PSYCHOPHARMACOTHERAPY

4.2. Long-term pharmacological treatment of bipolar disorders

Janusz Rybakowski

Key words: bipolar disorder; long-term treatment; mood-stabilizing drug; maintenance; prophylaxis; bipolar I; bipolar II

Summary

Several lines of clinical, genetic, and pharmacological evidence point to an association between bipolar and psychotic disorders. The goals of maintenance and prophylactic treatment of bipolar disorder include the prevention of new episodes and the improvement of social, family, and occupational functioning. This goal can be mainly achieved by using long-term adequate pharmacological treatment that is tolerable to patients. Among mood-stabilizers, the main drugs used for such treatment, the role of atypical antipsychotics has greatly increased in recent years.

Lithium still remains the drug that has produced the most convincing evidence of prophylactic action and has undergone the longest periods of observation. There has also been good confirmation for the maintenance efficacy of such anticonvulsant drugs as carbamazepine, valproate, and lamotrigine, the last having the strongest properties for prophylaxis of depressive episodes. The case for the usefulness of second-generation antipsychotic drugs in the long-term treatment of bipolar disorder has been rapidly accumulating.

Based on controlled trials, the best evidence for maintenance efficacy exists for olanzapine.

The vast majority of patients with bipolar illness experience inadequate response to monotherapy with mood-stabilizing drugs during long-term treatment. Some issues connected with polypharmacy targeting optimal maintenance results are discussed. In addition, the long-term management and the role of antidepressants in treatment of non-bipolar I illness is also briefly described.

4.2.1. Introduction

4.2.1.1. The place of bipolar disorders among psychotic disorders

In contemporary classifications, bipolar disorders (BDs) belong to mood (affective) disorders. However, several lines of evidence also point to their association with psychotic disorders. First, it is clinical. The previous name of bipolar disorder was manic-depressive psychosis, and in typical bipolar disorder (bipolar I), manic episodes frequently have a psychotic character with grandiose and/or persecutory delusions. Psychotic symptoms also occur in depression, and psychotic depression is significantly more frequent in bipolar than in the unipolar type of mood disorder. Second, recent molecular genetics studies seem to identify common genes predisposing to both schizophrenia and bipolar disorder: Of special interest may be some dopaminergic system genes connected with a predisposition to schizophrenia and to bipolar illness with psychotic features. Third, the efficacy of atypical antipsychotic (neuroleptic drugs) in acute phases and prophylaxis of bipolar mood disorder blurs the distinction between therapy of psychotic disorders and bipolar mood disorder.

4.2.1.2. The rationale for long-term treatment of bipolar disorder

Bipolar disorder is a lifelong illness with a heterogeneous course. The main elements of the illness are psychopathological phenomena of opposite poles, i.e. manic and depressive episodes. The current classification of BD is based on the severity of manic episodes or their equivalents. There is bipolar disorder, type I, in which the manic episodes occur, sometimes accompanied with mixed-state or psychotic features. Bipolar I illness has a prevalence of about 1% in the population. The prevalence of bipolar disorder, type II, with hypomanic

episodes, and bipolar spectrum disorder, with equivalents of hypomanic features may reach 3%–4% of the population. In the latter types, depressive episodes are much more frequent and long-lasting than hypomanic ones [Angst & Gamma, 2002]. The natural history of the illness shows that in 50% of cases, BD starts with a depressive episode [Perugi et al., 2000]. A recent study in Poland showed that bipolar mood disorders make up a substantial proportion of depressive outpatients treated by psychiatrists [Rybakowski et al., 2005].

Bipolar disorder is a highly recurrent condition. The probability of recurrence, as assessed by long-term follow-up studies, amounts to 100% of patients. Therefore, the best strategy for avoiding the deleterious consequences of recurrence is starting a long-term treatment early in the course of illness. Such a procedure is called maintenance or prophylactic treatment. Maintenance is usually defined as the duration of treatment between 6 months to 1 year and prophylaxis is more than one year, although sometimes the term "maintenance" is used for a more extended period of treatment.

The goals of maintenance and prophylactic treatment of BD include the prevention of new episodes and an improvement in social, family, and occupational functioning. This goal can mainly be achieved by using long-term adequate pharmacological treatment that is tolerable to patients. Augmentation of pharmacological treatment by various psychosocial interventions has been increasingly emphasized in recent years.

In this paper, the drugs used in the long-term treatment of bipolar illness will be presented, and the evidence for their efficacy will be discussed, based mainly on results from controlled trials. In addition, clinical issues connected with polypharmacy in long-term treatment of BD as well as treatment of non-bipolar I illness and the role of antidepressants will be considered.

4.2.1.3. Mood-stabilizing drugs

Mood-stabilizing (sometimes also called "mood-normalizing") drugs are the cornerstone of BD treatment. The "mood-stabilizing" property of a drug denotes therapeutic and prophylactic action in both psychopathological poles of BD. Such properties were convincingly demonstrated for the lithium ion, which is a prototype of mood-stabilizers [Bauer & Mitchner, 2004]. The prevention of manic and depressive recurrences in BD is probably the most important feature of a mood-stabilizer. The broader definition of mood-stabi-

lizing drug formulated by Bowden [2002] would include a drug that [Ahrens et al., 1995] benefits at least one primary aspect of bipolar illness (mania, depression, cycling frequency, number of episodes, subthreshold symptoms), [Altamura et al., 2003] is effective in acute and maintenance phase treatment, and [Amsterdam & Brunswick, 2003) does not worsen any aspect of the illness. In addition to lithium, such criteria have been met by some anticonvulsant drugs such as carbamazepine and valproate, and recently also by lamotrigine.

Conventional antipsychotic drugs, although efficacious for the treatment of mania, have not demonstrated a significant usefulness in the maintenance treatment of bipolar disorder. This was primarily because of a tendency to induce depressive symptoms and depressive recurrences in this group of patients during long-term administration. Second-generation antipsychotics have much weaker (if any) pro-depressant properties than conventional antipsychotics, and their tolerability, especially in long-term treatment, is more favourable. Clinical observations indicate that clozapine could have mood-stabilizing properties [Zarate, 1995]. At the turn of century, olanzapine was officially approved as the first atypical antipsychotic drug for the prophylaxis of bipolar mood disorder. On the basis of trials performed in recent years, such clinical attributes have also been suggested for other second-generation antipsychotics, namely for risperidone, quetiapine, ziprasidone, and aripiprazole.

Antidepressant drugs have been widely used for maintenance and sometimes prophylactic treatment of recurrent depression. However, their long-term administration in patients with bipolar disorder can result in an induction of the manic or hypomanic switch or in generation of a rapid cycling course of illness. On the other hand, long-term use of antidepressant drugs as an adjunct to mood-stabilizers may favourably influence the longitudinal course of the illness by alleviating or preventing depressive episodes, especially in patients with the non-bipolar I type of the illness.

4.2.2. Lithium

The seminal observations of Hartigan [1963] and Baastrup [1964] in the early 1960s set the stage for controlled trials aimed to determine the efficacy of lithium in preventing the recurrence of affective episodes. Hartigan's report, published in the *British Journal of Psychiatry* in 1963, was a 3-year observation of

lithium administration to 7 patients with manic-depressive illness and to 8 patients with recurrent depression. He found that in 6 patients from the first group and in 6 patients from the second group, there were no illness recurrences during the observation period. Hartigan suggested the possibility of a "prophylactic" action of lithium while Mogens Schou in the same year used terms such as "normothymic" or "mood-normalizing" to describe the effect of this ion [Schou, 1963]. In 1967, Baastrup and Schou summarized their experiences with long-term lithium treatment (mean: 6 years) in 88 patients with both unipolar and bipolar affective illness who had started lithium as inpatients of a psychiatric hospital in Glostrup (Denmark). They found that the mean duration of morbidity (depressive or manic) while staying on lithium was 2 weeks per year. This contrasted with the mean duration of morbidity preceding lithium treatment, which was 13 weeks per year. They argued that their results strongly suggest that lithium may possess "prophylactic" activity in mood disorders [Baastrup & Schou, 1967].

The results of controlled trials performed in 1970–1973 were unequivocally positive, showing that lithium is an effective prophylactic modality in preventing affective episodes in both bipolar and unipolar patients [Baastrup, 1964; Coppen et al., 1971; Cundall et al., 1972; Hullin et al., 1972; Melia, 1970; Prien et al., 1973; Stallone et al., 1973]. The total number of patients receiving lithium was 208 in these studies, and 212 received placebo. The relapse within 0.5–2 years of observation was 31% in the lithium group and 76% in the placebo group. Placebo-treated patients had a threefold increased rate of manic relapses and a twofold increased rate of depressive relapses compared to lithium-maintained patients.

The results of clinical observations on the prophylactic value of lithium carried out in the 1980s and later have been less optimistic. First, it was found that in naturalistic settings, the prophylactic effect of lithium was less marked than that obtained in controlled clinical trials performed in academic centres [Guscott & Taylor, 1994; Johnson & McFarland, 1996; Markar & Mander, 1989]. Second, in some patients, the effect of lithium tended to diminish over time, despite continuous drug administration [Maj et al., 1996]. Furthermore, the true fraction of excellent lithium responders, defined as patients experiencing no affective relapses, was estimated as no more than one-third of lithium-treated patients [Grof, 1999; Grof, 1998; Maj et al., 1998]. The nadir of sceptical attitudes towards lithium was reached in the late 1990s as expressed in a paper by Moncrieff [1997]. She argued that the results of previous pro-

phylactic trials with lithium hardly meet the contemporary criteria of evidence-based medicine.

A review paper of Baldessarini and Tondo [2000] addressed the issue of a possible decreasing prophylactic effect of lithium in consecutive decades. Based on the analysis of published reports as well as on the clinical effects on 360 bipolar patients who entered into lithium maintenance monotherapy after 1970, the authors did not find evidence that prophylactic lithium efficacy shows signs of abating.

At an outpatient clinic in the Department of Psychiatry, University of Medical Sciences in Poznan, where lithium prophylaxis was introduced at the beginning of 1970s, we attempted to compare patients entering lithium prophylaxis in two subsequent decades: the 1970s and 1980s. We were interested [Ahrens et al., 1995) in whether patients entering lithium in these two decades had different pre-lithium clinical characteristics; [Altamura et al., 2003] whether they differed in clinical course during 10 years of lithium prophylaxis; and (Amsterdam & Brunswick, 2003) whether any elements of this therapeutic procedure were different in these two decades. The inclusion criterion was that the patient had a diagnosis of bipolar affective illness and had been on lithium continuously for at least 10 years. We assumed that the evaluation of patients during such a long period of lithium administration would be necessary for an adequate assessment of the clinical course of illness on the drug. By 1999, such criteria were fulfilled by 60 patients initiating lithium during 1971–1980 and by 49 patients doing so in 1981–1989. No significant differences between the two groups of patients were found regarding the distribution of gender, the frequency of bipolar II category, the percentage of patients with a family history of affective illness, the rate of employment at the start of lithium, the age of illness onset, the age of starting lithium, or the period from onset of illness to the beginning of lithium prophylaxis.

Except for a trend to a greater number of depressive episodes in the first year of lithium prophylaxis, no significant differences between the two groups were found. The percentage of patients without episodes throughout 10 years of lithium prophylaxis (excellent lithium responders) was slightly lower in 1980s patients (27% vs. 35%) but insignificantly so [Rybakowski et al., 2001].

No significant difference was found between the two groups in terms of the frequency of somatic diseases and the percentage of recurrences apparently related to stress. The daily dose of lithium was slightly lower in the 1980s

group, and the mean lithium level was significantly lower in these patients (0.62 vs. 0.66 mmol/l, respectively). Consequently, the occurrence of such side-effects as thirst, polyuria, and tremor was insignificantly lower in patients in the 1980s compared with the earlier group*.

Therefore, despite some reservations, lithium still remains the most important agent for the long-term treatment of bipolar illness. The experiences with longitudinal lithium therapy amounting to a duration of 30 years or more do not exist for any other mood-stabilizing drug. The efficacy of long-term lithium efficacy in BD has been strongly supported by both clinical observations and also by most stringent analyses of clinical trials. The latest metaanalysis of long-term lithium efficacy in bipolar disorder was performed by Geddes et al. [2004] and included five randomized trials with 770 participants. The results showed that lithium was significantly more effective than placebo in preventing all relapses with a relative risk (RR)=0.65 and in preventing manic relapses (RR= 0.62), and less so for depressive relapses (RR=0.72).

Many years of lithium presence in psychiatric treatment have revealed, apart from mood-stabilizing action, several other interesting features of this drug. They include among others antiviral, immunomodulatory, and neuroprotective properties as well as antisuicidal activity, which, from a clinical point of view, could be very important.

The results of the first systematic study performed by German investigators convincingly demonstrated an antisuicidal effect of lithium long-term treatment. Sixty-eight patients with affective disorders and receiving lithium prophylaxis in a specialized lithium clinic were followed up for 8 years on average. They all attempted suicide at least once before onset of lithium prophylaxis. Fifty-five patients took their lithium regularly and 13 discontinued the drug during the period of follow-up. One-third of those patients who discontinued medication died from suicide, and multiple suicidal attempts were observed in this group of patients in a period from 2 weeks–44 months following lithium discontinuation. Only one suicide occurred in patients with regular lithium intake and proven compliance during the last check before death. The authors concluded, based on the results obtained, that lithium may have a specific antisuicidal effect even in patients not responding satisfactorily in terms of a reduced number of affective episodes [Müller-Oerlinghausen et al.,

* American recommendations for lithium concentration in prophylactic administration have been higher than in Europe (0.8-1.0 vs. 0.5-0.8 mmol/l, respectively) [Gelenberg et al., 1989].

1992]. Also in 1992, a paper was published showing that long-term treatment with lithium may exert a favourable effect on the mortality of patients with manic-depressive and schizoaffective illness. Such mortality is 2–3 times that of the general population. The data were gathered from 827 manic-depressive patients coming from four centres, receiving lithium for more than one year. The average duration of treatment was 81 months, and the total time on lithium was 5600 patient-years. The mortality risk was calculated for each patient. It was found that in the group of patients studied, the standardized mortality ratio did not differ from that of the general population [Müller-Oerlinghausen et al., 1992]. In a follow-up paper published 3 years later by the same group, it was postulated that a reduction in mortality rate by lithium in affective patients might be attributable to a reduction in both suicidal and cardiovascular mortality [Ahrens et al., 1995].

Long-term experiences with lithium prophylaxis have allowed delineation of a group of patients with a remarkable therapeutic response to lithium. In such patients, the illness simply "stopped" and no further recurrences were observed even in the course of many years of lithium treatment. Such a concept of "excellent lithium responders" was introduced by Paul Grof [1999]. It turned out that the percentage of "excellent lithium responders" is about one-third of all lithium-treated patients, while in the first years of lithium therapy it was estimated as 40%–50%. With the advent of molecular genetics, "excellent lithium responders" were regarded as a distinct clinical endophenotype of bipolar illness and used in such studies. Some chromosome loci (15q14 and 7q11.2) were identified as linked to excellent lithium response [Turecki et al., 2001]. In addition, some genes associated with a quality of response to lithium were found, such as phospholipase C [Turecki et al., 1998], tryptophan hydroxylase [Serretti et al., 1999], serotonin transporter [Rybakowski et al., 2005]], and brain-derived neurotrophic factor genes [Rybakowski et al., 2005].

4.2.3. Anticonvulsants

4.2.3.1. Carbamazepine

In the 1990s, carbamazepine was considered a main pharmacological alternative to lithium in the prophylaxis of bipolar illness. However, the possible mood-stabilizing properties of the drug had been first noticed by Japanese investigators, who described 20 years earlier in the early 1970s a favourable action of carbamazepine in the treatment of manic episodes, as well as the

possibility of prophylactic action [Okuma et al., 1973; Takezaki & Hanaoka, 1971].

Studies performed in the 1980s noted the positive effects of carbamazepine in bipolar disorder compared with placebo [Post et al., 1983]. Subsequent maintenance research has been also carried out comparing carbamazepine with lithium. In two such studies, it was concluded that the two drugs were equally efficacious [Lusznat et al., 1988; Placidi et al., 1986]. However, Placidi et al. [1986] first suggested that carbamazepine may be a better prophylactic drug in atypical forms, while lithium is superior in typical forms of bipolar mood disorder. On the other hand, in two other papers, a superior efficacy of lithium prophylaxis over carbamazepine was observed when the duration of drug-induced remission was analyzed [Coxhead et al., 1992; Watkins et al., 1987].

The biggest long-term study with carbamazepine in BD has been performed by German investigators. This study was an open-label randomized clinical trial that focused on the differential efficacy of carbamazepine and lithium for bipolar maintenance treatment. The study included 171 bipolar patients followed over 2.5-year period. It was found that carbamazepine was clearly inferior to lithium in bipolar I patients, especially those having a classical subtype of disorder. Such a subtype is characterized by the absence of mood-incongruent delusions and other psychiatric comorbidity, and by having a mania-depression–free interval sequence of illness. On the other hand, there was a trend favouring carbamazepine over lithium for prophylaxis of patients with the non-classical subtype of the disorder. A retrospective comparison was also done on the effect of carbamazepine and lithium on suicidal behaviour. In the carbamazepine group, four completed suicides and five suicidal acts occurred, while in the lithium group no suicidal act was observed [Greil et al., 1998].

Ten double-blind studies comparing carbamazepine to lithium were included in a meta-analysis on mood stabilizers performed by Davis et al. [1999]. Among 572 patients followed in maintenance treatment between 1 and 3 years, 55% of carbamazepine-treated patients versus 60% of lithium-treated patients experienced affective relapse. The authors suggested that the prophylactic efficacy of both drugs may be similar.

4.2.3.2. Valproate

The first evidence for a mood-stabilizing effect of valproic acid or its derivates came from the studies of French investigators in the 1960s and 1970s [Lambert et al., 1966; Lambert et al., 1971]. For the antimanic and possible prophylactic effect of the drug, they coined the term "thymoregulatrice". In the studies performed until the mid-1990s, valproic acid amide (valpromide) was primarily used, and more recently, sodium valproate or divalproex (sodium valproate and valproic acid in a 1:1 molar relationship) was employed, usually as a sustained-release formula.

Polish experiences with valpromide involved 37 patients with bipolar mood disorder and schizoaffective disorder to whom the drug, in doses of 600–1800 mg/day, was administered for a period of 1–6 years. A favourable prophylactic effect was observed in 23 patients (62%), regardless of diagnosis (bipolar I, bipolar II, schizoaffective). Such an effect was mostly exerted against manic and less so against depressive episodes. Rapid cycling was associated with poor response to valpromide monotherapy [Pużyński & Klosiewicz, 1984].

An open comparative study of valpromide vs. lithium was performed by French investigators in 1992 [Lambert & Venaud, 1992]. A total of 150 patients were randomized to valpromide, used in a dose of 1200 mg, or to lithium, with the dose adjusted according to serum level. During the 18-month observation, there were 0.51 episodes per subject in the valpromide group and 0.61 episodes per subject in the lithium group. The kind of episodes occurring with these drugs tended to suggest that both valpromide and lithium showed slightly less ability to prevent depressive episodes than manic ones.

Bowden et al. (2000) conducted the first double-blind, randomized, placebo-controlled maintenance study of bipolar I disorder that compared divalproex and lithium during a 1-year period. A total of 372 patients who had recovered from a manic episode were allocated to divalproex (concentration 71–126 μg/ml), lithium (0.8–1.2 mmol/l), or placebo. The mean duration of survival in the maintenance treatment for the three groups was 198, 152, and 165 days, respectively. Apart from this difference, fewer patients on divalproex than on lithium dropped out of the study because of intolerance or non-compliance (22% and 35%, respectively).

Gyulai et al. (2003) performed a post-hoc analysis of that study focusing on the maintenance efficacy of divalproex in the prevention of bipolar depression. They found that divalproex-treated patients had a reduced worsening of

depressive symptoms compared to lithium-treated patients during the one-year maintenance. Divalproex decreased the probability of depressive relapse in bipolar disorder, particularly in those patients who had previously experienced an antimanic response and in those with a more severe course of illness.

4.2.3.3. Lamotrigine

Lamotrigine is a relatively recent entry into the psychiatric armamentarium of mood-stabilizing drugs. Despite this, the drug has already reached a special category among them as a mood-stabilizer from below, having more antidepressant than antimanic properties [Ketter & Calabrese, 2002].

The first double-blind, placebo-controlled lamotrigine maintenance study was performed in patients with rapid cycling bipolar disorder. Initially, lamotrigine was openly added to the treatment regimen of 324 rapid cycling patients, of whom 182 stabilized and were randomly assigned to the double-blind 6-month maintenance study with either lamotrigine or placebo. During the 6-month observation phase, 56% of the placebo patients and 50% of the lamotrigine-treated patients required treatment of an emerging mood episode with additional pharmacotherapy. However, when overall survival was analyzed, this score was significantly longer for lamotrigine (median 14 weeks) than for placebo (median 8 weeks). The percentage of patients stable without relapse was 46% in lamotrigine and 26% in the placebo group. Greater differences arose when the data were analyzed separately for patients with bipolar I and bipolar II disorder. For patients with bipolar II disorder, median survival was 15 weeks with lamotrigine compared with 4 weeks for placebo, and percentages of patients without relapse were 46% and 18%, respectively [Calabrese et al., 2000].

In 2003, the results of two placebo-controlled studies appeared comparing the prophylactic efficacy of lamotrigine and lithium during an 18-month period. In the first study, 349 manic or hypomanic patients were enrolled, and lamotrigine was prescribed as an adjunctive or monotherapy. Of these, 175 patients were stabilized and randomized to maintenance treatment with lamotrigine (100–400 mg/day, n=59), lithium (0.8–1.1 mmol/l; n=46), or placebo (n=70). Both lamotrigine and lithium were superior to placebo in time required for additional pharmacological treatment of a mood episode. However, lamotrigine showed significantly greater efficacy for prolonging time to

a depressive episode compared with lithium. On the other hand, lithium, but not lamotrigine, was superior to placebo in prolonging the time to a manic, hypomanic, or mixed episode [Bowden et al., 2003]. In the second study, Calabrese et al. [2003] completed a double-blind 18-month maintenance comparison of lamotrigine and lithium in recently depressed bipolar I patients. A total of 463 patients with the most recent depressive episode in remission were randomized to lamotrigine (50, 200, or 400 mg/day; n=221), lithium (0.8–1.1 mmol/l; n=121), or placebo (n=121). Again, both lamotrigine (200 and 400 mg/day) and lithium were significantly superior to placebo in delaying time to intervention for any mood episode. Lamotrigine, but not lithium, was superior to placebo in terms of delaying time to intervention for depressive episodes. Lithium's superiority was also confirmed for delaying time to a manic or hypomanic episode.

An interesting paper also appeared comparing the clinical features of good prophylactic responders to lamotrigine or to lithium. Patients experiencing favourable action from lamotrigine more frequently had a chronic or rapid cycling course of illness. In such patients, the frequent clinical picture involved a comorbidity of anxiety disorders (panic attacks) and a tendency to psychoactive substance abuse. In their families, schizoaffective disorder, recurrent depression, or anxiety disorders often existed. Lithium responders tended to have a classical form of bipolar disorder, with a periodic course with full remission, and pure bipolar illness dominated the family history of such patients [Passmore et al., 2003].

4.2.4. Second-generation antipsychotic drugs

4.2.4.1. Clozapine

The usefulness of clozapine in the treatment of bipolar illness has long been recognized. We reported the remarkable antimanic effect of this drug in the early 1980s [Strzyzewski et al., 1981]. However, because of safety restrictions, this drug has been mainly used in treatment-resistant cases, including long-term administration in bipolar illness. Nevertheless, the results of such clinical, mostly naturalistic observations have been highly rewarding. It seems that although the results of controlled studies with clozapine are lacking, the drug could be considered for long-term mood stabilization in treatment-resistant and difficult cases of bipolar disorder.

The only randomized trial with long-term administration of clozapine was performed by American researchers [Suppes et al., 1999]. Thirty-eight treatment-resistant patients with bipolar or schizoaffective bipolar disorder were randomly assigned to a clozapine add-on treatment (19 patients) or treatment as usual (no clozapine) (19 patients) and followed up to 1 year. A significantly better clinical outcome was observed in the clozapine add-on group, reflected in scores on all rating scales except the Hamilton depression scale. Bipolar patients with and without psychotic features showed a similar degree of improvement. Total medication use significantly decreased in the clozapine group. No significant differences between groups in somatic complaints were noted except for initial sedation reported by some clozapine patients.

Ciaparelli et al. [2000, 2003] performed naturalistic long-term studies with clozapine. In the first study, 34 bipolar patients with psychotic features and 26 schizoaffective patients, bipolar type, received clozapine in flexible doses for 2 years. A significant improvement was observed in both groups of patients, exceeding in magnitude that obtained in patients with schizophrenia. In the second study, 37 bipolar and 30 schizoaffective patients receiving clozapine were observed for 4 years. The response to clozapine, defined as a 50% reduction of the Brief Psychiatric Rating Scale (BPRS) score was observed at the endpoint in 90% and 83.8% of patients, respectively.

4.2.4.2. Olanzapine

Olanzapine is the only second-generation antipsychotic that has been thoroughly examined in long-term treatment of bipolar disorder using double-blind, randomized controlled trials, with a variety of designs. They included comparison with placebo, comparison with standard mood-stabilizing drugs (lithium, valproate), and an addition of olanzapine to mood-stabilizers, which was compared with the addition of placebo. The results of all these studies strongly favour regarding olanzapine as a prophylactic agent in BD and using it in treatment standards for maintenance administration in this disorder or for an augmentation of conventional mood-stabilizers.

Long-term administration of olanzapine, mostly as an adjunctive therapy in bipolar disorder, was investigated initially in an open-label study. A total of 139 patients had either olanzapine monotherapy (57 patients) or the drug was added to lithium or fluoxetine (82 patients). After a mean 6.6 months of treatment with olanzapine at a mean dose of 13.9 mg/day, a significant improve-

ment of manic and depressive symptoms and a relapse rate of only 25.5% were observed [Sanger et al., 2001].

There is a randomized controlled trial of monotherapy with olanzapine vs. placebo of 12- month duration. A total of 361 patients achieving symptomatic remission after treatment of manic or mixed episode were included; 225 were randomized to olanzapine, 5–20 mg/day, and 136 to placebo. Relapse to an affective episode occurred in 46.7% of olanzapine-treated and in 80.1% of placebo-treated patients. Two-thirds of relapses with olanzapine were depressions [Tohen et al., 2003a]. Further analysis has shown that the preventive effect of olanzapine was better in patients with a manic index episode (relapse in 39.6% of patients) than with a mixed index episode (relapse in 59.2% of patients) [Tohen et al., 2003b].

There are two double-blind controlled trials comparing olanzapine with a mood stabilizer: one with lithium and a second with divalproex. In the first study, 431 patients who met symptomatic remission criteria after treatment of a manic or mixed episode were randomized to olanzapine (n=217) or lithium (n=214) for 52 weeks of double-blind treatment. Relapse to an affective episode occurred in 30% of olanzapine-treated and 38.8% of lithium-treated patients. However, the relapse into a manic episode was significantly lower with olanzapine (14.3% vs. 28%) [Tohen et al., 2002]. Olanzapine was also compared with divalproaex in a study of 47 weeks in duration. A total of 251 patients with acute manic or mixed episode were randomly allocated to either olanzapine (n=125) or divalproex (n=126). Over 47 weeks, there were no significant differences in relapse to an affective episode (42.3% for olanzapine and 56.5% for divalproex) [Tohen et al., 2003c].

4.2.4.3. Risperidone

The results of several maintenance trials with risperidone in BD strongly suggest that this drug may be of use for such indications, especially as an addition to a standard mood-stabilizing drug. However, there is no published controlled trial of risperidone as an add-on to a mood-stabilizer, and only one open study exists using risperidone as monotherapy for bipolar maintenance. The biggest trial of maintenance therapy (6 months) with risperidone, mean dose 3.9 mg/day, added to mood stabilizers covered 541 patients with BD or schizo-affective disorder, bipolar type. A total of 430 patients completed the study. The administration of risperidone resulted in a significant reduction of

both manic and depressive symptoms. The rate of relapse to the opposite pole occurred in 25% of patients [Vieta et al., 2001].

Recently, the results of the first maintenance (6 months) trial of risperidone, used as a monotherapy after manic episode in a mean dose of 4.2 mg/day, were reported. In 80 patients who completed the study, a significant efficacy of the drug was found against both manic and depressive symptoms. Risperidone was well tolerated. Extrapyramidal side-effects increased after the first month of therapy and showed a significant decrease after 6 months [Vieta et al., 2004].

Clearly, there is a need for randomized controlled studies with risperidone both as a monotherapy and in combination with mood stabilizers in long-term treatment of bipolar disorders. Apparently, such studies are currently under way, also using long-acting injectable preparations of risperidone.

4.2.4.4. Quetiapine, aripiprazole, ziprasidone

A paper by Altamura et al. [2003] deals with the possibility of prophylactic action of quetiapine in bipolar illness. In an open study performed in 28 bipolar outpatients, 14 were randomized to quetiapine and 14 to a classical mood stabilizer (valproate, lithium), and followed up to 12 months. BPRS scores in both groups significantly decreased over time. No significant difference was found in relapse prevention between both groups (8 mood episodes occurred in each group). Both treatments were well tolerated, and no patient complained of disturbing adverse events or discontinued the study because of side-effects or for lack of compliance. The authors argue that this observation may suggest a similar efficacy of quetiapine and classical mood stabilizers for recurrence prevention in bipolar illness. Quetiapine was also investigated as an adjunct to mood stabilizing drugs, and the results were presented during the American Psychiatric Association (APA) Annual Meeting in 2004. Twenty-one bipolar I outpatients inadequately responsive to standard treatments were treated in an open-label study with adjunctive quetiapine, mean 518 mg/day for 26–78 weeks. Significant differences in relapse rates before vs. during quetiapine treatment were found both for manic/mixed and depressive recurrences [Carta et al., 2004].

Aripiprazole was investigated in a 26-week, double-blind, placebo-controlled study involving 161 patients with a recent manic or mixed episode. Previ-

ously, the patients had been stabilized on aripiprazole, 15–30 mg/day for 6–18 weeks. The time to relapse of symptoms was significantly longer with aripirazole treatment, and significantly fewer aripiprazole-treated patients experienced affective relapse (25% vs. 43%, respectively). The only adverse events (≥10% incidence) more commonly reported with aripirazole than with placebo were anxiety and nervousness [McQuade et al., 2004].

Preliminary results of long-term treatment with ziprasidone following remission of a manic episode were also presented during the APA Annual Meeting in 2004. Ziprasidone, 40–160 mg/day, was investigated in 82 patients. A continued improvement on several measures was noted up to the 28th week of the study [Wechsler et al., 2004].

4.2.5. Combination therapy

The majority of the abovementioned trials focused on the long-term treatment of bipolar illness with drug monotherapy. However, the lesson learned from "excellent lithium responders" is evident: only one-third of patients treated with lithium do well in the long-term on monotherapy. It is conceivable that the percentages of patients with other mood-normothymic drugs are not higher and that the patients responding to monotherapy with a different mood-stabilizing drug may overlap. The proportion of patients with rapid cycling that responds to mood-stabilizer monotherapy may be even lower. Thus, the failure of an adequate response to monotherapy is experienced in long-term treatment by the vast majority of patients with bipolar illness. This outcome may prompt a search for a rational polypharmacy in order to obtain optimal therapeutic results in most patients.

An example of the synergistic effect of combination prophylactic therapy is that of lithium and carbamazepine. In a 3-year double-blind study, 52 patients were randomized to receive lithium or carbamazepine prophylaxis for 1 year, crossed-over to the second drug for the second year, and then given both drugs in combination in the third year. The percentage of patients who had marked or moderate improvement was higher on the combination therapy (55.2%) compared with lithium or carbamazepine as monotherapy (33.3% and 31.4%, respectively). The difference was even higher in patients with a history of rapid cycling, in whom the combination was successful in 56.3% vs. 28% lithium and 19% carbamazepine [Denicoff et al., 1997].

In many trials of long-term treatment with second-generation antipsychotic drugs, the assessment of their therapeutic efficacy was performed on an add-on basis to "classic" mood-stabilizers. The mood-stabilizing properties of risperidone or quetiapine in maintenance treatment were mostly inferred from their augmentation of the prophylactic effect of typical mood-stabilizers such as lithium or valproate. The first randomized placebo-controlled study of the combination of lithium or valproate with an atypical antipsychotic agent in the prevention of relapse of bipolar disorder was conducted with olanzapine. Patients achieving syndromic remission after treatment with olanzapine plus either lithium or valproate were randomized to olanzapine plus mood stabilizer (n=46) or placebo plus mood stabilizer (n=48) and followed up for 18 months. Median time to syndromic relapse was greater with combination therapy (94 vs. 41 days), while time to symptomatic relapse was significantly longer with adjunctive olanzapine (163 vs. 42 days) [Tohen et al., 2004].

4.2.6. Prophylaxis of bipolar II and the role of antidepressants

The majority of the trials mentioned above were conducted in patients with the bipolar I type of illness. However, in the light of the substantial prevalence of bipolar disorders other than type I, the recommendations for their maintenance treatment are badly needed. Because in such disorders depressive conditions significantly prevail, the long-term management of bipolar depression is also an important issue.

There is a scarcity of controlled trials assessing the efficacy of mood-stabilizing drugs in bipolar II patients. Such an assessment has usually been done by an analysis of a subset of bipolar II patients in the framework of a larger study. In the randomized trial of lithium vs. carbamazepine, these two drugs were shown to be equally efficacious in the maintenance treatment of bipolar II patients [Greil et al., 1998]. In the study of rapid cycling bipolar patients, lamotrigine was more effective in the maintenance treatment of those with the bipolar II type of illness [Calabrese et al., 2000].

The role of antidepressant drugs in the long-term treatment of bipolar illness remains controversial. There is a consensus that in bipolar I patients, antidepressants should be used concomitantly with mood-stabilizing drugs. They also should be discontinued after recovery from the depressive episode to prevent subsequent switch into mania or a rapid cycling course. However, in a proportion of patients (about 20%), the discontinuation of antidepressant

Table 4.2.1.

Recommended first-line prophylactic treatments for bipolar disorder (modification of Grunze et al., 2004)

Illness type	Monotherapy	Combination
Bipolar I regular	Lithium	+ MS or olanzapine
Bipolar I mania-dominant	Olanzapine	+ MS
Bipolar I depression dominant	Lamotrigine	+ MS (mainly lithium)
Bipolar I rapid cycling	_____	Lithium + Carbamazepine or Valproate
Bipolar I refractory	Clozapine	+ MS
Bipolar II regular	Lithium	+/or MS
Bipolar II rapid cycling	Lamotrigine	+ MS (mainly lithium)

MS – "classic" mood stabilizers (lithium, carbamazepine, valproate)

is connected with a depressive relapse and the continuation is not associated with an increased rate of switching into mania [Post et al., 2003]. There is less concern for long-term administration of antidepressants in bipolar II illness, and some authors even propose using these drugs as monotherapy on a maintenance basis [Amsterdam & Brunswick, 2003].

4.2.7. Conclusions

It seems that despite the heterogeneity and complex nature of bipolar illness, functional recovery may be possible by means of optimal long-term pharmacological treatment using monotherapy with mood-stabilizing drugs, or (more often) a combination of them.

According to the recent guidelines of the World Federation of Societies of Biological Psychiatry [Grunze et al., 2004], lithium monotherapy could still be considered the first choice treatment for classical bipolar I or bipolar II disorder without rapid cycling. For bipolar disorder I with rapid cycling, the best evidence exists for a lithium + carbamazepine or lithium + valproate combination, and for bipolar II with rapid cycling, for monotherapy with lamotrigine. Atypical psychotics, especially olanzapine, alone or in combination, are especially helpful in bipolar I disorder of mania-dominant type, and lamotrig-

ine is useful in bipolar I or II with depression-dominant type. Carbamazepine and valproate, alone or in combination with lithium, can be tried in cases of suboptimal lithium response or intolerance to this drug. Clozapine can be regarded as an option for very refractory cases of bipolar I illness (Table 1).

The optimization of long-term treatment of bipolar disorder may be further improved as the results of ongoing trials with second-generation antipsychotic drugs are analyzed, and these drugs will be prudently incorporated into the psychiatric armamentarium for the maintenance treatment of bipolar illness.

References

1. Ahrens B, Müller-Oerlinghausen B, Schou M, Wolf T, Alda M, Grof E et al. Excess cardiovascular and suicide mortality of affective disorders may be reduced by lithium prophylaxis. J Affect Disord. 1995; 33: 67-75.
2. Altamura AC, Salvadori D, Madaro D, Santini A, Mundo E. Efficacy and tolerability of quetiapine in the treatment of bipolar disorder: preliminary evidence from a 12-month open-label study. J Affect Disord. 2003; 76: 267-271.
3. Amsterdam JD, Brunswick DJ. Antidepressant monotherapy for bipolar type II major depression. Bipolar Disord. 2003; 5: 388-395.
4. Angst J, Gamma A. A new bipolar spectrum concept: a brief review. Bipolar Disord. 2002; 4 (suppl 1): 11-14.
5. Baastrup PC. The use of lithium in manic-depressive psychoses. Compreh Psychiatry. 1964; 5:396-408.
6. Baastrup PC, Schou M. Lithium as a prophylactic agent. Its effect against recurrent depression and manic-depressive psychosis. Arch Gen Psychiatry. 1967; 16: 162-172.
7. Baastrup PC, Poulsen JC, Schou M, Thomsen K. Prophylactic lithium: double-blind discontinuation in manic-depressive and recurrent depressive disorders. Lancet. 1970; 2: 326-330.
8. Baldessarini RJ, Tondo L. Does lithium treatment still work? Evidence of stable response over three decades. Arch Gen Psychiatry 2000; 57: 187-190.
9. Bauer MS, Mitchner L. What is a „mood stabilizer"? An evidence-based response. Am J Psychiatry. 2004; 161: 3-18.
10. Bowden CL, Calabrese JR, McElroy SL, Gyulai L, Wassef A, Petty F et al. A randomized, placebo-controlled 12-month trial of divalproate and lithium in treatment of patients with bipolar I disorder. Arch. Gen. Psychiatry. 2000; 57: 481-489.
11. Bowden CL. Pharmacological treatment of bipolar disorder: a review. In: Bipolar Disorders (Maj M, Akiskal HS, Lopez-Ibor JJ, Sartorius N, eds), John Wiley & Sons, Chichester, UK, 2002: 191-221.
12. Bowden CL, Calabrese JR, Sachs G, Yatham LN, Asghar S.A., Hompland M i wsp. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. Arch Gen Psychiatry. 2003; 60: 392-400.
13. Calabrese JR, Suppes T, Bowden CL, Sachs GS, Swann AC et al. A double-blind, placebo-controlled, prophylaxis study of lamotrigine in rapid-cycling bipolar disorder. J Clin Psychiatry. 2000; 61: 841-850.

14. Calabrese JR, Bowden CL, Sachs G, Yathan LN, Behnke K, Mehtonen O-P et al. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. J. Clin. Psychiatry. 2003; 64: 1013-1024.
15. Carta MG, Hardoy MC, Garofalo A, Carpiniello B. Quetiapine in long-term adjunctive treatment in refractory bipolar I disorder. Abstracts, American Psychiatric Association Annual Meeting, New York, May 1-6, 2004.
16. Ciaparelli A, Dell'Osso L, Pini S, Chiavacci MC, Fenzi M, Cassanio GB. Clozapine for treatment-refractory schizophrenia, schizoaffective disorder, and psychotic bipolar disorder: a 24-month naturalistic study. J Clin Psychiatry. 2000; 61: 329-334.
17. Ciapparelli A, Dell'Osso L, Bandettini di Poggio A, Carmassi C, Cecconi D, Fenzi M et al. Clozapine in treatment-resistant patients with schizophrenia, schizoaffective disorder, or psychotic bipolar disorder: a naturalistic 48-month follow-up study. J Clin Psychiatry. 2003; 64: 451-458.
18. Coppen A, Noguera R, Bailey J, Burns BH, Swani MS, Hare EH, Gardner R. Prophylactic lithium in affective disorders: controlled trial. Lancet 1971; 2: 275-279.
19. Coxhead N, Silverstone T, Cookson J. Carbamazepine versus lithium in the prophylaxis of bipolar affective disorder. Acta Psychiatr Scand 1992; 85: 114-118.
20. Cundall RL, Brooks PW, Murray LG. A controlled evaluation of lithium prophylaxis in affective disorders. Psychol Med. 1972; 2: 308-311.
21. Davis JM, Janicak PG, Hogan DM. Mood stabilizers in the prevention of recurrent affective disorder: a meta-analysis. Acta Psychiatr Scand. 1999; 100: 406-417.
22. Denicoff KD, Smith-Jackson EE, Disney ER, Ali SO, leverich GS, Post RM. Comparative prophylactic efficacy of lithium, carbamazepine, and the combination in bipolar disorder. J Clin Psychiatry. 1997; 58: 470-478.
23. Geddes JR, Burgess S, Kawton K, Jamison K, Goodwin GM. Long-term lithium therapy for bipolar disorder: systematic review and meta-analysis of randomized controlled trials. Am J Psychiatry. 2004; 161: 217-222.
24. Gelenberg AJ, Kane JM, Keller MB, Lavori P, Rosenbaum JF, Cole K, Lavelle J. Comparison of standard and low serum levels of lithium for maintenance treatment of bipolar disorder. N Eng J Med. 1989; 321: 1489-1493.
25. Greil W, Kleindienst N, Erazo N, Müller-Oerlinghausen B. Differenctial response to lithium and carbamazepine in the prophylaxis of bipolar disorder. J Clin Psychopharmacol. 1998; 18: 455-460.
26. Grof P. Excellent lithium responders: people whose lives have been changed by lithium prophylaxis. In: Birch NJ, Gallicchio VS, Becker RW (eds). Lithium: 50 Years of Psychopharmacology, New Perspectives in Biomedical and Clinical Research. Cheshire, Connecticut, Weidner Publishing Group, 1999:36-51.
27. Grof P. Has the effectiveness of lithium changed? Impact of the variety of lithium's effects. Neuropsychopharmacol. 1998; 19: 183-188.
28. Grunze H, Kasper S, Goodwin G, Bowden C, Möller H-J, WFSBP Task Force on Treatment Guidelines for Bipolar Disorders. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders, part III: maintenance treatment. World J Biol Psychiatry. 2004; 5: 120-135.
29. Guscott R, Taylor L. Lithium prophylaxis in recurrent affective illness. Efficacy, effectiveness and efficiency. Br J Psychiatry. 1994; 164: 741-746.
30. Gyulai L, Bowden CL, McElroy SL, Calabrese JR, Petty F, Swann AC et al. Maintenance efficacy of divalproex in the prevention of bipolar depression. Neuropsychopharmacol. 2003; 28: 1374-1382.
31. Hartigan GP. The use of lithium salts in affective disorders. Br J Psychiatry. 1963; 109:810-814.
32. Hullin RP, McDonald R, Allsopp MN. Prophylactic lithium in recurrent affective disorders. Lancet. 1972; 1: 1044-1046.

33. Johnson RE, McFarland BH. Lithium use and discontinuation in a health maintenance organization. Am J Psychiatry. 1996; 153: 993-1000.
34. Ketter T., Calabrese J.R.: Stabilization of mood from below versus above baseline in bipolar disorder: A new nomenclature. J. Clin. Psychiatry. 2002; 63: 146-151.
35. Lambert PA, Carraz G, Borselli S, Carbel S. Action neuropsychotrope d'un nouvel anti-epileptique: le depamide. Ann Med Psychol. 1966, 1, 707-710.
36. Lambert PA, Borselli S, Marcou G, Bouchardy M, Cabrol G. Action thymoregulatrice a long terme de Depamide dans la psychose maniaco-depressive. Ann Med Psychol... 1971; 2: 442-447.
37. Lambert PA, Venaud G. A comparative study of valpromide versus lithium in the prophylaxis of thymic disorders. Nervure. 1992; 5: 57-65.
38. Lusznat RM, Murphy DP, Nunn CMH. Carbamazepine vs. lithium in the treatment and prophylaxis of mania. Br J Psychiatry 1988; 153: 198-204.
39. Maj M, Pirozzi R, Magliano L, Bartoli L. Long-term outcome of lithium prophylaxis in bipolar disorder: a 5-year prospective study of 402 patients at a lithium clinic. Am J Psychiatry. 1998; 155: 30-35.
40. Maj M, Pirozzi R, Magliano L. Late non-response to lithium prophylaxis in bipolar patients: prevalence and predictors. J Affect Disord 1996; 39:39-42.
41. Markar HR, Mander AJ. Efficacy of lithium prophylaxis in clinical practice. Br J Psychiatry. 1989; 155: 496-500.
42. McQuade R, Sanchez R, Marcus R, Carson W, Rollin L, Iwamoto T, Stock E. Aripiprazole for relapse prevention in bipolar disorder in a 26-week trial. Int J Neuropsychopharmacol. 2004, 7 (Suppl.1), S160.
43. Melia PI. Prophylactic lithium: a double-blind trial in recurrent affective disorders. Br J Psychiatry. 1970; 116: 621-624.
44. Moncrieff J. Lithium: evidence reconsidered. Br J Psychiatry. 1997; 171: 113-119.
45. Müller-Oerlinghausen B, Müser-Causemann B, Volk J. Suicides and parasuicides in a high-risk patient group on and off lithium long-term medication. J Affect Disord. 1992; 25: 261-270.
46. Müller-Oerlinghausen B, Ahrens B, Grof E, Grof P, Lenz G, Schou M et al. The effect of long-term lithium treatment on the mortality of patients with manic-depressive and schizoaffective illness. Acta Psychiatr Scand. 1992; 86: 218-222.
47. Okuma T, Kishimoto A, Inue K. Anti-manic and prophylactic effect of carbamazepine (Tegretol) on manic depressive psychosis. Folia Psychiatr Neurol Japn. 1973; 27: 283-297.
48. Passmore MJ, Garnham J, Duffy A, MacDougall M, Munro A, Slaney C et al. Phenotypic spectra of bipolar disorder in responders to lithium versus lamotrigine. Bipolar Disord. 2003; 5: 110-114.
49. Perugi G, Micheli C, Akiskal HS, Madaro D, Socci C, Quilici C, Musetti L. Polarity of the first episode, clinical characteristics, and course of manic depressive illness: a systematic retrospective investigation of 320 bipolar patients. Compr Psychiatry. 2000; 41: 13-18.
50. Placidi GF, Lenzi A, Lazzerini F, Cassano GB, Akiskal HS. The comparative efficacy and safety of carbamazepine vs lithium: a randomized, double-blind 3-year trial in 83 patients. J Clin Psychiatry. 1986; 47: 490-494.
51. Post RM, Uhde TW, Ballenger JC, Squillace KM. Prophylactic efficacy of carbamazepine in manic-depressive illness. Am J Psychiatry. 1983; 140: 1602-1604.
52. Post RM, Leverich GS, Nolen WA, Kupka RW, Altshuler LL, Frye A et al. A re-evaluation of the role of antidepressants in the treatment of bipolar depression: data from the Stanley Foundation Bipolar Network. Bipolar Disord. 2003; 6: 396-406.
53. Prien RF, Caffey EM, Klett CJ. Prophylactic efficacy of lithium carbonate in manic-depressive illness. Arch Gen Psychiatry. 1973; 28: 337-341.
54. Pużyński S, Klosiewicz L. Valproic acid amide in the treatment of affective and schizoaffective disorders. J Affect Disord. 1984; 6: 115-121.

55. Rybakowski JK, Chlopocka-Wozniak M, Suwalska A. The propylactic effect of long-term lithium administration in bipolar patients entering lithium treatment in the 1970s and 1980s. Bipolar Disord. 2001; 3: 63-67.
56. Rybakowski JK, Suwalska A, Lojko D, Rymaszewska J, Kiejna A. Bipolar mood disorders among Polish psychiatric outpatients treated for major depression. J Affect Disord. 2005; 84: 141-147.
57. Rybakowski JK, Suwalska A, Czerski PM, Dmitrzak-Weglarz M, Leszczynska-Rodziewicz A, Hauser J. Prophylactic effect of lithium in bipolar affective illness may be related to serotonin transporter genotype. Pharamacol Rep. 2005; 57: 124-127.
58. Rybakowski JK, Suwalska A, Skibinska M, Szczepankiewicz A, Leszczynska-Rodziewicz A, Permoda A et al. Prophylactic lithium response and polymorphism of the brain-derived neurotrophic factor gene. Pharmacopsychiatry. 2005; 38: 166-170.
59. Sanger TM, Grundy SL, Gibson PJ, Namjoshi MA, Greaney MG, Tohen MF. Long-term olanzapine therapy in the treatment of bipolar I disorder: open-label continuation phase study. J Clin Psychiatry. 2001; 62: 273-281.
60. Schou M. Normothymics, "mood-normalizers". Are lithium and imipramine drugs specific for affective disorders? Br J Psychiatry. 1963; 108: 803-809.
61. Serretti A, Lilli R, Lorenzi C, Gasperini M, Smeraldi E: Tryptophan hydroxylase gene and response to lithium prophylaxis in mood disorders. J Psychiatr Res. 1999; 33: 371-377.
62. Stallone F, Shelley E, Mendlewicz J, Fieve RR. The use of lithium in affective disorders, III: a double-blind study of prophylaxis in bipolar disorder. Am J Psychiatry. 1973; 130: 1006-1010
63. Strzyzewski W., Rybakowski J., Chlopocka-Wozniak M., Czerwinski A.: Klozapina w leczeniu stanów maniakalnych. Psychiatr Pol. 1981; 15: 331-332.
64. Suppes T, Webb A, Paul B, Carmody T, Kraemer H, Rush AJ. Clinical outcome in a randomized 1-year trial of clozapine versus treatment as usual for patients with treatment-resistant illness and a history of mania. Am J Psychiatry. 1999; 156: 1164-1169.
65. Takezaki H, Hanaoka M. The use of carbamazepine in the control of manic-depressive psychosis and other manic-depressive states. Clin Psychiatry. 1971; 13: 173-183.
66. Tohen M, Marneros A, Bowden C, Calabrese J, Greil W, Koukopoulos A et al. Olanzapine versus lithium in relapse prevention in bipolar disorder: a randomized double-blind controlled 12-month clinical trial. Bipolar Disord 2002, 4 (Suppl.1), 135.
67. Tohen MF, Bowden CL, Calabrese JR, Sachs GS, Jacobs T, Baker RW, Evans AR. Olanzapine versus placebo for relapse prevention in bipolar disorder. Abstracts, APA 156th Annual Meeting, San Francisco, May 17-22, 2003a: 73.
68. Tohen M, Bowden CL, Rissen R, Detke HC, Calabrese JR. Olanzapine versus placebo in the prevention of relapse for mixed versus manic index episode patients. Scientific Abstracts, ACNP 42nd Annual Meeting, San Juan, Puerto Rico, December 7-11, 2003b: 97.
69. Tohen M, Ketter TA, Zarate CA, Suppes T, Frye M, Altshuler L et al. Olanzapine versus divalproex sodium for the treatment of acute mania and maintenance of remission: a 47-week study. Am J Psychiatry. 2003c; 160: 1263-1271.
70. Tohen M, Chengappa KN, Suppes T, Baker RW, Zarate CA, Bowden CL et al. Relapse prevention in bipolar disorder: 18-month comparison of olanzapine plus mood stabilizer v. mood stabilizer alone. Br J Psychiatry. 2004; 184: 337-345.
71. Turecki G, Grof P, Cavazzoni P, Duffy A, Grof E, Ahrens B et al. Evidence for a role of phospholipase C-gamma 1 in the pathogenesis of bipolar disorder. Mol Psychiatry. 1998; 3: 534-538.
72. Turecki G, Grof P, Grof E, D'Souza V, Lebuis L, Marineau C et al. Mapping susceptibility genes for bipolar disorder: a pharmacogenetic approach based on excellent response to lithium. Mol Psychiatry. 2001; 5: 570-578.
73. Vieta E, Goikolea J, Corballa B, Benabarre A, Reinares M, Martinez G et al. Risperidone safety and efficacy in the treatment of bipolar and schizoaffective disorders: results from a 6-month, multicenter open study. J Clin Psychiatry. 2001; 62: 818-825.

74. Vieta E, Brugue E, Goikolea JM, Sanchez-Moreno J, Reinares M, Comes M et al. Acute and continuation risperidone monotherapy in mania. Hum Psychopharmacol. 2004; 19: 41-45.
75. Watkins SE, Callender K, Thomas DR, Tidmarsh SF, Shaw DM. The effect of carbamazepine and lithium on remission from affective illness. Br J Psychiatry. 1987; 150: 180-182.
76. Wechsler RH, Warrington L, Dunn J, English P. Adjunctive ziprasidone in bipolar mania: short-term and long-term data. Abstracts, American Psychiatric Association Annual Meeting, New York, May 1-6, 2004.
77. Zarate CA. Is clozapine a mood stabilizer? J Clin Psychiatry. 1995; 56: 108-112.