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Sebastian Kliwicki, Maria Chłopocka-Woźniak, Ewa Rudnicka, Janusz Rybakowski

Efficacy of long-term lithium-treatment in bipolar disorder

*Skuteczność długoterminowego stosowania litu w chorobie afektywnej dwubiegunowej**

Klinika Psychiatrii Dorosłych, Uniwersytet Medyczny w Poznaniu

ABSTRACT

Objectives. The aim of the study was to investigate the efficacy of long-term lithium administration in a large group of patients with bipolar disorder (BP) and to define factors associated with the efficacy of lithium treatment.

Material and methods. The study included 111 patients (76 women, 35 men), aged 34-85 (mean age 61 years) receiving lithium for 5-39 years (mean length 18 years). Lithium efficacy was assessed using a three-step scale identifying Excellent Responders (ER), Partial Responders (PR) and Non-Responders (NR), as well as the Alda Scale rating lithium efficacy within the range of 0-10. Various clinical factors that can be linked with lithium efficacy were also analysed, including age at onset of the illness, polarity of the first episode, age at the first occurrence of elevated or depressed mood, number of affective episodes preceding lithium treatment, duration of the illness prior to lithium treatment, type of BP (I or II), family history of affective illness, comorbidity of anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder, alcohol and medication abuse/dependence, suicide attempts preceding lithium therapy and the duration of lithium treatment.

Results. Among the patients studied, 27% met the criteria for ER, 63% for PR and 10% for NR. The mean score on the Alda scale was 6.6±2.5. A better effect of lithium prophylaxis was shown in patients with a later onset of the illness, without a family history of affective illness, having family members who receive lithium, in women with comorbid anxiety disorder and in men without alcohol abuse/dependence.

Conclusions. There are no recurrences of BP in about 30% of patients in long-term lithium treatment, independently of the duration of lithium administration. Also, in the present study, several other factors were identified connected with lithium efficacy.

STRESZCZENIE

Cel pracy. Celem pracy była ocena skuteczności długotrwałego stosowania litu w dużej grupie pacjentów z chorobą afektywną dwubiegunową (CHAD) oraz określenie czynników związanych z tą skutecznością.

Materiał i metody. Badaniem objęto 111 pacjentów (76 kobiet, 35 mężczyzn) w wieku 34–85 lat (średnio 61 lat) leczonych litem przez okres 5–39 lat(średnio 18 lat). Ocena skuteczności litu została przeprowadzona za pomocą trzystopniowej skali wyróżniającej Excellent Responders (ER), Partial Responders (PR) i Non-Responders (NR) oraz tzw. skali Alda oceniającej skuteczność profilaktyki litem w skali 0–10. Analizowano również czynniki kliniczne mogące mieć związek ze skutecznością, takie jak wiek zachorowania, biegunowość pierwszego epizodu, wiek wystąpienia fazy podwyższonego i obniżonego nastroju, liczba epizodów afektywnych przed włączeniem litu, długość choroby przed włączeniem litu, typ choroby (CHAD I i II), obciążenie dziedziczne chorobą afektywną, przyjmowanie litu w rodzinie, współwystępowanie zaburzeń lękowych, zaburzeń obsesyjno-kompulsyjnych, zespołu stresu pourazowego, uzależnienia od alkoholu, uzależnienia od leków, występowania prób samobójczych przed rozpoczęciem podawania litu oraz długości leczenia litem.

Wyniki. W badanej grupie 27% pacjentów spełniało kryteria ER, 63% – PR i 10% – NR. Średnia punktacja w skali Alda wynosiła 6,6±2,5. Lepszy wynik profilaktyki litem uzyskano u osób z późniejszym początkiem choroby, bez obcią-

* Artykuł w języku polskim jest dostępny w wersji elektronicznej (fpn.ipin.edu.pl).

żenia genetycznego chorobą afektywną, posiadających w rodzinie osoby zażywające lit, u kobiet ze współwystępowaniem zaburzeń lękowych oraz u mężczyzn nie nadużywających alkoholu.

Wnioski. U ok. 30% pacjentów w trakcie długotrwałego stosowania litu nie dochodzi do nawrotów choroby niezależnie od długości jego stosowania. W obecnym badaniu wyodrębniono również szereg czynników związanych ze skutecznością stosowania litu.

Key words: bipolar affective illness, lithium, long-term treatment

Słowa kluczowe: choroba afektywna dwubiegunowa, lit, leczenie długoterminowe

INTRODUCTION

In 1963 the British psychiatrist Geoffrey Hartigan, published a paper reporting on a three-year long lithium treatment of seven patients with bipolar affective disorder (BP) and eight with recurrent depression (Hartigan 1963). In his research, six patients from each group experienced no relapses throughout the lithium treatment. Similar observations were reported a year later by Danish psychiatrist Paul Christian Baastrup, who investigated 88 patients suffering from rapid cycling bipolar disorder in the psychiatric hospital in Glostrup (Baastrup 1964). During his six-year long study, Baastrup observed a statistically significant reduction in the frequency of phases during the treatment. Moreover, when the phases did occur, their intensity was much lower than before the treatment (Baastrup and Schou 1967).

In 1970-1973, results of eight controlled placebo studies were published on the prophylactic efficacy of lithium, conducted in the UK, Denmark and the USA. The course of the affective illness was compared between a group of patients who were given a placebo and a group which continued to be treated with lithium. An analysis of these studies, which involved almost 800 patients, demonstrated that relapses were significantly less frequent (30% on average) in a group treated with lithium than in the placebo group (70% on average) (Schou and Thompsen 1976).

The first results of Polish research on the use and prophylactic qualities of lithium salts were published in *Psychiatria Polska* in 1971; a report by Warsaw psychiatrists on the use of lithium carbonate in patients from the Nowowiejski Hospital and an Outpatient Mental Clinic. The research involved 18 patients, treated with lithium doses from 500 to 1250 mg/day to reach the level of 0.6 mEq/l in the blood serum. Prior to lithium treatment, all patients suffered from frequent relapses and hospitalizations. Lithium carbonate was administered for periods of between 2 to 42 months. Four patients from the group resigned from the treatment. The analysis of the course of illness after introducing lithium carbonate confirmed the reports of international researchers, who suggested that the drug contributed to reducing the frequency and duration of relapses (Krzyżowski et al. 1971).

In 1980 another study including 61 patients, treated with lithium for a five-year period on average, was published by researchers from the Psychiatric Clinic in Poznań, who asserted a significant reduction of relapses throughout lithium treatment (71%) and also in the number of hospitalizations (by 72%) and continued remission in 44% of their patients (Rybakowski et al. 1980). The study was conducted with the aid of the mirror image method, comparing the course of the illness during the lithium therapy with the analogous period preceding the treatment.

Another analysis of long-term, ten-year treatment with lithium carbonate was conducted in a group of patients treated in the Outpatient Clinic of the Institute of Psychiatry and Neurology in Warsaw. Approximately 40% of bipolar affective disorder patients were reported to display reduced frequency of relapses after several years of effective treatment with lithium carbonate (Beręsewicz, 1996).

In 1999 a Canadian psychiatrist, Paul Grof, introduced the concept of "excellent lithium responders" (ER) for patients who show a very good response to lithium, with no relapses of BP in 10-year and longer periods of lithium treatment. He suggested that such a response was characteristic of approximately one third of BP patients. This was later confirmed by the results of a study published in 2001 by the Adult Psychiatry Clinic in Poznań. The study compared the prophylactic effect of lithium in patients whose treatment began in the 1970s with those who began treatment in the 1980s. The two groups comprised 60 and 49 patients respectively, and they were both monitored for 10 years. The percentage of patients with excellent response to lithium (without any relapses) was similar in both groups: 35% in the 1970s group and 27% in

the 1980s group, whereas the level of lithium in the blood serum was slightly higher in the former (Rybakowski et al. 2001).

Nivoli et al. (2010) conducted a meta-analysis of research on long-term treatment with lithium aimed at preventing relapses of bipolar disorder. The researchers analysed data available from randomized clinical trials (RCT) regarding long-term lithium treatment. Six of those involved 1561 patients (adult and children) with bipolar I and II affective disorder, 534 of whom were treated with lithium. The analysis showed that lithium was much more effective than placebo in preventing mania and hypomania but had a weaker impact on depressive episodes. The efficacy of lithium treatment was similar to the effects of valproic acid. Lithium was proven to be a little less effective than lamotrigine and less effective than olanzapine in the prophylaxis of manic and mixed episodes.

Since the very beginning of lithium use, attempts have been made to identify the factors that could be used as predictors of its beneficial prophylactic effects on bipolar disorder. In his recent work about excellent lithium responders, Grof says that he refers to patients suffering from classic BP, with a moderate frequency of episodes and symptomless periods of remission between the episodes. These patients usually have no other comorbid conditions, such as e.g. anxiety disorder (Grof 2010). Grof also says that in the ER group there is more frequent occurrence of bipolar disorder in patients' family histories.

In 2005 Kleindienst et al. conducted a meta-analysis of 42 clinical studies investigating the efficacy of the prophylactic use of lithium, and isolated five predictive factors. Lithium therapy seemed to have produced good effects in patients with a manic followed by depressive episode sequence at the beginning of the illness, and late onset of the illness. Patients who were frequently hospitalized, with rapid cycling BP and depressive-manic sequence, showed worse therapeutic responses to lithium. The authors also described six other factors which might have had an impact on lithium efficacy: isolated episodes, an occurrence of at least one episode with psychotic symptoms, high frequency of affective episodes, long break between the first and the following episode and comorbidity with a personality disorder.

It was the aim of this study to evaluate the overall efficacy of lithium in a large group of patients with bipolar disorder who have been treated with lithium in the long-term for the prevention of relapses of the illness, and also to define the predictors of lithium efficacy.

RESEARCH METHODOLOGY

1. The sample

The sample included 111 patients with bipolar affective disorder (diagnosed according to ICD-10 and DSM-IV) treated in the Outpatient Clinic of the Adult Psychiatry Clinic of the Poznań University of Medical Sciences. The group comprised 76 women and 35 men, with a mean age of 61 (SD=11 years, 34-85 span). The period of treatment with lithium carbonate was 18±9 years, spanning from 5 to 39 years. The concentration of lithium in these patients' blood serum ranged from 0.5 to 0.8 mmol/l.

Twenty three patients (18 women, 5 men) had taken lithium for 5-10 years and 54 patients (36 women and 18 men) for 11-20 years. 34 patients, including 22 women and 12 men, had taken lithium for prophylactic purposes for over 20 years. 30 patients received lithium in monotherapy and the remaining in combination therapy with other mood stabilizers, such as valproic acid, lamotrigine, and carbamazepine.

The group characteristics are presented in Table 1.

Table 1. Age of patients and length of lithium administration in the group of women and men

	Total (n=111)	**Women** (n=76)	**Men** (n=35)
Age (mean±SD)	61±11 (34-85)	62,5±11 (34-85)	57±10,5 (35-78)
Length of lithium treatment (mean±SD)	18±9 (5-39)	18±9 (5-39)	19±9 (5-38)
5-10 years	23 (20.7%)	18 (23.6%)	5 (14.3%)
11-20 years	54 (48.7%)	36 (47.5%)	18 (51.4%)
>20 years	34 (30.6%)	22 (28.9)%	12 (34.3%)

2. Evaluation of lithium efficacy

a. The 3-categories scale

This is a three-step scale for the evaluation of the prophylactic efficacy of the long-term use of lithium salts in patients with BP. Patients who show a very good response to lithium treatment (no affective episodes occurring in lithium therapy) have been identified as *excellent lithium responders* (ER). Patients with partial response to lithium therapy (50% reduction in affective episodes in treatment, as compared with the number of episodes preceding lithium therapy) have been labelled as *partial lithium responders* (PR). The group of patients who

responded weakly or showed no response (below 50% reduction in affective episodes during lithium therapy as compared with the number of episodes prior to taking lithium carbonate have been identified as *lithium non-responders* – NR).

b. Alda Scale

The scale was developed by Canadian researchers (Grof et al. 2002), and has been called the Alda Scale after Martin Alda, who made a particular contribution to its present form. The tool measures the efficacy of prophylactic lithium therapy on a ten-point scale. An analysis of the course of bipolar disorder is based on two criteria: A and B. The difference between the components A and B produces the final evaluation of the patient's clinical condition in lithium therapy. Criterion A assesses an association between the treatment and a clinical response on a scale of 0 to 10. Criterion B comprises five subscales B1 to B5, each of which is evaluated on a scale of 0 to 2, and includes additional factors affecting the results of treatment.

3. Evaluation of the factors linked with lithium efficacy

The study analysed the overall efficacy of lithium, along with clinical factors which might have an impact on it. Each patient's course of illness was assessed individually. The analysis considered the age at onset of the illness, polarity of the first episode, age of the first occurrence of elevated mood, age of the first occurrence of the depressed mood, number of affective episodes before taking lithium, the length of illness prior to the treatment, type of bipolar disorder (BP I, BP II), heredity, intake of lithium in the family, comorbidity of anxiety disorder, obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD), alcohol dependence/abuse, medication dependence/abuse, suicide attempts and length of treatment. The standardized questionnaire MINI (Sheehen et al., 1998) was used to evaluate the patient's overall psychiatric condition and comorbidity of other symptoms and disorders.

4. Methodology of statistical calculations

Statistical calculations of a correlation between the response to lithium treatment and the investigated clinical factors were performed using the statistical package STATISTICA for Windows version 10, Chi-square and Student's t-distribution. A level of significance (p-value) of less than 0.05 was accepted for the statistical analysis.

The study has been approved by the Bioethical Committee of the Poznań University of Medical Sciences.

RESULTS

1. Overall prophylactic efficacy of lithium

The 3-categories scale

ER: 30 patients showed a very good response to the lithium carbonate treatment, including 30% of all tested women and 20% of men.

PR: 70 patients showed partial response to the lithium treatment, including 61% of all women and 69% of men.

NR: the no-response group comprised 11 patients with weak or no response to the lithium treatment, which was 9% of all tested women and 11% of men.

Alda Scale

The patients in our sample scored on average 6.6±2.5 on the Alda Scale. The score for women was 6.7±2.5 and men's 6.3±2.2 points. 15 patients, i.e. 13% of the group, reached the highest score (10); 9-10 points were scored by 30 patients (27%), a 7-8 points score was confirmed in 29 patients (26%) and 5-6 points in 31 patients, which is 28% of the sample. 0-4 points was the score of 21 patients (19% of the group).

The women's mean score on the Alda scale was 6.7±2.6 points. A definite majority of women (84%) scored over 5 points. 16% of all women reached 10 points in the Alda scale.

The men's mean score on the Alda scale was 6.3±2.2 points. Out of 35 men, 7 (20%) scored 8 points, and nearly half scored between 3 and 5 points. A maximum 10 points was scored by 3 (8%) men and 4 scored only 3 points.

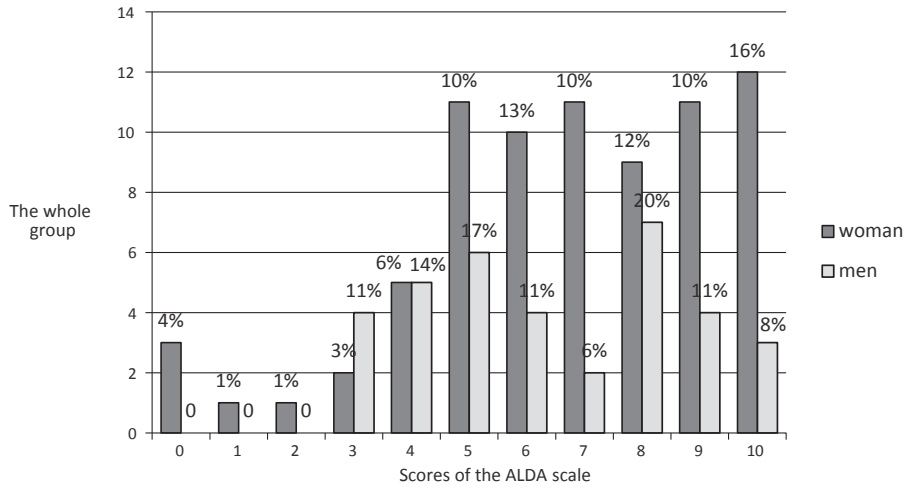
The distribution of ALDA scale scores for women and men is presented in Diagram 1.

2. Factors linked with lithium efficacy

The prophylactic efficacy of lithium measured with the Alda scale in relation to the age at onset, and course of the illness prior to lithium treatment, is presented in Table 2.

Higher Alda scale scores were reached by 42 patients whose illness began after their 34th birthday (38%), compared with 69 patients whose illness began at younger than 34 (62%). Yet the variation was not observed to be statistically significant (p=0.095). Patients with top scores (10 points) were oldest when they first fell ill with bipolar disorder.

In the case of women, the illness most often began with a depressive episode (59%) and in men with



Ill. 1. Distribution of scores of the Alda scale for 76 women and 35 men.

Table 2. Prophylactic efficacy of lithium measured with the Alda scale, in relation to the age at onset and the course of the illness preceding lithium treatment.

	ALDA SCALE		
	Total (n=111)	**Women (n=76)**	**Men (n=35)**
Age at onset of the illness <34	6,3±2,7	6,2±2,9	6,4±2,3
Age at onset of the illness >34	7,1±1,9	7,3±1,9	6,1±2,1
Beginning with a depressive episode	6.7±2.5	6.6±2.6	6.8±2.2
Beginning with a manic episode	6.5±2.5	6.9±2.6	6.0±2.2
Age at the first manic episode ≤34	6.2±2.8	6.1±3.1	6.4±2.5
Age at the first manic episode >34	6.9±2.2	7.1±2.2	6.3±1.9
Age at the first depressive episode ≤35	6.3±2.8	6.2±2.9	6.5±2.6
Age at the first depressive episode >35	6.9±1.9	7.4±1.9*	6.2±1.9
> 4 episodes of the illness before lithium treatment	6.6±2.5	6.6±2.1	6.8±3.3
≤ 4 episodes of the illness before lithium treatment	6.6±2.5	6.7±2.4	6.2±2.5
≤ 8 years preceding lithium treatment	6.4±2.6	6.3±2.8	6.6±2.5
> 8 years preceding lithium treatment	6.9±2.2	7.2±2.3	6.0±1.8

Student's t-distribution used for statistical calculations
* statistically significant correlation, p = 0.015

a manic episode (57%). The type of the first episode had no impact on the efficacy of lithium.

In our sample, patients whose first episode of mania occurred after 34 years of age showed a higher average score of response to lithium measured with the Alda scale, compared to those whose first manic episode took place before they were 34 years old. However, the difference was not statistically significant (p=0.08). Higher Alda scale scores were observed in women whose first depressive episode occurred after 35 years of age when compared to women who suffered from their first depressive episode before 35. The correlation was statistically significant (p=0.015).

In the whole group of patients the average number of BP episodes was 4±2. No significant correlation was observed between the response to lithium measured with the Alda scale and the number of episodes of the illness preceding the lithium treatment.

However, a better response to lithium measured with the Alda scale was observed in the group of women who were treated with lithium after more than 8 years from the onset of their illness compared to women whose treatment with lithium began earlier. The difference was not statistically significant (p=0.06).

The prophylactic efficacy of lithium measured with the Alda scale in relation to the type of ill-

ness, heredity and family history of taking lithium is shown in Table 3.

Alda scores were significantly higher in patients with BP II rather than BP I. The difference was also relevant in the group of women.

In our sample, 42 patients (38%) were affected by the family history of bipolar disorder (36 of BP I and 6 of BP II). Patients whose heredity involved bipolar disorder showed a significantly worse prophylactic response to lithium measured with the Alda scale. In the case of 17 patients (15%) at least one family member took lithium carbonate for its prophylactic effects. In this group the prophylactic effect of lithium measured with the Alda scale was better when compared with others. The difference was not statistically significant (p=0.064) in the whole group, yet it was confirmed in the group of men.

The prophylactic efficacy of lithium measured with the Alda scale in relation to the comorbidity of selected psychiatric disorders, dependency/abuse and suicide attempts prior to the lithium treatment is presented in Table 4.

Women with comorbid anxiety disorder scored higher on the Alda scale (mean 7.3) than women who did not suffer from anxiety (mean 6.3). However, the difference was not confirmed to be statistically significant (p=0.094). A reverse relationship was observed in the case of men: the mean result was 7.0 for

Table 3. Prophylactic efficacy of lithium measured with the Alda Scale in relation to the type of illness, heredity and presence of lithium treatment in the family.

	ALDA SCALE			
	Total (n=111)	**Women (n=76)**		**Men (n=35)**	
Type: bipolar I disorder	6.4±2.6	6.4±2.7		6.2±2.4	
Type: bipolar II disorder	7.2±2.1*	7.3±2.1*		6.6±1.9	
Hereditary taint	5.8±2.7	6.0±2.8		5.5±2.4	
		BP I	BP II	BP I	BP II
		n=25	n=4	n=11	n=2
No hereditary taint	7±2.2*	7.2±2.3		6.8±2	
Family members take lithium	7.6±2	7.4±1.9		7.8±2.2	
No family members take lithium	6.4±2.5	6.6±2.6		6.0±2.1*	

Student's t-distribution used for statistical calculations

Table 4. Prophylactic efficacy of lithium measured with the Alda scale in relation to comorbidity of selected psychiatric disorders, substance dependency/abuse and suicide attempts prior to lithium treatment.

	ALDA SCALE		
	Total (n=111)	**Women (n=76)**	**Men (n=35)**
Comorbid anxiety disorder	6.7±2.2	7.3±2	5.5±2.1*
No comorbid anxiety disorder	6.5±2.7	6.3±2.9	7.0±2.2
Comorbid OCD n=17	6.6±2.6	6.2±3.2	6.9±1.9
No comorbid OCD n=94	6.6±2.4	6.8±2.5	6.1±2.3
Comorbid PTSD	7.3±2.5	7.3±2.5	7.25±2.9
No comorbid PTSD	6.4±2.4	6.5±2.6	6.2±2.2
Alcohol dependence/abuse	5.9±2.4	6.5±2.6	5.4±2.2
No alcohol dependence/abuse	6.8±2.5	6.8±2.6	6.8±2.2
Medication dependence/abuse	6.3±2.7	6.5±2.9	6.1±2.3
No medication dependence/abuse	6.8±2.3	6.9±2.4	6.6±2.2
Suicide attempts preceding lithium treatment	6.1±2.6	6.0±2.7	6.5±2.6
No suicide attempts prior to the lithium treatment	6.8±2.3	7.0±2.5	6.3±2.4

Student's t-distribution used for statistical calculations

* Statistically significant correlation, p = 0.048

men without anxiety disorder, compared to the score of 5.5 for men with comorbid anxiety disorder. The difference was statistically significant (p=0.048).

Among the 17 patients who suffered from obsessive-compulsive disorder (OCD) there were 8 women (10.5%) and 9 men (26%). The Alda scores were a little higher for women without OCD and men with OCD but not in a statistically relevant way.

Post-traumatic stress disorder was observed in 26% of women and 11% of men. Patients with PTSD scored higher on the Alda scale than patients without it. This correlation was observed in relation to both men and women, yet it failed to reach the level of statistical significance.

Dependence on alcohol was confirmed in 17% of women and 34% of men. In the group of patients who depended on alcohol the mean result on the Alda scale was lower than the mean score in the group who suffered from no such addiction. Men who depended on alcohol scored significantly lower (5.4) when compared with other men in the group (6.8) but the difference was not statistically significant (p=0.083).

Medication dependence/abuse occurred in 44 patients, including 36% of women and 49% of men. Patients who were not dependent on medication scored higher on the Alda scale but the difference was not statistically relevant.

A better prophylactic effect of lithium carbonate was noted in the case of patients who had not attempted suicide prior to lithium treatment. Women whose history revealed no such incidents before lithium therapy scored higher on the Alda scale than female patients who had tried to commit suicide, but the difference was not statistically significant (0.07). None of the patients who had attempted suicide were in the NR group.

DISCUSSION

Many years of research into the efficacy of the prophylactic properties of lithium have allowed us to identify a group of patients whose lives have dramatically changed under the influence of the drug. Paul Grof, the Canadian psychiatrist, labelled this group as *excellent lithium responders* (ER). These are patients who have suffered from no relapses of the illness during the entire period of lithium monotherapy (10 years and longer), which is one third of all bipolar patients treated with lithium (Grof 1999).

In the current research conducted among patients who have received lithium for approximately 18 years, the ER criteria were met by 27% of patients, including 30% of women and 20% of men. Our study suggests that, on average, after 20 years of taking lithium carbonate every third patient will be free of symptoms. In the researched group 30% of patients scored 9-10 points on the Alda scale, which meant that they experienced no symptoms in lithium therapy. This is of course a combined effect of many psychosocial and biological factors.

In our sample, later age at onset of the first affective episode was linked with a better response to lithium therapy, and the person with the latest age at onset was found in the group of patients who had scored 10 on the Alda scale. There were no NR patients among those who became ill after 34 years of age. This confirms the data presented by Kleindienst et al. (2005) who, based on 10 studies involving 1,138 patients, showed a strong statistical correlation between later age at onset and a better prophylactic effect of lithium.

In the group of our patients, 60 people began their illness with an episode of depression and 17 of them showed a good response to lithium. An elevated mood episode marked the beginning of the illness in 51 patients, 13 of whom showed a very good response to lithium. In women, the illness began significantly more frequently with a depressive episode and in men with a manic episode. Our study showed no correlation between the type of the first episode of bipolar disorder (mania or depression) and the response to lithium. It should be mentioned, however, that Maj et al. (1989) showed a better effect of lithium treatment at the manic followed by depressive sequence of episodes, which was also confirmed by Kleindienst et al. (2005), based on the analysis of seven studies involving a total of 904 patients.

In our group of patients, the mean age of the occurrence of elevated mood as the first episode of bipolar disorder was 34, while in the group of patients with a good response to lithium the average age was 37. People who responded poorly to treatment with lithium carbonate experienced their first episode of elevated mood at a mean age of 28. There was also a better score on the Alda scale in the group of women whose first manic episode occurred after 34 years of age.

The mean age of the occurrence of the first depressive episode at the beginning of bipolar disorder was 34. Poor response to the prophylactic use of lithium was noted in patients who experienced their first depressive episode considerably earlier. The average age of the first depressive episode in the NR group was 26. Better results were noted in the group of women whose first depressive episode occurred after 35 as compared with a group of women who fell ill before 35.

No correlation was shown between the duration of the illness prior to the lithium treatment and response to the medication. These results differ from the conclusions reached by Franchini et al. (1999) and Ketter et al. (2006) who observed a better prophylactic effect of lithium in patients whose treatment began shortly after they became ill.

BP I was diagnosed in 79 patients in the group and BP II in 32 patients. Our study demonstrated a statistically significant correlation between a better response to lithium treatment (expressed by Alda score) and bipolar II disorder. This correlation was noted in relation to the whole group and the group of women with BP II. The relationship between the type of bipolar disorder and response to lithium was investigated by Kleindienst et al. (2005), based on 8 studies including altogether 1023 patients, without any unequivocal correlation being found.

In our group, patients whose history involved a hereditary component showed a worse response to lithium treatment. Patients who were not affected in this way showed statistically significant better scores on the Alda scale. These results are contrary to those presented by Mendlewicz et al. (1973) and Maj et al. (1984), who observed a reverse correlation, concluding that lithium produces better therapeutic effect in patients with a history of bipolar disorder in their family.

In our study group patients whose family members are also treated by lithium showed better prophylactic results. It is likely that a decision about introducing lithium in the treatment of other family members was linked with its efficacy in the case of a patient in our study group. This is also confirmed by Grof (2010), who says that a good response to lithium might be shown by a patient's relatives even in the next generation.

An interesting result of the present study is the finding of a different correlation between lithium efficacy and comorbid anxiety disorder in women and men. Women with comorbid anxiety disorder responded better to lithium therapy than men with the same comorbid disorder whose response to lithium carbonate was significantly worse. Young et al. (1993), who investigated the coexistence of anxiety disorder with bipolar disorder, did not find any correlation between these conditions and the response to lithium. Passmore et al. (2003), on the other hand, demonstrated on the basis of their observation of 164 persons from 21 families that lamotrigine produced a better therapeutic effect than lithium in patients with comorbid anxiety disorder.

Unlike other anxiety disorders, it has been observed that the co-occurrence of OCD was associated with a worse prophylactic effect of lithium, demonstrated in the Alda scale scores, in women than in men. Although these relationships did not reach statistical significance, this may indicate a distinct nature of OCD among other anxiety disorders, which has been considered in the latest edition of the DSM-5 (2013). In the available literature no studies have been found regarding the relationship between the response to lithium and the presence of obsessive-compulsive disorder.

24 patients in the study group were diagnosed with PTSD. These patients showed a better response to lithium, as measured on the Alda scale, compared to the patients without a PTSD diagnosis. A similar correlation obtained in men and women. We found no research on the relationship between the comorbidity of PTSD diagnosis and response to lithium treatment.

O'Connell et al. (1991) showed that dependence on alcohol and/or other substances was unconducive to a good response to lithium therapy. In our study, nearly 30% of the patients depended on medication, which was more than half of the patients with a poor response to the lithium treatment. Alcohol dependence was more often observed in men, who also showed a significantly worse response to the prophylactic properties of lithium. Kleindienst et al. (2005) analysed the impact of the dependence on alcohol and medication on lithium treatment, on the basis of the observation of 101 patients. However, they failed to confirm the existence of a correlation between comorbid alcohol or medication dependence and a prophylactic effect of lithium therapy.

A better prophylactic effect, measured on the Alda scale, was observed in patients who hadn't made suicide attempts preceding the lithium treatment, as compared with those who had. Following the introduction of lithium therapy, none of the patients displayed suicidal behaviour, which is linked with the anti-suicidal properties of lithium. None of the patients who had attempted suicide before lithium treatment was classified as NR. Lithium is a mood-stabilizing drug, with most frequently documented effects on suicidal behaviour, which was recently confirmed on the basis of the meta-analysis conducted by Cipriani et al. (2013).

CONCLUSIONS

1. Approximately 30% of bipolar disorder patients experience no relapses of the illness during long-term lithium therapy, independently of the duration of the treatment.

2. A beneficial effect of lithium is linked with older age at onset of the illness, bipolar II disorder, lack of 'hereditary taint', members of family taking lithium, comorbidity of anxiety disorder (in women) and lack of alcohol dependence (in men).

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Correspondence address:
Sebastian Kliwicki
Klinika Psychiatrii Dorosłych
Uniwersytet Medyczny w Poznaniu
ul. Szpitalna 27/33, 60-572 Poznań
phone: +48 698 007 302
e-mail: kliwicki@wp.pl