Lithium Therapy in Old Age: Recommendations from a Delphi Survey

Authors

Julia Christl[1], Bruno Müller-Oerlinghausen[2,3], Michael Bauer[4], Daniel Kamp[1], Fabian Fußer[5], Jens Benninghoff[6,7], Rosa A. Fehrenbach[8], Christian Lange-Asschenfeldt[1,9], Michael Rapp[10], Bernd Ibach[11], Rainer Schaub[12], Axel Wollmer[13], Timm Strotmann-Tack[14], Michael Hüll[15], Susanne Biermann[16], Katharina Roscher[17], Bernd Meissnest[18], Alexander Menges[19], Bernd Weigel[20], Dorothee Maliszewski-Makowka[21], Christian Mauerer[22], Martin Schaefer[23], Beate Joachimsmeier[24], Sarah Kayser[25], Lars Christian Rump[26], Tillmann Supprian[1]

Affiliations

1 Department of Psychiatry and Psychotherapy, Medical Faculty, Heinrich-Heine-University, Düsseldorf, Germany
2 Charité Universitätsmedizin Berlin, Berlin, Germany
3 Brandenburg Medical School Theodor Fontane, Faculty of Medicine and Psychology, Neuruppin, Germany
4 Department of Psychiatry and Psychotherapy, University Hospital Carl Gustav Carus, Medical Faculty, Technische Universität Dresden, Dresden, Germany
5 Klinik für Gerontopsychiatrie, Psychosomatik und Psychotherapie, Pfalzklinikum Klingenmünster, Klingenmünster, Germany
6 Zentrum für Altersmedizin und Entwicklungsstörungen, kbo-Isar-Amper-Klinikum München-Ost, Haar, Germany
7 LVR-Universitätsklinik Essen, Kliniken und Institut der Universität Duisburg-Essen, Essen, Germany
8 Saarland-Heilstätten GmbH, SHG-Kliniken Sonnenberg, Klinik für Gerontopsychiatrie, Saarbrücken, Germany
9 Oberberg Fachklinik Düsseldorf Kaarst, Kaarst, Germany
10 University of Potsdam, Research Area Cognitive Sciences, Division of Social and Preventive Medicine, Potsdam, Germany
11 Zentrum für Alterspsychiatrie und Privé, Clienia Littenheid AG, Littenheid und Universität Zürich, Zürich, Schweiz
12 Klinik für Gerontopsychiatrie und Psychotherapie, Klinikum am Weissenhof, Weinsberg, Germany
13 Klinik für Gerontopsychiatrie und Psychotherapie, Asklepios Klinik Nord-Ochsenzoll, Hamburg, Germany
14 Klinik für Gerontopsychiatrie und Psychotherapie, LVR-Klinik Viersen, Viersen, Germany
15 Zentrum für Psychiatrie Emmendingen, Emmendingen, Germany
16 LWL-Klinik Lengerich, Lengerich, Germany
17 Psychiatrische Klinik Lüneburg, Lüneburg, Germany
18 LWL-Klinikum Gütersloh, Gütersloh, Germany
19 Klinikum Freudenstadt, Freudenstadt, Germany
20 Bezirksklinikum Mainkofen, Mainkofen, Deggendorf, Germany
21 LVR-Klinik Bedburg-Hau, Bedburg-Hau, Germany
22 Bezirkskrankenhaus Bayreuth, Bayreuth, Germany
23 Klinik für Psychiatrie, Psychotherapie, Psychosomatik und Suchtmedizin, Evang. Kliniken Essen-Mitte, Essen, Germany
24 LWL Klinik Paderborn, Paderborn, Germany
25 Klinik für Allgemeine Psychiatrie und Psychotherapie mit Poliklinik Universitätsklinikum Tübingen, Tübingen, Germany
26 Department of Nephrology, Medical Faculty, University Hospital Düsseldorf, Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany

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Bibliography

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Georg Thieme Verlag, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence

Dr. med. Julia Christl
Department of Psychiatry and Psychotherapy,
Medical Faculty
Heinrich-Heine-University, Bergische Landstr. 2
40629 Düsseldorf
Germany
julia.christl@lvr.de

ABSTRACT

Introduction While lithium (Li) has been well established for the treatment of bipolar disorder, geriatric patients require special attention when it comes to issues of drug safety. Declining renal function, amongst other medical conditions, and polypharmacy may pose increased risks. Only a few previous studies have addressed the management of Li in geriatric patients.

Methods Twenty-four German medical experts on geriatric medicine and Li treatment participated in a Delphi survey, consisting of two rounds of questionnaires and a final formulation of treatment recommendations. Three major issues of Li therapy were outlined: initiation of treatment, monitoring of ongoing therapy, and withdrawal due to medical reasons. Final recommendations were consented to at a threshold of at least 80 % expert agreement.

Results Final consensus was achieved on 21 clinical recommendations. The approved recommendations covered aspects of necessary laboratory checks, concomitant medication, and target Li serum concentration in geriatric patients. Concerning the termination of Li therapy, an agreement was reached on the appropriate time span for tapering and on potential alternatives to Li. No consensus was achieved on whether concomitant dementia or frailty should be considered contraindications for Li treatment and the appropriate threshold of the estimated glomerular function rate for withdrawing Li.

Conclusion According to the view of German experts, Li may be used in geriatric patients, but it should be monitored carefully. However, the lack of consent in several specific treatment situations underlines the need for research on specific issues of Li therapy.

Introduction

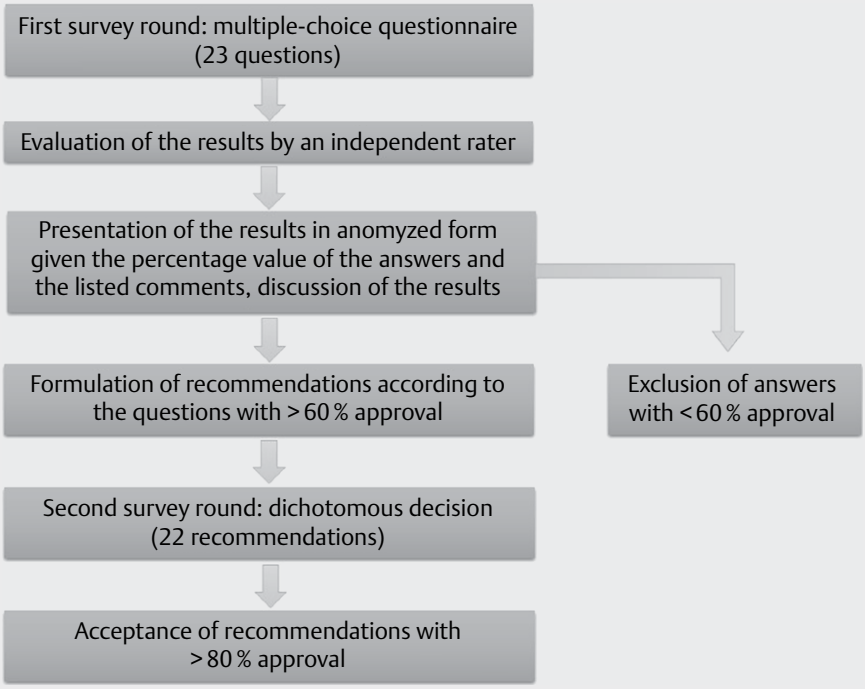
Lithium (Li) is considered the gold standard for the treatment of bipolar affective disorder in the prevention of manic and depressive episodes [1–4]. However, with patients growing older, several questions on appropriate drug monitoring, dosage, significant comorbid diseases, and appropriate control of renal function arise. The percentage of patients aged 60 years and older with bipolar disorder (old age bipolar disorder, OABD) is increasing. By 2030, one-half of patients with bipolar disorder will be 60 years or older [5]. Thus, national and international guidelines for Li treatment in older age ranges are becoming increasingly important.

Few studies have examined the efficacy and tolerability of Li in OABD indications, such as augmentation of antidepressant therapy in major depressive disorders. Sajatovic et al. (2005) surveyed the efficacy and tolerability of Li in the maintenance treatment of OABD and compared the effects with those of lamotrigine and a placebo [6]. Their results indicated that Li is successful in the prevention of manic, hypomanic, and mixed episodes. Compared to divalproex, Li was associated with a greater reduction in manic symptoms, while the tolerability of both pharmacological agents did not differ [7]. In a randomized controlled trial, Li was the more effective treatment option for therapy-resistant major depression compared to the monoamine oxidase inhibitor phenelzine. [8] Wilkinson et al. (2002) showed that the relapse risk of a major depressive episode in old age was significantly higher for the placebo than for Li [9]. Florenza et al. (2022) examined 986 participants aged 50 years or older with OABD and divided them into two groups: “lithium” or “non-lithium” users. The first group showed significantly lower depressive symptoms, demonstrated higher global functioning, and was prescribed fewer antipsychotic drugs [10]. An important argument for prescribing Li is its proven suicide-preventive effect [4]. Finally, a recent review reported a reduced risk for dementia in Li-treated patients with bipolar disorder (BD) [11].

In Ontario, Canada, a shift in the prescription patterns in favor of divalproex over Li for patients aged 65 years and older was noted. However, there was no convincing rationale for this change [12]. Shulman et al. (2019) conducted a Delphi survey on the maintenance therapy of Li in OABD. Li was endorsed as the first-line treatment option for maintenance therapy in OABD. In this survey, a consensus was achieved regarding necessary blood tests, Li serum levels, and signs of toxicity. Lamotrigine, quetiapine, olanzapine, and valproic acid were recommended as second-line choices for the maintenance treatment of OABD, but no consensus regarding the order of preference was achieved. In addition, there was controversy about the once or twice-daily dosage of Li. This survey did not focus on questions regarding concomitant diseases, medication, renal function, or the withdrawal of Li [13].

The review of Dols et al. (2016) showed that in most guidelines, specific recommendations for OABD are missing [14]. The guideline of NICE provides a specific recommendation only for the monitoring of Li therapy: in older individuals, the plasma Li level should be monitored every 3 months [1]. The CANMAT/ISBD guideline also recommends monitoring Li blood-levels and renal function at a minimum of every three to six months. After initiation of concomitant medication with non-steroidal anti-inflammatory drugs (NSAID), angiotensin II receptor blockers (ARB), angiotensin-converting enzyme inhibitors (ACEI), or thiazide diuretic, Li blood levels should be monitored five to seven days afterwards. A lower starting dosage of Li is recommended, along with an adjustment of dosage depending on tolerability and effectiveness [2]. The FDA guidelines for Li state that existing clinical studies did not include a sufficient number of geriatric patients to evaluate their therapeutic or prophylactic response [15]. The lack of clinical studies and the difficulties in conducting trials, for example on the modalities for withdrawal of Li, underline the importance of Delphi surveys.

While many clinicians argue that Li treatment in old age should be based on decisions surrounding each unique case, a repository of general recommendations based on a broader formalized consensus might still be desirable. The aim of the present Delphi Survey was to develop recommendations on issues of concomitant medication, comorbid diseases, and decisions on the initiation as



▶ **Fig. 1** Illustration of the Algorithm of the Delphi Process

well as potential withdrawal of Li therapy in old age. Additionally, we compared our results to those of the Delphi Survey by Shulman et al. (2019) [13].

Methods

Members of the "Working Group Geriatric Psychiatry" from the "Bundesdirektorenkonferenz" (federal medical director board) were invited to participate in the survey. From this group, 19 members joined the Delphi survey. Additionally, these psychiatrists were asked to nominate further experts on Li therapy or bipolar disorder. Based on recommendation, the list of experts was extended to include specialists who were not members of the Working Group. In the first round, a questionnaire with 22 multiple-choice questions was developed on the following topics: initiation of Li therapy, drug monitoring during ongoing treatment, and termination of Li therapy. The questions were based on existing reviews and guidelines. Each question was accompanied by a commentary section. An independent reviewer, who did not participate in the survey, analyzed the responses of experts. After the evaluation of the first round, the results were presented in an anonymized form to all participants and during a meeting of the Working Group. The comments were listed, and the percentage of the answers pertaining to each comment was calculated. The number of abstentions was also determined. For the second round, responses with a consensus above 60 % were transferred into recommendations. Each recommendation could be adopted or rejected (a binary "yes" or "no" decision), and additional commentaries were again permitted. A consensus of 100 % in the first round was considered as acceptance by all participants. Responses with less than 60 % consensus were excluded from the final survey. Recommendations of the second round, endorsed by at least 80 % of the participants, were considered as having achieved final consensus (▶ **Fig. 1**).

Results

All 24 participants completed the Delphi survey. Many participants made use of the commentary section in the first questionnaire, which helped to improve and specify the recommendations in the second questionnaire. The consensus was achieved on 21 recommendations pertaining to various aspects of from Li-therapy, including the indication, pre-treatment screening, dosage, ongoing treatment monitoring, and withdrawal. The final recommendations that achieved more than 80 % approval from the experts are summarized in ▶ **Table 1**. Seven suggested recommendations of the second questionnaire failed to reach a final consensus. ▶ **Table 2** summarizes these rejected recommendations and the comments of the experts.

Initiation of Lithium therapy

The consensus was achieved concerning the indication of a de novo Li therapy for the maintenance therapy of bipolar disorder, the augmentation in therapy-resistant depression, and the prevention of suicide in old age. Additionally, consensus was achieved among experts with regard to concomitant medication with ACEIs, diuretics, ARBs, and opioids and concomitant diseases like vascular encephalopathy, idiopathic Parkinson's syndrome, and syncope.

No consensus was achieved for the indications of manic episodes (< 57 % approval) and schizoaffective disorder (< 52 % approval). No consensus was obtained for the initiation of Li therapy

▶ **Table 1** Recommendations.

Recommendation	% of approval
Initiation of lithium therapy	
▪ A de-novo lithium treatment is indicated for inpatients with the following indications: • Maintenance therapy of bipolar disorder (type I and II) • Maintenance therapy for recurrent depressive disorder • Augmentation of therapy-resistant depressive episode • Lowering the suicide risk in patients with affective disorder	100
▪ The numerical age is no decision criteria for de-novo lithium therapy.	96
▪ Treatment with lithium can be initiated under medication with ACEIs, diuretics, ARBs, and opioids, if close monitoring of the lithium concentrations and renal function is provided. Before initiating treatment with lithium, a possible change of ACEIs, diuretics, ARBs, or opioids should be evaluated together with the internist.	88
▪ Mild cognitive impairment does not categorically exclude a de-novo lithium treatment. Before initiating lithium treatment, a neuropsychological examination and differential diagnosis are recommended. The lithium oncentration should be closely monitored.	96
▪ Previous falls are no contraindication for a de-novo lithium treatment.	92
▪ Vascular encephalopathy, idiopathic Parkinson's-syndrome, and syncopations are relative contraindications for a de-novo lithium treatment.	92
▪ Alternative to a measurement of the neck circumference, thyroid sonography is recommended before initiating lithium treatment.	88
▪ The following pre-treatment screenings are obligatory: • creatinine • eGFR • blood count • electrolytes (calcium included) • TSH, T_3, T_4 • ECG • weight • blood pressure and heart rate	100
▪ Lithium-carbonate (450 mg) should be initiated with 0.5 tablets for 4 days; after obtaining the lithium concentration, the dosage can be augmented to one tablet once or 0.5 tablets twice daily on day 5.	88
Monitoring during ongoing lithium therapy	
▪ 24-hour urine collection and EEG are not necessary for monitoring an established lithium therapy.	100
▪ In addition to creatinine, eGFR, blood count, electrolytes (calcium included), TSH, T_3, T_4, ECG, weight, blood pressure, and heart rate, the continuous monitoring of an established lithium therapy should include: • measurement of cystatin C • thyroid sonography • psychopathological examination • neurological examination	96
▪ The following lithium concentrations are recommended for a stable and lithium-responsive patient: 60–79 years: 0.4–0.7 mmol/L ≥ 80 years: 0.4–0.6 mmol/L	96
▪ After one lithium intoxication, the medication should not generally be ended. If the patient responded to lithium, the lithium intoxication did not cause chronic renal insufficiency or other injuries, and dementia was not the reason for intoxication.	92
Withdrawal from lithium therapy	
▪ If there are indications for reduced renal function, a nephrologist should be consulted.	96
▪ If the ending of the lithium therapy is decided, lithium should be withdrawn within three months.	96
▪ A malignant carcinoma or diabetes mellitus are no general contraindications for lithium therapy.	92
▪ The withdrawal from lithium cannot be dependent on the cognitive impairment due to dementia. In addition, the care and administration of the medication should be considered.	88
▪ For the neuropsychological evaluation, no specific neuropsychological tests can be recommended. The decision to withdraw from lithium therapy is not dependent on the results of the neuropsychological tests. Therefore, the clinical symptoms should be taken into consideration.	100
▪ Among the group of mood stabilizers, lamotrigine, and valproate are possible alternatives.	92
▪ Among the group of atypical antipsychotics, quetiapine is the first choice as an alternative to lithium.	88
▪ Other atypical antipsychotics, which can be prescribed as an alternative to lithium, are aripiprazole, olanzapine, and risperidone.	83

ACEIs: angiotensin converting enzyme inhibitors; ARBs: angiotensin receptor blockers; eGFR: estimated glomerular filtration rate; EEG: electroencephalogram; TSH: thyroid stimulating hormone.

▶ **Table 2** Points without consensus and possible arguments.

Questions without consensus	Discussion/arguments
Initiating a lithium therapy	
▪ In which indication would you start a de-novo lithium therapy? • acute manic episode? • schizoaffective disorder?	
▪ Would you initiate lithium therapy under simultaneous medication with NSAID or digoxine?	• Consultation of an internal specialist • Evaluation of the indication NSAID/digoxine • Under close monitoring of lithium concentration and eGFR • Close monitoring in the outpatient setting difficult • Risk of intoxication to high • Adherence? • Education of the patient about the risks
▪ How often would you monitor the lithium concentration and eGFR under simultaneous medication with ACE-inhibitors, diuretics, AT II antagonists, and opioids?	• First weekly, then monthly monitoring • After a change of dosage weekly • Stable dosage of the concomitant medication or lithium?
▪ Would you initiate a lithium therapy at an eGFR between 30 and 60 mL/min/1.73 m²?	• Consultation with a nephrologist • Renal function over the lifespan of the patient? • Measurement of cystatin C to optimize evaluation of renal function • Adherence? • Strong indication for lithium?
▪ Dementia is a contraindication for a de-novo lithium therapy	• Close monitoring of renal function • Control of adherence by relatives/caregiver • Mild cognitive impairment • Depression influences cognitive impairment negatively • Rather for augmentation than as maintenance therapy • Drinking protocols
▪ Frailty is a contraindication for a de-novo lithium treatment	• High risks for falls is a contraindication • Antipsychotic drugs have a higher risk for falls than lithium – alternatives? • What has a higher negative impact on quality of life?
▪ Would you initiate lithium therapy despite being underweight?	• Search for a possible cause of underweight: cancer, insufficient intake of food and liquid • Renal function must be normal • Underweight because of depression: lithium can be life-saving • Compliance of patient, liquid intake is sufficient • Weight controls • Close monitoring
▪ 24-hour urine collection as pre-treatment screening became obsolete. To evaluate the renal function further, an additional measurement of cystatin C to determine eGFR is recommended	• 24-hour urine collection is prone to error and often inaccurate • eGFR is sufficient
▪ Before initiating a de-novo lithium treatment, a neuropsychological evaluation is recommended	• Only if indicated
▪ Lithium aspartate or orotate are no alternatives to lithium carbonate	• Missing clinical evaluation and availability • No experience
Monitoring during ongoing lithium therapy	
▪ In which frequency would you recommend monitoring of • creatinine • eGFR • blood count • electrolytes (calcium included) • TSH, T_3, T_4 • ECG • weight • blood pressure and heart rate	• eGFR, creatinine weekly in the first month
Withdrawal from lithium therapy	
▪ At which eGFR would you end an established lithium therapy?	• Answers included a range between 60 and 30 mL/min/1.73 m² • Dynamic of renal function, continuous reduction of eGFR → withdrawal of lithium • Consultation with a nephrologist • Mental condition of the patient • If the patient is an excellent lithium-responder, withdrawal at 40–30 mL/min/1.73 m²

▶ **Table 2** Continued.

Questions without consensus	Discussion/arguments
▪ At which creatinine clearance would you end an established lithium therapy?	• Answers included a range between 90 and 30 mL/min
▪ If the patient is newly diagnosed with dementia, lithium should be withdrawn	• Dependent on the cognitive impairment • Compliance • Indication for lithium, when the patient has dementia • Control of adherence by relatives/caregivers
▪ Which of the following diagnosis would trigger the ending of lithium therapy? • Myocardial infarction • Cerebral ischemia • Intracerebral bleeding • Cachexia • Epilepsy • idiopathic Parkinson's-syndrome • Hyponatremia • Hypo-, hyperthyroidism	• Dependent on mental condition, patient excellent lithium-responder? • Relative contraindications • Dependent on risk-benefit-ratio • Combined treatment of epilepsy and bipolar disorders with anticonvulsant drugs • First attempt to reduce lithium • Cognition after intracerebral bleeding or cerebral ischemia, does the patient still benefit from lithium? • Multimorbidity

ACEIs: angiotensin converting enzyme inhibitors; ARBs: angiotensin receptor blockers; eGFR: estimated glomerular filtration rate; EEG: electroencephalogram; NSAID: non-steroidal anti-inflammatory drugs; TSH: thyroid stimulating hormone.

under simultaneous medication with NSAID and digoxin. One participant recommended an evaluation of the indication for the concomitant medication and consultation with an internal specialist. Lack of consensus also extended to questions surrounding the estimated glomerular filtration rate (eGFR): only 11 participants would initiate a Li therapy in a patient with an eGFR between 30 to 60 mL/min/1.73 m². In the commentary section, these participants argued that they would consult a nephrologist before initiating the medication and would monitor eGFR and Li levels more closely. No consensus was achieved concerning frailty (< 63 % approval) and dementia (< 63 % approval) as a contraindication. In an underweight patient, less than 57 % of the experts said they would initiate Li therapy. The responders commented that a differential diagnosis of underweight individuals should be undertaken. For most experts, a palliative care situation would be a contraindication for Li treatment. If the cause for cachexia is a major depressive disorder, Li can be effective. Before initiation of Li therapy, most participants recommended a neuropsychological examination (< 75 % approval). Others responded that neuropsychological examinations are only required if clinical impressions provide a rationale for conducting them. Most participants (< 75 %) would not conduct a 24-hour urine collection as a pre-treatment screening because of its frequent errors in the complete collection of urine in an out-patient setting. To further evaluate renal function, some participants recommended additional measurement of cystatin C to determine eGFR (< 67 % approval). Li carbonate was the preferred Li preparation. Because of their missing clinical evaluation and restricted availability, Li aspartate and orotate were not prescribed (< 79 % approval).

Monitoring of Lithium therapy

A Consensus was achieved concerning the concentration of Li in the blood of a stable and responsive Li patient and routine laboratory parameters that should be monitored during Li therapy. Additionally, consensus was reached on the recommendation that Li should not generally be withdrawn after one single intoxication. Participants noted the importance of evaluating the underlying reason and the risk for future intoxications. The preferences of the patients and their previous responsivity should also be considered.

No consensus was achieved concerning the frequency of laboratory checks. Most participants claimed that they would monitor the eGFR weekly (< 29 % approval) or monthly (< 71 % approval) during simultaneous medication with ACEIs, diuretics, ARBs, and opioids. In the commentary section, some participants expressed their view that they would monitor eGFR and Li concentration every week in the first month and on a monthly basis in subsequent months after therapy has been successfully established.

Withdrawal from Lithium therapy

The consensus was achieved on aspects related to the interval of withdrawal from Li, consultation of a nephrologist before the withdrawal of Li in a patient with a declining glomerular filtration rate, neuropsychological examination before withdrawal, and alternatives for Li. Most experts (92 %) agreed that malignant carcinoma or diabetes mellitus are not general contraindications for Li. Furthermore, 88 % of the experts would not make the decision to withdraw depending on the severity of the dementia. Optimized patient care and accurate supervision of medication dispensation were regarded as crucial to the decision of whether Li medication could be continued or stopped.

No consensus was achieved regarding Li-responsive patients with newly diagnosed dementia: less than 67 % of the participants would not terminate Li therapy in such cases. For most participants, the prominent psychopathology is relevant before ending an ongoing Li therapy in a patient with newly diagnosed dementia. It was suggested that the initial indication for Li should be considered.

Discussion

The efficacy of Li has been verified regarding the episode-preventive maintenance therapy of bipolar disorder [16], the augmentation strategy in therapy-resistant depression [9, 17–19], and its

suicide-preventive efficacy [20–22]. Li was also the preferred choice in the maintenance therapy of OABD in the Delphi Survey of Shulman et al. (2019) [13]. Regarding age, there is no evidence of a loss of efficacy in geriatric patients. Therefore, all experts favor Li for these indications. Patients' higher age was not regarded as a general contraindication. Moreover, consensus was achieved regarding the statement that mild cognitive impairment, several falls (more than two falls within the last six months), and simultaneous medication with ACEIs, diuretics, ARBs, and opioids are no absolute contraindications for a de-novo Li therapy. However, vascular encephalopathy, idiopathic Parkinson-syndrome, and syncope were regarded as relative contraindications. Nevertheless, at least in Parkinson's disease, a neuroprotective effect of Li was discussed, which would not support a labeling as a relative contraindication [23, 24]. However, this preliminary data did not lead to a general recommendation of Li in Parkinson's disease.

With respect to concomitant dementia or frailty, 63 % of the experts would not initiate a de-novo Li therapy. Florenza et al. (2022) supported the efficacy of Li, since Li users had higher global functioning and fewer depressive symptoms. Moreover, the study supported the hypothesis of a neuroprotective effect of Li because Li users performed better in cognitive assessments [10]. In the meta-analysis of Velosa et al. (2020), a higher risk of developing dementia (odds ratio (OR): 2.96) in patients with BD was depicted. However, Li use decreased the risk (OR: 0.51) [11]. A hippocampal volume reduction was shown for patients with BD compared to healthy controls, whereas for Li users, no difference in hippocampal volume compared to healthy controls was found. However, the listed trials might not really answer the question whether Li has protective effects and whether it should be started after dementia has developed [25].

In accordance with Shulman et al. (2019), consensus was also achieved regarding the serum reference levels for Li. However, the upper limit in our survey was set somewhat lower: for patients aged 65 to 79 years and for patients aged 80 years and older: serum level upper limits were 0.4 to 0.7 mmol/L and 0.4 to 0.6 mmol/L, respectively. The minimum limit did not differ. Shulman et al. (2019) concluded that lower serum levels might already be effective in old age [13]. In addition, they surveyed the reported therapeutic range of serum Li levels of the laboratories used by the experts. In most laboratories, the range was higher than the recommended, which increases the risk of intoxication for people of older age. Nolen et al. (2019) did not find a consensus regarding the optimal Li serum levels for the elderly, but the majority favored ranges similar to the present survey [26]. Rej et al. (2014) showed that the Li dose required to establish a Li blood concentration of 1.0 mmol/L decreases threefold across the lifespan [27]. With growing age and decreased eGFR, a smaller Li dose is required to achieve a given serum Li concentration, which is in accordance with Sproule et al. (2000) [28] and Rej et al. (2012) [29]. The association of Li dose/Li blood concentration is not correlated with sex, concurrent hydrochlorothiazide, loop diuretics, ARBs/ACEIs, NSAIDs, or aspirin use [27, 29]. Furthermore, patients with one daily dosage required a lesser dosage to establish equal concentration [27, 30]. However, the German guideline for bipolar disorder [3] recommends a twice-a-day dosage for geriatric patients to prevent serum concentration peaks. Shulman et al. (2019) did not achieve consensus in regard to once or twice daily dosage, which is similar to our results [13].

No consensus was achieved on the frequency of laboratory checks. Shulman et al. (2019) gave advice on blood monitoring: Li serum concentration and renal function should be monitored every 3–6 months [13]. In comparison to Shulman et al. (2019), in the present survey, there was a tendency for more frequent controls; 52 % of the experts suggested monthly checks, while a minority of 39 % of experts preferred quarterly controls of renal function. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) combined equation to estimate the eGFR with creatinine and cystatin C can improve the reliability and clinical significance of the calculated GFR [31, 32]. Thyroid sonography and neurological, and psychological examination are additional recommendations for monitoring a responsive and stable Li patient. No consensus was achieved concerning the cognitive screening instruments. Shulman et al. (2019) advised to evaluate cognitive functioning with the Mini-Mental Status Examination (MMSE) [33] and Montreal Cognitive Assessment Test (MoCa) [34] every 12 months [13]. In the present survey, the application of MMSE, MoCa, or a neuropsychological test battery (like the Consortium to Establish a Registry for Alzheimer's disease, CERAD [35]) were all possible options for cognitive testing. No specific screening instrument was recommended because the clinician should use the instrument with which she/he is familiar. The clinical presentation and global functioning of the patient and not only the result of a cognitive screening instrument are decisive factors in an evaluation. Shulman et al. (2019) did not recommend what consequences or action should be taken if the results of the screening instrument show cognitive impairment [13].

The risk of Li intoxication increases in elderly patients because of the decline in renal function and water volume. To prevent Li intoxication, comprehensive education of patients and caregivers on usage and risks is necessary before and during ongoing treatment. A survey of elderly patients' knowledge of Li therapy showed that many subjects were only poorly informed, which underscores the importance of continued education [36]. Therefore, experts agree that the decision to withdraw from Li should depend not only on the cognitive status alone but also on a consideration of the care setting and dispensation of the medication. Mild cognitive impairment was not considered as a contraindication for a de-novo Li therapy, but experts recommend an evaluation of differential diagnosis and closer monitoring of the Li concentration and renal function. No consensus was achieved concerning concomitant dementia; most experts (67 %) would not terminate Li in a stable and responsive patient with newly diagnosed dementia.

The consensus was reached on the statement that in case of the decision to stop Li, it should be tapered out over a period of 3 months if possible. In accordance with this survey, Tondo et al. (2019) [4] recommended a 20–25 % reduction in the daily Li dose every two weeks. However, the risk of relapse decreases with prolonged withdrawal from Li [37, 38]. The risk of relapse was 50 % in six months in patients with unipolar depression [38]. In addition, after withdrawal from Li, suicidal ideations may re-occur [39]. On the one hand, longer periods of tapering Li (more than six months) may reduce the risk of relapse. On the other hand, the decision to

discontinue Li therapy is likely to stem from significant contraindications in most cases and would thus be an urgent matter.

Quetiapine, lamotrigine, valproic acid, and olanzapine were the preferred alternatives to Li in the maintenance therapy of OABD in the Delphi Survey of Shulman et al. (2019) [13], which is in accordance with our results. The experts agreed that valproic acid and lamotrigine can be considered alternative mood stabilizers. Consensus regarding the order of preference was not achieved in the Delphi Survey of Shulman et al. (2019) [13]. In comparison to Shulman et al. (2019), in the group of atypical antipsychotics, quetiapine was the preferred alternative to Li compared to olanzapine, risperidone, and aripirazole. Lamotrigine has been shown to be effective in preventing depressive episodes in old age compared to placebo [6]. Nevertheless, Li is more effective in preventing hypomanic or manic episodes than lamotrigine [40]. Compared to valproic acid, Li-treated patients had lower relapse rates in old age [7], in congruence with the results of the BALANCE study [41]. Surprisingly, valproic acid did not cause more sedation compared to Li in the study of Young et al. (2017) [7]. Sajatovic et al. (2008) showed significant improvement in manic symptoms for quetiapine compared to placebo in patients older than 55 years. Common reported side effects were nausea, weight gain, dizziness, somnolence, and postural hypotension [42].

In summary, the present Delphi survey yields several clinical recommendations, which might be helpful in the Li treatment of elderly patients. Nevertheless, studies are urgently needed for important questions on Li therapy in OABD. However, the recruitment of a sufficient number of geriatric patients, and the feasibility of a randomized controlled trial are difficult to be realized, which underlines the importance of Delphi surveys. In addition, observational, multicenter studies could elucidate some clinical aspects. Additionally, there seems to be a gap in the knowledge concerning potential alternative drugs for older patients when termination of Li therapy becomes inevitable.

Contributors

Except for JC, all authors participated in the Delphi Survey. JC analyzed the answers of the participants in anonymized form. JC wrote substantial parts of the manuscript. TS, MS, and BMO contributed to the writing of the manuscript. LCR did not participate in the Delphi Survey, but stimulated and answered questions concerning renal function. All authors contributed to and have approved the final manuscript.

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Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] NICE-2014. Bipolar Disorder: Assessment and Management (NICE2014). Available at: https ://www.nice.org.uk/guida nce/cg185

[2] Yatham LN, Kennedy SH, Parikh SV et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord 2018; 20: 97–170

[3] DGBS e.V, DGPPN e.V. S3-Leitlinie zur Diagnostik und Therapie Bipolarer Störungen. Langversion 2019

[4] Tondo L, Alda M, Bauer M et al. Clinical use of lithium salts: Guide for users and prescribers. Int J Bipolar Disord 2019; 7: 16

[5] Sajatovic M, Strejilevich SA, Gildengers AG et al. A report on older-age bipolar disorder from the International Society for Bipolar Disorders Task Force. Bipolar Disord 2015; 17: 689–704

[6] Sajatovic M, Gyulai L, Calabrese JR et al. Maintenance treatment outcomes in older patients with bipolar I disorder. Am J Geriatr Psychiatry 2005; 13: 305–311

[7] Young RC, Mulsant BH, Sajatovic M et al. GERI-BD: A randomized double-blind controlled trial of lithium and divalproex in the treatment of mania in older patients with bipolar disorder. Am J Psychiatry 2017; 174: 1086–1093

[8] Kok RM, Vink D, Heeren TJ. Lithium augmentation compared with phenelzine in treatment-resistant depression in the elderly: an open, randomized controlled trial. J Clin Psychiatry 2007; 68: 1177–1185. DOI: 10.4088/jcp.v68n080.3

[9] Wilkinson D, Holmes C, Woolford J et al. Prophylactic therapy with lithium in elderly patients with unipolar major depression. Int J Geriatr Psychiatry 2002; 17: 619–622

[10] Forlenza O, Hajek T, Almeida OP et al. on behalf of the GAGE-BD initiative. Demografic and clinical characteristics of Lithium-treated older adults with bipolar disorder. Acta Psychiatr Scand 2022; 146: 442–455

[11] Velosa J, Delgado A, Finger E et al. Risk of dementia in bipolar disorder and the interplay of lithium: A systematic review and meta-analyses. Acta Psychiatr Scand 2020; 141: 510–521. DOI: 10.1111/acps.13153

[12] Shulman KI, Rochon P, Sykora K et al. Changing prescription patterns for lithium and valproic acid in old age: Shifting practice without evidence. BMJ 2003; 326: 960–961

[13] Shulman KI, Almeida OP, Herrmann N et al. Delphi survey of maintenance lithium treatment in older adults with bipolar disorder: An ISBD task force report. Bipolar Disord 2019; 21: 117–123

[14] Dols A, Kessing LV, Strejilevich SA et al. International Society for Bipolar Disorders Task Force for Older Adults with Bipolar Disorder. Do current national and international guidelines have specific recommendations for older adults with bipolar disorder? A brief report. Int J Geriatr Psychiatry 2016; 31: 1295–1300

[15] US Food and Drug Administration. Lithium carbonate https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/017812s027%2C018421s025%2C018558s021lbl.pdf

[16] Lahteenvuo M, Tanskanen A, Taipale H et al. Real-world effectiveness of pharmacologic treatments for the prevention of rehospitalization in a Finnish nationwide cohort of patients with bipolar disorder. JAMA Psychiatry 2018; 75: 347–355

[17] Bauer M, Adli M, Bschor T et al. Lithium’s emerging role in the treatment of refractory major depressive episodes: Augmentation of antidepressants. Neuropsychobiology 2010; 62: 36–42

[18] Buspavanich P, Behr J, Stamm T et al. Treatment response of lithium augmentation in geriatric compared to non-geriatric patients with treatment-resistant depression. J Affect Disord 2019; 215: 136–140

[19] Cooper C, Katona C, Lyketsos K et al. A systematic review of treatments for refractory depression in older people. Am J Psychiatry 2011; 168: 681–688

[20] Abou-Saleh MT, Müller-Oerlingshausen B, Copper AJ. Lithium in the episode and suicide prophylaxis and in augmenting strategies in patients with unipolar depression. Int J Bipolar Disord 2017; 5: 11

[21] Cipriani A, Hawton K, Stockton K et al. Lithium in the prevention of suicide in mood disorders: Updated systematic review and meta-analysis. BMJ 2013; 346: f3646

[22] Song J, Sjölander A, Joas E et al. Suicidal behavior during Lithium and Valproate treatment: A within-individual 8-year prospective study of 50.000 patients with bipolar disorder. Am J Psychiatry 2017; 174: 795–802

[23] Vallée A, Vallée JN, Lecarpentier Y. Parkinson's disease: Potential actions of lithium by targeting the WNT/β-catenin pathway, oxidative stress, inflammation and glutamatergic pathway. Cells 2021; 25: 230. DOI: 10.3390/cells10020230

[24] Lazzara CA, Kim YH. Potential application of lithium in Parkinson's and other neurodegenerative diseases. Front Neurosci 2015; 9: 403

[25] Haukvik UK, Gurholt TP, Nerland S et al.; ENIGMA Bipolar Disorder Working Group. In vivo hippocampal subfield volumes in bipolar disorder-A mega-analysis from The Enhancing Neuro Imaging Genetics through Meta-Analysis Bipolar Disorder Working Group. Hum Brain Mapp 2022; 43(1): 385–398. DOI: 10.1002/hbm.25249

[26] Nolen WA, Licht RW, Young AH et al. ISBD/IGSLI task force on the treatment with lithium. What is the optimal serum level for lithium in the maintenance treatment of bipolar disorder? A systematic review and recommendations from the ISBD/IGSLI Task Force on treatment with lithium. Bipolar Disord 2019; 21: 394–409. DOI: 10.1111/bdi.12805

[27] Rej S, Beaulieu S, Segal M et al. Lithium dosing and serum concentrations across the age spectrum: from early adulthood to the tenth decade of life. Drugs Aging 2014; 31: 911–916. DOI: 10.1007/s40266-014-0221-1

[28] Sproule BA, Hardy BG, Shulman KI. Differential pharmacokinetics of lithium in elderly patients. Drugs Aging 2000; 16: 165–177

[29] Rej S, Herrmann N, Shulman K. The effects of lithium on renal function in older adults–a systematic review. J Geriatr Psychiatry Neurol 2012; 25: 51–61. DOI: 10.1177/0891988712436690

[30] Singh LK, Nizamie SH, Akhtar S et al. Improving tolerability of lithium with a once-daily dosing schedule. Am J Ther 2011; 18: 288–291. DOI: 10.1097/MJT.0b013e3181d070c3

[31] Meeusen JW, Rule AD, Voskoboev N et al. Performance of cystatin C- and creatinine-based estimated glomerular filtration rate equations depends on patient characteristics. Clin Chem 2015; 61: 1265–1272. DOI: 10.1373/clinchem.2015.243030

[32] Grubb A, Nyman U, Björk J. Improved estimation of glomerular filtration rate (GFR) by comparison of eGFRcystatin C and eGFRcreatinine. Scand J Clin Lab Invest 2012; 72: 73–77

[33] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189–198

[34] Nasreddine ZS, Phillips NA, Bedirian V et al. The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005; 53: 695–699

[35] Fillenbaum GG, Mohs R. CERAD (Consortium to Establish a Registry for Alzheimer's Disease) neuropsychology assessment battery: 35 years and counting. J Alzheimers Dis 2023; 13:. DOI: 10.3233/JAD-230026

[36] Enudi W, Lawlor B, O'Connell HP. A survey of patients' knowledge about lithium therapy in the elderly. Prim Care Companion CNS Disord 2014; 16: PCC.13m01550. DOI: 10.4088/PCC.13m01550

[37] Volkmann C, Bschor T, Köhler S. Lithium treatment over the lifespan in bipolar disorders. Front Psychiatry 2020; 11: 377

[38] Ross J. Discontinuation of Lithium augmentation in geriatric patients with unipolar depression: A systematic review. Can J Psychiatry 2008; 53: 117–120

[39] Müller-Oerlinghausen B, Berghöfer A, Ahrens B. The antisuicidal and mortality-reducing effect of lithium prophylaxis: Consequences for guidelines in clinical psychiatry. Can J Psychiatry 2003; 48: 433–439

[40] Bowden CL, Calabrese JR, Sachs G et al. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. Arch Gen Psychiatry 2003; 60: 392–400

[41] Geddes JR, Goodwin GM, Rendell J et al. Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. The Lancet 2010; 375: 385–395

[42] Sajatovic M, Calabrese JR, Mullen J. Quetiapine for the treatment of bipolar mania in older adults. Bipolar Disord 2008; 10: 662–671

Notice
This article was changed according to the erratum on August 30, 2023.

Erratum
The 8th Citation, as well as the sentence which refers to it has been corrected.