Expert Opinion on Drug Safety

ISSN: 1474-0338 (Print) 1744-764X (Online) Journal homepage: https://www.tandfonline.com/loi/ieds20

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To cite this article: Elie Cheniaux & Antonio E. Nardi (2019) Evaluating the efficacy and safety of antidepressants in patients with bipolar disorder, Expert Opinion on Drug Safety, 18:10, 893-913, DOI: 10.1080/14740338.2019.1651291

To link to this article: https://doi.org/10.1080/14740338.2019.1651291

Accepted author version posted online: 31 Jul 2019.
Published online: 08 Aug 2019.

EXPERT OPINION ON DRUG SAFETY
2019, VOL. 18, NO. 10, 893–913
https://doi.org/10.1080/14740338.2019.1651291

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REVIEW

Evaluating the efficacy and safety of antidepressants in patients with bipolar disorder

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ABSTRACT

Introduction: The use of antidepressants (AD) in the treatment of bipolar depression is one of the most controversial issues in psychopharmacology. For some, AD are useful, but, for others, they should never be used in bipolar depression.

Areas covered: This review examines published clinical studies on the use of ADs in bipolar depression, addressing their clinical efficacy and the occurrence of side effects, manic switches, cycle acceleration, and suicidal behavior. Meta-analyzes and review articles on the subject are also discussed.

Expert opinion: Approved therapeutic options for bipolar depression are associated with not very high response rates and a high incidence of adverse effects. Patients with bipolar depression present very heterogeneous responses to the use of ADs. Some improve significantly, while others, especially those with concomitant manic symptoms, have had previous episodes of treatment-emergent mania or are rapid cyclers, exhibit manic switches or cycle acceleration. The authors conclude that the real question is not whether ADs should or should not be used in bipolar depression, but which patients benefit from these drugs and which ones are impaired. The concept of bipolar spectrum and a dimensional approach on bipolar/unipolar distinction may be useful for understanding the heterogeneity of responses to ADs.

ARTICLE HISTORY
Received 6 May 2019
Accepted 30 July 2019

KEYWORDS
Antidepressants; bipolar disorder; bipolar depression; efficacy; safety

1. Introduction

Bipolar disorder (BD) is a disabling, chronic, and severe mental disorder. It affects more than 1% of the world's population [1]. The clinical picture is characterized by depressive and manic episodes, as well as hypomanic and mixed episodes. In depression, there is sadness, decreased energy and motor activity, insomnia or excessive sleep, decreased or increased appetite, loss of libido, ideation and suicidal behavior, inhibition of thinking, among other changes. In mania, on the other hand, euphoria increased energy and motor activity, decreased need for sleep, increased libido, accelerated thinking, impulsivity and disinhibition are observed. Hypomanic episodes, compared to manic ones, have milder and less numerous symptoms, and do not lead to significant impairment. In mixed episodes, depressive and manic symptoms occur simultaneously. BD can be classified as type I and type II. In type I, by definition, at least one manic episode occurred, and depressive episodes may be absent; in type II, there was at least one depressive episode and one hypomanic episode, but never a manic episode [2].

1.1. The distinction between bipolar and unipolar depression

The occurrence of manic or hypomanic episodes is the distinguishing characteristic of BD from major depressive disorder (MDD) or unipolar depression. Current classification systems use the same diagnostic criteria for either bipolar or unipolar depression [3]. No single symptom or group of symptoms reliably distinguishes unipolar from bipolar depression [4], although some changes have been considered more common in bipolar depression than in unipolar depression: psychomotor retardation, pathological guilt, hypersomnia, and psychotic symptoms [5]. Some studies indicate that BD tends to manifest its symptoms earlier compared to MDD. A retrospective study with a large sample revealed that approximately one-third of patients with BD had onset of disease before age 13 and another one third, between the ages of 13 and 18 years [6]. In BD affective episodes are, on average, more numerous and shorter than in MDD. On the other hand, several structural and functional magnetic resonance imaging studies found significant differences between patients with bipolar depression and patients with MDD [7].

1.2. The predominance of depression in BD

Although what defines the diagnosis of BD is the occurrence of a manic episode, since in type I there is no need for depression [3], patients with BD, on average, stay longer in depression than in mania throughout the course of the disease [8]. A study with type I and type II bipolar patients found that they had stayed three times longer in depression than in mania or hypomania [9]. In addition, patients with type I BD have three times more depressive episodes than manic ones

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Article highlights

- The use of antidepressants (AD) in the treatment of bipolar depression is one of the most controversial issues in psychopharmacology.
- Approved therapeutic options for bipolar depression are associated with not very high response rates and a high incidence of adverse effects.
- Responses to ADs in bipolar depression are very heterogeneous and have not been adequately tested.
- The real question is not whether ADs should or should not be used in bipolar depression, but which patients benefit from these drugs and which ones are impaired.
- Considering a dimensional approach on bipolar / unipolar distinction, it can be presumed that patients with bipolar depression treated with ADs have a higher or a lower risk of manic switching or cycle acceleration depending on whether they are closer to one extreme or the opposite one on a continuum.

This box summarizes key points contained in the article.

[10]. In type II bipolar patients, depression may be even more prevalent [11].

1.3. The malignancy of depression in BD

Depressive episodes in BD are not benign. They are associated with intense subjective distress, significant occupational impairment, multiple psychiatric and medical comorbidities, cognitive dysfunction and reduced life expectancy [12].

1.4. Suicide in bipolar depression

Suicide is a relatively common outcome in BD. Among patients with BD, 25% to 50% attempt suicide at least once [13] and 8% to 19% die because of such attempts [14]. Among the risk factors for suicide in BD are previous suicide attempts, affective episodes of greater severity [13], presence of suicidal ideation [15] and depression [16]. In fact, more than two-thirds of the suicides completed by individuals with BD occur during a depressive episode [17].

1.5. Treatment of bipolar depression is poorly studied

Research on the treatment of bipolar depression has been minimal compared to mania and especially compared to unipolar depression. To date, twelve drugs have been approved by the Food and Drug Administration (FDA) for bipolar mania, but only four therapeutic options for bipolar depression: quetiapine, olanzapine/fluoxetine combination, lurasidone and cariprazine. The treatment of type II is even less studied than that of type I bipolar depression [18]. In the last decades, all clinical studies performed for the approval of a new antidepressant (AD) used samples consisting solely of patients with unipolar depression. The diagnosis of BD is usually an exclusion criterion [19].

1.6. Problems about the use of ADs in bipolar depression

In the last two decades, there has been increasing concern about the use of ADs in BD. Many authors believe that these substances could be ineffective in bipolar depression and potentially harmful to patients, increasing the risk for suicide, causing mania switches (treatment-emergent mania) or inducing rapid cycling [20]. However, physicians use ADs, associated or not with mood stabilizers (MSs), much more often than the expert consensus and the practical guidelines advocate [21]. In addition, ADs continue to be the class of medication most commonly prescribed for bipolar depression [22].

2. Therapeutic options for bipolar depression

As previously mentioned, quetiapine, olanzapine/fluoxetine combination, lurasidone and cariprazine were approved for the treatment of bipolar depression. The four therapeutic options were superior to placebo in large randomized clinical trials [23–26]. Olanzapine monotherapy [24] have also shown efficacy in at least one double-blind study. With the exception of fluoxetine, which is an AD, all these substances are atypical antipsychotics. In all of these studies, manic switch rates were not distinguished from placebo. On the other hand, despite the results found, some methodological critiques can be made to these clinical studies. Firstly, the samples were highly selected, excluding the most severe patients, that is, the most agitated or aggressive patients, or those presenting suicidal ideation or substance abuse. In addition, dropout rates were very high and, although the substance had outperformed placebo, response rates were not as high [27].

Lamotrigine, an anticonvulsant, has also been tested in the treatment of bipolar depression. In a large randomized clinical trial [28], this substance was superior to placebo in a secondary measure of efficacy, but there was no difference in a primary measure of efficacy. Subsequently, the results of five clinical studies were published together, which led to the conclusion that lamotrigine is not indicated in bipolar depression [29]. However, as evidenced by a naturalistic study [30], lamotrigine may be useful as an adjunctive treatment. This drug is associated with low rates of manic switches, but this can happen, especially if used alone [31]. Both discontinuation and rapid onset of lamotrigine may lead to severe cutaneous rash and Stevens-Johnson syndrome [32].

Lithium, alone or in combination, appears to be effective in the treatment of bipolar depression and is considered a first-line treatment by consensus specialists [33]. According to a meta-analysis of older studies [34], lithium is superior to placebo in bipolar depression. On the other hand, however, a review study [35] indicated a low response rate of 36%.

Finally, electroconvulsive therapy is an important option for the treatment of bipolar depression. In unipolar depression, this therapeutic modality is highly effective, being superior to the simulation of electroconvulsive therapy and to the use of ADs [36]. In bipolar depression, studies are far less numerous. However, a prospective clinical study of 2015 with a sample of patients with refractory bipolar depression [37] demonstrated that electroconvulsive therapy was superior to drug use.

3. Clinical studies on the use of ADs in bipolar depression

Regarding the use of ADs in bipolar depression, some questions need to be answered. Are they as effective as in unipolar depression? Are they tolerated and safe? How often do they lead to mania or hypomania? Do they cause cycle

acceleration? Do they increase the risk of suicide? And, within each of these questions, are there differences when considering different classes of ADs?

We conducted a broad review of clinical studies on the use of ADs in bipolar depression. In the Pubmed database, we use the terms 'depression', 'bipolar' and 'antidepressant'. Only original studies were selected. To be selected, a study should have a sample of patients with BD diagnosed according to modern criteria. In addition, patients should have been treated with an AD. There were no restrictions on the class of ADs, and studies with older antidepressants, such as tricyclics and MAOIs, were also included. We do not include review articles, letters to the editor or unpublished studies. In a complementary way, we have examined bibliographical references of recent clinical studies, review articles and meta-analyzes in search of additional original studies.

We found 73 original studies. In only eight of these studies [38–45], AD monotherapy was compared with placebo. Five of these eight studies had very small samples [38–42] and two of them [43,44] were continuation versus substitution studies. In these two studies, the samples consisted of patients who had improved with fluoxetine, and, in the second phase, the AD was maintained or replaced with placebo. Thus, in only one study among all 73 found [45], AD was not associated with another substance, there was comparison with placebo, placebo did not replace an AD that had been effective and sample size was significant. In that study, however, quetiapine was the major investigated substance and the AD was used merely as a comparator.

Among the 73 original studies, 33 were randomized. Among the randomized trials, 14 were placebo-controlled. Among the placebo-controlled studies, in eight the antidepressant was used as monotherapy. Among these eight studies, in only [45] one sample was more than 100 patients.

The presentation of the results of the clinical studies was organized based preferably on the substance tested. For a more general view on the use of ADs, or classes of ADs, in bipolar depression, we performed a review of the meta-analysis studies on the topic (Section 5).

3.1. Therapeutic response

In our review, we found 35 studies evaluating the therapeutic response of AD use in bipolar depression (see Table 1).

Six studies, only one controlled, one retrospective and five prospective, compared depressed bipolar and unipolar patients regarding response to ADs [41,46–50]. In the study by Tundo et al. [47], patients with BD were divided into two groups, type I and type II, and both were compared to patients with unipolar depression. In four studies [41,48–50], all patients with BD were type II. In the other study [46], there was no distinction between types I and II. In none of these studies was there a difference between groups of patients.

In three studies [46,47,51], the efficacy of a specific substance was not investigated and patients were treated with several ADs. None of these studies was controlled and one was retrospective. Initial response rates among patients with bipolar depression ranged from 48.7% to 75.5%.

In six controlled double-blind studies [38,41,52–55], the efficacy of imipramine in bipolar depression was evaluated. In the study by Agosti et al. [41], there were only type II bipolar patients, and in the study by Nemeroff et al. [55], patients from all groups were simultaneously using lithium. In the studies of Himmelhoch et al. [53] and Silverstone et al. [54], this tricyclic AD led to a significant improvement compared to baseline. In four studies, imipramine was compared to a monoamine oxidase inhibitor (MAOI). It was not distinguished from phenelzine [41] and moclobemide [54] and was inferior to tranylcypromine [53]. Thase et al. [52] performed a crossover study, with a very small sample. Of the twelve patients who had not responded to imipramine, nine improved with tranylcypromine, and of the four patients who had not responded to tranylcypromine, one improved with imipramine. Two studies compared imipramine with SSRIs. There was no difference between the therapeutic response with the tricyclic and that observed with paroxetine [55] or with fluoxetine [38]. Finally, imipramine was superior to placebo in one study [41], but was not distinguished from it in two other studies [38,55].

Five studies [38,39,48,56,57] evaluated the efficacy of fluoxetine monotherapy. Three of these studies were open-label and had samples with only patients with BD type II [48,56,57]. Amsterdam et al. [48] observed that the response among the depressed bipolar patients was similar to that found among the unipolar ones. The positive response rate was 59.5% in the study by Amsterdam et al. [56]. And in the study by Simpson et al. [58], 10 of the 16 patients presented a 'good' or 'very good' response. In two double-blind, randomized, controlled trials, fluoxetine did not differ from imipramine and placebo [38]; and was not distinguished from olanzapine/fluoxetine combination, olanzapine monotherapy and placebo [39].

Four controlled, double-blind, randomized studies evaluated the efficacy of olanzapine/fluoxetine combination [24,39,58,59]. In the study by Tohen et al., the combination was superior to olanzapine monotherapy and placebo. However, Amsterdam et al. [39], with a very small sample, found that olanzapine/fluoxetine combination was not distinguished from olanzapine alone, fluoxetine monotherapy or placebo. In the studies of Brown et al., olanzapine/fluoxetine combination was superior to lamotrigine in the short term, seven weeks [58], and in six months [59].

Three studies evaluated the efficacy of sertraline [60–62]. Altshuler et al. [60] found no difference between sertraline, sertraline/lithium combination and lithium monotherapy in a sample of depressed bipolar type II patients. Post et al. [61], in turn, compared sertraline with venlafaxine and with bupropion, and found no differences between the three ADs. In this study, patients in all three groups also used a MS. The same comparison was made by Leverich et al. [62], who also found no differences between the three substances associated with MS.

Six randomized controlled trials, five double-blind and one open-label, evaluated paroxetine [45,55,63–66]. Nemeroff et al. [55] found no difference between this AD and imipramine or placebo. In the study by Young et al. [63], the association of paroxetine with a MS was not distinguished from the association between two MSs. In the study by McElroy et al. [45], paroxetine was lower than quetiapine and equal to placebo. Shelton et al.

Table 1. Therapeutic response.

Study	Sample	Design	Methods	Therapeutic response
Ghaemi et al. (2004) [46]	41 BP and 37 UP depressed patients treated with AD	BP vs. UP patients	Retrospective	Short-term non-response: BP (51.3%) = UP (31.6%)
Tundo et al. (2015) [47]	49 BP type I, 52 BP type II and 154 UP depressed patients treated with AD	BP type I vs. BP type II vs. UP depressed patients	Prospective, open-label, 12 weeks	Positive response: BP type I (75.5%) = BP type II (75.0%) = UP (64.9%); Remission rate: BP type I = BP type II = UP
Amsterdam et al. (1998) [48]	89 patients with BP II depression and 89 with UP depression	FLX monotherapy: BP II vs. UP patients	Open-label, not controlled, 12 weeks	BP II = UP
Amsterdam (1998) [49]	17 patients with BP II depression and 31 UP depressed patients	VLFX monotherapy: BP II vs. UP patients	Open-label, not controlled, 6 weeks	Significant improvement; BP II = UP
Amsterdam et al. (2000) [50]	15 women with BP II depression and 17 with UP depression	VLFX monotherapy: BP II vs. UP patients	Open-label, not controlled, 6 weeks	Positive response: BP II (63%) = UP (60%)
Pacchiarotti et al. (2011) [51]	241 depressed BP patients	Investigation of an add-on treatment with AD	Prospective, not controlled, 8 weeks	Positive response: 138 patients (62.4%)
Agosti et al. (2007) [41]	62 BP type II and 248 UP patients depressed patients	BPII vs. UP; IMI vs. PHNZ vs. PCB	Double-blind, randomized, placebo-controlled, 6 weeks	Positive response: BP II = UP (with IMI, PHNZ or PCB); Positive response in BP II group: IMI = 57%, PHNZ = 52%, PCB = 23%
Thase et al. (1992) [52]	16 anergic depressed BP patients not responsive to IMI or TNCP	IMI vs. TNCP	Double-blind, crossover, 6 weeks: IMI replaced by TNCP (n = 12), TNCP replaced by IMI (n = 4)	Positive response: TNCP (9/12, 75%), IMI (1/4, 25%)
Himmelhoch et al. (1991) [53]	56 anergic patients with BP depression	TNCP (n = 28) vs. IMI (n = 28)	Double-blind, randomized, controlled, 6 weeks	TNCP and IMI significant improvement; TNCP > IMI
Silverstone (2001) [54]	156 patients with BP depression	MCLB (n = 78) vs. IMI (n = 78)	Double-blind, randomized, controlled, 8 weeks	MCLB and IMI significant improvement; MCLB = IMI
Nemeroff et al. (2001) [55]	117 patients with BP depression	IMI + Li (n = 39) vs. PRXT + Li (n = 35) vs. PCB + Li (n = 43)	Double-blind, randomized, placebo-controlled, 10 weeks	IMI = PRXT = PCB
Altshuler et al. (2017) [60]	142 BP type II depressed patients	Li (n = 49) vs. STRL (n = 45) vs. Li + STRL (n = 48)	Double-blind, randomized, controlled, 16 weeks	Positive response: Li (67,4%) = STRL (73.4%) = Li + STRL (47.9%)
Young et al. (2000) [63]	27 BP depressed patients	Li or DIVAL + PRXT (n = 11) vs. Li or DIVAL + second MS (n = 16)	Double-blind, randomized, 6 weeks	Both groups: significant improvement; Li or DIVAL + PRXT = Li or DIVAL + second MS
McElroy et al. (2010) [45]	740 BP depressed patients	QTP 300mg (n = 245) vs. QTP 600mg (n = 247) vs. PRXT (n = 122) vs. PCB (n = 126)	Double-blind, randomized, placebo-controlled, 8 weeks	QTP > PRXT and PCB; PRTX = PCB
Kupfer et al. (2001) [67]	33 BP depressed patients	CTLP as adjunctive treatment to MS	Prospective, open-label, 8 weeks	Response rates: 21 patients (64%)
Cohn et al. (1989) [38]	89 patients with BP depression	FLX vs. IMI vs. PCB	Double-blind, randomized, placebo-controlled, 6 weeks	Response rates: FLX (86%) = IMI (57%) = PCB (38%)
Amsterdam et al. (2010) [56]	148 BP type II depressed patients	FLX monotherapy	Open-lable, not controlled, 14 weeks	Positive response: 88 patients (59.5%)
Simpson et al. (1991) [57]	16 BP type II patients with a nonresponsive depression	FLX replacing previous treatment	Prospective, open-label, 10 months	10 patients: good or very good response; 3 pacients: fair response
Tohen et al. (2003) [24]	833 patients with BP I depression	OFC (n = 86) vs. OLZP (n = 370) vs. PCB (n = 377)	Double-blind, randomized, placebo-controlled, 8 weeks	OFC > OLZP > PCB
Amsterdam et al. (2005) [39]	34 BP depressed patients	OFC (n = 9) vs. OLZP (n = 8) vs. FLX (n = 8) vs. PCB (n = 9)	Double-blind, randomized, placebo-controlled, 8 weeks	OFC = OLZP = FLX = PCB
Brown et al. (2009) [59]	410 patients with BP I depression	OFC (n = 205) vs. LMTG (n = 205)	Double-blind, randomized,controlled, 45 weeks	OFC > LMTG
Brown et al. (2006) [58]	410 patients with BP I depression	OFC vs. LMTG	Double-blind, randomized,controlled, 7 weeks	OFC > LMTG
Shelton et al. (2004) [64]	30 BP depressed patients	PRXT + MS + PCB vs. RISP + MS + PCB vs. PRXT + RISP + MS	Double-blind, randomized, placebo-controlled, 12 weeks	PRXT + MS + PCB = RISP + MS + PCB = PRXT + RISP + MS
Sachs et al. (2007) [65]	366 BP depressed patients	AD (PRXT or BUP) + MS (n = 179) vs. PCB + MS (n = 187)	Double-blind, randomized, placebo-controlled, 26 weeks	Positive response: AD + MS (32.4%) = PCB + MS (38%)
Erfurth et al. (2002) [71]	13 BP patients with a severe depression	BUP as adjunctive treatment to other AD or MS	Prospective, open-label, 4 weeks	8/13 patients had positive response
Fogelson et al. (1992) [72]	11 BP patients with a nonresponsive depression	BUP as adjunctive treatment	Prospective, open-label, 6 weeks	7/11 patients had moderate-to-marked improvement

(*Continued*)

Table 1. (Continued).

Study	Sample	Design	Methods	Therapeutic response
Sachs et al. (1994) [73]	19 BP depressed patients	BUP + MS (n = 9) vs. DSPM + MS (n = 10)	Double-blind, randomized, controlled, 8 weeks	BUP + MS = DSPM + MS
Grossman et al. (1999) [74]	14 BP depressed patients	BUP (N = 7) vs. IDZX (N = 7)	Double-blind, randomized, controlled, 6 weeks	Significant improvement: BUP and IDZX
Vieta et al. (2002) [66]	60 patients with BP depression	PRXT + MS (n = 30) vs. VLFX + MS (n = 30)	Randomized, controlled, open, 6 weeks	PRXT + MS and VLFX + MS: significant improvement; PRXT + MS = VLFX + MS
Post et al. (2006) [61]	174 patients with BP depression	VLFX + MS (n = 65) vs. BUP + MS (n = 51) vs. STRL + MS (n = 58)	Randomized, controlled, 10 weeks	VLFX + MS = BUP + MS = STRL + MS
Leverich et al. (2006) [62]	228 BP depressed patients (acute phase); 87 in continuation phase	BUP + MS vs. STRL + MS vs. VLFX + MS	Randomized, controlled, 10 weeks (acute phase) and 1 year (continuation phase)	Both phases: BUP + MS = STRL + MS = VLFX + MS
Amsterdam et al. (2010) [69]	17 BP depressed type II patients non-responsive to Li	VLFX replacing previous Li	Prospective, open-label, 12 weeks	Significant improvement in median
Amsterdam et al. (2008) [76]	83 BP type II depressed patients	VLFX (n = 43) vs. Li (n = 40)	Prospective, randomized, open-label, 12 weeks	VLFX > Li
Amsterdam et al. (2016) [70]	129 depressed BP type II patients	VLFX (n = 65) vs. Li (n = 64)	Prospective, randomized, double-blind, controlled, 12 weeks	Response rate: VLFX (n = 67.7%) > Li (n= 34.4%)
Yatham et al. (2016) [75]	344 BP type I depressed patients	AGO + MS (n = 172) vs. PCB + MS (n = 172)	Double-blind, randomized, placebo-controlled, 8 and 52 weeks	AGO + MS = PCB + MS

AD: antidepressants; AGO: agomelatine; AMI: amitriptyline; BP: bipolar; BUP: bupropion; CTLP: citalopram; DIVAL: divalproex; DSPM: desipramine; ECT: electroconvulsive therapy; FLX: fluoxetine; IDZX: idazoxan; IMI: imipramine; Li: lithium; LMTG: lamotrigine; MCLB: moclobemide; MS: mood stabilizer; OFC: olanzapine/fluoxetine combination; OLZP: olanzapine; PHNZ: phenelzine; PRXT: paroxetine; PCB: placebo; QTP: quetiapine; RISP: risperidone; SSRI: selective serotonin reuptake inhibitors; STRL: sertraline; TNCP: tranylcypromine; UP: unipolar; VLFX: venlafaxine; YMRS: Young Mania Rating Scale

[64], in turn, compared paroxetine with risperidone and with the combination of these two substances and found no differences. Patients in the three groups were taking concomitantly a MS. In the study by Sachs et al. [65], the association of paroxetine or bupropion with a MS showed results similar to those obtained with the combination of placebo with a MS. Finally, Vieta et al. [66] found no difference between paroxetine and venlafaxine, both associated with a MS.

In the only study with citalopram [67], this AD was used as adjunctive treatment in 33 patients medicated with a MS. As a result, 21 of these patients had a positive response.

Eight studies evaluated venlafaxine [49,50,61,62,66,68–70]. In two studies [49,50], depressed bipolar type II patients and unipolar ones had similar responses to this AD. In a sample of patients not responding to lithium, Amsterdam et al. [69] observed an improvement when it was replaced by venlafaxine. In controlled studies with patients using MSs, venlafaxine was not distinguished from paroxetine [66], sertraline and bupropion [61,62]. Finally, in two controlled randomized studies with patients with BD type II, venlafaxine was superior to lithium [68,70].

The efficacy of bupropion was assessed in seven studies [61,62,65,71–74]. In two open-label studies with small samples [71,72], this AD led to an improvement for most patients when it was added to a MS. In a controlled, randomized, double-blind study [74], both bupropion and idazoxan led to a significant improvement in a sample of only 14 patients. In controlled studies with patient samples concomitantly using a MS, bupropion was not different from placebo [65], desipramine [73], sertraline, and venlafaxine [61,62].

Finally, agomelatine was evaluated in a single study [75]. Associated with a MS, this AD was not superior to placebo, also associated with a MS.

3.2. Adverse effects

In our review, we found 25 studies that evaluated the adverse effects associated with the use of ADs in bipolar depression (see Table 2).

Three studies [41,48,49] compared depressed bipolar patients with unipolar one for the occurrence of adverse effects on the use of ADs. Amsterdam [49] found a low incidence in both groups. In the other two studies [41,48], bipolar and unipolar patients had similar rates of withdrawal due to side effects.

Five controlled studies investigated the tolerability of imipramine in bipolar depression [38,41,52,54,55]. Cohn et al. [38] found a higher rate of withdrawal due to adverse effects with imipramine than with fluoxetine, but in the study by Agosti et al. [41], imipramine was not distinguished from phenelzine or placebo. In a crossover study [52], two of the twelve patients who switched to tranylcypromine dropped out because of side effects, which did not occur in any of the four patients who started using imipramine. Silverstone [54], on the other hand, observed a greater frequency of anticholinergic and weight gain effects with imipramine than with moclobemide. Finally, Nemeroff et al. [55], in a sample in which all patients also used lithium did not find differences between imipramine, paroxetine, and placebo on weight gain, although sexual dysfunction was more common with the tricyclic.

The tolerability of fluoxetine was assessed in five studies [38,44,48,56,57]. Dropout rates due to adverse effects

Table 2. Adverse effects.

Study	Sample	Design	Methods	Adverse effects
Amsterdam et al. (1998) [48]	89 patients with BP II depression and 89 with UP depression	FLX monotherapy: BP vs. UP patients	Short-term: open-label, not controlled, 12 weeks; Long-term: double-blind, placebo-controlled, 52 weeks	Short-term: dropouts for adverse effects: 11% (BP) = 9% (UP)
Amsterdam (1998) [49]	17 patients with BP II depression and 31 UP depressed patients	VLFX monotherapy: BP II vs. UP patients	Open-label, not controlled, 6 weeks	Low incidence
Agosti et al. (2007) [41]	62 BP type II and 248 UP patients depressed patients	BPII vs. UP; IMI vs. PHNZ vs. PCB	Double-blind, randomized, placebo-controlled, 6 weeks	Dropout for adverse effects: low incidence
Thase et al. (1992) [52]	16 anergic depressed BP patients not responsive to IMI or TNCP	IMI vs. TNCP	Double-blind, crossover, 6 weeks: IMI replaced by TNCP (n = 12), TNCP replaced by IMI (n = 4)	Dropouts for adverse effects: 2 patients with TNCP in crossover phase
Silverstone (2001) [54]	156 patients with BP depression	MCLB (n = 78) vs. IMI (n = 78)	Double-blind, randomized, controlled, 8 weeks	Anticholinergic effects and weight gain: IMI > MCLB
Nemeroff et al. (2001) [55]	117 patients with BP depression	IMI + Li (n = 39) vs. PRXT + Li (n = 35) vs. PCB + Li (n = 43)	Double-blind, randomized, placebo-controlled, 10 weeks	Sexual disfuction: more common with IMI; Weight gain: IMI (7.7%) = PRXT (5.7%) = PCB (7.0%)
Altshuler et al. (2017) [60]	142 BP type II depressed patients	Li (n = 49) vs. STRL (n = 45) vs. Li + STRL (n = 48)	Double-blind, randomized, controlled, 16 weeks	Dropout for adverse effects: Li = STRL = Li + STRL
Young et al. (2000) [63]	27 BP depressed patients	Li or DIVAL + PRXT (n = 11) vs. Li or DIVAL + second MS (n = 16)	Double-blind, randomized, 6 weeks	Dropouts for adverse effects: no patient of PRXT group; 2 patients of second MS group
Parker et al. (2006) [40]	10 BP type II patients (depressed or euthymic)	CTLP vs. PCB	Double-blind, randomized, placebo-controlled, crossover 9 months	CTLP = PCB
Kupfer et al. (2001) [67]	33 BP depressed patients	CTLP as adjunctive treatment to MS	Prospective, open-label, 8 weeks	"Level of reported adverse events relatively low"
Amsterdam et al. (2010) [56]	148 BP type II depressed patients	FLX monotherapy	Open-lable, not controlled, 14 weeks	Dropout for adverse effects: 5 patients (3.4%)
Cohn et al. (1989) [38]	89 patients with BP depression	FLX vs. IMI vs. PCB	Double-blind, randomized, placebo-controlled, 6 weeks	Dropouts for adverse effects: IMI (30%) > FLX (7%)
Simpson et al. (1991) [57]	16 BP type II patients with a nonresponsive depression	FLX replacing previous treatment	Prospective, open-label, 10 months	Dropout for adverse effects: 1/16 patient
Amsterdam et al. (2010) [44]	BP depressed type II patients remitted with FLX	FLX (continuation, n = 28) v. Li (substitution, n = 26) vs. PCB (substitution, n = 27)	Double-blind, randomized, placebo-controlled, 50 months	Dropout for adverse effects: FLX (3.6%) = Li (3.8%) = PCB: (3.7%)
Tohen et al. (2003) [24]	833 patients with BP I depression	OFC (n = 86) vs. OLZP (n = 370) vs. PCB (n = 377)	Double-blind, randomized, placebo-controlled, 8 weeks	Extrapyramidal symptoms: OFC = OLZP = PCB; weight gain, cholesterol levels and nonfasting glucose levels: OFC and OLZP > PCB; orthostatic hypotension: OFC > OLZP and PCB; elevated blood pressure: OFC > OLZP, OFC = PCB
Brown et al. (2009) [59]	410 patients with BP I depression	OFC (n = 205) vs. LMTG (n = 205)	Double-blind, randomized,controlled, 45 weeks	Adverse events in geral, weight gain and hypercholesterolaemia: OFC > LMTG
Brown et al. (2006) [58]	410 patients with BP I depression	OFC vs. LMTG	Double-blind, randomized,controlled, 7 weeks	Somnolence, increased appetite, dry mouth, sedation, weight gain, tremor, total cholesterol and triglyceride levels: OFC > LMTG
Sachs et al. (2007) [65]	366 BP depressed patients	AD (PRXT or BUP) + MS (n = 179) vs. PCB + MS (n = 187)	Double-blind, randomized, placebo-controlled, 26 weeks	Dropout for adverse effects: AD + MS (12.3%) = PCB + MS (9.1%)
Erfurth et al. (2002) [71]	13 BP patients with a severe depression	BUP as adjunctive treatment to other AD or MS	Prospective, open-label, 4 weeks	Dropouts for adverse effects: 2/13 patients
Vieta et al. (2002) [66]	60 patients with BP depression	PRXT + MS (n = 30) vs. VLFX + MS (n = 30)	Randomized, controlled, open, 6 weeks	PRXT = VLFX
McElroy et al. (2010) [45]	740 BP depressed patients	QTP 300mg (n = 245) vs. QTP 600mg (n = 247) vs. PRXT (n = 122) vs. PCB (n = 126)	Double-blind, randomized, placebo-controlled, 8 weeks	QTP: dry mouth, somnolence, sedation, and dizziness; PRXT: dry mouth, sedation, headache, insomnia, and nausea

(*Continued*)

Table 2. (Continued).

Study	Sample	Design	Methods	Adverse effects
Amsterdam et al. (2010) [69]	17 BP depressed type II patients non-responsive to Li	VLFX replacing previous Li	Prospective, open-label, 12 weeks	Dropout for adverse effects: no patient
Amsterdam et al. (2008) [76]	83 BP type II depressed patients	VLFX (n = 43) vs. Li (n = 40)	Prospective, randomized, open-label, 12 weeks	Dropout for adverse effects: 13 patients (15.7%)
Amsterdam et al. (2016) [70]	129 depressed BP type II patients	VLFX (n = 65) vs. Li (n = 64)	Prospective, randomized, double-blind, controlled, 12 weeks	Dropout for adverse effects: VLFX (3 patients) = Li (3 patients)
Yatham et al. (2016) [75]	344 BP type I depressed patients	AGO + MS (n = 172) vs. PCB + MS (n = 172)	Double-blind, randomized, placebo-controlled, 8 and 52 weeks	At least one emergent adverse effect: AGO + MS (69.6%) = PCB + MS (64.7%)

AD: antidepressants; AGO: agomelatine; AMI: amitriptyline; BP: bipolar; BUP: bupropion; CTLP: citalopram; DIVAL: divalproex; DSPM: desipramine; ECT: electroconvulsive therapy; FLX: fluoxetine; IDZX: idazoxan; IMI: imipramine; Li: lithium; LMTG: lamotrigine; MCLB: moclobemide; MS: mood stabilizer; OFC: olanzapine/fluoxetine combination; OLZP: olanzapine; PHNZ: phenelzine; PRXT: paroxetine; PCB: placebo; QTP: quetiapine; RISP: risperidone; SSRI: selective serotonin reuptake inhibitors; STRL: sertraline; TNCP: tranylcypromine; UP: unipolar; VLFX: venlafaxine; YMRS: Young Mania Rating Scale

with this AD ranged from 3.4% [56] to 11% [48]. Fluoxetine was better tolerated than imipramine [39], but did not differ in this aspect of lithium and placebo [44].

Three studies have addressed olanzapine/fluoxetine combination [24,58,59]. Tohen et al. [24] found that this combination was especially associated with weight gain, metabolic syndrome, orthostatic hypotension, and elevated blood pressure, but not with extrapyramidal effects when compared with olanzapine alone and with placebo. Brown et al. [58,59], in turn, observed that olanzapine/fluoxetine combination caused side effects than lamotrigine.

Only one study evaluated sertraline. Altshuler et al. [60] found that the rate of dropouts due to adverse effects with this AD was similar to those associated with lithium and with lithium/sertraline combination.

Five studies investigated the tolerability of paroxetine [45,55,63,65,66]. McElroy et al. [45] observed that paroxetine monotherapy was especially associated with dry mouth, sedation, headache, insomnia, and nausea. In other studies, paroxetine and other therapeutic options were associated with a MS. Nemeroff et al. [55] observed that there was less sexual dysfunction with paroxetine than with imipramine, but found no difference between paroxetine, imipramine, and placebo on weight gain. In the study by Vieta et al. [66], paroxetine and venlafaxine were similar in side effects. And, in two studies, paroxetine was not distinguished from a second MS [63] or placebo [65] regarding the rate of withdrawal due to adverse effects.

Only two studies evaluated citalopram [40,67]. As an adjunctive treatment to a MS, this AD has been associated with mild side effects [68]. And, in a controlled study [40], citalopram was as well tolerated as placebo.

Five studies on venlafaxine have been found [49,66,69,70,76]. In an open-label study [49], there was a low incidence of side effects with this AD. In a controlled study [66], venlafaxine had a similar tolerability to that of paroxetine. In the study by Amsterdam et al. [69], none of 17 patients discontinued treatment after lithium was replaced by venlafaxine. Amsterdam et al. [70] found similar rates of withdrawal due to adverse effects in the comparison between venlafaxine and lithium. Finally, in another study comparing venlafaxine and lithium [76], the dropout rate due to undesirable effects was 15.7%. However, the authors do not report the proportions of patients who were using one substance or another.

Two studies addressed bupropion [65,71]. In one of them [71], among 13 patients who used bupropion with an adjunctive treatment, two dropped out because of side effects. In the other study [65], in which this AD was also used as adjunctive treatment, bupropion did not differ from placebo in the rate of withdrawal due to adverse effects.

Finally, in the only study on agomelatine [75], used as adjunctive treatment, this AD did not differ from placebo in the incidence of side effects.

Table 3. Manic switches.

Study	Sample	Design	Methods	Mania/hypomania switches
Ghaemi et al. (2004) [46]	41 BP and 37 UP depressed patients treated with AD	BP vs. UP patients	Retrospective	BP (48.8%) > UP (0%)
Tundo et al. (2015) [47]	49 BP type I, 52 BP type II and 154 UP depressed patients treated with AD	BP type I vs. BP type II vs. UP depressed patients	Prospective, open-label, 12 weeks	2 BP type I patients and 1 BP type II patient
Amsterdam et al. (1998) [48]	89 patients with BP II depression and 89 with UP depression	FLX monotherapy: BP vs. UP patients	Short-term: open-label, not controlled, 12 weeks; Long-term: double-blind, placebo-controlled, 52 weeks	Short-term: 3.8% (BP) = 0.3% (UP); Long-term: 2% (BP) = 1% (UP)
Benazzi (1997) [77]	303 depressed patients (203 UP, 92 BP type II, 8 BP type I) treated with AD	BP II vs. UP patients	Naturalistic study, 3–6 months	BP II (17.3%) > UP (5.8%)
Amsterdam (1998) [49]	17 patients with BP II depression and 31 UP depressed patients	VLFX monotherapy: BP II vs. UP patients	Open-label, not controlled, 6 weeks	No patient
Amsterdam et al. (2000) [50]	15 women with BP II depression and 17 with UP depression	VLFX monotherapy: BP II vs. UP patients	Open-label, not controlled, 6 weeks	No patient
Altshuler et al. (2006) [78]	182 BP depressive patients treated with MS + AD (BUP, STRL or VLFX)	BP type I (n = 134) vs. BP type II (n = 48)	Prospective, randomized	BP type I (12%) > BP type II (2%)
Ghaemi et al. (2000) [84]	85 BP or UP patients	Investigation of the effect of AD use	Retrospective, longitudinal, 1 year	55% of the BP patients treated with AD
Goldberg et al. (2002) [83]	53 BP patients	Investigation of the effect of AD use	Retrospective	39.6% of the BP patients teated with AD
Gorwood et al. (2016) [86]	1242 depressed BP patients with MS who received a AD as add-on treatment	patients with antidepressant-emergent manic switch (n = 60) vs. patients with not	Prospective, 4 weeks	Manic switch associated to more past manic episodes and to prior manic switch
Altshuler et al. (1995) [82]	51 patients with refractory BP disorder (38 type I, 13 type II)	Life charting: proximity between AD iniciation and a manic episode or increase cycling	Retrospective, longitudinal, open-lable	35% had a manic episode "likely" induced by AD
Bottlender et al. (1998) [79]	158 BP depressed patients	AD treatment vs. non-AD treatment	Retrospective, longitudinal, open-lable	Mood switches: associated to AD treatment
Bauer et al. (2005) [80]	80 BP patients	Patient taking AD (n = 47) vs. not taking (n = 33)	Naturalistic, prospective	Patient taking AD (0.9%) = not taking (0.7%)
Boerlin et al. (1998) [88]	29 BP patients (79 depressed episodes)	MS (n = 31) vs. MS + AD (n = 48)	Naturalistic study	MS = MS + AD
Pacchiarotti et al. (2011) [89]	95 BP patients	AD vs. AD + MS	Retrospective and prospective, 10 years in median	AD > AD + MS
Viktorin et al. (2014) [21]	3240 BP patients	AD vs. AD + MS	Retrospective, 3 months	Increased risk: with AD, but not with AD + MS
Henry et al. (2001) [85]	44 BP patients (31 type I, 13 type II)	AD treatment vs. ECT	Naturalistic study, 6 weeks	24% of the patients treated with SSRI; AD = ECT
Serretti et al. (2003) [87]	416 BP patients	Prior history of manic switch during AD therapy (n = 169) vs. no history of manic switch during AD therapy (n = 247)	Retrospective	Manic switches: associated to type I BP, no use of MS, depressive polarity of the onset episode and less previous manic episodes
Lewis et al. (1982) [81]	53 BP patients	Trcyclic AD (n = 26) vs. no treatment (n = 27)	Retrospective	Triclyclic AD: 28%; no treatment: 41%
Himmelhoch et al. (1991) [53]	56 anergic patients with BP depression	TNCP (n = 28) vs. IMI (n = 28)	Double-blind, randomized, controlled, 6 weeks	TNCP (6 patients, 21%) = IMI (7 patients, 25%)
Silverstone (2001) [54]	156 patients with BP depression	MCLB (n = 78) vs. IMI (n = 78)	Double-blind, randomized, controlled, 8 weeks	MCLB (2 patients, 3.7%) = IMI (6 pacients, 11%)
Nemeroff et al. (2001) [55]	117 patients with BP depression	IMI + Li (n = 39) vs. PRXT + Li (n = 35) vs. PCB + Li (n = 43)	Double-blind, randomized, placebo-controlled, 10 weeks	PRXT (no patient) = IMI (3 patients, 7.7%) = PCB (1 patient, 2.3%)
Young et al. (2000) [63]	27 BP depressed patients	Li or DIVAL + PRXT (n = 11) vs. Li or DIVAL + second MS (n = 16)	Double-blind, randomized, 6 weeks	Emergence of a mixed state: no patient of PRXT group; 1 patient of second MS group
Kupfer et al. (2001) [67]	33 BP depressed patients	CTLP as adjunctive treatment to MS	Prospective, open-label, 8 weeks	6.7%
Amsterdam et al. (2010) [56]	148 BP type II depressed patients	FLX monotherapy	Open-lable, not controlled, 14 weeks	6 patients (4.1%)
Amsterdam et al. (2005) [43]	BP depressed patients remitted with FLX	FLX (continuation) vs. PCB (substituition)	Double-blind, randomized, placebo-controlled, 6 months	No patient
Amsterdam et al. (2010) [44]	BP depressed type II patients remitted with FLX	FLX (continuation, n = 28) v. Li (substitution, n = 26) vs. PCB (substitution, n = 27)	Double-blind, randomized, placebo-controlled, 50 months	FLX (10.7%) = Li (7.7%) = PCB (7.4%)

(*Continued*)

Table 3. (Continued).

Study	Sample	Design	Methods	Mania/hypomania switches
Altshuler et al. (2017) [60]	142 BP type II depressed patients	Li (n = 49) vs. STRL (n = 45) vs. Li + STRL (n = 48)	Double-blind, randomized, controlled, 16 weeks	Li (14.3%) = STRL (17.8%) = Li + STRL (10.4%)
Tohen et al. (2003) [24]	833 patients with BP I depression	OFC (n = 86) vs. OLZP (n = 370) vs. PCB (n = 377)	Double-blind, randomized, placebo-controlled, 8 weeks	OFC (6.4%) = OLZP (5.7%) = PCB (6.7%)
Amsterdam et al. (2005) [39]	34 BP depressed patients	OFC (n = 9) vs. OLZP (n = 8) vs. FLX (n = 8) vs. PCB (n = 9)	Double-blind, randomized, placebo-controlled, 8 weeks	No patient
Brown et al. (2009) [59]	410 patients with BP I depression	OFC (n = 205) vs. LMTG (n = 205)	Double-blind, randomized,controlled, 45 weeks	OFC (5.0%) = LMTG (7.3%)
Shelton et al. (2004) [64]	30 BP depressed patients	PRXT + MS + PCB vs. RISP + MS + PCB vs. PRXT + RISP + MS	Double-blind, randomized, placebo-controlled, 12 weeks	1 patient with PRXT + MS + PCB
Sachs et al. (2007) [65]	366 BP depressed patients	AD (PRXT or BUP) + MS (n = 179) vs. PCB + MS (n = 187)	Double-blind, randomized, placebo-controlled, 26 weeks	AD + MS (10.1%) = PCB + MS (10.7%)
Erfurth et al. (2002) [71]	13 BP patients with a severe depression	BUP as adjunctive treatment to other AD or MS	Prospective, open-label, 4 weeks	No patient
Fogelson et al. (1992) [72]	11 BP patients with a nonresponsive depression	BUP as adjunctive treatment	Prospective, open-label, 6 weeks	6/11 patients
Joffe et al. (2002) [90]	69 BP patients (51 type I, 18 type II)	SSRI vs. BUP	Naturalistic, prospective, open-label	SSRI = BUP
Sachs et al. (1994) [73]	19 BP depressed patients	BUP + MS (n = 9) vs. DSPM + MS (n = 10)	Double-blind, randomized, controlled, 8 weeks	BUP + MS (11%) < DSPM + MS (50%)
Vieta et al. (2002) [66]	60 patients with BP depression	PRXT + MS (n = 30) vs. VLFX + MS (n = 30)	Randomized, controlled, open, 6 weeks	PRXT (1 patient,3%) = VLFX (4 patients, 13%)
Post et al. (2006) [61]	174 patients with BP depression	VLFX + MS (n = 65) vs. BUP + MS (n = 51) vs. STRL + MS (n = 58)	Randomized, controlled, 10 weeks	VLFX (31%) > BUP (14%) and STRL (16%)
Leverich et al. (2006) [62]	228 BP depressed patients (acute phase); 87 in continuation phase	BUP + MS vs. STRL + MS vs. VLFX + MS; BP type I vs. BP type II	Randomized, controlled, 10 weeks (acute phase) and 1 year (continuation phase)	Both phases: BUP + MS = STRL + MS = VLFX + MS; BP type I > BP type II
Amsterdam et al. (2010) [69]	17 BP depressed type II patients non-responsive to Li	VLFX replacing previous Li	Prospective, open-label, 12 weeks	1 patient (5.9%)
Amsterdam et al. (2008) [76]	83 BP type II depressed patients	VLFX (n = 43) vs. Li (n = 40)	Prospective, randomized, open-label, 12 weeks	VLFX (2.4%) = Li (0%)
Amsterdam et al. (2016) [70]	129 depressed BP type II patients	VLFX (n = 65) vs. Li (n = 64)	Prospective, randomized, double-blind, controlled, 12 weeks	VLFX = Li
McElroy et al. (2010) [45]	740 BP depressed patients	QTP 300 mg (n = 245) vs. QTP 600 mg (n = 247) vs. PRXT (n = 122) vs. PCB (n = 126)	Double-blind, randomized, placebo-controlled, 8 weeks	QTP < PRXT and PCB; PRTX = PCB
Yatham et al. (2016) [75]	344 BP type I depressed patients	AGO + MS (n = 172) vs. PCB + MS (n = 172)	Double-blind, randomized, placebo-controlled, 8 and 52 weeks	8 weeks: AGO + MS (4.1%) = PCB + MS (3.5%)

AD: antidepressants; AGO: agomelatine; AMI: amitriptyline; BP: bipolar; BUP: bupropion; CTLP: citalopram; DIVAL: divalproex; DSPM: desipramine; ECT: electroconvulsive therapy; FLX: fluoxetine; IDZX: idazoxan; IMI: imipramine; Li: lithium; LMTG: lamotrigine; MCLB: moclobemide; MS: mood stabilizer; OFC: olanzapine/fluoxetine combination; OLZP: olanzapine; PHNZ: phenelzine; PRXT: paroxetine; PCB: placebo; QTP: quetiapine; RISP: risperidone; SSRI: selective serotonin reuptake inhibitors; STRL: sertraline; TNCP: tranylcypromine; UP: unipolar; VLFX: venlafaxine; YMRS: Young Mania Rating Scale

3.3. Manic switches

We found 45 studies on manic switches in patients with bipolar depression who were using an AD (see Table 3)

Six studies compared depressed bipolar patients with unipolar ones [46–50,77]. In two of these studies [46,77], the rate of manic switch was significantly higher among patients with BD. However, in the other four studies [47–50], no differences were found between the two groups of patients. Altshuler et al. [78] and Leverich et al. [62], on the other hand, observed that type I bipolar patients had more treatment-emergent mania than type II.

In a retrospective study, Bottlender et al. [79] compared patients with bipolar depression who had used ADs with those who had not used this type of substance and found that the former had more manic episodes. However, in a prospective naturalistic study, Bauer et al. [80] could not observe an association between the use of ADs and the development of a manic episode. Lewis et al. [81], on the other hand, found a greater proportion of manic episodes among non-treated patients than among those taking tricyclic ADs.

Three retrospective studies have found manic switches rates of 35% [82], 39.6% [83] and 55% [84], respectively, in patients with bipolar depression on AD use. In a naturalistic study, Henry et al. [85] observed that 24% of patients treated with SSRIs had a manic switch, a proportion similar to that found in patients undergoing electroconvulsive therapy.

Gorwood et al. [86] observed that treatment-emergent mania was associated with a previous history of treatment-emergent mania and a greater number of previous episodes of mania. In contrast, Serretti et al. [87] found an association with a smaller number of previous episodes of mania. Other elements related to manic switch found by these authors were type I of BD and the depressive polarity of the first episode of the disease. Four studies compared the use with non-use of a MS associated with AD [21,87–89]. In three of them [21,87,89], there were fewer manic switches among patients treated concomitantly with a MS.

Three controlled randomized studies evaluated the occurrence of manic episodes in patients with bipolar depression treated with imipramine [53–55]. Regarding manic switch rates, this AD was not distinguished from tranylcypromine [53], moclobemide [54], paroxetine or placebo [55].

Fluoxetine has been evaluated in five studies [39,43,44,48,56]. In two open-label studies with patients with type II BD, switch rates of 3.8% at 12 weeks, 2% at 52 weeks [48], and 4.1% at 14 weeks [44] were found. In controlled studies, fluoxetine was not distinguished from lithium [44], olanzapine/fluoxetine combination, olanzapine [39] or placebo [39,43,44].

Olanzapine/fluoxetine combination was evaluated in three randomized controlled trials [24,39,59]. According to the results, it was not differentiated from olanzapine monotherapy [24,39], fluoxetine [39], lamotrigine [59] or placebo [24,39] regarding the proportion of patients who switched into mania.

Six studies have addressed the use of paroxetine [45,55,63–66]. In five of these studies [55,63–66], all patients in the samples also received a MS. Regarding the manic switch rates in these five studies, paroxetine was not distinguished from imipramine [55], risperidone, paroxetine/risperidone combination [64], venlafaxine [66], a second MS [63] or placebo [55,65]. In the other study, in which the substances were used as monotherapy, paroxetine did not differ from placebo, but was more associated with manic switches than quetiapine [45].

Three studies evaluated sertraline [60–62]. Altshuler et al. [60] found no differences between sertraline, lithium and sertraline/lithium combination. In the other two studies, sertraline, venlafaxine, and bupropion, used as adjunctive treatments to a MS, were compared. Leverich et al. [62] found no differences between the three ADs, but in the study by Post et al. [61], venlafaxine led to more manic switches than sertraline and bupropion.

In the only study that addressed citalopram [67], this AD, used in combination with a MS, was associated with a switch rate of 6.7%.

Eight studies evaluated venlafaxine [49,50,61,62,66,69,70,76]. In the three open-label studies, the rates of manic switch with this AD were 0% [49], 0% and 5.9% [69], respectively. In two studies [70,76], venlafaxine was not distinguished from lithium. Vieta et al. [66] found no difference between venlafaxine and paroxetine. In two other studies [61,62], venlafaxine, sertraline, and bupropion have been used as adjunctive treatment to MSs. In the study by Post et al. [61], venlafaxine was associated with a higher rate of manic switch, but Leverich et al. [62] found no differences between the three ADs.

Six studies have addressed bupropion [61,62,71–73,90]. In all of these studies, except one [90], bupropion was used as an adjunctive treatment. Two studies were uncontrolled [71,72]. In the study by Erfurth et al. [71], none of the 13 patients presented a manic switch. Fogelson et al. [72], in turn, identified six patients from their eleven samples who switched into mania. In the study by Joffe et al. [90], there was no difference between bupropion and SSRIs. In a comparison with desipramine, bupropion was associated with lower cases of manic switch [73]. In two studies [61,62], bupropion was not distinguished from sertraline. Leverich et al. [62] found no difference between bupropion and venlafaxine, but Post et al. [61] observed that bupropion was less associated with manic switches than venlafaxine.

In the only study on agomelatine [75], this AD, in association with a MS, was not distinguished from placebo.

3.4. Cycle acceleration

In our review, we found 26 studies that evaluated the possibility of ADs causing cycle acceleration in BD (see Table 4).

Three studies compared depressed bipolar patients with unipolar ones [46,48,50]. In the retrospective study [46], more patients with BD presented cycle acceleration with the use of ADs than patients with unipolar depression, but two prospective studies [48,50] found no difference between the two groups. Vöhringer et al. [91], in turn, evaluated the number of new affective episodes within one to three years after the remission of a depressive episode with an AD and found no difference between patients with type I and type II BD.

Two retrospective studies found cycle acceleration rates of 23% [84] and 26% [82], respectively, in patients with BD who took ADs. In a naturalistic study of 13.7 years on average, Coryell et al. [92] did not observe an association between

Table 4. Cycle acceleration.

Study	Sample	Design	Methods	Cycle acceleration
Ghaemi et al. (2004) [46]	41 BP and 37 UP depressed patients treated with AD	BP vs. UP patients	Retrospective	BP (25.6%) > UP (0%)
Amsterdam et al. (1998) [48]	89 patients with BP II depression and 89 with UP depression	FLX monotherapy: BP vs. UP patients	Short-term: open-label, not controlled, 12 weeks; Long-term: double-blind, placebo-controlled, 52 weeks	Long-term: relapse rates similar in BP and UP patients
Amsterdam et al. (2000) [50]	15 women with BP II depression and 17 with UP depression	VLFX monotherapy: BP II vs. UP patients	Open-label, not controlled, 6 weeks	No patient
Ghaemi et al. (2000) [84]	85 BP or UP patients	Investigation of the effect of AD use	Retrospective, longitudinal, 1 year	23% of the BP patients with AD
Altshuler et al. (1995) [82]	51 patients with refractory BP disorder (38 type I, 13 type II)	Life charting: proximity between AD iniciation and a manic episode or increase cycling	Retrospective, longitudinal, open-lable	26% had cycle acceleration associated to AD
Coryell et al. (2003) [92]	345 BP patients	Investigation of AD treatment	Naturalistic, prospective, 13.7 years in median	AD treatment was not associated to the weeks preceding manic episodes
Yildiz et al. (2003) [93]	129 BP patients	use of AD prior to the first manic/hypomanic episode vs. non-use	Retrospective	Rapid cycling: no difference between the groups, but associated to AD use in female sub-sample
Bauer et al. (2005) [80]	80 BP patients	Patient taking AD (n = 47) vs. not taking (n = 33)	Naturalistic, prospective	Rapid cycling: patient taking AD = not taking
Schneck et al. (2008) [94]	1742 BP patients	AD treatment (n = 720) vs. non-AD treatment (n = 471)	Naturalistic, prospective, up to 1 year	Rapid cycling: AD treatment > non-AD treatment
Wehr et al. (1988) [95]	51 BP patients	Li + AD vs. Li + PCB	Double-blind, placebo-controlled, 59 months (in median)	Li + AD: 33% higher rate of rapid cycling
Altshuler et al. (2003) [96]	84 BP depressed patients who remitted with MS/AD combination	AD treatment stopped with 6 months after remission (n = 43) vs. not stopped (n = 41)	Prospective, not randomized, open-label, 1 year	Depressive relapse: AD stopped (70%) > AD not stopped (36%); Manic relapse: AD stopped (9 patients) > AD not stopped (6 patients)
Altshuler et al. (2001) [97]	44 BP depressed patients who remitted with MS/AD combination	AD treatment stopped with 6 months after remission (n = 25) vs. not stopped (n = 19)	Retrospective, 1 year	Depressive relapse: AD stopped > AD not stopped; Manic relapse: AD stopped = AD not stopped
Joffe et al. (2005) [98]	59 BP depressed patients who remitted with MS/AD combination	AD treatment stopped with 6 months after remission (n = 20) vs. not stopped (n = 39)	Retrospective, naturalistic, open-label, 1 year	Depressive relapse: AD stopped (90%) > AD not stopped (53.8%); Manic relapse: AD stopped (20%) = AD not stopped (12.8%)
Ghaemi et al. (2010) [99]	70 euthimic BP treated during depressive episode with AD and MS	AD continuation vs. descontinuation	Randomized, open-lable, 1–3 years	New depressive or manic episodes: AD continuation = descontinuation; rapid cycling was associated to more depressive episodes in AD continuation group
Vöhringer et al. (2015) [91]	70 euthimic BP treated during depressive episode with AD and MS	BP type I (n = 21) vs. type II (n = 49) patients	Randomized (AD continuation vs. descontinuation), open-lable, 1–3 years	New depressive or manic episodes: BP type I = type II
El-Mallakh (2015) [100]	68 BP depressed patients who remitted with MS/AD combination	Rapid cycler patients (n = 16) vs. non-rapid cycler (n = 51)	Prospective, randomized (AD treatment stopped after remission or not stopped)	In non-AD stopped group: rapid cycler patients had more depressive episodes; In AD stopped group: no difference between groups
Quitkin et al. (1981) [101]	75 BP type I patients	Li + IMI vs. Li + PCB	Double-blind, randomized, placebo-controlled, 19 months in median	Li + IMI: 2.4 times more manic episodes than Li + PCB
Kane et al. (1982) [42]	22 BP type II patients	Li vs. IMI vs. IMI + Li vs. PCB	Double-blind, randomized, placebo-controlled, 19 months	New episodes prevention: Li > IMI and PCB
Johnstone et al. (1990) [102]	13 depressed BP patients	Li vs. AMI + Li	Prospective, controlled, 3 years	New depressive episodes prevention: Li = AMI + Li
Amsterdam et al. (2015) [104]	55 depressed BP type II patients who responded to VLFX or Li	VLFX (n = 40) vs. Li (n = 15) continuation treatment	Prospective, randomized, controlled, 6 months	Relapse rate: VLFX (7.5%) = Li (26.7%)
Wehr et al. (1979) [103]	5 BP female patients	Li + DSPM vs. Li + PCB	Double-blind, crossover, 27 months (in median)	Li + DSPM: cycles 4 times more frequent
Parker et al. (2006) [40]	10 BP type II patients (depressed or euthymic)	CTLP vs. PCB	Double-blind, randomized, placebo-controlled, crossover 9 months	Depression severity, days depressed or high, % days impaired: CTLP < PCB

(*Continued*)

Table 4. (Continued).

Study	Sample	Design	Methods	Cycle acceleration
Amsterdam et al. (2005) [43]	BP depressed patients remitted with FLX	FLX (continuation) vs. PCB (substitution)	Double-blind, randomized, placebo-controlled, 6 months	Episode relapse: FLX (43%) = PCB (100%)
Amsterdam et al. (2010) [44]	BP depressed type II patients remitted with FLX	FLX (continuation, n = 28) v. Li (substitution, n = 26) vs. PCB (substitution, n= 27)	Double-blind, randomized, placebo-controlled, 50 months	Time to relapse: FLX > Li; FLX = PCB; Li = PCB; Proportion of patients: FLX (32.1%) = Li (57.7%) = PCB (51.9%)
Brown et al. (2009) [59]	410 patients with BP I depression	OFC (n = 205) vs. LMTG (n = 205)	Double-blind, randomized,controlled, 45 weeks	Rate of relapse: OFC (13.7%) = LMTG (18.2%)
Joffe et al. (2002) [90]	69 BP patients (51 type I, 18 type II)	SSRI vs. BUP	Naturalistic, prospective, open-label	SSRI = BUP

AD: antidepressants; AGO: agomelatine; AMI: amitriptyline; BP: bipolar; BUP: bupropion; CTLP: citalopram; DIVAL: divalproex; DSPM: desipramine; ECT: electroconvulsive therapy; FLX: fluoxetine; IDZX: idazoxan; IMI: imipramine; Li: lithium; LMTG: lamotrigine; MCLB: moclobemide; MS: mood stabilizer; OFC: olanzapine/fluoxetine combination; OLZP: olanzapine; PHNZ: phenelzine; PRXT: paroxetine; PCB: placebo; QTP: quetiapine; RISP: risperidone; SSRI: selective serotonin reuptake inhibitors; STRL: sertraline; TNCP: tranylcypromine; UP: unipolar; VLFX: venlafaxine; YMRS: Young Mania Rating Scale

the use of an AD and the occurrence of new manic episodes. Four studies [80,93–95] compared the use of an AD with non-use of this type of substance, and two of them [94,95] found an association between rapid cycling and AD treatment.

Four studies [96–99], with samples formed by bipolar patients who had remission of a depressive episode using an AD associated with a MS, compared patients who continued to use AD with those who interrupted the medication. In three [96–98] of these four studies, there were more depressive relapses between patients who had the AD removed, and in the remaining study [99], there was no difference between the two groups. In one [97] of these four studies, there were more manic episodes in patients with the AD discontinued, and, in the other three studies [97–99], no difference was found between groups. In two studies [99,100] in which a bipolar depressive episode was treated with an AD and a MS, an association was found between rapid cycling and a greater recurrence of depressive episodes in follow-up of patients who maintained the use of AD.

Four controlled studies have addressed tricyclic ADs [42,101–103]. Quitkin et al. [101] found more manic episodes following-up patients with BD who used the lithium/imprimanine combination than those taking lithium associated with placebo. Kane et al. [42], in turn, observed that patients taking imipramine or placebo had more affective episodes than those treated with lithium. In the study by Wehr et al. [103], the lithium/desipramine combination was associated with a greater number of episodes than the lithium/placebo combination. In contrast, Johnstone et al. [102] found no difference between the lithium/amitryptiline combination and the use of lithium monotherapy.

A single study evaluated venlafaxine. Amsterdam et al. [104] found no difference between this AD and lithium regarding the rate of recurrence of affective episodes in a six-month follow-up.

Four controlled studies have addressed the risk of cycle acceleration in the use of SSRIs [40,43,44,90]. With a sample of only 10 patients with BD type II, Parker et al. [40] observed, over a nine-month period, a worse outcome with placebo than citalopram. In two studies [43,44], the samples were composed of patients who had remission of a depressive episode with fluoxetine, which was then maintained or replaced. In these studies, in relation to recurrence rates, fluoxetine was not distinguished from lithium [44] nor from placebo [43,44]. Joffe et al. [90] found no difference between SSRIs and bupropion.

Finally, in the study by Brown et al. [59], olanzapine/fluoxetine combination was not distinguished from lamotrigine in the rate of recurrence of affective episodes.

3.5. Suicidal risk

We found 12 studies addressing the occurrence of suicidal ideation or behavior in patients with BD using ADs (see Table 5).

Two naturalistic studies [105,106] could not find an association between long-term use of ADs and an increased risk of suicidal behavior. In addition, in one of these studies [106], with a follow-up of 27 years, the occurrence of suicidal behavior was more associated with periods when ADs were not used. In contrast, in two retrospective studies [89,107], patients who used an AD alone had a higher frequency of suicidal behavior than those who took the AD in combination with a MS.

Table 5. Suicide.

Study	Sample	Design	Methods	Suicidal risk
Leon et al. (2014) [106]	206 BP type I patients and 139 BP type II patients	Periods with AD vs. periods with not AD	Naturalistic, 27 years	Suicide behavior in BP type I and type II patients: periods with AD < periods with not AD
Bauer et al. (2006) [105]	425 depressed BP patients	AD treatment vs. non-AD treatment	Naturalistic, 18 months	Suicidality not associated to AD treatment
Tundo et al. (2015) [47]	49 BP type I, 52 BP type II and 154 UP depressed patients treated with AD	BP type I vs. BP type II vs. UP depressed patients	Prospective, open-label, 12 weeks	Suicide attempt: 1 BP type I patient
Yerevanian et al. (2007) [107]	405 BP patients	AD vs. MS vs. AD + MS	Retrospective, 3 years in median	Suicidal behavior event rates: AD > AD + MS > MS
Pacchiarotti et al. (2011) [89]	95 BP patients	AD vs. AD + MS	Retrospective and prospective, 10 years in median	Suicide attempts: AD > AD + MS
Sachs et al. (2007) [65]	366 BP depressed patients	AD (PRXT or BUP) + MS (n = 179) vs. PCB + MS (n = 187)	Double-blind, randomized, placebo-controlled, 26 weeks	1 patient with PCB + MS had suicidal ideation
Brown et al. (2009) [59]	410 patients with BP I depression	OFC (n = 205) vs. LMTG (n = 205)	Double-blind, randomized,controlled, 45 weeks	Suicidal attempt ou ideation: OFC, 3 patients; LMTG, 7 patients
Brown et al. (2006) [58]	410 patients with BP I depression	OFC vs. LMTG	Double-blind, randomized,controlled, 7 weeks	Suicidal and self-injurious behavior: LMTG (3.4%) > OFC (0.5%)
Amsterdam et al. (2010) [56]	148 BP type II depressed patients	FLX monotherapy	Open-lable, not controlled, 14 weeks	1 patient (0.7%): suicide attempt
Amsterdam et al. (2010) [69]	17 BP depressed type II patients non-responsive to Li	VLFX replacing previous Li	Prospective, open-label, 12 weeks	No patient
Amsterdam et al. (2008) [76]	83 BP type II depressed patients	VLFX (n = 43) vs. Li (n = 40)	Prospective, randomized, open-label, 12 weeks	1 patient with Li had suicidal ideation
Yatham et al. (2016) [75]	344 BP type I depressed patients	AGO + MS (n = 172) vs. PCB + MS (n = 172)	Double-blind, randomized, placebo-controlled, 8 and 52 weeks	Suicide attempts: 2 patient (1.2%) with AGO + MS, 5 patients (2.9%) with PCB + MS

AD: antidepressants; AGO: agomelatine; AMI: amitriptyline; BP: bipolar; BUP: bupropion; CTLP: citalopram; DIVAL: divalproex; DSPM: desipramine; ECT: electroconvulsive therapy; FLX: fluoxetine; IDZX: idazoxan; IMI: imipramine; Li: lithium; LMTG: lamotrigine; MCLB: moclobemide; MS: mood stabilizer; OFC: olanzapine/fluoxetine combination; OLZP: olanzapine; PHNZ: phenelzine; PRXT: paroxetine; PCB: placebo; QTP: quetiapine; RISP: risperidone; SSRI: selective serotonin reuptake inhibitors; STRL: sertraline; TNCP: tranylcypromine; UP: unipolar; VLFX: venlafaxine; YMRS: Young Mania Rating Scale

Several studies, controlled [58,59,65,75,76] and uncontrolled [47,56,69], found very low rates of suicidal ideation or behavior related to AD use. In two of these studies [65,75], the AD was associated with a MS. Paroxetine, bupropion [65], olanzapine/fluoxetine combination [58,59], fluoxetine [56], venlafaxine [69,76] and agomelatine [75] were the therapeutic options evaluated. Olanzapine/fluoxetine combination was compared with lamotrigine in two studies by the same authors. Each patient group consisted of 205 patients. In the short-term, 7-week study, lamotrigine was more associated with suicidal and self-injurious behavior: 3.4% versus 0.5%, respectively [58]. However, in the 45-week follow-up study, no significant differences were found between the two treatment options [59].

4. AD in the therapeutic guidelines for bipolar depression

The World Federation of Societies of Biological Psychiatry published in 2010 [108] an update of its guidelines for the treatment of BD. The authors set five levels of recommendation. At level 1, they include only quetiapine. At level 2, there is no therapeutic option. At level 3 are fluoxetine, lamotrigine, olanzapine, valproate, olanzapine/fluoxetine combination, the combination of lithium and lamotrigine, modafinil as adjunctive treatment and N-Acetylcysteine associated with a MS. Other ADs appear only at lower levels: sertraline or venlafaxine associated with MS, and tranylcypromine as adjunctive treatment, at level 4; and imipramine associated with lithium, and paroxetine or bupropion associated with MS, at level 5.

The Canadian Network for Mood and Anxiety Treatments and the International Society for Bipolar Disorders have presented therapeutic guidelines for bipolar depression [33]. According to the authors, the first-line options are quetiapine, lurasidone with lithium or divalproex, lithium, lamotrigine, lurasidone monotherapy, and lurasidone as adjunctive treatment. Among the second-line options are divalproex, a SSRI or bupropion as adjunctive treatment, electroconvulsive therapy, cariprazine, and olanzapine/fluoxetine combination.

The International College of Neuro-Psychopharmacology has produced an algorithm to guide the treatment of bipolar depression [109]. As a first step, the options are quetiapine or lurasidone. In the case of an unsatisfactory response, the following step is followed: olanzapine/fluoxetine combination, olanzapine, combination of a MS with lurasidone, modafinil or pramipexole, or lithium plus lamotrigine, replacing the first option; or the addition of escitalopram or fluoxetine. Third step: valproate, aripiprazole, imipramine, phenelzine, lamotrigine or lithium plus L-sulpiride. Finally, the fourth step: tranylcypromine, lithium, venlafaxine plus an antimanic agent, armodafinil or intravenous ketamine with a MS, lithium plus fluoxetine or lamotrigine, levothyroxine plus a MS or lithium plus oxcarbazepine.

The UK National Institute for Health and Care Excellence (NICE) published a clinical guideline on assessment and management of BD in 2014 [110]. Its recommendations regarding the treatment of bipolar depression are as follows. If the depressive episode is of moderate or severe severity and the patient is not taking any medication, olanzapine/fluoxetine combination

or quetiapine should be started as monotherapy. Other options would be monotherapy olanzapine or lamotrigine. If there is no response to olanzapine/fluoxetine combination or quetiapine, consider lamotrigine as monotherapy. If the patient is already using a MS, that is, lithium or valproate, it should be maintained and associated with the above-mentioned options.

The British Association for Psychopharmacology also published guidelines on the treatment of bipolar depression [111]. The therapeutic option with the highest level of recommendation was lurasidone. In a second level, quetiapine, olanzapine/fluoxetine combination, and olanzapine alone were included. Lamotrigine as an adjunctive treatment and ADs were placed at a level well below the others.

The Royal Australian and New Zealand College of Psychiatrists also developed clinical guidelines for the treatment of bipolar depression [112]. According to these therapeutic guidelines, as an initial option, an atypical antipsychotic (quetiapine, lurasidone or olanzapine) or a MS (lithium, valproate or lamotrigine) may be used as monotherapy. If there is no positive response, the antipsychotic or MS may be associated with a MS or AD. In relation to ADs, the following recommendations are made: whenever possible, their use should be avoided; and should not be prescribed if manic symptoms are present, if there is motor agitation or rapid cycling, if BD is type I, or if there is a manic-switch history related to treatment.

The Japanese Society of Mood Disorders [113] recommends, for the treatment of bipolar depression, quetiapine, lithium, olanzapine, and lamotrigine. It also recommends the combination of lithium with lamotrigine and electroconvulsive therapy. Tricyclic ADs and the use of any AD in monotherapy are contraindicated.

The Taiwanese Society of Biological Psychiatry and Neuropsychopharmacology [114] includes as first-line options for the treatment of bipolar depression quetiapine, lamotrigine, and valproate. Lithium monotherapy or in combination with valproate or lamotrigine, and the combination of valproate/lamotrigine are the second-line options. As third-line treatments are olanzapine, olanzapine/fluoxetine combination, quetiapine/SSRI combination, and combination of lithium (or valproate) with an AD (fluoxetine, sertraline, paroxetine or bupropion).

The Indian Psychiatric Society includes a wide variety of options as first-line treatments for bipolar depression [115]. Lithium, lamotrigine, quetiapine, olanzapine/fluoxetine combination, valproate with lithium, valproate with AD, MS or antipsychotics with AD, psychosocial intervention, and electroconvulsive therapy are recommended.

5. Meta-analysis studies on the use of ADs in bipolar depression

Gijsman et al. [116] performed in 2004 a systematic review and meta-analysis of 12 controlled studies, with a total of 1,088 patients randomized. The authors found that ADs were more effective than placebo. The rate of manic switch with ADs was similar to that of placebo, being higher with tricyclic ADs than with the other ADs combined (10% vs. 3.2%).

In the Sidor & MacQueen meta-analysis [117], fifteen studies were included, corresponding to a total of 2,373 patients. The authors concluded that ADs were no superior to placebo or any other option for the treatment of bipolar depression. Regarding manic switch, ADs were not associated to a higher risk than the other therapeutic options.

Vázquez et al. [118] performed a meta-analysis that included 10 placebo-controlled studies of 1,432 depressed bipolar patients. According to the results, the ADs led to a therapeutic response significantly superior to the placebo.

McGirr et al. [119] conducted a meta-analysis of placebo-controlled studies in which a second-generation AD was combined with a MS or atypical antipsychotic. Six studies were found, including a total of 1,383 patients. The authors observed a significant reduction in severity scores of depressive symptoms; however, there was no difference from placebo in rates of clinical response and remission. On the other hand, treatment with ADs was not associated with the risk of manic switch during acute episode, but in the long-term follow-up, this association was found.

In an earlier review article, Peet [120] found a high rate of manic switch with tricyclics (11.2%), superior to that observed with SSRIs (3.7%) or placebo (4.2%). Recently, a systematic review and meta-analysis on manic switch in the treatment of bipolar depression with ADs was carried out. Fornaro et al. [121] found 51 studies, which included 10,098 patients. Treatment-emergent mania rates were 30.9% in retrospective studies, 14.4% in prospective open studies, 11.8% in randomized controlled trials, and 30.9% in cross-sectional studies.

Ghaemi et al. [122] performed a meta-analysis of seven studies that evaluated the long-term use of ADs in BD for at least 6 months. In comparison to the use of a MS alone or with non-treatment, ADs were associated with a lower risk for recurrence of a depressive episode, but a greater risk for the development of a manic episode. However, when the AD/MS association was compared to the use of the stabilizer alone, no differences were found.

In the meta-analysis of Liu et al. [123], long-term studies of at least 4 months with ADs in the treatment of bipolar depression were included. Eleven controlled randomized studies were found, with 692 patients. ADs, combined or not with a MS, were superior to placebo in preventing new depressive episodes without increasing the risk of manic episodes. On the other hand, compared to MS monotherapy, AD monotherapy increased the risk of manic switch and was not effective in preventing new depressive episodes.

6. The debate over the use of ADs in bipolar depression

The issue of the use of ADs in BD represents one of the most controversial in psychopharmacology. For some, these substances are ineffective and dangerous and should only be used as a last resort, but for others they are quite useful, despite some risks [124].

Beyer [18] emphasizes that there are very few placebo-controlled studies on the treatment of bipolar depression with ADs, which leads to many doubts about the efficacy and safety of this therapeutic option. For him, on the face of it, it is a paradox that ADs are so widely prescribed in BD. This probably occurs because of the limited number, poor efficacy, and tolerability of other treatments, and pressure from patients seeking rapid improvement in depressive symptoms.

For Ghaemi [125], based on clinical studies and his personal experience, antidepressants are ineffective in bipolar depression, do not prevent new depressive episodes and lead to mood destabilization after the acute phase. In addition, according to the author, tricyclics and venlafaxine cause mania.

Goodwin [5] believes that bipolar depression has a lower response to antidepressants compared to unipolar depression. Thus, according to him, if a patient with depression needs to use several antidepressants successively to improve, it is likely that he actually has BD.

For Malhi [126] the prescription of antidepressants should be avoided in patients with BD with these characteristics: history of treatment-emergent mania or poor response with this class of medications, manic symptoms during depression and rapid cycling. For other patients with bipolar depression, according to the author, antidepressants could be helpful.

For Azorin & Kaladjian [127], in the acute phase of bipolar depression, antidepressants may be prescribed in the most severe cases and when the risk of manic switch and destabilization is lower. In BD type II, the prescription of antidepressants would be safer, in contrast with what would happen in patients with a history of substance abuse and a high number of previous affective episodes. In the maintenance treatment, according to the authors, antidepressants are useful for a small fraction of patients with type I BD and for a greater proportion of type II patients.

Antosik-Wójcińska et al. [128] conducted a review of clinical studies on the use of antidepressants in bipolar depression. The authors report the increased risk of manic switch in BD type I and with tricyclic antidepressants and venlafaxine. They report that, after treatment of the acute phase, withdrawal of the antidepressant is related to an increased risk of recurrence of depression. In addition, the authors approve antidepressant monotherapy in BD type II.

Pacchiarotti et al. [129] published in 2013 recommendations on the use of antidepressants in BD. According to the authors, in the acute treatment of a depressive episode, adjunctive antidepressants may be used when there is a history of positive response to these substances, but should be avoided if there are concomitant manic symptoms, psychomotor agitation, rapid cycling or a history of treatment-emergent mania. Antidepressant monotherapy is contraindicated, especially in BD type I. In addition, among antidepressants, norepinephrine-serotonin reuptake inhibitors, and tri- and tetracyclics should not be the first option.

Based on a systematic review on the topic, Salvi et al. [130] argue that a portion of patients with bipolar depression may benefit from the use of antidepressants and that the risk of inducing mania is reduced if MSs are associated and tricyclics are avoided. In addition, the continued use of antidepressants after remission of the acute episode may reduce the recurrence of depressive episodes without increasing the frequency of manic episodes.

In a recent review article, Gitlin [22] summarizes the results obtained in clinical studies on the use of ADs in BD. According to him: the efficacy of these substances in bipolar depression is not well established; when associated with MSs, ADs do not induce a manic switch; modern ADs, especially in association with a MS, do not seem to cause cycle acceleration; the use of ADs in patients with type II BD is probably safe; and, finally, a subgroup of bipolar patients develops positively with the AD/MS association in maintenance treatment, without causing instability. Thus, for Gitlin, the question is not whether ADs can or cannot be used in BD, but which are the patients that evolve positively and those that evolve poorly with these medicines.

For Fornaro [131] the results of clinical studies on the treatment of bipolar depression with ADs are contradictory and inconclusive. He believes this is due to the use of different definitions of bipolar depression, methodological limitations of the studies and non-uniform interpretations of the meta-analyzes. In his article, the author emphasizes the idea that the samples are not homogeneous. In that sense, among patients who are experiencing a bipolar depressive episode but do not meet the mixed state criteria, some would have more concomitant manic symptoms than others. Thus, there would be quantitative differences between them and the response to ADs would vary depending on how mixed that depressive episode is, resulting in heterogeneous clinical outcomes.

7. Conclusion

BD is a serious and disabling mental disorder and presents a high prevalence. Depressive episodes occur in both BD and MDD. Based only on symptomatology, that is, without information on previous manic episodes, it is not possible to distinguish bipolar depression from unipolar depression. In BD, depressive episodes are generally more numerous and longer than manic ones. Thus, on average, patients remain much longer in depression than in mania during the course of the disease. Depressive episodes are associated with major occupational impairment, cognitive dysfunction, various comorbidities, and, more seriously, suicidal ideation and behavior. Treatment of bipolar depression is poorly studied. Clinical studies on the treatment of mania, and especially unipolar depression, are much more numerous. Although ADs have a high response rate in unipolar depression, their use in BD is very controversial. For many authors, in bipolar depression, these substances are less effective, cause manic switches and cycle acceleration, and increase the risk of suicide. Despite this, ADs are widely prescribed for the treatment of bipolar depression.

To date, only quetiapine, olanzapine/fluoxetine combination and lurasidone have been approved for the treatment of bipolar depression. In randomized clinical trials, monotherapy olanzapine and cariprazine were superior to placebo. Lamotrigine and lithium, especially as adjunctive treatments, are also considered useful. Finally, electroconvulsive therapy proved to be efficacious in a comparison with drugs in a sample of patients with refractory bipolar depression.

In our review, we found only one study that presented good methodological quality. In all others, there was no comparison with placebo, the sample was too small or the AD was associated with another substance, mainly MSs. Thus, the interpretation of the results of the published clinical studies is quite limited.

Available data indicate that the therapeutic response to ADs in bipolar depression is similar to that observed in unipolar depression. In addition, no differences were found between type I and type II bipolar depression in response to

ADs. However, very few studies have been conducted on these issues. Few studies have also evaluated AD response rates in bipolar depression, but the results were not very different from those found for unipolar depression.

In studies on the therapeutic efficacy in bipolar depression, imipramine was equal to or inferior to MAOIs, did not differ from SSRIs, and was better than or equal to placebo. Fluoxetine was not distinguished from imipramine, olanzapine/fluoxetine combination, olanzapine monotherapy or placebo. Olanzapine/fluoxetine combination was superior to olanzapine monotherapy, lamotrigine, and placebo. In the comparison of sertraline with lithium, venlafaxine or bupropion, no differences were found. Paroxetine was not distinguished from imipramine, venlafaxine, risperidone, MSs, and placebo, and was inferior to quetiapine. Citalopram has proved to be useful as an adjunctive treatment in patients using a MS. Venlafaxine was not distinguished from paroxetine, sertraline, and bupropion, but was superior to lithium. Bupropion was not distinguished from placebo, desipramine, sertraline, and venlafaxine. Agomelatine was no better than placebo.

The incidence of adverse effects does not appear to distinguish bipolar depression from unipolar depression. In studies on the tolerability of ADs in bipolar depression, imipramine was inferior to fluoxetine, but was not distinguished from phenelzine and placebo. On the other hand, this tricyclic was associated with anticholinergic effects, weight gain and sexual dysfunction. Fluoxetine was better tolerated than imipramine, but was not distinguished from lithium and placebo. Olanzapine/fluoxetine combination was less well tolerated than olanzapine monotherapy, lamotrigine, and placebo. Sertraline did not differ from lithium and lithium/sertraline combination. Paroxetine, on the other hand, was similar to imipramine, venlafaxine, a second MS and placebo. Citalopram, bupropion, and agomelatine were not distinguished from placebo. Venlafaxine was as well tolerated as paroxetine or lithium.

As would be expected, some studies have shown that patients with bipolar depression present more manic switches than those with unipolar depression. In addition, BD type I was more associated to treatment-emergent mania than BD type II. The combination of a MS with the AD decreases the risk of switching. In more than one-quarter of the studies on the risk of manic switching with AD, all patients in the samples were using a MD, which is a confounding factor. Therefore, in these studies, the results of comparisons of AD with other AD or with other substances should be considered with caution.

Regarding the rates of manic switches, imipramine was not distinguished from tranylcypromine, moclobemide, paroxetine or placebo. Fluoxetine did not differ from lithium, olanzapine/fluoxetine combination, olanzapine or placebo. Olanzapine/fluoxetine combination did not differ from olanzapine, fluoxetine, lamotrigine or placebo. Paroxetine was not distinguished from imipramine, risperidone, paroxetine/risperidone combination, venlafaxine, a MS or placebo, but was more associated with manic switches than quetiapine. Sertraline presented similar results to those obtained with lithium, sertraline/lithium combination and bupropion. In one study, sertraline was not distinguished from venlafaxine, but, in another, it was less associated with manic switches than venlafaxine. No difference was found in the comparison of venlafaxine with lithium or paroxetine. In one study, venlafaxine was not distinguished from sertraline or bupropion, but, in another, it led to a greater proportion of manic switches. Bupropion did not differ from sertraline, but led to lower manic switch taxes than desipramine and venlafaxine.

Possibly cycle acceleration with the use of ADs is more associated with BD than with unipolar depression, but no difference was found between BD type I and type II. Among the four studies, two evidenced an association between the use of ADs and the development of rapid cycling in patients with BD. On the other hand, however, four other studies have shown that, after an episode of bipolar depression, the maintenance of an AD was not associated with a greater recurrence of affective episodes when compared to the discontinuation of medication. Follow-up of patients taking tricyclic ADs showed cycle acceleration. Surprisingly, venlafaxine was not distinguished from lithium in recurrence of new affective episodes. SSRIs, particularly fluoxetine, were not associated with an increased risk of rapid cycling.

The studies are contradictory as to whether ADs in monotherapy, that is, not associated with a MS, increase the risk of suicide in BD. In any case, rates of suicidal behavior in bipolar patients treated with ADs are quite low. One study found that suicidal or self-injurious behaviors were less frequent with olanzapine/fluoxetine combination than with lamotrigine.

Due to the risk of manic switch and cycle acceleration, ADs are not included or are among the last options for the treatment of bipolar depression by the main therapeutic guidelines.

The meta-analysis studies present divergent results. Two meta-analyses indicated that, in an acute episode of bipolar depression, ADs would be superior to placebo, but two others did not prove the effectiveness of these substances. Regarding the short-term manic-switch risk, no study found differences between ADs and placebo or another drug. However, the use of tricyclics was associated with a higher rate of treatment-emergent mania in comparison with other ADs. Based on long-term studies, some meta-analyzes have concluded that maintaining an AD after the remission of an acute episode reduces the recurrence of depression. On the other hand, the meta-analyzes are divided on whether the prolonged use of ADs would increase the chances of new manic episodes. However, in the vast majority of original studies, the AD was associated with a MS. Moreover, when this association was compared to MS monotherapy, there was no difference. In addition, AD monotherapy was associated with a greater number of manic episodes in the long term, without prevention of new depressive episodes, when

compared to MS monotherapy. Thus, the authors of two meta-analyzes have concluded that MSs, not ADs, would be useful in maintenance treatment.

The authors' opinions on the use of ADs in BD are heterogeneous. Several of them point to the lack of evidence of the efficacy of these drugs, but others admit that these substances may be useful, especially in more severe cases and in BD type II. One reason for not using ADs in BD is the risk of a manic switch. For authors who advocate the use of ADs in BD, this risk is reduced if the substance is associated with a MS; if manic symptoms, rapid cycling and a prior history of treatment-emergent mania are absent; and if venlafaxine and tricyclics are avoided. Finally, regarding the use of ADs as maintenance treatment, the positions are equally divergent. For some authors, ADs cause instability in the course of the disease, but, for others, they can prevent the recurrence of depressive episodes without increasing the frequency of manic episodes, especially if associated with a MS.

The contradictions between the results of the clinical studies and between the conclusions of the review studies and meta-analyses are quite evident. This is likely to be due to the methodological limitations of the vast majority of studies and to the great heterogeneity between studies with regard to methods and patient samples.

On the other hand, we need to mention a major limitation of our review. The topic covered was very broad and the studies reviewed were very heterogeneous, which hinders a critical analysis of the results and a generalization of the conclusions.

8. Expert opinion

Treating bipolar depression is a major challenge in psychiatric practice, something much more complex than treating bipolar mania. Firstly, FDA has approved only four therapeutic options for the treatment of bipolar depression: quetiapine, olanzapine/fluoxetine combination, lurasidone and cariprazine. However, quetiapine and olanzapine/fluoxetine combination are especially associated with weight gain and metabolic disruption as well as sedation, which significantly restricts the prescription of these substances [132]. Lurasidone and cariprazine do not have this adverse effect profile, but it very often causes akathisia [26,133]. In addition, in clinical studies with these drugs, although the reduction in severity of symptoms was significantly greater than with placebo, response rates were not as high: 56.1% with olanzapine/fluoxetine combination [24], 61% with quetiapine [134], 53% with lurasidone [25], and 49.7% with cariprazine [26]. Electroconvulsive therapy, in turn, appears to be as effective in bipolar depression as it is in unipolar depression [37], but its prescription is greatly limited by the stigma associated with this treatment [135].

The authors who condemn the treatment of bipolar depression with ADs, however, do not oppose the use of olanzapine/fluoxetine combination, which contains an AD. We can speculate that most of the AD effect of this combination is due to fluoxetine, an AD. On the other hand, the results of the meta-analysis performed by Wen et al. [136] demonstrate that the augmentation of ADs with atypical antipsychotics in patients with MDD is better than placebo in improving response and remission rates. Blockade of 5-HT 2 receptors may be related to an alleged AD effect of atypical antipsychotics, particularly olanzapine [137], which in the study by Tohen et al. [24], was superior to placebo in the treatment of bipolar depression, although inferior to olanzapine/fluoxetine combination. However, according to the same meta-analysis [136], the addition of an atypical antipsychotic to an AD entails higher rates of withdrawal due to adverse effects. In relation to weight gain and the metabolic syndrome, olanzapine appears to be worse than the other atypical antipsychotics [132]. Another problem related to olanzapine/fluoxetine combination is related to the long half-life of this AD [138]. Fluoxetine, like other SSRIs, is less associated with manic switches than the tricyclics and venlafaxine. In addition, the association with an antimanic agent, olanzapine [139], further reduces the chances of inducing a manic episode. However, if despite everything the manic switch occurs, withdrawal of fluoxetine will only aid in reversing the manic episode after an excessively long time. Thus, although the association between an atypical antipsychotic and an AD in the treatment of depression seems to be interesting, the choice of olanzapine and fluoxetine has some drawbacks. Clinical studies evaluating the efficacy of the combination of another atypical antipsychotic, more tolerated, with another SSRI, with a shorter half-life, would be most welcome.

On the other hand, in a recent review of randomized clinical trials on the treatment of bipolar depression, Vázquez et al. [140] classified ADs, especially the more modern ones, as the option with the most favorable risk/benefit ratio, considering efficacy and tolerability. In a relatively recent meta-analysis, Taylor et al. [141] recommended SSRIs, among other options, for the treatment of bipolar depression and, moreover, stated that tricyclic ADs are effective.

It is a fact that the effectiveness of ADs in bipolar depression has not been proven. However, to date, this issue has not been adequately tested. In only a single large controlled study, the AD was used alone and compared with placebo [45]. Thus, it is also not possible to say that this type of substance is useless in BD.

As ADs are associated with high response rates in unipolar depression [2], which, concerning symptomatology, is identical to unipolar depression [4], it could be assumed that they would be the best option for the treatment of bipolar depression, just below electroconvulsive therapy, if there was no risk of mania switching or cycle acceleration. Tricyclics and venlafaxine are associated with higher rates of treatment-emergent mania. A review of the results of randomized studies and meta-analyzes that directly compared two ADs found that clomipramine, venlafaxine, and escitalopram had demonstrated superior efficacy to the others in MDD treatment [142]. So, we can speculate that the higher the AD action of a substance, the greater the likelihood of it inducing a manic switch. Therefore, if the medicine is very good, paradoxically this is bad. Consequently, psychiatrists are forced to use a lower therapeutic option, either a less effective AD or another type of substance, such as an atypical antipsychotic or a MS.

In clinical practice, we often find patients with bipolar depression who, after attempts at various therapeutic options, only present a positive response when using an AD, often a tricyclic. A significant portion of these patients do not present a manic switch induced by this medicine. After remission of the depressive episode, one issue to be resolved is about how long the AD should be maintained. Meta-analysis studies indicate that maintaining the AD in the long term would prevent the recurrence of depressive episodes, but they are divided as to the risk of new manic episodes. We have observed that the manic switch occurs more frequently in the first few days after the introduction of the AD and that, if it does not occur immediately, the tendency is also that it will not occur in the medium term. The challenge in clinical practice, however, is to be able to identify previously that patients will not present a treatment-emergent mania.

Despite the great controversy over whether ADs should be used in depression, there is a relative consensus on what care should be taken in relation to the prescription of these substances to reduce the risk of a manic switch. According to the findings of several meta-analyses and review articles, ADs are safer in type II than type I BD; and should be avoided in patients who are experiencing mixed depression, in those who have had previous episodes of treatment-emergent mania and in rapid cyclers. SSRIs should be preferred over tricyclics and venlafaxine and should be associated with a MS or an atypical antipsychotic. Besides these guidelines, in our personal practice, we consider two other elements as indicative of the non-use of ADs in a bipolar depressive episode: the recent occurrence of a manic episode and, in relation to the course of the disease, manic predominant polarity.

We identify with Gitlin's position [22]. For him, the question is not whether it is correct or not to use ADs in bipolar depression, but to which patients these substances may be beneficial and to which ones are harmful. Fornaro's opinion [131] is somewhat similar. For him, patients with bipolar depression are very heterogeneous, because some of them have more, while others have less, mixed characteristics, which would lead to a great variety of responses to the treatment with ADs.

Authors such as Angst [143] and Goodwin [5] question the categorical approach to bipolar/unipolar distinction. For them, according to the concept of bipolar spectrum, a dimensional approach, which takes into account quantitative differences, would be more valid. Thus, BD type I and MDD (or unipolar depression) would be the extremes of a continuum. Consistent with this position, we believe that patients suffering from a mood disorder are heterogeneous not because some are bipolar and others are unipolar, but because the level of bipolarity is variable. That is, some patients would be 'more bipolar' than others. For example, if the patient has, as characteristics, manic predominantly polarity, a history of early onset of illness and of very numerous and short affective episodes, rapid cycling, the presence of manic symptoms during depressive episodes, a hyperthymic or cyclothymic temperament, a family history of BD, a good response to lithium and the occurrence of manic switches induced by ADs, then he or she would be 'very bipolar'. Alternatively, if the patient does not have these characteristics or has opposite characteristics, he would be 'very little bipolar'. Between these two extremes, there would be innumerable levels of bipolarity. There could even be 'almost nothing bipolar', but never a non-bipolar, that is, a unipolar, even if the patient had never had a manic or hypomanic episode. This conception would explain the wide range of responses to ADs in bipolar depression. Thus, the 'more bipolar' a patient is, the more likely manic switches and cycle acceleration would occur due to treatment with an AD.

Funding

This paper was not funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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