ANTIDEPRESSANT ACTIVITY OF MOOD STABILIZERS

Janusz K. Rybakowski

Abstract

There is some evidence that the efficacy of antidepressant drugs in both unipolar and bipolar depression is decreasing and also for a possible usefulness of mood-stabilizing drugs in the pharmacotherapy of both these depressive states. In past two decades the number of drugs fulfilling the criteria for a mood stabilizer i.e. a drug which favourably influences mood abnormalities in bipolar disorder. has greatly increased. This article examines the utility of mood stabilizers, both classic (lithium, carbamazepine, valproate) and those of the second generation (atypical antipsychotics and lamotrigine) as antidepressants, in the treatment and prophylaxis of depression in bipolar and unipolar mood disorders. Clinical data show that lithium, quetiapine and lamotrigine are useful in the treatment and prophylaxis of bipolar depression and that they may have some therapeutic effects in the acute episode, as well as in the prophylaxis of unipolar depression. On the other hand, lithium, carbamazepine, atypical antipsychotics and lamotrigine have all been shown to augment antidepressants in treatment-resistant depression, both bipolar and unipolar.

Key words: mood stabilizer, antidepressant drug, unipolar depression, bipolar depression, lithium, quetiapine, lamotrigine

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A crisis of confidence in antidepressants

The introduction to psychiatry of antidepressant drugs in the 1950s made a breakthrough in the therapy of depression. Also, studies on the pharmacological mechanisms of antidepressant action made an important contribution to the understanding of the pathogenesis of depression, especially for the role of neurotransmitters such as serotonin or of catecholamines. To a much lesser extent, they paved the way for the introduction of antidepressant drugs with novel mechanisms of action. Half of century after their introduction, the results of some studies performed in the last decade have caused some undermining of the value of antidepressant drugs in the treatment of depression, both in the course of recurrent major depressive disorder and in bipolar mood disorder (bipolar depression).

The main goal of treatment of the acute episode of major depressive disorder is achieving remission. However, the results of the American STAR-D* study showed that such an effect, after 3 months of antidepressant monotherapy is achievable in only one third of depressed patients. (Trivedi et al. 2008). Some meta-analyses have shown that, in mild-to-moderate depression, the placebo-antidepressant drug difference is fairly small (Fournier et al. 2010). Furthermore, in recent years, the number of patients with treatment-resistant depression (defined as a lack of response after two adequate treatments with antidepressant drugs) has been growing. The percentage of such patients has been estimated as being 10-30% (Al-Harbi 2012), and the options in them include optimization, substitution, combination or augmentation of antidepressant treatment (Joffe et al. 1996). Among methods of augmenting antidepressants, an important place has been given to mood stabilizing drugs, both classic ones such as lithium as well as novel substances showing mood-stabilizing properties such as atypical antipsychotics or lamotrigine.

Severe doubts have been raised about the use of antidepressants in bipolar depression. As early as the late 1980s, Akiskal and Mallya (1987) suggested the clinical importance of the concept of a bipolar spectrum, based on the fact that even a subtle bipolarity may not respond well to antidepressants. Seventeen years later, Ghaemi et al. (2004) analyzed the clinical records of an antidepressant trial of 41 patients with bipolar depression and 37 with unipolar depression, similar in age and sex distribution. They found that short-term non-
response was significantly more frequent in bipolar (51.3\%) than in unipolar (31.6\%) depression. Furthermore, in an American study published in 2007, it was demonstrated that depression in bipolar mood disorder may be, to a great extent, “insensitive” to antidepressants. The paradigm was a comparison of adding an antidepressant, or a placebo, to the mood stabilizer in bipolar patients during a depressive episode. After 26-week observation a durable recovery was obtained in 23.5\% of those subjects receiving a mood stabilizer plus adjunctive antidepressant therapy (paroxetine or bupropion), but a similar improvement was noted in 27.3\% of subjects receiving a mood stabilizer plus a matching placebo (Sachs et al. 2007).

On the other hand, several studies and reviews indicate that antidepressants may be equally effective in bipolar as in unipolar depression. This was demonstrated in a naturalistic study of 2032 patients comparing bipolar I and unipolar ones (Möller et al. 2001), in a research of 50 bipolar and 50 unipolar patients (Bottlender et al. 2002) as well as in review of twelve randomized trials including 1088 patients (Gijsman et al. 2004). Amsterdam and Garcia-Expola found similar short-term efficacy of venlafaxine in bipolar II and unipolar depressed women, and Baldessarini et al. (2007) reported that during 2000-2003 in the USA, antidepressants were prescribed to 50\% of bipolar patients.

A number of studies have been performed showing the relationship between features of bipolarity and an inferior response of depression to antidepressant drugs. The all-Poland multicenter study with the acronym TRES-DEP (treatment-resistant depression) performed in the year 2007 was specifically designed to test any association between bipolarity and treatment-resistant depression. One thousand and fifty-one patients entered the study, classified into non treatment-resistant (NTR) depression (482 patients) and treatment-resistant (TR) depression (569 patients). The groups did not differ as to age, gender, education and marital status. However, the indices of bipolarity assessed according to the Hypomania Checklist-32 (HCL-32) and the Mood Disorder Questionnaire (MDQ) were significantly higher in the TR group (Rybakowski et al. 2011). In a separate analysis of TRES-DEP it was found that treatment-resistance was also associated with earlier onset of depression and more depressive episodes, the features apparently connected with bipolarity (Dudek et al. 2010). A recent review of the literature performed by Correa et al. (2010) included 196 articles published in the decade 1998-2008. It strongly suggests that in a population of treatment-resistant depression patients there are high rates of hidden bipolar disorder. Furthermore, in patients diagnosed with bipolar mood disorder, antidepressants may not be robustly effective and are poorly tolerated.

In the past 20 years, the number of drugs fulfilling the criteria for a mood stabilizer has greatly expanded. At the same time these drugs are being increasingly used for the augmentation of antidepressants in treatment-resistant depression and some have been shown to possess antidepressant activity, either as monotherapy or in combination. This has resulted in a gradual focus on the possible usefulness of mood-stabilizing drugs in the pharmacotherapy of depressive states, both unipolar and bipolar.

First and second generation mood stabilizers

A classification of mood stabilizers based on the chronology of their introduction for the treatment of bipolar mood disorder was proposed by the author of this review (Rybakowski 2007). A mood stabilizer can be defined as a drug that, if used as monotherapy it 1) acts therapeutically in mania or/and in depression; 2) acts prophylactically against manic or/and depressive episodes, as demonstrated in a trial of at least one year’s duration and 3) does not worsen any therapeutic or prophylactic aspect of the illness outlined above. The introduction of the first generation of mood stabilizers fulfilling the criteria mentioned above occurred nearly half a century ago. The mood-stabilizing property of lithium was first suggested in the early 1960s (Hartigan 1963), that for valproates at the turn of the 1960/1970s (Lambert et al. 1971), and for carbamazepine in the early 1970s (Okuma et al. 1973). The first suggestion that the atypical antipsychotic drug, clozapine, had a mood-stabilizing action was advanced in the mid-1990s (Zarate et al. 1995), and in the following years, the mood-stabilizing properties have been confirmed for such atypical antipsychotic drugs as olanzapine, quetiapine, aripiprazole and risperidone (Rybakowski 2007, 2008; Quiroz et al. 2010). A suggestion for its being a mood-stabilizing drug was made for lamotrigine in the early 2000s (Ketter & Calabrese 2002). It has therefore been proposed to name lithium, carbamazepine and valproate 1st generation mood stabilizers, and atypical neuroleptics and lamotrigine 2nd generation mood stabilizers (Rybakowski 2007).

In 2006, Spanish researchers introduced the term “predominant polarity” (manic or depressive) to describe the different courses of bipolar mood disorders (Colom et al. 2006). Such a classification can also be adopted for existing mood stabilizing drugs. Clozapine, which exerts strong antipsychotic and antimanic effects may be placed at one edge of the continuum, being “a mood stabilizer from above” where the administration of the drug starts during a severe manic episode of the illness, especially one with psychotic features. Other atypical antipsychotics, such as olanzapine, aripiprazole and risperidone, belong to a similar category. Lithium, carbamazepine and valproate also have stronger antimanic than antidepressant activity although, out of these three 1st generation mood stabilizers, lithium exerts the most pronounced antidepressant action. Quetiapine has turned out to be the most balanced mood-stabilizer, being equally effective against both psychopathological poles. And finally, lamotrigine may be placed on the opposite pole of this continuum, exerting a predominantly antidepressant effect, being “a mood stabilizer from below” and the administration of lamotrigine typically starts during a depressive episode. Therefore lithium, quetiapine and lamotrigine have become the most important drugs used for the treatment of depression. This was also reflected in a recent study on the polarity index of pharmacological agents used for maintenance treatment of bipolar disorder (Popovic et al. 2012).
Lithium, quetiapine and lamotrigine - mood stabilizers with apparent antidepressant properties

The antidepressant effects of lithium have been known since the 1970s. In our own study performed at that time, we found a therapeutic effect of lithium in both unipolar and bipolar depression (Rybakowski et al. 1974). In his review paper from the late 1980s Johnson (1987) stated that lithium exerts a marked antidepressant effect, although one slightly inferior to that of tricyclic antidepressant drugs. According to this review, lithium is also efficacious in preventing affective recurrences in both unipolar and in bipolar mood disorders, although lithium only is recommended as a drug of choice in the latter. It should be mentioned that in Hartigan’s (1963) paper which first demonstrated a prophylactic effect of lithium in mood disorders, half of his patients were suffering from unipolar depression. A recent meta-analysis by Guzzetta et al. (2007) reported a significant anti-suicidal effect of lithium in the long-term treatment of recurrent major depressive disorder.

The antidepressant effect of lithium in bipolar depression has long been acknowledged and in America lithium is recognized as the first-line treatment of bipolar depression (Thase 2005, Ansari et al. 2010). However, some doubts have recently been raised in this respect as in a double-blind controlled study, lithium monotherapy was shown to be no more effective than a placebo, while quetiapine was (Young et al. 2010). The role of lithium for the prophylaxis of bipolar depression has never been questioned, although in a comparison study, the drug was found to be slightly less effective than lamotrigine in preventing depressive episodes (Goodwin et al. 2004). Credit for lithium prophylaxis of depression was obtained in a recent BALANCE study which compared valproate, lithium and combinations of both over 2 years of observation with 110 patients in each group. The lowest percentage of depressive recurrences was in patients on lithium alone (32%), compared to those on drug combination (35%) and valproate monotherapy (45%) (Balance 2010). Lithium has also been mentioned as significantly preventing bipolar depressive episodes in a recent meta-analysis by Popovic et al. (2011). An additional asset of long term lithium prophylaxis is the fact that lithium among all mood stabilizing drugs may prevent suicidal behaviour in mood disorders to the greatest extent (Baldessarini et al. 2006).

Lithium was the first mood stabilizer to provide evidence of being efficacious in the augmentation of antidepressant drugs in treatment-resistant depression. The initial paper on this topic was published in the early 1980s by Canadian investigators (DeMontigny et al. 1981). Our own study, reported 11 years later, presented 51 patients with treatment-resistant depression in whom the lithium augmentation effect was superior in bipolar depression (79%) but was also considerable in unipolar depressed patients (46%) (Rybakowski and Matkowski 1992). In one study, the augmentation was not obtained with low dose of lithium carbonate (250 mg/day) but was present with that of 750 mg/day (Stein and Bernard 1993), and in other study, lithium did not augment nortriptyline in patients with a previous failure of five or more antidepressant treatment (Nierenberg et al. 2003). The most recent review on this issue was performed by Bauer et al (2010). According to them, the augmentation of antidepressants with lithium is currently the best-evidenced augmentation therapy in the treatment of depressed patients who do not respond to antidepressants. Most of these studies have involved patients with unipolar depression and included all the major classes of antidepressants. A meta-analysis of placebo-controlled trials revealed a mean response rate of 41.2% in the lithium group versus 14.4% in the placebo group.

The antidepressant effect of quetiapine monotherapy in unipolar depression has been demonstrated in two studies showing the efficacy of this drug when given as 150 mg or 300 mg/day in the treatment of an acute depressive episode of unipolar depression (Cutler et al. 2009, Weisler et al. 2009). Also, in one controlled study lasting 52 weeks, a prophylactic effect of quetiapine (50-300 mg/day) against depressive recurrences was found (Liebowitz et al. 2010). However, the most significant antidepressant effect of quetiapine monotherapy has been demonstrated in bipolar depression in the course of both bipolar I and bipolar II disorders (Suppes et al. 2008, 2010). The results of these studies have created a situation in which quetiapine is currently recommended as the monotherapy of choice for the treatment of bipolar depression in most of the guidelines (Grunzweig et al. 2010). That quetiapine is also effective in preventing bipolar depressive episodes was shown in a recent meta-analysis (Popovic et al. 2011).

The usefulness of quetiapine as augmentation strategy in treatment-resistant unipolar depression was also demonstrated recently. In an open-label study, Anderson et al. (2009) showed a significant improvement in patients with treatment-resistant depression after the addition of quetiapine (in an average dose of 245 mg) to a monoamine reuptake inhibitor. In a double-blind, placebo-controlled study including 446 patients, quetiapine, 300 mg/day, was significantly more effective than placebo as adjunctive therapy in patients with major depression inadequately responding to ongoing antidepressant treatment with SSRI or SNRI, while quetiapine, 150 mg/day, was not (El-Khali et al. 2010).

Lamotrigine has been called a “mood stabilizer from below” since the drug has substantial antidepressant properties, expressed to greatest extent among all current mood stabilizers (Ketter and Calabrese 2002). A review of lamotrigine in the treatment of unipolar depression has been recently performed by Zavodnick and Ali (2012). According to this review, the most robust effect of lamotrigine was found among patients who were treated for over 8 weeks and who received higher dosages of the drug. In patients with unipolar depression, better effects were demonstrated in those with more treatment-resistance as well as those with comorbid anxiety and borderline personality disorders.

Based on a meta-analysis of Geddes et al. (2009) showing the advance of lamotrigine over placebo, specifically in more severely depressed patients, the use of lamotrigine monotherapy for acute bipolar depression may be recommended. Lamotrigine exerts a significant effect on preventing depressive recurrences in bipolar mood disorder (Popovitz et al. 2011), being in this
respect more efficacious than lithium (Goodwin et al. 2005). Of interest is a study showing the beneficial effects of lamotrigine in recurrent brief depression (Ravindran and Ravindran 2007). The latter condition, due to its extremely high number of recurrences, shows some resemblance to bipolar disorder and even short lasting depressive episodes may generate serious suicidal behaviour.

A number of studies have investigated the augmentation of antidepressant drugs by lamotrigine in treatment-resistant depression, some of them comparing the efficacy of lamotrigine with lithium. Based on their retrospective chart review of 34 patients with major depressive disorder where lamotrigine was added to antidepressants Guitierrez et al. (2005) suggested the use of this procedure as an efficacious strategy in treatment-resistant depression. However, such a desirable effect was not confirmed in a placebo-controlled study performed on a small sample of patients by Santos et al. (2008). On the other hand, several open-label studies, including ours, revealed comparable results for lamotrigine and lithium augmentation of antidepressants on most outcome measures (Rybakowski and Tuszewska 2006, Schindler and Angeleescu 2007, Ivkovics et al. 2009).

Antidepressive properties of other mood stabilizing drugs

The antidepressant effect of carbamazepine has been already shown in mid-1980s (Post et al. 1986). In our own study performed in the early 1990s, we found a therapeutic effect of carbamazepine which was better in bipolar than unipolar depression and in patients with concomitant irregular EEG recordings and structural brain abnormalities (Matkowski and Rybakowski 1992. More recently, Chinese researchers have demonstrated the effectiveness of carbamazepine in the acute episode of major depression by means of a double-blind, randomized, placebo controlled study (Zhang et al. 2008). In the early 1990s Austrian psychiatrists observed a prophylactic effect of carbamazepine in patients with unipolar depression (Stupperich et al. 1994), and a few studies of effective antidepressant augmentation by carbamazepine, appeared at that time (De la Fuente and Mendlewicz 1992, Navarre et al. 1994). In our own study comparing carbamazepine with lithium, a significant augmentation effect of carbamazepine was found in both bipolar and unipolar depression, although the effect was less robust than that of lithium (Rybakowski et al. 1999). In a recent review paper, valproate has been also found to have some utility in treating bipolar depression (Smith et al. 2010). On the other hand, augmentation of antidepressants with valproate in unipolar depression has not been reported. In conclusion, the data on both anti-convulsant drugs have been insufficient to make a strong recommendation for their use in the treatment of depression.

The strategy of augmenting antidepressants in treatment-resistant depression with atypical antipsychotic drugs, most of which meet the criteria for mood-stabilizers, has gained increasing popularity. Atypical antipsychotics, in contrast to most first generation antipsychotics (e.g. haloperidol), are not depressiogenic, and indeed some of them have a clear antidepressant effect. In a meta-analysis based on 10 clinical trial reports where aripiprazole and ziprasidone data were not included, Papacostas et al. (2007) showed that the pooled remission and response rates for adjunctive atypical antipsychotics vs placebo were 47.5% vs 22.3% and 57.2% vs 35.4%, respectively.

A combination of olanzapine, an atypical antipsychotic drug with mood-stabilizing properties, with the antidepressant fluoxetine has also been recommended for the treatment of bipolar depression. Recently, Bobo and Shelton (2009) made a review of four randomized, double-blind, acute phase studies of this combination in patients with major depressive disorder who had previously responded inadequately to antidepressant monotherapy. A rapid reduction of depressive symptoms was found in all these studies after combination treatment. However, in their more recent paper the same authors (Bobo and Shelton 2010) raise some reservations about the long term use of such a combination, due to the significant metabolic side-effects of olanzapine.

The efficacy of aripiprazole as an adjunctive treatment for unipolar depression, where the use of selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors (SNRI) antidepressants has been initially insufficient was initially reported in a small number of patients (Hellerstein et al. 2008). A recent study where a post-hoc, pooled analysis of two large, placebo-controlled studies involving 741 patients was made, revealed a significant effect for aripiprazole vs placebo in the core symptoms of depression (Nelson et al. 2010). Aripiprazole, in daily 2-15 mg doses, gained an American Food and Drug Administration recommendation for augmenting SSRI and SNRI antidepressant drugs in treatment-resistant depression. Citrome (2010) performed a comparison of aripiprazole, olanzapine, or quetiapine as adjuncts to an antidepressant in major depressive disorder. He did not find any differences in clinical efficacy, as the mean number to treat (NNT) value for all three drugs was about 7.

Following anecdotal reports of possible risperidone augmentation of antidepressants in treatment-resistant depression, a placebo-controlled trial on 97 patients with unipolar non-psychotic major depression not responsive to antidepressant monotherapy was performed (Keitner et al. 2009). The patients were randomized to either risperidone 0.5-3 mg/day or a placebo in a double-blind study. After 4 weeks treatment, 52% of the risperidone augmentation group remitted (MADRS £10) compared to 24% of the placebo group. Successful augmentation of antidepressants by risperidone in major depressive disorder has also been demonstrated in a recent meta-analysis (Owenby et al. 2011). However, in a study of Rapaport et al. (2006), the long-term benefits of such procedure are questioned.

The data on another atypical antipsychotic, ziprasidone, are insufficient as there is only one open investigation into the antidepressant augmentation by this drug (Dunner et al. 2007). Sixty-four subjects with treatment-resistant depression were randomly allocated to sertraline monotherapy, sertraline plus ziprasidone 80 mg/day or sertraline plus ziprasidone 160 mg. It was found that adjunctive ziprasidone, 80 mg/day, was
Mood stabilizers in unipolar and bipolar antidepressant-refractory depression

The use of mood stabilizers in the treatment of depression has become particularly relevant in recent years as treatment-resistant depression, both unipolar and bipolar, has become a major therapeutic issue in psychiatry. A substantial percentage of major depressive patients do not achieve remission after two apparently adequate trials of antidepressant therapy, and the number of such patients has tended to increase. In recent years considerable research has been carried out on the role of bipolarity (the lifetime occurrence of manic or hypomanic symptoms) in depression poorly responding to antidepressant drugs. Also, the effective treatment of bipolar depression has proved a difficult task. All these findings suggested the possible use of mood-stabilizing drugs as antidepressants for both the treatment and prophylaxis of bipolar and unipolar depression, and to augment antidepressants in treatment-resistant depression. This has been partially reflected in the current recommendations for the pharmacotherapy of mood disorders both acute episode and long-term.

In the treatment of an acute episode of unipolar major depression, a careful application of antidepressant drug has been recommended as the initial step. In treatment-resistant depression, defined as a failure of remission after two adequate courses of antidepressant drugs, augmentation of antidepressants is suggested. In the majority of such strategies, 1st or 2nd generation mood stabilizing drugs (lithium, atypical antipsychotics, lamotrigine) are recommended. In unipolar depression, antidepressants are also used longitudinally for the prevention of new episodes. However, in cases with frequent recurrences, despite good compliance, adding a mood stabilizer to the antidepressant may be considered. In highly suicidal cases, adding lithium could be an important option. Despite the results of some old (lithium) (Johnson et al. 1987) and new (quetiapine) (Liebowitz et al. 2010) studies showing the prophylactic action of mood stabilizer monotherapy in unipolar depression, such a strategy has not been recommended so far.

Existing treatment guidelines do not deal with brief recurrent depression, characterized by short (1-3 day) and frequently recurrent (10-20/year) episodes. In view of the poor efficacy of antidepressants and some promising reports of using a mood stabilizers (lamotrigine), (Ravindran and Ravindran 2007), trials with other mood stabilizers of the 1st generation, or with quetiapine could be warranted.

Current guidelines for treating bipolar depression indicate limitations concerning the use of antidepressant drugs which, in bipolar I disorder, have only been accepted concomitant with mood stabilizers. A preferred therapeutic procedure in bipolar depression would be monotherapy or a combination of 1st (lithium) or 2nd generation (quetiapine, lamotrigine) mood stabilizing drugs. (Grunze et al. 2010). A specific place in this respect has been occupied by quetiapine monotherapy, the treatment with which is now accepted in most therapeutic guidelines. Also, lamotrigine and lithium are regarded as monotherapy but more frequently in combination. In America, another mood-stabilizing, atypical antipsychotic, olanzapine, in combination with fluoxetine has also been approved. Quetiapine, lamotrigine and lithium are currently considered the best drugs for a prophylaxis of depressive episodes in bipolar illness with predominant depressive polarity. They are used either as monotherapy, in combination, or with other mood stabilizing agents. The very strong antisuicidal efficacy of lithium should also be mentioned here.

Mood stabilizing drugs are now recommended for the augmentation of treatment-resistant depression in the course of both bipolar and unipolar mood disorders. The use of lithium for both conditions has long been known and accepted (Bauer et al. 2010), and trials with lamotrigine seem promising (Rybakowski Tuszewska 2006, Schindler and Angeleescu 2007, Ivkovics et al. 2009). However, a conspicuous feature recently has been the numerous papers on such atypical antipsychotics as olanzapine (with fluoxetine), aripiprazole, risperidone and ziprasidone, all of which show favourable results of their add-on strategy to antidepressants in treatment-resistant depression (Bobo and Shelton 2009, Dunner et al. 2007, Nelson et al. 2010, Owenby et al. 2011).

Recommendations regarding the treatment of a mixed depression, i.e. a major depressive episode accompanied by at least three subsyndromal manic or hypomanic symptoms which is frequently present in bipolar patients are lacking (Goldberg et al. 2009). A thorough assessment of such symptoms in patients with unipolar depression found the frequency of mixed depression to be about 30% (Benazzi 2007). In bipolar patients, a phenomenon similar to a mixed depressive episode can be induced by treatment with antidepressants and is then called antidepressant-associated chronic irritable dysphoria (ACID) (El-Mallakh and Karipott 2005). The findings from the STEP-BD study showed that, in bipolar depression accompanied by manic symptoms, antidepressants do not hasten the time to recovery relative to treatment with mood stabilizers alone, and treatment with antidepressants may indeed lead to (hypo) manic symptoms of greater severity (Goldberg et al. 2008). This may indicate that, in mixed depression, the use of antidepressants alone does not result in a favourable therapeutic outcome, and such a condition could be regarded as a category of depression unsuitable for, or resistant to, treatment with antidepressant drugs. Therefore, the pharmacological approach here could initially involve mood stabilizing drugs alone or in approved combination, similar to that adopted in treating depression in the course of rapid cycling bipolar illness.

Mechanisms of antidepressant action of mood stabilizers

The pharmacological mechanisms governing the antidepressant effect of mood-stabilizing drugs as well as those augmenting antidepressants used in treatment-resistant depression may be manifold. The majority of related studies suggest that the antidepressant
mechanism of mood-stabilizing drugs may be connected with their effect on the catecholaminergic (noradrenergic and dopaminergic) and/or serotonergic systems. A link between lithium augmentation of antidepressants and an increase in central serotonin neurotransmission has been postulated (Scheuch et al. 2010). The antidepressant activity of quetiapine could be connected with the effect of its active metabolite, N-desalkyl-quetiapine, which has been proven to be a potent norepinephrine (NE) reuptake inhibitor and a partial serotonin SHT1 receptor agonist, both effects being attributed to the pharmacological profile of some antidepressant drugs (Jensen et al. 2008). Other antipsychotic drugs with mood-stabilizing properties, such as olanzapine, aripiprazole, risperidone and ziprasidone, may exert their antidepressant action by a partial 5-HT1A agonism or/and 5HT, antagonism (Bortolozzi et al. 2010, Schmidt et al. 2001, Stark et al. 2007). The addition of aripiprazole to SSRI drugs was found to reverse the inhibitory action of these drugs on noradrenergic and dopaminergic (DA) neuronal firing, thus augmenting NE and DA neurotransmission (Chemoloz et al. 2009). A combination of aripiprazole and serotonergic antidepressants was also found to increase antidepressant activity as measured by a swimming test, the most widely used animal model of antidepressant effect (Bourin et al. 2009).

In addition to serotonin and catecholamines, other neurotransmitters and intracellular messengers may be involved in the antidepressant effect of mood stabilizers. Glutamatergic (NMDA) modulation may play a role in the antidepressant action of lamotrigine (Hunt et al. 2008). Mann et al. (2009) suggest that the antidepressant effect of both lithium and carbamazepine may be related to the inhibition of specific adenylyl cyclase isomorphs, an effect which is not exerted by valproate.

Recent experimental research has shown that mood stabilizers, of both the 1st and 2nd generation, (lithium, olanzapine, quetiapine, lamotrigine) by exerting an antidepressant action enhance an intracellular neuroprotective cascade, especially via their effect on the brain-derived neurotrophic factor (BDNF) system (Hashimoto et al. 2002, Park et al. 2006, Hammonds et al. 2009, Li et al. 2011). BDNF was found to exert an antidepressant action itself (Stuciak et al. 1997), and treatment with either antidepressants or mood-stabilizing drugs is connected with an increase in serum BDNF (Molendijk et al. 2011, Rybakowski and akatisia (aripiprazole).

**References**


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disorder. Psychopharmacology 206, 335-344.

Hammonds MD, Shim SS (2009). Effect of 4-week treatment with lithium and olanzapine on levels of brain-derived neurotrophic factor, B-cell CL/Lymphoma 2 and phosphorylated cyclic adenosine monophosphate response element-binding protein in the sub-regions of the hippocampus. Basic Clin Pharmacol Toxicol 105, 113-119.


