Review

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Therapeutic and Pharmacologic Differences between Medications Used in the Treatment of Bipolar Disorders: Seven-Year Update

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A detailed review was published in 2004 on the therapeutic properties of the medications used in the treatment of bipolar disorders (Tamayo, JM et al. Actas Esp Psiquiatr 2004;32(Supl. 1):3-17). At the time it could be concluded that although mood stabilizers (euthymics) share some action mechanisms, they are also significantly different from each other with respect to their therapeutic properties in the various phases of bipolar disorders. This led to a proposed change in their generic classification as "mood stabilizers" to a new classification that includes: antimanic medications, partial mood stabilizers, and euthymics.

Since then, several randomized, double-blind studies and meta-analyses that explore the effectiveness and tolerability of these medications have been published. This updated review aims to assess the validity of the proposed classification in the light of new evidence.

Key words:
Euthymiants, Bipolar Disorder, Antimanics, Mood stabilizers

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Diferencias terapéuticas de los medicamentos para el tratamiento de los trastornos bipolares: siete años después

En el 2004 fue publicada una revisión detallada sobre las características terapéuticas de los medicamentos utilizados en el tratamiento de los trastornos bipolares [Tamayo JM et al. Actas Esp Psiquiatr 2004;32(Suppl. 1):3-17]. En aquél momento se podía concluir que si bien los eutimizantes compartían algunos mecanismos de acción, eran a la vez sustancialmente diferentes respecto a sus propiedades terapéuticas en las diferentes fases de los trastornos bipolares llevando a proponer un cambio en su clasificación genérica como "estabilizadores del estado de ánimo" a una nueva incluyendo: antimaníacos, estabilizadores parciales del ánimo y eutimizantes.

Desde entonces, han sido publicados varios estudios doble-ciego aleatorizados y meta-análisis, explorando la eficacia y tolerabilidad de estos medicamentos. Esta revisión actualizada pretende evaluar, a la luz de la nueva evidencia, la validez de la propuesta de clasificación publicada en ese entonces.

Palabras claves:
Eutimizantes, Trastorno Bipolar, Antimaníacos, Estabilizadores del ánimo

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SOME CLINICO-EPIDEMIOLOGICAL CHARACTERISTICS OF THE BIPOLAR DISORDERS

Bipolar disorders (BDs) share the presence of depressive symptoms and a high risk of recurrence and chronification with unipolar depressive disorders and, in the case of Bipolar Disorder II (BD II), a greater prevalence in women. However, the presence of manic or hypomanic episodes distinguishes one condition from the other.[1, 2] BDs can be subdivided into different types depending on the episodes that the patient has presented throughout life. Bipolar Disorder I (BD I) differs from other BDs in that at least one manic or mixed episode has occurred. BD II is characterized by one or more depressive episodes with at least one hypomanic episode with a minimum duration of 4 days. The cyclothymic disorder is characterized by a chronic recurrent pattern of oscillation between hypomanic and depressive symptoms of less severity than observed in BD I or II, although 15% to 50% of these patients will progress to BD I or especially to BD II.[3]

An international cross-sectional study (11 countries) conducted in more than 61,000 adults living in the community using DSM-IV criteria and the CIDI (Composite International Diagnostic Interview) scale of the WHO showed

that the prevalences in the community were 0.6% BD I, 0.4% BD II, 1.4% sub-threshold BD and 2.4% for the bipolar spectrum in general. The prevalence of the bipolar spectrum varies significantly between countries, ranging from 0.1% in India to 4.4% in the United States (USA), suggesting that cultural factors could greatly influence the detection of the disorder. However, for the authors the rates of prevalence, severity, impact and comorbidities of BDs are "remarkably similar" at the international level. This study made it possible to confirm that symptom severity and suicidal behavior increased from sub-threshold BD to BD I, but that the functional alterations are similar in all the BD subtypes and depend to a great extent on the presence of depressive symptoms.[4]

The differences between the different subtypes of bipolar disorders are substantial and go beyond the symptomatology and severity of the affective episodes. For example, the study of the National Institute of Mental Health Collaborative Depression of the United States showed that the percentage of weeks in which subjects with BD I and II experienced depression was 31% and 52%, respectively, in a 15-year follow-up. In contrast, the weeks of hypomanic, manic or mixed episodes reported was 10% and 1.6%, respectively.[5, 6] In comparison with pure manic episodes, mixed manic episodes occurred more often in female patients, had a greater frequency of episodes in the previous 12 months, more suicide attempts, a greater rapid cycling rate (RC), less social activities and more occupational impairment. During 24 months of follow-up, the group with mixed episodes had a significantly lower recovery rate than patients with pure manic episodes (36% versus 46%, p = 0.006).[7] Although only 10% to 15% of patients present four or more episodes a year, patients who develop an RC pattern present a very high risk of suicide attempts and attain only partial remissions or exhibit a marked tendency to change polarity.[8] In addition, women seem to have a greater risk of RC.[9, 10] Finally, patients with a predominantly depressive polarity tend to present an onset of disease in the depressive phase, an earlier age of onset, longer disease duration, more suicide attempts and more delayed BD diagnosis than patients with predominantly manic polarity. [11]

With respect to comorbidity, 65% of patients with BDs exhibit one or more Axis I comorbidity diagnoses in the course of life, whereas more than 40% of patients have 2 or more diagnoses and 25% have 3 or more.[12] Among the most common Axis I comorbidities in patients with BD are substance abuse/dependence disorders (40-60%) and anxiety disorders (50%). The international mental health study showed that up to three fourths of patients with BD exhibit at least one other psychiatric condition in comorbid form, panic attacks being the most frequent comorbidity (present in almost 50% of patients), followed by alcohol abuse (34.2%).[4] The most common nonpsychiatric comorbidities include cardiovascular diseases and obesity.[13, 14]

With regard to treatment, fewer than half of international patients with BDs receive mental health treatment. In low income countries, only 25.2% of patients report a contact with the mental health system at some time in their lives.[4] As for studies that evaluate the effectiveness and safety of medicinal products for the treatment of BDs, the majority usually include only patients with BD I. Few double-blind, randomized studies have focused exclusively on patients with BD II or other subtypes of bipolarity. As has been mentioned, there are substantial differences in the course and prognosis of different bipolar subtypes. An independent evaluation of the pharmacologic effect of euthymics in each subtype is necessary. On the other hand, evaluations of therapeutic pharmacologic effect in bipolar patients in special situations, such as comorbidity, gender, RC, mixed episodes or high rates of suicide are usually scant and the available evidence often cannot be extrapolated. A still greater problem is suggested by a sub-analysis of data from an international multicenter study of patients with BD I.[15] The authors found that demographic and cultural diversity can contribute to variations in the study results. The dosage, disease severity and response to placebo vary substantially among countries like India, Russia and the U.S.A. Other authors conclude that international multicenter studies are usually accompanied by factors that complicate the interpretation of the data related to differences in the nature and severity of BD, cultural conceptions of BD, diagnostic criteria, the measurement of severity and adverse event notifications, among others.[16]

THERAPY OF BIPOLAR DISORDERS

The treatment of BDs can reduce the associated morbidity and mortality, diminish the frequency, severity and psychosocial consequences of the affective episodes, and improve psychosocial functioning in periods of euthymia (normal mood). Nevertheless, it is calculated that only one third of the persons with BD receive treatment. Management includes pharmacologic intervention (for the control of the acute episode and the maintenance phase), the development of daily activity patterns and individual and group psychotherapy.[17, 18] The objectives of intervention vary with the disease phase and prevailing mood. In the acute phase, treatment is designed to stabilize the mood of the present episode in order to achieve remission (defined as a complete return to the basic level of functioning and the virtual absence of symptoms), guarantee the safety of the patient and those around them, prevent cycling from one episode to another and prevent suicidal behavior. In the maintenance phase, the aim of treatment is to optimize protection against recurrence and reduce the frequency of depressive, mixed, manic or hypomanic episodes. At the same time, attention

must be given to improving the patient's functioning and reducing subsyndromic symptoms and the adverse effects of treatment, to treating comorbidities and cognitive problems, increasing knowledge of the patient and family members about the disease and improving compliance with treatment.

At present it is thought that most first-line treatments for the acute manic episode produce an appreciable clinical effect within no more than 10 to 14 days. When selecting the primary treatment, the general rule is to use what was successful in the treatment of the index episode. Although treatment guides recommend monotherapy as a first-line strategy,[19] multiple drug treatments are often used without the support of evidence or, sometimes, without clear or adequate optimization of the monotherapy.[20-22] For example, Perlis et al.[23] mention that it is likely that differences in the effectiveness of the acute treatment of mania between monotherapy with second-generation antipsychotics (SGAs) and the addition of another medication are small, if any can be found. A recent meta-analysis reports that more than 50% of patients with a manic episode respond properly to monotherapy with lithium, anticonvulsants or SGAs.[24]

However, the literature suggests that some patients do not respond to acute treatment with monotherapy, especially if they have a bipolar depressive episode.[22, 24] These patients usually need combination therapy and the best strategy is to begin with the better studied medications and then to try less tested agents if these drugs are ineffective or not tolerated. If the symptoms cannot be controlled within the recommended time for observing an appreciable clinical effect, the first step must be to optimize the dose of the current medication to ensure that the blood levels are within therapeutic range. It is also important to identify problems of noncompliance with the medication, a frequent cause of relapses. If the symptoms continue, other options include adding or switching to another medication, again emphasizing the optimal dose and compliance with the therapeutic regimen. It is recommended that each pharmacotherapeutic regimen be evaluated for at least 2 weeks before concluding that the patient is unlikely to respond (generally defined as a reduction in the symptoms targeted by therapy of less than 30%). In patients with severe or treatment-refractory disease, electroconvulsive therapy (ECT) and experimental or novel treatments can be considered. In addition, there is some evidence, as yet limited, that coadjuvant psychosocial interventions can help to increase the response to pharmacologic treatment.[25]

Seven years ago an evidence-based definition was proposed that allowed the classification of these medications according to their effectiveness in different phases of BD[26]:

1. Antimanic agents: The antimanic agents that have been demonstrated to be effective in the control of manic episodes when used in monotherapy, but lack double-blind, randomized, placebo-controlled studies that demonstrate their effectiveness in the control of depressive symptoms or BD prophylaxis.
2. Partial mood stabilizers: mood stabilizing agents with demonstrated effectiveness in the control of manic episodes and/or the prevention of manic recurrences, but not in the control of the depressive episodes or the prevention of recurrences. Or those that, in inverse form, are effective in the control of depressive episodes and/or in the prevention of depressive recurrences, but not in the control of manic episodes or in the prevention of manic recurrences.
3. Euthymics: agents used as monotherapy that in double-blind, randomized, placebo-controlled studies have been demonstrated to be effective in the control of mixed and depressive manic episodes; and that have also been demonstrated to be effective in the prophylactic management of patients with BD for both the prevention of both manic and depressive episodes.

This classification, like others, does not include concepts like 'bipolar antidepressants,' medications that would only be effective in the bipolar acute depressive phase. The use of monotherapy with antidepressants in bipolar patients in the depressive phase is not justified but contraindicated in various therapy guides.[17, 19]

Finally, it should be highlighted that effectiveness in double-blind, randomized studies is usually measured on the basis of the change in the total score of different scales validated for this purpose. However, other aspects that go beyond the changes in mood states that are also part of the syndromic picture of bipolar patients, such as cognitive alterations or compromised functionality, are rarely considered as measures of primary effectiveness and, therefore, information on the impact of pharmacologic treatments on those points is usually scarce.

DRUG THERAPY OF THE MANIC EPISODES

Patients with BDI who present acute manic or mixed episodes usually require a rapid and aggressive intervention for the control of agitation, affective symptoms and, in some cases, psychotic symptoms. Different studies have demonstrated that antipsychotics usually act more rapidly in the control of agitation, excitation, grandiosity, hostility and psychotic disorganization than lithium or anticonvulsants.[27, 28] Despite this, the use of conventional antipsychotics as antimanics must be evaluated in relation to the risk of adverse effects. Patients with bipolar disorder have higher rates of incidence of extrapyramidal symptoms (EPS) than observed in patients with schizophrenia,[29, 30] they have high rates of tardive dyskinesia[31] and they have been associated to a greater risk of depressive episodes and rapid cycling.[32, 33]

Study or Subroup	MDR Events	MDR Total	placebo Events	placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
lithium						
Bowden, 1994	18	36	19	74	22.8%	1.95 [1.17, 3.23]
Bowden, 2005	52	98	26	97	32.7%	1.91 [1.32, 2.76]
Keck, 2009	73	160	57	165	45.7%	1.32 [1.01, 1.73]
Total (95%CI) I^2 = 40%	**143**	**294**	**103**	**336**	**100.0%**	**1.62 [1.23, 2.13]**
valproate						
Bowden, 1994	33	69	19	74	14.7%	1.86 [1.18, 2.95]
Bowden, 2006	92	192	63	185	50.1%	1.41 [1.10, 1.80]
Tohen, 2008	75	201	31	105	26.0%	1.26 [0.89, 1.79]
Wagner, 2009	18	76	17	74	9.2%	1.03 [0.58, 1.84]
Total (95%CI) I^2 = 0%	**218**	**538**	**130**	**438**	**100.0%**	**1.39 [1.16, 1.65]**
oxcarbazepine						
Wagner, 2006 ER-CBZ	42	59	26	57	100.0%	1.56 [1.13, 2.16]
Weisler, 2004	42	101	23	103	36.1%	1.86 [1.21, 2.86]
Weisler, 2005	73	120	33	115	63.9%	2.12 [1.54, 2.92]
Total (95%CI) I^2 = 0%	**115**	**221**	**56**	**218**	**100.0%**	**2.02 [1.56, 2.62]**
haloperidol						
McIntyre, 2005	56	99	35	100	25.2%	1.62 [1.18, 2.22]
Smulevich, 2005	68	144	46	140	26.6%	1.44 [1.07, 1.93]
Vieta, 2008	94	171	18	88	19.2%	2.69 [1.74, 4.15]
Young, 2009	82	165	58	153	29.0%	1.31 [1.02, 1.69]
Total (95%CI) I^2 = 64%	**300**	**579**	**157**	**481**	**100.0%**	**1.63 [1.25, 2.12]**
aripiprazole						
Keck, 2003a	49	123	23	120	16.1%	2.08 [1.36, 3.18]
Keck, 2009	73	155	57	165	28.5%	1.36 [1.04, 1.78]
Sachs, 2006	73	137	43	135	26.0%	1.67 [1.25, 2.24]
Young, 2009	78	167	58	153	29.4%	1.23 [0.95, 1.60]
Total (95%CI) I^2 = 44%	**273**	**582**	**181**	**573**	**100.0%**	**1.49 [1.22, 1.83]**
olanzapine						
Tohen, 1999	34	70	16	69	19.4%	2.09 [1.28, 3.43]
Tohen, 2000	35	54	24	56	30.7%	1.51 [1.05, 2.17]
Tohen, 2007	52	107	12	54	16.9%	2.19 [1.28, 3.74]
Tohen, 2008	82	215	31	105	33.0%	1.29 [0.92, 1.82]
Total (95%CI) I^2 = 27%	**215**	**446**	**83**	**284**	**100.0%**	**1.63 [1.28, 2.08]**
quetiapine						
Bowden, 2005	57	107	27	97	49.3%	1.91 [1.33, 2.76]
McIntyre, 2005	43	101	35	100	50.7%	1.22 [0.86, 1.73]
Total (95%CI) I^2 = 68%	**100**	**208**	**62**	**197**	**100.0%**	**1.52 [0.97, 2.37]**
risperidone						
Hirschfeld, 2004	54	125	32	134	24.0%	1.81 [1.26, 2.60]
Khanna, 2005	107	146	52	144	42.5%	2.03 [1.60, 2.58]
Smulevich, 2005	74	154	46	140	33.5%	1.46 [1.10, 1.95]
Total (95%CI) I^2 = 33%	**235**	**425**	**130**	**418**	**100.0%**	**1.77 [1.44, 2.17]**
ziprasidone						
Keck, 2003b	66	131	23	66	40.8%	1.45 [1.00, 2.10]
Potkin, 2005	63	137	19	65	31.9%	1.57 [1.03, 2.39]
Vieta, 2008	66	178	18	88	27.2%	1.81 [1.15, 2.86]
Total (95%CI) I^2 = 0%	**195**	**446**	**60**	**219**	**100.0%**	**1.58 [1.25, 2.00]**
Total (95%CI)	**1824**	**3798**	**697**	**2299**	**100.0%**	**1.61 [1.49, 1.75]**

Heterogeneity: Tau^2 = 0.01; Chi^2 = 28.23, df = 21 (P = 0.013); I^2 = 26%; Test for overall effect: Z = 11.29 (P < 0.00001)
Response is defined as a reduction of ≥ 50% with respect to baseline points in the measure of primary efficacy after 7 to 10 weeks of treatment. M-H, Mantel–Haenszel (ref. 24)

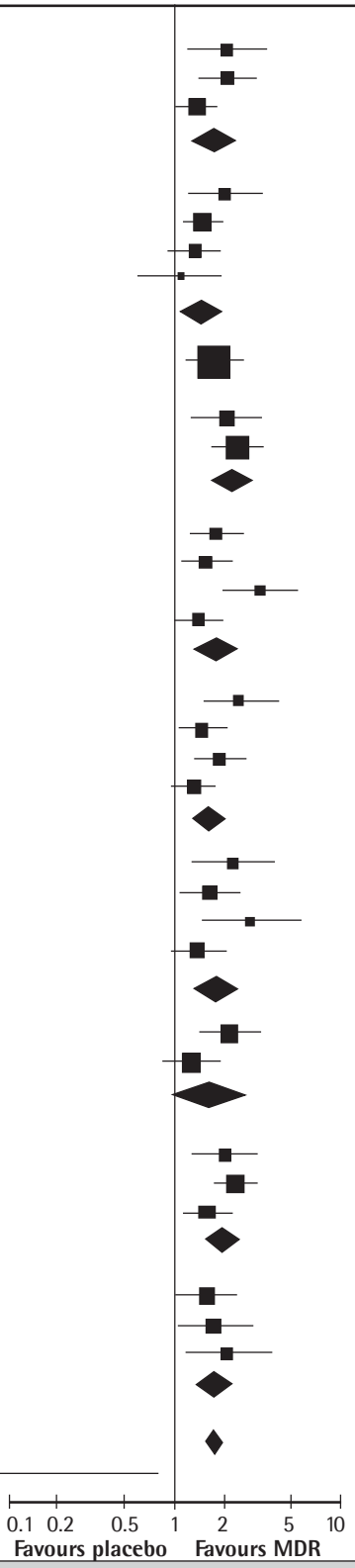

Figure 1 Random relative risk (RR) and 95% confidence intervals (CI) for response rates in monotherapy (MDR) vs. placebo in the treatment of acute mania episodes.

Recent studies suggest that the use of injectable SGAs in monotherapy form permit the control of acute manic episodes that is at least similar to that observed with conventional antipsychotics but with a lower incidence of adverse events (AEs).[34-37]

With respect to the management of the manic/acute mixed episode in the patient who does not require parenteral management, some expert consensus recommendations and treatment guides suggest that the treatment of choice is monotherapy with a mood stabilizing agent like lithium, carbamazepine or valproic acid, followed by combined therapy with a mood stabilizer plus a SGA.[19, 38, 39] However, two recent meta-analyses show that SGA monotherapy is equally effective in the treatment of acute episodes of mania.[24, 40] One of these meta-analyses[24] included data from 31 randomized controlled studies and found that monotherapy with lithium, valproic acid or SGA (n = 3798) is associated to a greater probability of response (defined as a reduction of at least 50% on the scale of primary effectiveness, usually the Young Mania Rating Scale, or YMRS) [RR = 161 (95% CI, 1.49-1.75)], although with a greater risk of interruption due to AEs [1.57 (95% CI, 1.22-2.03)] than patients treated with placebo (n = 2299). Additional comparisons demonstrated that the patients treated with mood stabilizers (lithium, oxcarbazepine or valproate; n = 1112) had a greater probability of response [1.57 (95% CI, 1.36-1.81)] with a greater risk of interruption due to AEs [2.07 (95% CI, 1.46-2.93)] than patients treated with placebo (n = 975). Likewise, patients treated with SGA (n = 2107) had a greater probability of response [1.59 (95% CI, 1.44-1.75)] with a greater risk of interruption due to AEs [1.36 (IC 95%, 1.03-1.79)] than patients treated with placebo (n = 1691) (Figure 1).

Other later meta-analyses and double-blind studies have also confirmed the effectiveness of lithium,[40] anticonvulsants[40, 41] and SGA[40, 42-46] in the control of manic episodes. One of them reported negative results for valproate versus placebo (n = 225).[41]

With respect to the treatment of children and adolescents with bipolar disorder, lithium was until a few years ago the only treatment approved by the FDA for the treatment of children over 12 years. However, the level of evidence on the management of acute manic episodes with this drug and anticonvulsants in adolescents is based on few randomized studies and[47] several randomized, double-blind, placebo-controlled studies have suggested recently the effectiveness of several SGAs in acute manic episodes in children and adolescents: aripiprazole,[48, 49] olanzapine[50] and risperidone.[51] A recent comparative analysis based on 9 double-blind studies concluded that SGAs exhibit more effectiveness than lithium and anticonvulsants in the treatment of manic episodes, although with greater rate of adverse events like weight gain and drowsiness.[52]

Despite the available evidence, combined therapy continues to be the universally accepted method of treatment for manic patients not refractory to monotherapy, the same as 7 years ago.[20, 22] In patients who do not respond to monotherapy, a meta-analysis suggests that combined therapy (a SGA plus lithium or an anticonvulsant) can offer a slightly higher response rate, although with diminished tolerability.[53] However, Cipriani et al.[54] have questioned the utility of this meta-analysis because the sample sizes and heterogeneity of the studies lead to a biased result that favors combined therapy. In addition, in all the studies on which this meta-analysis is based, the monotherapy that was ineffective for the control of the manic episode is used as the comparator of the combined therapy. On the other hand, it should be taken into account that drug interactions, lower tolerability, decreased compliance and greater costs can jeopardize the hypothetical benefits of combined therapy.

DRUG THERAPY OF THE MIXED EPISODES

The same as 7 years ago, few studies have evaluated the impact of pharmacologic treatments or electro-convulsive therapy (ECT) in the acute phase and maintenance of patients with mixed episodes. Most of these publications are post hoc analysis of double-blind studies or open-label studies. Considering these limitations, it could be said that the presence of mixed affective episodes or a pattern of rapid cycling continues to be a risk factor for poor response to lithium. Valproate in patients with mixed manic episodes, administered as monotherapy or associated to other antimanics, has been shown to have a broader spectrum of effectiveness than carbamazepine or lithium. Recent studies suggest that the SGAs (especially olanzapine and aripiprazole) can be as effective as valproate in this type of patients.[55, 56] In some cases, ECT is necessary for the control of this type of episodes.[57]

DRUG THERAPY OF THE DEPRESSIVE EPISODES

Neither evidence-based guides[17, 19] nor a recently published meta-analysis[58] recommend antidepressant monotherapy for the management of bipolar depressive episodes, but approximately 50% of patients are treated initially with an antidepressant, more than twice as many as those who receive anticonvulsants as the first option.[59] The guides also suggest that clinicians interrupt antidepressant treatment during the manic episodes and recommend considering the use of other medications that have been demonstrated to be effective in patients with bipolar depression. Despite these recommendations, more than 15% of patients continue to receive antidepressant treatment during manic episodes.[60] The possibility that antidepressants might cause a change of polarity in the

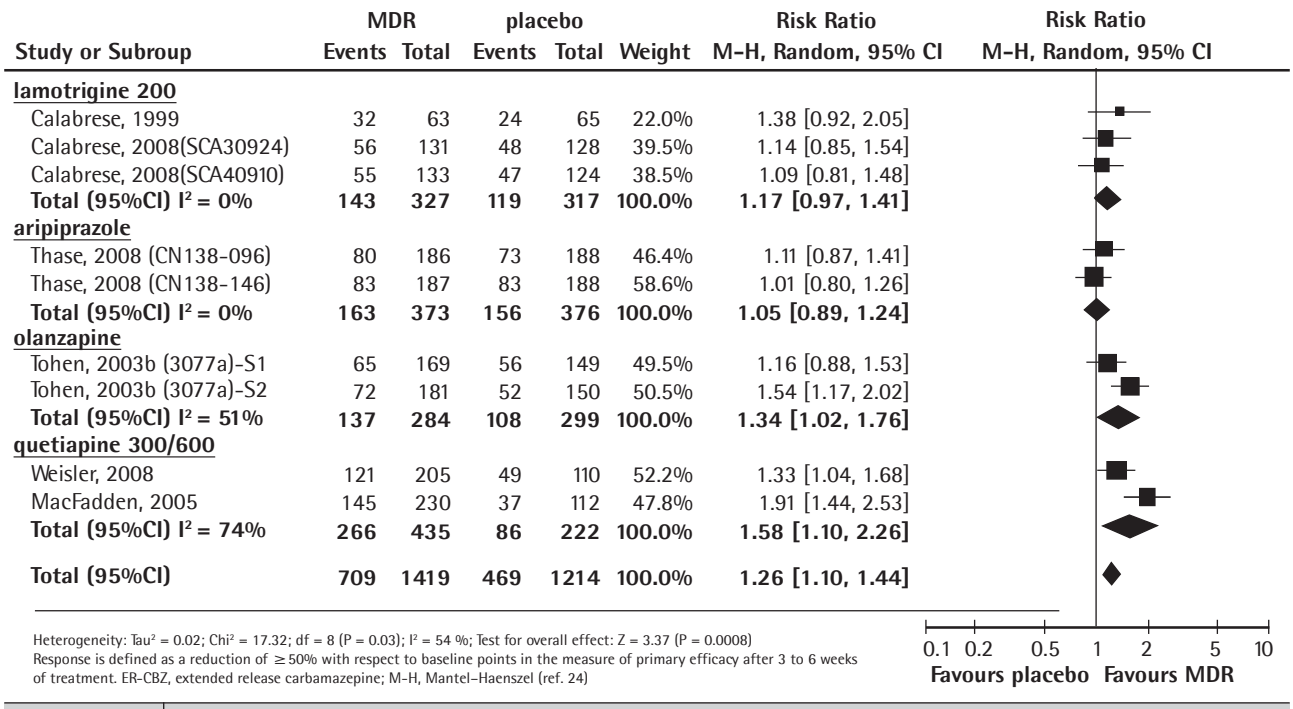

Figure 2 Random relative risk (RR) and 95% confidence intervals (CI) for response rates in monotherapy (MDR) vs. placebo in the treatment of bipolar depression episodes.

manic episodes is a common concern.[17] Nonetheless, most studies do not suggest an increased risk of change of polarity with antidepressants (3.8% vs. 4.7% for placebo), although the rate of change of polarity with tricyclic antidepressants (TCAs) seems to be greater than with selective serotonin reuptake inhibitors (SSRIs) or monoamine oxidase inhibitors (MAOIs).[61] Venlafaxine can also lead to a greater rate of change to mania or hypomania than other antidepressants like the SSRIs and bupropion.[62] A meta-analysis has confirmed that the conversion to manic episodes was observed exclusively with TCAs [RR = 1.93 (95% CI, 1.13-3.30)],[63] whereas another meta-analysis has confirmed that the concomitant use of euthymics reduces the risk of conversion to mania compared to the use of antidepressants in monotherapy.[64] Moreover, for Licht et al.,[65] using the criteria of Bradford-Hill, the conversion rates seen with antidepressants in association with euthymics in patients with BD must be attributed to the natural history of the disease and not to the use of those medications. For these authors, many states of treatment-induced emergent mania (TEM) attributed to antidepressants may be due to a shortening of the depressive episode without a direct effect of the antidepressant on the conversion. They conclude: "antidepressants do not prevent mania." Another serious problem reported in the literature is that antidepressants could reduce the duration of the bipolar cycle and induce RC. As in the case of research on the change of mood polarity, the body of proof in relation to RC is small. Even so, shortening of the cycle duration has been served with TCAs[66] but not with SSRIs[67]. Finally, a recent publication of a study of 144 patients with BD I with 9.5 years of follow-up concluded that almost 40% of the patients treated with antidepressants presented at least one mixed manic episode and that the appearance of this type of episodes was associated to a larger number of suicide attempts ($p < 0.001$), a greater rate of treatment-induced emergent manias ($p = 0.010$) and more time with the disease ($p = 0.022$). The authors found that the presence of mixed mania was associated significantly with the use of dual antidepressants ($p = 0.041$) but not with TCAs or SSRIs.[68] A previous *post hoc* analysis based on a double-blind study controlled with the combination of fluoxetine and olanzapine in patients with bipolar depression showed that the frequency of mixed depression in the 8 weeks of treatment was comparable to the frequency observed in patients treated with olanzapine monotherapy or placebo, and that the response rates with olanzapine + fluoxetine in such patients were comparable to those of patients without concomitant manic symptoms and higher than those of patients with mixed depression treated with placebo.[69]

Cruz and Vieta[70] claim that the effectiveness and safety of antidepressants in bipolar depression are still a matter of

debate and that meta-analyses of the topic[58, 61] include studies of poor quality and varied effect sizes that can significantly bias conclusions.

Some studies even suggest that selective serotonin reuptake inhibitors (SSRI) or dual serotonin and noradrenalin reuptake inhibitors (SNRI) are effective as monotherapy in the control of acute depressive phases in patients with BD II.[71-73] With regard to BDI, two studies have demonstrated that the combination of fluoxetine with olanzapine is more effective than olanzapine alone in the treatment of patients with type I bipolar depression, but the effect of monotherapy with fluoxetine was not evaluated.[74, 75] In combination with other euthymics, the available evidence does not seem to support the use of antidepressants in type I bipolar depression.[76] Even McElroy et al.[77] found that quetiapine, unlike paroxetine, is significantly more effective than placebo in patients with bipolar depression I or II. In general, the risk of a change of polarity, RC or tachyphylaxis in bipolar patients treated with antidepressant monotherapy form would seem to contraindicate its use.[10, 78, 79] It should be noted, however, that a recent meta-analysis failed to observe differences between the use of antidepressants in monotherapy or associated to euthymics and a hypothetical increase in the risk of long-term recurrences (10 years).[64] Another review also could not confirm a greater risk of RC or suicide with the use of antidepressants in BD and the author concludes that most of the evidence has been obtained from small studies with several methodological biases, leading to an over-interpretation of the risks of using those medications. [80]

On the other hand, in depressive episodes it is essential to reduce or discontinue conventional antipsychotics if they are administered concomitantly with other euthymics, because this single measure can lead to diminished depressive symptoms.[81]

As far as the use of monotherapies in patients with bipolar depression, a meta-analysis included 9 randomized, controlled studies. The general relative risk (RR) with regard to response in patients with bipolar depression treated with monotherapy (n = 1419) was 1.26 (95% CI, 1.11-1.44), but with a risk 1.77 (95% CI, 1.38-2.26) times greater of interruption of the therapy as a result of AEs compared to patients treated with placebo (n = 1214).[24] As for anticonvulsants, two meta-analyses that included 4 double-blind studies with small sample sizes suggest greater antidepressant response rates for patients treated with valproate versus placebo [RR = 2.00 (95% CI, 1.13-3.53) and RR = 2.10 (95% CI, 1.10-4.03)].[82, 83] A small study in ambulatory patients with bipolar depression (67% with RC) showed that 38.5% of patients with BD I showed a response in comparison with 10.7% of the placebo group (p = 0.017).[41] On the other hand, in contrast with general perception and the recommendations of some guides supported by experts,[39] a meta-analysis that includes the data of three randomized controlled studies concludes that patients with BD I treated with lamotrigine (≥ 200 mg/day) (n = 327) have a similar opportunity for response and remission as patients treated with placebo (n = 317). Similar results were observed when patients with BD I and patients with BD II were taken into account and when all the doses of lamotrigine studied were considered.[24] Another meta-analysis of 5 studies with lamotrigine, all of them negative, confirms that the effectiveness of lamotrigine is marginal with respect to placebo [RR = 1.14 (95% CI, 1.00-1.30)].[84] A third meta-analysis shows that only in patients with marked severity (score of more than 24 on the Hamilton depression scale) is a significant difference appreciated versus placebo in favor of lamotrigine [RR = 1.21 (95% CI, 1.06-1.41)].[85] With respect to SGAs, patients treated with aripiprazole (n = 373) had a similar opportunity for response and remission as the patients treated with placebo (n = 376) in two controlled double-blind studies.[86] The only two monotherapies that have exhibited statistically significant response rates compared to placebo in two meta-analyses were olanzapine [RR = 1.34 (95% CI, 1.02-1.76) and 1.28 (95%CI, 1.05-1.57)] and quetiapine [RR = 1.58 (95% CI, 1.10-2.26) and 1.37 (95% CI, 1.24-1.51)][24, 87] (Figure 2).

In the case of refractoriness there is little evidence of differences in the magnitude and rate of response with electroconvulsive therapy (ECT) in patients with bipolar depression are compared to patients with unipolar depressive disorder. Some small studies, however, show that patients with bipolar depression seemed to have more rapid clinical improvement, requiring fewer treatments then unipolar patients.[88-90] With respect to RC, these patients exhibit clearly lower response rates to lithium, anticonvulsants or antipsychotics and may require combinations of two or three medications.[91] As mentioned previously, although it is debated whether antidepressant use in patients with BDs is useful, the first reports refer mainly to TCAs, which have been associated with a high risk of RC. Nevertheless, more recent and substantive evidence indicates that, in the worst of cases, the risk of changing polarity and perhaps also of RC and the appearance of suicidal tendencies has been overestimated and is applicable to new antidepressants.[80] With regard to lamotrigine, a double-blind, placebo-controlled study that showed that lamotrigine was superior to placebo in patients with BD I and RC after 26 weeks of treatment (p = 0.037) did not demonstrate a significant difference (p = 0.427) when these patients were analyzed independently.[92] In patients with impaired thyroid function, L-thyroxine (0.025-0.5 mg/day) or liothyronine has been demonstrated to be effective in association with anticonvulsants or lithium.[93, 94] ECT, together with certain psychopharmaceuticals, can also be considered a valid option for the treatment of RC patients with refractory bipolar depression.[95]

PROPHYLACTIC PHARMACOTHERAPY OF BIPOLAR DISORDERS

The primary goal of maintenance treatment of BDs is to prevent recurrences. The long-term treatment must be considered seriously after the stabilization of the first episode because the prevention of recurrence in the first stages of disease can lead to a more benign general course. Several studies have found that discontinuing maintenance treatment with lithium or other medications produces high recurrence rates compared to continuing treatment, the risk of recurrence being especially high in the first year after interruption.[96] The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study found that patients with problems of substance abuse have an increased risk of recurrence of the manic symptoms, whereas patients with an existing anxiety disorder or eating disorder in the course of life have a greater risk of recurrence of depressive symptoms.[97] Another natural history study of 154 patients with BDs, with an 18-month follow-up, shows that proper and uninterrupted maintenance was greater in patients who did not present a new affective episode, did not require hospital management, did not have a pattern of RC or did not have some concomitant personality disorder.[98]

There is considerable debate about the optimal duration of maintenance treatment, especially after a depressive episode. As BD is currently recognized as a chronic, recurrent and disabling disease, several authors recommend long-term maintenance, including after the first episode.[99]

The lack of compliance with prescribed treatment is a serious obstacle for the effective prevention of recurrence. A study in patients who received long-term treatment with lithium or anticonvulsants found that almost 50% of the participants (n = 98) were considered noncompliant with the drug regimen at some time during the 2 previous years, and that almost one third of patients missed 30% or more of their medications in the previous month.[100] The lack of compliance may be due to multiple factors, including age (more frequent in young people), substance abuse, the side effects of medications, unwillingness to forego the good moods, and generally negative feelings about taking the medication and having a chronic mental disease.[21] In an effort to increase compliance with treatment, clinicians must maintain a supportive relation with patients and ask about patients' compliance with and expectations of treatment. Patients and their families must be encouraged to consult the doctor if drug-related problems occur.[100]

Despite the use of evidence-based pharmacologic treatments, affective recurrence is observed in at least half of the persons who have BDs with intervals of up to 2 years.[100] In addition to complete syndromic recurrence, patients diagnosed with BDs often experience subsyndromic levels of affective symptoms. For example, the data of a long-term natural history study in the United States (NIMH Depression Collaborative Study) show that patients diagnosed of BD II and patients diagnosed of BD I invest a considerable part of their days experiencing depressive or hypomanic subsyndromic affective symptoms (16.2% and 14.1%, respectively), or symptoms consistent with minor depression, dysthymia or hypomania (27% and 20.1%, respectively).[101] Consequently, patients with BD II have a somewhat smaller percentage of asymptomatic days than patients with BD I (44.2% vs. 53.4%).[5, 6] The recent results of the STEP-BD study identify residual manic symptoms as significant predictors of the time to manic or depressive recurrence. The presence of residual manic symptoms in the phase of recovery and the proportion of elevated mood days in the previous year is associated significantly with a shorter time to the recurrence of the manic, hypomanic or mixed episode. With each additional hypomanic or manic symptom, the risk of recurrence increases by 20%.[102]

If the patient responds to acute treatment with monotherapy, that medication generally must be continued in the maintenance phase as monotherapy. In the case of persistence or reappearance of affective symptoms, the present standard of practice is to continue treatment with the index medication and add a second medication to try to achieve the desired response. If the second medication is not effective, a third medication can be added or used to replace one of the two prior medications, and this process is repeated until remission or at least an acceptable response is achieved. No consensus opinion exists about how long the patient should continue with these complex regimens and, for that reason, it is not surprising that an increasing number of persons with BDs are being treated with up to 3, 4 and 5 medications approved for the condition.[101-104] Effective maintenance therapy is especially crucial for the prevention of depressive episodes, due to the risk of suicide. Although it is likely that all the effective maintenance therapies reduce the risk of suicide by diminishing the probability of recurrences, only lithium is backed by empirical evidence showing that it can reduce the risk of suicidal behavior and the number of consummated suicides.[105]

Some evidence-based guides, such as those of the Canadian Network for Mood and Anxiety Treatments (CANMAT) and the International Society for Bipolar Disorders (ISBD), suggest that lithium, divalproate, olanzapine, quetiapine and depot risperidone can be effective in the prevention of manic or depressive episodes in bipolar patients. Lamotrigine in the prevention of depressive episodes and aripiprazole in the prevention of manic episodes are also considered as first-line treatments.[39] A recent review of 15 studies designed to evaluate the prophylactic effect of euthymics in patients with BD concluded that aripiprazole, olanzapine, quetiapine, depot risperidone and lithium are effective in the prevention of manic recurrences as they present the necessary number to

Table 1 Adverse events most commonly observed with medications used in the treatment of BDs

Medication	Adverse event	Frequency	Mechanism	Treatment	Therapeutic options
Lithium	polydipsia and polyuria	35.9%	nephrogenic diabetes insipidus	reduce PL one half + amiloride and K+ supplements	carbamazepine, divalproate, SGAs
	cognitive dysfunction	28.2%	anticholinergic	PL lower than 0.68 mEq/L	SGAs
	weight gain (2-12 kg)	18.9%	fluid retention, increased appetite, hypothyroidism	diet and exercise, non-thiazide diuretics	addition of topiramate as second option, aripiprazole
	tremor	15%	anti-dopaminergic	β-blockers	carbamazepine, divalproate, SGAs
	hypothyroidism	5-35%	antithyroid receptor antibodies	suspension and thyroxine administration	carbamazepine, divalproate, SGAs
	congenital malformations	4-12%*	organ toxicity	prevent administration (risk/benefit)	SGAs first trimester
Oxcarbazepine	dizziness, ataxia, diplopia, drowsiness	30-50%	slowing of neuronal conduction	dose reduction	lithium
	aplastic anemia, agranulocytosis	0.5/100 ml **	idiosyncratic reaction	suspend immediately	another euthymic (exc. CBZ)
	AV block		rapid Na+ channel blocker	suspend immediately	another euthymic (exc. CBZ)
	skin rash	10%	idiosyncratic reaction	suspend immediately	SGA, lithium
	hepatotoxicity	10-15%	idiosyncratic reaction	suspend immediately	lithium
	hyponatremia	23%	antidiuretic effect	dose reduction, electrolyte correction	SGA, divalproate
	thrombocytopenia	10%	idiosyncratic reaction	suspend immediately	SGA, lithium
	delayed fetal growth	5.3%	epoxide hydrolase deficiency	prevent administration	SGAs first trimester
	congenital malformations (cardiac, vertebral, esophageal, hypoplasias)	5.2-5.7%	neural tube defects, folic acid deficiency	prevent administration (risk/benefit), folic acid (?)	SGAs first trimester
Divalproate	nausea	23%	?	dose reduction (titration)	SGAs
	drowsiness	19%	GABAergic effect	dose reduction (titration)	lithium
	tremor, ataxia, vertigo	16%	GABAergic effect	dose reduction (titration)	quetiapine (?), olanzapine (?)
	weight gain	12-44%	increased appetite	diet and exercise	topiramate as second option, aripiprazole
	alopecia	2.6-12%	idiosyncratic reaction	zinc supplement	any other euthymic
	liver disease	1/600 in children	necrosis and idiosyncratic steatosis	suspend immediately	lithium
	polycystic ovarian syndrome	0-11%	hyper-androgenism (?)	controversial; may require suspension and hormone treatment	lithium, SGA
	pancreatitis	rare	idiosyncratic reaction	suspend immediately	SGA, lithium
	congenital malformations (cardiac, vertebral) and delayed growth	7-11%	neural tube defects due to free radicals	prevent administration (risk/benefit), folic acid (?), selenium (?)	SGAs first trimester

Table 1 Continuation

Medication	Adverse event	Frequency	Mechanism	Treatment	Therapeutic options
Lamotrigine	dizziness, ataxia, diplopia, drowsiness	14-38%	slowing of neuronal conduction	dose reduction	lithium (?), SGA (?)
	agitation, anxiety, confusion, mania, psychosis	?	NMDA receptor blockade	dose reduction	SGAs
	congenital malformations	1.8%	neural tube defects	prevent administration (risk/benefit), folic acid (?)	SGAs (?)
	severe skin rash	10%	idiosyncratic reaction	suspend immediately	SGA, lithium
SGAs	drowsiness (quetiapine > olanzapine)	15-46%	anti-H_1 effect	dose reduction, evening administration	other SGAs, lithium
	transitory elevation of hepatic transaminases	<4%	?	spontaneous normalization in the first 6 weeks	lithium in the case of persistence
	weight gain (olanzapine > quetiapine > risperidone)	25%-50%	increased appetite (various mechanisms postulated)	diet, exercise, metformin, topiramate	aripiprazole, ziprasidone
	extrapyramidal symptoms (akathisia, tremor) (risperidone, aripiprazole, ziprasidone, asenapine)	up to 25%	blockade of striatal D2 receptors	dose reduction, anticholinergics (?), β-blockers	quetiapine, olanzapine, divalproate
	galactorrhea, gynecomastia, osteoporosis (risperidone, paliperidone >> olanzapine)	up to 25%	hyper-prolactinemia	suspend	other SGAs, lithium, carbamazepine

PL = plasma levels; AP = antipsychotics; CBZ = carbamazepine; BZD = benzodiazepine
* versus 2% to 4% in controls; ** versus 0.2/100ml in controls. (adapted from ref. 26)

treat (NNT) to observe benefits with respect to placebo, less than 10. Similarly, lamotrigine, quetiapine and lithium presented significant NNTs in the prevention of depressive recurrences.[106]

As for the general prophylactic value (prevention of both manic and depressive episodes) of the euthymics, as of 1990 twelve placebo-controlled studies that evaluated the prophylactic value of lithium had been published. When the combined rate of recurrences of these studies was estimated, it was found that recurrences were present in 80% of the patients who received placebo and in 35% of the patients who received lithium.[107] Three meta-analyses confirm that lithium is effective in the general prevention of affective recurrences in patients with BD I in comparison with placebo [HR = 0.68 (95% CI, 0.53-0.86), RR = 0.65 (95% CI, 0.50-0.84)][108, 109] and OR = 0.29 (95% CI, 0.09-0.93).[108-110] Nevertheless, one of these meta-analyses that included 9 randomized studies (n = 825) that compared lithium to placebo for a period of 12 to 24 months indicated that lithium reduces the risk of recurrences in only 42% (95% CI, 30% - 52%).[110] Poor prophylactic response to lithium is particularly common in patients with mixed affective episodes, rapid cycling, patients with continuous transition from depressive to manic episodes without an intermediate period of euthymia (normal mood), negative familial history of BD, more than 3 affective episodes, concomitant use of substances of abuse, BD secondary to general medical conditions, or presentation or exacerbation of other pathologies like acne, psoriasis, cognitive dysfunction, renal or thyroid insufficiency.[26, 109, 111] On the other hand, the risk of general recurrence (either manic or depressive) depends significantly on how lithium is discontinued. A joint analysis of the available studies indicates that, in comparison with the gradual suspension of lithium, rapid cessation (i.e., in fewer than 14 days) is associated with a significant reduction in the time to recurrence of mania (5 times) or depression (2.8 times), as well as suicide attempts (2 times). In addition,

Table 2 Highest risk pharmacologic interactions observed with medications used in the treatment of BDs

Medication	Interaction	Mechanism	Therapeutic options
Lithium	NSAIDs	reduction of renal clearance	salicylates
	thiazide diuretics	decrease in Na+ resorption in renal tubules	spironolactone
	α-methyldopa, β-blockers, metronidazole, ACEIs , los sodium intake	increase in plasma lithium levels due to renal retention	calcium channel blockers (may reduce lithium levels)
	haloperidol (neurotoxicity or extrapyramidalism)	antidopaminergic summation with haloperidol	SGAs
Oxcarbazepine	phenobarbital, phenytoin, theophylline	metabolic induction of OxCBZ	increase OxCBZ dose
	medications metabolized by CYP3A4	metabolic inhibition	reduce dose (avoid QTc prolongers)
	contraceptives, haloperidol, anticonvulsants, TCAs	metabolic induction of OxCBZ	increase dose of other medications
Divalproate	medications metabolized by CYP3A4	metabolic induction or inhibition	increase or reduce dose (avoid QTc prolongers)
Lamotrigine	CBZ, phenobarbital, primidone	metabolic induction of LTG	increase LTG dose
	divalproate	metabolic inhibition	reduce dose
SGAs	substances metabolized by CYP3A4 (quetiapine, ziprasidone)	metabolic inhibition or induction	increase or reduce dose (avoid QTc prolongers)
	substances metabolized by CYP2D6 (risperidone, paliperidone, aripiprazole)	metabolic inhibition	reduce dose
	substances metabolized by CYP1A2 (olanzapine, asenapine)	metabolic induction or inhibition	increase dose, especially in female smokers

NSAIDs = nonsteroid anti-inflammatory drugs; ACEIs = angiotensin-converting enzyme inhibitors; TCAs = Tricyclic antidepressants; OxCBZ = Oxcarbamazepine; CBZ = carbamazepine; LTG = lamotrigine (adapted from ref. 26)

the risk of recurrence after a rapid interruption was greater in patients with BD II than in patients with BD I.[112]

The possible reduction of the prophylactic effect with time (although different from placebo) is not only observed with lithium. Although several studies document the effectiveness of divalproate in acute patients and in patients with mixed mania or rapid cycling, more double-blind studies are required to evaluate their long-term effectiveness. A Cochrane review, not updated, found that the time to occurrence of an affective episode does not differ between divalproate and lithium. No significant differences were observed in the number of patients who left the study due to recurrence.[113] Nevertheless, a prospective, international, multicenter, natural history study (BALANCE) with 110 patients per treatment arm demonstrated that lithium (0.4-1 mmol/L) is superior to valproate (750-1250 mg/day) in the prevention of recurrences, generally after 24 weeks of treatment [HR = 0.71 (95% CI, 0.51-1.00)],[114] and the time to recurrence is significantly longer (14.7 months vs. 6.2 months, respectively).[115] In any case, the low doses of valproate and the accepted lower limit for lithium plasma concentrations could have influenced the results. A subanalysis of a maintenance study suggests that concentrations of at least 6 mmol/L are necessary in the case of lithium to observe an adequate prophylactic effect with the cation.[116]

With regard to other euthymics, a meta-analysis also demonstrated effectiveness in the general prevention of affective recurrences in patients with BD I, compared to

placebo, for olanzapine [RR = 0.58 (95% CI, 0.49-0.69)], lamotrigine [RR = 0.84 (95% CI, 0.71-0.99)] and valproate [RR = 0.63 (95% CI, 0.44-0.90)].[108] Another meta-analysis also demonstrated that the general prophylactic effect versus placebo is also superior for valproate, lamotrigine, olanzapine and aripiprazole.[117] Similarly, another meta-analysis demonstrated that olanzapine as monotherapy is superior to placebo in the prevention of recurrences of any type [RR = 0.58 (95% CI, 0.49-0.69).[118] With respect to aripiprazole, however, a recent systematic review to identify placebo-controlled, double-blind studies of the prophylactic effect of this SGA in patients with BDs advises of limitations in the interpretation of some studies. The authors find that the duration of treatment and low rate of completers (2.1% of 567 patients at 72 weeks) of the only study found are insufficient to support the prophylactic effectiveness of aripiprazole.[119] Finally, a placebo-controlled, double-blind study demonstrated the general prophylactic effectiveness of long-acting injectable risperidone ($p < 0.001$).[120]

Other meta-analyses have compared several euthymics with each other in the general prophylaxis of BDs. One of them demonstrated that lithium is superior to carbamazepine [OR = 0.48 (95% CI, 0.27-0.84)] and has a prophylactic effect equivalent to lamotrigine, valproate and olanzapine (although lithium has a lower hospitalization rate than olanzapine [OR = 1.78 (95% CI, 1.08-2.93)]).[117] Another study that compared carbamazepine and lithium showed that both euthymics can be equally effective in the prevention of recurrences in general in patients with BD.[121] Another meta-analysis concluded that olanzapine is as effective as lithium or valproate in the prevention of any affective episode.[122] Finally, a double-blind controlled study demonstrated the general prophylactic effectiveness of lamotrigine and lithium without any significant differences between the two compounds [RR = 0.92 [95% CI, 0.60-1.40)].[123]

With respect to the control of manic/mixed recurrences, a recent meta-analysis concludes that only olanzapine and aripiprazole are superior to placebo and that lithium is superior to placebo in the prevention of re-hospitalization for mania or additional interventions for the control of those episodes.[117] Another meta-analysis, nevertheless, found that lithium is more effective than placebo [RR = 0.63 (95% CI, 0.44-0.91)] and similar to olanzapine [RR = 0.37 (95% CI, 0.24-0.57)] in the prevention of manic recurrences (108). An additional meta-analysis confirmed that olanzapine in monotherapy is superior to placebo in the prevention of manic recurrences.[118] A placebo-controlled, double-blind study demonstrated the general prophylactic effectiveness of long-acting injectable risperidone for manic episodes.[120]

With respect to meta-analyses that compare several euthymics to each other, one of them found that lithium is inferior to olanzapine.[117] This was confirmed by another meta-analysis in which olanzapine was superior to lithium or valproate in the prevention of manic episodes [RR = 0.37 (95% CI, 0.24-0.57)].[122] A double-blind, controlled study does not show any differences in the prophylactic effectiveness of lamotrigine or lithium for manic episodes [RR = 1.91 (95% CI, 0.73-5.04)].[123]

A double-blind, placebo-controlled study has demonstrated that the use of sustained-release injectable risperidone is effective in the prevention of recurrences in patients with an index episode of mania ($p < .001$).[120] This has been confirmed in the natural history of the disorder in Spain in an open-label study with 14 bipolar patients who exhibited multiple recurrences due to poor therapeutic compliance.[124] Finally, a comparative study not controlled with placebo suggests that asenapine, in magnitude similar to olanzapine, could be effective in the prevention of affective recurrences in patients with an index episode of mania.[125]

With respect to depressive recurrences, the duration of antidepressant therapy after a bipolar depressive episode is still matter of debate, although nobody doubts the importance of maintaining long-term use of the euthymic or mood stabilizer. In the meta-analysis by Beynon et al.,[117] the authors conclude that only valproate and imipramine are superior to placebo in the prevention of depressive recurrences in patients with BDs. Lamotrigine has been found to be superior to placebo in reducing additional interventions to prevent depressive episodes. However, the addition of imipramine to the prophylactic therapy with lithium does not diminish the risk of future depressive episodes and, as shown in a previous study,[126] the risk of manic episodes may be duplicated. A meta-analysis confirms that lithium does not exhibit significant effectiveness in the prevention of depressive recurrences [RR = 0.84 (95% CI, 0.65-1.10)].[108] With regard to other euthymics, the same meta-analysis only finds effectiveness in the prevention of depressive recurrences for valproate in comparison with placebo [RR = 0.40 (95% CI, 0.20-0.82)].[108] Meta-analysis with olanzapine in monotherapy also does not demonstrate the superiority of this SGA over placebo in the prevention of depressive recurrences [RR = 0.78 (95% CI, 0.58-1.04)].[118] A double-blind, placebo-controlled study demonstrated that long-acting injectable risperidone is not superior to placebo in the prevention of depressive recurrences in patients with BD with an index episode of mania ($p = 0.805$).[120]

With respect to meta-analyses that compare several euthymics, none of the studies has demonstrated the superiority of any medication over the others in the prevention of depressive recurrences.[117, 122] A double-blind controlled study also failed to demonstrate the prophylactic effectiveness of lamotrigine with respect to lithium in

depression [RR = 0.69 (95% CI, 0.41-1.22)].[123] Likewise, an as yet unpublished maintenance study[127] suggests that continued treatment with extended release (XR) quetiapine in comparison with placebo and lithium increases the time to recurrence of any phase in patients with an episode index of type I or II bipolar depression.

As has been mentioned, for patients who present a recurrence during their monotherapy treatment, combined therapy can offer a better alternative, but the larger number of AEs demands that each treatment be individualized.[128] Olanzapine plus lithium or valproate in symptomatic remission,[129] lamotrigine plus lithium,[130] and quetiapine plus lithium or valproate[131, 132] are backed by some evidence supporting their use in the maintenance phase of patients with BD I with a previous manic episode. It must be considered, however, that in the case of associations with lithium or valproate in these studies only patients who had a history of poor response to lithium or valproate in the mania phase were included, which introduces a bias in the monotherapy comparator group. Moreover, the BALANCE naturalistic study brings into question the effectiveness of combined therapy with lithium in comparison with monotherapy with this cation in the prophylactic phase of treatment of BDs.[114] In a meta-analysis the authors conclude that despite the extended use of combined therapy in the maintenance phase of BDs, no adequate evidence exists to support this practice as the front-line treatment.[117] A European naturalistic study with 1076 bipolar patients concluded that patients treated with olanzapine monotherapy (29%) had fewer recurrences than patients in combined therapy with olanzapine plus traditional mood stabilizers (71%) (p = 0.01). In addition, patients treated with combined therapy had a greater risk of adverse events like tremor (OR 2.37, 95% CI 1.44–3.89) and polyuria (OR 3.08, 95% CI 1.45–6.54), although there was more weight gain with monotherapy.[133] Another meta-analysis found that patients with BD treated with various SGAs experienced more dry mouth (number needed to harm, or NNH = 4), tremor (NNH = 6), sedation (NNH = 8), sexual dysfunction (NNH = 8) and constipation (NNH = 11) than patients treated with SGA in monotherapy.[134]

Few studies have evaluated the preventive effect and safety of long-term combined maintenance therapy with antidepressants. Antidepressants in monotherapy are not recommended for the maintenance of patients with BDs who recovered from a depressive episode.[135] Some authors maintain that when antidepressants are combined with lithium, anticonvulsants or SGAs, no additional benefit is evident in comparison with monotherapy.[76] Nevertheless, in the case of a bipolar depressive episode that is considered refractory to treatment with euthymic monotherapy, or in the case of a depressive episode that occurs during maintenance therapy in the form of relapse or recurrence, an antidepressant can be considered. Evidence from several studies suggests that if the patient exhibited an adequate response during the acute depressive phase, combination treatment can continue with positive results and no additional risks for patients. Several studies coincide in reporting that those patients who interrupted the antidepressant after achieving remission of a bipolar depressive episode presented a depressive recurrence within a significantly shorter time than those that continued to take the antidepressant. In addition, these studies confirmed that the use of antidepressants associated with euthymics was not accompanied by a greater risk of manic recurrences in the long term.[75, 136-139] However, more research is required to establish a definitive conclusion.

COMMON ADVERSE EVENTS OF MEDICATIONS USED IN THE TREATMENT OF BIPOLAR DISORDER

Due to the variety of effective therapeutic options existing, clinicians can make a selection of medications on the basis of their long-term tolerability and not only on the basis of their effectiveness. The presence of adverse events (AE) is one of the first reasons for discontinuing therapy and for poor treatment compliance in patients with BD.[140] The rates of discontinuation for AEs are usually higher with active medications like lithium, valproate and olanzapine than with placebo according to a meta-analysis on the prophylactic effect of euthymics. Lamotrigine had the same tolerability as placebo.[108] In another meta-analysis comparing SGA with traditional mood stabilizers, weight gain was the only AE more common with SGAs.[52] A meta-analysis with olanzapine showed that the rate of withdrawals motivated by AEs with this SGA is no greater than the rate observed with placebo in bipolar patients receiving long-term treatment [RR = 0.59 (95% CI, 0.21-1.67)].[122] The generalized use of SGAs in patients with BD has motivated physicians to consider the risks that these medications represent. In a meta-analysis the risks of withdrawal for different AEs were compared in patients with bipolar disease versus patients with schizophrenia. In acute mania, no SGA was accompanied by more withdrawals due to AEs than in schizophrenia, but in bipolar depression both olanzapine (NNH = 24) and quetiapine (NNH = 7) led to more withdrawals due to AEs than in schizophrenia.[141] Table 1 offers an updated summary of the most common adverse events with medications for the control and prevention of BDs, while Table 2 presents the pharmacologic interactions with the highest risk (adapted from ref. 26).

CONCLUSIONS

Seven years ago, a review proposed a new definition of the medications used in the treatment of BDs based on randomized, placebo-controlled, double-blind studies.[26] New studies published since then have confirmed the

utility of that classification and show that antimanic agents (medications that have been demonstrated to be effective in the control of manic episodes alone) consist only of conventional antipsychotics. However, due to the high risk of extrapyramidal, cardiovascular and induced dysphoria AEs and the availability of various effective medications for the control of manic agitation and acute manic episodes per se, they are currently excluded as first-line therapy in patients with BDs. As far as the SGAs are concerned, risperidone and ziprasidone could be considered as exclusively antimanics, few studies existing on maintenance in monotherapy and these few being of open-label design. These medications are accompanied by a lower incidence of EPS than conventional antipsychotics. In the case of clozapine, although it has been used in several open-label studies as monotherapy or associated with euthymics in patients refractory to treatment, the use of this agent as an antimanic of first choice is limited by its profile of adverse events and the blood monitoring requirements.

As for the partial mood stabilizers (medications with demonstrated effectiveness in the control of manic episodes and in the prevention of manic recurrences, or medications that are effective in the control of depressive episodes and prevention of depressive recurrences), aripiprazole, in the control of manic episodes and prevention of manic recurrences, and lamotrigine, in the control of depressive episodes (partially demonstrated and only in patients with marked severity) and in the prevention of new depressive episodes both meet the criteria for inclusion in this category because more than one double-blind, placebo-controlled study demonstrates that they are not effective in the control and prevention of opposing episodes.

Finally, euthymics (medications that have been shown to be effective, used in monotherapy, in the control of manic, mixed and depressive episodes, and in the prevention of manic and depressive episodes) include lithium (except in mixed mania and, possibly, RC), valproate (which requires more studies in the bipolar depressive phase), olanzapine (not as effective in the prevention of depressive episodes as monotherapy compared to combination with fluoxetine) and quetiapine (whose effectiveness in acute mania must be confirmed in studies with a rapid titration scheme and whose prophylactic effect against manic recurrences is supported by unpublished data).

Combined therapies with different medications merit separate mention. These medications continue to be accepted as an alternative in patients refractory to the use of a single medication or in patients with mixed mania or RC or with bipolar depressive episodes. Nevertheless, more studies are necessary to affirm that combined therapy offers more benefits than monotherapy for the management of the different phases of patients with BDs, especially if we take into account the higher cost, diminished likelihood of compliance and greater rates of AEs.

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