Psychiatr. Pol. 2015; 49(6): 1223–1239
PL ISSN 0033-2674 (PRINT), ISSN 2391-5854 (ONLINE)
www.psychiatriapolska.pl
DOI: http://dx.doi.org/10.12740/PP/37914

Efficacy and safety of antidepressants' use in the treatment of depressive episodes in bipolar disorder – review of research

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Summary

The use of antidepressants in treatment of depression in course of bipolar disorders (BD) is controversial. In case of no improvement during monotherapy with mood stabilizer, the use of antidepressants is often necessary. The safety of this group (in context of phase change, mixed states and rapid cycling) is essential and is the subject of many research. In the paper, the authors review the literature concerning efficacy and safety of antidepressants use in the treatment of affective disorders and long-term impact on the course of the disease. Selection of articles has been made by searching the Medline and Pubmed databases using keywords: antidepressant drugs, bipolar depression, bipolar disorder, efficacy, safety, mania, hypomania. The risk of mania is greater in bipolar disorder type I, than in type II or during treatment with Tricyclic antidepressants (TCAs) and treatment with venlafaxine. The use of SSRIs and bupropion is associated with a relatively small increase of phase change risk. There are different opinions concerning recommended duration of antidepressant treatment. Generally the use of antidepressant should end after 2–3 months of remission, the risk of recurrence of depression after discontinuation of antidepressants is, however, higher than in case of continuation. In BD type II or BD spectrum, antidepressant monotherapy is allowed in severe depression. In bipolar disorder type I and in case of phase change after the use of antidepressants in the past, use of antidepressants should be very cautious. Antidepressants are contraindicated in rapid cycling and in mixed episodes. Further work is needed to evaluate the efficacy and safety of antidepressants use.

Key words: bipolar disorder, antidepressant drugs, bipolar depression

The study was not sponsored.

Introduction

In the course of bipolar disorder (BD) appear both hypomanic or manic episodes and depressive episodes. In the natural course of the disease, the depressive episodes appear on average 3 times more often than hypomanic and manic episodes [1–4]. Depression is associated with an increased risk of suicide [5] and impaired psychosocial functioning. [6] First generation mood stabilizers, such as lithium carbonate, valproic acid and carbamazepine, and second generation mood stabilizers such as atypical antipsychotics, are effective in mania prevention, but are not always sufficiently effective in the treatment of depressive phases. Mood stabilizer with proven antidepressant efficacy is quetiapine, also lamotrigine and –according to some researchers – olanzapine. Lithium also has therapeutic effect in a bipolar depressive episode. It is effective in reducing suicidal thoughts and tendencies, what is particularly important in this group of patients. The use of antidepressants in the treatment of depressive episodes in the course of BD is controversial (in context of their efficacy, safety, phase change, mixed states induction and long-term influence on the course of the illness, including a risk of rapid cycling), although this group of drugs is commonly used in the population of patients with the diagnosis of bipolar disorder.

Literature data indicate that the induction of phase change to hypomania or mania is associated with aggravation of the course of the illness [7]. This is important in assessing the suitability of this group of drugs in the treatment of bipolar disorder [8–15]. In this paper, the authors review the literature concerning the efficacy and safety of the use of antidepressants in the treatment of affective disorders, mainly focusing on the use of antidepressants in the treatment of bipolar disorder. Selection of articles has been made by searching the databases Medline and Pubmed using keywords: antidepressant drugs, bipolar depression, bipolar disorder, efficacy, safety, mania, hypomania. Among the selected publications authors chose papers concerning the treatment of depressive episodes in bipolar disorder with the use of antidepressants.

The efficacy of antidepressants in bipolar disorder

The results of a prospective study conducted by Bottlender et al. [16], which included 50 patients with a diagnosis of bipolar disorder and 50 patients with unipolar depression, did not confirm that antidepressants were less effective in a population of patients with bipolar depression than in unipolar depression. Amsterdam et al. [17] compared the efficacy of fluoxetine, olanzapine and combined fluoxetine plus olanzapine therapy in the treatment of depressive episodes in the course of bipolar disorder. 34 patients with bipolar disorder were randomised to treatment with fluoxetine, olanzapine, the combination of fluoxetine with olanzapine and placebo-treated group of patients. The assessment of mental state was conducted with the use of the 28-point Hamilton Depression Rating Scale (HAM-D28) Montgomery–Asberg Depression Rating Scale (MADRS) and the Young Mania Rating Scale (YMR). In all study groups similar significant improvement in mental state has been shown.

In another study, Amsterdam et al. [18] demonstrated that fluoxetine monotherapy, compared to the lithium and placebo monotherapy, is effective in preventing the recurrence in the population of patients with bipolar II disorder. The risk of recurrence in the group treated with fluoxetine was two times lower than in the group treated with lithium. Current experts' guidelines do not recommend antidepressant monotherapy in the treatment of depressive episodes in the course of bipolar II disorder. This is in contradiction with clinical practice, because according to research antidepressants are most often used by clinicians in the treatment of depression in bipolar II disorder.

Amsterdam et al. [19] also showed that in the group of patients with no improvement during monotherapy with lithium adding venlafaxine may give good results. In this study, group of 40 patients was treated with lithium monotherapy at first. In the group of patients who did not respond to treatment, adding venlafaxine gave a significant improvement in mental state [19].

The effectiveness of antidepressants in bipolar disorder was also confirmed in the study of Vieta et al. [20]. The authors evaluated the efficacy of venlafaxine or paroxetine in patients with depression in the course of bipolar disorder receiving mood stabilizers. The randomised study included 60 patients, 30 people received paroxetine and 30 – venlafaxine. To assess the efficacy of treatment the 17-item Hamilton Depression Rating Scale (HAMD-17), Clinical Global Impression (CGI), and the Young Mania Rating Scale (YMS) were used. The efficacy of both drugs was similar [20]. In a different double-blind, placebo-controlled study, Sachs et al. [21] obtained different results. Analysing the improvement and remission rates in the groups treated with paroxetine or bupropion in combination with mood stabilizers in comparison with placebo and mood stabilizer monotherapy, no statistically significant difference was observed. The observation period was 26 weeks. Antidepressant therapy was not more effective in patients with bipolar II disorder in comparison to the patients with bipolar I disorder. Parker et al. [22] tried to answer the question of whether SSRIs have mood stabilizing potential. The study included 10 patients with a diagnosis of bipolar II disorder, who had never received psychotropic drugs. After 3 months without active treatment, participants were randomly assigned to 2 groups. The first group of patients received placebo, while the second group received escitalopram in a dose of 10 mg/d for 3 months. After 3 months the conversion of both groups was made, showing that treatment with escitalopram was associated with a reduction in depressive symptoms, improvement of functioning, reduction in the number of days of depression and a decrease in the number of days with elevated mood compared to placebo [22]. Of course, it is difficult to generalise on the basis of such a small group of respondents.

In 2007 Agosti and Stewart [23] published the results of a randomised, placebo-controlled study, which compared the efficacy of therapy with imipramine and phenelzine (MAO inhibitor – MAOI). The randomised study involved 70 people with a diagnosis of bipolar II disorder, which were divided into two groups. In the first group, patients received imipramine 250 mg/d, and in the second – phenelzine 6 mg/d. Response to the treatment was observed in 57% of patients treated with imipramine and 52% of patients treated with phenelzine. In the placebo-group response was observed only in 23% of respondents.

In 2010 Pihatsch et al. [24] published the results of a study comparing the effectiveness of adding paroxetine or amitriptyline in patients currently treated with lithium. The study involved 40 people with a diagnosis of bipolar I/II disorder. Patients were randomly assigned to two groups receiving paroxetine or amitriptyline. Observation of the mental state lasted 6 weeks. Both treatments were equally effective, reduction of the scores in the Hamilton Depression Rating Scale was observed (14.9 for paroxetine and –15.5 for amitriptyline). In the group receiving paroxetine treatment effect was observed earlier, from 3rd week of the treatment. Treatment with paroxetine was associated with a lower risk of side effects.

McElroy et al. [25] compared the efficacy in the treatment of depressive episodes of paroxetine monotherapy (20 mg/d) and quetiapine monotherapy (at a dose of 300–600 mg/d). Assessment made after eight weeks of treatment showed no statistically significant improvement in the reduction of depressive symptoms in the group treated with paroxetine in comparison to placebo, however, in the group receiving quetiapine a significant improvement was observed.

A comprehensive meta-analysis published by Sidor et al. [26] found no benefit from the use of antidepressants (bupropion, tricyclic antidepressants, venlafaxine) in the treatment of bipolar depression compared to placebo and drugs from other groups [26].

As regards to the effectiveness of antidepressants in the treatment of bipolar depression and unipolar depression, the results of studies conducted by Tondo et al., published in 2012, are worth mentioning [16]. Researchers assessed the course of the illness in the group of 1,036 patients diagnosed with depression. Patients were treated in the Mood Disorders Centre in Cagliari. 878 patients received treatment with antidepressants, 93 patients (10.6%) were diagnosed with bipolar II disorder, 117 (13.3%) were diagnosed with bipolar II disorder, and 668 (76.1%) with unipolar depression. 158 patients were not enrolled for treatment with antidepressants, because of the predominance of manic episodes. The criterion for inclusion in the study was to obtain at least 14 points in the 21-item Hamilton Depression Rating Scale (HDRS-21). The results of treatment were evaluated on the basis of the reduction of the score in HADRS-21. Criterion of response was at least 50% decrease of the score in the scale, and the criterion of remission was less than 7 points in HDRS-21. The results showed a better response to treatment in patients with a diagnosis of bipolar I/II depression than in the group with unipolar depression. The time required to achieve remission in patients with a diagnosis of bipolar I/II depression was shorter than in the group of patients with a diagnosis of unipolar depression.

Another issue is to evaluate the efficacy of antidepressant after obtaining remission of depressive symptoms. Ghaemi et al. [27] carried out STEP-BD study that showed no significant benefit of continuation of antidepressant medication after remission. In the group treated with antidepressant, time to onset of a new episode of depression was indeed longer, but the treatment did not reduce the incidence of new depressive episodes, compared to the group that received only mood stabilizers [27].

The results of studies concerning the efficacy of antidepressants in bipolar disorder are summarised in Table 1.

Table 1. **The effectiveness of antidepressants in bipolar disorder**

Study	Subject	Group size	Results	Comments
Bottlander et al. [40]	Assessment of antidepressants in bipolar disorder and unipolar depression treatment	50 patients with bipolar disorder, 50 patients with unipolar depression	Similar effectiveness in both groups	Prospective study
Amsterdam et al. [17]	Assessment of fluoxetine, olanzapine and combination of fluoxetine and olanzapine effectiveness	32 patients with bipolar I disorder and 2 patients with bipolar II disorder	Similar effectiveness in 3 groups. No increase in the risk of phase change was observed during antidepressants monotherapy	Randomised and double-blind study
Amsterdam et al. [18]	Assessment of fluoxetine and lithium treatment effectiveness in recurrence prevention in comparison with placebo	81 patients, 28 receiving fluoxetine, 26 receiving lithium, 27 receiving placebo	Recurrence risk was twice smaller during treatment with fluoxetine in comparison with lithium treatment	Randomised and double-blind study
Amsterdam et al. [19]	Assessment of effectiveness and safety of venlafaxine in a group of patients with bipolar II disorder previously treated with lithium with no remission	40 patients treated with lithium; 17 patients with bipolar II disorder treated with venlafaxine (previously treated with lithium with no remission)	Significant improvement after venlafaxine implementation	Open study, no placebo control
Vieta et al. [20]	Assessment of effectiveness of adding paroxetine or venlafaxine to mood stabilizer	60 patients with bipolar disorder; 30 with paroxetine, 30 treated with venlafaxine	Adding AD was effective in depression reduction	Randomised study
Sachs et al. [21]	Assessment of effectiveness of paroxetine or bupropion in combination with mood stabilizer	366 bipolar patients; 187 patients receiving placebo + mood stabilizer, 179 patients receiving AD + mood stabilizer	Effectiveness of AD in comparison to mood stabilizer + placebo was not proved	Randomised and double-blind study
Parker et al. [22]	Comparison of effectiveness of escitalopram compared to placebo	10 patients with bipolar II disorder	Reduction of depressive symptoms in escitalopram group. The use of escitalopram did not affect the risk of phase change	Study without randomisation and placebo control

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Agosti et al. [23]	Effectiveness of phenelzine or imipramine compared to placebo	70 patients with bipolar II disorder	Effectiveness of the treatment with phenelzine or imipramine compared to placebo	Randomised and double-blind study
Phitash et al. [24]	Effectiveness of implementing treatment with amitriptyline or paroxetine in a population of patients receiving lithium	40 patients with bipolar I/II disorder	Similar effectiveness in both groups	Randomised study
McElroy et al. [25]	Effectiveness of quetiapine in comparison with paroxetine and placebo	740 patients with bipolar I/II disorder; 245 patients treated with quetiapine 300 mg/d, 247 patients treated with quetiapine 600 mg/d, 122 patients treated with paroxetine 20 mg/d, 126 receiving placebo	Quetiapine was more effective in comparison with paroxetine and placebo	Randomised and double-blind study
Sidor et al. [26]	Effectiveness of ADs in bipolar depression treatment	meta-analysis of (15 studies 1,469 patients)	Treatment with ADs was not more effective than treatment with other drugs or placebo	Randomised and double-blind study
Tondo et al. [16]	Effectiveness of ADs in bipolar and unipolar depression treatment	873 patients; 93 patients with bipolar I disorder, 117patients with bipolar II disorder, 668 patients with unipolar depression	ADs treatment was more effective in bipolar patients	
Ghaemi et al. [27]	Effectiveness of ADs in preventing recurrence of depression	70 patients with bipolar I disorder, 32 patients treated with ADs after remission, 38 patients not continuing ADs treatment after remission	ADs treatment was not effective in preventing depression in comparison to treatment with mood stabilizers	Randomised study

The safety of the use of antidepressants in bipolar disorder

The relationship between the use of antidepressants and the occurrence of episodes of abnormally elevated mood was observed after the introduction of imipramine treatment in the 1950s [28–30]. The occurrence of high mood episode during antidepressant treatment may indicate that a primary diagnosis of a single episode of depression or unipolar disorder was a mistake. This situation often occurs in young patients during their first episode of depression [31]. The risk factors of high mood episode are: the occurrence of excessive agitation during antidepressant treatment [32–34], as well as the early age of onset [35, 36] and cyclothymic [37] or hyperthymic [38] type of temperament.

Current guidelines for treating bipolar depression in the course of bipolar I and bipolar II disorder recommend avoiding the use of antidepressants because of the risks of inducing a phase change, however, studies conducted in recent years indicate that this risk during treatment with SSRIs may be less than commonly believed.

In a study conducted by Leverich et al. [39] authors observed phase change to hypomania in 11.4% patients and to mania in 7.9% patients during 10 weeks of acute phase treatment after adding antidepressant medication to the treatment with mood stabilizers. The authors compare the risk of phase change in the treatment with sertraline, bupropion and venlafaxine and estimate that the risk is the highest for venlafaxine and the smallest for bupropion [28]. The risk of phase change may be higher because of the dual mechanism of action of venlafaxine (an inhibitor of serotonin and noradrenaline reuptake) compared to SSRIs (selective serotonin reuptake inhibitors) or dopaminergic actions of bupropion.

Tondo et al. [16] evaluated the course of illness in 1,036 patients diagnosed with depression in the course of bipolar disorder and unipolar depression. In the study group 878 patients were taking antidepressants, 93 patients were diagnosed with bipolar I disorder and 117 with bipolar II disorder, 668 were diagnosed with unipolar depression. 158 patients were not enrolled for the treatment with antidepressants, because of the predominance of manic phases. The risk of phase change to hypomania, mania or mixed episode during the three-month treatment with antidepressants was 15.8% in the group with a diagnosis of bipolar II disorder, 8.60% in the group with bipolar I disorder and 0.56% in the group with unipolar depression (probably the primary diagnosis was incorrect). In patients with a diagnosis of bipolar II disorder phase change occurred 4 weeks earlier and in the group of patients with bipolar I disorder 8 weeks earlier than in a population of patients with a diagnosis of unipolar depression. The authors pointed out that, paradoxically, the risk of phase change was greater among patients who received antidepressants in combination with mood stabilizers. Of course, it is possible that mood stabilizers were recommended in these patients who before the start of the study had evaluated risk of phase change. Summing up, the results of studies conducted by Tondo et al. indicate at least good antidepressant efficacy in the treatment of bipolar depression, but such treatment is not fully safe. The occurrence of phase change is higher in AD group than spontaneous phase change that occurs in approx. 3% of people with bipolar disorder who do not receive antidepressants [16].

Bottlender et al. [40] in a prospective study, involving a total of 100 patients (50 with a diagnosis of bipolar disorder and 50 with unipolar repression) assessed the efficacy and safety of antidepressants in the course of bipolar depression and unipolar depression. In the study group mania occurred in 12% of patients with bipolar disorder [40].

In the study of Amsterdam et al. [17] 34 patients with bipolar disorder were randomly assigned to treatment with fluoxetine, olanzapine, fluoxetine in combination with olanzapine and placebo-treated group of patients. Treatment with fluoxetine monotherapy and in combination with olanzapine was not associated with an increased risk of mania [17].

In another study conducted by Amsterdam et al. [18], authors showed that fluoxetine monotherapy was not associated with significant risk of phase change even in comparison with lithium and placebo [18].

In accordance with the works of Amsterdam [19] adding venlafaxine in the treatment of patients who did not achieve the improvement of mental state during lithium monotherapy is not associated with a significant increase in the risk of phase change.

In a meta-analysis conducted by Gijsaman et al. [41], researchers demonstrated the effectiveness of bipolar depression treatment with antidepressants. The meta-analysis of four randomised controlled trials, involving a total of 662 patients showed significant increase of response and remission rate in patients taking antidepressants compared to placebo group, but the majority of patients in the active treatment group also received mood stabilizers. The risk of phase change for SSRIs was 3.2% and was not significant compared to placebo, whereas in the group treated with TCAs phase change occurred in 10%.

According to Gijsaman et al. [41] SSRIs are not only effective in the treatment of depression in the course of bipolar disorder, but also the risk of phase change during treatment is low. Presented meta-analysis was widely commented, it was pointed out that a small risk of a phase change could be related with the short observation period, a large proportion of patients with bipolar II disorder and the fact that the majority of respondents received antidepressants in combination with mood stabilizers.

McElroy et al. [25] analysed the results of the study EMBOLDEN II and noted that in a population of 740 patients with bipolar disorder treatment with paroxetine was not associated with significantly increased risk of phase change [25].

Viktorin et al. [42] using the Swedish national registries assessed the risk of phase change after using antidepressants as monotherapy and in combination with mood stabilizers [42]. The study involved 3,240 patients with a diagnosis of bipolar disorder, of which 1,641 were treated with combination therapy: mood stabilizer + antidepressant and 1,117 were treated with antidepressant monotherapy. The risk of phase change was greater in patients treated with antidepressants monotherapy, while in the group receiving mood stabilizers an increased risk of manic episodes was not observed during 3 months of therapy. In the period from 3 to 9 months of adding antidepressant to mood stabilizer the risks of phase change significantly decreased [42].

In a meta-analysis conducted by Tondo et al. [43] authors demonstrated that antidepressant treatment increases the risk of phase change both for bipolar and unipolar disorder, phase change was observed in 15.3% of patients with bipolar disorder, and

in 5.97% of the subjects with a diagnosis of unipolar depression (it should be understood that the diagnosis was erroneous). In the group which was not treated with antidepressants phase change was observed in 13.8% of patients with bipolar disorder and in 1.24% of patients treated for unipolar depression. Surprisingly, the results of the study did not confirm the beneficial effect of mood stabilizers in the prevention of mania, both in the group receiving them as monotherapy or in combination with antidepressants. These results can be explained by the fact that mood stabilizers were used in a group of severely ill patients with a higher risk of spontaneous phase change, and the follow-up period was too short (5 months). The determination of the potential long-term benefits associated with mood stabilizers use could not be observed in such a study with so short follow-up period [43].

A meta-analysis conducted by Sidor et al. [26] analysed the safety of antidepressants in the treatment of depressive episodes in the course of bipolar disorder compared to placebo and drugs from other groups. Results of the study have not shown that treatment with antidepressants was associated with a significant increase of phase change risk. It is also noted that in the observed population phase change occurred in the group receiving bupropion less often than in the group treated with TCA or SNRI (venlafaxine) [26].

As part of the STEP-BD study, Christine et al. [44] evaluated the risk of phase change during treatment with an antidepressant. Prospective study, which involved 338 patients with bipolar disorder receiving antidepressants, showed that phase change occurred more often in a group of patients with short history of illness, with a history of multiple antidepressant treatments and history of phase change during antidepressant treatment. In the 12-week follow-up phase change occurred in 44% of patients [44].

The study conducted by Vieta et al. [20] involved 60 patients, 30 people were randomly assigned to a group receiving paroxetine and 30 to a group receiving venlafaxine. Phase change occurred in 13% of patients receiving venlafaxine, and only in 3% of patients treated with paroxetine.

The double-blind, placebo-controlled study conducted by Sachs et al. [21] did not show that treatment with antidepressants was associated with an increased risk of phase change [21] in groups treated with paroxetine or bupropion in combination with mood stabilizers, compared to the placebo group and patients receiving mood stabilizers as monotherapy. The observation period was 26 weeks.

The results of recent studies (2014) published by Leon et al. [45] assessing the risk of suicide during treatment with antidepressants in a group of 206 subjects with a diagnosis of bipolar I disorder and 139 people with bipolar II disorder, indicate that in patients with bipolar I disorder antidepressant treatment reduces the risk of suicide attempt by an average of 54%. Also, patients with bipolar II disorder had benefits from taking antidepressants – researchers found that in the periods in which patients received antidepressants occurred up to 35% less suicidal attempts than in the periods when the patients were taking mood stabilizers only. In a group of patients with unipolar depression no beneficial effects of antidepressants on the risk of suicide were observed. The study was a long-term, multicentre, prospective study with a 27-year follow-up period. The results indicate that treatment with antidepressants can have a protective effect in the population of patients with bipolar disorder, significantly reducing the risk of suicide.

The risk of inducing a phase change is different for bipolar I and bipolar II disorder. Most studies evaluated the efficacy and safety of antidepressants in bipolar I disorder. According to some experts, bipolar I and bipolar II disorders are so different from each other in terms of the course of the illness that should be treated almost like two different illnesses. In one of the publications analysing the risk of phase change during the treatment of acute phase with monotherapy of antidepressant in patients diagnosed with bipolar I and bipolar II disorder, David et al. [46] demonstrated that the risk of phase change was greater in bipolar I disorder than in bipolar II disorder. The phase changed in 14.2% of patients with bipolar I disorder and only in 7.1% of patients with a diagnosis of bipolar II disorder. The authors also reported that the observed episodes of elevated mood in the group of patients with bipolar II disorder were less severe and met the criteria for hypomania [46]. The authors suggest that antidepressants are safer in the treatment of depressive phases of bipolar II disorder. Therefore, the guidelines for the treatment of bipolar I and bipolar II disorder should be different and take into account the different course of the illness.

When it comes to safety of the use of antidepressants in the context of the occurrence of mixed states conclusions are based on the results of two retrospective observational studies [47, 48] which found that the use of antidepressants in bipolar disorder both lifetime and during the last six months was associated with a higher incidence of mixed states. The study of US population [49] found that 32% of patients with bipolar I disorder who have experienced an episode of mania or mixed state, were treated with antidepressant during the period prior to this episode. Antidepressant treatment was associated with more frequent hospitalisations in the 12 months of follow-up.

The results of studies concerning the safety of the use of antidepressants in bipolar disorder are summarised in Table 2.

Table 2. **The safety of the use of antidepressants in bipolar disorder**

Study	Subject	Group size	Results	Comments
Leverich et al. [39]	The risk of phase change after adding antidepressant to mood stabilizer	159 patients with bipolar disorder, 50 people receiving bupropion, 50 receiving sertraline 59 people receiving venlafaxine	Phase change to hypomania occurred in 11.4% of patients, in 7.9% to mania during10 weeks of observation	The greatest risk of phase change for venlafaxine, the smallest for bupropion
Tondo et al. [16]	The risk of phase change during the treatment with antidepressants in a group of patients with bipolar I disorder, bipolar II disorder and unipolar depression	93 patients with bipolar I disorder, 117 with bipolar II disorder, 668 with unipolar depression	Phase change risk was 15.8% in bipolar II disorder group, 8.60% in bipolar I disorder 0.56 % in unipolar depression group	Study without randomisation and placebo control

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Bottlender et al. [40]	Assessment of effectiveness and safety of depressive episodes therapy with antidepressants	50 patients with BD, 50 patients with RD	Phase change in 12% bipolar patients	Prospective study
Amsterdam et al. [17]	Assessment of phase change risk during fluoxetine, olanzapine and combined fluoxetine + olanzapine treatment	34 patients with bipolar disorder	Treatment with fluoxetine and fluoxetine with olanzapine did not increase phase change risk	Randomised and double-blind
Amsterdam et al. [18]	Assessment of phase change risk during treatment with lithium, fluoxetine compared to placebo	81 bipolar II patients treated with fluoxetine, 28 patients treated with lithium, 28 with placebo	No phase change risk increase during treatment with fluoxetine compared to treatment with lithium and placebo	Randomised and double-blind study
Amsterdam et al. [19]	Assessment of effectiveness and safety of venlafaxine in a group of patients previously treated with lithium with no remission	17 patients with bipolar II disorder treated with venlafaxine, 40 patients treated with lithium	Venlafaxine was effective and did not increase phase change risk	Open study, without placebo control
Gijsmann et al. [41]	Effectiveness and safety of bipolar depression treatment with ADs	662 BD patients, meta-analysis of 4-studies	No phase change risk increase during treatment with SSRIs; during treatment with tricyclic antidepressants phase change was observed in 10% patients	Most patients received also mood stabilizers
Viktorin et al. [42]	Phase change assessment in a group treated with ADs monotherapy and in combination with mood stabilizer	3,240 bipolar patients; 1,641 receiving AD+mood stabilizer , 117 treated with AD monotherapy	The risk of phase change was higher during monotherapy with antidepressants	

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Tondo et al. [43]	Phase change risk assessment during the treatment with ADs	114,521 patients, 56,212 receiving ADs, 58,309 not receiving ADs, 7,915 patients was diagnosed with bipolar disorder, 102,501 with unipolar depression	Phase change risk increase in a group treated with ADs. In bipolar group treated with ADs phase changed in 15.3%, in bipolar group not treated with ADs phase changed in 1.8% of patients	
Sidor et al. [26]	Assessment of safety during bipolar depression treatment	meta-analysis f 15 studies (1,469 patients)	No phase change risk increase during treatment with ADs in comparison to placebo and other drugs	Randomised study. The lowest phase change risk in bupropion group
Christine et al. [44]	Phase change risk assessment during treatment with ADs	338 patients with bipolar disorder	Phase change risk increase	Prospective study
Vieta et al. [20]	Phase change risk assessment after adding venlafaxine or paroxetine in a group treated with mood stabilizer	60 patients with bipolar disorder; 30 treated with venlafaxine, 30 with paroxetine	Phase change risk was higher during treatment with venlafaxine (13%), small risk during treatment with paroxetine (3%)	No placebo control
Sachs et al. [21]	Phase change risk assessment after adding AD to mood stabilizer compared to placebo	179 patients receiving AD + mood stabilizer, 187 patients receiving placebo + mood stabilizer	No phase change risk increase after adding AD compared to placebo	Placebo-controlled and double-blind study
David et al. [46]	Phase change risk assessment after adding antidepressant in bipolar I and bipolar II group	777 patients; 462 patients with disorder, 315 with bipolar II disorder	Significant phase change risk increase in bipolar I group (14.2%) in comparison to bipolar II group (7.1%)	

Recapitulation

The use of antidepressants in bipolar depression treatment is still controversial. In the course of bipolar disorders depression is more common than episodes of mania/

hypomania [50, 51], for this reason the effective treatment of depression is essential not only for psychosocial and professional functioning of subjects, but also for the course of illness and prognosis. Treatment of bipolar depression is difficult, requiring proper and thorough assessment of the current clinical state and in-depth analysis of the course of the illness. Results of researches indicate that antidepressants are potentially efficient in the treatment of bipolar depression. Literature data are also confirmed by naturalistic clinical observations. In case of lack of improvement during monotherapy with mood stabilizer, the use of antidepressants is often necessary. The safety of antidepressants in the context of phase change risk, mixed states and rapid cycling induction is essential and this is the subject of many current studies. It should be noted, however, that most of these studies does not analyse the population of patients with bipolar I and bipolar II disorder separately, which seems to be the most appropriate due to the course of the illness. Also, considering the whole group of antidepressants is inappropriate, because the risk of phase change is different for TCAs, SSRIs and SNRIs. Risk of mania induction may be higher in patients with bipolar I disorder than bipolar II disorder, and during the treatment with tricyclic antidepressants and venlafaxine monotherapy [52, 41]. In view of the studies, it appears that the use of SSRIs, trazodone and bupropion is associated with relatively low risk of phase change. When it comes to the use of mirtazapine and mianserin in bipolar disorder, these drugs seem to be as safe, and perhaps safer, as SSRIs and bupropion, but there are no double-blind studies, which could confirm the data from the clinical observations. There are different opinions concerning recommended duration of antidepressant treatment. Generally antidepressant treatment should end after 2–3 months of the remission [53]; the risk of recurrence of depression after discontinuation of antidepressants is, however, higher than in case of continuation [54, 55]. The potential benefits of the use of anti-depressive drugs may refer to patients with a predominance of depressive phases and a history of a positive response to treatment with antidepressants. In bipolar II disorder or BD spectrum antidepressant monotherapy is allowed in severe depression. In bipolar I disorder and in case of phase change after the use of antidepressants in the past, use of antidepressants should be very cautious. Antidepressants are contraindicated in rapid cycling and in mixed episodes [56, 57].

The conclusions from the presented studies coincide with the recommendations of the International Society for Bipolar Disorders (ISBD) [58]. Antidepressants may be used for an acute bipolar I or bipolar II disorder depressive episode when there is a history of previous positive response to antidepressants. These drugs should be avoided in depressive episode with two or more concomitant core manic symptoms in the presence of psychomotor agitation or rapid cycling. When it comes to maintenance treatment antidepressants may be considered if a patient relapses into a depressive episode after discontinuation of antidepressant therapy [56]. Antidepressant monotherapy should be avoided in bipolar I and bipolar II in depression with two or more core manic symptoms. To minimise the risk of switch to mania, hypomania, or mixed states and rapid cycling, bipolar patients starting antidepressants should be observed for signs of hypomania or mania and increased psychomotor agitation, in which case antidepressants should be discontinued. The use of antidepressants is not recommended

when there is a history of mania, hypomania, or mixed episodes during antidepressant treatment in the past. The use of antidepressant should be avoided in bipolar patients with a high mood instability and high number of episodes.

According to ISBD recommendations antidepressants should also not be used during mixed states and in a population of bipolar patients with predominance of mixed states [58].

Treatment with SNRIs or tri- and tetracyclics should be considered only after other antidepressants have been tried, and needs special caution [58].

Due to the small number of studies and ambiguous results, some differences in the opinions of experts on the risk of phase change and aggravation of the course of the illness, further work is needed to evaluate the efficacy and safety of the use of antidepressants. It seems necessary to search for new effective therapies and optimising existing therapeutic strategies.

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