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Why inositol supplementation may help to recover side effects induced by mood stabilizers and anticonvulsant drugs

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ABSTRACT

INTRODUCTION. Lithium, valproic acid and carbamazepine are the most used mood stabilizers and anticonvulsant drugs. They share the depletion of myo-inositol in the central nervous system as mechanism of action. However, such therapies may expose patients to several side effects that negatively influence their quality of life, leading to a poor compliance and a poor prognosis. Gathering scientific evidence explaining why myo-inositol supplementation may recover side effects without dampening the central therapeutic action of these drugs is the purpose of this review.

MATERIALS AND METHODS. We reviewed literature searching through different databases. We used different keywords, including mood stabilizers, anticonvulsant drugs, mechanisms of action, inositol depletion, bipolar disorder, and epilepsy.

RESULTS. We reported all the most common complications in patients taking lithium, valproic acid or carbamazepine related to inositol depletion in peripheral tissues. Interestingly, the efficacy of myo-inositol supplementation in recovering the adverse effects occurring during the treatment corroborates its use in such patients.

CONCLUSIONS. Concerning the chronic use of these drugs, it is intriguing to explore the role of myo-inositol supplementation to recover, or altogether avoid, the emerging side effects without dampening the central therapeutic action, thanks to a dosage that poorly crosses the blood brain barrier.

INTRODUCTION

Inositols are natural molecules involved in several biochemical and metabolic functions in different organs and tissues. They are essential components of the cells, playing crucial roles as second messengers both in several pathways (cellular growth, signal transmission of neurotransmitters and hormones, membrane biogenesis) and physiological processes, such as reproductive, endocrine and metabolic pathways. Among the five natural stereoisomers, myo-inositol (myo-ins) is the most abundant one.

It plays a crucial role also in brain functionality as a precursor molecule for inositol lipid synthesis, but also as a physiologically important osmolyte[1]. As a key precursor of membrane phosphoinositide and phospholipids, myo-ins is involved in the cell membrane and myelin sheath structures[2]: higher levels of inositol in brain (up to 10 mM), compared to those in cerebrospinal fluid (100-500 µM) or in other tissues[3], can correlate to the continuous synthesis and turnover of membrane phospholipids, which are needed for both neuronal plasticity and increased synapse formation[4].

Myo-ins levels in brain cells depend on 3 routes:

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(i) recycling of inositol phosphates[5], (ii) surrounding environment inositol transporters[6,7] or, in the absence of exogenous inositol, (iii) synthesis de novo, which is primarily responsible for maintaining intrinsic myo-ins levels into the brain[8]. In particular, since the blood brain barrier (BBB) may slow inositol uptake in brain[9], the inositol de novo synthesis and the recycling of inositol phosphates are the main sources in cerebral tissue[10].

Inositol phospholipids play a central role in those cellular pathways regulating neuronal function and neurotransmission, such as the ion-channels activation or the production of the second messengers[5]. Myo-ins is involved in the phosphatidylinositol second messenger system, which plays a crucial role in neurotransmitter systems via two second messengers, diacylglycerol (DAG) and inositol trisphosphate (InsP3). Each of them, in turn, initiates separate cascades of cellular events, including the activation of protein kinase C (PKC) and the mobilization of calcium (Ca^{2+}), respectively[11].

Excessive activation of the InsP3/Ca^{2+} signalling is one of the biochemical features of bipolar disorder (BD), a chronic psychiatric condition characterized by alternated episodes of extreme mania and depression[12]. Such a condition is often characterized by negative social consequences with increased disability and poor quality of life (QoL) for both patients and their relatives[13,14].

The excessive activation of the InsP3/Ca^{2+} signalling characterizes the occurrence of manic episodes driving the neuronal excitatory-inhibitory imbalance with the overactivation of the neuronal phosphoinositide signalling pathway in patients with BD[15]. Several studies indicated altered levels of phosphoinositide and myo-ins in the brain of patients with BD[16-18]: in particular, higher levels of myo-ins characterize the manic phase[19], while lower levels of myo-ins identify the depressive phases[20].

Therefore, most of the drugs used in BD aim to induce the depletion of inositol, specifically myo-ins, in the CNS as a mechanism of action, dampening the overactive InsP3/Ca^{2+} cerebral signalling[21]. This therapeutic mechanism of action confirms that the alterations of myo-ins levels and related pathways are a crucial therapeutic target in mood disorders.

MYO-INOSITOL DEPLETION AS A MECHANISM OF ACTION OF THERAPEUTIC APPROACHES FOR BD

Mood stabilizers are the gold standard treatment for patients with BD, either in acute or long-term therapy[22]. They aim to keep a balanced mood, even though residual clinical symptoms and dysfunctions can persist even during the treatment[23].

The main mood stabilizers for the treatment of BD, include lithium (Li), as the eligible one, and the anticonvulsants, such as valproate (VA), carbamazepine (CBZ), oxcarbazepine and lamotrigine, along with some atypical antipsychotics, such as quetiapine, risperidone, olanzapine, ziprasidone and aripiprazole. Interestingly, even though structurally dissimilar, Li, VA and CBZ share the depletion of myo-ins in the CNS, as a common therapeutic outcome among various mechanisms of actions[24,25]. These medications act by normalizing the altered phosphatidylinositol cycle activity observed in patients with BD[26], confirming that the excessive activation of the neuronal phosphoinositide signalling pathway[15] is a crucial pathogenetic mechanism. The induced reduction of free intracellular levels of myo-ins can slow the recycling of inositol-containing metabolites (phosphoinositides), which are required for the maintenance and the efficiency of signal transduction[26]. This leads to the stabilization of the structural integrity of neurons and to the enhancement of synaptic plasticity, with a consequent dampening of the overactive neurotransmission.

Experimental evidence gave rise to the "inositol depletion hypothesis"[27,28], highlighting the depletion of inositol in overactivated neural circuits as the principal initial event in the mechanism of action shared by Li and the most used anticonvulsant drugs[21].

At first, Berridge et al suggested the evidence of the inositol-depletion mechanism[29], with the attempt to explain the effects of Li on InsP3 mediated signalling. They highlighted the involvement of the inositol signalling cellular pathway in the pathogenesis of BD. Previous studies demonstrated that Li induced a decrease in cellular concentration of myo-ins in certain areas of the brain of patients with BD[30] by inhibiting the two main intracellular routes to produce inositol, (i) the recycling and (ii) the de novo synthesis of inositol. Experimental studies further corroborated this mechanism of action by revealing a reduction of InsP3 levels in rat cerebral cortex slices after Li administration[31]. Allison et al demonstrated that Li administration induced a 30% decrease of myo-ins levels in rat cerebral cortex, which was evident until 6 hours after Li injection and for 24 hours[32].

Likewise, chronic treatments based on the anticonvulsants VA and CBZ induced inositol depletion in the CNS. VA treatment led to a reduced intracellular basal concentration of InsP3 observed both in rat and in human brain[30]. Clinical evidence further revealed that VA is effective both in the manic and in the mixed state of BD, resulting as a useful mood stabilizer, especially in those patients not responsive to Li[33,34].

CBZ, in turn, causes inositol depletion, possibly by preventing its proper uptake[35]. Indeed, all of the three drugs, Li, VA and CBZ can reduce myo-ins cellular uptake by inhibiting the Na+-Myo-Ins transporters (SMIT1), which is largely responsible for its uptake from the extracellular fluid into the brain[36]. They all targeted SMIT1 mRNA levels as demonstrated both in astrocytes of murine models and in human astrocytoma cell lines. However, the effect occurs only after prolonged treatments, underlining that SMIT1 may not be the primary target of these drugs[37]. Even though the effectiveness of CBZ in the treatment of patients with BD[35], a clinical study reported that about 68% of patients treated with CBZ discontinued treatment early due to the lack of efficacy or to the occurrence of side effects[38]. This evidence underlines that considering the adverse effects during pharmacological treatments is crucial to optimize patients' prognosis.

Indeed, chronic administration of Li, as well as VA and CBZ, even though it provides beneficial effects on mood, exhibits a narrow therapeutic window with some risks and complications. The chronic use of Li, VA and CBZ may expose patients to peripheral side effects related to several pathological conditions, such as Polycystic Ovary syndrome (PCOS), hypothyroidism, hormonal and metabolic imbalances, like weight gain, hyperinsulinemia, dyslipidaemia[39,40]. All these pathological conditions can worsen patients QoL weakening their adherence to the therapy.

Notably, all these effects correlate with an altered myo-ins metabolism in the related peripheral tissue. Sherman et al reported that the inositol depletion occurring in the CNS after Li administration correlates with reduced levels of myo-ins in peripheral tissues, such as kidney and testes[41].

The impairment of kidney function occurs in up to 70% long-term patients causing excessive urination and thirst (polyuria and polydipsia)[39,42]. Myo-ins depletion in renal tissue is associated with its increased degradation in animal models of metabolic diseases, such as diabetes mellitus, dietary-induced obesity, and hypertension[43]. Chang et al demonstrated that myo-ins depletion is a persistent feature of hypertensive and insulin-resistant states, correlating with an increased activity of the myo-ins degrading enzyme, the myo-ins oxygenase (MIOX).

About a third of patients under chronic Li administration exhibit cardiac alterations[44]. Indeed, InsP3 signalling also plays a role in cardiac myocytes, since its alterations can cause the initiation and/or progression of arrhythmias, hypertrophy and heart failure[45].

Another target of Li and anticonvulsant drugs is the thyroid functionality. Indeed, myo-ins is a second messenger of the thyroid-stimulating hormone (TSH)[46] and about 20% of patients taking Li exhibit hypothyroidism[47], while up to 50% may develop goiter. Li may inhibit thyroid hormone release that is a crucial process in the development of hypothyroidism.

Notably, one of the most common causes of patients' dropout is weight gain. A meta-analysis on 14 trials from Gitlin et al demonstrated that patients taking Li and anticonvulsants exhibit a significant weight gain (>7 %) compared to those receiving placebo[39]. Up to 50% of patients taking VA undergoes a significant weight gain (>10% gain from baseline weight), which influences treatment acceptability[48].

Furthermore, another side effect, more specific for VA and CBZ chronic administration[49], is the occurrence of polycystic ovary syndrome (PCOS)[50,51]. In a meta-analysis, the raw incidence of PCOS in VA-treated women is approximately 1.95-fold than in other antiepileptic drugs[52]. VA administration also correlates with an increase in androgen levels, causing a condition of hyperandrogenism that is a typical pathological feature of PCOS. Interestingly, the hormonal and endocrine imbalance typical of these patients clearly correlated to altered inositol metabolism. Patients with PCOS are generally characterized by an altered ratio between myo-ins and its stereoisomer, D-chiro-inositol (D-chiro-ins), in favour of the former. These patients tend to exhibit insulin resistance, resulting in a reduced intracellular conversion of myo-ins to D-chiro-ins, which is mediated by an insulin-sensitive epimerase enzyme[53-55]. An opposite situation occurs in the ovaries of patients with PCOS that maintain a normal sensitivity to insulin[56-58], thus becoming enriched in D-chiro-ins and depleted in myo-ins. Physiologically ovarian myo-ins acts as the second messenger of the Follicle-stimulating hormone (FSH) signalling pathway, while D-chiro-ins is responsible for insulin mediated androgen synthesis. The latter also inhibits the aromatase enzyme, which is responsible for the conversion of androgens into estrogens[59,60]. Therefore, in women with PCOS the altered ratio occurring in ovaries in favour of D-chiro-ins promotes hyperandrogenism and the related features (hirsutism, acne), with a reduced efficiency of myo-ins-mediated FSH signalling.

The observed reduction of estradiol and progesterone and the increase of testosterone, can induce hypogonadism, resulting in amenorrhea or oligomenorrhea, along with sexual dysfunction and lower fertility in these women.
The dermatological adverse effects, mainly acne, normally occur in the first weeks of the pharmacological treatment. They are not highly common (3.4-4.5% of lithium-treated patients), but they contribute to weaken patients' adherence to the therapy and to worsen their QoL[39]. Li-associated psoriasis has an estimated prevalence ranging from 1.8 to 6% of treated cases, and it is one of the major reasons for a poor compliance in patients[61]: it can make existing psoriasis worse and even trigger new cases. Noteworthy, a recent work by Owczarczyk-Saczonek Agnieszka et al identified an intriguing role for inositols, in particular D-chiro-ins, as a local adjuvant treatment of mild plaque psoriasis, opening novel fields of application[62].
Finally, such drugs may expose to teratogenic risk, increasing the occurrence of neural tube defects (NTDs); therefore, pregnant women should avoid their use[63]. Interestingly, previous studies revealed a protective role of myo-ins supplementation during the periconceptional period in preventing the risk of NTDs, especially for those folic acid resistant[64]. Indeed, the active myo-ins uptake mechanism in the embryonic stages, when the neural tube is closing, is likely to be an important determinant of physiological development[64,65]. However, in clinical practice, women under anticonvulsants or mood stabilizers are strictly recommended to concomitantly take anti-conceptional drugs in order to avoid the occurrence of congenital fetal malformations.
Overall, therapies based on mood stabilizers and anticonvulsants deserve a proper monitoring of side effects, due to inositol depletion, in order to optimize patients' compliance and improve the QoL.

RECOVERING SIDE EFFECTS OF THE THERAPIES: A LESSON FROM MYO-INOSITOL

Monitoring side effects during the pharmacological administration of Li, VA and CBZ may optimize the acceptability and the effectiveness of the therapies in patients with BD, ensuring the best QoL possible.
Clinical studies highlighted that myo-ins supplementation led to positive effects in most of the previously reported pathological conditions due to myo-ins crucial role in the physiology of the involved tissues.
Regarding thyroid dysfunctions, a recent study from Nordio et al revealed that the administration of myo-ins plus selenium is significantly effective in restoring euthyroidism in patients with subclinical hypothyroidism or autoimmune thyroiditis[66].
Furthermore, considering the occurrence of PCOS phenotype in patients treated with VA or CBZ, several studies highlighted the beneficial effects of myo-ins in improving hormonal profile, hyperandrogenism[67], menstrual cycle and oocyte quality in patients with PCOS[68,69]. In addition, clinical studies pointed out the beneficial effects of the combination between myo-ins and D-chiro-ins. The combined ratio of 40:1, in favour of myo-ins, positively affects the hormonal profile in overweight women with PCOS[70,71], also improving metabolic parameters like levels of insulin, triglycerides, lipids[72] and weight gain. Later studies revealed that the addition of α-lactalbumin (α-LA) to inositol administration can optimize the beneficial effects in women with PCOS, overcoming the common problem of inositol resistance occurring in these patients[73]. Indeed, in vitro studies and clinical data corroborated the ability of αα-LA in improving inositols intestinal adsorption, ensuring a higher effectiveness of inositol-based therapy[74].
Overall, the use of myo-ins supplementation is generally recognized as safe (GRAS) by experts. Previous studies reported that a dosage of myo-ins up to 30 grams/daily can induce only mild gastrointestinal symptoms experienced for the first month, while the dosage of 4 grams/daily of inositol, which is commonly used in clinical practice, is completely free of side effects[75].
However, a crucial point in patients with BD under such pharmacological therapies is to evaluate whether myo-ins supplementation may reduce the central pharmacological therapeutic effect by increasing the levels of myo-ins into the brain. Interestingly, some studies addressed this issue by demonstrating that inositol supplementation can recover some of the unwanted peripheral effects of Li, without diminishing the beneficial effect of the pharmacological treatment.
Bersudsky et al reported that inositol supplementation both in rats and in patients ameliorated Li-induced polyuria-polydipsia[76], which are among the most common unwanted events. Rats treated with Li and concomitantly with myo-ins, exhibited lower polydipsia compared to controls. Likewise, patients under Li treatment taking 3 grams/daily of myo-ins exhibited an improvement in polyuria and polydipsia, without any effects on Li central therapeutic effect[76].
Furthermore, Allan et al demonstrated that myo-ins administration in patients with psoriasis under Li treatment recovered the Psoriasis Area and Severity Index (PASI),

further helping psoriasis aggravated by the treatment[77]. In this study, fifteen patients with psoriasis, who were taking Li, were administrated with 6 grams/daily of myo-ins. Such dosage significantly induced beneficial effects on the psoriasis phenotype without dampening the central effect of myo-ins depletion and without any negative effects on mood disorder. This result suggests a crucial therapeutic use for inositols, up to 6 grams/daily, in patients with psoriasis who need to continue Li treatment for the management of BD. Subsequently, Kontoangelos et al provided a case report of a bipolar patient that discontinued Li treatment due to a severe psoriatic exacerbation. After myo-ins administration (3 grams/daily), skin condition significantly improved, while patient's mood remained stable[78]. This study demonstrated the effectiveness of a lower dose myo-ins compared to the study of Allan, to recover psoriatic plaque phenotype, also in the case of a discontinuous Li treatment.

Scientific evidence reported that myo-ins is poorly absorbed from the periphery into the brain, so large doses are required to penetrate into the CNS, when it is administered exogenously[10]. Previous studies on pathological conditions that require higher levels of inositol in brain, like depression and premenstrual dysphoric disorder, reported beneficial effects of myo-ins supplementation by using a dosage of 12 grams/daily[79]. These data confirm that a high myo-ins dosage is necessary to cross the BBB.

Noteworthy, the combined ratio of 40:1, in favour of myo-ins, is effective to recover endogenous conditions, including metabolic impairments and endocrine alterations, heart defects, thyroid alterations[54,57,80-84]. However, as reported in recent reviews[85,86], the iatrogenic depletion of inositols needs a higher amount of inositols. The tailored combined ratio of 80:1 myo-ins:D-chiro-ins provides a large amount of myo-ins and an adequate one of D-chiro-ins immediately functionable, which is needed for the metabolic boost, thus recovering the altered inositol metabolism. Such ratio may guarantee a recovery of inositol eumetabolism in patients taking Li, VA or CBZ, improving those pathological conditions reported as side effects.

This therapeutic strategy may overcome the iatrogenic depletion of inositols bridging the gap in clinical practice. Such ratio in a clinical dosage of 4 grams/daily may further improve adherence to the therapy, by counteracting side effects of mood stabilizer-based therapy, without interfering with the pharmacological therapies nor worsening patients' mood.

CONCLUSIONS

Li, VA and CBZ are the most used treatments in patients with BD. They induce the inositol depletion in the central nervous system, dampening the overactive InsP3/Ca^{2+} signalling. The "inositol depletion hypothesis" was put forward to explain the effect of Li and anticonvulsant drugs on manic depressive psychosis: brain myo-ins levels fall as these drugs negatively affect its biosynthesis and uptake, confirming the crucial role of myo-ins in the pathogenesis of BD. However, this depletion may expose patients taking pharmacological therapy to side effects in peripheral tissues, which share an alteration of inositol levels as a common feature. Therefore, considering that myo-ins poorly crosses the blood brain barrier, its administration can be useful to overcome, or altogether avoid, the adverse effects occurring during the pharmacological treatment without dampening the central positive effect. The beneficial effects of inositol supplementation on several pathological conditions, like hypothyroidism, obesity, PCOS – and concomitantly – the promising effects of myo-ins on psoriasis and polyuria in patients taking lithium may open the possibility to counteract side effects related to the treatment of BD.

Therefore, supplementation of inositols in a controlled dosage (up to 6 grams/daily), can effectively recover the adverse effects without hindering the beneficial central action of the pharmacological treatment. Furthermore, the safety and the wide use in various pathological conditions make the application of inositols intriguing to propose as a concomitant supplementation in patients taking Li or anticonvulsant drugs, with the final aim to optimize patients' compliance and their QoL.

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.

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Data Availability

Not applicable.

Author Contributions

VU conceptualized the work. ZK, EL, MMO and VRU searched literature for appropriate articles and drafted the original paper. ZK and VU critically revised the article. All authors read and approved the final version of the paper.

REFERENCES

1. Fisher SK, Novak JE, Agranoff BW. Inositol and higher inositol phosphates in neural tissues: homeostasis, metabolism and functional significance. J Neurochem 2002;82(4):736-754.
2. Haris M, Cai K, Singh A, Hariharan H, Reddy R. In vivo mapping of brain myo-inositol. Neuroimage 2011;54(3):2079-2085.
3. Deranieh RM, Greenberg ML. Cellular consequences of inositol depletion. Biochem Soc Trans 2009;37(Pt 5):1099-103.
4. Brand A, Richter-Landsberg C, Leibfritz D: Multinuclear NMR studies on the energy metabolism of glial and neuronal cells. Dev Neurosci 1993;15(3-5):289-298.
5. Balla T: Phosphoinositides: tiny lipids with giant impact on cell regulation. Physiol Rev 2013;93(3):1019-1137.
6. Berry GT, Mallee JJ, Kwon HM, Rim JS, Mulla WR, Muenke M, et al. The human osmoregulatory Na+/myo-inositol cotransporter gene (SLC5A3): molecular cloning and localization to chromosome 21. Genomics 1995;25(2):507-513.
7. Nikawa J, Tsukagoshi Y, Yamashita S. Isolation and characterization of two distinct myo-inositol transporter genes of Saccharomyces cerevisiae. J Biol Chem 1991;266(17):11184-11191.
8. Parthasarathy LK, Seelan RS, Tobias C, Casanova MF, Parthasarathy RN. Mammalian inositol 3-phosphate synthase: its role in the biosynthesis of brain inositol and its clinical use as a psychoactive agent. Subcell Biochem 2006;39:293-314.
9. Spector R. Myo-inositol transport through the blood-brain barrier. Neurochem Res 1988;13(8):785-787.
10. Levine J, Rapaport A, Lev L, Bersudsky Y, Kofman O, Belmaker RH, et al. Inositol treatment raises CSF inositol levels. Brain Res 1993;627(1):168-170.
11. Kim H, McGrath BM, Silverstone PH. A review of the possible relevance of inositol and the phosphatidylinositol second messenger system (PI-cycle) to psychiatric disorders--focus on magnetic resonance spectroscopy (MRS) studies. Hum Psychopharmacol 2005;20(5):309-326.
12. Cerullo MA, Adler CM, Delbello MP, Strakowski SM. The functional neuroanatomy of bipolar disorder. Int Rev Psychiatry 2009;21(4):314-322.
13. Fajutrao L, Locklear J, Priaulx J, Heyes A: A systematic review of the evidence of the burden of bipolar disorder in Europe. Clin Pract Epidemiol Ment Health 2009;5:3.
14. Oldis M, Murray G, Macneil CA, Hasty MK, Daglas R, Berk M, et al. Trajectory and predictors of quality of life in first episode psychotic mania. J Affect Disord 2016;195:148-155.
15. Berridge MJ. The Inositol Trisphosphate/Calcium Signaling Pathway in Health and Disease. Physiol Rev 2016;96(4):1261-1296.
16. Kato T, Shioiri T, Takahashi S, Inubushi T. Measurement of brain phosphoinositide metabolism in bipolar patients using in vivo 31P-MRS. J Affect Disord 1991;22(4):185-190.
17. Kato T, Shioiri T, Murashita J, Hamakawa H, Inubushi T, Takahashi S. Phosphorus-31 magnetic resonance spectroscopy and ventricular enlargement in bipolar disorder. Psychiatry Res 1994;55(1):41-50.
18. Silverstone PH, McGrath BM, Kim H. Bipolar disorder and myo-inositol: a review of the magnetic resonance spectroscopy findings. Bipolar Disord 2005;7(1):1-10.
19. Davanzo P, Thomas MA, Yue K, Oshiro T, Belin T, Strober M, et al. Decreased anterior cingulate myo-inositol/creatine spectroscopy resonance with lithium treatment in children with bipolar disorder. Neuropsychopharmacology 2001;24(4):359-369.
20. Frey R, Metzler D, Fischer P, Heiden A, Scharfetter J, Moser E, et al. Myo-inositol in depressive and healthy subjects determined by frontal 1H-magnetic resonance spectroscopy at 1.5 tesla. J Psychiatr Res 1998;32(6):411-420.
21. Williams RS, Cheng L, Mudge AW, Harwood AJ. A common mechanism of action for three mood-stabilizing drugs. Nature 2002;417(6886):292-295.
22. Ventimiglia J, Kalali AH, McIntyre R. Treatment of bipolar disorder. Psychiatry (Edgmont) 2009;6(10):12-14.
23. Altamura AC, Lietti L, Dobrea C, Benatti B, Arici C, Dell'Osso B. Mood stabilizers for patients with bipolar disorder: the state of the art. Expert Rev Neurother 2011;11(1):85-99.
24. Nasrallah HA, Ketter TA, Kalali AH. Carbamazepine and valproate for the treatment of bipolar disorder: a review of the literature. J Affect Disord 2006;95(1-3):69-78.
25. Tondo L, Alda M, Bauer M, Bergink V, Grof P, Hajek T, et al. Clinical use of lithium salts: guide for users and prescribers. Int J Bipolar Disord 2019;7(1):16.
26. Di Daniel E, Cheng L, Maycox PR, Mudge AW. The common inositol-reversible effect of mood stabilizers on neurons does not involve GSK3 inhibition, myo-inositol-1-phosphate synthase or the sodium-dependent myo-inositol transporters. Mol Cell Neurosci 2006;32(1-2):27-36.
27. Harwood AJ. Lithium and bipolar mood disorder: the inositol-depletion hypothesis revisited. Mol Psychiatry 2005;10(1):117-126.
28. Yu W, Greenberg ML. Inositol depletion, GSK3 inhibition and bipolar disorder. Future Neurol 2016;11(2):135-148.

29. Berridge MJ, Downes CP, Hanley MR. Neural and developmental actions of lithium: a unifying hypothesis. Cell 1989;59(3):411-419.
30. Seelan RS, Parthasarathy LK, Parthasarathy RN. Lithium modulation of the human inositol monophosphatase 2 (IMPA2) promoter. Biochem Biophys Res Commun 2004;324(4):1370-1378.
31. Kennedy ED, Challiss RA, Nahorski SR. Lithium reduces the accumulation of inositol polyphosphate second messengers following cholinergic stimulation of cerebral cortex slices. J Neurochem 1989;53(5):1652-1655.
32. Allison JH, Blisner ME, Holland WH, Hipps PP, Sherman WR. Increased brain myo-inositol 1-phosphate in lithium-treated rats. Biochem Biophys Res Commun 1976;71(2):664-670.
33. Kravitz HM, Fawcett J. Efficacy of divalproex vs lithium and placebo in mania. JAMA 1994;272(13):1005-1006.
34. Pope HG, Jr., McElroy SL, Keck PE, Jr., Hudson JI. Valproate in the treatment of acute mania. A placebo-controlled study. Arch Gen Psychiatry 1991;48(1):62-68.
35. Chen CH, Lin SK. Carbamazepine treatment of bipolar disorder: a retrospective evaluation of naturalistic long-term outcomes. BMC Psychiatry 2012;12:47.
36. van Calker D, Belmaker RH. The high affinity inositol transport system--implications for the pathophysiology and treatment of bipolar disorder. Bipolar Disord 2000;2(2):102-107.
37. Lubrich B, van Calker D. Inhibition of the high affinity myo-inositol transport system: a common mechanism of action of antibipolar drugs? Neuropsychopharmacology 1999;21(4):519-529.
38. Ketter TA, Kalali AH, Weisler RH, Group SPDS. A 6-month, multicenter, open-label evaluation of beaded, extended-release carbamazepine capsule monotherapy in bipolar disorder patients with manic or mixed episodes. J Clin Psychiatry 2004;65(5):668-673.
39. Gitlin M. Lithium side effects and toxicity: prevalence and management strategies. Int J Bipolar Disord 2016;4(1):27.
40. Murru A, Popovic D, Pacchiarotti I, Hidalgo D, Leon-Caballero J, Vieta E. Management of adverse effects of mood stabilizers. Curr Psychiatry Rep 2015;17(8):603.
41. Sherman WR, Munsell LY, Gish BG, Honchar MP. Effects of systemically administered lithium on phosphoinositide metabolism in rat brain, kidney, and testis. J Neurochem 1985;44(3):798-807.
42. Bone S, Roose SP, Dunner DL, Fieve RR. Incidence of side effects in patients on long-term lithium therapy. Am J Psychiatry 1980;137(1):103-104.
43. Chang HH, Chao HN, Walker CS, Choong SY, Phillips A, Loomes KM. Renal depletion of myo-inositol is associated with its increased degradation in animal models of metabolic disease. Am J Physiol Renal Physiol 2015;309(9):F755-763.
44. Swedberg K, Winblad B. Heart failure as complication of lithium treatment. Preliminary report of a fatal case. Acta Med Scand 1974;196(4):279-280.
45. Kockskamper J, Zima AV, Roderick HL, Pieske B, Blatter LA, Bootman MD. Emerging roles of inositol 1,4,5-trisphosphate signaling in cardiac myocytes. J Mol Cell Cardiol 2008;45(2):128-147.
46. Nordio M, Pajalich R. Combined treatment with Myo-inositol and selenium ensures euthyroidism in subclinical hypothyroidism patients with autoimmune thyroiditis. J Thyroid Res 2013;2013:424163.
47. Lazarus JH. Lithium and thyroid. Best Pract Res Clin Endocrinol Metab 2009;23(6):723-733.
48. Verrotti A, D'Egidio C, Mohn A, Coppola G, Chiarelli F. Weight gain following treatment with valproic acid: pathogenetic mechanisms and clinical implications. Obes Rev 2011;12(5):e32-43.
49. Viswanathan LG, Satishchandra P, Bhimani BC, Reddy JY, Rama Murthy BS, Subbakrishna DK, et al. Polycystic ovary syndrome in patients on antiepileptic drugs. Ann Indian Acad Neurol 2016;19(3):339-343.
50. Bilo L, Meo R. Polycystic ovary syndrome in women using valproate: a review. Gynecol Endocrinol 2008;24(10):562-570.
51. Genton P, Bauer J, Duncan S, Taylor AE, Balen AH, Eberle A, et al. On the association between valproate and polycystic ovary syndrome. Epilepsia 2001;42(3):295-304.
52. Hu X, Wang J, Dong W, Fang Q, Hu L, Liu C. A meta-analysis of polycystic ovary syndrome in women taking valproate for epilepsy. Epilepsy Res 2011;97(1-2):73-82.
53. Larner J, Craig JW. Urinary myo-inositol-to-chiro-inositol ratios and insulin resistance. Diabetes Care 1996;19(1):76-78.
54. Sortino MA, Salomone S, Carruba MO, Drago F. Polycystic Ovary Syndrome: Insights into the Therapeutic Approach with Inositols. Front Pharmacol 2017;8:341.
55. Sun TH, Heimark DB, Nguygen T, Nadler JL, Larner J. Both myo-inositol to chiro-inositol epimerase activities and chiro-inositol to myo-inositol ratios are decreased in tissues of GK type 2 diabetic rats compared to Wistar controls. Biochem Biophys Res Commun 2002;293(3):1092-1098.
56. Carlomagno G, Unfer V, Roseff S. The D-chiro-inositol paradox in the ovary. Fertil Steril 2011;95(8):2515-2516.
57. Dinicola S, Chiu TT, Unfer V, Carlomagno G, Bizzarri M. The rationale of the myo-inositol and D-chi-

ro-inositol combined treatment for polycystic ovary syndrome. J Clin Pharmacol 2014;54(10):1079-1092.
58. Unfer V, Porcaro G. Updates on the myo-inositol plus D-chiro-inositol combined therapy in polycystic ovary syndrome. Expert Rev Clin Pharmacol 2014;7(5):623-631.
59. Kalra B, Kalra S, Sharma JB. The inositols and polycystic ovary syndrome. Indian J Endocrinol Metab 2016;20(5):720-724.
60. Kamenov Z, Gateva A. Inositols in PCOS. Molecules 2020;25(23)5566.
61. Jafferany M. Lithium and skin: dermatologic manifestations of lithium therapy. Int J Dermatol 2008;47(11):1101-1111.
62. Owczarczyk-Saczonek A, Czerwinska J, Wygonowska E, Kasprowicz-Furmanczyk M, Placek W. D-chiro-inositol as a treatment in plaque psoriasis: A randomized placebo-controlled clinical trial. Dermatol Ther 2021;34(1):e14538.
63. Iqbal MM, Sohhan T, Mahmud SZ. The effects of lithium, valproic acid, and carbamazepine during pregnancy and lactation. J Toxicol Clin Toxicol 2001;39(4):381-392.
64. Greene ND, Copp AJ. Inositol prevents folate-resistant neural tube defects in the mouse. Nat Med 1997;3(1):60-66.
65. D'Souza SW, Copp AJ, Greene NDE, Glazier JD. Maternal Inositol Status and Neural Tube Defects: A Role for the Human Yolk Sac in Embryonic Inositol Delivery? Adv Nutr 2021;12(1):212-222.
66. Nordio M, Basciani S. Treatment with Myo-Inositol and Selenium Ensures Euthyroidism in Patients with Autoimmune Thyroiditis. Int J Endocrinol 2017;2017:2549491.
67. Zacche MM, Caputo L, Filippis S, Zacche G, Dindelli M, Ferrari A. Efficacy of myo-inositol in the treatment of cutaneous disorders in young women with polycystic ovary syndrome. Gynecol Endocrinol 2009;25(8):508-513.
68. Pundir J, Psaroudakis D, Savnur P, Bhide P, Sabatini L, Teede H, et al. Inositol treatment of anovulation in women with polycystic ovary syndrome: a meta-analysis of randomised trials. BJOG 2018;125(3):299-308.
69. Unfer V, Facchinetti F, Orru B, Giordani B, Nestler J. Myo-inositol effects in women with PCOS: a meta-analysis of randomized controlled trials. Endocr Connect 2017;6(8):647-658.
70. Benelli E, Del Ghianda S, Di Cosmo C, Tonacchera M. A Combined Therapy with Myo-Inositol and D-Chiro-Inositol Improves Endocrine Parameters and Insulin Resistance in PCOS Young Overweight Women. Int J Endocrinol 2016;2016:3204083.
71. Le Donne M, Metro D, Alibrandi A, Papa M, Benvenga S. Effects of three treatment modalities (diet, myoinositol or myoinositol associated with D-chiro-inositol) on clinical and body composition outcomes in women with polycystic ovary syndrome. Eur Rev Med Pharmacol Sci 2019;23(5):2293-2301.
72. Diamanti-Kandarakis E, Dunaif A. Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. Endocr Rev 2012;33(6):981-1030.
73. Montanino Oliva M, Buonomo G, Calcagno M, Unfer V. Effects of myo-inositol plus alpha-lactalbumin in myo-inositol-resistant PCOS women. J Ovarian Res 2018;11(1):38.
74. Monastra G, Sambuy Y, Ferruzza S, Ferrari D, Ranaldi G. Alpha-lactalbumin Effect on Myo-inositol Intestinal Absorption: In vivo and In vitro. Curr Drug Deliv 2018;15(9):1305-1311.
75. Carlomagno G, Unfer V. Inositol safety: clinical evidences. Eur Rev Med Pharmacol Sci 2011;15(8):931-936.
76. Bersudsky Y, VI, Grisaru N, Yaroslavsky U, Gheorghiu S, Ivgi D, Kofman O, Belmaker RH. The effect of inositol on lithium-induced polyuria/polydipsia in rats and humans. Human Psychopharmacology: Clinical & Experimental 1992;7(6):403-407.
77. Allan SJ, Kavanagh GM, Herd RM, Savin JA. The effect of inositol supplements on the psoriasis of patients taking lithium: a randomized, placebo-controlled trial. Br J Dermatol 2004;150(5):966-969.
78. Kontoangelos K, Vaidakis N, Zervas I, Thomadaki O, Christaki S, Stavrianeas NG, et al. Administration of inositol to a patient with bipolar disorder and psoriasis: a case report. Cases J 2010;3:69.
79. Cantelmi T, Lambiase E, Unfer VR, Gambioli R, Unfer V. Inositol treatment for psychological symptoms in Polycystic Ovary Syndrome women. Eur Rev Med Pharmacol Sci 2021;25(5):2383-2389.
80. Iervolino M, Lepore E, Forte G, Lagana AS, Buzzaccarini G, Unfer V. Natural Molecules in the Management of Polycystic Ovary Syndrome (PCOS): An Analytical Review. Nutrients 2021;13(5):1677.
81. L'Abbate S, Nicolini G, Forini F, Marchetti S, Di Lascio N, Faita F, et al. Myo-inositol and d-chiro-inositol oral supplementation ameliorate cardiac dysfunction and remodeling in a mouse model of diet-induced obesity. Pharmacol Res 2020;159:105047.
82. Benvenga S, Nordio M, Lagana AS, Unfer V. The Role of Inositol in Thyroid Physiology and in Subclinical Hypothyroidism Management. Front Endocrinol (Lausanne) 2021;12:662582.
83. Dinicola S, Unfer V, Facchinetti F, Soulage CO, Greene ND, Bizzarri M, et al. Inositols: From Establi-

shed Knowledge to Novel Approaches. Int J Mol Sci 2021;22(19).
84. Lagana AS, Garzon S, Casarin J, Franchi M, Ghezzi F. Inositol in Polycystic Ovary Syndrome: Restoring Fertility through a Pathophysiology-Based Approach. Trends Endocrinol Metab 2018;29(11):768-780.
85. Lepore E, Lauretta R, Bianchini M, Mormando M, Di Lorenzo C, Unfer V. Inositols Depletion and Resistance: Principal Mechanisms and Therapeutic Strategies. Int J Mol Sci 2021;22(13):6796.
86. Janiri L, D'Ambrosio F, Di Lorenzo C. Combined treatment of myo-inositol and d-chiro-inositol (80:1) as a therapeutic approach to restore inositol eumetabolism in patients with bipolar disorder taking lithium and valproic acid. Eur Rev Med Pharmacol Sci 2021;25(17):5483-5489.