Up-date in the treatment of rapid cycling and other refractory bipolar disorders

I. Fernández Pérez, M. J. de Frutos, E. Luján and J. Ortiz del Romero

Hospital Psiquiátrico de Madrid. Madrid. Spain

Actualización en el tratamiento de pacientes cicladores rápidos y otros bipolares resistentes

Summary

Introduction. *Up-date in the treatment of rapid cycling and other resistant bipolar disorders.*

Methods. *A Medline research of the literature was performed in several databases as Pub-Med, Cochrane and Embasse, from 1998 to December 2001. We have also reviewed bibliography supplied by different laboratories and several monographies.*

Results. *30 articles were selected: 11 reviews, 17 open-labeled studies and 2 articles on general recommendations. From the 17 open-labaled studies, 10 were on topiramate (25 to 400 mg/day) as a coadjuvant of another stabilizer. Improvement ranged from 40 to 70%; 4 adding gabapentin to the previous treatment, at the dosage of 60 to 5,600 mg/day, 27 and 92% showed improvement; 1 with mexiletine (200 to 1,200 mg/day) in which 46% were full responders, 15% partial responders and 38% had no response, 100% response in manic or mixed and 38% in depressed patients; and 2 with lamotrigine (50 to 500 mg/day) in which 52 to 80% showed improvement. With risperidone at the dosage of 2-3 mg/day as coadjuvant, improvement was seen in 62%. Olanzapine had direct short-term antimanic effects, with 49% improvement in single drug therapy and 57% as coadjuvant.*

Conclusions. *More double-blind studies are necessary to assess efficacy in monotherapy or as coadjuvants, in short-term or even in monotherapy, and to compare the different treatments with each other as well as with the conventional treatment. The authors agree in pointing out the efficacy of gabapentin and topiramate associated to another stabilizer, and also of lamotrigine in depressed phases*

Key words: *Rapid cycling. Refractory bipolar disorder. Treatment.*

Resumen

Introducción. *Actualización en el tratamiento de pacientes cicladores rápidos y otros bipolares resistentes.*

Métodos. *Se han realizado varias búsquedas bibliográficas en diferentes bases de datos como Pub-Med, Cochrane y Embasse, desde el año 1998 hasta diciembre de 2001. Ha sido revisada bibliografía aportada por casas comerciales y diversas monografías.*

Resultados. *Se han seleccionado 30 artículos: 11 revisiones, 17 estudios abiertos y dos artículos sobre recomendaciones globales. De los 17 estudios abiertos, 10 han sido sobre el topiramato (25 a 400 mg/día) como coadyuvante de otro estabilizador; la mejoría osciló entre un 40 y un 70%; cuatro añadiendo gabapentina al tratamiento previo, a dosis de 60 a 5.600 mg/día, con mejorías entre el 27 y el 92%; uno con mexiletina (200 a 1.200 mg/día), donde tuvieron una respuesta completa en el 46%, parcial en el 15% y ausencia de respuesta en el 38%, respuesta del 100% en maníacos o mixtos y del 38% en sujetos con depresión, y dos con lamotrigina (50 a 500 mg/día), con una mejoría del 52 al 80%. Con risperidona a dosis de 2-3 mg/día como coadyuvante se ha visto mejoría en un 62%. La olanzapina tiene efectos antimaníacos a corto plazo, con mejorías del 49% en monoterapia y del 57% como coadyuvante.*

Conclusiones. *Son fundamentales más estudios doble ciego para valorar la eficacia en monoterapia o como adyuvantes a corto plazo o en mantenimiento y comparando los fármacos entre sí y con el tratamiento convencional. Los autores coinciden en señalar la posible efectividad de la gabapentina y el topiramato asociándolos a otro estabilizador, así como de lamotrigina en fases depresivas.*

Palabras clave: *Cicladores rápidos. Trastorno bipolar refractario. Tratamiento.*

INTRODUCTION

The concept of rapid cycling (RC) was introduced by Dunner and Tieve in 1974 to designate those patients who present 4 or more yearly episodes and it is mainly used in the context of manic-depressive disease and its different subtypes. Prevalence of rapid cyclers in the bipolar population generally ranges from 15-20%[1,6,31] although this seems to be increasing in recent years due to the greater use of antidepressant agents[2-4,28], above all tricyclics, and intermittent use[28]. It is also related with greater frequency in hypothyroid patients, in those who have neurological disorders and those who take corticosteroids.

Correspondence:
Isabel Fernández Pérez
P.º de las Delicias, 65 A, esc. 2, 6.º C
28045 Madrid (Spain)
E-mail: prinfresa@hotmail.com

Lithium (Li) is the standard treatment for acute manic episodes and to prevent bipolar disorder relapses. However, between 20-30% of the patients[5] do not respond to its administration. In RC, treatment failure with Li increases up to 80%[6]. As an alternative, several epilepsy drugs, that traditionally were valproate (Val) and carbamazepine (CBZ), are used.

The need to search for other drugs to improve treatment in those cases that do not adequately respond has increased interest in new epilepsy drugs such as topiramate (Top), gabapentin (Gab) or lamotrigine (Lam) and for atypical antipsychotic agents such as clozapine (clz), olanzapine (olz) or risperidone (ris). Top shares pharmacological properties with Val and CBZ, blocks the sodium channels (as both drugs) and increases GABA activity as occurs with Val, modulates neuroexcitation mediated by glutamate and some calcium channels and is a weak inhibitor of carbon anhydrase. Gab is structurally analogue to GABA, however its action does not seem to be equivalent; it is calcium antagonist in neocortex and hippocampus, it does not metabolize or bind to proteins, it is eliminated by the kidney and its low toxicity makes it useful in the elderly and in those who take other drugs. In the case of Lam, it blocks the sodium channels, 5-HT_3 receptors and inhibits presynaptic release of glutamate. Clz and Olz are dibenzodiazepines, partial antagonists of the D_2 receptor and strong ones of the D_1 and D_4 ones, with potent 5-HT_2 and 5-HT_3 antiserotoninergic action, α_1 and α_2 antiadrenergic (above all clz) action, potent anticholinergic and H1 antihistaminic action. Ris is a benzisoxazole derivative, potent D_2 antagonist and without D_1 action, it is the most potent 5-HT_{2A} and 5-HT_{2C} antiserotoninergic, and is also α_1 and α_2 antiadrenergic and H_1 antihistaminic.

METHODS

To make this review, several searches were performed on the existing bibliography in different databases such as Pub-Med, Cochrane and Embasse. The terms that give the name to the review were introduced (rapid, cycling, treatment, resistance and bipolar disorder) and the search was limited to publications from the year 1998 to December 2001, that were in English, that dealt with humans and that included summaries. Those articles that dealt with bipolar disorder in general and were not about resistant patients and those that did not include treatment were rejected. The term «rapid cycling» has still not been included as such in the MeSH and was searched for as an exact concept. References from these articles were also studied to specify some features that seemed to be useful.

Bibliographic sources supplied by commercial firms were also reviewed in regards to studying efficacy of some drugs more, drugs which in the existing bibliography seemed to have a more important role than at present.

Finally, it should be mentioned that different monographs were used. They have contributed the overall view of the articles and the point from which we have begun for the review.

A total of 30 articles were reviewed (table 1): 11 reviews, 17 open studies and two articles on the global recommendations. Of the 17 open studies, 10 were on Top, four on Gab, one on mexiletine and two on Lam.

TABLE 1. 30 articles reviewed

Type of article (n.º)	*Drug studied*	*Reference*
Reviews (11)		1-4, 15-17, 25-28
Open studies (17)	10 topiramate	5-14
	4 gabapentin	18-21
	1 mexiletine	22
	2 lamotrigine	23, 24
Treatment guides (2)		29, 30

RESULTS

Topiramate

We found 10 articles[5-14] out of all the bibliographic search (table 2) that evaluated the efficacy of Top (at a dose of between 25 to 400 mg/day) as coadjuvant treatment to patients who were previously receiving Li, CBZ, Gab, Val or Lam. Assessment of clinical improvement in these studies was performed with the HAM-D (Hamilton depression scale), YMRS (Young mania rating scale), AEG (functionality scale), SCID (present mood scale) and CGI (bipolar disorder scale). Improvement in these cases ranged from 40% to 70%, it being observed in four of these studies that there was weight loss in patients who had a BMI >28 that ranged from 11 ± 6 kg. Dropouts went from 0% in the L. Plon et al. and KN. Roy

TABLE 2. Topiramate in the treatment of bipolar patients refractory to conventional tr eatment

Study	*Sample*	*Design*	*Results (Improvement, %)*
Kusukumar et al. (1999)	19 RC	Retrospective	53
Kusukumar et al. (p 6. 032)	27 RC	Open	69
Plon et al. (1999)	4 RB	Cases	50 clara, 50 leve
Vieta et al. (1999)	21 RB	Open prospective	40
Vieta et al. (p 16. 04)	22 RB	Open prospective	67
Roy Chengappa et al. (1999)	16 RB	Open	56
Roy Chengappa (p 6. 036)	20 (RC 6)	Open	60
Sachs et al (1999)	14 (RC 7)	Retrospective	61
Hussain et al. (1999)	45 RB	Open	61
Heinz et al. (2000)	11 RB	Open on-off	70
Vieta et al. (2001)	21 RB	Open, case series	38.1 mania 19 depresion

Chengappa et al. studies to 50% in the G. Sachs et al. study. Most of these were caused by side effects, the most frequent being: sedation, concentration difficulty, ataxia, headache, tremors, and psychotic symptoms. In other cases, it was the lack of efficacy that led to the drop-out. In another article[14], assessment was also performed with the HDRS-17 (Hamilton depression scale) but the mean dose of Top was 75-200 mg/day, finding 38.1% of improvement in the mania and 19% improvement in the depression with moderate side effects of paresthesia type or CNS impairments at 2 weeks.

Gabapentin

In the 4 studies reviewed in which Gab was added (table 3) to the previous treatment of Li, Val, CBZ or Ris, the Gab doses were 60 to 5600 mg/day. The clinical assessment was performed with the HDRS scale, the Beck mania scale and the CGI and improvement ranged from 88% to 53%, although Botts et al.[16], in their review, found that improvement ranged from 27% to 92%. Drop-outs in these 4 studies went from 0% in the Afftshuler et al. study[18], in spite of the side effects, and 28.5% in the E. Vieta et al. one[15]; in the review, the drop-outs ranged from 42% to 58% due to side effects, relapses and inefficacy. The most frequent side effects found were: drowsiness, decreased coordination, dizziness, gastrointestinal problems and malleolar edemas. In another study[19], efficacy of Gab as coadjuvant with a follow-up greater than 6 months was assessed, using the HAMB and YMRS scales, including patients with intolerance or inefficacy with at least two mood stabilizers. The mean dose was 300 to 600 mg/day and neither antidepressants nor electroconvulsive treatment (ECT) were used nor were the doses of other concomitant treatments modified. Significant improvement was observed in the depressive and manic symptoms as well as in global functioning and maintenance at 6 months without finding polarity changes in the course of the disease with treatment. In addition, no excessive side effects were found, the most frequent being sedation, sexual alterations, insomnia, as well as a high incidence of tremors and ataxia, above all when associated to Gab and CBZ.

In the review of Gotor[20], it was considered that using Gab as an antimanic agent is less effective than Li, that larger doses and longer latencies are necessary, although it is superior to Li as a stabilizer in patients with unstable and emotionally changing evolution as well as in the control of impulses. Al-though Gab is inferior to Li in the prophylaxis, it is useful to improve its efficacy when used jointly. It has doubtful effects on the stabilization of the RC, but does not worsen its course[21].

TABLE 3. Gabapentin in the treatment of bipolar patients refractory to conventional tr eatment

Study	*Sample*	*Design*	*Results (Improvement, %)*
Vieta et al. (1999)	21 RB	Open	53
Kennet et al. (1999)	10 RB	Open	88
Affshule et al. (1999)	28 (RC 5)	Open prospectivo	71
Trevor Young et al. (1990)	37 RB	Open prospectivo	Significant in mania and depresion

Mexiletine

Schaffer et al.[22] performed an open study with 20 RC subjects treated for 6 weeks with mexiletine (drug with antiarrhythmic, anticonvulsant and analgesic properties), at a dose between 200-1200 mg/day. The patients included had not responded or tolerated either Li or other anticonvulsants such as CBZ or Val. The HAM-D and MSRS scales were used, elaborating an intermediate scale between both MSRS, that represented depressive and manic symptoms. They found a complete response in 46% of the subjects, partial in 15% and absence of response in 38%, establishing a differentiation between manic subjects or those with mixed state where the complete or partial response was 100%, and the subjects with depression with complete or partial response of 38%.

Lamotrigine

In a bibliographic review of 11 studies with Lam, either in single drug therapy or associated to another mood stabilizer, improvement was observed using a dose of 50 to 500 mg/day that went from 52 to 80%, even though study drop-outs were not analyzed. The most frequent side effects were: dizziness, migraines, nausea, tremor, drowsiness, fatigue, anxiety and skin rashes in 10% during the first 6 weeks, that substantially increased if Val was added. In addition Stevens-Johnson syndrome appeared occasionally and was fatal. Calabrese et al.[23] performed a double blind, prophylaxis placebo controlled clinical trial with Lam in single drug therapy in RC. It is the first controlled study of a drug in a prospective cohort of RC patients. A sample of 324 RC of both genders, in good physical and psychic conditions and without laboratory analysis alterations (including normal ECG and thyroids) was used. Patients with axis II pathology, with risk of suicide, with scores >2 on item 3 of the Hamilton scale, with psychiatric comorbidity and patients under previous treatment in the last 6 months with Lam, if it lasted more than 6 weeks or if any allergic reaction, including rash, was produced were excluded. In a first open or preliminary phases, they received Lam for 6 weeks in ascending dose of up to 300 mg/day. After 182 patients, without side effects or re-intensification went on to the second double blind, randomized, placebo controlled phase, and were administered doses of Lam of up to 500 mg/day. It was well tolerated, with a type and frequency of side effects equal to the placebo except for mild weight increase. The results in the Lam

group were greater time passing without needing to add another drug (80% should be added due to depression) although it was not statistically significant, greater global survival (17 weeks with Lam compared to 7 weeks with placebo) and at 6 weeks and greater percentage of stable patients at 6 months (41% compared to 26%), it being effective, above all, in BPII RC.

In an open longitudinal study in RC[24], efficacy of Li and Lam as mood stabilizer was compared. It included 14 RC patients who were treated for 1 year with either of the two, observing that with Li, 43% had less than 4 episodes and 57% more, but with Lam 86% reduced the number of episodes below 4% and 14% exceeded this value.

In another review article of Calabrese et al.[17], it is mentioned that most RC have depression, this being more frequent and severe than in the rest of the bipolar subjects. Administration of Li and Val, in spite of having an 85% antimanic effect and 60% antidepressant one, stabilizes at least half of the patients. Within this article, there is a clinical trial that assesses the efficacy of the combined treatment with Li and Val for 6 months in a prospective cohort of 215 patients diagnosed of bipolar type I and II RC disorder, with a manic-hypomanic episode in the 3 months prior to the study, with therapeutic concentrations and with or without comorbidity with alcohol or other drugs. It was observed that most of the RC occurred in the depressive phase of the disease and that combined treatment with Li and Val had elevated efficacy in the control of mania-hypomania, but little for depression (antimanic effect in 88 non-comorbid patients, 86 comorbid ones; antidepressant effect in non-comorbid-comorbid: 61-57 patients; mood state stabilization: 50 in non-comorbid and 43 in comorbid). It was observed that the RC without comorbidity with alcohol-drugs are more frequently BP type II women; they initiate their disease with depressive phases and they have good drug compliances on the contrary to the comorbids who are more frequently BP type I men with a grea-ter relative incidence of mixed mania-state. The fact of comorbidity does not modify the disease evolution itself, although as it causes lower drug compliance, it gives rise to a larger number of relapses, and thus, to a worse prognosis.

Antipsychotics

Regarding the use of antipsychotic agents in bipolar disorder[28], a series of problems with typical APS are posed, such as lack of efficacy in maintenance, worsening of the disease course, scarce data supporting its efficacy as prophylaxis, as well as that the concomitant use with mood stabilizers obscures their efficacy.

Although clozapine has properties as a mood stabilizer in single drug therapy, it presents several risks and limitations such as the risk of agranulocytosis and seizures, drug interactions (the risk of agranulocytosis increases with CBZ) and high cost, more studies being necessary for more conclusive data (table 4).

TABLA 4. Studies with clozapine

Study	*n*	*Criterion response*	*Improvement (%)*	*Treatment type*
Zarate et al.	17	CGI-I	65	Single drug therapy
Calabrese et al.	25	YMRS, BPRS	72	Single drug therapy

BPRS: Brief Psychiatric Rating Scale.

Risperidone has been shown to be ineffective to treat mania in single drug therapy, it being effective as coadjuvant treatment and it is more effective at low doses (2-3 mg/d). It is considered to be more effective in the short term than as maintenance treatment (table 5).

Short term antimanic effects have been found with olz, but there are no studies on its efficacy in prophylaxis. More studies are available than with the remaining atypical drugs (table 6).

Regarding side effects, the risk of tardive dyscinesia that can appear in the course of the psychosis is emphasized, this being, above all, at the onset of treatment. This was 0.3% for ris and 0.52% for olz. Extrapyramidal symptoms are less frequent with clz and ris than with typical neuroleptics (NLPs). An acathisia having similar seriousness and frequency was found, but the Parkinsonism was clearly inferior.

Combinations

Bowden et al.[25] reviewed the different treatments of bipolar disease, recommending the administration of Val in RC patients, later associating other mood state stabilizers, antipsychotics and thyroid hormones. According to these authors, 13% to 20% of the bipolars are RC and 82% of them respond poorly to Li, although there are practically no rando-mized and placebo controlled studies. Good antimanic effect has been observed with Val, although with poor antidepressant effect. CBZ produces 32% response in depression and 52% in mania, although it would be necessary to associate it to NLPs, AD and/or Li to be efficacious. According to Okuma,

TABLA 5. Studies with risperidone

Study	*n*	*Criterion response*	*Improvement (%)*	*Treatment type*
Dwight et al.	8	YMRS, HAM-D	50	Single drug therapy
Jacobsen	13	CGI	62	Adjuvant
Tohen et al.	13	BPRS	62	Adjuvant
Sajatovic et al.	5	CGI, YMRS, BPRS	0	Single drug therapy
Ghaemi				
Calabrese et al.	25	YMRS, BPRS	72%	Single drug therapy

TABLA 6. Studies with olanzapine

Study	*n*	*Criterion response*	*Improvement (%)*	*Treatment type*
Tohen et al.	73	BPRS, MADRS	Depressive symptoms	Single drug therapy
Sanger et al.	139	YMRS	49 mania	Single drug therapy
McElroy et al.	14	CGI-BP	57	Adjuvant

rapid cycling predicts poor response to Li and CBZ. According to Bauer and Whytrow, thyroid hormones together with mood state stabilizers are adequate in the prevention of RC. Clozapine is efficacious in subjects who are RC or previously intolerant to Li, epilepsy agents and typical NLPs, although its long term administration is not recommended due to the risk of agranulocytosis until clear benefits exist. Other treatments given as alternative or associated to lithium are: NLPs, AD, BZPs, calcium channel blockers, Lam, TEC and total sleep deprivation.

Furthermore, Hilty, et al.[27] reviewed bipolar disorder in adults, finding that patients rapid RC pattern in acute episodes seem to respond better to Val than to Li. In a 15 month prospective study, 54% of the patients with mania and 87% with mixed mania had marked response to Val, also as prophylaxis. As an optional treatment, they also considered adding thyroid hormone as a stabilizer until 150% of the normal thyroid function is reached, using a combination of stabilizers, clz alone or combined with Li or Val.

The Goodwin[26] group compared Li and anticonvulsant therapy in the prevention of suicide asso-ciated with affective disorders and they established differences for the RC such as worse response to Li in single drug therapy. They cite a recent retrospective 5 year study on RC who were treated with Li alone or combined with CBZ where improvement was faster in those who received anticonvulsant therapy together with Li. They describe a study with 101 RC, where Val showed a marked prophylactic effect against mania or mixed episodes, with poor or marked antidepressant effect.

Bauer et al.[29] established some guidelines for the treatment of this type of patients where they established that, in spite of the fact that lack of response to Li is a marker of RC, there are few data that indicate that these respond better to other anticonvulsants, so that they continue to recommend Li as first line treatment for these patients, assuring that the optimum dose of the former is used before changing to another anticonvulsant agent. They propose three steps in the treatment (fig. 1).

Similar indications were established in the *First International Exchange on Bipolar Disorder*[30] in the year 2000, where they recommended combined treatment with mood stabilizers, antipsychotics, thyroid hormones and nimodipine as adjuvant in these patients.

In their study, Tondo et al.[2] stated that the RC in bipolar disorder predict greater future morbidity and worse response to treatment. They found that the risk

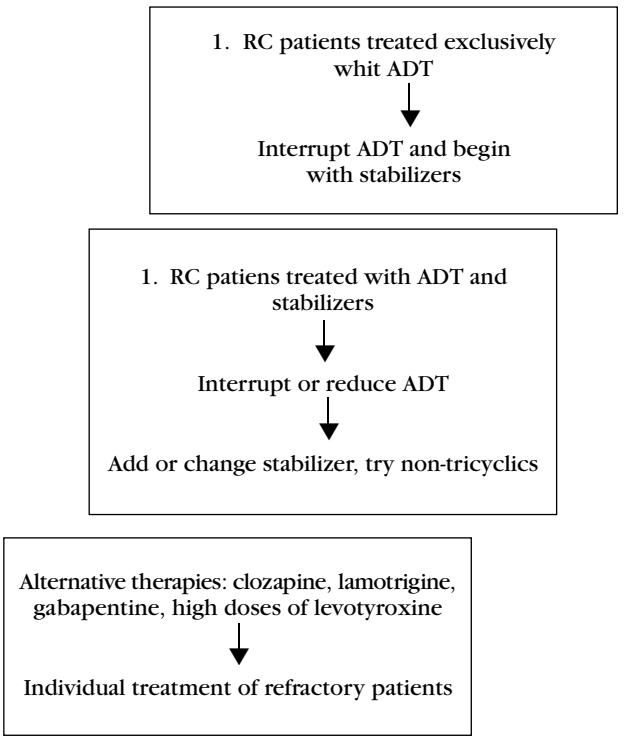

Figure 1. Therapeutic steps.

of RC was 5.1 times greater in type II bipolar patients than in type I (30.3%/6.0%), in less excess in women than in men (17.9%/11.5%), and associated with premorbid cyclothymia, first depressive episodes and older age at onset.

DISCUSSION

In the studies that we have reviewed[32-36], the limited number of patients that the sample often had stands out. This is partially due to the difficulty to select a sufficient number of patients for the sample, since the prevalence of refractory bipolar disorder is low (15-20%) within the bipolar patients, that account for somewhat more than 1% of the psychiatric disease[5]. They indicate the results with mexiletine because, in spite of being a drug that is used little in this disorder, the results obtained are superior to the placebo and can be a pathway for future investigations. More specific related bibliography has not been found.

In relationship with the side effects (table 7), we find some differences between one drug and another, which often leads us to consider different options that have a similar therapeutic effectivity according to each patient in particular. In the case of Lam, a double blind study obtained 52% improvement that was earlier in those who were in the depressive phase of the disease. However, this drug has the disadvantage of being associated to the serious Steven-Johnson syndrome, which makes it necessary for the clinician to use low doses (25 mg/kg),

TABLE 7. Side effects of the drugs studied

Drug	*Side effects*
Topiramate	Sedation, concentration difficulty, ataxia, headache, tremors and psychotic symptoms
Gabapentin	Drowsiness, coordination disorder, dizziness, gastric problems and malleolar edemas
Lamotrigine	Dizziness, migraine, nausea, drowsiness, tremor, fatigue, anxiety, skin rash and even Steven-Johnson syndrome
Clozapine	Tachicardia, constipation, sedation, agranulocytosis and seizures
Olanzapine	Constipation, drowsiness, weight increase, hypotension
Risperidone	Dyscinesias, hypotension, sedation, anxiety, hyperprolatinemia

this being even lower (12.5 mg/kg) in those who have some erythematous reaction as a background, and to not associate it to valproate that interacts with lamotrigine and decreases its metabolization. Gab has the fundamental advantage of its practical absence of side effects and in the case of Top, the weight loss produced in some patients with a BMI greater than 28 could also be considered as an advantage in some patients (table 7).

CONCLUSIONS

We find that future investigations are essential to explain many of the doubts posed from the results of the studies. We consider that more double blind clinical trials are needed since most of the studies found are retrospective and not prospective, and the degree of evidence of the former is less and, with thus, the reliability of the results is also less. It is important to know if the drugs studied function in single drug therapy or as adjuvant, since, as Sheila et al. found in their review, when Gab was used in single drug therapy, improvement did not exceed 27%, data similar to those obtained with placebo. It would also be useful to assess efficacy, directly comparing the different drugs to each other and with the conventional treatment, as well as their efficacy in maintenance treatment.

In spite of the limitations of the designs due to the limited number of patients and the fact that most of the studies are open or retrospective, the authors coincide in pointing out the possible effectivity of Gab and Top, associating them to another stabilizer. The use of Lam seems promising, principally in those patients in the depressive phase. However, more double blind studies are necessary so that the statistical significance of the findings makes it possible to generalize the results and to make recommendations on the use of these drugs systematically. The most potent drug industry is exerting pressure by performing more studies whose efficacy is sometimes doubtful to the detriment of the initial drugs that no one studies any longer. This opens the way for new studies.

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