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BRIEF REPORT

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Prescribing lithium for the management of persons suffering from bipolar disorders: expert consensus based on a Delphi study

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Abstract

Background According to international guidelines, lithium treatment represents the gold standard for the appropriate management of persons with bipolar disorder. However, prescription rates in ordinary practice are not in line with clinical guidelines' suggestions. Clinicians prefer to use drugs other than lithium, considering its low therapeutic window, the need for regular lab tests and its side effects profile. Based on these premises, a Delphi-method study focused on highly-debated aspects of lithium treatment in bipolar disorder has been promoted with the aim to reach a consensus among an expert panel of Italian psychiatrists.

Methods The Delphi method is a structured technique aimed to obtain a consensus from repeated rounds of questionnaires where opinion/agreement among experts are important. A Steering Committee of experts has developed a 24-items questionnaire exploring: (1) the use of lithium as first choice for treating different phases of bipolar disorder; (2) the side effect and tolerability profile of lithium treatment as hampering factors for its use in clinical practice; (3) the lithium prescribing in special target population, such as adolescents, elderly patients, and pregnant women.

Results The questionnaire was delivered to a panel of 100 Italian psychiatrists, experts in the field of managing people with bipolar disorders. An almost complete positive consensus was reached for statements dealing with the use of lithium treatment as first choice in the management of patients with bipolar disorder, and as the first choice for preventing manic/hypomanic and depressive episodes.

Conclusions Current clinical guidelines and scientific evidence support the use of lithium as first choice treatment in patients with bipolar disorder. However, over the last decades a downward tendency in lithium's prescription has been registered worldwide. The present Delphi study confirmed the "good clinical reasons" for supporting lithium prescription in clinical practice. Our findings should be used to develop clinical practice guidelines and reduce the discrepancy between international guidelines and ordinary care.

Keywords Lithium, Bipolar disorder, Clinical guidelines, Pharmacological management

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Background

Lithium represents the gold-standard treatment for persons with bipolar disorder and it is a useful treatment also in patients with refractory unipolar depression (Ercis et al. 2023). Lithium has anti-suicidal effects in patients with bipolar or major depressive disorder as well as neuroprotective properties in neurogenerative diseases (Singh et al. 2023; Nierenberg et al. 2023; Fiorillo et al. 2023; Janiri et al. 2023; Sartorius 2023; Holm et al. 2024). Moreover, people with bipolar disorder treated with lithium reported a reduced rate of both depression- and mania-related hospitalizations, thus, representing the ideal mood stabilizers for these patients (Singh 2025; Berk et al. 2024).

Current clinical guidelines and scientific evidence support use of lithium as first choice treatment option in patients with bipolar disorder (Sampogna et al. 2022a; Jauhar and Young 2019). Over the last decades, a downward tendency to use lithium has been reported, so that lithium has been defined a "forgotten" and old-fashioned drug (Di Vincenzo et al. 2022; Lähteenvuo et al. 2023).

In an observational study carried out in Germany, Kriner et al. (2023) showed a significant decrease in the proportion of prescriptions for mood stabilizers by 2018 (from 58.6% to 49.5%), particularly for lithium (from 31.4% to 26.2%), and an increased prescription of antipsychotics (from 38.4% in 2009 to 53.1% in 2018). In a national survey carried out in Spain, Pérez de Mendiola et al. (2021) found that the main reasons for psychiatrists to not prescribe lithium were its side effects. They reported that most psychiatrists prescribe lithium following conservative plasma concentrations (0.6–0.8 mmol/L). Furthermore, lithium was not used in adolescent patients due to concerns related to its side effects and the need to constantly monitor its plasma levels (Bohlken et al. 2020).

The declining lithium prescription rate has been recently witnessed as a worldwide tendency (Shuy et al. 2024; Rhee et al. 2020). The Global Bipolar Cohort collaborative network has found that lithium was prescribed to 29% of patients, with significant different prescription patterns according to geographic regions (Singh 2025).

Despite the clinical efficacy of lithium treatment and its anti-suicidal effects, its use in clinical practice is far from suggestions from clinical guidelines (Baldessarini and Tondo 2022; Galynker et al. 2024; Branje 2024). In Italy, the QUADIM study (D'Avanzo et al. 2023) highlighted a significant treatment gap for patients with bipolar disorders not only in terms of lack of continuity of care and low intensity of care, but also regarding to the prescriptive patterns. In fact, Italian psychiatrists prefer prescribing second generation antipsychotics or other types of mood stabilizers compared to lithium to patients with bipolar disorder. These prescription patterns reflect the organizational and practical difficulties reported by Italian mental health care professionals, which prefer to use drugs other than lithium, considering its low therapeutic window and need for regular lab tests. Further possible factors hampering the use of lithium in clinical practice include the profile of possible serious adverse events, which should increase when patients have many comorbid physical diseases, as in the case of people with bipolar disorders.

Residents and early career psychiatrists are often untutored on lithium use and feel uncomfortable in prescribing it (Ruffalo 2017), although a greater awareness on lithium use has been recently reported by them (Hidalgo-Mazzei et al. 2023). These data highlight the need to improve education on the use of lithium in bipolar disorder and to provide good clinical practice suggestions (Skokauskas et al. 2024; Liu et al. 2023).

Based on these premises, a Delphi-method study focused on highly-debated aspects of lithium treatment in bipolar disorder has been promoted with the aim to reach a consensus among an expert panel of Italian psychiatrists.

Materials and methods

The Delphi method is a structured technique aimed to obtain a consensus opinion from a panel of experts by repeated rounds of questionnaires in highly debated areas and where opinion/agreement among experts are important (Nasa et al. 2021; Fiorillo et al. 2024). In particular, the decision to adopt the Delphi method was due to the need to reach consensus on controversial aspects on the lithium treatment in patients with bipolar disorder. This analysis was deemed to be timely and urgent due to the alarming finding from the QUADIM study on the treatment gap in patients with bipolar disorders (D'Avanzo et al. 2023). The results of the Delphi study, as a form of expert opinion research, addressing relevant questions for the appropriate pharmacological management of patients with bipolar disorders, should be used for developing clinical guidelines tailored to the Italian context, in order to reduce the existing discrepancy between clinical guidelines and clinical practice in Italy.

A Steering Committee made of seven Italian key opinion leaders (KOLs) in the field of bipolar disorder identified highly debated topics on lithium use in clinical practice. The Steering Committee conducted an extensive literature search regarding relevant topics on the clinical management of persons with bipolar disorder, focusing on lithium treatment. The final Delphi questionnaire included 24 statements grouped in three main domains: (1) the use of lithium as first choice for treating different phases of bipolar disorder; (2) the side effect

and tolerability profile of lithium treatment as hampering factors for its use in clinical practice; (3) the lithium prescribing in special target population, such as adolescents, elderly patients, and pregnant women.

The development of the Delphi survey followed a multistep procedure: (1) analysis of available literature and expert discussion on the use of lithium in clinical practice; (2) identification of an initial list of relevant topics; (3) submission of the provisional draft of the Delphi questionnaire to external validators (see Acknowledgment for panel members' names) for revision/approval; (4) distribution of the final approved/validated version of the Delphi questionnaire to participants of the expert panel. The Delphi Questionnaire consists of 24 items, dealing with the main strengths and difficulties of prescribing lithium treatment in clinical practice (Appendix 1).

For each statement, participants had to express their level of agreement according to a 5-point Likert scale: 1 = strongly disagree; 2 = disagree; 3 = agree; 4 = more than agree; 5 = strongly agree. In accordance with the Delphi standards (Nasa et al. 2021), a consensus is reached when the sum of items 1 and 2 (Disagreement) or of items 4 and 5 (Agreement) reaches the threshold of 66%. When the sum of the responses for a negative (1 and 2) or a positive consensus (4, and 5) is below 66%, the consensus is not reached (Giannarou and Zervas 2014; Walker and Selfe 1996).

Experts invited to participate in the Delphi study were defined according to the following criteria: (1) having more than 10 years of experience in clinical practice; (2) working in in-patient/out-patient units with a subspecialty in managing people suffering from mood disorders (including both unipolar and bipolar disorders); (3) having treated at least 100 patients with bipolar disorder/per year; (4) being member of national and/or international scientific associations with a focus/section on bipolar disorder (i.e., Società Italiana di Psichiatria, European Psychiatric Association, Società Italiana di Psicopatologia, International Society for Bipolar Disorders). Participants were recruited through direct/personal email invitation. Participants filled an information and consent form on a secure data collection platform (hosted on a private domain). Participants agreed to be recontacted in case of "no agreement". A second round of the Delphi process was implemented for items on which a consensus was not found. The Steering Committee provides scientific references for supporting the agreement process.

The experts were invited to fill in the questionnaire between May and August 2024 and between October and November 2024 (second round). Items included in the second round have been reported in Appendix 2.

Participants received a brief introduction to the project with its objectives and process, and a link to fill in the questionnaire. Participants had about one hour to complete the questionnaire. Collected personal data included the following socio-demographic information: gender, age, and geographic region. Moreover, respondents had to fill in the following yes/no questions: having more than 10 years of experience in clinical practice; working in in-patient/out-patient units with a subspecialty in managing people suffering from mood disorders (including both unipolar and bipolar disorders); having treated at least 100 patients with bipolar disorder/per year; being member of national and/or international scientific associations with a focus/section on bipolar disorder. Only invited participants stating "yes" at each of the above-mentioned items were considered eligible and therefore took part to the Delphi study.

The study is based on a survey that does not involve the participation of human subjects nor patient data management and does not aim to modify the current clinical practice of participants. Consequently, the study did not require any ethical approval. All experts involved in the Delphi survey were informed of the study's objectives and the possibility of publishing the results in a peer-reviewed article. The participation was on a voluntary basis. The required sample of experts participating to the Delphi has been set to 100 persons. All data were anonymously analyzed using SPSS Statistical Software, version 20.0.

Results

One-hundred and twenty experts were invited to participate; 83.3% (N = 100) agreed to participate, reaching the required fixed sample size. 56.3% of experts (N = 54) were male, with a mean working experience in mental health of 18.9 years (sd: 11.1), mainly at university hospital settings (32.3%, N = 31). Respondents were distributed through the entire country: 40.6% were from Central Italy, 35.4% from Southern Italy and 24% from Northern Italy.

At the first round of the Delphi survey, agreement was not reached for 8 items out of 24 (Fig. 1). In particular, a positive agreement was reached for 6 items (25% of cases), while a negative agreement was obtained for 10 items (41.6% of cases). No agreement was reached on statements dealing with: using lithium as first choice for the treating depressive episodes; using lithium for treating acute manic episodes; timing of periodical lab tests (Table 1).

Consensus statements: positive agreement

A strong positive agreement (higher than 85%) was reached for six items, suggesting a shared view on the utility of lithium treatment as first choice for the management of patients with bipolar disorder. All statements

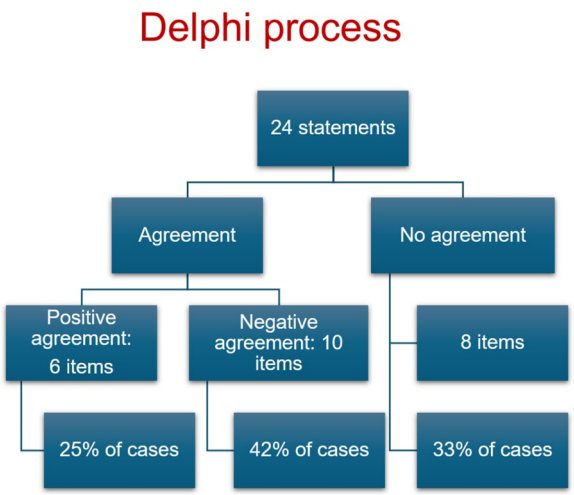

Fig. 1 Delphi process—first round

and items of the consensus, with the percentages of agreement and disagreement, are reported in Table 1.

As regards the statements dealing with the use of lithium treatment as first choice in the management of patients with bipolar disorder,

An almost complete agreement (ranging from 81 to 92%) was reached for items stating that lithium treatment represents the first choice for the pharmacological management of patients with bipolar disorder and that lithium represents the first choice for preventing manic/hypomanic and depressive episodes.

The statement on good clinical practice to be adopted before starting lithium treatment reached a good level of positive consensus, with 88% of participants agreeing that routine lab test should always be prescribed.

A strong positive consensus (84%) was shared by experts regarding the anti-suicidal effects of lithium in people suffering from mood disorders.

Consensus statements: negative agreement

A strong negative consensus was reached for statements dealing with the prescription of lithium treatment only in adult patients with bipolar disorder (86%) and with the difficulties in anticipating possible pharmacological interactions in case of polytherapy.

Statements dealing with lithium prescription in special target population (e.g., pregnant women, elderly people, adolescents) reached an almost complete negative agreement, with values ranging from 87% (no need for interrupting lithium treatment in patients suffering from hypothyroidism) to 68% of negative agreement (no need for suspending immediately lithium treatment in pregnant women).

As regards the long-term management of lithium treatment, a strong negative consensus (80%) has been reached for dosing lithium plasma levels every month (Table 1).

No agreement found: second round of Delphi

A second round of the Delphi panel was carried out only on the eight items for which "no-agreement" was reached at the first round (Appendix 2). A total of 75 out of 100 former experts provided their feedback, with an attrition rate of 25%. As reported in Fig. 2, a positive agreement was reached for four further items, while a negative agreement was reached for three items. No agreement was reached for the item stating that "The pharmacological regimen of patients suffering from bipolar disorder includes mood stabilizer drugs only" (Table 2).

A positive consensus was found on statements related to the use of lithium as first choice treatment for the management of bipolar depression as well as severe form of depressive disorders, on the easiness of use slow-release lithium formulation and on the regular 3-months lab check of lithium concentration. A negative agreement was reached on statements dealing with lithium prescription as first choice treatment in acute manic episode, with the regular 6-month lab check and with the complexity of pharmacological regimen including lithium.

Discussion

According to several international guidelines, lithium should be considered the first-choice treatment for patients suffering from bipolar disorder, including adolescents, elderly people, patients with substance use disorders, and pregnant women. However, several real-world studies have documented that clinicians' preference in using lithium in clinical practice is quite poor (Koistinaho et al. 2023; Gomes-da-Costa et al. 2022; Greil et al. 2023; Hickie and Crouse 2024; Hsu et al. 2022; Galderisi 2024; Wampold and Flückiger 2023; Reed 2024), and that other medications are preferred, due to some misconceptions related to the higher manageability of other compounds compared to lithium. Rather than patients' nonadherence, a key factor influencing clinician's reluctance in prescribing lithium treatment is the need for regular blood monitoring, which seems to play a crucial hampering role in lithium prescription, as it happens for clozapine use in patients with schizophrenia (Kessing 2019, 2024; Laforgue et al. 2021).

Thus, a substantial gap between guideline recommendations and current clinical practice exists, which can be partly explained by the complex phenomenology of bipolar disorder but reflects the need for a better medical education of psychiatrists and the need to disseminate good clinical practice recommendations in real-world

Table 1 Delphi survey—Prescribing lithium in clinical practice—first round—Positive agreement items (N = 6)

	Level of agreement				
	Negative Agreement		No agreement	Positive agreement	
	1	2	3	4	5
During the maintenance phase of the treatment plan of patients with bipolar disorder, it is not possible to completely tapering and interrupting the pharmacological treatment	0	4% 4	10% 9	45	86% 33
Lithium is considered the first line treatment for the pharmacological management plan of patients with bipolar disorder	0	2% 2	8% 7	35	90% 47
Lithium is considered the first line treatment for the pharmacological management of prevention of depressive episode in patients with bipolar disorder	0	4% 4	14% 13	49	81% 25
Lithium is considered the first line treatment for the pharmacological management of prevention of manic/hypomanic episode in patients with bipolar disorder	1	3% 2	4% 4	34	92% 50
Lithium is the only drug with anti-suicidal evidence-based properties	0	8% 7	9% 8	39	84% 37
Before starting lithium treatment, routine lab test should be performed	2	4% 2	8% 7	39	88% 41
The pharmacological management plan of patients suffering from bipolar disorder does not include any preventive treatment	76	99% 14	0% 0	1% 0	1
The lithium plasma level concentration should be checked every month during the maintenance phase	15	80% 58	11% 10	8	9% 0
Lithium treatment is indicated only for adult patients with bipolar disorder	26	86% 52	10% 9	4% 4	0
In case of a polytherapy regimen, including lithium, pharmacological interaction cannot be predicted in advance	26	92% 58	7% 6	1% 1	
A patient suffering from hypothyroidism must immediately interrupt lithium treatment	36	87% 43	13% 12	0% 0	0
A pregnant patient treated with lithium, in a stable phase of the disorder, should interrupt lithium treatment	21	68% 41	11% 10	21% 18	1
An elderly patient with bipolar disorder should not be treated with lithium	18	84% 58	13% 12	3% 3	0
In adolescent patient, at first affective episode, lithium treatment should not be started	19	69% 44	24% 22	7% 4	2
Lithium treatment is NOT usually started in a patient with substance abuse disorder and affective symptoms	21	88% 59	11% 10	1% 1	0
Using lithium slow-release formulation does NOT reduce the incidence of side-effects, including tremors and nausea	11	68% 51	19% 17	13% 11	1
The pharmacological regimen of patients suffering from bipolar disorder includes mood stabilizer drugs only	10	55% 40	22% 20	23% 17	4
Lithium is considered the first line treatment for the pharmacological management of depressive episode in patients with bipolar disorder	1	16% 14	37% 34	46% 28	14
Lithium is NOT considered the first line treatment for the pharmacological management of acute manic episode in patients with bipolar disorder	12	34% 19	31% 28	35% 28	4
The long-term management plan of lithium-based treatment in patients with bipolar disorder is more complicated compared to other mood stabilizers	18	58% 35	26% 24	15% 12	2
The slow-release lithium formulation are easier to be used compared to the immediate-release ones	2	14% 11	21% 19	65% 44	15
The lithium plasma level concentration should be checked every three months during the maintenance phase	5	29% 21	21% 19	51% 36	10
The lithium plasma level concentration should be checked every six months during the maintenance phase	6	42% 32	19% 17	40% 28	8
In patient with unipolar depression, with high number of episodes per year, lithium treatment is selected as first line choice	0	23% 21	25% 23	52% 38	9

settings (González-Pinto et al. 2021; Sampogna et al. 2022b). Moreover, it may be that lithium prescribing trends over the past decades have been influenced by aggressive marketing by second-generation antipsychotic companies, lack of education among trainees on lithium subtleties and some attitudes among seasoned psychiatrists to consider lithium a second-choice treatment. Practicing psychiatrists (both early career and more senior ones) should be incentivized to adhere to evidence-based guidelines and training and education on lithium use should be reintroduced and disseminated (Fitzgerald et al. 2022; Flett and Hewitt 2024).

With this Delphi study we aimed to highlight the most common difficulties limiting lithium use in clinical practice. In particular, the Italian expert panel confirmed the international clinical guidelines by stating that lithium is a first-choice drug for people with bipolar disorders. The findings of the present Delphi study can be useful to reach consensus on relevant questions for the appropriate pharmacological management of patients with

bipolar disorders. The consensus should be used for developing clinical guidelines tailored to the Italian context, in order to reduce the existing discrepancy between clinical guidelines and clinical practice in Italy. Moreover, our findings could highlight the need to develop educational material for practicing psychiatrists, residents and fellows on lithium subtleties (Sampogna et al. 2024; Gitlin and Bauer 2024; Zachar 2023; Gitlin 2016; Fusar-Poli et al. 2024; Stanghellini 2024; Fisher 2024).

The Delphi expert panel clearly confirmed—with a positive agreement higher than 85%—that lithium treatment should be used as first choice for the management of patients with bipolar disorder. In particular, the panel agreed that lithium should represent the first choice for the prevention of manic/hypomanic and depressive episodes. These statements are in line with the most recent evidence that lithium significantly reduces the risk of new (manic and depressive) episodes compared to placebo (Volkmann et al. 2020; Yildiz et al. 2023; Nestsiarovich et al. 2022). For the optimal efficacy in long-term treatment of patients with bipolar disorder, target serum levels should generally be around 0.6–0.8 mmol/L (Nolen et al. 2019; Parker et al. 2017; Ulrichsen et al. 2023). However, for patients unable to adhere to lithium treatment, prescribing second generation antipsychotics should be considered, with a personalized and individualized selection of the most appropriate drug for each patient (Jauhar and Young 2019). A recent longitudinal cohort study by Lintunen et al. (2025) has compared the relapse ratio in patients taking lithium compared to those treated with second generation antipsychotics, confirming that olanzapine, risperidone, aripiprazole and lithium were associated with a decreased risk of relapse in patients with bipolar disorders.

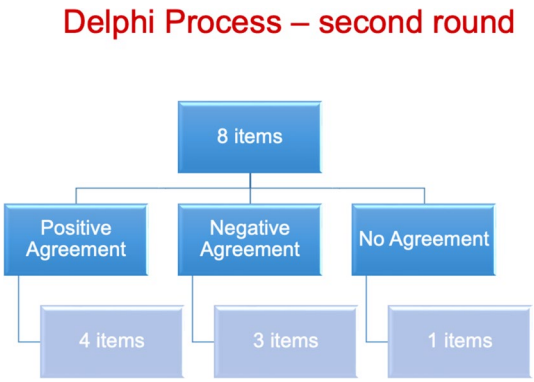

Fig. 2 Delphi process—Second round

In order to improve good clinical practice, the expert panel agreed that routine lab tests should always be prescribed before starting a lithium treatment. In particular, routine lab tests before initiating lithium treatment should include kidney function tests, urine analysis, Cystatin C, and a broader panel including cell blood count/platelet count. Moreover, clinicians should consider checking body weight, estimated glomerular filtration rate, full blood count, thyroid function tests, and calcium levels. An electrocardiogram (ECG) is recommended for patients with cardiovascular diseases, such as arrhythmias, or other cardiovascular risk factors (Mehta and Vannozzi 2017).

However, no agreement was found regarding the timing of periodical lab test in the maintenance phase (Nederlof et al. 2019). Most guidelines (Malhi et al. 2020a, 2020b, 2017; Yatham et al. 2018; Kriner et al. 2024) suggest checking lithium levels every three months during the first year of treatment and then every six months. Exceptions should be made for patients with known risk factors for toxicity, including patients aged over 65 years, those with renal or thyroid impaired functioning, raised calcium levels, taking interacting medicines, and with poor medication

Table 2 Delphi survey—prescribing lithium in clinical practice—second round

	Level of agreement		
	Negative Agreement	No agreement	Positive Agreement
Lithium is considered the first line treatment for the pharmacological management of depressive episode in patients with bipolar disorder	20% 1 14	14% 11	66% 44 8
The slow-release lithium formulation are easier to be used compared to the immediate-release ones	3% 0 2	19% 15	78% 43 18
The lithium plasma level concentration should be checked every three months during the maintenance phase	21% 1 20	13% 5	66% 39 13
In patient with unipolar depression, with high number of episodes per year, lithium treatment is selected as first line choice	18% 2 12	10% 8	72% 48 8
Lithium is NOT considered the first line treatment for the pharmacological management of acute manic episode in patients with bipolar disorder	66% 20 32	7% 9	27% 15 2
The long-term management plan of lithium-based treatment in patients with bipolar disorder is more complicated compared to other mood stabilizers	79% 19 43	9% 7	12% 19 0
The pharmacological regimen of patients suffering from bipolar disorder includes mood stabilizer drugs only	81% 11 52	5% 4	14% 11 0
The lithium plasma level concentration should be checked every six months during the maintenance phase	49% 5 33	8% 6	44% 30 4

adherence (Millischer et al. 2022; Nielsen et al. 2018). In these cases, lithium level should be checked every three months. The panel quite unanimously agreed that there is no need for checking lithium level every month.

Panelists highlighted the relevant anti-suicidal effect of lithium, considering that the management of patients with suicidal ideation/suicidal behavior/suicidal risk is one of the most challenging tasks for healthcare clinicians (Cipriani et al. 2013, 2005; Perna et al. 2024). Lithium is effective in reducing the risk of suicide in patients with affective disorders over the long-term course (Cipriani et al. 2013; Pompili et al. 2022; Sampogna et al. 2024; Kotzalidis et al. 2024; Joffe 2002). Data also suggest that the overall mortality in patients with mood disorders is reduced when lithium is prescribed (Shine et al. 2015). However, it must be considered that a randomized controlled trial involving veterans has recently found lack of a positive effect (Katz et al. 2022).

Experts reached a positive consensus on the management of lithium treatment in target population, with no need for interrupting lithium treatment in patients suffering from other physical illnesses like hypothyroidism or for suspending immediately lithium treatment in pregnant women (Fung et al. 2023; Bocchetta et al. 2017; Lastname, et al. 2017). The issue of stopping lithium in pregnancy represents a growing concern in clinical practice. A recent cohort study using individual-level data of pregnancies by Wittström et al. (2024) confirmed that the prevalence of lithium use in pregnant women varied markedly between countries and populations. The extreme heterogeneity in lithium prescription in pregnant women affected from bipolar disorder is in line with the controversial data collected so far. Given the severe and chronic nature of bipolar disorder and the high risk of relapse, the continuation or the initiation of lithium treatment in pregnant patients should be always considered. However, the benefits of relapse prevention must be carefully weighed against potential adverse effects on both mother and child (Volkmann et al. 2020).

Lithium dosage should be adapted according to sociodemographic and clinical characteristics, since its profile of efficacy, tolerability, and side effects may vary from one group to another (Sproule et al. 2000; Gitlin and Bauer 2023). In fact, elderly people usually require lower doses of lithium to achieve effective serum concentrations, due to pharmacokinetic modifications and to the reduced renal excretion (Aprahamian et al. 2014). On the other hand, an increase of renal lithium excretion has been observed in pregnant women, which may require increased lithium doses to obtain a meaningful clinical effect. Of course, the risk of toxicity of high lithium doses should be balanced with the positive effects of increasing lithium dosage. These examples highlight the need for a careful physical and laboratory examination of patients taking lithium, which cannot be limited to the assessment of lithium serum levels. Old age and comorbid substance use disorder do not appear to be relevant hampering factors for clinicians to starting lithium therapy (Berk et al. 2024).

While there was no consensus on the use of lithium during acute manic episodes in bipolar disorder, the panel agreed that lithium is a first-choice treatment strategy for the maintenance phase of bipolar disorder. This finding highlight that the notion of lithium as maintenance treatment is widely accepted, but there is still much work to do about its use in acute phases, despite FDA recent approval for mania (Pérez de Mendiola et al. 2021).

The present Delphi study has some limitations, that should be acknowledged. Firstly, invited experts were all Italian, mainly working in academic settings, and thus results cannot be easily generalizable to other settings or countries. However, it should be considered that the aim of a Delphi study is not to capture the clinical practice in Italy, but to explore experts' opinions and knowledge on the use of lithium in clinical care. It would be interesting to involve a larger panel of experts, working in different settings or coming from countries with different background, in order to identify any difference in relation to setting and region. Second, the Delphi method is used to analyse and summarize experts' opinions, but not necessarily a consensus is reachable for all statements due to controversies in the field. Third, only a few demographic-type information about respondents have been collected. Moreover, a self-reported procedure for confirming the fulfilment of eligibility criteria of invited clinicians has been adopted. Therefore, the adopted procedure should have biased the recruitment process and can limit replicability of our survey in other contexts.

Finally, the Steering Committee decided to include the topic of the optimal timing for lab tests in patients taking lithium treatment. Although clinical guidelines suggest performing lab test before starting lithium treatment and after six-months treatment, the Steering Committee aimed to establish a level of consensus among the invited Italian expert clinicians. The decision to include several statements—dealing with the same topics—should have create confusion in respondents and should have biased our results. Moreover, a question on lithium using among individuals with chronic kidney disease (CKD) or those who develop early-stage CKD has not been included. Although this is a major concern for prescribers, limited data on the progression to end-stage kidney disease are available (Gislason et al. 2024; Chang and Ho 2020),

which could have biased the opportunity to reach a consensus.

Conclusions

Current clinical guidelines and scientific evidence support the use of lithium as first choice treatment in patients with bipolar disorder. However, over the last decades a downward tendency in lithium's use has been registered worldwide. The present Delphi study confirmed the "good clinical reasons" for supporting lithium prescription in clinical practice (Ratcliffe 2024; Berking 2024). Our findings should be used to develop clinical practice guidelines and reduce the discrepancy between international guidelines and ordinary care.

Appendix

Appendix 1: First round—Delphi study—Prescribing lithium in clinical practice

1. The pharmacological regimen of patients suffering from bipolar disorder includes mood stabilizer drugs only.

2. During the maintenance phase of the treatment plan of patients with bipolar disorder, it is not possible to completely tapering and interrupting the pharmacological treatment.

3. The pharmacological management plan of patients suffering from bipolar disorder does not include any preventive treatment.

4. Lithium is considered the first line treatment for the pharmacological management plan of patients with bipolar disorder.

5. Lithium is considered the first line treatment for the pharmacological management of depressive episode in patients with bipolar disorder.

6. Lithium is considered the first line treatment for the pharmacological management of prevention of depressive episode in patients with bipolar disorder.

7. Lithium is considered the first line treatment for the pharmacological management of prevention of manic/hypomanic episode in patients with bipolar disorder.

8. Lithium is NOT considered the first line treatment for the pharmacological management of acute manic episode in patients with bipolar disorder.

9. Before starting lithium treatment, routine lab test should be performed.

10. The long-term management plan of lithium-based treatment in patients with bipolar disorder is more complicated compared to other mood stabilizers.

11. The slow-release lithium formulation are easier to be used compared to the immediate-release ones.

12.1 The lithium plasma level concentration should be checked every month during the maintenance phase.

12.2 The lithium plasma level concentration should be checked every three months during the maintenance phase.

12.3 The lithium plasma level concentration should be checked every six months during the maintenance phase.

13. Lithium treatment is indicated only for adult patients with bipolar disorder.

14. In case of a polytherapy regimen, including lithium, pharmacological interaction cannot be predicted in advance.

15. Lithium is the only drug with anti-suicidal evidence-based properties.

16. A patient suffering from hypothyroidism must immediately interrupt lithium treatment.

17. A pregnant patient treated with lithium, in a stable phase of the disorder, should interrupt lithium treatment.

18. An elderly patient with bipolar disorder should not be treated with lithium.

19. In adolescent patient, at first affective episode, lithium treatment should not be started.

20. Lithium treatment is NOT usually started in a patient with substance abuse disorder and affective symptoms.

21. Using lithium slow-release formulation does NOT reduce the incidence of side-effects, including tremors and nausea.

22. In patient with unipolar depression, with high number of episodes per year, lithium treatment is selected as first line choice.

Appendix 2: Second round—Delphi study—Prescribing lithium in clinical practice

1. The pharmacological regimen of patients suffering from bipolar disorder includes mood stabilizer drugs only
2. Lithium is considered the first line treatment for the pharmacological management of depressive episode in patients with bipolar disorder
3. Lithium is NOT considered the first line treatment for the pharmacological management of acute manic episode in patients with bipolar disorder
4. The long-term management plan of lithium-based treatment in patients with bipolar disorder is more complicated compared to other mood stabilizers
5. The slow-release lithium formulation are easier to be used compared to the immediate-release ones

6. The lithium plasma level concentration should be checked every three months during the maintenance phase
7. The lithium plasma level concentration should be checked every six months during the maintenance phase
8. In patient with unipolar depression, with high number of episodes per year, lithium treatment is selected as first line choice

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