

Studi sperimentali

Lithium treatment in elderly patients affected by mood disorders

Trattamento con litio in pazienti anziani affetti da disturbo dell'umore

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SUMMARY. Objective. The aim of this study is to provide information about lithium effectiveness and safety in the treatment of old patients with mood disorders. **Methods.** The study is naturalistic in nature and design and considers all patients aged ≥ 75 years attending our center in the past 10 years. We obtained patients' socio-demographic and clinical characteristics, the worst Global Assessment of Functioning score assigned in the course of treatment, the Clinical Global Impression (CGI) score at the beginning of treatment, the CGI-Improvement (CGI-I) highest score achieved in the follow-up, and drop-out rates. We compared patients treated with lithium, in some cases associated with other psychotropic medications, and patients treated with psychotropic medications other than lithium. Furthermore, we analyzed lithium side effects and causes of lithium withdrawal. **Results.** In the considered period, 25 lithium-treated patients achieved higher CGI-I scores after treatment in comparison with 138 patients not receiving lithium. Drop-out rates were similar in the two groups. Mean dose of lithium was 390 ± 178.5 mg/day. Among lithium treated patients, neither hypothyroidism nor renal failure were significant problems. Thyroxine treatment was prescribed to 8 (32%) lithium-treated patients. Lithium was withdrawn in 6 (24%) patients, respectively for ineffectiveness, heart disease (unrelated to lithium), erratic and unpredictable metabolism of lithium, poor compliance (two cases), and mitigation of the disease. **Conclusions.** Lithium remains irreplaceable and maintains a high effectiveness in the treatment of elderly patients. Low doses and frequent monitoring are recommended.

KEY WORDS: bipolar disorder, elderly, lithium, side effects, suicide, treatment.

RIASSUNTO. Scopo. Scopo dello studio è fornire informazioni sull'efficacia e sicurezza del litio nel trattamento dei pazienti con disturbi dell'umore. **Metodi.** Lo studio, condotto secondo un disegno naturalistico, ha incluso tutti i pazienti di età ≥ 75 anni afferiti presso il nostro centro negli ultimi 10 anni. Sono stati raccolti i dati relativi alle caratteristiche socio-demografiche e cliniche dei pazienti, il punteggio più basso di Global Assessment of Functioning attribuito durante il trattamento, il punteggio di Clinical Global Impression (CGI) all'inizio del trattamento, il punteggio più alto al CGI-Improvement (CGI-I) durante il follow-up e il tasso di drop-out. I pazienti trattati con litio, in alcuni casi in associazione ad altri farmaci psicotropi, sono stati confrontati con i pazienti trattati con farmaci psicotropi diversi dal litio. Inoltre, sono stati valutati gli effetti collaterali del litio e le cause di interruzione della terapia. **Risultati.** Nel periodo preso in esame, i 25 pazienti trattati con litio hanno mostrato un CGI score più elevato rispetto ai 138 pazienti che non ricevevano il litio. I tassi di drop-out sono risultati simili nei due gruppi. La dose media di litio è stata di $390 \pm 178,5$ mg/die. Tra i pazienti in trattamento con litio né l'ipotiroidismo, né l'insufficienza renale sono stati problemi significativi. La tiroxina è stata prescritta in 8 (32%) pazienti del gruppo in trattamento con litio. In 6 (24%) pazienti è stata necessaria l'interruzione della terapia, rispettivamente, per inefficacia, cardiopatia (non correlata al litio), incostante e imprevedibile metabolismo del litio, scarsa aderenza alla terapia (due casi) e attenuazione del disturbo. **Conclusioni.** Il trattamento con litio è tuttora insostituibile e dimostra di essere altamente efficace nel trattamento di pazienti anziani. Si raccomanda la somministrazione di basse dosi con frequente monitoraggio.

PAROLE CHIAVE: disturbo bipolare, anziano, litio, effetti collaterali, suicidio, trattamento.

INTRODUCTION

Lithium remains the best treatment in bipolar disorder and recurrent unipolar depression. No drug is as effective as lithium in preventing suicidal ideation or behavior¹. Mood disorders are associated with high risk of suicide². Old age may be an independent additional risk factor for suicidality³. For these reasons, lithium is the ideal treatment for many old patients. However, lithium has a narrow therapeutic index, especially in the elderly, for age-related pharmacodynamic and pharmacokinetic changes⁴, higher rates of medical comorbidities and polypharmacy⁵, increased brain vulnerabili-

ty resulting from cerebrovascular disorders, parkinsonism and dementia⁶.

Furthermore, monitoring requirements discourage clinicians from using lithium. As a consequence, there are few studies on lithium in the elderly and recommendations for clinical use are based on extrapolations from pharmacokinetic studies or reports from mixed age patient studies⁵. However, data from younger patients cannot be properly used to define dosing and maintenance of serum concentrations in the elderly because of age-related changes.

The aim of this study is to provide information about lithium effectiveness in the treatment of elderly patients and to

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highlight the main problems encountered in the management of elderly patients treated with this drug.

METHODS

We considered all patients aged ≥ 75 years attending our private practice in the last 10 years. We obtained patients' socio-demographic and clinical characteristics, the worst Global Assessment of Functioning (GAF) score assigned in the course of treatment, the Clinical Global Impression (CGI) score at the beginning of any treatment, the CGI-Improvement (CGI-I) highest score achieved in the follow-up, the cause of drug withdrawal. We compared patients treated with lithium, in some cases associated with other psychotropic medications (Li group) and patients treated with psychotropic medications other than lithium (no-Li group). Furthermore, we analyzed lithium side effects and causes of lithium withdrawal.

In the analysis, we used the χ^2 test and the Fisher's exact test for categorical variables, the t-test for continuous variables, and the Mann-Whitney U test for ordinal variables. All tests were two-tailed. Statistical significance was set at $p < 0.05$.

RESULTS

In the considered period, we treated 163 subjects aged ≥ 75 years. 25 were in the Li group (8 men, 17 women; mean age 80.1 ± 4.3 years) and 138 in the no-Li group (40 men, 98 women; mean age 81.3 ± 4.7 years). The two groups were similar in gender ratio, age, civil status, and parenting. In the Li group, 22 patients suffered from bipolar disorder and 3 patients from recurrent unipolar depression. In the no-Li group, 51 patients suffered from bipolar disorder, 35 from unipolar depression (single episode or recurrent) and 52 from other mental disorders. Bipolar disorder diagnosis was more frequent in the Li group ($\chi^2=20.284$; degrees of freedom (df) =1; $p=0.000$). GAF score was higher in the no-Li group (43.5 ± 10.7) than in the Li group (33.2 ± 11.6) ($t=4.338$; $df=152$; $p=0.000$). CGI score at the beginning of treatment was higher in the Li group (5.5 ± 0.5) than in the no-Li group (4.8 ± 0.65) (ZT=4.676; $p=0.000$). Both these differences suggest severer psychopathology in the Li group. Mean duration of lithium treatment was 31.3 ± 35.0 months. Mean daily dose of lithium was 390 ± 178.5 mg (range: 150-750). Mean minimal lithium plasma level was 0.32 ± 0.14 mEq/L (range: 0.2-0.7). Mean maximal lithium plasma level was 0.83 ± 0.5 mEq/L (range: 0.4-2.5). Three (12%) patients of the Li-group had attempted suicide before lithium treatment. None of them attempted suicide during lithium treatment (Fisher's exact test: $p=0.235$). Suicidal ideation was present in 8 patients before lithium and in 2 patients after lithium, absent in 16 patients before lithium and in 17 patients after lithium, data were missing in 1 patient before lithium and in 6 patients after lithium (Fisher's exact test: $p=0.282$). In comparison with other psychopharmacological treatments, lithium was associated with higher CGI-I scores (Table 1). Six (24%) patients exhibited symptoms of acute lithium intoxication. Lithium plasma level was high in 5 of them (1.0; 0.9; 1.1; 1.8; 2.5 mEq/L) and unavailable in one. Four (16%) patients presented relatively high levels of lithium plasma level (0.83; 0.9; 0.9; 1.03 mEq/L) without signs of intoxication. Five (20%) patients had a $>7\%$ increase from

baseline body weight. Neither hypothyroidism nor renal failure were significant problems. No patient showed deteriorating renal function. Thyroxine treatment (a proxy for hypothyroidism) was prescribed to 8 (32%) of lithium-treated patients, 7 women (41.2%) and 1 man (12.5%). Four of them had been treated with thyroxine also before lithium.

Drop-out rates were not different between lithium and other treatments. Lithium was withdrawn in 6 (24%) patients, hereafter described:

- Case 1. An 89-year-old man, assuming 150 mg of lithium tid, unexpectedly presented a lithium plasma level of 2.5 mEq/L. Six months before, on the same dose, lithium plasma level was 0.6 mEq/L. Lithium was tapered to 150 mg/day. Lithium plasma level remained high (1.0 mEq/L). Therefore we substituted lithium with valproate and risperidone. In the following months, he presented suicidal ideation for the first time, but never attempted suicide.
- Case 2. A 78-year-old woman, assuming 150 mg/day of lithium, underwent several episodes of pulmonary embolism leading to heart failure. We withdrew lithium. In the following 10 months, her mood remained stable until death for heart failure.
- Case 3. A 78-year-old man, assuming 150 mg/day of lithium, withdrew lithium for ineffectiveness. We had treated him with low doses of lithium (150-300 mg/day), achieving low lithium plasma levels (0.24-0.39 mEq/L) because of poor renal functioning (creatinine: 1.21-2.22 mg/dL).
- Case 4. A 78-year-old man, assuming 600 mg/day of lithium, presented acute lithium intoxication (confusion, tremor and sedation; plasma level: 1.1 mEq/L). He had not been visited by any physician in the last months. We withdrew lithium for poor compliance. He continued treatment with olanzapine and valproate, and remained well until death for hematological disease.
- Case 5. A 77-year-old woman, assuming 450 mg/day of lithium, presented acute lithium intoxication (confusion,

Table 1. Number of patients treated with different drugs, categorized by the score of Clinical Global Impression-Improvement

CGI-I score	Li	VPA	Ox-CBZ	LTG	SSRI	AD	AP
1	13	11	2	0	4	7	30
2	8	35	4	1	3	7	25
3	1	20	1	1	6	7	10
4	1	8	1	3	7	12	8
≥ 5	0	1	1	0	16	26	6
NA	2	26	4	0	7	9	17
Mann-Whitney test		ZT= 3.195; $p=0.001$	ZT= 1.996; $p=0.046$	ZT= 3.080; $p=0.002$	ZT= 4.705; $p=0.000$	ZT= 6.143; $p=0.000$	ZT= 2.358; $p=0.018$
Other drug vs lithium							

CGI-I = Clinical Global Impression-Improvement; NA = not assessed; Li = lithium; VPA = valproate; Ox-CBZ = ox-carbazepine; LTG = lamotrigine; SSRI = selective serotonin reuptake inhibitors; AD = all antidepressants (including SSRIs); AP = antipsychotics.

- tremor, dysarthria, and ataxia: lithium plasma level: 1.8 mEq/L). The etiology of intoxication was unknown. She had not changed lithium dosage, assumed any other drug, or changed diet or salt intake. Two months before, lithium plasma level was 0.51 mEq/L. Possibly, she was dehydrated for poor water intake. She refused lithium. Thereafter, her compliance with treatment was poor and she deteriorated.
- Case 6. A 90-year-old woman, assuming 150 mg/day of lithium, presenting mild creatinine increase (1.31 mg/dL) and a lithium plasma level of 0.6 mEq/L, slowly withdrew lithium after 3 years of well being. In the following 12 months, she remained well continuing treatment with quetiapine (300 mg/day).

DISCUSSION

The research on lithium is declining. Lithium effectiveness can be appreciated only after months or years of treatment. Unfortunately, randomized controlled trials on lithium are not conducted over long periods, and naturalistic studies can be of value. Lithium is very effective in the treatment of mood disorders and presents an unparalleled action in the prevention of suicidal ideation and behavior. Even very low levels of lithium in drinking water may play a role in reducing suicide risk within the general population⁷. Patients with a particularly high risk of suicide, e.g., patients with agitated depression who have anxiety associated with depression⁸ are likely to get special benefit from treatment with lithium.

In clinical practice, the use of lithium in older adults is decreasing⁹. Non psychiatrists doctors and young psychiatrists are not familiar with its use and neglect lithium, fearing its side effects.

This study investigates an unexplored clinical area. The study design does not allow comparison between lithium and other drugs in the treatment of mood disorders since treatments were selected on the basis of patients' diagnostic features and clinical characteristics. Clinical assessments were made unblindly by only one senior psychiatrist (MR) who personally visited the patients, acquiring a direct and exhaustive knowledge of patients' clinical course. Furthermore, patients' temperament was not specifically investigated although it is an important factor influencing the clinical course and the response to treatment¹⁰. Despite the methodological limitations, the results of the study provide evidence that lithium maintains strong effectiveness in old patients. Although patients of the Li group were more severely affected (as indicated by lower GAF score and higher CGI score), they achieved higher CGI-I scores after treatment.

The potential chronic side effects of lithium, hypothyroidism or renal failure, were not significant problems in this sample. Old patients treated with lithium for decades and not yet presenting these side effects are unlikely to develop them in the future and, if ever, they develop these symptoms gradually and slowly. Lithium induced chronic renal failure is unlikely in old patients starting lithium for the first time. Actually, lithium chronic renal toxicity may become manifest after at least a decade of treatment¹¹.

While chronic side effects of lithium are quite harmless in the elderly, acute side effects are dangerous.

In this sample, the reasons for the suspension of lithium were the following:

- a) Unmanageable plasma levels due to erratic and unpredictable lithium metabolism. Lithium intoxication can occur suddenly, without apparent reason, even when using low doses (cases 1 and 5). Brain lithium concentrations usually correlate with serum lithium levels in young patients, but not in older subjects¹². Therefore, the use of lower doses of lithium in old patients is mandatory.
- b) Occurrence of severe heart disease, independent of the use of lithium (case 2).
- c) Ineffectiveness of the drug (case 3).
- d) Poor compliance which is more frequent in elderly patients due to age-related cognitive decline or lack of care giving relatives (cases 4 and 5).
- e) Mitigation of the disease. Especially in the elderly, long-term psychopathological stability may suggest trying to quit lithium slowly (case 6).

Consistently with the results of Eastham et al.¹³, in our experience, elderly patients require more frequent clinical and laboratory monitoring and lithium dosages 25% to 50% lower than those used in younger individuals. Despite possible adverse effects, lithium can be valuable in the treatment of elderly patients with mood disorders.

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