

# Lithium and valproate in manic and mixed states: a naturalistic prospective study

*Litio e valproato nel trattamento degli episodi maniacali e misti: studio prospettico osservazionale*

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## Summary

### Objectives

Lithium is still recommended as a first-choice treatment for acute bipolar mania, especially in pure euphoric mania of mild to moderate severity. Despite the large quantity of evidence supporting the efficacy of lithium, in clinical practice its use has often been limited because of management issues related to its narrow therapeutic index. International guidelines suggest combining lithium with a second mood stabilizer (anticonvulsant or atypical antipsychotic) for treatment of mixed states, rapid cycling and severe forms of mania with atypical features, which are classically considered to be poorly responsive to lithium alone. To date, however, the specific modalities of these associations on the basis of different clinical presentations have been poorly investigated in clinical trials. In this study, we aimed to evaluate the modalities of use of lithium in a naturalistic setting of manic and mixed bipolar patients, and to investigate the effects of its combination with valproate on the clinical course.

### Materials and methods

Seventy-five bipolar I patients (DSM-IV-TR) in a manic (14.7%) or mixed (85.3%) phase, treated with lithium alone or in association with valproate, were recruited at the day hospital of the Psychiatric Unit of the Department of Clinical and Experimental Medicine, University of Pisa, and followed-up in a naturalistic trial for an average period of 6 months. Diagnosis was confirmed using SCID-I. All subjects recruited underwent at least two standardized evaluations of clinical course, assessed by the

CGI-BP, at baseline and at each subsequent check of serum lithium levels. Variables concerning clinical features of patients and clinical course of episodes were analyzed by comparison between the two treatment groups (lithium monotherapy vs. lithium plus valproate).

### Results

The group of subjects treated with the combination of lithium and valproate ( $n = 41$ , 54.7%) was composed mainly of men, had a higher percentage of rapid cyclers and a higher severity of psychotic symptoms at baseline. The two treatment groups did not differ in the other demographic and clinical features analyzed. Patients treated with lithium plus valproate had a higher remission rate at endpoint than subjects treated with lithium monotherapy. The association of valproate significantly reduced the severity of specific symptomatological dimensions, such as mixed, anxiety and psychotic features.

### Conclusions

Our data confirm the use of combination therapy in more severe forms of mania. Prospective data on the clinical course have shown that the combination of lithium with valproate is associated with a greater improvement of specific symptomatological dimensions, which are poorly responsive to lithium monotherapy.

### Key words

Lithium • Valproate • Mania • Mixed state • Treatment • Bipolar disorder

## Introduction

Although in the last decades many pharmacological alternatives to lithium have become available, the drug is still recommended as a first-choice treatment for acute bipolar mania, as supported by the results of several clinical trials<sup>1,2</sup>.

Lithium monotherapy is indicated especially for patients with a classical (euphoric) presentation of mania of mild to moderate severity<sup>3,4</sup>. On the contrary, international

guidelines for the treatment of bipolar disorder (BD)<sup>5-8</sup> suggest combining lithium with a second mood stabilizer (anticonvulsant or atypical antipsychotics) for the treatment of severe and atypical manifestations of mania, with psychotic symptoms and high rates of psychiatric comorbidity<sup>9-14</sup>. This is consistent with common clinical practice, where is often necessary to use a polypharmacotherapy to treat different psychopathological dimensions of manic and mixed episodes<sup>15-17</sup>. To date, however, few

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studies have systematically investigated the efficacy of combination treatments in comparison with monotherapy consisting of single antimanic agent, and a proper algorithm regarding the specific modalities of these associations according to different clinical presentations is still lacking<sup>18-21</sup>.

Many questions concerning the optimal conditions of use of lithium remain open. Most of the studies with lithium have been conducted with very strict diagnostic inclusion criteria for BD, with exclusion of patients presenting atypical symptoms and psychiatric comorbidity. Thus, the results of these studies may not be generalized to the wide range of bipolar conditions<sup>22</sup>. This modality of patient selection, which is very restrictive compared to the current concept of bipolar spectrum<sup>23,25</sup>, helps to explain the discrepancy between "efficacy" and "effectiveness" of this treatment. Furthermore, the risk of toxicity related to the narrow therapeutic index of lithium has often limited its use in clinical practice, while increasing the prescription of other antimanic agents, such as valproate<sup>26,27</sup>. The optimal serum lithium concentration maintaining its therapeutic efficacy while minimizing side effects, also remain a debated question, as well as if specific combination treatments may have a selective efficacy on specific psychopathological dimensions.

The present study evaluated the prescribing patterns of lithium in a naturalistic setting of manic and mixed bipolar patients, and investigated the effects of its combination with valproate on clinical course.

## Materials and methods

In May 2010, the Psychiatric Unit of the Department of Clinical and Experimental Medicine, in collaboration with the Section of Pharmacology of the Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, started a naturalistic prospective study, still on-going, to evaluate the use of lithium in BD<sup>28</sup>. As part of this study, 75 patients (30 men and 45 women, mean age  $37.45 \pm 14.54$  years) in a manic ( $n = 11$ , 14.7%) or mixed ( $n = 64$ , 85.3%) episode according to DSM-IV-TR criteria<sup>29</sup>, and treated with lithium alone or in combination with valproate, were recruited and followed-up.

Patients were recruited among subjects consecutively admitted at the day hospital of the Psychiatric Unit during a 2-year period (May 2010-March 2012). All patients treated with antipsychotics or other mood stabilizers, with substance/alcohol abuse until three months before study entry and/or with severe somatic disorders were excluded. All subjects participated voluntary in the study after written informed consent for the assessment procedures was obtained.

The collection of data at baseline took place during an

interview lasting about two hours, often in the presence of a family member, using the SCID-I (Structured Clinical Interview for DSM-IV-TR Axis I Disorders)<sup>30</sup> to establish the diagnosis of BD type I and the presence of a manic or mixed episode. To complete the diagnostic picture, information obtained from every available source was used: medical history, previous medical data and information from first-degree relatives.

The 75 patients recruited underwent at least two standardized assessments of the symptomatology through the administration of the Clinical Global Impression Bipolar Version Scale (CGI-BP)<sup>31</sup>. In addition to baseline evaluations, the CGI-BP was administered at each subsequent check of serum lithium levels. All baseline and follow-up assessments were performed by resident clinicians not directly involved in the clinical management of the patients and trained to use the assessment scales. Clinicians from the Section of Pharmacology analyzed blood samples of patients to determine serum lithium levels.

Each patient was followed-up for an average period of 6 months. The frequency of clinical and biological assessments was established by independent psychiatrists who were in charge of the therapeutic management of patients, on the basis of variations in clinical symptoms. In the present study, data from clinical and biological evaluations that had a minimum interval of 14 days and a maximum of 42 days (mean interval 25 days) were analyzed.

Considering pharmacological treatment, 34 patients (45.3%) were treated with lithium monotherapy and 41 patients (54.7%) were treated with the combination of lithium and valproate. The daily dose was of  $664 \pm 165$  mg/day for lithium carbonate (range: 450-1200 mg/day) and  $822 \pm 294$  mg/day for sodium valproate (range: 500-1250 mg/day). The mean serum lithium level (mean  $\pm$  SD; mEq/l) was  $0.50 \pm 0.16$ , while those of valproate (mean  $\pm$  SD; mg/l) was  $54.68 \pm 23.41$ . Variables concerning the clinical features of the sample and the clinical course of episode were analyzed by comparison between the two treatment groups.

Episodes were considered to be in remission when the CGI-BP score for global illness severity achieved and maintained a value of 1 (normal, not ill) or 2 (minimally ill) for at least two subsequent evaluations during the observational period. Symptomatic improvement was assessed by the reduction, between baseline and endpoint, of at least 3 points in the CGI-BP scores indicating the severity of different symptomatological dimensions of a manic/mixed episode.

## Statistical analysis

Comparison of categorical variables between the two groups was carried out using chi-square analysis, whereas that of dimensional variables by the t-test. A p value

**TABLE I.**  
Demographic and clinical features. *Caratteristiche cliniche e demografiche.*

	Lithium (n = 34)	Lithium + Valproate (n = 41)		
	N (%)	N (%)	$\chi^2$	p value
Gender (female)	26 (76.5%)	19 (46.3%)	7.030	.007
Marital status (married)	9 (26.5%)	16 (39%)	1.318	.184
Employment (employed)	23 (67.6%)	30 (73.2%)	.274	.393
Index episode (Mixed)	28 (82.4%)	36 (87.8%)	.441	.366
Polarity of onset (Manic/Mixed)	9 (40.9%)	18 (56.2%)	1.227	.203
Rapid cyclers	2 (5.9%)	12 (29.3%)	6.695	.009
Comorbidity PD	14 (41.2%)	20 (48.8%)	.434	.336
Comorbidity OCD	10 (52.6%)	5 (35.7%)	.930	.271
Previous alcohol/substances abuse	2 (12.5%)	8 (36.4%)	2.720	.099
	M $\pm$ DS	M $\pm$ DS	F	p value
Mean age	38.00 $\pm$ 14.00	36.97 $\pm$ 15.16	.299	.766
Schooling (years)	13.88 $\pm$ 3.05	12.83 $\pm$ 3.63	.971	.388
Serum lithium level (mEq/l)	0.49 $\pm$ 0.15	0.50 $\pm$ 0.17	.186	.853
Numbers of previous episodes:				
Manic	3.86 $\pm$ 4.25	3.12 $\pm$ 3.09	.148	.707
Mixed	7.25 $\pm$ 3.41	5.00 $\pm$ 3.50	3.144	.086
Depressive	4.75 $\pm$ 2.95	4.21 $\pm$ 2.54	.246	.624
Severity of illness <sup>*</sup>	4.2 $\pm$ 1.1	4.4 $\pm$ 1.2	.616	.435
Severity of psychopathological dimensions of episode <sup>†</sup> :				
Manic symptoms	4.0 $\pm$ 1.0	4.1 $\pm$ 0.9	.476	.493
Mixed symptoms <sup>‡</sup>	4.4 $\pm$ 1.0	4.7 $\pm$ 0.9	1.339	.252
Depressive symptoms <sup>‡</sup>	3.8 $\pm$ 0.9	3.7 $\pm$ 0.8	.574	.452
Anxiety symptoms	4.0 $\pm$ 1.0	4.4 $\pm$ 0.9	1.843	.179
Psychotic symptoms <sup>§</sup>	3.7 $\pm$ 0.9	4.8 $\pm$ 1.1	8.566	.006

<sup>\*</sup> Scores at baseline assessed by the CGI-BP subscale for overall illness severity; <sup>†</sup> Scores at baseline assessed by the CGI-BP subscale for severity of various psychopathological dimensions; <sup>‡</sup> Evaluated on 64 patients with mixed episode; <sup>§</sup> Evaluated on 36 patients with psychotic symptoms.

less than 0.05 was considered statistically significant. All statistical analyses were carried out using the Statistical Package for Social Science, version 16.0.

## Results

Comparing the demographic and clinical features of subjects between the two treatment groups, it emerged that the group of patients taking lithium and valproate was composed mainly of men (53.7% vs. 26.5%;  $\chi^2 = 7.030$ ;  $p = .007$ ); furthermore, these patients had a higher percentage of rapid cycling (29.3% vs. 5.9%;  $\chi^2 = 6.695$ ;  $p = .009$ ) and a higher CGI-BP score for the severity of

psychotic symptoms at baseline (4.8  $\pm$  1.1 vs. 3.7  $\pm$  0.9;  $T = 8.566$ ;  $p = .006$ ), compared with those without valproate (Table I). The two treatment groups did not differ in terms of polarity of onset, number of previous episodes, rate of psychiatric comorbidity, polarity of index episode or in severity of current episode assessed by the CGI-BP. At endpoint, patients treated with the combination of lithium and valproate showed a higher remission rate than those treated with lithium alone, although the difference did not reach statistical significance (68.3% vs. 47.1%,  $\chi^2 = 3.456$ ;  $p = .052$ ). In particular, the association of valproate produced a significantly higher improvement of mixed (72.2% vs. 42.9%,  $\chi^2 = 5.630$ ;  $p = .017$ ), psy-

**TABLE II.**

Clinical course: remission of episode and improvement of psychopathological dimensions at endpoint. *Decorso clinico: remissione dell'episodio in atto e miglioramento delle singole dimensioni psicopatologiche al termine del periodo di osservazione.*

	Lithium (n = 34)	Lithium + Valproate (n = 41)	$\chi^2$	p value
% patients with remission of manic/mixed episode*	16 (47.1%)	28 (68.3%)	3.456	.052
% patients with symptomatic improvement <sup>†</sup>				
Manic symptoms	17 (50%)	29 (70.7%)	3.369	.055
Mixed symptoms <sup>‡</sup>	12 (42.9%)	26 (72.2%)	5.630	.017
Depressive symptoms <sup>‡</sup>	15 (53.6%)	18 (50%)	.080	.488
Anxiety symptoms	15 (44.1%)	33 (80.5%)	10.671	.001
Psychotic symptoms <sup>§</sup>	7 (46.7%)	17 (81%)	4.629	.037
Impulsivity	17 (54.8%)	23 (57.5%)	.050	.506

\* Remission: score of 1 (normal, not ill) or 2 (minimally ill) on CGI-BP subscale for overall illness severity maintained for at least two subsequent evaluations; <sup>†</sup> Symptomatic improvement: reduction of at least 3 points in the CGI-BP scores for the severity of various psychopathological dimensions at endpoint; <sup>‡</sup> Evaluated on 64 patients with mixed episode; <sup>§</sup> Evaluated on 36 patients with psychotic symptoms.

chotic (81% vs. 46.7%,  $\chi^2 = 4.629$ ;  $p = .037$ ) and anxiety symptoms (80.5% vs. 44.1%,  $\chi^2 = 10.617$ ;  $p = .001$ ). In contrast, there were no significant differences between the two groups in terms of depressive symptoms and impulsivity (Table II).

## Discussion and conclusions

Although the efficacy of lithium in the treatment of acute mania has been widely documented, in clinical practice it is often necessary to use complex drug combinations for management of different clinical manifestations<sup>1 2 14 16</sup>. However, no specific indications are still available to guide these association strategies.

Our data on the use of lithium in clinical practice, in monotherapy or in combination with valproate, showed that more than 50% of the sample was treated with the combination of the two drugs. Most patients receiving lithium plus valproate were male and rapid cyclers; furthermore, combination treatment was associated with a higher severity of psychotic symptoms at baseline. This is consistent with the common practice to administer polypharmacotherapy for the management of more severe forms of BD<sup>9 11 14</sup>.

Patients treated with the combination of lithium and valproate showed greater rates of clinical improvement at endpoint compared with subjects with lithium alone. In particular, co-administration of valproate significantly reduced the severity of specific psychopathological dimensions, such as mixed, anxiety and psychotic symptoms, which are poorly responsive to lithium alone<sup>10 14 17</sup>.

The present study suffers from some limitations: first, it is naturalistic and second, it was carried out in a small

sample of patients followed-up for an average period of 6 months. Therefore, the results are not generalizable to the wide spectrum of bipolar conditions.

Further investigations will be necessary to better define possible advantages resulting from the association of lithium with valproate, and in particular, if serum lithium levels may be reduced when lithium is co-administered with valproate, while enhancing its antimanic properties and minimizing side effects related to high dosages of the drug.

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