






Delphi survey of maintenance lithium treatment in older adults with bipolar disorder: An ISBD task force report

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Objectives: Despite the growing numbers and proportion of older adults with bipolar disorder (OABD), there are very limited guidelines for the use of lithium with its double-edged potential for effectiveness and toxicity in this population. The primary aims of this Delphi survey were: (a) To determine the place of lithium among the preferred choices for maintenance treatment of OABD. (b) To provide detailed clinical guidelines for the safe and effective use of lithium in OABD.

Methods: In the face of limited evidence, the Delphi survey method was used to achieve consensus by a group of 25 experts in OABD from nine countries. An oversight committee monitored and analyzed the results of each survey and formulated more focused questions with each subsequent iteration.

Results: A 100% response rate was achieved for all three iterations of the survey. Lithium was the preferred choice for maintenance monotherapy in OABD. Serum levels of 0.4–0.8 mmol/L were recommended for ages 60–79 and serum levels of 0.4–0.7 mmol/L were recommended for ages 80 and over. Specific recommendations achieved consensus for second line monotherapy as well as for other drugs to be used in combination with lithium if necessary. Guidelines for routine monitoring of lithium in OABD were provided for laboratory investigations and clinical assessments.

Conclusions: Lithium remains the preferred choice for maintenance monotherapy in OABD. Laboratories should report the therapeutic range for serum levels of lithium separately for older adults.

KEYWORDS

Delphi, lithium, maintenance, older adults

1 | INTRODUCTION

Older adults with bipolar disorder (OABD), generally regarded as age 60 years or over, represent 6% of geriatric psychiatry

outpatient visits and 10% of geriatric psychiatry inpatients.¹ OABD is expected to comprise 50% of all cases of bipolar disorder by 2030.² Despite these significant numbers, international guidelines for the treatment of bipolar disorders have generally

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not considered the specific management needs associated with OABD to date.³

Based on a recent review of clinical practice guidelines (CPGs) and pharmaco-epidemiological data for all ages, lithium remains the first-line treatment for maintenance monotherapy despite the availability of several other choices for mood stabilization.⁴⁻⁶ Treatment with lithium has been shown to reduce the risk of suicide^{7,8} and psychiatric admissions.⁴ Emerging epidemiological and neurophysiological evidence suggests that lithium may have neuroprotective properties and reduce the risk of dementia^{9,10} and conceivably of cancer.¹¹ The results of neuroimaging studies have suggested that adults with bipolar disorder treated with lithium have better preserved cortical gray matter volume.^{12,13} Notably, OABD who were using lithium reported positive attitudes toward treatment.¹⁴

On the other hand, lithium, just like all of the other mood stabilizers including antipsychotic agents, represents a double-edged sword for older adults. One concern has been its possible role in increasing the risk of chronic renal failure^{15,16} although there is also considerable recent epidemiological evidence that the risk is not as concerning as originally considered.¹⁷ Other concerns include hypothyroidism,¹⁸ hypercalcemia,¹⁹ neurotoxicity,²⁰ and parkinsonism.²¹ As the cohort of bipolar patients successfully maintained on lithium reaches their 70's and 80's, the age associated decrease in renal clearance may lead to higher lithium levels. This in turn leads to increased risk of side effects and outright toxicity if typical adult doses are not lowered.^{20,22} Several commonly used drugs in older adults, such as diuretics, ACE Inhibitors and non-steroidal anti-inflammatory drugs, can interact with lithium and cause higher serum levels, thereby increasing the risk of toxicity.²³ Furthermore, symptoms of toxicity (eg, tremor, gastrointestinal upset, and neurological disturbance) can be misinterpreted as other conditions commonly seen in later life, such as parkinsonism or dementia.²¹ A "prescribing cascade" may ensue,²⁴ with additional medications introduced unnecessarily to assist in the management of the observed symptoms (eg, dopaminergic agents, cognitive enhancers, and gastrointestinal drugs). Clearly, more evidence and guidelines are needed that balance the risks and benefits of lithium use in OABD.^{25,26}

The first randomized control study of lithium for OABD was only recently published.²⁷ The investigators compared the efficacy of lithium and divalproex in older adults for acute mania and mixed presentations, but not for maintenance therapy. Both drugs were shown to be efficacious and well tolerated, although lithium was associated with greater reduction in mania scores. While the evidence for its effectiveness remains high, the use of lithium in OABD has been declining compared to atypical antipsychotic agents and divalproex—a phenomenon for which there is no good supportive evidence.^{28,29} This increasing reluctance to prescribe lithium in OABD is most likely due to concerns about its toxicity, limited experience of younger clinicians with the use of lithium, and the impact of pharmaceutical marketing.²⁹

The most recent reviews of CPGs on the use of lithium for all ages recommend a target maintenance therapeutic serum level range of

0.6-0.8 mmol/L. The recently recommended therapeutic range is lower than the ones provided by most laboratories around the world which do not take into account the age of patients, phase of illness, or medical comorbidities. Malhi et al⁶ have summarized the limited recommendations in CPGs for older adults which are not detailed. Their recommended therapeutic range was 0.6-0.8 mmol/L but reported other ranges that varied from 0.4 to 1.3 mmol/L. Moreover, they noted that one of the limitations of CPGs is the lack of sensitivity to real world presentations.⁶

In the face of compelling evidence for the effectiveness of lithium in bipolar disorder and its potential for neuroprotection combined with the lack of specific and detailed guidelines for its use in OABD, the ISBD task force on OABD conducted a Delphi survey of maintenance treatment for lithium in older adults in order to provide better direction for clinicians on the safety and effectiveness of lithium use in this vulnerable population. This survey focused on the question of maintenance therapy in OABD because of the clinical concern that the large cohort of adults who has been maintained on mood stabilizers for many years are now reaching old age. This study aims to fill the gap in data for this phase of treatment in OABD. Clinical experience also suggests that lithium toxicity may be missed in older adults and that the "therapeutic" range for lithium reported by most labs could be misleading and lead to a false sense of "safe practice," especially to clinicians with limited experience in the use of lithium in OABD.

The primary aims of the survey were:

1. To determine the place of lithium among the preferred choices for maintenance treatment of OABD.
2. To provide clinical guidelines for the safe and effective use of lithium in OABD.

2 | METHODS

2.1 | Study Design and Procedure

In the face of very limited systematic evidence for maintenance treatment in OABD, the Delphi method was chosen as a technique for obtaining consensus from a group of experts. Such panels generally consist of 10-25 experts.³⁰ The Delphi method has been used since the 1950's as a means of achieving consensus of expert opinion on a wide range of real-world knowledge.³¹ It consists of a series of surveys where each wave represents a refinement of the previous one through a systematic process of feedback from the group.³⁰ This leads to a progressive move toward consensus.^{30,31} This is viewed as a type of "virtual meeting" that anonymizes the experts to each other and facilitates independent thought and the gradual formation of a considered opinion through a systematic process of communication and feedback.³⁰ An oversight committee is commonly set up to monitor unintentional bias. Because of the interest in correcting a perceived loss of confidence in the use of lithium in OABD, the potential bias in this initiative needed checks and balances. Without

more valid evidence for lithium use in OABD, a systematic approach to expert consensus is the best way of providing direction to clinicians—perhaps enhancing the current clinical practice guidelines (CPG's) whose methodology varies considerably.⁶

Three iterations, not more than 15-20 minutes in length, were sent electronically to each expert at approximately 1-month intervals (see Supporting information S1, S2, S3). All questions were framed within the clinical scenario of maintenance treatment in OABD. The first iteration was open-ended and asked about demographic features of the participant experts, their choice of mood stabilizers by order of preference, suggested therapeutic range for lithium levels, recommended routine laboratory investigations and clinical assessments during lithium maintenance, and clinical signs of lithium toxicity. Other prescribing practices were explored including the impact of subtype diagnosis and dosing schedules.

The questions separated the recommendations into two broad age groups within OABD, ages 60-79 and 80 years, or over. Each survey asked the experts to comment on the items presented and provide a brief rationale for each answer. Participants were given opportunities to identify other areas of concern or controversy. Each iteration was reviewed by an oversight committee (KS, OA, NH, AS, SS, AD, MS). The members of the oversight committee were also respondents in the survey. A cumulative impression of the group judgment for each item was presented by the oversight committee to the experts for the purpose of reviewing or revising their answers. The next iteration was then sent to all participants with each iteration comprised of questions that narrowed the focus based on previous responses. These iterations continued until consensus was reached (at least 80% agreement for each item) or the pre-set limit of three iterations elapsed, in which case non-consensus items were identified.

A flow chart describing the Delphi Method is presented in Figure 1.

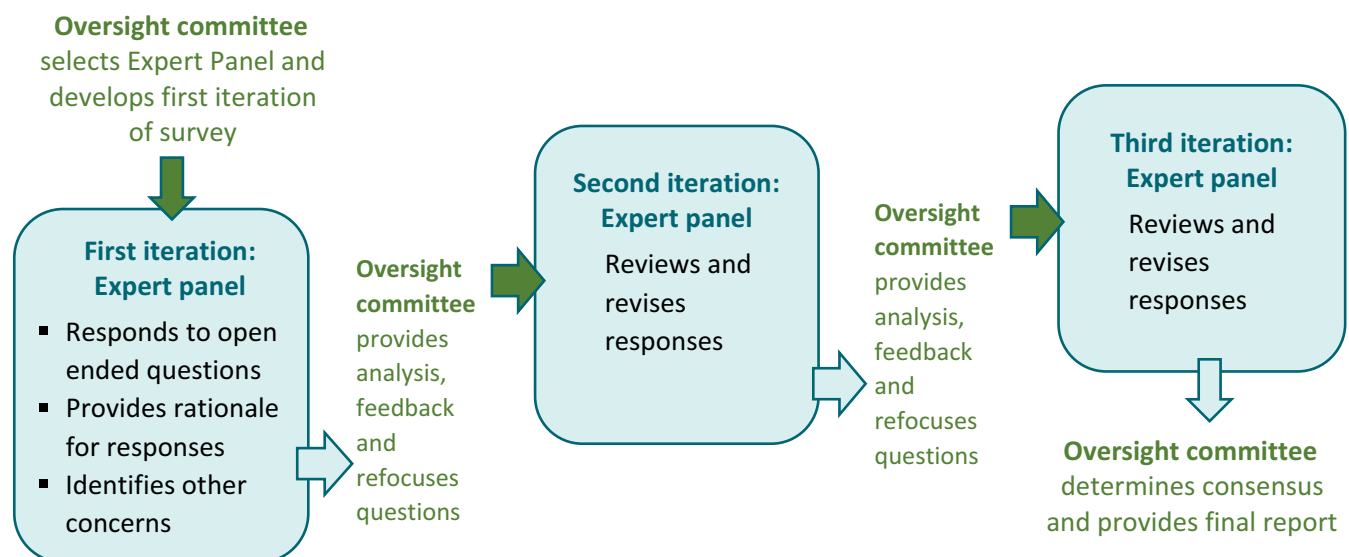


FIGURE 1 The Delphi method: A systematic feedback process toward achieving consensus [Colour figure can be viewed at wileyonlinelibrary.com]

2.2 | Participants

An invitation to participate on the panel was extended to all the physician members of the ISBD OABD task force. This proved to be an excellent convenience sample from which to identify the best available internationally representative experts in this clinical arena. Members of the task force were then asked to nominate other potential experts for inclusion on the panel. Twenty-seven experts were invited to take part in the Delphi survey. One did not respond to two invitations and another reported limited experience with OABD. This left an expert group of 25 psychiatrists, 23 of whom identified themselves as geriatric psychiatrists and two as general psychiatrists with expertise in bipolar disorders. Table S4 summarizes the list of the experts involved in this survey and their countries of origin.

3 | RESULTS

3.1 | Response rate

A complete response rate of 100% was achieved for all three iterations of the survey.

3.2 | Preferred choice for the maintenance of OABD

There was 100% consensus that lithium should be the drug of choice for maintenance monotherapy in OABD. Second line medications considered appropriate for monotherapy maintenance of OABD included lamotrigine, olanzapine, quetiapine, and valproate (See Table 1). No consensus was achieved regarding order of preference and hence the results of this question were reported as a group of optional choices listed in alphabetical order.

If maintenance of OABD with lithium requires adjunctive treatment, the following group of medications were recommended (once

TABLE 1 Recommendations for maintenance therapy for older adults with bipolar disorder (OABD)

Target serum lithium range		First-line choices to COMBINE with lithium maintenance treatment for OABD	Second-line choices for monotherapy treatment for OABD
Age	mmol/L		
60-79	0.4-0.8	Lamotrigine	Lamotrigine
80+	0.4-0.7	Quetiapine	Olanzapine
		Valproate	Quetiapine
			Valproate

again no consensus was achieved regarding order of preference): lamotrigine, quetiapine, and valproate. The experts (84%) did not recommend a different therapeutic range for lithium when used in combination with another psychotropic agent.

3.3 | Advice for the safe use of lithium in OABD

After the third iteration, the expert panel achieved consensus regarding the target serum concentration of lithium: 0.4 to 0.8 mmol/L for OABD aged 60 to 79 years and 0.4 to 0.7 mmol/L for those aged 80 years or over. Sixty-four percent of panel members indicated that the diagnosis of bipolar I and II should not influence the target therapeutic range. There was no consensus regarding the preferred pattern for the daily dosing of lithium: once or twice per day.

Recommendations for maintenance therapy for older adults with bipolar disorder (OABD) can be seen in Table 1.

Table 2 shows the therapeutic ranges of the serum concentration of lithium reported by the local laboratories used by the expert panelists. We requested this information to determine the current practice of laboratories in reporting the therapeutic range for serum lithium levels and to ascertain whether local laboratories provided separate guidelines for older adults. The most common level at the lower limit of the therapeutic range was 0.6 mmol/L (45%) while the most common level for upper limit was 1.2 mmol/L (60%). The current ranges reported by the labs are well above the range recommended by the experts and by recent CPG's for all adults. None of the labs reported a separate therapeutic range for older adults.

TABLE 2 Therapeutic range for serum lithium levels in labs used by experts

Range	No. labs
0.6-1.2	7
0.5-1.2	3
0.5-1.0	3
0.4-1.3	2 ^a
0.6-1.5	1
0.6-1.0	1
0.7-1.2	1
0.8-1.2	1
No specific therapeutic range; intoxicated level alerted when >1.5 mmol/L	1

^aOne lab was used by multiple experts.

A summary of the consensus recommendations regarding the routine assessment of OABD receiving maintenance treatment with lithium can be seen in Table 3. On that basis, it is recommended that OABD maintained on lithium should be assessed by a clinician at least every 6 months.

Table 4 describes the expert consensus regarding the common signs of lithium toxicity among OABD.

4 | FURTHER RESEARCH

From comments received, experts suggested that further research is needed in OABD on the following:

1. Lithium's long-term effects on renal function and specifically the concern about chronic renal failure
2. Lithium's and the atypical antipsychotics' effect on metabolic function
3. Guidelines for the use of other mood stabilizers such as lamotrigine, quetiapine, olanzapine, and risperidone
4. The potential neuroprotective properties of lithium and potential for protection from cancers.

5 | DISCUSSION

The results of this survey indicate that lithium remains the preferred choice of experts for mood stabilization during the maintenance phase of OABD. This recommendation must be viewed in the context of a significant and steady decline in use of lithium in this population, likely as a result of excessive anxiety about its safety profile in later life and the lack of pharmaceutical marketing. Hence these findings should provide some reassurance and guidance for clinicians to be more confident in their use of lithium in older adults. The recommended maintenance serum range for lithium for ages 60-79 is 0.4 to 0.8 mmol/L, while for people aged 80 years or over is 0.4 to 0.7 mmol/L. Surprisingly there was not much difference in the recommended therapeutic range for these two age groups. The most obvious difference compared with published guidelines pertains to the lower therapeutic limit of 0.4 mmol/L compared to 0.6 mmol/L recommended by Malhi et al⁶ and 0.5 mmol/L recommended by Wijeratne and Draper.³² Our group of experts concluded that

TABLE 3 Routine laboratory and clinical monitoring

Frequency	Lab testing	Clinical assessments
3-6 months	Lithium level Serum creatinine eGFR BUN	Tremor Gait
6-12 months	Thyroid function (TSH) Fasting glucose Fasting cholesterol (lipids) Triglycerides Weight (including waist circumference) Calcium	
12 months	Hematology	Routine cognitive screening (MMSE and/or MoCA)
As concerns rise		General and comprehensive neurological assessments

TABLE 4 Common signs of lithium toxicity among OABD

Consensus reached
<ul style="list-style-type: none"> • Impaired ability to sustain and shift attention • Delirium • Tremor of the extremities • Ataxia • Gastrointestinal symptoms such as nausea and vomiting
Consensus not reached
<ul style="list-style-type: none"> • Diarrhea • Hyperreflexia • Polyuria and polydipsia

0.4 mmol/L may be sufficient for a proportion of OABD. The recommended upper limits of lithium in the serum in this survey were also well below those recommended by others, implying that our experts believe that a lower concentration of lithium may be more effective in later than early life, or that concerns about adverse effects demand greater caution when using lithium in older age. Some experts seemed to favor slightly higher serum lithium levels for Bipolar I patients but this did not achieve consensus. Increased efforts should be made to have laboratories report levels specifically for older adults that are in keeping with those recommended by clinical practice guidelines and by this survey. Certainly, the current therapeutic range for lithium levels reported by laboratories is much higher than is recommended by the most recent clinical practice guidelines^{6,33} and the results of this survey for OABD. This current practice by local laboratories puts older adults at risk of lithium toxicity and adds urgency to this clinical issue. Providing separate more appropriate therapeutic ranges of serum lithium levels for older adults should help to minimize the risk of toxicity in this vulnerable population.²⁰

With regard to lithium administration, the experts did not reach consensus on the value of twice compared to once daily dosing. The uncertainty in the literature on this point was reflected by the fact that some experts gave the same reason (less stress on the kidneys) for both options. The majority favored once daily dosing but this did not reach the consensus threshold.

Guidelines for safe monitoring of lithium levels and related laboratory and clinical testing suggest that older adults with bipolar disorder should be seen routinely at least every three to six months with specific laboratory tests and clinical assessments administered as described in the results: renal functioning every 3-6 months, metabolic and endocrine testing every 6 months, and hematology yearly. Routine clinical assessment of gait and tremor should take place every 3-6 months and routine cognitive testing should be done annually using the MMSE³⁴ or MoCA.³⁵ By seeing OABD every 3-6 months, clinicians will be able to monitor the clinical course and detect significant clinical or medical concerns at an early stage. In centers where the availability of psychiatrists is limited, family physicians or allied health professionals can supplement the necessary frequency of clinical monitoring. Special attention must be given to the signs of lithium toxicity in order to avoid the “prescribing cascade” that mistakes lithium side effects and signs of toxicity for another disorder such as parkinsonism, dementia, or gastrointestinal disorder. As most side effects of lithium are dose dependent, these guidelines offer room to lower the dose and serum level without loss of effectiveness.

The safety measures recommended for lithium use in this survey should not suggest that the other possible choices for mood stabilizers are safer and without their own risks. Indeed, there is much that we do not know about the adverse effects of the atypical antipsychotics and other mood stabilizers in OABD inviting more specific research on this issue. Notwithstanding the potential side effects and toxicity associated with lithium use in OABD, the experts still concluded that lithium is the preferred choice for maintenance treatment in OABD. Similarly, despite the consensus in this survey, it should be clear that maintenance treatment with lithium is not necessarily the best option for all OABD and clinicians must continue to make individualized choices based on multiple factors.

Given the scope of the Delphi survey the oversight team decided not to drill down on the question of lithium's effects on long-term renal function. Some members of the OABD task force argued in favor of reassuring clinicians about the long-term safety of lithium with regard to

chronic kidney disease. However, since this was not explicitly addressed in the survey we are unable to comment definitively on that issue in our recommendations which must reflect the results of the Delphi survey and not simply the opinion of the OABD task force members.

Lessons learned from the use of a Delphi survey include the need to remain focused on specific goals and objectives while avoiding excessive time and energy on controversial areas that are unlikely to achieve consensus. Specifically, we avoided a focus on the controversial area of lithium and renal function and limited our focus to the specific place and use of lithium in the maintenance treatment of OABD. We also refrained from drilling down on the other recommended mood stabilizers.

The successful recruitment of experts was done by personal connections as far as possible with individualized invitations rather than "cold call" emailing that is much less likely to attract participation. Utilizing an existing structure, such as the OABD task force, from which to recruit experts ensured a high degree of interest and motivation to participate in a survey that may take three over four iterations. The use of brief questionnaires, timely feedback and short intervals between iterations helped to maintain motivation and interest in the study and continued participation in the survey on repeated iterations. Our 100% response rate for all three iterations is a testament to those factors and avoided the potential for a low response rate with multiple iterations, one of the common limitations of a Delphi survey.

It was important to identify quickly those issues for which consensus was not possible or likely, and not try to force consensus. The oversight team helped to formulate the next iteration of questions designed to sharpen the focus of the survey and obtain as much consensus as possible. It made most sense to use the Discussion to elaborate on the issues where there was no consensus. Use of the oversight team to review results objectively and avoid unintended guidance of responses due to preconceived ideas was critical.

In the face of very limited published data to inform clinical practice, it has been argued that consensus expert opinion must be explicitly recognized by CPG authoring groups.³³ Given the impact that CPG's have on clinical practice, this is an important consideration for maintenance treatment of OABD. Expert opinion is based on a combination of vast clinical experience and accumulated knowledge from a wide range of sources which should strengthen the credibility of CPGs which tend to focus on published "evidence." A "hybrid" CPG that includes both published data and expert opinion may be more relevant and practical for clinicians.³³ The recent CANMAT and ISBD bipolar disorder guidelines provide an example of such a hybrid section on older adults but still lack specifics with regard to therapeutic serum levels of lithium and relevant laboratory and clinical investigations for OABD.³⁶ A hybrid approach also addresses some of the concerns about real world effectiveness raised by Malhi et al⁶ in their critical review of CPGs. Future CPGs for OABD should incorporate expert consensus recommendations until such time as RCT data are available to guide practice.

These guidelines for OABD could help to stem the unwarranted decline in lithium prescriptions that has been evident in recent years. Pending further systematic data regarding the use of lithium for maintenance therapy in OABD, these Delphi survey recommendations offer robust guidance to clinicians on how best to use lithium for the effective and safe maintenance treatment of OABD.

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Expert panel members are listed in supplemental Appendix S4. OABD task force members are listed in supplemental Appendix S5. The authors thank Rhona Shulman for help in the design of the Figure, Tables and formatting of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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