Review article

Treating bipolar depression – antidepressants and alternatives: a critical review of the literature

Tundo A, Cavalieri P, Navari S, Marchetti F. Treating bipolar depression – antidepressants and alternatives: a critical review of the literature.

Objective: Although depressive symptoms are preponderant in the course of bipolar (BP) disorders, the treatment of BP depression remains a controversial issue with different clinical approaches available. This review addresses the issues of whether antidepressants (ADs) are effective in treating acute and long-term BP depression, risks linked to ADs and what alternatives to ADs are available.
Methods: We searched the MEDLINE databases using the following syntax: [bipolar depression AND unipolar depression AND (antidepressants OR anticonvulsants OR lithium OR antipsychotics OR dopamine-agonists OR psychoeducation OR psychotherapy OR electroconvulsive therapy OR transcranial magnetic stimulation)]. The search included studies published up to 31 May 2009 and conducted on adults.
Results: In the acute treatment of BP depression ADs are effective with no differences among drug classes. However, neither the switch into (hypo)mania induction rate nor the suicide risk linked to AD use are definitely established. The effectiveness of long-term AD use is limited to highly selected samples of patients with positive acute response. The risk of long-term ADs causing cycle acceleration and rapid cycling induction concerns a subpopulation of patients. Valid alternatives to ADs in treating acute BP depression are quetiapine, an olanzapine–fluoxetine combination, and electroconvulsive therapy for more severe patients. Lamotrigine is effective and safe in preventing depressive relapses. Psychotherapy and psychoeducation represent effective adjunctive treatments.
Conclusion: In the treatment of BP depression there is not a specific effective treatment for all the patients. Interventions should therefore be personalised and the scientific evidence should be adapted to each patient's clinical features.

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Introduction

Bipolar (BP) disorder is a debilitating, chronic illness presenting depression as its predominant mood state (1–5). The depressive phase recurs more frequently and lasts longer than (hypo)mania (2,3,6,7); it also typically presents marked suicide attempts and completed suicide risks (8) and causes a greater disruption in patients' daily functioning (including work, social life and family life) (6).

Despite the prevalence of depressive symptoms in BP disorders, the acute and long-term treatment of BP depression remains a controversial issue and different approaches have been investigated. Different guidelines (9,10) and several authors (11,12) recommend a conservative use of antidepressants (ADs), by limiting their prescription to more severe and more resistant episodes (10) and always in combination with mood stabilisers (9,10). Moreover, Ghaemi

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et al. (11) recommend that AD use be discontinued as soon as feasible after symptom remission, underscoring that the gold-standard therapy for moderate- and mild-severity episodes is treatment with lithium or lamotrigine. Restrictions on the use of ADs are in fact justified by both the high AD non-response rate in the acute treatment of BP depression and the risk of switching into (hypo)mania and cycle acceleration/rapid cycling (11).

Conversely, however, World Federation of Societies of Biological Psychiatry (WFSBP) guidelines (13) and Möller et al. (14,15) claim that ADs in combination with mood stabilisers should represent the core treatment for BP depression. These authors maintain that studies examining AD use in the acute phase of BP depression have yielded more solid evidence of efficacy than mood stabiliser efficacy studies have, and that the risk of cycle acceleration is currently over-estimated, when compared to the risk of suicidal behaviour (14,15).

Given the controversial issue of BP depression treatment, the purpose of this article was to respond to the following questions, in light of literature findings:

1 How effective are ADs in treating acute BP depression?
2 What risks are linked to short-term AD treatment in BP depression?
3 How effective are ADs in preventing depressive relapses?
4 What are the risks of long-term AD use in BP patients?
5 What alternative treatments to ADs are available? How effective are they?

Methods

This article is based on a review conducted by an electronic search of the relevant literature published from January 1972 to May 2009 on MEDLINE, Pubmed. Keywords were [bipolar depression AND unipolar depression AND (antidepressants OR anticonvulsants OR lithium OR antipsychotics OR dopamine-agonists OR psychoeducation OR psychotherapy OR electroconvulsive therapy OR transcranial magnetic stimulation)]. The search was limited to studies conducted on adult patients. Other citations of interest were further identified from references reported in the accessed articles.

Results

AD efficacy in treating acute BP depression

ADs versus placebo and ADs versus ADs. Gijsman et al. (16) have systematically analysed the few studies available examining acute AD efficacy (as monotherapy or in combination with a mood stabiliser) versus placebo. The authors conducted a meta-analysis of five randomised, controlled, double-blind trials by comparing short-term AD treatment (4–10 weeks) to placebo in patients with BP depression (DSM IV-TR criteria) (17–21). The ADs examined (selegiline, tranilcipromine, fluoxetine, imipramine and paroxetine) showed higher efficacy than placebo did. Indeed, two studies (22,23), examining bupropion versus placebo, showed evidence for the effectiveness of bupropion as first AD choice in BP depression. Yet, Gijsman et al. (16) excluded these two studies from their meta-analysis because their inclusion criteria were based on the DSM II diagnosis of 'BP depression', which corresponds to the modern criteria (DSM-IV-TR) of 'recurrent major depression'.

With respect to the issue of the specific efficacy of different AD classes in the short-term treatment of BP depression, the few randomised and double-blind studies published showed that monotherapy with tranilcipromine was more effective than monotherapy with imipramine (24,25). Conversely, no efficacy differences were observed in studies comparing moclobemide versus imipramine (26); bupropion versus desipramine (4,27); venlafaxine versus paroxetine (28) and sertraline versus venlafaxine versus bupropion (29). The ADs examined in these studies were always in combination with a mood stabiliser.

The literature available shows that ADs are more effective than placebo in the short-term treatment of BP depression and that different classes of AD present a similar efficacy profile.

ADs in BP depression versus unipolar depression. Preliminary research data indicate that unipolar (UP) depression and BP depression are distinct nosological entities with their own specific biological substrates (30,31). Ghaemi et al. (32) have hypothesised that ADs may be less effective in treating BP depression than they are for UP depression. Yet, little evidence concerning the relative efficacy of ADs on the two subtypes of depression is available to date.

The few studies published on the topic have shown that venlafaxine is equally effective in the short-term treatment of both UP and BP-II depression (33,34). Moreover, in a large naturalistic cohort of 2032 consecutively admitted inpatients with UP and BP-I depression, it was found that, even after considering different outcome criteria, ADs were similarly effective in treating the two subtypes of depression (35). In line with these results are findings by Bottlender et al. (36) who found similar response rates between UP and BP depressed inpatients matched by age, gender and illness duration. All

participants were treated with ADs and BP patients were also given mood stabilisers or antipsychotics. Indeed, a double-blind study on the short-term treatment (6 weeks) of depression found no differences in the response rates of patients with BP-II versus UP depression (37).

Conversely, in Ghaemi et al.'s (32) retrospective observational study examining 41 patients with BP-I and BP-II depression and 37 patients with UP depression who were all taking ADs, BP patients were found to have lower response rates at 4 weeks than UP patients did, and patients with UP depression relapsed more frequently after discontinuing ADs. These effects were similar for different classes of ADs and were not dependent on the use of a mood stabiliser in BP patients. The authors interpreted their findings by concluding that ADs are less effective in short-term treating BP than UP depression.

Although discordant, the available data tend to support the hypothesis of equivalent antidepressant efficacy in the short-term treatment of both UP and BP depression. Owing to limited evidence, however, further research is required to confirm these conclusions.

ADs plus mood stabiliser versus mood stabiliser alone. One randomised study found that the adjunctive treatment with an AD (paroxetine) was as effective as adjunctive treatment with a second mood stabiliser [lithium or valproate (AV)] in BP-I and BP-II depressed patients ($n = 27$) already taking a mood stabiliser (lithium or AV) (38). Similarly, a double-blind, placebo-controlled study showed, in a retrospective evaluation, that the short-term (26 weeks) addition of paroxetine or bupropion to mood stabiliser therapy ($n = 179$) conferred no benefits over the addition of placebo ($n = 187$), in terms of stable recovery (39).

Nemeroff et al. (20) showed that the antidepressant efficacy of paroxetine or imipramine–lithium combination in BP depressed patients was higher than a placebo–lithium combination. This difference, however, was observed only in patients with low serum lithium levels (<0.8 mequiv./l). The authors, therefore, concluded that antidepressant treatment might represent useful adjunctive therapy for BP patients who are unable to tolerate high lithium concentrations.

Conversely, however, Tohen et al. (21) found that, over 8 weeks, in a randomised, double-blind study of 833 patients with BP-I depression, the antidepressant efficacy of the olanzapine (7.4 mg/die) plus fluoxetine (39.3 mg/die) combination (OFC) was superior to both olanzapine monotherapy (9.7 mg/die average dosage) and placebo. Similarly, a randomised, double-blind study of 410 patients with

BP-I depression found that OFC was more effective than lamotrigine, over 7 weeks of treatment (40).

Although discordant, the results from the few literature studies available suggest not a greater efficacy for an AD-mood stabiliser combination than for mood stabiliser monotherapy.

AD efficacy in BP type I and II depression. To our knowledge, the literature available provides a paucity of information regarding how BP diagnostic subtypes influence the efficacy of ADs. In two distinct studies, Himmelhoch et al. (24) and than Silverstone (26) found that BP-I and BP-II depressed patients had comparable response and remission rate. In the other studies there was no direct comparison between two groups.

The findings are few and do not enable to define a role of antidepressant treatment in the two subtypes.

What risks are linked to short-term AD treatment in BP depression?

Switch. The literature regarding depression to (hypo)mania switches generally focuses on the issues of how frequently the phenomenon occurs, how the risk varies in function of AD class, the potential role of mood stabilisers in preventing switch and what its clinical predictors might be. Two literature reviews (41,42) estimated that the switch risk in patients with BP disorder treated with ADs can soar from 10 to 70% and from 20 to 40%, respectively. It is not clear, however, whether the reported switch phenomenon is part of the natural history of BD, whether it worsens the course of an already severe illness or whether it might result from a *de novo* adverse drug event (43). In fact, findings from some studies suggest that the switch rate is independent from AD administration and therefore that AD use does not necessarily worsen the course of illness (14,44–47). In Gijsman et al.'s (16) meta-analysis and in Sachs et al.'s (39) double-blind, placebo-controlled study, short-term AD treatment was associated with a switch risk that did not significantly differ from placebo (3.8 and 4.7% in Gijsman et al.'s study (16), 10.1 and 10.7% in Sachs et al.'s study (39), respectively). Similarly, two prospective studies (44,48) showed that the switch rate was independent from AD administration and a review literature (49) suggested that the AD-mood stabiliser combination did not increase the switch rate when compared with that of mood stabiliser alone. Some studies have found that switch risk differs by AD class and is higher for tricyclic ADs (TCAs) (11.2–33%) and lower for selective serotonin reuptake inhibitors (SSRIs) (3.7–12%) (36,50–52). The lowest risk has been reported for paroxetine in combination with mood stabilisers (20,28,38). Results for venlafaxine are controversial: two studies showed

higher switch rates than for paroxetine (28) and for bupropion and sertraline (53), respectively, but a third study found no switch effects (33). Many open clinical trials (54–56) conducted with small sample sizes have highlighted that bupropion use is associated with a low risk of switch induction and cycle acceleration. Moreover, two controlled double-blind, randomised trials showed a significantly lower incidence of bupropion-induced mania than rates observed for desipramine (27) and venlafaxine (53).

It is still unclear whether mood stabiliser use might reduce the risk of switching or not. One study attributed this protective function exclusively to lithium (57), but other studies (36,58) have shown that anticonvulsants present the same property. Furthermore, the results of one study (20) suggested that mood stabilisers prevent only spontaneous switch, but findings from another two studies suggested that mood stabilisers prevent only AD-induced switch (39,51).

Several studies have addressed potential risk factors for AD-related switching. The data yielded thereof show that female gender, depression-mania-interval episode sequence, substance abuse, depressive mixed state, high number of previous depressive episodes and previous AD trials, all predict (hypo) manic switch during AD treatment (29,57,59–65).

Switch in BP type I and II depression. Several (49,66) but not all (67) studies show that the relative risk of AD-switch induction is greater in BP I than in BP II disorder. Recent meta-analysis (66) found that AD association switch in BP I and II disorders in acute trials were 14.2 and 7.1% respectively. Yet, Licht et al. (49) in a review literature found that the risk of AD switch induction is greater in BP I than in BP II disorder receiving the same treatment modalities.

There is evidence that ADs may induce hypo (mania) in a subgroup of BP patients with specific risk factors and in BP I patients. Indeed, the switch risk is higher with TCAs than with other AD classes. Moreover, the issues of AD induction rates and of whether mood stabiliser use might reduce switch risk remain unclear.

Suicide. There is a lack of knowledge about the effect of ADs on suicidal behaviour in patients with BDs. Some studies (68–70) suggest a potentially higher risk of suicidal behaviour in adolescent and adult patients with depression treated with ADs (particularly, with SSRIs), and other studies have not observed this type of association (71,72).

Specifically, with respect to BP depression, a retrospective study found that patients treated with ADs had significantly higher rates of suicidal behaviour than patients on mood stabilisers without AD treatment did (73). Indirect evidence suggests that ADs may induce suicidal behaviour specifically in a subset of with BP depression patients with anxious features and that this type of induction might be prevented by the co-administration of lithium (74).

Conversely, two studies (75,76) specifically assessing the effect of ADs on the suicidality of patients with BP depression failed to reveal a significant correlation between AD administration and suicidal ideation or attempts (75,76). Indeed a retrospective study examining a sample of patients with BP-I and II depression found that AD treatment improved depressive symptoms and also suicidal ideation in patients with major depression, independently from diagnosis (77). AD treatment in this study was also associated with an emerging suicidal ideation rate that was below the reported general population rate.

Although controversial, the available evidence does not clearly support the hypothesis that ADs increase the risk of suicidality in adults with BP depression. Further prospective randomised studies are needed to explore the association between AD exposure in BP depression and the rate of new onset suicidal ideation and suicidal behaviours.

Efficacy of ADs in preventing depressive relapse

There is an evident disparity between the broad empirical clinical use of ADs for preventing depressive relapses in BD and the American Psychiatric Association (APA) guideline recommendation to discontinue AD within the first 3–6 months after the remission of depression (10).

A metanalysis of seven randomised controlled trials examining the long-term (up to 6 months) efficacy of ADs in BP depression suggested that long-term adjunctive AD treatment was not superior to the use of mood stabiliser alone in preventing BP depressive relapses (78).

Conversely, data from observational studies (79,80) indicate that AD discontinuation significantly increases depressive relapse risk within 1 year, as compared to combined AD-mood stabiliser treatment. Furthermore, the risk of relapse into mania did not appear to be associated with AD therapy continuation.

In particular, a randomised study concluded that patients achieving a positive acute AD response to an AD-mood stabiliser combination will maintain response with the same continued treatment (81). Moreover, this study's switch rate into mania with continued AD treatment did not differ from the natural switch rate.

Results are controversial between naturalistic studies, indicating the effectiveness of ADs in preventing depressive relapses, and randomised studies,

failing to observe such effect. These differences may be because of the fact that the naturalistic studies presented highly selected samples (i.e. patients showing positive acute response to ADs and requiring long-term AD treatment on clinical judgment) predominately under SSRIs or new generation ADs. Therefore, the results cannot be generalised to all patients with BDs and to all AD classes.

What are the risks of long-term AD treatment in BP depression?

Cycle acceleration and rapid cycling course. Although there is no general consensus on the issue (82), some authors suggest that long-term AD use in patients with BDs might induce mood destabilisation and a relapse rate increase of up to four episodes per year (i.e. rapid cycling) (83). The statement that AD use in patients with BDs is associated with rapid cycling (83) is supported by findings from three earlier, randomised clinical trials examining TCA use (50,84,85) and from several naturalistic studies (7,32,86–91). Nevertheless, one large-scale naturalistic study did not observe an association between AD administration and cycle acceleration (92) and the hypothesised interaction has been recently questioned elsewhere (83,93).

These discordant results could indicate that not all patients with BDs are prone to cycle acceleration during AD treatment, but that only a specifically predisposed subpopulation are.

Reports on long-term AD use are limited and do not allow for a clear association of AD use with cycle acceleration and rapid cycle course.

What alternative treatments to AD are available? How effective are they?

Given the controversial issue of AD use in BP depression, several observational and experimental studies have focused on examining the antidepressant efficacy of other treatments.

Mood stabilisers

Lithium. The APA practice guidelines (10) cite lithium as the first-line treatment for acute BP depression. A preliminary, open-label study of a small sample of patients ($n = 10$) yielded a 70% rate of positive response to lithium (94) and five double-blind trials showed lithium to be superior to placebo in treating BP depression, although lithium actually showed rather low antidepressant efficacy (95–99). Moreover, lithium is the only documented drug that has shown specific suicidality prevention efficacy in individuals affected by BP depression (100,101).

Yet, one literature review (102) concluded that the antidepressant efficacy of lithium monotherapy in BDs is less impressive than frequently claimed. Some authors have reported full antidepressant activity with serum lithium levels of >0.8 mequiv./l, although this value also tends to be linked to a low tolerability profile (20).

With respect to maintenance studies, two meta-analyses found only equivocal support for the proposal that lithium treatment reduces the risk of depressive episodes (103,104).

Lamotrigine. The APA guidelines (10) recommend the use of lamotrigine (LMT) as a first-choice treatment alternative to lithium in BP depression. Regarding the issue of acute efficacy, a systematic review and metanalysis (105) from randomised controlled trials compared LMT and placebo and found evidence that LMT has a beneficial effect on depressive symptoms in BP depression. The pool effect was modest, although the advantage over placebo was larger in more severely depressed patients. LMT was found to be as effective as lithium in a randomised open label monotherapy with either LMT or lithium for the acute (16 weeks) treatment of BP-II depression (106). Moreover, LMT added to lithium therapy was found to be more effective than lithium plus placebo in treating BP depression (107).

With respect to long-term efficacy, recent literature reviews report the efficacy of LMT in decreasing depressive BP symptoms and in preventing relapse (108,109).

Other anticonvulsants. Several small-scale randomised blinded studies suggest the acute (110,111) and long-term (112) efficacy of AV in BP depression, although no adequately powered studies examining this topic have yet been conducted.

Studies examining the effects of carbamazepine are few and have been inadequately conducted to determine the possible effectiveness (113), and other anticonvulsants (gabapentin and topiramate) have shown little or no effectiveness in treating BP depression (114–117).

Dopamine-agonists

Pramipexole. One study (118) examined 21 patients with BP-II depression treated with either lithium or AV and randomly assigned to additional treatment with pramipexole (PMX) or placebo for 6 weeks. PMX showed a significantly higher antidepressant effect than placebo did (60 and 9%, respectively), with low switch rates into (hypo)mania. These findings are consistent with the results of two preliminary studies on treatment-resistant depression (119,120).

Indeed, more recently, a systematic review (121) found that PMX had a large effect size in the treatment of BP (and also UP) depression, with a low short-term rate of switch into (hypo)mania.

Modafinil. In a 6-week randomised controlled trial, adjunctive modafinil was significantly better than placebo in improving depressive symptoms in patients with BP depression who had not responded to lithium or to AV, with or without concomitant ADs (122).

Atypical antipsychotics

Olanzapine. An olanzapine–fluoxetine combination (OFC) showed an AD efficacy over 8 weeks that was superior to both olanzapine monotherapy and placebo (21) in patients with BP-I depression. Indeed OFC was more effective than LMT even when associated with more treatment-emergent adverse events, greater weight gain and some elevated metabolic factors in the acute treatment of BP-I depression (40). Similarly, a study confirmed the superior efficacy of OFC versus LMT in improving depressive symptoms in patients with BDs (123).

With respect to the issue of maintenance treatment in BP depression, OFC showed greater symptom improvement over 25 weeks than LMT did, although the relapse incidence in the OFC group did not significantly differ from that of the LMT group (124).

Quetiapine. The results from two randomised studies (the BOLDER studies) confirmed a significantly higher antidepressant efficacy for quetiapine monotherapy (600 or 300 mg/die) than for placebo in BP-I and II depression, as well as acute antisuicidal properties, with no increase in induced mania risk. A positive response was observed for rapid cycling patients (125,126): a *post hoc* analysis of the Bolder studies' results confirmed the superior efficacy of quetiapine versus placebo in terms of acute antidepressant efficacy and other measures, such as quality of life (127–130).

Other antipsychotics. Some studies have observed that risperidone can improve depressive symptoms in patients with BP and schizoaffective disorder (131–133), although these findings require further validation.

A randomised placebo-controlled study showed that aripiprazole monotherapy was not significantly more effective than placebo over 8 weeks in the treatment of BP depression (134), and findings on aripiprazole augmentation in treatment-resistant depression have been controversial (135,136).

Physical treatment

Electroconvulsive therapy. Electroconvulsive therapy (ECT) is an evidence-based option for BP depression and achieves response rates ranging from 43 to 100% (137,138). Its use is currently limited to patients with severe and psychotic depression, especially those at high suicide risk. It is also a valuable treatment option for BP depression that does not respond to pharmacological treatment (139–141) and for pregnant women with BP depression (142).

Repetitive transcranial magnetic stimulation. The efficacy of repetitive transcranial magnetic stimulation (rTMS) in treating BP depression has been little investigated. Specifically, only three controlled studies have been published to date and two of these were limited by small sample size (143–145). The largest study (144), a single-blind, randomised, sham-controlled trial, conducted over 2 weeks in 23 patients with BP-I and II depression failed to find a statistically significant antidepressant superiority for left dorsolateral prefrontal cortex rTMS. A recently conducted open-label study, however, found that augmentative low-frequency rTMS was effective and well tolerated in a small sample of patients with drug-resistant BP depression (146).

Psychotherapy and psychosocial intervention

Little is known about the specific role of psychotherapy in managing acute BP depression. To our knowledge, only one psychotherapy study specifically examining the treatment of acute BP depression has been published. This trial (147) showed Interpersonal and Social Rhythm Therapy to be a promising form of monotherapy intervention for a subset of individuals presenting acute BP-II depression (7 of 17 responders). The small sample size and absence of a control group, however, limited the generalisability of the findings.

A number of psychological and psychosocial forms of intervention have been tested as adjunctive therapies to pharmacological treatment for BP prophylaxis, i.e. individual and group psychoeducation, systematic care, family focused therapy, cognitive behaviour therapy, interpersonal and social rhythm therapy (148). Overall, the available data shows that treatment emphasising medication adherence and early recognition of mood symptoms has a stronger influence on manic relapse rates. Conversely, treatment focusing on cognitive and interpersonal coping strategies has a stronger impact on depressive relapse rates.

The available literature suggests that pharmacological alternatives to ADs for treating acute BP depression are still quite limited. The evidence supports the

efficacy of quetiapine monotherapy and, to a lesser extent, that of OFC. The efficacy of lithium and LMT seems less impressive than claimed to be. PMX has shown promise for intervening in treatment-resistant depression and ECT has been confirmed as a valuable antidepressant alternative, although currently, its use is limited to more severe patients.

With respect to the issue depressive relapse prevention, LMT shows evidence of being effective and safe, but the data on lithium remain controversial. Moreover, psychosocial intervention has been shown to be effective as adjunctive treatment.

Discussion

The treatment of BP depression represents a challenge for clinicians having to rely on contradictory and frequently limited scientific evidence when attempting to manage this severe psychopathological condition, which also presents high suicidality and disability risks. Nevertheless, a critical evaluation of the literature can yield several useful indications for clinical practice.

ADs are the first-line treatment for most patients with acute BP depression. Some, but not all, studies show that ADs are more effective than placebo and are as effective in treating BP depression as they are for UP depression, with no AD class differences observed. Moreover, there is no clear evidence of increased suicide risk for adult patients with BP depression using ADs. In susceptible individuals, ADs and especially TCAs may induce a depression-to-mania (or -hypomania) switch, but there is no current consensus on whether mood stabilisers can prevent this phenomenon.

Overall, there are suggestions that ADs might have a greater utility in patients with BP-II than BP-I depression since there is greater tolerability and less risks of switching.

The studies reviewed also suggest the efficacy of quetiapine monotherapy and, to a lesser extent, of OFC as the best pharmacological option in treating acute BP depression. Although ECT is the best validated non-pharmacological alternative to AD use, because of stigma, a scarcity of specialised centres and younger clinicians' limited experience with the technique, ECT is used exclusively for severe or treatment-resistant forms.

Long-term AD use is a more complex issue, given that AD treatment to avoid depressive recurrences is not suitable for all patients, as shown by the negative results yielded by randomised controlled trials. Nevertheless, a subpopulation of patients with BDs requires long-term adjunctive AD therapy in combination with mood stabilisers, as shown by the naturalistic studies examining this topic. A

key problem with long-term AD use – especially TCA use – can be that of rapid cycling induction. This course, however, concerns a restricted group of individuals with specific susceptibility, given that the rapid cycle pattern occurs in 5–15% of patients with BDs and is not related to AD use ('spontaneous rapid cycling') in more than one third of this subgroup percentage (90). Hence, when considering the serious, although infrequent, risk of cycle acceleration, clinicians should carefully monitor the follow-up of patients on AD maintenance and should be ready to modify the therapeutic strategy before rapid cycling sets in.

LMT, in monotherapy or in association with lithium, is effective in preventing depressive relapses; the data on lithium, however, remain controversial. Structured psychosocial intervention is an important component of the long-term management of BP depression and should be used in conjunction with pharmacotherapy.

Conclusion

In conclusion, no specific treatment for all patients with BP depression is currently available. In clinical practice, treatment should be highly personalised by taking the scientific evidence into consideration and adapting it to each patient's clinical features. In light of the available evidence, we believe that the issue is not whether ADs should or should not be used, but in what circumstances and for which patients.

The current lack of data on the biological, demographic and clinical characteristics of BP patient subgroups responding to various antidepressant strategies requires that further research be conducted on the topic.

Acknowledgement

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