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Safety of inositol supplementation in patients taking lithium or valproic acid: a pilot clinical study

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Abstract. – OBJECTIVE: Mood stabilizers like lithium (Li) and valproic acid (VPA) act *via* cellular depletion of inositol in the central nervous system (CNS). However, such depletion also involves peripheral tissues, thus exposing patients to various side effects. Preclinical and clinical studies revealed the effectiveness of inositol supplementation to recover such pathological conditions. Nevertheless, the risk of reducing the effectiveness of pharmacological therapies by raising inositol levels in the CNS, still represents a matter of concern. This study adds new insights on this aspect, highlighting the safety of a tailored dosage of inositol in patients taking Li or VPA.

PATIENTS AND METHODS: We enrolled 15 patients over 18 years of age taking Li and/or VPA. They assumed 2 gr of myo-inositol (myo-ins) and D-chiro-inositol (D-chiro-ins) in the combined 80:1 ratio, plus 50 mg of α-lactalbumin (α-LA), twice a day for a total period of 6 months (T1). Evaluating the interference of such dietary supplementation with pharmacological therapy was the primary outcome. Monitoring blood levels of thyroid (fT3, fT4, TSH) and metabolic markers (fasting insulin, glucose, HOMA-IR index, triglycerides, HDL, LDL) were secondary outcomes. The analysis was carried out by comparing values at baseline (T0) and T1 (6 months).

RESULTS: After 6 months, pharmacological therapy was still suitable for patients, requiring no changes nor adjustments. Instead, inositol treatment improved those borderline values about thyroid functionality and glucose and lipid metabolism.

CONCLUSIONS: This pilot study demonstrated that the dosage of 4 gr/daily of inositol is safe in patients taking Li/VPA, as we recorded no interference with the pharmacological therapy. Moreover, such treatment may counteract or even prevent side effects, thus improving patients' quality of life.

Key Words:
Myo-inositol, D-chiro-inositol, 80:1, α-lactalbumin, Lithium, Valproic acid.

Introduction

Lithium (Li) and valproic acid (VPA) are commonly used drugs in the management of neurological and psychiatric conditions, including bipolar disorder (BD)[1]. BD is a severe mental illness affecting patients' mood, characterized by alternating manic and depressive phases[2]. As mood stabilizers, the pharmacological activity of Li and VPA prevents the occurrence of manic episodes also reducing the severity and the frequency of mania[3]. Among their mechanisms of action, Li and VPA induce the reduction of brain levels of inositol, according to the "inositol depletion hypothesis[4-6]".

The term inositols refers to a group of stereoisomers, among which myo-inositol (myo-ins) is the most abundant. It is physiologically involved in brain functionality and its levels correlate with the alternation of mood phases: higher levels of myo-ins in brain correlate with manic phases of BD[7], while lower levels correlate with depressive ones[8]. Both Li and VPA dampen manic phases by targeting myo-ins metabolism and its absorption through the inhibition of the involved enzymes and transporters[9].

Notably, depletion of inositol induced by mood stabilizers involves not only the central nervous system (CNS), but also peripheral tissues, thus exposing patients to several undesired reactions[10]. As a matter of fact, pathological side effects emerging during Li and VPA treatments share the altered metabolism of inositol in related tissue. Inositol plays a central role in physiology and functionality of different tissues, acting as second messenger of hormones like Thyroid-Stimulating Hormone (TSH)[11], Follicle-Stimulating Hormone (FSH)[12] and insulin[13]. Indeed, most of patients taking Li or VPA may experiment pathological

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conditions including polyuria and polydipsia[14,15], dermatological problems[16,17], hypothyroidism[18], hormonal and metabolic unbalances[17], gynecological disorders[19] as the polycystic ovary syndrome (PCOS), cardiac alterations[17,20-23]. In line with this, preclinical and clinical evidence revealed that inositol administration has positive effects on these pathological conditions. Previous studies[24,25] demonstrated that adding myo-ins to selenium-based treatments ensured euthyroidism in patients with subclinical hypothyroidism and autoimmune thyroiditis. A 6-month supplementation with myo-ins significantly recovers the levels of TSH and thyroglobulin antibodies in 84 patients with Hashimoto's thyroiditis and subclinical hypothyroidism, compared to selenium treatment[26]. Thyrocytes indeed need myo-ins for the physiological biosynthesis of thyroid hormones, thyroxine (T4) and triiodothyronine (T3).

In addition, several studies[27,28] revealed that inositol supplementation restores metabolic parameters related to glucose and lipid metabolism. Drug-induced depletion of myo-ins exposes patients to conditions of insulin resistance and increased body weight, also influencing levels of D-chiro-inositol (D-chiro-ins), another stereoisomer involved in glucose metabolism. While myo-ins drives glucose uptake into the cells, D-chiro-ins boosts metabolism by storing glucose into glycogen and thus enhancing insulin pathway. In fact, overweight/obese patients with PCOS experience greater benefits in terms of Body Mass Index (BMI), waist, hip circumference taking the combined administration of myo-ins and D-chiro-ins rather than diet or myo-ins alone[29-31]. The co-administration for three months also improves glycated hemoglobin and fasting glycaemia in patients with type-2 diabetes, and lipid profile in patients with metabolic syndrome[32,33].

Noteworthy, *in vitro* and *in vivo* studies revealed that adding the prebiotic agent α-lactalbumin (α-LA) to inositols, improves their intestinal absorption acting on the intestinal tight junctions. In this way, such addition overcomes the problem of inositol resistance[34-36], according to which most of patients cannot absorb these molecules.

Considering that the abovementioned side effects depend on the depletion of inositol in related peripheral tissues and that inositol eumetabolism may contribute to a healthy state, treatments based on such molecules may also recover peripheral depletion during Li or VPA therapies. However, such approach could theoretically reverse the inositol depletion also in the CNS that is one of the mechanisms of action of Li and VPA, thus risking dampening the central therapeutic effect of these drugs. In this regard, previous studies[37] reported that dosages of inositol up to 6 gr per day do not influence the central effect of drugs nor mood of patients, and that only dosages of 12-18 gr per day can cross the blood brain barrier (BBB). Allan et al[38] demonstrated that supplementation with 6 gr/daily of myo-ins improved the severity of psoriatic plaques in patients treated with Li and exhibiting related psoriasis. Indeed, the treatment reduced Psoriasis Area Severity Index (PASI) without influencing patients' mood nor compliance to pharmacological therapy.

Our study highlights the safety of inositol supplementation in patients taking Li or VPA, also demonstrating the non-interference with pharmacological treatments, and opening its use in psychiatric field. Indeed, a recent investigation depicted a therapeutic gap since psychiatrists have no tools to counteract side effects in clinical practice, beside adjusting drugs' dosage and/or type of pharmacological treatment[39].

By taking into account the blood levels of specific markers and the possible interactions with the pharmacological therapy, this study provides awareness about the safety of such tailored dosage, giving evidence of a promising tool in clinical practice without interfering with the central therapeutic effect.

Patients and Methods

Between March 2021 and January 2022, a total of 15 patients (12 males and 3 females) were enrolled in this pilot study. All the participants provided their informed consent after explanation of the study purpose. The study was conducted privately at Don Guanella Institute (Rome, Italy) following the Ethical Principles of the Helsinki Declaration and the national law. The inclusion criteria were: (I) age over 18 years and (II) ongoing treatment with Li and/or VPA. Recruited patients exhibited no altered blood levels of the evaluated markers at the baseline (T0). Patients were treated with 2 gr of myo-ins and D-chiro-ins in the combined 80:1 ratio, plus 50 milligrams of α-LA, twice a day for a total period of 6 months (T1). The exclusion criteria were: (I) the assumption of dietary supplements based on inositols, (II) a low-calory dietary regimen, (III) a condition of alcohol abuse.

The primary outcome of the study was the safety of inositol supplementation in patients treated with Li or VPA, taking into account possible interferences with ongoing pharmacological therapies. Patients filled in a questionnaire about their compliance and the occurrence of side effects during the inositol administration. As secondary outcomes, we monitored levels of the following blood markers: free thyroxine (fT4) and free triiodothyronine (fT3), TSH, fasting insulin, glucose, triglycerides, High-Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL). Patients taking pharmacological treatments interfering with the evaluated blood markers, such as levothyroxine or statins, were excluded from the analysis of thyroid and lipid markers, respectively.

Statistical Analysis

Statistical analysis was carried out using GraphPad Prism Software. Wilcoxon Signed-Rank Test was used to compare changes in blood levels of markers related to thyroid functionality (fT3, fT4, TSH), glucose metabolism (glycaemia, HOMA-IR), lipid metabolism (triglycerides, LDL, HDL) and Body Mass Index (BMI) from T0 (baseline) to T1 (after 6 months of inositol treatment). The analysis of the fasting insulin was carried out by using the paired *t*-test, as the mean and the median values matched for this marker.

In the case of the Wilcoxon test, data were represented using individual values with median - 25th percentile - 75th percentile; in the case of the paired *t*-test, data were represented using individual values with mean and standard deviation. We considered statistically significant results with a p-value ≤ 0.05.

Results

All the recruited patients fulfilled the inclusion criteria, 3 patients taking Li and 12 patients taking VPA; however, none of them still presented side effects or altered values of the blood markers.

The questionnaires highlighted no need for adjusting the pharmacological therapy during dietary supplementation with inositols. The treatment did not influence patients' compliance to pharmacological therapy, supporting the safety of the dosage of 4 gr/daily of inositol in such patients.

Inositol supplementation proved devoid of negative effects on the evaluated blood markers. On the contrary, such treatment induced a significant improvement in blood levels of HDL indicating a positive effect on lipid metabolism (Figure 1H, median value T0: 49.50 mg/dL - 25th percentile 40.25 - 75th percentile 54.25; median value T1: 49.00 mg/dL - 25th percentile 40.25 - 75th percentile 61.00; p-value < 0.05).

We further stratified data on blood markers, including in the analysis only those patients exhibiting borderline values at the baseline (T0). We divided them in the following subgroups: (i) borderline values for thyroid markers (n=6 patients), (ii) borderline values for glucose metabolic markers (n=4 patients) and (iii) for lipid metabolic markers (n=9 patients).

In the subgroup (i), the levels of fT4 significantly increased after 6 months of inositol administration compared to the baseline (Figure 2B, median value T0: 0.80 ng/dL -25th percentile 0.71 - 75th percentile 0.83; median value T1 1.14 - 25th percentile 1.04 - 75th percentile 1.23; p-value $<$ 0.05), without exceeding the physiological values.

The analyses of the subgroup (ii) revealed that the administration of inositols for 6 months led to a significant reduction of fasting insulin levels compared to the baseline (Figure 2D, mean value T0: 21.00 ± sd. 0.82; mean value T1: 17.25 ± sd. 0.50; p-value < 0.001). The treatment also induced a slight decrease in the HOMA-IR index, without reaching statistical significance (Figure 2F).

Finally, lipid metabolic markers of the subgroup (iii) exhibited no altered levels after inositol administration keeping values within the physiological range.

Discussion

The results of this study demonstrated the safety of a specific dosage of inositols in patients with BD taking Li and/or VPA. Such therapies reduce the onset and the severity of manic phases by targeting inositol content in the CNS. However, drug-induced depletion of inositol involves not only the CNS, but also peripheral tissues, thus exposing patients to side reactions related to altered inositol metabolism. They include PCOS, hypothyroidism, cardiac alterations, increased body weight, altered glucose and lipid metabolism. All these conditions weaken patients' compliance and worsen their quality of life. Nevertheless, to date, psychiatrists have no tools to counteract such collateral reactions in patients taking Li and/or VPA, they just consider them as part of the pharmacological therapy itself.

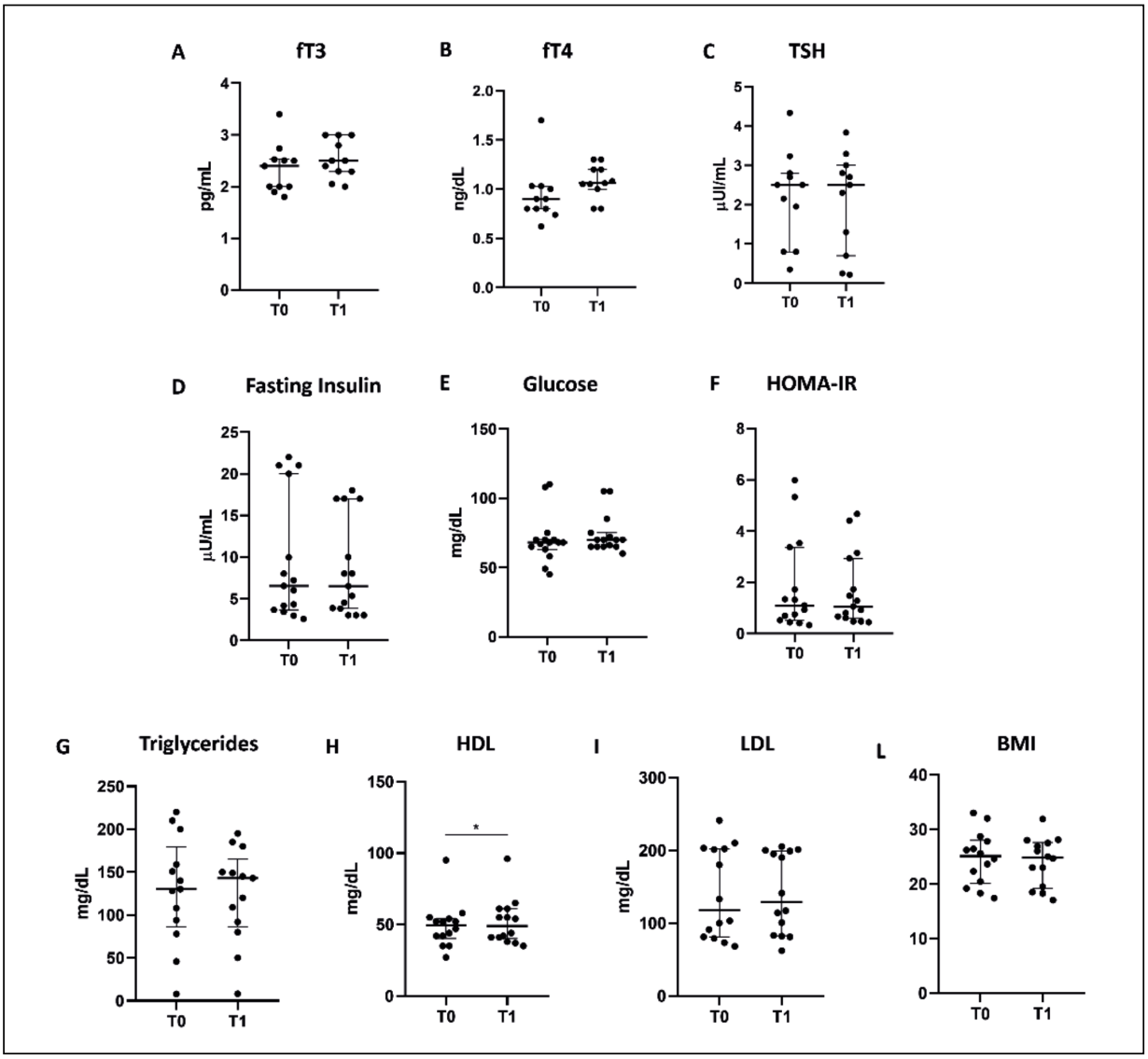

Figure 1. Blood levels of markers for thyroid functionality, glucose and lipid metabolism, and BMI. Comparison of blood markers for thyroid functionality (**A-C**), glucose (**D-F**) and lipid metabolism (**G-I**), and BMI (**L**) at baseline (T0) and after 6 months of inositol treatment (T1). Data are represented as individual values at T0 and T1 with median – 25th percentile – 75th percentile (*$p < 0.05$ by Wilcoxon Signed-Rank test).

This study addresses the concerns still existing in clinical practice by demonstrating that the dosage of 4 gr/daily of inositols is safe in such patients, opening toward a more awareness application in psychiatric field.

With regard to the general safety of inositol, the Food and Drug Administration indicated it among the compounds generally recognized as safe (GRAS). A dosage ranging 12-30 gr/daily can induce only mild gastrointestinal symptoms, while the dosage of 4 gr/daily, commonly used in clinical practice, is completely free of side effects[40]. Noteworthy, regarding the concomitant assumption of Li or VPA, previous works have already revealed that a dosage up to 6 gr/daily of inositol in patients taking Li, improves the side effect of psoriasis, without influencing pharmacological therapy nor mood[38].

This study finally overcomes the concern about reduced effectiveness of pharmacological therapies derived from the exogenous administration of inositols. The dosage of the study, in a ratio of 80:1 between myo-ins and D-chiro-ins, does not influence pharmacological therapy, in-

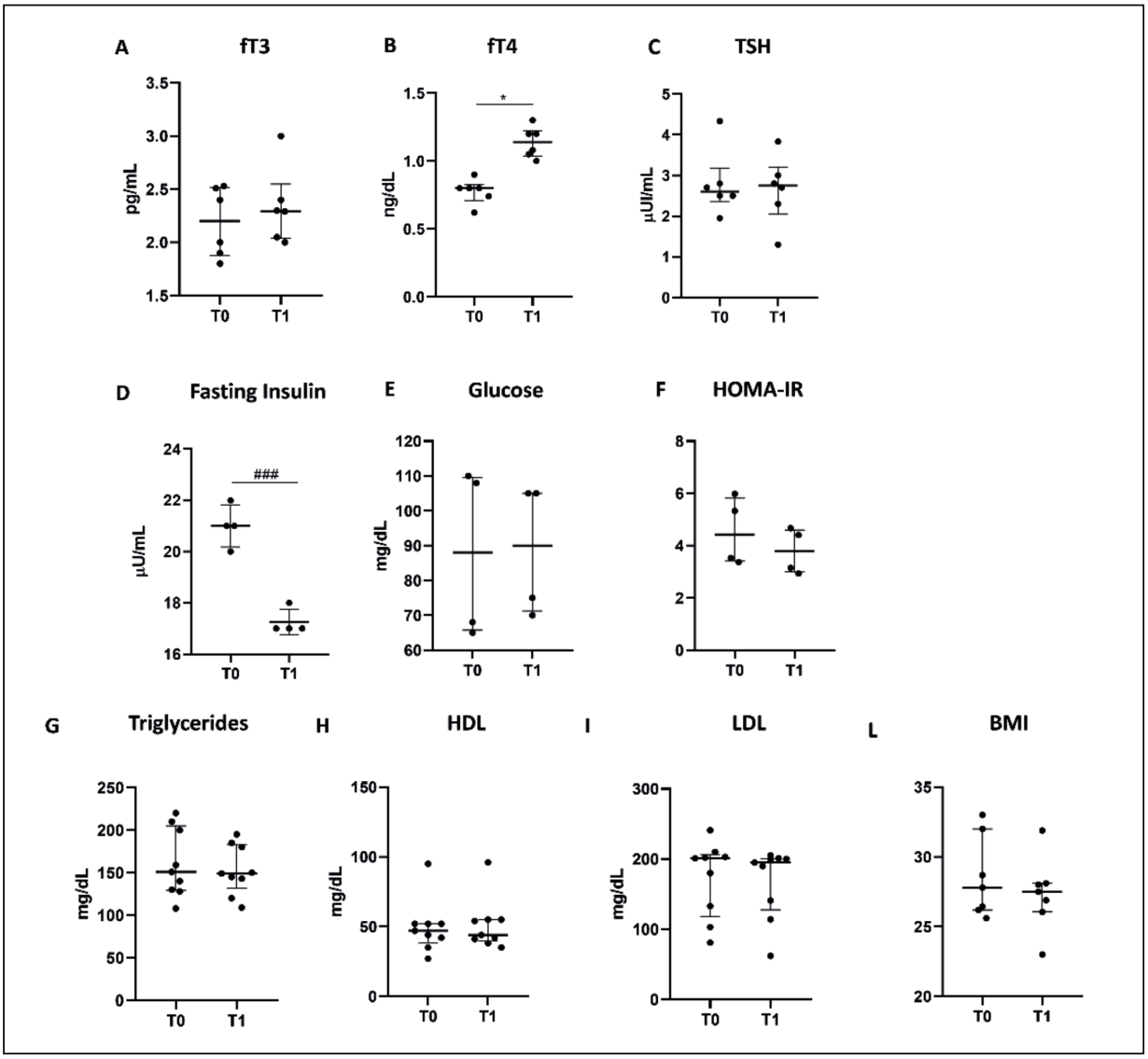

Figure 2. Blood levels of markers for thyroid functionality, glucose and lipid metabolism and BMI after stratification of the data. Patients were stratified and only those with borderline values for the evaluated parameters were included. Graphs report the comparison of blood markers for thyroid functionality (**A-C**), glucose (**D-F**) and lipid metabolism (**G-I**), and BMI (**L**) at baseline (T0) and after 6 months of inositol treatment (T1). Data are represented as individual values with median – 25th percentile – 75th percentile (**A-C; E-L**); (**D**) data are represented as individual values with mean and standard deviation (*$p < 0.05$ by Wilcoxon Signed-Rank test; #$p < 0.05$ by paired *t*-test).

stead it guarantees beneficial effects on collateral pathological conditions.

After 6-month administration of inositols, blood levels of HDL significantly improved, while levels of triglycerides of all patients were under 200 mg/dl without exceeding the physiological range. Considering that Li treatment may interfere with cardiac functionality by inducing arrhythmias and heart failure, the significantly increased levels of HDL and the lower levels of triglycerides after inositol supplementation may suggest a protective role against cardiovascular risk, likely reducing heart attacks and ictus. In addition, a previous review by Tabrizi et al[33] found that combined inositol administration improved lipid profile by reducing levels of total cholesterol, low density lipoprotein (LDL) and triglycerides in patients with metabolic syndrome.

The administration of inositols also improved those borderline values about thyroid and metabolic markers, supporting our hypothesis that not only it does not interfere with pharmacological

therapy, but it also improves some of the evaluated markers. In particular, increased levels of fT4, with the constant levels of TSH, indicate an improvement in TSH signaling and thyroid functionality after 6 months of treatment. Alterations in thyroid physiology are very common in such patients: hypothyroidism indeed occurs in about 20% of patients taking Li or VPA[18], while about 50% may develop goitre[41]. As reported in previous studies[11,25,26], inositol supplementation positively influences thyroid functionality recovering signaling pathway of TSH. Indeed, myo-ins regulates the biosynthesis of hydrogen peroxide for the organification of iodide and the biosynthesis of thyroid hormones (fT4, fT3), which are involved in the regulation of metabolic processes of the whole body.

Moreover, decreased levels of myo-ins correlate with reduced levels of D-chiro-ins and with reduced cellular uptake of glucose, consequently leading to high levels of glycaemia and insulin-resistance[12]. The significant decrease in fasting insulin and the slight decrease in HOMA-IR index after 6-month of inositol supplementation corroborate positive effects of inositols in improving glucose and lipid metabolism. Being second messengers of the insulin signaling pathway, myo-ins and D-chiro-ins improve insulin sensitivity and regulate insulinemia. Indeed, these results suggest beneficial effects of inositols on metabolic parameters, thus opening their use in patients under Li or VPA. Metabolic alterations in such patients are very frequent, and about 50% of them experiment increased body weight and obesity during treatments[22].

This pilot study addresses the gap still remaining in clinical practice about the risk of a reduced effectiveness of pharmacological therapy in the case of inositol supplementation. Indeed, as myo-ins poorly passes the BBB[42], a dosage of 4 gr is completely safe on patients' mood. The results from the questionnaires revealed no changes in patients' mood nor the occurrence of adverse effects related to inositol supplementation, so that the psychiatrist did not modify dosages of pharmacological therapies.

Limitations and Strengths

Clearly, the low number of patients' cohort and the absence of overt adverse effects at the enrolment, could represent limiting aspects of the study. However, it consists of a pilot clinical study, and we decided to focus the analysis on patients under Li or VPA treatment that exhibited no side effects in order to assess the inositol safety on pharmacological outcomes and patients' mood. Our findings support the use of inositols even before starting the pharmacological therapies, thus preventing the onset of such collateral effects and providing a tailored use in clinical practice. Janiri et al[43] have already reported that the 80:1 ratio of inositols may guarantee a recovery of inositol eumetabolism in patients taking Li or VPA, improving those adverse conditions occurring during pharmacological therapies.

Overall, this study corroborates evidence about the safety of 4 gr/daily of inositol in patients taking Li or VPA, opening a more aware use of such molecules in psychiatric field for both preventing and recovering side effects.

Conclusions

Drugs like Li or VPA expose patients to the risk of side effects that may weaken their compliance and reduce their quality of life. Such pathological conditions, including alterations in thyroid functionality, cardiac system, metabolism and hormones, correlate with lower inositol levels in peripheral tissues. This iatrogenic abnormality represents a reflection of the therapeutic central depletion of inositol induced by pharmacological therapy.

Literature supports the effectiveness of combined inositol supplementation to recover or prevent such conditions, suggesting that inositol treatment may be beneficial when associated to therapies with Li or VPA. However, whether inositol supplementation interferes with the pharmacological regimen is still a matter of concern.

This pilot study demonstrates that inositol administration is safe in patients taking Li and VPA, as it does not interfere with the pharmacological outcome, also improving blood levels of metabolic markers, as the HDL value. Moreover, in patients with borderline values, inositol supplementation induces beneficial effects on thyroid and metabolic parameters, as observed for fT4, fasting insulin and HOMA-IR after 6 months of treatment. The present results pave the way for the use of inositols in psychiatric field, with the aim of both preventing and recovering side effects in patients using Li or VPA, thus filling the still existing therapeutic gap in clinical practice.

Conflicts of Interest

Elisa Lepore and Vittorio Unfer are employees at Lo.Li. Pharma S.R.L. (Rome, Italy). All other authors declare no conflict of interest.

Ethics Approval

The study was conducted privately, following the Ethical Principles of the Helsinki Declaration and the national law.

Data Availability

Data will be available upon reasonable request.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

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No funding for the study.

Authors' Contributions

TC: study concept, data collection, editing; EL: analysis, writing; VRU: literature review, editing; VU: study concept, analysis, data checking, editing.

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