Review

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Use of antiepileptic drugs in bipolar disorder

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Objective. Bipolar disorder is a chronic difficult to treat disease that generates a high degree of incapacity. Although lithium remains the first choice drug, some patients do not respond and others show adverse reactions. One alternative to lithium is the use of certain antiepileptic drugs. Data on the efficacy of old and new antiepileptic drugs in bipolar disorder obtained in controlled clinical trials are reviewed.

Development. Results in many clinical trial support the use of some old antiepileptic drugs such as carbamazepine and sodium valproate in monotherapy in the acute treatment of severe, mixed or mild manic episodes as well as in the management treatment of bipolar disorder. Overall, new antiepileptic drugs show a better profile of adverse reactions with fewer interactions than lithium, but data on their efficacy in bipolar disorder remain scarce. Oxcarbazepine efficacy in mania is similar to that of the carbamazepine. Lamotrigine is becoming the best alternative to lithium in depressive episodes. Topiramate does not appear to be effective in acute treatment of manic episodes. Levetiracetam seems to produce some benefits, but controlled, randomized and double blind clinical trials are not yet available. Data on gabapentin efficacy are controversial.

Conclusions. Although lithium is still the first choice for the treatment of bipolar disorder, carbamazepine and valproate are also first choice drugs. Oxcarbazepine and lamotrigine may be a good option in some patients. Other new antiepileptic drugs may also be effective in bipolar disorder but more solid evidence of their efficacy is needed.

Key words:
Antiepileptic drugs. Bipolar disorder. Rapid cycling.

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Utilización de los antiepilépticos en el trastorno bipolar

Objetivo. El trastorno bipolar es una enfermedad crónica de difícil manejo terapéutico que genera altos índices de discapacidad. Aunque el litio es el fármaco de primera elección, hay pacientes que no responden o que presentan efectos secundarios. Una alternativa al litio es el uso de determinados antiepilépticos. Se revisan los datos sobre la eficacia de los antiepilépticos clásicos y nuevos en el tratamiento del trastorno bipolar obtenidos en ensayos controlados.

Desarrollo. Los resultados de numerosos ensayos clínicos avalan el empleo de los antiepilépticos clásicos como carbamazepina y valproato en monoterapia en el tratamiento agudo de los episodios maníacos severo, mixtos o leves, así como en el tratamiento crónico del trastorno bipolar. Los nuevos antiepilépticos presentan en general un perfil de reacciones adversos e interacciones más favorable que el litio, pero los datos sobre su eficacia en el trastorno bipolar son todavía escasos. La eficacia de la oxcarbazepina en la manía es similar a la de la carbamazepina. La lamotrigina se perfila como la mejor alternativa al litio en episodios depresivos. El topiramato no parece aportar beneficio en la manía aguda. El levetiracetam parece aportar un beneficio, pero no se dispone de ensayos con asignación aleatoria, doble ciego y controlados con placebo, y la gabapentina no está claro si aporta o no un beneficio.

Conclusiones. El litio continúa siendo el tratamiento de elección del trastorno bipolar, pero la carbamazepina y el valproato pueden considerarse también fármacos de primera línea. Oxcarbazepina y lamotrigina pueden ser una buena opción en algunos pacientes. Otros nuevos antiepilépticos pueden aportar beneficios en el trastorno bipolar, pero se necesitan pruebas más sólidas de su eficacia.

Palabras clave:
Antiepilépticos. Trastorno bipolar. Cicladores rápidos.

INTRODUCTION

Bipolar disease is a difficult to treat chronic disease that generates high incapacity indexes. Recurrence of its epi-

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sodes causes significant deterioration of the bipolar patient's work and social setting, with frequent hospitalizations and high suicide rates of 10 %-15 %[1].

It is characterized by the cyclic appearance of depressive, manic or mixed episodes that may alternate with normality periods [2]. Mood stabilizers are considered the key to drug intervention for both treatment of the acute episodes and their prophylaxis. They may be administered in combination or not with antipsychotics and/or antidepressive agents.

Lithium, which has been used since 1949 for the treatment of mania, is the drug of choice in bipolar disorder. It is used in both the acute and maintenance phase. However, its use is limited by: *a)* a narrow optimum interval (0.6-0.8 mEq/l) that requires periodic control of serum lithium to avoid serum levels ≥ 2 mEq/L that may cause toxicity[3,4]; *b)* a profile of unfavorable adverse effects, since 75 % of the patients with lithium suffer some type of side effect such as tremor, confusion, polyuria, polydypsia, weight increase, nausea, vomiting, changes in the ECG, hypothyroidism or renal disorders[4]; *c)* delayed and incomplete responses, since it is estimated that almost 40 % of the patients do not respond well to lithium from the beginning (especially rapid cycling patients) or due to loss of efficacy with time[5].

Thus, lithium is not considered a fully satisfactory treatment for these patients. This has motivated the search for alternatives that improve these patients' treatment. In recent years, some old and other new antiepileptics have been profiled as reasonable alternatives to lithium.

There are data that support the efficacy of some classical antiepileptics (carbamazepine, valproate) as mood stabilizers. Besides contributing benefit in lithium refractory forms, they present a different profile of side effects than lithium and are better tolerated. The new antiepileptics (gabapentin, lamotrigine, levetiracetam, oxcarbazepine and topiramate), which have fewer adverse effects and less interactions than classical antiepileptics, seem to have less teratogenic risk, and do not require periodic monitoring, could also be an alternative in the treatment of bipolar disorder in resistant cases[6].

Data available on efficacy, tolerability, indications and level of evidence of the main antiepileptics used in the treatment of bipolar disorder obtained in controlled clinical trials are reviewed.

CLASSICAL ANTIEPILEPTICS

The carbamazepine and valproate used since the decade of the seventies in psychiatry are, together with lithium, the drugs used in treatment of acute mania and in maintenance treatment (relapse prophylaxis) of bipolar disorder, sometimes associated to antipsychotics and/or antidepressives.

Carbamazepine

The action mechanism of carbamazepine in bipolar disorder has been related with its capacity to inhibit amygdaline discharges and thus the development of sensitization phenomena (kindling)[7].

Acute treatment

In mania, carbamazepine was superior to placebo in the trial with random and crossed allotment[8] and comparable to lithium in two randomized and double blind trials[9,10] (table 1). In one of the studies, significant improvement was observed in both groups (lithium and carbamazepine) and the patients with lithium showed a slightly higher improvement than patients with carbamazepine, however the difference was not statistically significant[10].

In bipolar depression, carbamazepine has shown that it is more effective than placebo in the depressive phase of bipolar disorder in at least two controlled and double blind clinical trials[11,12].

Management treatment

Efficacy of carbamazepine in the management treatment of bipolar disorder is debatable. A meta-analysis published in 1995 that included 4 randomized and double blind trials with 206 patients compared carbamazepine with lithium without finding differences[13] (table 1). However, the weak statistical power of the studies included does not make it possible to consider that the «lack of statistical significance» implies «equality of efficacy.»

In a subsequent randomized and double blind trials with 52 patients comparing lithium with carbamazepine and with its combination, a significant superiority of lithium versus carbamazepine was observed in the percentage of patients in whom it was possible to suppress manic episodes (11 % with lithium, 4 % with carbamazepine and 33 % with lithium + carbamazepine; $p < 0.01$)[14]. In this study, the rapid cyclings patients responded poorly to lithium (28 %) and to carbamazepine (19%), and better to the combination of both drugs (56.3 %, $p < 0,05$). Thus, the lithium + carbamazepine combination seems to be more effective than lithium alone to prevent manic episodes in rapid cycling patients and in mixed mania.

Finally, a recent study of 171 patients found that the capacity of lithium to prevent new manic episodes was significantly greater than that of carbamazepine ($p < 0.01$) in patients with classic symptoms (type I bipolar disorder) and similar to carbamazepine in bipolar subjects with atypical symptoms[15].

Available studies have made it possible to identify bipolar patients who may benefit from treatment with carbamaze-

Table 1 Clinical trials on the use of carbamazepine in bipolar disorder

Reference	N	Diagnosis	Study type	Objectives	Study result
Acute treatment					
11	22	Bipolar disorder	Double blind	To compare CBZ and placebo	CBZ better than placebo (7 out of 9 manics with partial of marked improvement 5 out of 13 despressive with significant improvement)
9	52	Hospitalized patients with mania	Controlled with random allotment	To compare CBZ and lithium	CBZ the same as lithium
10	34	Patients with mania	Controlled with random allotment	To compare CBZ and lithium	CBZ the same as lithium
Management treatment					
13	179	Patients hospitalized with mania episode (50 % resistant to lithium)	Metanalysis: 4 double blind trials	To compare CBZ and lithium	CBZ the same as lithium (however the study's statistical power is weak)
14	52	Out-patients with bipolar disorder	Crossed double blind	To compare CBZ, lithium and CBZ + lithium	Lithium better than CBZ ($p < 0.01$). Rapid cyclings patients responded better to the CBZ + lithium ($p < 0.05$)
15	171	Patients with bipolar disorder	Double blind	To compare CBZ and lithium	Lithium better than CBZ in patients with classical symptoms ($p < 0.01$) and similar in atypical ones

CBZ: cabamazepine.

pine with the following predictive markers: *a)* bipolar patients who have not received treatment with mood stabilizers previously[16]; *b)* patients with atypical symptoms and signs[15,17]; *c)* dysphorics and rapid cyclings patients; *d)* patients resistant to treatment with lithium; *e)* those under 30 years and *f)* patients with no family history of bipolar disorder[18,19]. Although an optimum interval of serum concentrations of carbamazepine for bipolar disorder has not been established, that established in epilepsy (4-12 mg/l) is used to minimize toxicity risk[20]. Carbamazepine is approved in Spain for the second choice treatment of severe and mixed manic episode and mild manic episode.

Valproate

The mechanism though which it exercises its mood stabilizing action is unknown. It may be related with its gabaergic effects[21] since it has been observed that patients with high levels of plasma GABA have a better response to valproate[22].

Acute treatment

In mania, Cochrane[23] has reviewed 10 randomized clinical trials (assessed as class B, that is, unclear according to the Cochrane criteria) that were double blind (except one) and controlled (with placebo, lithium, olanzapine, haloperidol or carbamazepine) (table 2). Eight assessed valproate efficacy in acute mania episodes and two in mixed mania. It was concluded that valproate was more effective than placebo in mania treatment (RR: 0.62; 95 % CI of 0.51 to 0.77), but no significant differences were observed between valproate and lithium (RR: 1.05; 95 % CI of 0.74 to 1.50), or between valproate and carbamazepine (RR: 0.66; 95 % CI of 0.38 to 1.16). This review also suggests that valproate may be less effective than olanzapine in the control of manic symptoms, although olanzapine produced greater weight gain and sedation. There were no significant differences regarding haloperidol.

There are no trials published in bipolar depression with random and controlled allotment that assesses efficacy of valproate in depressive episodes.

Management treatment

Efficacy and tolerability of valproate was investigated in a systematic review, comparing it with placebo and other mood stabilizers[24]. Only one randomized and controlled clinical trial was identified[25]. The study compared divalproex (a valproate preparation used in the USA) with lithium and placebo for a 12 month period in patients with type I bipolar disorder. Divalproex was not superior to the placebo or to lithium in the prevention of new episodes, although withdrawals due to new episodes were lower in the dival-

Table 2 Clinical trials on the use of sodium valproate in the acute treatment of bipolar disorder[23]

Reference	N	Diagnosis	Trial duration	Study type	Objectives	Doses and/or levels	Study result
53	43	Bipolar disorder	21 days	Double blind	To compare VPA and placebo	VPA 50-100 mg/l	VPA more effective than placebo
26	27	Mania	21 days	Double blind	To compare VPA and lithium	VPA 1,500-3,000 mg/day	VPA same as lithium
54	179	Patients hospitalized with mania episode (50 % resistant to lithium)	21 days	Multicenter. Double blind	To compare VPA, lithium and placebo	VPA < 150 mg/l	VPA more effective than placebo and same as lithium
55	36	Patients hospitalized with manic or mixed episodes	36 days	Single blind	To compare VPA and haloperidol	VPA 50 mg/l y haloperidol 0.2 mg/kg/day	VPA same as haloperidol
56	136	Patients hospitalized with manic	21 days	Multicenter. Double blind	To compare VPA and placebo	VPA 20 mg/kg/day	VPA more effective than placebo
57	30	Out-patients with bipolar disorder	4 weeks	Double blind	To compare VPA and lithium CBZ	VPA 1,000-2,200 mg/day and CBZ 800-1,600 mg/day	VPA same as CBZ
58	42	Manic or mixed episode bipolar patients	6 weeks	Double blind	To compare VPA, CBZ and lithium	VPA 85-110 mg/l, CBZ 7-10 mg/l and lithium 0.8-1.2 mEq/l	VPA same as CBZ and lithium
59	251	Type I BD in manic or mixed hospitalized patients	Unknown	Double blind	To compare VPA and olanzapine	VPA 50-125 mg/l and olanzapine 5-20 mg/day	VPA same as olanzapine
60	120	Unknown	12 weeks	Double blind	To compare VPA and olanzapine	VPA 750-3,250 mg/day. Olanzapine 2-25 mg/day	VPA same as olanzapine

CBZ: cabamazepine; VPA: sodium valproate.

proex group than in the placebo one (RR: 0.63; 95 % CI of 0.44 to 0.90). In regards to tolerability, drop-outs motivated by adverse reactions in the divalproex group were more frequent than in the placebo group (RR: 1.87, 95 % CI of 1.01 to 3.47), but less frequent than in the lithium group (RR: 0.62; 95 % CI of 0.42 to 0.92)[25].

The available clinical trials suggest that patients with better response to valproate are: *a)* patients with dysphoric or mixed episodes and *b)* rapid cyclings patients[26,27]. Furthermore, the association of lithium and valproate in both groups has shown that it is more effective than monotherapy[26,28]. On the other hand, a relationship has been demonstrated between valproate efficacy and/or toxicity in bipolar disorder (both in acute situation and in maintenance treatment and its serum levels. This is because levels between 45 and 100-125 mg/l were more effective than levels below 45 mg/l and better tolerated than levels above 125 mg/l[29]. Valproate, together with lithium, is considered a first line drug in the treatment of severe or mixed manic episode (in mixed episodes, valproate is preferred to lithium), of mild manic episode and as maintenance therapy of bipolar disorder in the USA[1]. However, it is not authorized in these indications in Spain.

NEW ANTIEPILEPTICS

The new antiepileptics tested in bipolar disorder (oxcarbazepine, lamotrigine, topiramate, gabapentin and levetiracetam) generally have fewer side effects and fewer interactions than the classical antiepileptics[30]. Due to their characteristics, they could be a good alternative for bipolar patients, including resistant cases[6].

Oxcarbazepine

It is a structural analogue of carbamazepine with a similar spectrum. The main difference with carbamazepine is its pharmacokinetic characteristics. It produces less enzymatic induction, so that it produces fewer interactions[30].

Acute treatment

In mania, a double blind, placebo controlled trial in which oxcarbazepine was introduced and withdrawn in six patients with mania reduced manic symptoms in 50 % of the patients

versus 26 % with the placebo[31] (table 3). In two other double blind trials, it was observed that oxcarbazepine efficacy in acute mania was similar to that obtained with lithium or haloperidol[32]. However both studies lack the necessary statistical power to clarify if there were any differences between the efficacy of oxcarbazepine and lithium. We have not found data from controlled clinical trials in depression.

The profile of adverse effects and interactions of oxcarbazepine is more favorable than that of carbamazepine. The American Society of Psychiatry[1] proposed oxcarbazepine as a second choice drug in the treatment of severe or mixed manic episode and of mild manic episode. However, this indication is still not authorized in Spain.

Lamotrigine

Its action mechanism is unknown, although it has been suggested that its mood regulating capacity could be associated to inhibition of presynaptic glutamate release (alterations of the glutamergic system have been shown in depression), blockage of calcium channels (there are significant increases in intracellular calcium concentrations in bipolar patients) or serotoninergic receptor blockage[33,34].

Acute treatment

There are three controlled clinical trials in mania, but with significant methodological limitations. Two trials did not find significant differences between lamotrigine and placebo or gabapetin, however, this was attributed to the small sample size of the studies and high indexes of response to placebo[35,36] (table 4). The third trial compared lamotrigine with lithium and also did not find significant differences. However, in this case, besides a small sample, low blood lithium levels were found[37]. A fourth randomized trial was conducted in 45 hospitalized patients with mania, in which efficacy and tolerability of lamotrigine versus olanzapine and lithium were evaluated, showed a significant improvement in the different treatment groups[38].

There is a multcenter, double blind trial in depression that included 195 patients with type I bipolar disease in depressive phase treated with 50 mg/day or 200 mg/day of lamotrigine or with placebo. In this trial, a significantly greater improvement was found in the two lamotrigine groups than in the placebo group[39]. Favorable response was observed in 56 % of the patients treated with 200 mg/day of lamotrigine versus 37 % of those receiving placebo. Furthermore, a greater incidence of maniac, hypomanic or mixed episodes in patients treated with lamotrigine (5.4 %) than in the placebo group (4.5 %) was not found in this study.

Management treatment

In a randomized and double blind trial that included 175 patients in which lamotrigine was compared with lithium and placebo for 18 months, lamotrigine and lithium prolonged the time to appearance of any episode more than the placebo (lamotrigine vs. placebo, $p < 0.05$; lithium vs. placebo, $p < 0.01$)[40] (table 4). In this study, lamotrigine prolonged time to appearance of a depressive episode and lithium prolonged time to appearance of a maniac, hypomanic or mixed episode regarding the placebo. The greater efficacy of lamotrigine in the depressive episodes and of lithium in the manic ones was confirmed in another study having a similar design conducted in 463 patients with bipolar disorder in which capacity of lamotrigine or lithium to suppress depressive and manic episodes at one year of

Table 3 | **Clinical trials on the use of oxcarbazepine in the treatment of bipolar disorder**

Reference	N	Diagnosis	Study type	Objective	OXC dose (mg/day	Study result
31	6	Mania	Double blind. Placebo controlled. On-off-on design	To compare OXC and placebo	1,800-2,100	OXC better than placebo (51% reduction in symptoms with OXC versus 26 % with placebo)
32	38	Acute mania	Double blind	To compare OXC and haloperidol	2,400 (mean)	OXC same as with haloperidol in reduction of manic symptoms after 2 weeks of of treatment
32	52	Acute mania	Double blind	Compared OXC and lithium	1,400 (mean)	OXC same as with lithium in reduction of manic symptoms after 2 weeks of treatment

BD: bipolar disorder; OXC: oxcarbazepine

Table 4 Clinical trials on the use of lamotrigine in bipolar disorder treatment

Reference	N	Diagnosis	Study type	Objective	Lamotrigine dose (mg/day)	Study result
Acute treatment						
39	195	Type I BD. Depressive phase	Double blind,	To compare LTG and placebo	50 or 200	LTG better than placebo
35	31	Type I and II BD. Unipolar depression	Double blind and crossed	To compare LTG, gabapentin and placebo	274 (mean)	LTG (52 %) better tha gabapentin (26 %) and better than placebo (23 %)
36	16	Mania, hypomania. Mixed states	Double blind	To compare LTG and placebo	200	LTG same as placebo. (probably due to low no. of study)
37	30	Type I BD. Manic phase	Double blind	To compare LTG and lithium	100	LTG same as lithium
38	45	Acute mania	Double blind	To compare LTG, lithium and olanzapine	100	LTG same as lithium and same as olanzapine
Management treatment						
41	463	Type I BD	Double blind	To compare LTG, lithium and placebo	50, 200 or 400	LTG better than placebo in depressive episodes. Lithium better than placebo in manic, hypomanic or mixed episodes
40	175	Type I BD	Double blind	To compare LTG, lithium and placebo	100-400	LTG better than placebo in depressive episodes Lithium better than placebo in manic, hypomanic or mixed episodes
42	182	TYPE I or II BD. Rapid cycling patients	Double blind	To compare LTG and placebo	100-500	LTG (41 %) better than placebo (26 %)

LTG: lamotrigine; BD: bipolar disorder.

treatment was assessed[41]. In this study, depressive episodes were suppressed in 57 % of the patients with lamotrigine, 46 % of those treated with lithium and 45 % of those who received placebo and manic episodes were suppressed in 77 %, 86 % and 72 % of the patients respectively. In rapid cycling, whose prevalence generally ranges from 15 %-20 % of the patients with bipolar disorder, there are two clinical trials that verify efficacy of lamotrigine as a good option for maintenance treatment. In the first double blind trial, efficacy of lamotrigine in monotherapy was compared with that of gabapentin in monotherapy and with placebo in 31 patients refractory to conventional treatment (11 with type I bipolar disorder, 14 with type II bipolar disorder and 6 with unipolar depression), 23 of whom were rapid cycling[35]. A total of 52 % of the patients responded to lamotrigine, 26 % to gabapetin and 23 % to placebo ($p < 0.05$). The main adverse effect was weight gain/loss, since weight was lost with lamotrigine (–0.96 ± 3.11 kg) and gained with gabapentin (1.83 ± 5.04 kg). In the second double blind, placebo controlled trial conducted in 182 rapid cycling patients, 41 % of the patients with lamotrigine did not have relapses for 6 months versus 26 % of those receiving placebo ($p < 0.05$)[42].

The main disadvantage of lamotrigine is the risk of serious skin disorders (Stevens-Johnson's Syndrome, toxic epidermal necrolysis, angiodema) that appear more frequently in the 4th-6th week of treatment with an 0.1 % incidence in adults and 1 %-2 % in children. Gradual introduction of lamotrigine with slow dose escalation may avoid this type of adverse reaction.

Lamotrigine has been shown to be effective for acute and management treatment of depression in bipolar disorder, rapid cyclers and bipolar patients refractory to other treatments. The effect of lamotrigine in mania is still not explained. Lamotrigine is authorized in Spain to prevent depressive episodes in patients with bipolar disorder.

Topiramate

It is structurally different from other antiepileptics. Its action mechanism as a mood stabilizer, not explained at present, could be related with the mechanisms proposed for its anticonvulsive action such as inhibition of voltage dependent sodium channels, facilitation of GABA action on

the $GABA_A$ receptor and antagonism of the glutamergic excitory action on the kainate receptor[30].

Most of the data available with topiramate come from open label trials, with potential risk of false positives due to biases[43]. In a single blind preliminary trial in which topiramate was compared with bupropion in patients with bipolar depression, improvement was observed in 56 % of the patients with topiramate and in 59 % of those treated with bupropion. However, there were no significant differences between both drugs[44].

In unpublished data, presented in the 2004 American Psychiatric Association Annual Meeting on four, double blind placebo controlled clinical trials that compared topiramate with placebo, it was not observed that topiramate was effective in acute treatment of mania. In two of these trials, topiramate was compared with lithium, the efficacy of lithium being greater than that of topiramate[45] (table 5).

Topiramate is not authorized in Spain for the treatment of bipolar disorder. However, a possible advantage of topiramate is that it may produce weight loss, especially in the first two months of treatment on the contrary to other mood stabilizers such as valproate that generally lead to weight gain[30,46].

Gabapentin

Gabapentin has better tolerability and fewer interactions than other antiepileptics. The anticonvulsant action mechanism is not well known. It is possible that inhibition of the sodium channels, increase of GABA release and reduction of glutamic release, as well as fixation of a regulatory subunit of voltage dependent calcium channel are involved[30].

Most of the studies published are open label, non-controlled studies with small and heterogeneous samples[47]. In a placebo controlled trial in type I bipolar patients in whom mania, hypomania or mixed episodes persisted in spite of baseline treatment (lithium, valproate or association of both), gabapentin or placebo were added. Improvement was observed in both groups. However this was significantly greater in the placebo group than in the gabapentin group ($p < 0.05$)[48] (table 5).

At present, gabapentin is being studied as a potentiator of other mood stabilizer agents or for cases with a large component of anxiety. However, there are still no double blind, placebo controlled studies that demonstrate its efficacy. Gabapentin is not authorized in Spain for the treatment of bipolar disorder.

Levetiracetam

Its action mechanism as a mood stabilizer is unknown. However, it has a certain gabaergic facilitating action that could be involved in this effect.

A decrease in mood condition has been observed in epileptic patients treated with levetiracetam. This infers that levetiracetam could have antimanic properties. There are three cases of bipolar patients, two of them being rapid cycling patients, who improved their depressive and manic/mixed symptoms when levetiracetam was associated to their conventional treatment[49,50]. However, no randomized and double blind, placebo controlled clinical trial has verified this effect.

CONCLUSION

Antiepileptics are a heterogeneous group of drugs, to which properties and uses different from the initially recogni-

Table 5 Clinical trials on the use of topiramate and gabapentin in bipolar disorder treatment

Reference	N	Diagnosis	Study type	Antiepileptic dose (mg/day)	Study result
Topiramate					
44	36	Type I and II BD	Simple blind	50-300	It reduces the baseline HDRS-17 score ≥ 50 % in 56 % of the patients with topiramete and in 59 % of those with bupropion, without significant difference between both drugs
45		Type I BD			
Gabapentin					
48		Type I BD	Placebo controlled trial	900-3,600	Decrease in YMRS scale inplacebo group (–9) than in gabapentin group

BD: bipolar disorder; HDRS-17: Hamilton Depression Rating Scale-17 items. YMRS: Young Mania Rating Scale.

zed antiepileptic use have been attributed in recent decades. In fact, their use for treatment of neuropathic pain treatment (trigeminal neuralgia, postherpetic neuralgia, phantom limb, etc.), non-neuropathic pain (migraine) and psychiatric condition has increased considerably[51].

Classic antiepileptics, carbamazepine and valproate, used in the bipolar disorder since the 1970's, presently have sufficient data to support their use in monotherapy in the acute treatment of severe or mixed manic episodes and in the mild ones as well as in management treatment. These drugs have demonstrated a clear benefit in patients with dysphoric or mixed mania, rapid cycling and lithium resistant patients. However, of the two, only carbamazepine is authorized in Spain for this indication[52].

With the new antiepileptics having a profile of clearly more favorable adverse effects than that of lithium and fewer interactions, the present data are less solid and sometimes contradictory. The doubtful quality of many of the available, non-randomized open studies, and with small samples and non-standardized assessment scales, makes it difficult to obtain conclusions. However, they manifest beneficial effects and specific advantages that stress the convenience of conducting double blind, placebo controlled trials that confirm their efficacy and clarify their role in the treatment of bipolar disorder.

Oxcarbazepine, whose profile is superimposable to that of carbamazepine in mania, has less induction risk and thus interactions. Lamotrigine is profiled, with a moderate degree of evidence, as the best alternative to lithium in depressive episodes without inducing an increase in manic or hypomanic episodes and it is authorized for this indication in Spain. Topiramate does not seem to have any benefit in acute treatment of mania and there are no randomized, double blind and placebo controlled trials with levetiracetam. It is not clear if gabapentin has a benefit or not.

Table 6 shows the possible role of antiepileptics in the acute and chronic treatment of bipolar disorder and levels of evidence that support it.

Table 6 **Therapeutic options recommended and evidence level in bipolar disorder treatment**

	First option	Second option
Manic episode		
Mild	Lithium (I), VPA (I), atypical antipsychotic (olanzapine) in monotherapy	CBZ (II) or OXC (II)
Severe and mixed	Lithium (I) or VPA (I)* + atypical antipsychotic	CBZ (II) or OXC (II) ± atypical antypsychotic
Depressive episode	Lithium (I) or LTG (II)	Lithium + antidepressive (III)
Maintenance	Lithium (I) or VPA (I)	LTG, CBZ, OXC (II) TPM, GBP, LEV (III)

Evidence level is indicated between parenthesis. Level I: recommendation with solid clinical tests. Level II: recommendation with moderate clinical tests. Level III: it can be recommended in specific circumstances. CBZ: carbamazepine; GBP: gabapentin; LTG: lamotrigine; LEV: levetiracetam; OXC: oxcarbazepine; TPM: topiramate; VPA: sodium valproate. *VPA is preferable in mixed episodes. Modified from Hirschfeld RMA, et al[1].

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