

# Anticonvulsants and antipsychotics in the treatment of Bipolar Disorder

## Anticonvulsivantes e antipsicóticos no tratamento do transtorno bipolar

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### Abstract

Bipolar disorder is a complex medical condition, and up to the date there is no single treatment with proven efficacy in the control of all aspects of the illness. The available literature on the use of anticonvulsants (valproate, carbamazepine, oxcarbazepine, lamotrigine, gabapentin, topiramate, clonazepam) and atypical antipsychotics (clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole) for acute and prophylactic treatment of bipolar disorder was reviewed. There is a large amount of evidence that lithium is efficacious in the prophylaxis of episodes and better for acute mania than for depressive episodes. Other data show that carbamazepine and valproate are effective in acute manic episodes. Lamotrigine apparently reduced cycling and showed efficacy in depressive episodes. Based on the available data, olanzapine was found to be the most appropriate atypical antipsychotic agent for the treatment of manic bipolar patients, although there are also studies suggesting the efficacy of risperidone, aripiprazole and clozapine. The preliminary data evaluating the efficacy of quetiapine and ziprasidone in bipolar disorder are still very limited. There is no consistent information supporting the prophylactic use of newer antipsychotics.

**Keywords:** Bipolar disorder/drug therapy; Antipsychotic agents/therapeutic use; Anticonvulsivants/therapeutic use

### Resumo

O transtorno bipolar é uma condição médica complexa e até o momento não há um tratamento único comprovadamente eficaz no controle de todos aspectos da doença. Foram revisadas a literatura disponível sobre o uso de anticonvulsivantes (valproato, carbamazepina, oxcarbazepina, lamotrigina, gabapentina, topiramato, clonazepam) e antipsicóticos atípicos (clozapina, risperidona, olanzapina, quetiapina, ziprasidona e aripiprazole) no tratamento agudo e profilático do transtorno bipolar. Existe um acúmulo de evidências acerca da eficácia do lítio na profilaxia e de ser melhor no tratamento da mania aguda do que nos episódios depressivos. Outros dados indicam que a carbamazepina e o valproato são eficazes na mania aguda. A lamotrigina parece reduzir ciclagem e ser eficaz em episódios depressivos. Baseado nas informações disponíveis, as evidências apontam a olanzapina como o antipsicótico atípico mais apropriado no tratamento de pacientes bipolares em mania, embora existam estudos sugerindo a eficácia da risperidona, aripiprazol e da clozapina. Resultados preliminares avaliando a eficácia de ziprasidona e quetiapina no transtorno bipolar ainda são bastante limitadas. Não há dados consistentes apoiando o uso profilático dos novos antipsicóticos.

**Descritores:** Transtorno bipolar/quimioterapia; Agentes antipsicóticos/uso terapêutico; Anticonvulsivos/uso terapêutico

### Introduction

In the last years the treatment of bipolar disorder (BD) has considerably changed with the regular use of valproate, carbamazepine (CBZ), lamotrigine (LTG) and other anticonvulsants associated with or replacing lithium. It may be highlighted that the interest of the pharmaceutical industry in the BD field has an important role to support its widespread use. This interest has also changed the traditional therapeutic concepts leading to new recommendations (algorithms) and options of pharmacological treatment. Lithium, valproate, CBZ and LTG are well-established treatments, among which lithium shows the most robust evidence of prophylactic efficacy<sup>1</sup> and sodium valproate has some evidence of efficacy on rapid cycling.<sup>1-3</sup> There has been growing evidence about the efficacy of other anticonvulsants, atypical antipsychotics and the combination of treatments.<sup>4</sup> Typical antipsychotics are still used in acute mania, but studies about prophylaxis are still lacking. Bipolar patients may be particularly prone to tardive

dyskinesia induced by these medications.<sup>5-6</sup> Currently, the use of typical antipsychotics is only justified by financial reasons and in resistant cases. The treatment of bipolar depression is a major issue as the use of antidepressant medications may induce manic cycling and the use of mood stabilizers is recommended as first-choice treatment (e.g., LTG). Whenever indicated, antidepressants should be used in association with mood stabilizers. Therefore, it is important to examine the current pharmacological management of BD considering the available evidence which has increased in volume and quality in order to prevent sub-therapeutics.<sup>1</sup> This article critically reviews the evidence on the use of anticonvulsants and antipsychotics in the treatment of BD and highlights practical aspects of the treatment.

### Rationale for the use of anticonvulsivants

In the last decades much attention has been given to the use of classical anticonvulsants in psychiatry due to the observations

of psychiatric symptoms among patients with temporal epilepsy. In the '50s these observations led to the use of phenytoin among psychiatric patients, with inconsistent results. From the '60s onwards the use of CBZ has become widespread in psychiatric hospitals in Japan, where lithium was not commercialized, culminating in the first reports about its efficacy in the treatment of BD and the theories to explain the efficacy of anticonvulsants, such as the kindling phenomenon.<sup>7</sup> The kindling model and the evidence of a beneficial psychotropic effect among epileptic patients stimulated the research of other anticonvulsants, but not all of them were efficient on bipolar subjects, as occurred with gabapentine, vigabatrin, tiagabine, and topiramate which were useful in some refractory cases. The minimal efficacy of some anticonvulsants on mood disorders suggests the revision of the concept that the reduction in kindling would be beneficial in BD. These differential effects of lithium, CBZ, valproate, valpromide and LTG may explain their differential efficacy.<sup>7</sup>

### Valproic acid, sodium divalproate (valproate)

Valproate, among other actions, augments the gabaergic function, by means of increase in the release of the gamma-aminobutyric acid (GABA) and decrease of its catabolization, and through the increase in the density of type B GABA receptors.<sup>8</sup> Its tolerability and safeness are well-established<sup>12</sup>, and the main side-effects are gastrointestinal and neurological.<sup>9</sup> Severe adverse reactions, such as pancreatitis and hepatotoxicity, are extremely rare and are generally associated with polytherapy. In mania the dose should be rapidly adjusted up to the point of reaching the desired clinical effect, and initial doses corresponding to 20 mg/kg/day may be used,<sup>10-11</sup> respecting the maximum dose of 60 mg/kg/day. It is suggested the maintenance of serum levels between 50 and 120 mcg/ml.<sup>12</sup>

The efficacy of valproate in the treatment of acute mania was proved by 16 non-controlled studies and 6 controlled studies. As a rule, the results indicate that valproate was efficient in nearly 60% of the cases, including those which had unsatisfactory response to lithium, showing higher results than those with placebo and comparable to those with lithium.<sup>13-16</sup> Mixed episodes have also good acute and prophylactic responses.<sup>17-18</sup> The following factors were described as predictors of good response in the treatment of acute mania: the presence of depressive symptoms, diagnosis of mixed episodes, rapid cycling, comorbidity with anxiety disorders, with alcohol abuse, substance abuse, mental retardation, and antecedents of head trauma and neurological lesions.<sup>5,15,19</sup> The prophylactic antidepressant action seems higher than the acute one, only 30% above in open studies.<sup>19</sup> Patients with comorbidity with anxiety disorders and type II bipolar depressed patients may show satisfactory response.<sup>20</sup>

Several open studies suggested its efficacy in the prophylactic treatment of manic and depressive episodes, with responses in nearly 63% of assessed patients.<sup>18</sup> Rapid cycling, type II bipolar disorder and the presence of neurological abnormalities are mentioned as predictive factors of good response.<sup>15,21</sup> The controlled study performed by Bowden et al<sup>3</sup> did not identify significant differences between lithium and valproate in the prevention of manic and depressive relapses. Tohen et al<sup>21</sup> have recently observed an equivalence between divalproate and olanzapine in the prevention of relapses along a 47-week period.

Open studies showed positive results in the treatment of BD among children and adolescents,<sup>22</sup> but controlled studies are still being developed. It was discussed the risk of development of polycystic ovaries among adolescents, but the studies were performed among epileptic youngsters.<sup>23</sup> Weight gain hampers compliance with treatment among adolescents. Its use is contraindicated in pregnancy, particularly in the first trimester.<sup>24</sup>

The risk of developing biphid spine is 1% to 5%, compared to 0.06% among controls. The efficacy in the administration of folate to prevent this malformation has not been determined.<sup>25</sup> According to Chaudron and Jefferson,<sup>25</sup> breastfeeding newly born babies receive low concentration of valproate, but signs of liver dysfunction, hematological abnormalities or effects on the central nervous system should be observed.<sup>25</sup>

Case reports and retrospective studies indicated that it is efficacious and well tolerated among the elderly.<sup>26-27</sup> Valproate binds strongly to the plasmatic proteins and it is a weak inhibitor of the 2D6 fraction of cytochrome P450. It may inhibit the metabolism of tricyclic antidepressants and displace diazepam, raising its plasmatic levels and increasing the possibility of side-effects.<sup>28</sup>

### Gabapentine

Gabapentine is an aminoacid which is structurally related to GABA and acts mainly augmenting the gabaergic function as it influences the synthesis and concentration of GABA, blocking calcium channels and binding to the gabapentine receptor, related to voltage-dependent calcium channels.<sup>29</sup> It is not metabolized and does not interact with other substances. It is excreted by the kidneys and, in cases of renal insufficiency, doses should be adjusted. Its wide therapeutic range (900 to 3,600 mg/day) may hamper compliance with treatment.<sup>30</sup> Its main side-effects are sedation, ataxia (as a rule mild and transient) and edema of inferior limbs.<sup>12</sup>

The results of open studies on acute mania<sup>31</sup> suggested that the association with gabapentine could be useful in the treatment of mania, including in cases of poor response to previous treatments, although controlled studies have not confirmed these results.<sup>31-32</sup> In one controlled study by Frye et al<sup>32</sup> the antidepressant efficacy of gabapentine was comparable to placebo. We did not find up to now controlled prophylactic studies.

### Topiramate

Topiramate is an anticonvulsant with wide potential of action. Among its effects, there are augmentation of activity of GABA, decrease in the activity of voltage-sensitive calcium channels, inhibition of carbonic anhydrase and antagonism of glutamate activity on non-NMDA receptors.<sup>29</sup> The main side-effects reported were somnolence, fatigue, concentration problems, dizziness, nausea, vomiting, anorexia and weight loss, paresthesias, mental confusion, and depression, which are more intense at the beginning of treatment and related to the rapid increase of doses. Hepatic alterations were also described.<sup>33-34</sup>

Open studies suggested beneficial effects of the association with topiramate, especially in cases of mania or mixed states, with poor response to previous treatments, in which nearly 50% (n=225) of patients responded positively.<sup>35</sup> The results of one double-blind placebo-controlled study (n=97) showed that 512 mg/day of topiramate were not significantly superior to placebo.<sup>35-36</sup> In bipolar depression, open studies suggested a possible beneficial effect in cases of poor response to treatments and its association promoted response in 54% of the patients.<sup>36</sup> In another single-blind study<sup>37</sup> there were no significant differences between topiramate (mean dose: 176 mg/day) and bupropione (mean dose: 250 mg/day), only higher weight loss (1.2 kg and 5.8 kg respectively). In some open studies it was observed some efficacy in the addition of topiramate for patients with history of poor response to other mood stabilizers, including cases of rapid cycling.<sup>36</sup> Controlled studies are needed to better assess its efficacy in prophylactic treatment. Animal studies related the exposure to topiramate to cranio-facial malformations and demonstrated that topiramate is excreted in the milk of rats, but there are no conclusive data on humans and caution is recommended in its use on nursing infants.<sup>24</sup>

### Carbamazepine

CBZ is a composite with anticonvulsant and antinociceptive properties. It is believed that its basic mechanisms of action are due to effects in the neuronal ionic channels, such as the blockade of sodium channels in order to reduce the neuronal excitability, and in the signal transduction and synaptic systems.<sup>38</sup> Due to the self-inducement of hepatic enzymes, after being continuously used during 3 to four weeks its half-life decreases from 30-40 hours to 10-20 hours, what requires the adjustment of the dose. CBZ reduces the plasmatic concentration of several substances, decreasing its effect; on the other hand, some drugs may inhibit the metabolism of CBZ, leading to a risk of toxicity.<sup>39-40</sup> The main intoxication symptoms are accentuated dizziness and somnolence, persistent diplopia, seizures, irregular, slow or superficial breath, severe trembling, tachycardia or arrhythmia. Among the pharmacodynamic interactions, the association of lithium with CBZ may increase the risk of confusional states and the combination with clozapine, the risk of agranulocytosis.<sup>29,40</sup>

At the beginning of treatment the hepatic parameters and the hemogram should be normal, as well as electrolytes among the elderly, although the risk of hepatic insufficiency and blood discrasias is rare. As an equivalence between serum levels and the clinical response in BD was not established, the dose should be individualized according to its efficacy and tolerability. Antimanic posology is between 1000 and 1200 mg/day. In stable or depressed patients doses should be slowly increased from 400 to 1600 mg/dia.<sup>39-40</sup>

The efficacy of CBZ in the treatment of acute mania was the object of 15 controlled studies with placebo, antipsychotics and lithium. However, these studies were invalidated due to the combined use of other active substances, such as antipsychotics and/or lithium, and pointed to antimanic efficacy in nearly 60% of the cases.<sup>41</sup> Considering only the six studies in which CBZ was used alone (only the use of hypnotics was allowed), its antimanic efficacy was near to 50%.<sup>42</sup> Despite that, it is less convincing than lithium or valproate.<sup>2</sup> The use of CBZ in the treatment of bipolar depression was investigated in few controlled studies, which demonstrated a therapeutical response nearly between 30% and 44% of patients.<sup>39,42</sup> It is deemed insufficiently studied and there was no recent interest in exploring its antidepressant efficacy. Two big prospective studies compared CBZ to lithium in maintenance treatment.<sup>42-43</sup> In the first one, a 2.5-year open prospective study with 171 patients, lithium was superior among type I bipolar patients and was comparable among type II ones.<sup>42,13</sup> There was favorable response to lithium in the reduction of suicide behavior and to CBZ regarding the patient's satisfaction. However, the inter-episodic symptomatology (higher need of combined treatment of antipsychotics and antidepressants) and the rate of withdrawal with rehospitalization was significantly higher in the CBZ group when compared to those who received lithium (42% versus 17%).<sup>13</sup> In the second study, a 2-year double-blind prospective study with 94 patients who had not received any prophylactic treatment, lithium was also more efficient in the prevention of recurrences.<sup>43</sup>

Exposure to CBZ is associated with a 1% risk of defects in the closing of the neural tube and with 2.3% to 5.7% of major congenital malformations.<sup>44-45</sup> Among elderly people and especially with high doses, carbamazepine may cause hyponatremia and hydric intoxication.<sup>46</sup> Besides, cases of congestive cardiac insufficiency and alterations in the cardiac conduction associated with CBZ were described.<sup>47</sup> CBZ's potential of pharmacological interaction should be more closely observed.

### Oxcarbazepine

Oxcarbazepine (OXC) is a CBZ-derived 10-keto, whose effect is probably due to the blockade of voltage-sensitive sodium and calcium channels.<sup>48</sup> It has not a self-inducing effect and induces

less the metabolism of other drugs than CBZ; nevertheless, it inhibits the 2C19 isoenzyme and induces the metabolism in a lower degree through the 3A4 isoenzyme.<sup>49</sup> Therefore, there is no need of repeated serum doses, but there is risk of increase in the serum level of other substances, including oral contraceptives, stemming from the replacement of CBZ by OXC. The profile of side-effects caused by OXC is more favorable than CBZ's, being indicated in cases of intolerance and good clinical response to CBZ. It is estimated that this replacement in equipotent doses reduces in 75% the side-effects, among them the risk of skin rash.<sup>39</sup> OXC is less sedative and effects such as aplastic anemia, hepatotoxicity and teratogenicity are not known.<sup>29,49</sup> The main side-effects stem from its action on the central nervous system and use to be mild and transient.<sup>12</sup> The most common ones are headache, somnolence, dizziness and nausea; OXC may cause dose-dependent hyponatremia, evident among 2.5% of patients and more frequent than with CBZ. In cases of hydric intoxication the restriction of liquids may be necessary.<sup>49</sup>

The initial treatment requires assessment of electrolytes and initial doses from 600 to 1200 mg/day may suffice or should be augmented to 1400 to 2400 mg/day in order to obtain the desired effect.<sup>12</sup> Contrarily to CBZ, it does not interfere in the metabolism of other anticonvulsants, but reduces the plasmatic levels of felodipine, verapamil and estrogens among women who take oral contraceptives.<sup>12</sup>

There are only two small-sized controlled studies on mania which pointed to a similar efficacy to that of haloperidol and lithium.<sup>46</sup> However, it has been recently investigated in naturalistic studies,<sup>49-50</sup> due to its theoretically similar response to CBZ and to its higher tolerability, used alone or associated on different groups of patients with bipolar disorder, pointing to efficacy in half of them. There are few data on the teratogenicity of OXC, but it passes through the placenta and is eliminated in the maternal milk.<sup>24</sup>

### Lamotrigine

LTG is a phenyltriazine-derived anticonvulsant indicated in the combined treatment of partial seizures, with or without secondary generalization among adolescents and adults.<sup>51</sup> It apparently has the same effect of OXC, blocking voltage-sensitive sodium and calcium channels.<sup>47</sup> Due to the risk of skin rash the dosis should be slowly increased and 50 to 200 mg/day generally suffice.<sup>39</sup> When patients take valproate, the initial doses should be halved and when patients also take CBZ, the initial dose should be doubled. As a rule, it is well-tolerated by most of patients, although in the first 8 weeks it may cause benign skin rash in nearly 10% of patients and severe rash in less than 0.1% of them.<sup>13,51</sup> It may be withdrawn and gradually reintroduced in benign cases. In rare cases severe reactions, such as Stevens-Johnson syndrome may occur.<sup>56</sup> Side-effects such as insomnia and transient headache<sup>39</sup> may occur in 10% of treated patients, it does not cause weight gain and rarely provokes dizziness, trembling, diplopia, ataxia, nausea, blurred vision and somnolence.<sup>29</sup> LTG does not affect the metabolism of other drugs, but the substances which inhibit cytochrome P450, fraction 3A4 (e.g., CBZ), reduce the serum levels of LTG. Valproate inhibits the metabolism of LTG doubling its half-life<sup>50</sup> and phenitoin, phenobarbital and primidone decrease its plasmatic levels in nearly 40%.

There are few controlled studies on mania. In one small, 4-week study, 30 manic hospitalized patients were randomized to take LTG or lithium. The differences were not significant, probably due to the low doses of lithium.<sup>52</sup> The same problem occurred in other controlled study, which compared LTG, lithium, and olanzapine between groups of 15 patients, in which significant differences were found in therapeutic responses.<sup>53</sup> There are

two unpublished negative studies up to now.<sup>39</sup> It is the only anticonvulsant superior to placebo in the treatment of bipolar depression. In one double-blind placebo-controlled study,<sup>54</sup> 195 type I bipolar patients were assigned to take 50 mg or 200 mg of LTG, or placebo. After seven weeks, 56%, 48% and 29%, respectively, had therapeutical responses. It was significantly more efficient than placebo, without increasing the risk of cycling to mania or hypomania. LTG was superior (41%) to placebo (26%) in the prophylaxis of rapid cycling among 324 type I and II bipolar patients, randomized to doses of 100 to 300 mg/day LTG or placebo for 6 months.<sup>55</sup> Two 18-month, separate, controlled, prospective studies compared lithium, LTG and placebo in the maintenance treatment of type I bipolar patients<sup>56-57</sup> with depression or mania, hypomania or mixed state<sup>62</sup> and of patients whose last episode was mania, hypomania or mixed state, those who received lithium took significantly more time to develop new episodes and those from the LTG group took more time to have depression. In the prophylaxis of patients whose last episode was depression, 463 bipolar subjects stabilized with monotherapy were randomized to 5 groups: LTG 50 mg, 200 mg or 400 mg; lithium (0.8 – 1.1 mEq/l) or placebo.<sup>56-57</sup> The results were similar to the former study and there were no significant differences between LTG and lithium, taking into account the time span until a therapeutical intervention to control manic or depressive episodes was needed.<sup>56-57</sup>

LTG was associated with a risk of more than 3% of congenital malformations in samples with more than 300 pregnant women.<sup>45</sup> When used in association with valproate, this risk increased to 11.9%; therefore, it should not be used in pregnant or breastfeeding women, due to the risk of skin rash on lactants.<sup>29</sup>

### Benzodiazepines

For several reasons clonazepam and lorazepam have been used in the acute treatment of mania.<sup>58</sup> Insomnia worsens mania and benzodiazepines promote sleep improvement. These drugs have a high therapeutical rate and although inducing somnolence, dizziness and ataxia, their safety profile is favorable when compared to extrapyramidal reactions or tardive dyskinesia seen with antipsychotics, to which bipolar patients are at higher risk.<sup>59</sup> Despite the methodological limitations found<sup>60</sup> in metaanalyses about the use of clonazepam and lorazepam in acute mania, it was concluded that clonazepam is efficient and safe in the treatment of acute mania and that the results with lorazepam remain uncertain. With regard to the prophylactic treatment the results were controversial.<sup>61</sup> As an adjunctive medication, clonazepam could reduce the frequency of cycles, and some patients taking neuroleptics plus lithium can benefit from the replacement by clonazepam plus lithium, although there is no consensus regarding the lower relapse risk during the replacement.<sup>62-63</sup>

### Antipsychotics

Before the use of lithium salts, typical antipsychotics were the main treatment for agitation and psychotic symptoms in mania<sup>65</sup> and, currently, the use of atypical antipsychotics has been rising due to their better tolerability and efficacy. They are called atypical for being similar to clozapine and causing less extrapyramidal side-effects.

The therapeutic action of antipsychotics is probably due to the antagonism to D<sub>2</sub> dopaminergic receptors in the mesolimbic pathway. Other dopaminergic pathways, such as the nigrostriatal, tuberoinfundibular and mesocortical, besides other neurotransmission systems, such as the histaminergic (H<sub>1</sub>), noradrenergic (α<sub>1</sub>, α<sub>2</sub>), and cholinergic (muscarinic M<sub>1</sub>) are also

blocked by these medications. It is believed that these blockades are more related to the side-effects than to the therapeutical effect. Their action on affective symptoms and the lower probability of extrapyramidal symptoms is probably due to a potent antagonism to 5-HT<sub>2</sub> receptors and to the weaker blockade of D<sub>2</sub> receptors.<sup>65</sup> Aripiprazole shows partial agonism, rather than antagonism, of D<sub>2</sub> receptors, besides an action on the serotonergic system (antagonism 5-HT<sub>2</sub> and agonism 5-HT<sub>1A</sub>),<sup>66</sup> what confers it a different profile of action.

Chlorpromazine and haloperidol were the most studied typical antipsychotics in acute mania. Most studies have compared these antipsychotics with lithium or CBZ, with similar results and with limitations due to the small number of participants.<sup>67</sup> Haloperidol (n=53) has been tested for three weeks in one double-blind controlled randomized study against risperidone (n=52) and placebo (n=51), in adjunctive treatment to lithium or to valproate in acute mania, being both superior to placebo.<sup>68</sup> Haloperidol (n=219) has been recently compared to olanzapine (n=234) for 12 weeks in acute mania without significant difference regarding remission (46.1% vs. 52.1%).<sup>69</sup>

Clozapine, the first atypical medication, was never tested in a double-blind controlled study against placebo or other active medication on bipolar subjects. This is partially due to the inherent risk of agranulocytosis, although case reports and open studies have indicated efficacy with resistant bipolar subjects. In one open study, 30 hospitalized patients with acute mania and taking lithium were randomized for a 3-week treatment with chlorpromazine or clozapine, without significant difference in the response, but the mean dose of clozapine was low (166 mg/day vs. 310 mg/day).<sup>70</sup> Another open study in 22 manic patients with refractory psychotic symptoms, in which clozapine was used during a 12-week period up to the maximum dose of 550 mg/day, showed a 20% improvement in 77.3 % of patients.<sup>71</sup>

Risperidone showed efficacy in acute mania as an adjunctive therapy to mood stabilizers in two 3-week double-blind multicentric placebo-controlled studies. The first one was a comparison to haloperidol, associated with lithium or valproate.<sup>5</sup> The second one involved 151 patients randomized to risperidone (n=75) or placebo (n=76), using CBZ, lithium or valproate. Patients who used CBZ had risperidone levels 40 % below normal without significant alteration, but in the association with lithium or valproate the difference favoring risperidone was significant.<sup>72</sup> Two studies comparing placebo to risperidone in monotherapy of acute mania are being currently developed, with results favoring the active medication.<sup>73</sup>

The efficacy of olanzapine in acute mania and in mixed state was established from the results of two double-blind multicentric placebo-controlled studies of three- to four-week periods.<sup>74-75</sup> Doses utilized varied from 5 to 20 mg/day, and of 254 patients, 48.6% and 65% responded to olanzapine and 24%, 2% and 43% to placebo. It was also tested as an adjunctive therapy to lithium or valproate in manic or acute mixed episodes. After 6 weeks, there was significant response to olanzapine regarding the control group (67.7% and 44.7%, respectively).<sup>76</sup> In the 12-week double-blind controlled study already mentioned the efficacy was similar to haloperidol, although with less extrapyramidal effects and higher weight gain. It was also described higher efficacy in 125 patients with manic or mixed episodes compared to valproate after three weeks (n=123),<sup>77</sup> being equal after 12 weeks in 120 patients (n=63 for valproate and 57 for olanzapine).<sup>78</sup>

Compared to other antipsychotics there are still few studies assessing their efficacy. Ziprasidone, 80-160 mg/day, was more efficient than placebo in acute mania and in mixed states in one

three-week study with 210 patients.<sup>79</sup> Aripiprazole, 15 to 30 mg/day, was superior to placebo (40% vs. 19%) in 262 patients in one controlled study after three weeks.<sup>80</sup> Another placebo-controlled study being currently performed has shown similar results.<sup>72</sup> Quetiapine was studied as an adjunctive therapy to valproate in 30 adolescents (aged 12 to 18) with manic or mixed episodes, with 450 mg/day for six weeks. The response was significant (87%) compared to placebo (53%).<sup>81</sup> Studies on quetiapine in monotherapy, compared to lithium or haloperidol, are being developed with promising results.<sup>72</sup>

There are no controlled studies proving the prophylactic efficacy of typical antipsychotics in depression. In one double-blind controlled study assessing withdrawal in manic patients remitted for six months, comparing perphenazine against placebo, patients who were still using the antipsychotic had a faster depressive relapse.<sup>82</sup> Nonetheless, long-term use of typical antipsychotics in BD is frequent, occurring among 34 to 95 % of patients in naturalistic studies with 6-month to one-year follow-up.<sup>83</sup> Olanzapine was the only antipsychotic investigated in bipolar depression in double-blind randomized and controlled studies. It has shown efficacy regarding placebo alone (5 to 20 mg/day) or associated with fluoxetine (6+25 mg/day, 6+50 mg/day or 12+50 mg/day), in one 8-week multicentric study with 833 patients. All treatments obtained response significantly higher than placebo (remission of 24.5% with placebo, 32.8% with olanzapine and 48.8% with the combination olanzapine-fluoxetine). However, the number of patients needed for this response was only 86 in the group olanzapine-fluoxetine compared to 370 patients who used only olanzapine. The antidepressant action of the medication was therefore modest. There was no difference in the induction of mania between the three treatment groups.<sup>84</sup>

There are few prophylactic studies with atypical antipsychotics. In one 1-year open study, clozapine was compared to the usual treatment in 38 bipolar or schizoaffective patients resistant to treatment, showing global improvement, including of non-psychotic ones, without differences in the treatment of depressive symptoms.<sup>85</sup> Olanzapine was also studied in the prophylaxis of bipolar disorder. In one 47-week double-blind randomized controlled study, after acute treatment of mania, olanzapine (5 to 20 mg/day) was comparable to valproate (500 to 2500 mg/day) regarding depressive or manic relapses (42.3% for olanzapine and 56.5% for valproate), despite the remission of the manic episode being faster with olanzapine.<sup>86</sup> In one 52-week placebo-controlled prophylactic study of 310 bipolar patients, olanzapine was superior to placebo in the prevention of both manic and depressive episodes.<sup>87</sup> In other study, comparing the use of lithium for one year in 431 patients with manic or mixed episodes, those who used olanzapine had lower chance of relapse of manic episodes and treatment withdrawal, and equal chance of relapse of depressive episodes.<sup>87</sup>

There is few evidence of teratogenic effects of antipsychotics, however, they cross the blood-placenta barrier and may alter the neurotransmission of the developing brain. Their use should be restricted to cases in which there is real need. Phenothiazines, when used in the first trimester of pregnancy, seem to be related to additional fetal malformations in 1 to 4 cases per each 1000 gestations.<sup>88</sup> Among atypical antipsychotics there are case reports of neonatal convulsions, hypotonia of the newborn and malformations in up to 6% of gestations with clozapine.<sup>89</sup> Mothers who use antipsychotic medications should not breastfeed, as they pass to the baby through the maternal milk. Lower doses of antipsychotics should be used in the elderly and the use on children has been scarcely studied, but quetiapine may be an important alternative in acute mania.<sup>88</sup>

## Conclusion

Due to the complexity of bipolar disorder and the variability of clinical characteristics and course, there is no unique treatment or a combination of treatments which function for all patients. However, several general principles may improve the management of BD such as monitoring the disorder through a graphic representation of the course of the affective disorder; treating incisively comorbidities and side-effects; focusing psychotherapy in the adherence to treatment, promoting the psychoeducation of patients, family members and friends; emphasizing the change in the life style aimed at the circadian integrity and regularity in activities; being alert to suicidal behaviors; using antidepressants cautiously, and prescribing combined treatment for patients not responsive to monotherapy. However, in our milieu it is rising the number of patients who receive anticonvulsants as first choice treatment and patients for whom the replacement of lithium is hastily performed, without observing the possible beneficial effect, even though partial, or waiting more time to assess the prophylaxis.

The evidence of efficacy of medications in bipolar disorder can be summed up as follows:<sup>4,89</sup> lithium shows more evidence of prophylactic efficacy; lithium, typical antipsychotics, CBZ, valproate and atypical antipsychotics are efficient in the treatment of acute mania; CBZ, valproate and olanzapine seem efficacious in preventing mania, but as well as lithium they are less effective in the prevention of depression; in rapid cycling CBZ or valproate may improve the symptoms, but only LTG has shown to be able to decrease cycling in placebo-controlled, randomized studies, especially with type II bipolar patients; for bipolar depression, lithium and olanzapine showed modest efficacy and LTG has the most robust effects. As mania responds well to a medication and the depressive symptoms to others, combined treatment may be the option.

Whenever prescribing combined treatment it is fundamental to monitor the pharmacological interactions, safety on pregnancy, the relationship therapeutic efficacy – toxicity, side-effects, impact on mortality, as well as the cost of the treatment. All mood stabilizers should be administered in lower doses when combined, decreasing thus the burden of side-effects and increasing compliance with treatment.

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