studies and their use in clinical practice can not be recommended. The results of randomized clinical trials on the use of AEDs in patients with trigeminal neuralgia are illustrated in *Table 1*.

Carbamazepine

Carbamazepine can be considered the drug of choice for the treatment of trigeminal neuralgia [2, 3]. Its effect on pain suppression probably occurs via central and peripheral mechanisms. Carbamazepine exerts a use-dependent inhibition of sodium channels and reduces the frequency of sustained repetitive firing of action potential in neurons [4].

The experience with carbamazepine dates back to 1962 when Bloom first described its analgesic effect in patients with trigeminal neuralgia [5]. Since then several randomized clinical trials, reviewed by Beghi [4], have documented the effectiveness of carbamazepine [6-12]. In these trials, carbamazepine, used at a daily dose ranging from 100 to 2 400 mg, was manifestly superior to placebo [6-9] and more effective or better tolerated than other active comparators such as tizanidine [10], tocainide [11] and pimozide [12].

Carbamazepine effectively relieves the pain of trigeminal neuralgia in 70 to 80% of patients initially. Effective pain relief continues in approximately 50% of cases after prolonged administration. In order to avoid initial toxicity, the starting dose may be 100-200 mg/day. The daily dose should be then increased gradually until pain relief or adverse effects occur, up to 1 000-1 200 mg. Due to the spontaneous remission of pain and the toxic effects during chronic treatment with carbamazepine, drug discontinuation is recommended after two-three months in patients with pain relief. In patients not responding to carbamazepine, other anticonvulsants such as phenytoin, gabapentin, lamotrigine or topiramate could be attempted as monotherapy or in combination. In a controlled study of patients with trigeminal neuralgia, optimal pain control was documented at the concentration range of 5.7 to 10.1 µg/mL [13]. The metabolite of carbamazepine, carbamazepine-10,11-epoxide, has antineuralgic efficacy comparable to the parent compound [14].

Phenytoin

Evidence for the efficacy of phenytoin in trigeminal neuralgia is based only on uncontrolled studies [2]. Pain relief is obtained in approximately 60% of patients initially. As tachyphylaxis may develop within a short time, only about 20-30% of patients will experience sustained pain relief. Phenytoin should be used at dosages ranging from 300 to 600 mg/day. The greatest practical value of phenytoin lies in the management of patients presenting with acute neuralgic crisis. Since phenytoin, unlike carbamazepine, can be administered intravenously, crescendo attacks can be controlled rapidly with a loading dose of 12 mg/kg at 50 mg/min. A combination of carbamazepine and phenytoin has been claimed to be effective when either drug alone is inadequate.

Valproic acid

The effectiveness of valproic acid for the pain of trigeminal neuralgia was initially evaluated in a single, open-label trial, where it demonstrated some benefit [15]. In a subsequent double-blind trial, Desai *et al.* [16] studied the effect of sodium valproate 800 to 1600 mg/day in patients with trigeminal neuralgia resistant to carbamazepine. During three months of follow-up, eight out of 10 patients receiving valproic acid alone reported a 50 to 75% improvement (as defined as a reduction in the frequency of attacks), as compared to only two out of 10 control patients receiving carbamazepine alone.

Lamotrigine

In a double-blind, placebo-controlled, crossover study, lamotrigine, at a maintenance dose of 400 mg/day, was administered as add-on treatment to 14 patients with trigeminal neuralgia refractory to carbamazepine or phenytoin [17]. Lamotrigine was significantly superior to placebo ($P = 0.011$), based on a composite efficacy index. Seven out of 13 patients experienced unwanted effects,

Table 1. Randomized clinical trials of anti-epileptics for the treatment of trigeminal neuralgia.

Study (Ref.)	No. treated (diagnosis)	Design	Daily dosage	Duration	Main outcome
Carbamazepine (CBZ)					
Rockliff and Davis, 1966 [6]	9	db, pc, co	600 mg	three days	CBZ preferred by 8/9; CBZ and placebo equally effective in 1/9
Campbell <i>et al.</i> , 1966 [7]	77	db, pc, co	400-800 mg	four weeks	Responders: CBZ 57%; placebo 15%
Killian and Fromm, 1968 [8]	42 (30 with trigeminal neuralgia)	db, pc, co	400-1 000 mg	10 days	CBZ: mild improvement to complete recovery in all patients; placebo: minimal or no improvement in all patients
Nicol, 1969 [9]	64 (54 with trigeminal neuralgia)	db, pc, pco	100-2 400 mg	two weeks	Responders: CBZ 15/20; placebo 6/24
Vilming <i>et al.</i> , 1986 [10]	12	db, ac, pg	CBZ: 900 mg, tizanidine: 18 mg	three weeks	Responders: CBZ 4/6; tizanidine 1/5
Lindstrom and Lindblom, 1987 [11]	12	db, ac, co	CBZ: max tolerated dose, Tocainide: 60 mg/kg	two weeks	CBZ and tocainide equally effective (12/12)
Leichin <i>et al.</i> , 1989 [12]	48	db, ac, co	CBZ: 300-1 200 mg, pimoziide: 4-12 mg	eight weeks	Responders: CBZ 27/48; pimoziide 18/48
Valproic acid (VPA)					
Desai <i>et al.</i> , 1991 [16]	40	db, pc, pg	VPA: 800-1 600 mg, CBZ: 600-900 mg, Baclofen: 25-75 mg	10 days	Responders: VPA + CBZ + baclofen 10/10; VPA 8/10; CBZ 2/10; baclofen 7/10
Lamotrigine (LTG)					
Zakrzewska <i>et al.</i> , 1997 [17]	14	db, pc, co, ao	400 mg	31 days	Responders: LTG 11/13; placebo 2/14

db = double-blind; **pc** = placebo-controlled; **co** = crossover; **pco** = partial crossover; **pg** = parallel group; **ac** = active control; **ao** = add-on

including dizziness, somnolence, constipation, nausea and diplopia.

Gabapentin and Topiramate

Small, open-label studies have suggested that gabapentin and topiramate may be effective in the treatment of refractory trigeminal neuralgia in patients with multiple sclerosis [18, 19]. Gabapentin, 900 to 2 400 mg/day, induced complete pain relief in six out of seven patients [18]. Pain relief reached the maximum effect within two weeks and was maintained for up to one year. Topiramate, 200 to 300 mg/day, had a beneficial effect in five out of six multiple sclerosis patients [19]. Relief of pain typically occurred within one week of therapy and patients remained pain-free for at least six months.

Neuropathic pain

Neuropathic pain is a form of chronic pain caused by injury to or disease of central and peripheral nervous system. It includes trigeminal neuralgia, already covered in the previous section, neuralgias affecting other cranial

or peripheral nerves (glossopharyngeal, superior laryngeal), postherpetic neuralgia, diabetic neuropathy, central post-stroke pain syndrome, phantom limb pain, tabetic pain, cancer pain and others. Neuropathic pain responds poorly to standard therapeutic approaches for pain and to standard doses of opioid analgesics [20, 21]. Over the past two decades, knowledge of the pathogenesis of neuropathic pain has increased significantly. Neuropathic pain, whether of peripheral or central origin, is characterized by a neuronal hyperexcitability in damaged areas of the nervous system [20-22]. Such a hyperexcitability is due to a series of molecular changes in the peripheral nociceptor, dorsal root ganglia, the dorsal horn of the spinal cord, and the brain. These changes include abnormal expression of sodium channels, increased activity at glutamate receptors, changes in gamma-aminobutyric acid inhibition, and an alteration of calcium influx into cells. The similarities between the biochemical and molecular changes observed in some epilepsy and neuropathic pain models justify the use of AEDs in the management of neuropathic

pain. Carbamazepine and phenytoin were the first AEDs to be used in controlled clinical trials (Table 2). The availability of newer AEDs has marked a new era in the treatment of neuropathic pain. While gabapentin has the most clearly documented analgesic effect, other agents, including lamotrigine, topiramate and pregabalin, have also been under investigation (Table 2).

Carbamazepine

Six randomized clinical trials have evaluated the efficacy of carbamazepine, administered at daily dosages ranging from 150 to 1 000 mg, in neuropathic pain other than trigeminal neuralgia [23-28]. Two of these studies were performed in patients with painful diabetic neuropathy: in one study the drug was compared with placebo [23], and in the other with nortriptyline-fluphenazine [24]. Carbamazepine was more effective than placebo and similar to the tricyclic-neuroleptic combination in the treatment of diabetic neuropathy. The efficacy of carbamazepine in patients with postherpetic neuralgia was assessed in two studies [25, 26]. In the first trial, the combination carbamazepine-clomipramine was more effective than transcutaneous nerve stimulation [25], while in the second, the drug was less effective than prednisolone [26]. In one study of patients with central post-stroke pain, there was no statistically significant difference between carbamazepine and placebo in pain relief [27]. In a more recent double-blind, placebo-controlled, crossover study in patients with Guillain-Barré syndrome in the intensive care unit, the pain score was significantly ($P < 0.001$) lower during carbamazepine than placebo phase [28]. Case reports and open series indicate that carbamazepine may be effective also in glossopharyngeal neuralgia, phantom limb pain, multiple sclerosis and thalamic syndrome [29].

Phenytoin

Few randomized placebo-controlled studies have evaluated the efficacy of phenytoin, administered orally at an average dose of 300 mg/day, in patients with diabetic neuropathy [30, 31] and Fabry's disease [32]. While the results of studies in patients with diabetic neuropathy were conflicting, phenytoin was more effective than aspirin 1 700 mg/day and placebo in patients with Fabry's disease. In a recent double-blind, placebo-controlled, crossover study, a two hour intravenous infusion of 15 mg/kg phenytoin showed a significant analgesic effect in acute exacerbation of neuropathic pain [33]. Although these studies provide some evidence for the efficacy of phenytoin in the management of neuropathic pain, data on its utility are still lacking.

Gabapentin

Gabapentin has been recently approved in several countries for the symptomatic treatment of neuropathic pain in adults, particularly diabetic neuropathy and postherpetic neuralgia. Although its mode of action is not fully understood, gabapentin appears to have a unique effect on

voltage-dependent calcium ion channels at the postsynaptic dorsal horns and may, therefore, interrupt a series of events that possibly lead to the experience of a neuropathic pain sensation [34]. Data from case reports, open studies and randomized, placebo-controlled trials have documented the efficacy of gabapentin in the treatment of painful diabetic neuropathy, postherpetic neuralgia, and other neuropathic pain syndromes [35]. In particular, gabapentin appears to relieve symptoms of allodynia, burning pain, shooting pain, and hyperesthesia.

In a double-blind trial, 165 patients with chronic painful diabetic neuropathy were randomly assigned to receive gabapentin (titrated from 900 to 3 600 mg/day or maximum tolerated dosage) or placebo [36]. At the eight-week study end point, for the intention-to-treat population, the gabapentin group had a significant improvement ($P < 0.001$) in mean daily pain scores compared with the placebo group. Pain relief was already observed during the second week of treatment after the gabapentin dosage reached 1 800 mg/day and was maintained after further dosage increase and for the overall duration of the study. In a trial with a very similar design, gabapentin was compared with placebo in 229 patients with postherpetic neuralgia [37]. The average daily pain score, the primary efficacy parameter, was significantly reduced ($P < 0.001$) in the gabapentin-treated group compared with the placebo-treated group from week two until the end of study week eight, without signs of tolerance. In both studies, symptoms frequently associated with chronic pain were also evaluated; sleep, mood and quality of life were improved during gabapentin treatment. One randomized, double-blind crossover study compared gabapentin (900 to 1 800 mg/day) and amitriptyline (25 to 75 mg/day) in patients with peripheral diabetic neuropathy [38]. At the end of the six-week study period, both drugs provided a significant and comparable analgesic effect. In the gabapentin-treated group, sedation and dizziness were the most common adverse effects, while in the amitriptyline group dry mouth and weight gain were the most frequent. In a seven-week, randomized, double-blind, placebo-controlled trial, the efficacy and tolerability of fixed doses of gabapentin, 1 800 and 2 400 mg/day were assessed in 334 patients with postherpetic neuralgia [39]. At the end of the study, the difference in mean pain scores between gabapentin and placebo was 18.8% for the 1 800 mg dose and 18.7% for 2 400 mg dose ($P < 0.01$, both gabapentin groups *versus* placebo). Statistically significant reductions in daily pain scores for gabapentin and placebo were already achieved at week one, when the gabapentin dose was 1 200 mg/day. Gabapentin was well tolerated, with the most common adverse effects being dizziness and somnolence. A large eight-week, double blind, placebo-controlled trial evaluated the efficacy and safety of gabapentin, 900 to 2 400 mg/day, in patients with a wide range of neuropathic pain syndromes with at least two of the following symptoms: allodynia, burning pain, shooting pain or hyperalgesia [40]. At the end of treatment,

Table 2. Randomized clinical trials of anti-epileptics for the treatment of neuropathic pain.

Study (Ref.)	No. treated (diagnosis)	Design	Daily dosage	Duration	Main outcome
Carbamazepine (CBZ)					
Rull <i>et al.</i> , 1969 [23]	30 (diabetic neuropathy)	db, pc, co	Up to 600 mg	two weeks	Responders: CBZ 28/30; placebo 19/30
Gomez-Perez <i>et al.</i> , 1996 [24]	16 (diabetic neuropathy)	db, pc, co	CBZ: 600 mg, fluphenazine + nortriptyline: 1.5 mg + 30 mg	four weeks	No difference between treatments
Gerson, 1977 [25]	29 (post-herpetic neuralgia)	ac, co	CBZ + clomipramine: 150-1 000 mg + 10-75 mgTCN	eight weeks	CBZ + clomipramine more effective than TCN
Kezkes and Basheer, 1980 [26]	40 (acute <i>herpes zoster</i>)	db, ac, pg	CBZ: 400 mg, prednisolone: 40 mg	four weeks	CBZ less effective than prednisolone in reducing pain severity
Leijon and Boivie, 1989 [27]	15 (stroke)	db, pc, ac, pg	CBZ: up to 800 mg, amitriptyline: up to 75 mg	four weeks	Responders: CBZ 5/14; amitriptyline 10/15; placebo 1/15
Tripathi and Kaushick, 2000 [28]	12 (Guillain-Barrè syndrome)	db, pc, co	300 mg	seven days	CBZ more effective than placebo
Phenytoin (PHT)					
Saudek <i>et al.</i> , 1977 [30]	12 (diabetic neuropathy)	db, pc, co	300 mg	23 weeks	PHT similar to placebo
Chadda and Mathur, 1978 [31]	40 (diabetic neuropathy)	db, pc, co	300 mg	two weeks	Responders: PHT 28/38; placebo 10/38
Lockman <i>et al.</i> , 1973 [32]	eight (Fabry's disease)	db, pc, ac, co	PHT: up to 300 mg, Aspirin: 1 700 mg	three weeks	PHT superior to aspirin in relieving subjective pain
McCleane, 1999 [33]	20 (acute exacerbation of neuropathic pain)	db, pc, co	15 mg/kg infusion	two hours	PHT superior to placebo in decreasing burning, shooting and overall pain
Gabapentin (GBP)					
Backonja <i>et al.</i> , 1998 [36]	165 (diabetic neuropathy)	db, pc, pg	900-3 600 mg	eight weeks	Response rate: GBP 47.6%; placebo 20.0%
Rowbotham <i>et al.</i> , 1998 [37]	229 (post-herpetic neuralgia)	db, pc, pg	900-3 600 mg	eight weeks	Response rate: GBP 29.4%; placebo 12.1%
Morello <i>et al.</i> , 1999 [38]	21 (diabetic neuropathy)	db, ac, co	900-1 800, amitriptyline 25-75	six weeks	Response rate: GBP 52%; amitriptyline 67%
Rice and Maton, 2001 [39]	334 (post-herpetic neuralgia)	db, pc, pg	1 800 mg 2 400 mg	seven weeks	Response rate: GBP 1800 32.2%; GBP 2400 34.3%; placebo 14.4%
Serpell <i>et al.</i> , 2002 [40]	305 (various neuropathic pain syndromes)	db, pc, pg	900-2 400 mg	eight weeks	Response rate: GBP 21.9%; placebo 14.9%
Lamotrigine (LTG)					
Simpson <i>et al.</i> , 2000 [45]	42 (painful HIV-associated neuropathy)	db, pc, co	300 mg	14 weeks	LTG more effective than placebo in reducing pain
Vestergard <i>et al.</i> , 2001 [46]	30 (central post-stroke pain)	db, pc, co	200 mg	eight weeks	LTG more effective than placebo in reducing pain
McCleane, 1999 [47]	100 (various neuropathic pain conditions)	db, pc, pg	200 mg	eight weeks	LTG had no effect in reducing pain

db = double-blind; pc = placebo-controlled; co = crossover; pg = parallel group; ac = active control; TNS = transcutaneous nerve stimulation

mean daily pain scores were significantly reduced with gabapentin compared with placebo ($P < 0.05$). The most common adverse effects were mild to moderate dizziness and somnolence, most of which were transient and occurred during the titration phase. Gabapentin also appears to be effective in a variety of other painful neuropathic

syndromes such as neuropathic pain after traumatic spinal cord injury [41], Guillain-Barrè syndrome [42], postamputation phantom limb pain [43] and postoperative pain [44]. Treatment with gabapentin should be started at a dose of 900 mg/day (300 mg on day 1, 600 mg on day two, and 900 mg on day three). Additional titration to 1800 mg/day

is recommended for greater efficacy. Doses of up to 3 600 mg/day may be needed in some patients. Adverse effects are typically mild to moderate and usually tend to disappear within approximately 10 days from the beginning of treatment.

In summary, based on the positive results of these studies, its favourable tolerability profile and low potential for drug interactions, gabapentin should be considered an important agent in the management of neuropathic pain syndromes.

Lamotrigine

There is a limited and conflicting evidence on the effectiveness of lamotrigine in the management of a variety of painful neuropathic syndromes. In a double-blind, placebo-controlled study of 42 patients with HIV-associated, painful neuropathy, the mean reduction in pain score from baseline to week 14 was significantly greater ($P < 0.05$) in patients treated with lamotrigine at 300 mg/day, than in those receiving placebo [45]. However, the frequency of rash was greater than in lamotrigine studies in epilepsy. In addition, a placebo-controlled, crossover, eight-week trial, showed that lamotrigine, 200 mg/day, was more effective than placebo ($P < 0.01$) in 27 patients with central post-stroke pain [46]. In contrast to the positive results of these studies, in a randomized, double-blind, placebo-controlled trial, lamotrigine at doses of up to 200 mg/day had no analgesic effect in 100 patients with a variety of neuropathic pain conditions [47].

Topiramate

Evidence from pilot controlled trials and open-label studies indicates that topiramate may provide consistent pain relief in patients with neuropathic pain, especially diabetic neuropathy, in whom other analgesics, including other antiepileptic drugs, have failed [48]. Further studies in randomized controlled trials are needed to document these initial observations.

Pregabalin

In a recent, multicenter, eight-week, double-blind, placebo-controlled trial in 173 patients with postherpetic neuralgia, pregabalin, a new AED not yet available for clinical use, administered at doses of 300 or 600 mg/day, was significantly more effective than placebo ($P = 0.0001$) in reducing pain [49].

Migraine

The pharmacological treatment of migraine may be acute (abortive, symptomatic) or preventive (prophylactic). While triptans and ergotamine derivatives are the primary agents for migraine attacks, established drugs currently used for the prevention of migraine include beta-blockers, calcium channel antagonists, antidepressants, serotonin antagonists and nonsteroidal anti-inflammatory drugs. In

recent years, new agents, mostly AEDs, have been investigated based on their action on the metabolism of GABA and glutamic acid and, possibly, on a presumed neurogenic vascular effect [50]. In this respect, there is an increasing recognition of the role that cortical hyperexcitability and an imbalance between GABAergic inhibition and amino acid-mediated excitation may play in the pathophysiology of migraine. To date, valproic acid is the only AED approved for migraine prevention, while other newer agents, such as gabapentin and topiramate, are being evaluated (Table 3).

Valproic acid and divalproex sodium

Valproic acid (sodium valproate) was approved for migraine prophylaxis by the US Food and Drug Administration (FDA) in 1996. It is usually used in the form of divalproex sodium, an oligomeric complex composed of valproate sodium and valproic acid in a 1:1 ratio. The mechanism of action of valproic acid in migraine prophylaxis may be related to facilitation of GABAergic neurotransmission and attenuation of neurogenic inflammation [51].

Double-blind, placebo-controlled studies and a variety of open trials reviewed by Silberstein [51], have documented that valproic acid is an effective preventive treatment for migraine. In summary, randomized, placebo-controlled trials [52-55] showed that response rate among patients treated with valproic acid, 800 to 1 500 mg/day, ranged from 43 to 86% compared with 14 to 21% in those receiving placebo. The drug seemed to reduce the number, severity and duration of migraine attacks with a modest dose-response effect. Adverse effects, mostly gastrointestinal, occurred in 19 to 86% of cases (7 to 79% with placebo). Data from the two multicenter studies [54, 55] indicated that valproic acid was equally as effective in migraine with aura as in migraine without aura.

At present, there are no large comparative studies of valproic acid and traditional agents for the preventive treatment of migraine. In a small single-blind, crossover comparative study of divalproex, propranolol and placebo in 37 patients with migraine without aura, assessment of migraine frequency revealed a significant response (defined as a greater than 50% reduction in either mean migraine frequency or mean number of days with migraine compared with baseline) in 66% of patients treated with divalproex, dose range from 750 to 2 000 mg/day, in 63% of patients treated with propranolol, dose range from 120 to 240 mg/day, and in 19% of those receiving placebo [56].

In an open-label, long-term efficacy and safety study of divalproex for migraine prophylaxis, 163 patients were treated for up to three years [57]. The starting dose of divalproex was 500 mg/day, with adjustment of dose and frequency possible after one to three days. Treatment lasted more than 180 days for 71% of patients and more than 360 days for 48% of patients. Improvements in the

Table 3. Randomized clinical trials of anti-epileptics for the treatment of migraine.

Study (Ref.)	No. treated	Design	Daily dosage	Duration	Main outcome
Valproic acid (VPA)					
Hering and Kuritzki, 1992 [52]	29	db, pc, co	800 mg	eight weeks	Response rate: VPA 86%
Jensen <i>et al.</i> , 1994 [53]	43	db, pc, co	1 000-1 500 mg	12 weeks	Response rate: VPA 50%; placebo 18%
Mathew <i>et al.</i> , 1995 [54]	107	db, pc, pg	500-1 500 mg	12 weeks	Response rate: VPA 48%; placebo 14%
Klapper 1997 [55]	176	db, pc, pg	500-1 500 mg	12 weeks	Response rate: VPA 43%; placebo 21%
Topiramate (TPM)					
Edwards <i>et al.</i> , 2000 [58]	30	db, pc, pg	200 mg	18 weeks	Response rate: TPM 47%; placebo 7%
Storey <i>et al.</i> , 2001 [59]	40	db, pc, pg	25-200 mg (mean 125 mg)	16 weeks	Response rate: TPM 26%; placebo 10%
Gabapentin (GBP)					
Mathew <i>et al.</i> , 2001 [60]	143	db, pc, pg	900-2 400 mg	12 weeks	Response rate: GBP 46%; placebo 16%
Lamotrigine (LTG)					
Steiner <i>et al.</i> , 1997 [63]	77	db, pc, pg	200 mg	12 weeks	Attack rates reduced by 11% with LTG and 32% with placebo

db = double-blind; pc = placebo-controlled; co = crossover; pg = parallel group

four-week, change-from-baseline migraine rates were seen during each of the three- and six-month time intervals. Nausea (42%), infection (39%), alopecia (31%), and tremor (28%) were the most commonly reported adverse effects, but most of these resolved spontaneously with continuing treatment. The incidence of tremor, however, remained relatively constant at 20 to 30% throughout the study.

Divalproex has been used in the acute treatment of migraine. Small open studies have suggested that intravenous valproic acid is effective in acute migraine treatment [51]. Moreover, evidence from open-label trials has indicated that divalproex may be useful as preventive therapy in patients with episodic or chronic cluster headache [51].

The following practical recommendations have been proposed for the optimal use of valproic acid in migraine [51]:

- before initiating treatment, a physical medical examination and a thorough medical history, with special attention to hepatic, hematological and bleeding abnormalities, should be performed;

- to minimize gastrointestinal side effects an enteric-coated formulation should be preferably used. The starting dose is 250 mg at bedtime, slowly increasing up to 500-750 mg/day;

- follow-up serum concentrations of valproic acid should be obtained to evaluate compliance and toxicity;

- during the first six-nine months patients should be controlled on a regular basis (every one-two months);

- it is not necessary to monitor blood and urine in healthy and asymptomatic patients receiving monotherapy;

- if mild elevation of serum hepatic aminotransferase levels occurs, valproic acid should be continued at the same dosage or a lower dosage until enzyme levels normalize. If the hepatic aminotransferase elevations are much higher, valproic acid has to be discontinued;

- if tremor (which may occur in 10% of treated patients) is bothersome, the dose of valproic acid should be reduced or, alternatively, propranolol may be used;

- valproic acid should be avoided in very young children with a suspicion of a metabolic disorder, in patients with preexisting liver disease and in pregnant women.

Topiramate

Topiramate is a promising agent for migraine prevention. Two, relatively small, placebo-controlled trials have evaluated the effect of topiramate prophylaxis in patients with migraine. In the first trial [58], 30 patients who had migraine with or without aura were randomized to topiramate prophylaxis ($n = 15$) or placebo ($n = 15$). The study included a 4-week baseline phase, followed by a six-week titration and a 12-week maintenance phase. Eleven patients reached a topiramate dose of 200 mg/day (mean 173 mg/day). After 18 weeks of treatment, the mean 28-day migraine frequency was reduced by 29% in patients receiving topiramate and by 7% in those receiving placebo. Percentage of responders (subjects with $\geq 50\%$ reduction in 28-day migraine frequency) were 47% in the topiramate group and 7% in the placebo group ($P = 0.035$). Therapy was well-tolerated and discontinuation rates were similar in the two study groups. Adverse effects included paresthesia, diarrhea, altered taste and somnolence. The second study [59] lasted 20 weeks

(baseline, titration and maintenance phase of four, eight, and eight weeks), and included 40 patients who were randomly assigned to receive topiramate ($n = 19$), dose ranging from 25 to 200 mg/day, or placebo ($n = 21$). The mean 28-day migraine frequency was reduced by 36% in topiramate-treated patients as compared with 14% in placebo recipients ($P = 0.004$). In addition, 26% of patients on topiramate and 9.5% of those on placebo achieved a 50% reduction in migraine frequency. Adverse effects that occurred more frequently in topiramate-treated patients included paresthesia, weight loss, altered taste, anorexia and memory impairment.

In summary, the available data suggest that topiramate may be effective in migraine prevention. Further evaluation in double-blind, placebo-controlled trials with larger populations is needed to confirm these preliminary findings.

Gabapentin

Gabapentin is under investigation for its possible use for the prevention of migraine. In a recent 12-week multicentre prophylaxis trial of 143 patients with migraine, randomized to receive either gabapentin ($n = 98$) or placebo ($n = 45$), the median four-week migraine rate was 2.7 for patients treated with gabapentin, maintained on a stable dosage of 2 400 mg/day, and 3.5 for those treated with placebo ($P = 0.006$), compared with 4.2 and 4.1, respectively, during the baseline period [60]. Additionally, the proportion of patients showing at least 50% reduction in the migraine rate was 46.4% with gabapentin and 16.1% with placebo ($P = 0.008$). Dizziness, somnolence, and asthenia were the most commonly reported adverse effects in the gabapentin group. The Authors concluded that gabapentin was an effective and well-tolerated prophylactic agent for migraine. However, the use of a 'modified' intention-to-treat approach represents an important limitation of this study. Therefore, despite possible advantages of gabapentin over valproate in terms of tolerability and drug interaction potential, there are still no convincing data to support the use of gabapentin for the prophylaxis of migraine.

Lamotrigine

There is limited information concerning the possible use of lamotrigine in migraine treatment. While two open studies suggested that lamotrigine may be useful for preventing aura associated with migraine [61, 62], the results of a 12-week, double-blind, placebo-controlled trial in which 37 patients received lamotrigine, 200 mg/day, and 40 received placebo, indicated that lamotrigine is not effective for migraine prophylaxis [63].

Essential tremor

Essential tremor is a progressive neurological disorder characterized by oscillating movements caused by alternative contraction of agonist and antagonist muscles.

Beta-receptor blocking agents (propranolol and analogues) and the anticonvulsant primidone are considered first-line pharmacological treatment in patients with essential tremor [64]. The new anticonvulsant agents gabapentin and topiramate may represent alternative therapeutic options.

Primidone

Several open and randomized clinical trials, reviewed by Koller *et al.* [65], have documented the efficacy of primidone in essential tremor. The drug was used at dosages ranging from 50 to 1 000 mg/day. The impact of treatment was evaluated clinically and reduction of tremor was assessed with an accelerometer. Daily doses of primidone 250, 750 and 1 000 mg showed comparable efficacy and caused a tremor decrease by 60 to 70%. Adverse effects such as somnolence, fatigue, vertigo, nausea and unsteadiness, were often experienced at the beginning of treatment unless low doses (25 to 50 mg/day) were used and titrated slowly. In the only study comparing primidone with propranolol, the two agents were found to be equally effective [66]. Unlike primidone, phenobarbital and phenylethylmalonamide, the active metabolites of primidone, showed little or no evidence of efficacy in essential tremor.

Other antiepileptics

Other AEDs that may be useful in the treatment of essential tremor include gabapentin and topiramate. In a double-blind, placebo-controlled trial in 20 patients with essential tremor, gabapentin, 1 800 mg/day, added to baseline antitremor medication for 2 weeks, had only a limited treatment benefit [67]. By contrast, in a double-blind, three-way placebo- and propranolol-controlled crossover study in 16 patients with essential tremor, gabapentin, 1 200 mg/day, and propranolol, 120 mg/day, demonstrated significant and comparable efficacy in reducing tremor [68]. In a recent double-blind, placebo-controlled, crossover trial, topiramate, 400 mg/day or maximum tolerated dose, given as monotherapy or adjunctive treatment, showed a significant effect in 24 patients with essential tremor [69]. The most common adverse effects were appetite suppression/weight loss and paresthesias.

Other nonepileptic neurological conditions

In addition to the previously mentioned categories, AEDs appear to be promising in the treatment of a variety of other nonepileptic neurological conditions, including myotonia, spasticity, amyotrophic lateral sclerosis, neonatal cerebral haemorrhage, Parkinson's disease [1]. However, evidence for the efficacy of AEDs in these disorders is still inadequate and most studies are too small to detect a true difference between treatments.

Use of antiepileptic drugs in psychiatric disorders

In the last three decades, AEDs have become an integral part of the pharmacological treatment of many psychiatric conditions, in particular bipolar disorder, and an ever-increasing number of other potential indications, ranging from impulse control disorders to aggressive behavior, substance use disorders, and refractory anxiety disorders.

Bipolar disorder

Bipolar disorder is a severe, chronic and potentially life-threatening illness of recurrent mood episodes, i.e., mania, hypomania, depression and mixed states (concomitant manic and depressive symptoms), and rapid cycling (four or more episodes per year). It is subdivided into bipolar I (manic and depressive episodes) and bipolar II disorder (hypomanic and depressive episodes).

Lithium has been, for many years, the treatment of choice for bipolar disorder. The growing awareness of the limitations of lithium treatment prompted the search for alternative treatment options. In this regard, the discovery of the mood-stabilizing properties of some AEDs has significantly broadened the array of treatment options for bipolar disorder. AEDs, such as carbamazepine and valproic acid, have joined lithium as standard, brief-term treatment of manic episodes and mixed-states, and long-term prevention of relapses of bipolar disorder. Notwithstanding their efficacy and relative safety, even carbamazepine and valproic acid have important limitations and negative effects. A significant subgroup of bipolar patients, especially those characterized by a very unstable or chronic course, shows varying degrees of resistance to these drugs. Moreover, both carbamazepine and valproic acid may cause side effects, such as weight gain and impairment of cognitive functioning, which may significantly reduce compliance, and compromise long-term treatment. In addition, long-term tolerance to the mood stabilizing effect has been reported for lithium, carbamazepine and valproic acid, either in monotherapy or in combination [70, 71]. Finally, traditional mood stabilizers have shown significant efficacy on the (hypo)manic phases of bipolar disorder, but only marginal efficacy on the depressive phases, that respond less to these treatments and often require the association of antidepressants, which often themselves become the cause of side effects, manic switches, cycle acceleration, and chronicity.

The availability of a new generation of AEDs has broadened the therapeutic choices for the treatment of bipolar patients who are resistant or intolerant to traditional mood stabilizers. Among the new AEDs, lamotrigine, oxcarbazepine, gabapentin, and topiramate appear to be promising in the treatment of refractory bipolar disorder, as a monotherapy as well as in combination with traditional mood stabilizers, while preliminary evidence exists also for tiagabine and zonisamide. In general, these drugs have

a more favourable tolerability profile and a lower potential for drug interactions as compared to traditional mood stabilizers, and this may significantly improve compliance with treatment. As carbamazepine and valproic acid are well established agents in the treatment of bipolar disorder, in this section more emphasis is given to studies documenting the potential role of newer AEDs in this condition. Therefore, only results of randomized clinical trials on the use of new AEDs in patients with bipolar disorder are reported in *Table 4*.

Carbamazepine

At least 12 double-blind randomised controlled trials were reported in the '80s and early '90s, showing that carbamazepine is superior to placebo and comparable to lithium and antipsychotics in the treatment of acute mania [72-83]. However, only six of these studies [72-75, 78, 83] have not been biased by the concomitant use of lithium and antipsychotics. Summarizing this literature [84, 85], it has been possible to conclude that: 1) carbamazepine is effective in 50% of the cases, *versus* 56% of lithium and 61% of neuroleptic monotherapy (these differences are not statistically significant); 2) carbamazepine acts more rapidly than lithium, and it similar to antipsychotics in its antimanic effects; 3) in general, carbamazepine is better tolerated than lithium and antipsychotics in patients that remain in treatment, although the number of drop-out for adverse events is similar. In responders, the blood levels are similar to those utilized in epilepsy, 4-15 µg/mL, with daily dosages ranging from 400 to 2 000 mg/day.

Three, small, double-blind, placebo-controlled, crossover studies examined the efficacy of carbamazepine [82, 86, 87] in a total of 40, bipolar, depressed patients; of these patients 27 (68%) responded to carbamazepine treatment, and placebo substitution led to relapse of the depressive symptoms in 50% of the cases.

The efficacy of carbamazepine in the maintenance treatment of bipolar disorder was examined in only a small, double-blind, placebo-controlled trial (carbamazepine: $n = 12$; placebo: $n = 10$) [88]. Results indicated that 60% of patients randomized to carbamazepine, and 22% randomized to placebo were stable during the one-year study period. A number of other controlled studies compared carbamazepine with lithium, and reported that up to two-thirds of patients responded to carbamazepine [79, 89-92].

In summary, carbamazepine seems to have some efficacy in the long-term, maintenance treatment of bipolar disorder, but further studies are needed before firm conclusions can be drawn. The drug seems to be more effective in preventing manic rather than depressive recurrences, and long-term tolerance to this therapeutic effect (tachyphylaxis), has been described [93]. However, it is difficult to exclude the possibility that the loss of efficacy observed with carbamazepine during maintenance treatment of selected bipolar patients, might be due to the progression of

Table 4. Randomized clinical trials of new antiepileptics for the treatment of bipolar disorder.

Study (Ref.)	No. treated (diagnosis)	Design	Dosage	Duration	Main outcome
Lamotrigine (LTG)					
Calabrese <i>et al.</i> , 1999 [110]	195 (bipolar I: major depressive episode)	db, pc, pg	50-200	seven weeks	LTG 50 mg/day: 41%, LTG 200 mg/day: 51%, placebo: 26%
Calabrese <i>et al.</i> , 2000 [111]	182 (rapid-cycling bipolar disorder)	db, pc, pg	50-400 mg (mean: 288 mg/day)	26 weeks	LTG better than placebo on a number of outcome measures
Bowden <i>et al.</i> , 2003 [113]	175 (recently manic or hypomanic patients with bipolar I disorder)	db, pc, ac, pg	LTG: 100-400 mg/day, Lithium: 0.8-1.1 mEq/L	18 months	LTG effective in long-term maintenance, particularly for prophylaxis of depression
Oxcarbazepine (OXC)					
Muller and Stoll 1984 [115]	20 (acute mania)	db, ac, pg	OXC: 900-1 200 mg/day, haloperidol: 15-20 mg/day	two weeks	Both groups showed a significant improvement of manic symptoms, faster in the OXC group
Emrich 1985 [114]	12 (acute mania)	db, ac, pg, co	OXC: 1 800-2 100 mg/day, VPA: 1 800-3 800 mg/day	Not reported	VPA and OXC showed a significant improvement of manic symptoms in comparison with placebo
Emrich 1990 [116]	38 (acute mania)	db, ac, pg	OXC: 2 400 mg/day (mean dose), haloperidol: 42 mg/day (mean dose)	two weeks	Both drugs resulted in a statistically significant improvement; no significant difference in efficacy between the two groups
	52 (acute mania)	db, ac, pg	OXC: 1 400 mg/day (mean dose), Lithium: 1 100 mg/day (mean dose)	two weeks	Both drugs resulted in a statistically significant improvement; no significant difference in efficacy between the two groups
Gabapentin (GBP)					
Frye <i>et al.</i> , 2000 [112]	31 (bipolar patients refractory to standard mood stabilizers)	db, pc, ac, co	GBP: mean = 3 987 mg/day, LTG: mean = 274 mg/day	six weeks	LTG superior to placebo; No significant difference between GBP and placebo
Pande <i>et al.</i> , 2000 (126)	116 (patients with resistant bipolar disorder)	db, pc, ao	900-3 600 mg/day	eight weeks	No statistically significant difference between adjunctive treatment with GBP and placebo
Topiramate (TPM)					
Mc Intyre <i>et al.</i> , 2000 [141]	36 (bipolar I and II depression)	sb, ac, pg	TPM: 50-300 mg/day, bupropion SR: 100-400 mg/day	eight weeks	TPM improves depressive symptoms and produced more weight loss than bupropion

sb = single-blind; **db** = double-blind; **pc** = placebo-controlled; **co** = crossover; **pg** = parallel group; **ac** = active control

the illness, rather than the development of tolerance. Interestingly, some of the predictors of poor lithium response, such as the severity of the manic symptomatology, the presence of rapid cycling (four or more episodes/year), or mixed states, and the lack of positive family history for mood disorders [94, 95], have been associated with a favourable response to carbamazepine.

Valproic acid

Although valproic acid has been used in bipolar patients resistant or intolerant to lithium or carbamazepine for its safety and tolerability, it is today considered the first choice drug for the treatment of acute mania. Numerous open-label and controlled studies have clearly indicated

that valproic acid is effective in the treatment of acute mania [96-101]. In controlled trials [97-101], valproic acid has been shown to be superior to placebo and comparable to lithium in the short-term treatment of manic episodes; about 60% of patients treated with valproic acid showed marked to moderate improvement of acute symptomatology. The antimanic response was obtained two weeks after that the blood level of valproic acid had reached 50 µg/mL or more. However, there is preliminary evidence of a more rapid antimanic action when using high doses from the beginning. In an open study with blind evaluation of the outcome, 19 manic patients were treated with 20 mg/kg/day of valproic acid (oral loading) from the first day of treatment; 10 (53%) of these patients presented a significant clinical response after five days, with minimal side effects [102].

A placebo-controlled, parallel-design study, examined the efficacy of valproic acid monotherapy in acute bipolar depression [103]. After a single-blind placebo lead-in for up to 14 days, patients were randomized to treatment with valproic acid or placebo for eight weeks. Intent-to-treat analysis indicated that nine out of 21 (43%) subjects randomized to valproic acid and six out of 22 (27%) randomized to placebo met criteria for recovery ($P = 0.4$). Mean changes from baseline in the Hamilton Depression Rating Scale (HDRS) scores were greater in the valproic acid group, and were significant at weeks two and five, but not at the end-point, compared with the placebo group. The negative findings in this study could be due to a smaller sample size. A double-blind study compared the efficacy of adding a second mood stabilizer versus addition of paroxetine in the treatment of bipolar depression [104]. Twenty-seven patients with bipolar depression, on either lithium or valproic acid, were randomly assigned to addition of a second mood stabilizer (lithium for those on valproic acid and valproic acid for those on lithium), or paroxetine for six weeks. Both groups improved with no significant difference between the groups. Combination of lithium plus valproic acid would be an appropriate strategy for bipolar I depressed patients with a previous history of severe or refractory manic episodes, as the goal in such patients would be to relieve depressive symptoms with the least risk of inducing a manic switch.

In a placebo-controlled trial of the efficacy of valproic acid in the maintenance treatment of bipolar disorder, Bowden *et al.* [105] randomized 372 patients who met recovery criteria within three months of an index manic episode, to maintenance treatment with divalproex, lithium, or placebo in a 2:1:1 ratio. On the primary efficacy measure of time-to-any-mood episode, the divalproex group did not differ significantly from the placebo group. However, divalproex was superior to placebo in terms of lower rates of discontinuation for either a recurrent mood episode or depressive episode. Divalproex was also superior to lithium in terms of a longer duration of successful prophylaxis in the study and less deterioration in depressive

symptomatology. A controlled prospective study compared the efficacy of valproic acid ($n = 78$) with lithium ($n = 72$) in 150 patients (121 were bipolar and 29 were unipolar), over a two-year period [106]. The number of episodes decreased from 4.12 during the two years prior to the study to 0.51 in the valproic acid group, and from 3.92 to 0.61 in the lithium group; there was no significant difference in efficacy between the two groups. There were, however, fewer drop-outs (10%) in the valproic acid group compared with the lithium group (25%).

In summary, valproic acid is the first choice drug for the treatment of acute mania. In addition, it seems to be effective in the maintenance treatment of bipolar disorder, but this needs to be confirmed in further double-blind trials. Predictors of response to valproic acid seem to include rapid cycling course, depressive symptoms during mania, late age-at-onset, and mania associated with mental retardation or secondary to medical or neurological illness [107].

Lamotrigine

Initial open prospective trials provided evidence that lamotrigine may be an effective treatment option for patients with refractory forms of bipolar disorder [108]. More recently, a considerable number of systematic studies has indicated that lamotrigine may be an efficacious and well-tolerated treatment in bipolar disorder. Its efficacy principally addresses acute bipolar depression and continuation treatment, especially prophylaxis against depressive symptomatology [109]. On the other hand, lamotrigine has not been shown to have clear efficacy in the treatment of mania or unipolar depression.

With regard to bipolar depression, the double-blind seven-week comparison between lamotrigine at 50 or 200 mg/day and placebo, in 195 bipolar one patients experiencing a major depressive episode, showed that depressive symptomatology showed a significant improvement in both 50 and 200 mg/day groups [110]. According to the Clinical Global Impression (CGI) scale, 41% of the patients receiving 50 mg/day and 51% of those taking 200 mg/day of lamotrigine reported a clinical remission *versus* 26% of subjects treated with placebo. The incidence of rash was comparable between the lamotrigine and placebo groups, and there were no reports of severe rash among study participants. In a controlled study of patients with rapid-cycling bipolar disorder, Calabrese *et al.* [111] compared lamotrigine and placebo during a 26-week randomised phase. Lamotrigine was better than placebo on a number of outcome measures, in particular in bipolar II patients. These findings support the efficacy of lamotrigine in rapid cycling bipolar II disorder, which is often resistant to standard mood stabilizers, and are consistent with data reported by Frye *et al.* [112] comparing lamotrigine, gabapentin and placebo in resistant bipolar patients.

In a recent study [113], the long-term efficacy and tolerability of lamotrigine was compared with lithium and placebo in recently manic or hypomanic patients with bipolar I disorder. After an eight- to 16-week open-label phase during which treatment with lamotrigine was initiated and other psychotropic drug regimens were discontinued, patients were randomized to lamotrigine (100-400 mg daily), lithium (0.8-1.1 mEq/L), or placebo, as double-blind maintenance treatment, for a period of 18 months. Of 349 patients who met screening criteria and entered the open-label phase, 175 met stabilization criteria and were randomized to double-blind maintenance treatment (59 patients with lamotrigine, 46 with lithium and 70 with placebo). Both lamotrigine and lithium were superior to placebo at prolonging the time-to-intervention for any mood episode. Lamotrigine was superior to placebo at prolonging the time-to-a-depressive episode. Lithium was superior to placebo at prolonging the time-to-a-manic, -hypomanic, or -mixed episode. As a general conclusion of this study, lamotrigine was effective and well-tolerated in the long-term maintenance treatment of bipolar disorder, particularly for prophylaxis of depression.

In summary, lamotrigine can be considered useful in monotherapy or in combination with other mood stabilizers in bipolar depression and in rapid cycling bipolar II patients. Preliminary evidence indicates that it may also be effective in long-term prophylaxis, particularly preventing depressive episodes. On the other hand, lamotrigine does not appear to have anti-manic properties.

Oxcarbazepine

The availability of open clinical observations and controlled studies for oxcarbazepine treatment of bipolar disorder is still rather limited, but the data currently available seem to be promising.

Concerning the use of oxcarbazepine in acute mania, the first controlled, double-blind and cross-over study compared the efficacy of oxcarbazepine and valproic acid *versus* placebo in 12 patients with a diagnosis of manic psychosis [114]. The doses of oxcarbazepine ranged from 1 800 to 2 100 mg/day. All subjects showed a significant improvement of manic symptoms in comparison with placebo, and a good tolerability to the treatment. Valproic acid and oxcarbazepine showed similar efficacy. Another two-week, randomized controlled study compared the efficacy of oxcarbazepine (dose range 900-1 200 mg/day), and haloperidol (dose range 15-20 mg/day) in 20 patients with acute mania [115]. Both groups showed a statistically significant improvement in manic symptoms. These findings prompted the execution of two, two-week, double-blind, multicentric international studies that compared oxcarbazepine, lithium, and haloperidol in patients with acute mania [116]. In the first one (oxcarbazepine *versus* haloperidol), 38 manic patients were evaluated. The mean oxcarbazepine dose was 2 400 mg/day, while the

mean haloperidol dose was 42 mg/day. At the end of the two-week observation period, both drugs resulted in a statistically significant improvement in manic symptoms, measured by the Bech-Rafaelson Mania Scale (BRMS), compared to baseline, with no significant difference in efficacy between the two groups. Oxcarbazepine was significantly better tolerated, as the incidence of side effects was 3.5 times less in the oxcarbazepine group than among haloperidol-treated subjects. In the second controlled study (oxcarbazepine *versus* lithium), 52 manic patients were evaluated. Mean dosages were 1 400 mg/day for oxcarbazepine and 1 100 mg/day for lithium. At the end of the observation period, there was a significant improvement in manic symptoms compared to baseline, with no significant difference in efficacy and tolerability between the two groups.

Other studies have evaluated the prophylactic efficacy of oxcarbazepine in preventing bipolar relapses compared with lithium, in two small groups of manic ($n = 15$) and schizoaffective ($n = 15$) patients. In one, the authors found that no conclusions about the prophylactic efficacy of oxcarbazepine could be drawn, but treatment with oxcarbazepine at a dose level of 900 mg/day was related to a reduction in the frequency and intensity of manic and depressive episodes similar to that with lithium therapy [117]. Another study found that subjects treated with oxcarbazepine had more frequent relapses than those treated with lithium [118]; it must be noted however, that this study was limited by the fact that some patients treated with oxcarbazepine were non-responders to lithium, and there was a higher dropout rate in the oxcarbazepine group.

Our group [119], conducted a chart review on 48 patients with DSM-IV bipolar I disorder. All patients were resistant or intolerant to standard mood stabilizers. Oxcarbazepine was used either as monotherapy ($n = 9$), or added to the ongoing treatments ($n = 39$) with conventional mood stabilizers, antidepressants, and antipsychotics to which patients had not responded after a period of at least 12 weeks. The mean duration of oxcarbazepine treatment was 23.6 weeks (range 4-64), with a mean final dose of $1\ 218 \pm 48$ mg/day (range 600-2 400 mg/day). Oxcarbazepine induced an improvement in bipolar symptoms and global functioning in more than 60% of our patients. In particular, the drug seems to be more effective in manic and mixed, than in depressive, symptomatology. In our sample in fact, non-responders showed more frequent depression during the index episode compared to responders. Moreover, two patients interrupted the oxcarbazepine during the observation period due to the reappearance of depression.

In conclusion, knowledge of the mood stabilizing properties of oxcarbazepine is still rather limited. Future placebo-controlled studies are particularly needed to specifically investigate the antidepressant, anti-anxiety and anti-

manic properties of oxcarbazepine. Because of its favourable tolerability and drug interaction profile in comparison with other mood stabilizers, oxcarbazepine appears to be a promising agent as an adjunct treatment for those patients who have partial or no response to standard therapeutic regimens.

Gabapentin

A relevant number of case reports and open studies, reviewed by Carta *et al.* [120], involving at least 600 patients, indicate that gabapentin may be effective as an adjunctive treatment of acute (hypo)mania, and may play an important role in treatment of refractory bipolar disorder. Available data on the comparison of gabapentin as a single or adjunct treatment indicate that it may be efficacious if administered alone, in a subgroup of bipolar patients with mild or moderate symptoms, whereas it may be useful in association with standard mood stabilizers in severe manic or mixed states.

Most studies evaluated the efficacy of gabapentin in acute treatment of manic or hypomanic episodes [120, 121] and reported rates of response ranging from 37% to 92%. Several studies [122-124] suggest that gabapentin may be also useful as an additional treatment for bipolar mixed states, which have partial or no response to traditional mood stabilizers. These studies, however, are conflicting. A study by our group of 21 patients with bipolar mixed state [123], found that gabapentin has remarkable efficacy on depressive symptoms, while the effects on the manic features were limited. However, another study found that a one-month treatment with gabapentin was useful for both manic and depressive symptoms [124].

Data on the efficacy of gabapentin in long-term maintenance treatment are still limited. A recent study by Schaeffer and Schaeffer [125], re-evaluated the effectiveness in long-term maintenance treatment in a group of bipolar subjects that were refractory to traditional mood stabilizers but who had responded to short-term adjunctive treatment with gabapentin. Thirty-nine percent of the group had experienced significant benefit from the adjunctive treatment with gabapentin.

While open studies are in overall agreement about the efficacy of gabapentin in bipolar spectrum disorders, results from the controlled studies available tend to contradict these findings [112, 126]. Frye *et al.* [112] reported a crossover comparison of gabapentin, lamotrigine and placebo in 31 bipolar patients who were refractory to standard mood stabilizers. Single lamotrigine treatment was superior to placebo (52% of patients who received lamotrigine responded versus 23% of the placebo group), while there were no significant differences between gabapentin and placebo. Another study by Pande *et al.* [126] found no statistically significant differences between adjunctive treatment with gabapentin and placebo in 116 patients with resistant bipolar disorder. However, it must be noted that some methodological limitations in the latter study

may have reduced the validity of the results (reduced compliance, non-homogeneous composition of the sample, frequent modification of the associated mood-stabilizer treatments in the placebo group). Several hypotheses have been developed to explain the controversial results of the controlled studies. Some authors [126, 127] suggest that gabapentin may be efficacious on one or more symptom dimensions that are not adequately catered for by the rating scales used in controlled studies. In this regard, it must be noted that gabapentin appears to have also an important anti-anxiety effect, as indicated by its efficacy in controlled studies on panic disorder [128] and social phobia [129].

In a recent study [130], we evaluated the predictors of response for gabapentin as an adjunctive treatment in a sample of 43 subjects with DSM-III-R bipolar disorder, who were resistant to standard mood stabilizers. Gabapentin was administered as an adjunctive treatment for an eight-week period, in combination with other mood stabilizers, benzodiazepines, antidepressants, and neuroleptics. Eighteen (41.9%) out of 43 patients who began treatment were considered responders. From our data, gabapentin seems to have antidepressant and anxiolytic properties. The improvement in depressive and anxiety symptoms was independent of the severity of the manic features. On the other hand, manic symptoms did not show a significant improvement, not even in those patients where they were the dominant clinical feature.

Other recent studies have reported the efficacy of gabapentin on major depression in unipolar and bipolar patients [131, 132]. The observation of a specific efficacy in bipolar patients who have co-morbid panic disorder or alcohol abuse (and maybe social phobia) appears to be of great importance. If these findings were to be confirmed in larger samples, these properties would have great relevance for clinical practice.

The very favourable pharmacological profile of this drug, in comparison with traditional mood stabilizers, underscores the great tolerability and safety of gabapentin as an adjunct treatment for those patients who have partial or no response to standard therapeutic regimens.

Topiramate

The use of topiramate in the treatment of bipolar disorder has been recently reviewed [133]. Initially, topiramate was evaluated in mood disorders refractory to previous treatments, including the newer AEDs. Marcotte [134], reviewed charts of 58 consecutive patients (39 outpatients and 19 inpatients). Forty-four patients had rapid cycling bipolar disorders characterized by manic, hypomanic, or mixed episodes; 18 patients had previously failed to respond to lamotrigine and/or gabapentin in addition to conventional mood stabilizers. The mean duration of topiramate treatment was 16.0 weeks and the mean dose level approximately 200 mg/day. Thirty-six (62%) out of the 58 patients exhibited marked or moderate improvement.

Adverse events were predominantly related to the gastrointestinal tract (i.e., nausea, and diarrhoea) and central nervous system (i.e., paresthesias, somnolence, fatigue, impaired concentration and memory). Chengappa *et al.* [135] reported data on 20 patients, 18 with DSM-IV bipolar I disorder and two subjects with resistant schizoaffective disorder bipolar type. Topiramate was started at 25 mg/day and increased by 25-50 mg every three-seven days up to a target dose of between 100 and 300 mg/day, as other medications were held constant for five weeks. By week five, 12 (60%) subjects were responders; all patients lost weight with a mean loss of 9.4 lb in 5 weeks, with a significant reduction in body mass index (BMI). McElroy *et al.* [136] evaluated the response of 56 bipolar outpatients who had been treated with adjunctive topiramate in an open-label, naturalistic fashion. Of the 54 patients who completed at least two weeks of treatment, 30 had manic, mixed, or cycling symptoms, 11 had depressed symptoms, and 13 were relatively euthymic at the time topiramate was begun. Patients who had been initially treated for manic symptoms displayed significant reductions in standard ratings scores after four weeks, after 10 weeks, and at the last evaluation. Those patients who were initially depressed or treated while euthymic showed no significant changes. Patients as a group displayed significant decreases in weight and body mass index from topiramate initiation to week four, to week 10, and to the last evaluation. The effect of adjunctive topiramate was also evaluated in 11 patients in an on-off study design [137]. Topiramate was added after stable plasma levels of concomitant mood stabilizers had been reached, and was titrated within one week to a final dose range of 25 to 200 mg/day. Topiramate was discontinued after 10 days, while concomitant medication remained unchanged. After five days, topiramate was reintroduced at similar or increased dosages for another seven days. Seven of the 11 patients initially showed a good response with > 50% reduction in Young Mania Rating Scale (YMRS) score. One patient showed psychotic features following a rapid increase in topiramate dosage and dropped out on day 10. After discontinuation of topiramate, seven of the remaining 10 patients worsened, two remained stable, and one discontinued follow-up after good recovery. After reintroducing topiramate, all patients improved again within a week. With the exception of the patient who developed psychosis, topiramate was well tolerated and did not interfere with plasma levels of concomitant medication, except for the level of carbamazepine in one patient.

The employment of topiramate as a monotherapy (dose range 50-1 600 mg/day) was firstly evaluated by Calabrese *et al.* [138], who conducted an open study on ten manic inpatients. After a mean period of 16 days (maximum 28 days), three patients showed a marked improvement, one moderate, four minimal or absent and two patients were judged worsened; the drug appeared to be well tolerated. Ghaemi *et al.* [139] in a retrospective study

reported on 76 patients with bipolar spectrum disorders that were treated with topiramate. Results showed that 47% of subjects ($n = 36$) had a "mild" improvement, 13% ($n = 10$) a "moderate" or "marked" improvement; 50% of the sample subjects showed a weight loss, the size of which was directly related to the dosage of topiramate. Most frequently reported side effects, in addition to weight loss, were cognitive difficulties, sedation, paresthesia, nausea, insomnia, and headache.

As regard treatment-resistant bipolar patients, Guille and Sachs [140] reported data on 14 patients attending a bipolar clinic who were treated with topiramate for an average of 22.4 weeks. Nine of these patients (64%) experienced an increased level of functioning and a decrease in symptom severity during treatment with adjunctive topiramate. Eleven patients remained on treatment for longer than two weeks. Eight patients (73%) experienced a significant improvement in their co-morbid conditions.

McIntyre *et al.* [141] evaluated the efficacy and tolerability of topiramate and bupropion SR, when added to mood stabilizer under single-blind conditions (rater-blinded), in patients meeting DSM-IV criteria for bipolar I and II depression. A total of 36 out-patients with HDRS scores = 16 were randomized to receive escalating doses of either topiramate (50-300 mg/day) or bupropion SR (100-400 mg/day) for eight weeks. A significant and comparable reduction in depressive symptoms was observed from baseline to endpoint following topiramate (56%) and bupropion SR (59%) treatment. Both topiramate and bupropion SR were generally well-tolerated; 13 patients discontinued the study: two because of lack of efficacy, one due to withdrawal of consent and 10 following side-effects (six in the topiramate and four in the bupropion SR-treated group). Topiramate produced greater weight loss (mean = 5.8 kg) than bupropion (mean = 1.2 kg). These preliminary data suggest that adjunctive topiramate may reduce depressive symptom severity in acute bipolar depression.

The preliminary results concerning the use of topiramate in bipolar disorder appear promising, especially for adjunctive treatment for patients who are non-responders to other mood stabilizers. The appetite-reducing effect of the drug, which was remarkably demonstrated in the various studies, has interesting prospects for the treatment of the patients with bipolar disorder and co-morbid bulimia nervosa, binge-eating disorder or obesity. The antidepressant efficacy of this compound requires confirmation via double-blind, placebo-controlled studies. In addition, topiramate offers a favourable side-effect profile, which includes decreased appetite and weight loss in some patients.

Tiagabine and zonisamide

Tiagabine and zonisamide have only been evaluated in few, small, open case-series. Initially, a 14-day open trial with tiagabine was conducted in eight acutely manic

inpatients with DSM-IV bipolar I disorder, two of them as monotherapy and six as an add-on to previously insufficient mood-stabilizing medications [142]. None of the patients showed clear-cut relief from manic symptoms during the two-week observation period. Subsequently, Schaffer *et al.* [143] treated in an open fashion with adjunctive tiagabine at a low-dose range (1-8 mg/day), 22, adult, bipolar outpatients, who were considered unsatisfactory responders to standard medications. After six months, eight (36%) of the patients were considered responders. All 14 non-responders had to discontinue tiagabine because of unacceptable, but reversible, side effects; one non-responder experienced breakthrough absence seizures. Finally, 17 treatment-refractory patients participating in the Stanley Foundation Bipolar Network long-term follow-up study were offered open treatment with add-on tiagabine [144]. Four patients discontinued low-dose tiagabine prior to the second visit and were excluded from data analysis; 13 patients received a mean of 38 days of treatment at a mean dose of 8.7 mg/day of tiagabine. Only three (23%) patients showed noticeable or very noticeable improvement, and 10 (77%) patients showed no change, or worsening. Significant adverse events were noted, including two presumed seizures.

Available evidence appears to indicate a limited efficacy of tiagabine for acute mania. Moreover, an unfavorable side-effects profile is reported, in particular at high doses. At the moment, tiagabine cannot be recommended for use in patients with bipolar disorder.

The effect of adjunctive zonisamide (100-600 mg/day) was examined in 24 patients (15 bipolar manic, six schizoaffective manic, and three excited schizophrenic) [145]. Approximately 71% of all the patients and 80% of the bipolar group had more than a moderate global improvement; 25% of all the patients and 33% of the bipolar manic patients showed remarkable global improvement. No serious adverse reactions were found and no patients required zonisamide withdrawal. One patient developed both leukocytosis and mildly abnormal liver function tests. One developed leukocytosis and another reported mild sleepiness. These reactions disappeared when zonisamide was discontinued. Further controlled studies are necessary in order to confirm a possible role for zonisamide in the treatment of bipolar disorder.

Other psychiatric disorders

AEDs have been utilized in a variety of other psychiatric conditions characterized by "atypical" anxiety, impulsivity and aggressive behaviour. Preliminary evidence exists also for atypical psychosis, and eating and personality disorders [146, 147]. Most information in this widening spectrum of indications is based on case series, open studies and small controlled trials and it should be considered preliminary.

Conclusions

In addition to their use for the management of epilepsy, some traditional and newer AEDs may represent the treatment of choice, or a valuable alternative to standard treatments, in a variety of nonepileptic neurological and psychiatric conditions, including trigeminal neuralgia, neuropathic pain, migraine prophylaxis, essential tremor and bipolar disorder. However, evidence for the efficacy and safety of AEDs, especially the newer compounds, for many of these disorders is still inadequate. Therefore, there is an ongoing need for controlled studies with a large number of patients and greater homogeneity of diagnosis in order to establish the efficacy of individual AEDs in the management of clinical conditions other than epilepsy. Finally, when considering the use of AEDs for nonepileptic indications, their safety profile must be weighed against their reported efficacy. In this respect, newer (AEDs) appear to have a more favourable tolerability and drug interaction profile as compared to older compounds, with subsequent advantages in terms of compliance with treatment [148]. □

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