Psychiatr. Pol. 2024; 58(2): 223–236
PL ISSN 0033-2674 (PRINT), ISSN 2391-5854 (ONLINE)
www.psychiatriapolska.pl
DOI: https://doi.org/10.12740/PP/169407

Sixty years of recurrence prevention in mood disorders

Janusz Rybakowski

Department of Adult Psychiatry, Poznań University of Medical Sciences
Corresponding member of the Polish Academy of Sciences

Summary

In 2023, we observed the sixtieth anniversary of the article by a British psychiatrist, Geoffrey Hartigan, demonstrating, for the first time, the possibility of preventing the recurrence of mood disorders by using lithium salts. Herein, a history of prevention of recurrences of mood disorders both worldwide and in Poland will be presented concerning both lithium and other mood-stabilizing drugs. The merit for verifying the prophylactic lithium effect in the 1960–1970s should be given to Danish researchers, Mogens Schou and Poul Baastrup. In Poland, the first paper on prophylactic lithium appeared already in 1971. In the 1970s, French researchers showed prophylactic activity of valproic acid amide, and Japanese researchers – of carbamazepine. In the 1980s, studies on valproic acid amide were performed in the 2nd Psychiatric Clinic of the Institute of Psychiatry and Neurology led by Prof. Pużyński. Since the mid-1990s, 2nd generation mood-stabilizing drugs have been introduced, including some atypical antipsychotics (clozapine, olanzapine, quetiapine, aripiprazole, risperidone) and an anticonvulsant drug, lamotrigine, showing prophylactic activity in bipolar mood disorder. The studies on lithium resulted in the identification of factors connected with its prophylactic efficacy as well as the antisuicidal, antiviral, and neuroprotective effects of this drug. From a sixty-year perspective following Hartigan's article, it seems that his pioneering concept on the possibility of pharmacological influence on the course of mood disorders was fully confirmed. Current Polish recommendations on pharmacological prophylaxis of mood disorders were presented in the books *Standardy leczenia niektórych zaburzeń psychicznych* and *Psychofarmakologia kliniczna*, both published in 2022.

Key words: bipolar mood disorder, prevention of recurrences, mood-stabilizing drugs

Introduction

In 2023, we observed the sixtieth anniversary of an article demonstrating, for the first time, the possibility of preventing the recurrence of mood disorders by using lithium salts. The author of the paper was a British psychiatrist, Geoffrey Philip Hartigan (1917-1968), known as "Toby", working in St. Augustine's Hospital in Chartham Down

[1]. Among 45 patients receiving lithium carbonate in this hospital during a period of six years, he presented his observations on long-term lithium administration (≥ three years) in seven patients with bipolar mood disorder (BD) and eight patients with recurrent depression. It transpired that in six persons from the first group and six from the second group there were no recurrences of the illness. This publication appeared 14 years after John Cade's article showing the therapeutic effect of lithium in manic states [2]. The next year after Hartigan's paper, a Danish psychiatrist, Poul Christian Baastrup, also presented his observations on the "prophylactic" effect in 11 BD patients receiving lithium for three years [3].

The pioneering idea of Hartigan was to point out the possibility of the favorable effect of lithium administration on the long-term course of mood disorders, including also recurrent depression. He referred to the terms "normothymotics" and "mood-normalizers", which were proposed by a Danish psychiatrist, Mogens Schou, in the article published in the same issue of the British Journal of Psychiatry, for lithium and imipramine, as the drugs normalizing moods in BD and unipolar depression, respectively [4]. Hartigan's demonstration of the preventive action against manic and depressive recurrences justified naming lithium a drug normalizing (stabilizing) mood. For such drugs, the name "mood-stabilizer" is presently used although in Polish and Russian psychiatric literature the term "normothymic drugs" has been employed.

In this article, a history of prevention of recurrences in mood disorders both worldwide and in Poland will be presented, concerning both lithium and other mood-stabilizing drugs, on the sixtieth anniversary of Geoffrey Hartigan's publication. The prevention of BD recurrences will be mostly discussed although such proceedings in unipolar mood disorder (recurrent depression) will be also noticed.

Worldwide studies on lithium prophylaxis in 1960-1990

In 1967, a paper by Danish psychiatrists mentioned in the introduction (Poul Baastrup and Mogens Schou) appeared, summarizing the experiences of lithium administration at an average of six years in 88 patients with bipolar and unipolar mood disorders treated in Glostrup psychiatric hospital. The periods of disturbed mood (mania or depression) during a year were compared. The results showed that the mean duration of disturbed mood during lithium administration was more than six-fold shorter compared to the period before lithium. This indicated a high probability of a favorable prophylactic effect of lithium on the course of mood disorders [5].

However, in the next year, a highly critical article against Danish research on the possibility of lithium prophylaxis appeared. It was published in the prestigious journal "Lancet", authored by the British psychiatrists Barry Blackwell and Michael Shepherd, and titled: "Prophylactic lithium: another therapeutic myth?". The authors voiced strong doubts about the results of the Danish researchers and postulated performing double-blind studies to verify them [6].

As if in response to the recommendation of the British authors, in 1970-1973, the results of eight placebo-controlled studies carried out in Europe (Denmark and UK) and the USA assessing the prophylactic efficacy of lithium were published. The patients participating in the trials had in the last two years at least two episodes of the illness. In the majority of the studies, a comparison of the course of the illness was made between patients in which lithium was replaced by a placebo and those continuing lithium (so-called "discontinuation design"). A recurrence of the illness was defined as a condition requiring psychiatric hospitalization or antidepressant/antimanic treatment. The overall analysis revealed that the percentage of patients with recurrences of depression or mania was significantly lower during lithium administration (mean 30%) than during placebo (mean 70%) [7].

The 1980s and 1990s made an apogee of lithium studies in mood disorders, mainly for prophylactic purposes. In some countries, a considerable percentage of patients with mood disorders were receiving the drug. In 1990-1994, a scientific journal "Lithium" was running. In 1989, a scientific society IGSLI (International Group for Study of Lithium-treated Patients) was initiated. Its creators were the Danish researcher Mogens Schou, Canadian psychiatrist of Czechoslovakian origin, Paul Grof, and German researcher, Bruno Müller-Oerlinghausen. The latter, at the beginning of the 1990s, led the clinical studies performed in countries of the IGSLI members showing that long-term lithium administration prevents suicides [8].

The 1990s also mark the beginning of the anti-pharmacological activity of a British psychiatrist, Joanna Moncrieff, who undermined the prophylactic properties of lithium in her two papers, recognizing significant methodological flaws in previous lithium research [9, 10]. Her articles were noted although had no impact on the practice of prophylactic lithium administration. Such contestant activity of the author has been going on until the present. As evidence of this is her recent article in "Molecular Psychiatry", where the role of serotonin in the pathogenesis of depression is denied as well as the therapeutic action of serotonergic antidepressants [11].

Studies on lithium prophylaxis in Poland, 1970-1990

The first Polish paper on the prophylactic effect of lithium salts was published in "Psychiatria Polska" already in 1971. It was about lithium administration to patients of the Nowowiejski Hospital and Outpatient Psychiatric Clinic in Warsaw. Eighteen patients were included, receiving lithium carbonate in doses of 500-1250 mg per day, to obtain a serum lithium concentration of about 0.6 mmol/l. All patients before starting lithium had frequent recurrences and hospitalizations. The duration of lithium treatment ranged from 2 months to 6.5 years. Four subjects of this group gave up lithium treatment. The analysis of disease course after the introduction of lithium corroborated the foreign studies suggesting that the drug contributed to a decrease in the duration and frequency of illness recurrences [12].

Five years later, a paper appeared coming from a Kraków center, with Ewa Broszkiewicz as the first author [13]. Among assessed patients, there were 11 receiving lithium for more than three years and 26 patients for which lithium was given for 2-3 years. Many patients had interruptions in lithium administration. In the first group, among five patients with continuous lithium treatment, the number of hospitalizations dropped from seven before lithium to zero on lithium. In 19 patients from the second group taking lithium continuously, the number of hospitalizations decreased from 31 before lithium to five on lithium.

In 1980, a paper was published in "Psychiatria Polska" coming from a Poznań center, analyzing 61 patients receiving lithium carbonate for an average of five years. All patients in the two years preceding lithium administration had at least two episodes of the illness. The "mirror image" method was applied to compare the course of the illness during lithium treatment with the analogous period before starting lithium. The analysis of all patients revealed that during lithium treatment, the number of recurrences decreased by 71%, and the number of hospitalizations by 72%. In 44% of patients, there were no recurrences [14]. In the same year, the Poznań center presented results obtained from the same group of patients showing a significant prophylactic lithium effect on depressive episodes and sex-related differences in lithium's prophylactic efficacy [15].

In 1996, the analysis of long-term lithium treatment (more than 10 years) was performed on a group of 30 patients attending the outpatient clinic of the Institute of Psychiatry and Neurology in Warsaw. During this period, in 18 patients (60%) with BD, nearly a total elimination of illness recurrences was noted. In the majority of the remaining ones, a favorable effect of lithium was observed in the first years of administration, while the recurrences appeared in the following years, mainly as depressive episodes [16].

Studies on the prophylactic effect of valproates and carbamazepine

At the beginning of the 1970s, clinical observations appeared showing that anticonvulsant drugs, such as valproates and carbamazepine, may have properties that prevent the recurrence of mood episodes in BD. French researchers led by Pierre Lambert found such action of valproic acid amide. They coined the French term "thymorégulatrice" to describe such an effect, which can allude to such names as "mood-normalizing" or "normothymic" [17]. The merit for demonstration of the prophylactic action of carbamazepine should be given to Japanese researchers led by excellent psychopharmacologist, Teruo Ōkuma (1926-2010) [18].

The studies on the prophylactic action of valproic acid amide were carried out in the 2nd Psychiatric Clinic of the Institute of Psychiatry and Neurology in Warsaw under the leadership of Prof. Stanisław Pużyński, and the first publication on this topic appeared in 1984. It was found that lithium administration for 26-51 months in 15 pa-

tients with BD or schizoaffective illness resulted in a reduction in the number, duration, and severity of mood episodes, mostly manic ones, as well as a significant decrease in the number and duration of hospitalizations [19]. In the next year, in "Psychiatria Polska" the experiences on a greater number of patients were presented (22 with BD and 15 with schizoaffective illness) confirming the prophylactic efficacy of the drug, used in the majority of patients in doses of 600-900 mg/day [20].

The studies on valproates in the USA in the 1990s were carried out under the leadership of eminent BD specialist, Charles Bowden. Valproic acid amide was not used anymore and the equimolar combination of sodium valproate and valproic acid named "divalproex" was employed. Besides the strong antimanic activity of this drug, its prophylactic effect preventing BD recurrences was demonstrated, similar to that of lithium [21]. Due to the intensive promotion of this drug by pharmacological companies, at the beginning of the 21st century, the use of valproates significantly increased, which resulted, among others, in a decrease in lithium administration. Such a situation imposed attempts to verify the real efficacy of both drugs, reflected by the project having the acronym BALANCE (**Bi**polar **A**ffective disorder **L**ithium/**AN**ti**C**onvulsant **E**valuation). In this study, the prophylactic efficacy of divalproex monotherapy, lithium monotherapy, and the combination of both drugs was assessed for two years in 330 BD patients (110 in each group). Better prophylactic efficacy of lithium monotherapy compared with divalproex monotherapy was found, while combined treatment with these drugs was the most effective [22].

In the 1980s and 1990s, the discoveries on carbamazepine in mood disorders, including its prophylactic effect can be a merit of American psychiatrists, the eminent BD specialists, such as Robert Post and Terrence Ketter [23]. In the 1990s, carbamazepine became the second drug after lithium used for the prophylaxis of mood disorders in Europe. In the late 1990s, German psychiatrists attempted to compare the prophylactic efficacy of carbamazepine and lithium within a study having the acronym MAP (**M**ulticenter study of long-term treatment of **A**ffective or schizoaffective **P**sychoses), where such an efficacy was assessed during 2.5 years. It was found that lithium was more efficacious in "classic" forms of BD, while carbamazepine – in atypical ones, e.g., with psychiatric comorbidity or mood-incongruent delusions [24]. The introduction of a carbamazepine derivative, oxcarbazepine, into psychiatric treatment in the 1990s should be mentioned. The prophylactic efficacy of oxcarbazepine in BD was demonstrated in many studies, also indicating that some pharmacokinetic and clinical properties of this drug can be more favorable than those of carbamazepine [25].

Introduction of the second generation of mood-stabilizing drugs

Lithium, valproates, and carbamazepine initiated a new category of psychotropic drugs known as "mood stabilizers". Such drugs can be defined as therapeutically effective in an acute episode of mania and/or depression and possessing prophylactic

activity (prevention of recurrences), evidenced by observation lasting at least one year. They should not cause worsening in any BD episodes. Such criterion is therefore not met by typical antipsychotic drugs which may cause depression and by antidepressant drugs which can induce mania. The author of this paper proposed in 2007 a distinction between mood-stabilizing drugs based on the chronology of their introduction. Lithium, whose prophylactic properties were first observed in the 1960s, as well as valproates and carbamazepine introduced in the 1970s, were defined as mood-stabilizing drugs of the first generation [26].

More than three decades passed from Hartigan's paper when American psychiatrists observing the effects of clozapine, a drug introduced to the USA several years earlier, suggested that it can possess mood-stabilizing properties. In 1995, a paper appeared with Carlos Zarate as the first author [27], where 17 BD patients successfully receiving clozapine for the treatment of mania were followed up for 16 ± 6 months. In 11 of them (65%), during the administration of clozapine there were no recurrences or hospitalizations. Twenty years later, Chinese authors performed a meta-analysis on the long-term treatment of clozapine where 15 papers were covered including more than 1,000 patients. In the article, the long-term efficacy of clozapine, both therapeutic and prophylactic was confirmed [28]. The predictive factors for good antimanic and prophylactic effects of clozapine were severe manic episodes with psychotic symptoms and psychomotor agitation. Thus, clozapine initiated the second generation of mood-stabilizing drugs [26].

The next atypical antipsychotic drug showing prophylactic efficacy in BD was olanzapine. The best preventive effect of olanzapine was noted in patients in whom the drug was therapeutically effective in acute manic episodes [29]. For the prevention of manic episodes, olanzapine turned out to be more efficacious than lithium [30], whereas the combination of olanzapine with lithium or valproate was prophylactically more effective than each of these drugs used alone [31].

Quetiapine, another atypical antipsychotic drug, proved to possess therapeutic and prophylactic properties for both psychopathological poles, i.e., mania and depression. For the prevention of depressive episodes, quetiapine was equally efficacious as lithium [32]. Similar to olanzapine, better prophylactic activity of quetiapine was observed when the drug was combined with lithium or valproate [33]. A four-year observation of the prophylactic efficacy of quetiapine used as monotherapy or combination therapy revealed that the percentage of patients free of recurrences on quetiapine alone was 29.3%, whereas in combination with lithium or valproate was 80% and 78.3%, respectively [34].

The prophylactic effect of aripiprazole, mostly against manic episodes, was demonstrated in a two-year study, published in 2007 [35]. Evidence was also obtained for better prophylactic efficacy of this drug when combined with lithium or valproate [36]. In 2010, the conclusions of a two-year study revealed a prophylactic effect of

long-acting injectable (LAI) risperidone, also mostly against manic episodes [37]. Previously, risperidone was found to augment the prophylactic effect of first-generation mood stabilizers [38].

The antipsychotics mentioned above such as clozapine, olanzapine, quetiapine, aripiprazole, and risperidone meet the criteria for second-generation mood-stabilizing drugs [26, 39]. It is worth mentioning that good results were recently obtained in the prevention of recurrences by LAI aripiprazole and risperidone [40]. There have been promising effects for prophylaxis of BD recurrences of other atypical antipsychotic drugs such as ziprasidone [41], asenapine [42], and paliperidone [43]. However, these drugs do not meet the criteria for mood stabilizers given above regarding monotherapy, duration of treatment, or efficacy in acute episodes. A candidate for the second-generation mood-stabilizing drugs can be lurasidone, similar to aripiprazole, classified as a third generation antipsychotic. It has been found that lurasidone exerts therapeutic action in bipolar depression as well as prophylactic activity in BD when administered long-term both as monotherapy or in combination with lithium or valproate [44, 45].

In addition to atypical antipsychotic drugs, the second generation of mood stabilizers was enhanced by a new anticonvulsant drug, lamotrigine. Among all mood-stabilizing drugs, lamotrigine exerts the strongest antidepressant activity and is thus regarded as a "mood stabilizer from below". Lamotrigine is effective in the treatment of bipolar depression and the prophylaxis of BD, preventing mostly depressive recurrences [46]. In a 1.5-year comparative study of lithium and lamotrigine, it was found that lithium was significantly better in the prevention of manic episodes while lamotrigine was superior in the prevention of depressive ones [47]. Predictive factors for the prophylactic efficacy of lamotrigine are different from those for lithium and clozapine. A good prophylactic effect of lamotrigine can be obtained in patients with chronic depressive episodes, rapid cycling, and comorbid anxiety conditions, e.g., panic disorder [48].

Lithium research at the turn of the century

In 1999, half a century after the introduction of lithium into contemporary psychiatry [2], and 36 years after Hartigan's article [1], a Canadian psychiatrist of Czechoslovakian origin, Paul Grof, presented the concept of "excellent lithium responders" (ELR) which assumes the existence of a group of BD patients in whom lithium monotherapy results in total elimination of the illness' recurrences [49]. At the Poznań center, an assessment of the percentage of ELR was performed, showing that about one-third of BD patients were free of recurrences during 10 years of lithium administration [50]. Several clinical factors connected with good prophylactic efficacy of lithium have been indicated, such as: moderate number of affective episodes with distinct periods of remission, the episode sequence mania-depression-remission, the absence of rapid cycling, and psychiatric comorbidity [51]. In their last meta-analysis, Kessing et al.

[52] indicated that in the BD population, lithium monotherapy is prophylactically more effective compared with monotherapy of any other mood-stabilizing drug. Recently, the Poznań center presented the case of a female patient receiving lithium for 50 years, with excellent results in many areas of health and social functioning [53].

Longitudinal lithium administration is associated with many favorable occurrences, the most important of which is preventing suicides. In this respect, lithium exerts the strongest effect among all mood-stabilizing drugs [8, 54]. In a Polish-American study, with the participation of the Department of Adult Psychiatry, Poznań University of Medical Sciences and the Depression Research Unit, University of Pennsylvania in Philadelphia, the antiviral effect of lithium against herpes viruses was shown. In lithium-treated patients, total elimination or significant decrease of labial herpes recurrences was observed [55]. Long-term lithium use exerts neuroprotective action, reflected in a decreased risk of dementia [56]. In a recent meta-analysis, a significant prophylactic effect of lithium was evidenced in unipolar depression which could confirm the results of the original Hartigan paper published sixty years ago [57].

Recurrence prevention in mood disorders sixty years after Hartigan's article

Sixty years of clinical experience have shown the unquestionable efficacy of mood-stabilizing drugs in the prevention of BD recurrences. As mentioned, BD patients in whom lithium monotherapy results in the total elimination of recurrences constitute about 30% [50]. A similar percentage of excellent prophylactic efficacy can probably be obtained with other mood-stabilizing drugs used in monotherapy, although the clinical characteristics of such responders could be specific for each drug, an example of which are patients with a good response to lamotrigine [48]. Therefore, it transpires that in the majority of BD patients, for obtaining optimal prophylactic effect, combination therapy with mood-stabilizing drugs is needed. The results of studies on the combination of atypical antipsychotic drugs with lithium or valproate have shown a better prophylactic effect compared to monotherapy with each of these drugs [31, 33, 36]. There have also been comparative analyses of various configurations of mood stabilizers [58].

The results of clinical studies have been reflected in the Polish recommendations for the prevention of recurrences in BD, which are included in the recent edition of standards for pharmacological treatment of psychiatric disorders, published in 2022 [59]. In the book, indications for drugs used in both monotherapy and combination therapy in BD of type I and II are presented. In the "classic" type of BD I, with moderate frequency of episodes, distinct periods of remission, and absence of major pathology of the central nervous system, lithium salts constitute the drug of choice. In the case of suboptimal effect after a year of treatment, combination therapy can be started, adding a second mood-stabilizing drug of the first or second generation. In BD with predominant manic episodes, it is recommended to continue olanzapine administration after a manic episode, especially if the drug had a beneficial effect in such an

episode. In the case of suboptimal effect after a year, a combination of olanzapine with one of the first-generation mood-stabilizers could be recommended. If side effects of olanzapine appear (e.g., excessive weight gain) the drug can be changed to quetiapine or aripiprazole. In BD type I with predominant depressive episodes, after such an episode administration of lamotrigine or quetiapine is recommended. In the case of suboptimal effect, a combination of lamotrigine or quetiapine with a first-generation mood-stabilizing drug is suggested, preferably with lithium, or a combination of lamotrigine with quetiapine. In the form of illness with atypical features (mixed episodes, mood-incongruent delusions, comorbidity of anxiety disorders), anticonvulsant drugs (valproates, carbamazepine, or lamotrigine) are indicated as the first choice. In the case of suboptimal effect, lithium or atypical mood-stabilizing antipsychotics could be added. In treatment-resistant BD I, the drug of choice is clozapine as monotherapy, with an option of adding a first-generation mood stabilizer, preferably lithium, which can prevent leukopenia. In the rapid-cycling form, combination therapy should be introduced from the start, beginning with a combination of two first-generation mood-stabilizing drugs, and a second-generation mood stabilizer can be later added as the third drug.

In the classic type of BD type II, lithium salts are the drug of choice which can be combined with another first-generation mood stabilizer. In the majority of such patients, there is a possibility of long-term administration of antidepressant drugs. Similar to BD I, in the atypical form of BD II (e.g., pathological EEG), initial recommendations point to carbamazepine or valproates, and after a suboptimal effect, lithium can be added. In the majority of such patients, antidepressant drugs can be administered. Promising experiences have been obtained for lamotrigine monotherapy in BD II with rapid cycling [60]. After a suboptimal effect, a first-generation mood stabilizer can be added, preferably lithium, and next, an atypical antipsychotic, as the third drug. In this form of illness, antidepressant drugs should be rather avoided.

Polish standards of BD prophylaxis take into account a drug choice based on the clinical characteristics of a patient. The use of lithium should be considered in each patient with a high risk of suicide. Such risk factors should be assessed based, among others, on family history of suicide, previous suicidal behavior in the patient as well as present life situation and clinical status of the patient. In a patient showing the clinical characteristics of ELR, lithium monotherapy could be sufficient. In the remaining patients showing a high risk of suicide, lithium should constitute an essential element of combination mood-stabilizer therapy. When structural changes of the brain by magnetic resonance or computer tomography or abnormal EEG findings are discovered, anticonvulsant drugs of the first generation (valproates, carbamazepine, or oxcarbazepine), or second generation (lamotrigine) are indicated. In the presence of manic mixed states, the anticonvulsants (valproate, carbamazepine) or some atypical mood-stabilizing antipsychotics (olanzapine, clozapine, quetiapine) show the best effect. In the presence of depressive mixed states, lithium, lamotrigine, and quetiapine

are indicated as monotherapy or in combination. In comorbid anxiety disorders, lamotrigine should be considered. In patients abusing alcohol or psychoactive substances, anticonvulsant drugs of the first or second generation as well as some atypical antipsychotics (clozapine, quetiapine) show beneficial effects. Among the first-generation mood stabilizers, the most neutral for weight gain is carbamazepine, and from the second-generation drugs – aripiprazole and lamotrigine.

The prophylaxis of depressive recurrences in unipolar mood disorder was described in the textbook "Psychofarmakologia kliniczna" published in 2022 [61]. In patients showing indications for pharmacological prophylaxis, the long-term administration of antidepressants is applied. However, lithium administration is also worth considering, especially in patients with poor prophylactic efficacy of antidepressants, with high suicidal tendencies as well as in those with good effects of lithium augmentation of antidepressants [62].

Thus, analyzing the events from the perspective of sixty years following Geoffrey Hartigan's article, it seems that his pioneering idea on the possibility of pharmacological influence on the course of mood disorders has been fully confirmed.

References

1. Hartigan GP. *The use of lithium salts in affective disorders.* Br. J. Psychiatry 1963; 109: 810–814.
2. Cade JFK. *Lithium salts in the treatment of psychotic excitement.* Med. J. Aust. 1949; 36(10): 349–352.
3. Baastrup PC. *The use of lithium in manic-depressive psychosis.* Compr. Psychiatry 1964; 5(6): 396–408.
4. Schou M. *Normothymotics, "mood-normalizers": Are lithium and the imipramine drugs specific for affective disorders?* Br. J. Psychiatry 1963; 109: 803–809.
5. Baastrup PC, Schou M. *Lithium as a prophylactic agent. Its effect against recurrent depression and manic-depressive psychosis.* Arch. Gen. Psychiatry 1967; 16(2): 162–172.
6. Blackwell B, Shepherd M. *Prophylactic lithium: Another therapeutic myth? An examination of the evidence to date.* Lancet 1968; 291(7549): 968–971.
7. Schou M, Thompsen K. *Lithium prophylaxis of recurrent endogenous affective disorders.* In: Johnson FN, ed. *Lithium research and therapy.* London: Academic Press; 1975. pp. 63–84.
8. Rybakowski J. *Lit – niezwykły lek w psychiatrii.* Poznań: Wydawnictwo Termedia; 2019. https://www.termedia.pl/Ksiazka/-279.
9. Moncrieff J. *Lithium revisited. A reexamination of the placebo-controlled trial of lithium prophylaxis in manic-depressive disorder.* Br. J. Psychiatry 1995; 167(5): 569–574.
10. Moncrieff J. *Lithium: Evidence reconsidered.* Br. J. Psychiatry 1997; 171: 113–119.
11. Moncrieff J, Cooper RE, Stockmann T, Amendola S, Hengartner MP, Horowitz MA. *The serotonin theory of depression: A systematic umbrella review of the evidence.* Mol. Psychiatry 2023; 28: 3243–3256. Doi: 10.1038/s41380-022-01661-0.

12. Krzyżowski J, Skaryszewska-Sawicka J, Marcjan K. *Profilaktyczne działanie soli litu w psychozach afektywnych.* Psychiatr. Pol. 1971; 5: 283–288.
13. Broszkiewicz E, Gątarski J, Polewka A, Zelewska M. *Problem wskazań do profilaktycznego stosowania litu.* Psychiatr. Pol. 1976; 10: 647–653.
14. Rybakowski J, Chłopocka-Woźniak M, Kapelski Z. *Ocena kliniczna skuteczności profilaktycznej długotrwałego stosowania węglanu litu u chorych z endogennymi zespołami depresyjnymi.* Psychiatr. Pol. 1980; 14: 357–361.
15. Rybakowski J, Chłopocka-Woźniak M, Kapelski Z, Strzyzewski W. *The relative prophylactic efficacy of lithium against manic and depressive recurrences in bipolar patients.* Int. Pharmacopsychiatry 1980; 15(2): 86–90.
16. Beręsewicz M. *Wyniki długotrwałej (powyżej 10 lat) kuracji węglanem litu.* Psychiatr. Pol. 1996; 30: 583–592.
17. Lambert PA, Borselli S, Marcou G, Bouchardy M, Cabrol G. *Action thymorégulatrice a long terme de Depamide dans la psychose maniaco-dépressive.* Ann. Med. Psychol. 1971; 2: 442–447.
18. Okuma T, Kishimoto A, Inue K. *Anti-manic and prophylactic effect of carbamazepine (Tegretol) on manic depressive psychosis.* Folia Psychiatr. Neurol. Jpn. 1973; 27(4): 283–297.
19. Pużyński S, Kłosiewicz L. *Valproic acid amide in the treatment of affective and schizoaffective disorders.* J. Affect. Disord. 1984; 6(1): 115–121.
20. Kłosiewicz L. *Zapobiegawcze działanie amidu kwasu walproinowego w chorobach afektywnych.* Psychiatr. Pol. 1985; 19: 23–29.
21. Bowden CL, Calabrese JR, McElroy SL, Gyulai L, Wassef A, Petty F et al. *A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. Divalproex Maintenance Study Group.* Arch. Gen. Psychiatry. 2000; 57(5): 481–489.
22. BALANCE investigators and collaborators; Geddes JR, Goodwin GM, Rendell J, Azorin J-M, Cipriani A, Ostacher MJ et al. *Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): A randomized open-label trial.* Lancet 2010; 375(9712): 385–395.
23. Post RM, Ketter TA, Denicoff K, Pazzaglia PJ, Leverich GS, Marangell LB et al. *The place of anticonvulsant therapy in bipolar illness.* Psychopharmacology (Berl.) 1996; 128(2): 115–129.
24. Kleindienst N, Greil W. *Differential efficacy of lithium and carbamazepine in the prophylaxis of bipolar disorder: Results of the MAP study.* Neuropsychobiology 2000; 42(Suppl 1): 2–10.
25. Rybakowski J. *Okskarbazepina w chorobie afektywnej dwubiegunowej.* Farmakoter. Psychiatr. Neurol. 2018; 34(2): 131–138.
26. Rybakowski JK. *Two generations of mood stabilizers.* Int. J. Neuropsychopharmacol. 2007; 10(5): 709–711.
27. Zarate CA, Tohen M, Banov MD, Weiss MK, Cole JO. *Is clozapine a mood stabilizer?* J. Clin. Psychiatry 1995; 56(3): 108–112.
28. Li XB, Tang YL, Wang CY, Leon de J. *Clozapine for treatment-resistant bipolar disorder: A systematic review.* Bipolar Disord. 2015; 17(3): 235–237.
29. Tohen MF, Calabrese JR, Sachs GS, Banov MD, Detke H, Risser R et al. *Randomized, placebo-controlled trial of olanzapine as maintenance therapy in patients with bipolar I disorder responding to acute treatment with olanzapine.* Am. J. Psychiatry 2006; 163(2): 247–256.

30. Tohen M, Greil W, Calabrese JR, Sachs GS, Yatham LN, Oerlinghausen BM et al. *Olanzapine versus lithium in the maintenance treatment of bipolar disorder: A 12-month randomized double-blind controlled clinical trial.* Am. J. Psychiatry 2005; 162(7): 1281–1290.
31. 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(4): 337–345.
32. Ketter TA, Miller S, Dell'Osso B, Wang PW. *Treatment of bipolar disorder: Review of evidence regarding quetiapine and lithium.* J. Affect. Disord. 2016; 191: 256–273.
33. Suppes T, Vieta E, Gustafsson U, Ekholm B. *Maintenance treatment with quetiapine when combined with either lithium or divalproex in bipolar I disorder: Analysis of two large randomized, placebo-controlled trials.* Depress. Anxiety 2013; 30(11): 1089–1098.
34. Altamura AC, Mundo E, Dell'Osso B, Tacchini G, Buoli M, Calabrese JR. *Quetiapine and classical mood stabilizers in the long-term treatment of bipolar disorder: A 4-year follow-up naturalistic study.* J. Affect. Disord. 2008; 110(1–2): 135–141.
35. Keck PE, Calabrese JR, McIntyre RS, McQuade RD, Carson WH, Eudicone JM et al.; Aripiprazole Study Group. *Aripiprazole monotherapy for maintenance therapy in bipolar I disorder: A 100-week, double-blind study versus placebo.* J. Clin. Psychiatry 2007; 68(10): 1480–1491.
36. Marcus R, Khan A, Rollin L, Morris B, Timko K, Carson W. *Efficacy of aripiprazole adjunctive to lithium or valproate in the long-term treatment of patients with bipolar I disorder with an inadequate response to lithium or valproate monotherapy: A multicenter, double-blind, randomized study.* Bipolar Disord. 2011; 13(2): 133–144.
37. Quiroz JA, Yatham LN, Palumbo JM, Karcher K, Kushner S, Kusumakar V. *Risperidone long-acting injectable monotherapy in the maintenance treatment of bipolar I disorder.* Biol. Psychiatry 2010; 68(2): 156–162.
38. Vieta E, Goikolea J, Corballa B, Benabarre A, Reinares M, Martínez G et al.; Group for the Study of Risperidone in Affective Disorders (GSRAD). *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(10): 818–825.
39. Rybakowski JK. *Meaningful aspects of the term 'mood stabilizer'.* Bipolar Disord. 2018; 20(4): 391–392.
40. Keramatian K, Chakrabarty T, Yatham LN. *Long-acting injectable second-generation/atypical antipsychotics for the management of bipolar disorder: A systematic review.* CNS Drugs 2019; 33(5): 431–456.
41. Bowden CL. *The role of ziprasidone in adjunctive use with lithium or valproate in maintenance treatment of bipolar disorder.* Neuropsychiatr. Dis. Treat. 2011; 7: 87–92.
42. Szegedi A, Durgam S, Mackle M, Yu SY, Wu X, Mathews M et al. *Randomized, double-blind, placebo-controlled trial of asenapine maintenance therapy in adults with an acute manic or mixed episode associated with bipolar I disorder.* Am. J. Psychiatry 2018; 175(1): 71–79.
43. Berwaerts J, Melkote R, Nuamah I, Lim P. *A randomized, placebo– and active-controlled study of paliperidone extended-release as maintenance treatment in patients with bipolar I disorder after an acute manic or mixed episode.* J. Affect. Disord. 2012; 138(3): 247–258.
44. Pikalov A, Tsai J, Mao Y, Silva R, Cucchiaro J, Loebel A. *Long-term use of lurasidone in patients with bipolar disorder: Safety and effectiveness over 2 years of treatment.* Int. J. Bipolar Disord. 2017; 5(1): 9.

45. Calabrese JR, Pikalov A, Streicher C, Cucchiaro J, Mao Y, Loebel A. *Lurasidone in combination with lithium or valproate for the maintenance treatment of bipolar I disorder.* Eur. Neuropsychopharmacol. 2017; 27(9): 865–876.

46. Besag FMC, Vasey MJ, Sharma AN, Lam ICH. *Efficacy and safety of lamotrigine in the treatment of bipolar disorder across the lifespan: A systematic review.* Ther. Adv. Psychopharmacol. 2021; 11: 20451253211045870.

47. Goodwin GM, Bowden CL, Calabrese JR, Grunze H, Kasper S, White R. *A pooled analysis of 2 placebo-controlled 18-month trials of lamotrigine and lithium maintenance in bipolar I disorder.* J. Clin. Psychiatry 2004; 65(3): 432–441.

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(2): 110–114.

49. 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. pp. 36–51.

50. Rybakowski JK, Chłopocka-Woźniak M, Suwalska A. *The prophylactic effect of long-term lithium administration in bipolar patients entering treatment in the 1970s and 1980s.* Bipolar Disord. 2001; 3(2): 63–67.

51. Rybakowski JK, Ferensztajn-Rochowiak E. *Updated perspectives on how and when lithium should be used in the treatment of mood disorders.* Expert Rev. Neurother. 2023; 23(2): 157–167. Doi: 10.1080/14737175.2023.2181076.

52. Kessing LV, Bauer M, Nolen WA, Severus E, Goodwin GM, Geddes J. *Effectiveness of maintenance therapy of lithium vs other mood stabilizers in monotherapy and in combinations: A systematic review of evidence from observational studies.* Bipolar Disord. 2018; 20(5): 419–431.

53. Ferensztajn-Rochowiak E, Chłopocka-Woźniak M, Rybakowski JK. *Ultra-long-term lithium therapy: All-important matters and a case of successful 50-year lithium treatment.* Braz. J. Psychiatry 2021; 43(4): 407–413.

54. Lewitzka U, Severus E, Bauer R, Ritter P, Müller-Oerlinghausen B, Bauer M. *The suicide prevention effect of lithium: More than 20 years of evidence – a narrative review.* Int. J. Bipolar Disord. 2015; 3: 32.

55. Rybakowski JK, Amsterdam JD. *Lithium prophylaxis and recurrent labial herpes infections.* Lithium 1991; 2: 43–47.

56. Rybakowski JK, Suwalska A, Hajek T. *Clinical perspectives of lithium's neuroprotective effect.* Pharmacopsychiatry 2018; 51(5): 194–199.

57. Undurraga J, Sim K, Tondo L, Gorodischer A, Azua E, Tay KH et al. *Lithium treatment for unipolar major depressive disorder: Systematic review.* J. Psychopharmacol. 2019; 33(2): 167–176.

58. Kishi T, Ikuta T, Matsuda Y, Sakuma K, Okuya M, Nomura I et al. *Pharmacological treatment for bipolar mania: A systematic review and network meta-analysis of double-blind randomized controlled trials.* Mol. Psychiatry 2022; 27(2): 1136–1144.

59. Rybakowski J. *Farmakoterapia choroby afektywnej dwubiegunowej.* In: Jarema M, ed. *Standardy leczenia farmakologicznego niektórych zaburzeń psychicznych.* Gdańsk: Via Medica; 2022. pp. 93–127.

60. Bowden CL, Calabrese JR, McElroy SL, Rhodes LJ, Keck PE Jr, Cookson J et al. *The efficacy of lamotrigine in rapid cycling and non-rapid cycling patients with bipolar disorder.* Biol. Psychiatry 1999; 45(8): 953–958.

61. Jaracz J. *Farmakologiczna profilaktyka nawrotów depresji.* In: Rybakowski J, ed. *Psychofarmakologia kliniczna.* Warszawa: Państwowy Zakład Wydawnictw Lekarskich; 2022. pp. 448–461.

62. Bauer M, Adli M, Ricken R, Severus E, Pilhatsch M. *Role of lithium augmentation in the management of major depressive disorder.* CNS Drugs 2014; 28(4): 331–342.

Address: Janusz Rybakowski
Department of Adult Psychiatry
Poznań University of Medical Sciences
Corresponding member of the Polish Academy of Sciences
e-mail: janusz.rybakowski@gmail.com