Treatment adherence and tolerability of immediate- and prolonged-release lithium formulations in a sample of bipolar patients: a prospective naturalistic study.

Running head: naturalistic study comparing different lithium formulations

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Conflict of interests

PG acted as consultant to Lundbeck, Angelini, FB-Health. He received a scholarship / research support from Lundbeck and Angelini. He is a member of the speaker / advisory board of Sanofi-Aventis, Lundbeck, FB-Health, Angelini. Other authors declare that they have no competing interests.

Funding

The company Angelini S.p.A. provided funding for the activation of professional services in support of clinical and research activities (contracts, scholarships).

Abstract

Objectives

The aim of this study was to compare treatment adherence and tolerability of immediate-release (IR) and prolonged-release (PR) lithium formulations in bipolar patients during a one-year follow-up.

Methods

This is a naturalistic, prospective study conducted in 70 bipolar patients receiving lithium therapy for the first time. During follow-up, in addition to the routine psychiatric evaluation, data were collected regarding patient's therapeutic adherence, possible side effects of the treatment, and serum levels of lithium, creatinine and thyroid stimulating hormone.

Results

At baseline, the whole sample included 30 (43%) patients on PR lithium formulations and 40 (57%) on IR formulations. At final evaluation, a total of 37 patients (53%) were considered lost to follow-up. Both PR and IR patients showed significantly improvement in the Functioning Assessment Short Test (FAST) and the Clinical Global Impressions for Bipolar Disorder (CGI-BP) scores during the follow-up . At the first follow-up visit, the mean plasma lithium level of PR patients was higher than IR patients (0.61 versus 0.47, respectively; p=0.063), as well as the therapeutic adherence (85% versus 64%, respectively; p=0.089). Fine tremor and gastrointestinal symptoms were more frequently detected in IR patients compared to PR ones at each follow-up visit, with the sole exception of GI symptoms at the last evaluation, which were nearly not detected in both patient groups.

Conclusion

Lithium PR therapy could provide potential advantages over IR formulations, such as reduced adverse events and improved therapeutic adherence, aided by fewer daily administrations required. Future naturalistic studies and clinical trials with a longer follow-up duration are needed.

Key Words: Lithium; Prolonged-release lithium; Immediate-release lithium; Bipolar Disorder.

Introduction

Lithium is considered a first-line treatment in the major Bipolar Disorder (BD) therapy guidelines and still plays a prominent role in acute and long-term management of the illness, even if a variety of anticonvulsants and modern antipsychotics have emerge (Goodwin et al., (2016); Grande et al., (2016); Sani et al., (2017)). The promotion of lithium alternatives has also led, in some cases, to unjustified implications that lithium has inferior efficacy to other alternatives, especially in certain diagnostic subgroups (rapid cycling course or with mixed states). Lithium is effective in the management of mania and in the prophylactic treatment of BD patients, preventing both manic and depressive episodes (Malhi et al., (2012)). In addition to its prophylactic efficacy, lithium has an independent protective effect against suicide and suicidal behaviours (Baldessarini et al., (2006)). Recent research indicates that lithium also exhibits a neuroprotective effect, suggesting its possible role in the prevention of neurodegenerative manifestations associated or not with BD (Forlenza et al., (2019); Rybakowski et al., (2018)).

Lithium is rapidly and completely absorbed from the upper gastrointestinal (GI) tract, is not metabolized, and more than 95% is excreted unchanged by the kidney at a constant rate proportional to the glomerular filtration rate. The specific biochemical mechanism of action of lithium remains only partially understood. Certainly, lithium has multiple levels of action: it alters sodium transport across the cell membrane, affects second messenger signaling, and interferes with neurotransmitter systems (Malhi et al., (2013)).

It is worth noting that lithium has a narrow therapeutic index. The generally recommended minimum effective serum level of lithium for maintenance treatment is between 0.6 and 0.8 mEq/L (Severus et al., (2008)). Serum lithium concentrations below 0.5 mEq/L are rarely effective. On the contrary, lithium levels above 1.5-2.00 mEq/L are always associated with more or less severe symptoms of intoxication. Below these levels, however, the threshold for symptoms onset differs considerably. Age, gender, renal function, changes in diet and fluid intake, fever, and several pharmacological

treatments, such as angiotensin-converting enzyme (ACE) inhibitors, diuretics, non-steroidal anti-inflammatory drugs (NSAIDs) can all influence serum lithium concentrations and should be considered in the clinical assessment. (Malhi et al., (2012)).

Common side effects of lithium treatment are GI symptoms (anorexia, nausea, vomiting, diarrhea), fine-hand tremor, muscle weakness, cognitive effects, polyuria, polydipsia, and weight gain. Dermatological complications include exacerbation of psoriasis and acne and increased hair loss. Lithium can also have effects on electrocardiogram and laboratory parameters, such as changing serum electrolyte concentrations. In the medium term, due to the competition of lithium with iodine, hypothyroidism is common but easily managed with the administration of low doses of thyroid hormones to control the increase in thyroid stimulating hormone (TSH) (Yatham et al., (2018)). Renal alterations such as reduced urinary concentrating may occur, but only a few patients develop renal failure after years/decades of treatment (McKnight et al., (2012)). Adequate monitoring of patients taking lithium is needed to optimize dosage, maximize effectiveness, and minimize possible side effects and toxicity.

Different lithium preparations (carbonate immediate-release, IR and sulfate prolonged-release, PR), now also available in Italy, may have different pharmacokinetic characteristics. IR lithium formulations are associated with rapid fluctuations in plasma concentration with a peak serum concentration 1–2 hours after oral administration. These fluctuations may be associated with possible acute side effects during the peak and followed by a potential reduction in therapeutic efficacy during the fall in serum level. PR lithium preparations, on the other hand, would reduce the frequency and amplitude of concentration peaks, reducing the incidence and intensity of some adverse effects related to the rapid rise in serum lithium levels, and, perhaps allowing for a stable pharmacological response (Durbano et al., (2002)). Additionally, PR lithium formulations are related to higher serum lithium concentrations than those with the IR formulation. Finally, the PR formulation may allow for once-

a-day intake, simplifying the administration regimen and consequently favoring adherence to drug treatment and the therapeutic compliance (Girardi et al., (2016)).

Several studies in BD patients have reported poor adherence to lithium therapy. One study, for example, reported that 32% of patients with BD type I did not adhere to therapy, especially those with comorbid personalities and substance use disorders (Murru et al., (2013)). Subjective sensations of cognitive impairment, weight gain and tremors are the main reasons for discontinuing or non-adherence to treatment, while polyuria and polydipsia, also frequent adverse events, usually do not lead patients to discontinue treatment (Gitlin et al., (1989)).

Only a few studies have explored the potential advantages of PR lithium formulations over IR formulations (Castrogiovanni, (2002); Durbano et al., (2002)) and detailed information on the long-term effectiveness and tolerability of PR compounds is lacking. The aim of this one-year naturalistic follow-up was to prospectively assess the treatment adherence and tolerability of different lithium formulations in BD patients treated with lithium for the first time by comparing therapeutic adherence, side effects, and serum lithium concentrations between PR and IR patients.

Methods

Study design and patient sample

This is a naturalistic, prospective, and observational follow-up study conducted in 70 adult BD patients receiving lithium therapy for the first time. Enrolment took place between February 2019 and September 2020 at the Psychiatry Unit 2 of the University of Pisa, both in the psychiatric ward and in the outpatient clinic.

The study duration was 1 year for each patient and included 4 visits: screening for study inclusion and concomitant assessment at baseline, and follow-up visits at 3 (T1), 6 (T2) and 12 (T3) months (± 2 week).

The inclusion criteria for this study were age ≥18 years, a diagnosis of BD according to DSM-5

diagnostic criteria (American Psychiatric Association, (2013)), and being on lithium therapy (IR or PR) for the first time for up to three months. All patients were either hospitalized in the psychiatric unit at the moment of the enrolment or were recruited during an outpatient visit. Patients unable to read or understand informed consent, who reported pregnancy or breast-feeding or who participated in another interventional study were excluded from the present study. Patients receiving other pharmacological treatments were not excluded, with the exception of medications that interfere pharmacokinetically with lithium, such as ACE inhibitors, diuretics, and NSAIDs.

According to the naturalistic and non-interventional approach of this study, all diagnostic and therapeutic procedures, as well as the follow-up visits, were part of routine clinical practice. Therapeutic choices were made by the treating psychiatrist based on his/her clinical experience and guidelines; the decision to initiate mood-stabilizing therapy with lithium salts, the choice of lithium salt formulation (IR or PR), and its dosage were made regardless of the patient's inclusion in this study.

Data collection and assessing instruments

In the baseline consultation, participating psychiatrists recorded socio-demographic variables (gender, age, education level, job and marital status) along with several clinical variables regarding the course of BD (current affective episode, age at first psychiatric treatment, history of psychotic symptoms, suicide attempts, and hospitalizations), psychiatric and medical comorbidities (panic disorder, substance abuse, eating disorders, attention deficit/hyperactivity disorder - ADHD, cardiologic and metabolic diseases) and psychiatric family history. All psychiatric diagnoses were made by the participating psychiatrists according to DSM criteria through the Structured clinical interview for DSM-5, clinical version (SCID-5-CV)(First et al., (2016)).

In addition to serum creatinine and TSH levels, the dosage and formulation of lithium salt therapy and any other concomitant psychopharmacological treatments were also collected in the baseline assessment.

During the follow-up visits, in addition to the routine psychiatric evaluation, data were collected regarding possible side effects of the treatment (tremor, GI symptoms, cognitive effects, polyuria/polydipsia, weight gain, dermatological symptoms), any change in lithium dose or formulation, serum lithium levels, creatinine levels (at 6 and 12 months) and TSH levels (at 12 months). Patients' therapeutic compliance was assessed clinically during each follow-up visit by collecting information from the patient and the patient's family members/caregivers.

The global severity of the episodes was assessed by the severity subscale of the Clinical Global Impressions – Bipolar Version (CGI-BP)(Guy, (1976)), a version of CGI which preserves the fundamental assets of the original global rating instrument while focusing on the specific components of BD. Different areas of functioning have been investigated through the administration of the Functioning Assessment Short Test (FAST)(Rosa et al., (2007)). This scale is organized into 6 clusters (autonomy, occupational functioning, cognitive functioning, financial management, social functioning and leisure time), whose items are evaluated from absence of difficulty to high difficulty. Both scales were administered at baseline, and at each visit of follow-up.

Statistical analysis

Sociodemographic and clinical variables were compared between patients taking IR lithium salts and patients taking PR formulations. Descriptive analyses have been reported in terms of mean and standard deviations for continuous variables and number and percentages for categorical ones. Comparisons between the two subgroups were performed by independent-sample Student' t-test for continuous variables (Mann-Whitney U-test when appropriated) and chi-square analysis for categorical ones. Pairwise comparisons between the mean scores of the CGI-BP (severity subscale) and FAST scores at baseline and final assessment were conducted by paired t-test. Mean scores on both scales at the end of follow-up are reported using the last observation carried forward method (LOCF), including only patients who have achieved at least T1 (3 months). Given the high possibility of both type I and type II errors, our results must be considered preliminary. Consequently, we have

considered a significance level of p-value < .05, but we also have also commented on the significant differences at a p-value <.10. We used the statistical routines of IBM SPSS Statistics for Mac, Version 25.0 (SPSS Inc., USA).

Ethic information

All subjects provided written informed consent for the study participation. This study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) and the study protocol was approved by the Ethics Committee of the Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy (Protocol n. 57192; 12/11/2018).

Results

Socio-demographic characteristics of the sample

In our study, patients were predominantly female (63%) and the mean age was 37.8 years (range 18 to 68), with a normal distribution (Table 1). Approximately half of the patients were single at the time of assessment, 24% were married, 16% divorced and 7% widowed. Regarding work status, half of the patients were employed or students, while 34% had no job and 14% were disabled or retired. Finally, as regards the highest level of education achieved by the patients, almost half of the sample had a high school diploma, a third had a secondary/elementary school diploma and only 21% had a college degree. The two groups did not show significant differences in sociodemographic variables.

INSERT TABLE 1

Clinical characteristics of the sample

Of the total sample of 70 individuals, at baseline, 30 (43%) were on PR and 40 (57%) on IR lithium therapy; 17 (24%) patients were diagnosed with BD type I and 53 (76%) with BD type II (Table 2).

At baseline evaluation, 14% were euthymic, 23% had an ongoing manic or hypomanic episode, 40% were depressed, and 23% presented mixed features. The mean age at first psychiatric treatment was 25 years (range 13 to 60). Of the entire sample, 24% had a history of psychotic symptoms, 19% have

attempted suicide at least once, and 64% have been previously or currently hospitalized in a psychiatric setting. No significant differences were found between PR and IR patients with regards to the above clinical characteristics.

Among lifetime psychiatric comorbidities, panic disorder was the most frequently detected (51%); substance use disorder was more frequent in the IR group than in the PR group, albeit with weak significance (respectively, 35% vs 17%; p=0.088). Of the entire sample, 11% had cardiological comorbidity and nearly 20% showed a metabolic disorder. As expected, mood disorders were the most represented in the psychiatric family history of these patients (76%), followed by panic disorder (24%) and substance use disorder (16%). With the exception of substance abuse, the two groups showed similar psychiatric comorbidity and familiarity.

At baseline, two-thirds of patients were taking antiepileptics as additional mood stabilizers (valproic acid, carbamazepine, lamotrigine) and/or antidepressants (selective serotonin reuptake inhibitors - SSRI, tricyclics), 46% were on typical or atypical antipsychotic treatment, and 30% were taking benzodiazepines. Stimulant medications for ADHD were prescribed in 7% of the sample with a slightly higher prevalence in the PR group than in the IR group (respectively, 13% vs 2%, p=0.082).

INSERT TABLE 2

Follow-up

Of the total sample at baseline, 54 (77%) patients were available to re-evaluation 3 months later (PR group 26, 37%; IR group 28, 40%), 42 (60%) reached 6 months of follow-up (PR group 21, 30%; IR group 21, 30%), and finally 33 (47%) patients were followed up for the entire duration of the study (PR group 17, 24%; IR group 16, 23%). Thirty-seven patients were considered lost to follow-up: 24 (60%) in IR group and 13 (43.3%) in PR group (χ^2=1.911; p=167). In all of these cases, the reason was the patients' lack of willingness or commitment to cooperate in accordance with study procedures. Considering the 54 patients who reached at least 3 months of follow-up, we found that FAST and CGI-BP (severity subscale) scores showed a statistically significant improvement in both the PR and

IR groups.

INSERT TABLE 3

Lithium administration was once daily in the case of PR formulations and twice daily for IR compounds. At baseline, the mean prescribed lithium dose for the whole sample was 15±7 mmol/day, while at final evaluation, it increased to 22±10 mmol/day (Table 4). Mean lithium dosages were similar for both patients groups at baseline and at each follow-up visit. In contrast, at the T1 visit, the mean plasma lithium level of PR patients was higher than IR patients (0.61 versus 0.47, respectively; p=0.063). In addition, PR patients appeared to show a more stable trend in mean plasma lithium concentration throughout the study period (range 0.61-0.66 mEq/L) than IR patients (range 0.47-0.60 mEq/L), although no significant differences were found between the two groups at the following follow-up visits. Creatinine and TSH levels appeared to be stable during the one-year follow-up in both patient groups.

INSERT TABLE 4

During follow-up, possible side effects of lithium treatment were evaluated (Table 5). Self-reported weight gain was the most frequent side effect found in both groups. In the PR group, polyuria/polydipsia was another common symptom observed while, among IR patients, fine tremor and GI symptoms (nausea, vomiting, diarrhea) were particularly frequent. The latter were more frequently detected in IR patients compared to PR ones at each follow-up visit, with the sole exception of GI symptoms at the last evaluation, which were nearly not detected in both patient groups. Cognitive effects and dermatologic symptoms (acne, psoriasis) were less represented in the sample, without significant differences between subgroups. Therapeutic adherence resulted slightly higher at the first follow-up visit in PR patients compared to IR ones (respectively, 85% vs 64%, p=0.089) while no differences were found in subsequent follow-up evaluations.

INSERT TABLE 5

Discussion

In this study, as expected, we observed significant improvement in both clinical and functional outcome of BD patients treated with IR or PR lithium formulations for one year, as assessed by the CGI-BP and FAST scales. Obviously, given the naturalistic setting of the study, causal relationships cannot be delineated nor can the influence of other concomitantly prescribed psychopharmacological therapies on the final outcome be assessed. However, of particular interest appears to be the reduction in FAST total scores in BD patients after one year of lithium treatment, which reflects functional improvement in daily functioning, regardless of the emergence of new affective episodes or chronic mood instability.

As expected, at baseline, the two patient groups were comparable with regard to clinical features of BD, as well as psychiatric family history. Although not significant, there is a younger age trend in PR patients compared to IR ones. This finding seems to reflect clinical practice, in which PR lithium is often preferred in young patients in order to strengthen therapeutic adherence by reducing daily administrations and to reduce the acute and long-term side effects related to peaks in serum lithium concentration (Bowden, (1998)). By increasing the number of subjects in our sample, the observed trend may be confirmed. In line with this view, we also observed that PR patients were more often prescribed stimulants for the treatment of ADHD than those with IR. Indeed, ADHD is considerably more common in the young population (Chung et al., (2019)). On the contrary, the increased use of IR lithium in patients with substance/alcohol abuse could be related to the greater confidence of psychiatrists in prescribing an already familiar and well-known lithium formulation to complicated and poorly compliant patients to avoid overdosage risks.

During follow-up, patients in the two groups were taking comparable doses of lithium. Despite this, PR patients reached therapeutic serum lithium levels earlier and kept them more stable and slightly higher than IR patients, especially in the first months of therapy. In PR patients, lithium levels remained consistently within the recommended therapeutic ranges (between 0.6 and 0.8 mEq/l) throughout the duration of the study, while in IR patients these levels fluctuated between 0.5 and 0.6

mEq/l. Our results are in line with some previous studies comparing once-a-day PR formulations and multiple daily IR formulations showing reduced fluctuations in serum lithium concentrations in the first group of patients compared to the others (Castrogiovanni, (2002); Durbano et al., (2002)).

In our one-year follow-up, no major increases in creatinine or TSH were found in either group of patients, reflecting the absence of renal and thyroid abnormalities. Obviously, especially for the evaluation of the impact of lithium on the renal function, longer prospective studies that follow patients for years/decades are needed. As previously mentioned, lithium treatment can impair the renal concentration ability and cause polyuria and secondary increase in thirst. In most patients, this effect is modest and less than 5% of cases develop severe renal failure over the long term (McKnight et al., (2012)). In a small study of 56 patients comparing the impact of PR and IR formulations on renal function, the authors found less impairment of the kidney's ability to concentrate urine in patients treated with PR lithium compared to the others (Wallin and Alling, (1979)). A review on BD patients treated with lithium for the first time showed that a single daily dosing was associated with a reduction in urinary frequency and with less pathological damage at renal biopsy compared to multiple daily regimens, although the available evidence are still inconclusive and insufficient (Carter et al., (2013)).

In the medium term, hypothyroidism is the most frequent endocrine disorder caused by lithium, is more common in women than in men and increases with age (Kirov et al., (2005)). Prevalence rates in the literature range from 0% to 23% (Bocchetta and Loviselli, (2006)). However, it appears that thyroid dysfunctions are more frequently detected in BD patients than in normal population regardless of lithium treatment, possibly due to an increased susceptibility to autoimmune disorders (Barbuti et al., (2017)). Although there is a lack of data on this topic in the literature, lithium IR and PR formulations do not appear to have a different impact on the thyroid gland and on the risk of developing hypothyroidism.

When interpreting the results of the present study, the relatively high rate of patients lost to follow-

up should be taken into account. This finding seems to be largely related to the tertiary level specialization in mood disorders of our psychiatric unit, which implies the admission of patients with BD from all over Italy and therefore easily lost after recruitment. Unfortunately, we cannot provide an estimation of the percentage of patients who discontinued lithium among those lost to follow-up.

Although there was a trend towards a higher frequency of patients lost to follow-up in the IR group, the rate did not significantly differ between the two patients groups. Adherence to treatment, as assessed during follow-up visits by participating psychiatrists, was greater in the first months of treatment in patients who were prescribed lithium PR than in others. Some naturalistic studies have shown that a major cause of lithium treatment failure is associated with poor treatment compliance. The latter, in turn, appears to be related, among other variables, to the number of daily administrations, with the single daily doses preferred by patients over multiple administrations (Castrogiovanni, (2002); Girardi et al., (2016); Lavantes et al., (1999)).

Additionally, the reduced rates of adverse effects with PR lithium formulations could further promote adherence to treatment. In fact, several lithium side effects seem to be related to the rate of increase in serum lithium concentration. The slower rise in serum lithium levels of PR lithium formulations compared to IR compounds could consequently reduce the rate or severity of several adverse events (Bowden, (1998); Castrogiovanni, (2002)). In our sample, tremor and GI symptoms were found less frequently in the PR group than in the IR group. Tremor tended to persist in patients for the duration of follow-up while GI symptoms, such as nausea and diarrhea, tended to disappear over time even in the IR group. Other side effects were found equally in the two groups and included: increased need to drink and polyuria (15-20%), patient-reported weight gain (25-30%), cognitive dysfunction/dulling (approximately 10%), and exacerbation of psoriasis in three cases. Consistent with our findings, an observational study involving a small sample of patients switching from IR lithium formulations to once-daily PR formulations showed that the latter were associated with a lower incidence of adverse events, including tremor, GI symptoms, somnolence, and polyuria (Durbano et al., (2002)). Although

some previous Authors have found that polyuria/polydipsia and GI symptoms, such as diarrhea, occurred at higher rates with lithium PR formulations compared to lithium IR formulations (Carter et al., (2013); Fyrö et al., (1970)), our study found no differences in the rates of these side effects between the two groups of patients.

As previously mentioned, the reduced rate of adverse events with PR versus IR formulations could improve patient compliance and reduce drug discontinuation rate, although there is a lack of studies assessing this issue.

Limitations

The present study showed several limitations that should be taken into account. The main limitation of the present study is the low number of subjects and the relatively high rate of patients lost to follow-up. Given the possibility of both type I and type II error, our results should be considered preliminary. Another important limitation is the naturalistic setting of this follow-up, which does not allow an adequate evaluation of the impact of other psychopharmacological therapies on the side effects encountered in patients with BD. A third limitation could be represented by the methodological design of the present study, in which some variables of interest (therapeutic adherence and side effects) were clinically evaluated, without the use of specific assessment scales. Finally, the absence of a blinding assessment may also have played a role in influencing the psychiatrist's evaluations.

Conclusions

Lithium salts still represent the mainstay in the treatment of BD. At the moment, in Italy, two different lithium formulations are available: IR lithium carbonate and PR lithium sulphate. The latter seem to provide potential benefits over IR formulations, in particular more stable serum lithium concentrations and a more gradual increase in lithium levels, potentially reducing some of the adverse events, such as tremors and GI symptoms, and improving therapeutic adherence by lowering the number of daily administrations. Given the lack of information on the comparison between IR and PR lithium formulations, further prospective and longer naturalistic studies as well as randomized

clinical trials are needed in the future.

Acknowledgements

None.

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