

## Outcomes of patient education practices to optimize the safe use of lithium: A literature review

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### Abstract

**Introduction:** Lithium is commonly used to treat various psychiatric disorders and is particularly effective in the maintenance phase of bipolar disorder. Unfortunately, this drug has a narrow therapeutic index and, if not monitored regularly, can result in toxicity. Therefore, for lithium to be prescribed safely, clinicians must ensure that patients are well educated on lithium toxicity, its prevention, and symptom recognition. This article summarizes studies that investigated lithium education strategies to help promote the safe use of lithium.

**Methods:** Four electronic databases were searched using key terms and subject headings. Reference lists of relevant papers were also reviewed. The search was limited to literature published in English, without year limits. Eligible studies examined lithium patient education and the impact on patients' knowledge of safe lithium use.

**Results:** Of a total of 517 citations that were retrieved from the electronic database search, 12 were selected for inclusion in this review. Most of the studies included assessed the effect of lithium education on various aspects of patients' knowledge, including but not limited to, lithium toxicity. Of the studies assessing the correlation between lithium knowledge and lithium levels, most demonstrated a positive correlation between lithium knowledge and lithium levels that were more stable and within the higher end of the recommended therapeutic range.

**Conclusions:** Studies evaluating lithium patient education and its effect on improving the safe use of lithium are limited. Nevertheless, this literature review highlights that lithium patient education is critical to promote its safe use.

**Keywords:** lithium patient education, lithium safety outcomes, lithium toxicity

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### Introduction

Lithium is used to treat a variety of psychiatric disorders and has demonstrated efficacy in the maintenance phase of bipolar disorder.<sup>1,2</sup> Notably, lithium has multiple drug interactions, undergoes significant renal excretion, and has a narrow therapeutic window that, if not adequately monitored, can result in toxicity, even at doses considered to be therapeutic.<sup>3</sup> Lithium toxicity has been divided into 3 categories: acute, acute-on-chronic, and chronic.<sup>4</sup> Stud-

ies<sup>5,6</sup> have shown that toxicity is more likely to result from chronic, therapeutic administration rather than from acute poisoning or overdose. Chronic and acute-on-chronic intoxication have been suggested to be triggered by concurrent illness, drug interactions, or gradual dehydration, resulting in reduced renal excretion of lithium.<sup>4,7</sup> Toxicity associated with lithium maintenance treatment is prevalent; approximately 75% to 90% of patients have reported signs and symptoms of toxicity at some point during their treatment.<sup>8</sup> Studies<sup>9-11</sup> also suggest that the serious neurologic consequences of toxicity are usually in the context of chronic or acute-on-chronic administration of lithium. Prior to 1975, mortality ranged from 9% in patients who presented with toxicity from chronic poisonings to 25% in acute poisonings.<sup>10</sup> These results probably overestimated mortality because of the presence of publication bias.<sup>11</sup> More recent data<sup>12,13</sup> suggest mortality rates of equal to or less than 1%, possibly due to improved lithium therapy monitoring.

The literature<sup>2,8,9,11,14,15</sup> recommending strategies to reduce lithium toxicity and its associated costs is extensive. Individualized prescribing, regular monitoring practices, and clinician's awareness of the associated risk factors, as well as patient education, have been recommended. For lithium to be used safely, patients need to be well aware of the features of lithium toxicity, and clinicians must provide this education early during treatment initiation, as well as in a regular and consistent manner. Patient-reported instruments, such as the Lithium Knowledge Test (LKT) and the Lithium Attitudes Questionnaire (LAQ), have been used to assess patients' lithium knowledge and compliance attitudes, which are important if therapy with lithium is to be safe and effective.<sup>16,17</sup> The LKT scores are obtained by adding up the responses to a total of 20 questions, whereas the LKT hazard scores (LHS) are obtained by adding together the responses to the questions on symptoms of toxicity. Studies<sup>18-20</sup> reveal that adequate lithium knowledge (as assessed by LKT scores) is associated with shorter duration of treatment, younger age, and positive attitudes toward treatment with lithium. Intensifying patient education, especially in older adults, seems to be an important strategy to potentially prevent lithium toxicity with chronic use.<sup>15</sup>

Many specialized lithium outpatient clinics, inpatient psychiatric services, and reputable Web sites provide information, psychoeducation, and brochures about lithium to patients.<sup>16,20,21</sup> Studies<sup>15,22,23</sup> have not only assessed patients' lithium knowledge and attitudes, but also correlated these with adherence, mood control, and therapeutic drug levels. This article summarizes studies evaluating the relationship between patients' lithium knowledge and safer utilization patterns of lithium.

Studies assessing the impact of lithium educational strategies on toxicity-related outcomes are also reported.

## Methods

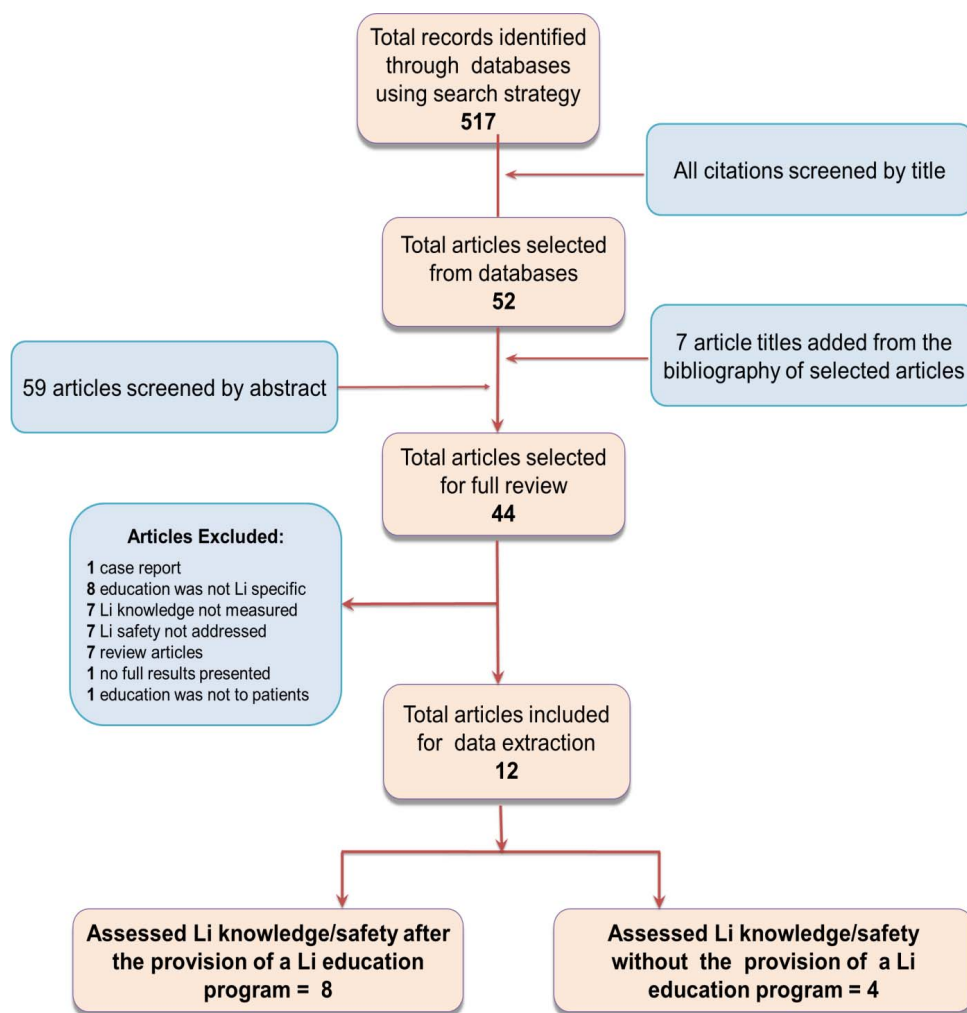
For this review, a computerized search was conducted using PubMed Central, MEDLINE, Embase, and Google Scholar databases, without year limits. In order to identify studies describing lithium patient education and the impact on patients' knowledge on safe use of lithium, the following key words were used: *lithium education*, *lithium counseling*, *lithium toxicity*, and *lithium knowledge*. The initial screening of article titles and abstracts was conducted by one reviewer (M.Z.). Studies were selected for full review based on the following inclusion criteria: articles in English language that describe a lithium patient education strategy or studies reporting any form of assessment of patients' knowledge on the safe use of lithium. Articles were excluded if educational strategies were not focused on lithium safety or if the impact of lithium education was not evaluated. All review articles were also excluded. The full texts of all potentially relevant articles were retrieved and equally distributed among 5 reviewers (M.Z., Y.E.T., M.A., M.F., N.E.H.) to confirm eligibility.

## Results

Of the 517 citations identified in the initial electronic database searches, 52 full-text articles were retrieved to undergo a more comprehensive examination based on the inclusion/exclusion criteria. An additional 7 citations were identified through a review of the references of potentially relevant articles, for a total of 59 articles to be examined more thoroughly by the reviewers. As shown in the Figure, of the 44 articles that qualified for full review, 12 were included. Data in these 12 articles were independently extracted by the same 5 reviewers using a standardized data collection tool.

The results of the 12 articles included in this review<sup>15,16,19,20,24-31</sup> are summarized in Tables 1 and 2. As highlighted in Table 1, 8 of the 12 included studies<sup>16,20,24-26,29-31</sup> examined the impact that educational strategies had on patients' lithium knowledge. Table 2 summarizes the studies<sup>15,19,27,28</sup> that assessed lithium knowledge without a lithium patient education intervention. A total of 7 studies<sup>15,19,26,27,29-31</sup> reported lithium levels as toxicity outcomes.

As summarized in Table 1, a variety of educational strategies were described in these studies, including verbal and written communication, visual education via videos, and psychoeducation. The LKT (and the related LHS) was the preferred instrument used to assess patient knowl-



**FIGURE:** Flow diagram of the literature review process

edge about lithium therapy and its safety profile (in 8 of the 12 included studies<sup>15,16,19,20,25,27,29,30</sup>); however, in some studies,<sup>20,30,31</sup> modified versions of the LKT were used.

In most studies<sup>15,19,26,27,29-31</sup> included in this review (7 of 12), researchers investigated the correlations and/or associations of the patients' lithium knowledge with lithium blood levels. In 6 of these 7 studies<sup>15,19,26,27,29,30</sup> it was concluded that lithium levels were generally more stable and within the therapeutic range in those individuals with higher lithium knowledge scores. However, not all studies reported an association with decreased incidence of lithium toxicity or improved lithium tolerability.

## Discussion

Current literature evaluating the relationship between patients' lithium knowledge, use patterns, and patient outcomes is scarce. Despite the availability of several

validated questionnaires, such as the LKT (and related LHS) and LAQ, patients' knowledge of and attitudes toward lithium treatment and its associated risks appear to be rarely evaluated using these tools.

None of the studies included in this review described educational strategies using technology. This may be explained by the fact that most of the studies found on this topic are more than a decade old, when technology applications for this use were not yet widely available to consumers. In addition, it has been reported that in mental health, these types of treatment innovations tend to be delayed, often related to the stigma that is prevalent in the provision of mental health services.<sup>32</sup> In 2015, Hidalgo-Mazzei and colleagues<sup>33</sup> described the development and planned validation of a smartphone application to monitor signs and symptoms of bipolar disorder, offering customized embedded psychoeducation contents, but validation of this instrument has not yet been published. However, this type of educational strategy has already been shown to improve treatment

**TABLE 1: Studies assessing lithium (Li) knowledge after the provision of Li education program**

Study, y	Study Design and Population	Li Assessment Tool	Li Educational Strategy	Li Levels Assessed?	Findings
Anderson and Sowerbutts <sup>24</sup> (1998)	Survey of 67 of 99 pts attending an outpatient affective disorders clinic in Scotland at a minimum of every 3 mo intervals completed the Q (68% response rate).	Semistructured Q developed by the authors based on the information of Li leaflets. Q was self-administered.	Pts received Li pamphlets. Education was reinforced with verbal information, and some pts viewed a videotape.	No	Li knowledge was not significantly influenced by age, duration of treatment, type of Li education, or length of time since Li education. The only significant effect on levels of knowledge was having received more than 1 form of Li education (most commonly written and verbal).
Clarke and Pickles <sup>25</sup> (1994)	Face-to-face interviews of 25 pts with learning disability taking Li, and their caregivers.	LKT, LAQ, and LQ (which includes a hazard score)	Caregivers and some pts received Li information from a variety of health care professionals on a one-to-one basis.	No	Knowledge (as measured by LKT) was associated with more positive attitudes (measured by the LAQ). Overall hazard scores related to the LKT and LQ were high.
Colom et al <sup>26</sup> (2005)	Subanalysis of BPAD pts taking Li obtained from a larger study on the efficacy of group psychoeducation. There were 44 pts assigned to the control group and 49 assigned to the psychoeducation program.	Li knowledge was not assessed.	Psychoeducation comprised 21 group sessions aimed at improving illness awareness and treatment adherence. The program was conducted by 2 experienced psychologists.	Yes	Pts in the psychoeducation group maintained higher (0.785 mEq/L versus 0.671 mEq/L) and more stable (0.75–0.79 mEq/L versus 0.64–0.72 mEq/L) Li levels compared with the control group.
Doğan and Sabanciogullari <sup>29</sup> (2003)	The study compared a total of 26 pts (14 study and 12 control) with BPAD who had taken Li for 10 y (1992-2002). The study pts received individual education.	Medication assessment Q (20 questions) designed by the authors.	Two sessions, consisting of education about BPAD, causative factors, clinical symptoms, goals of Li therapy, its SEs, and Li monitoring.	Yes	An increase in medication knowledge and more regular medication use were observed among the study group members. Percent of pts with Li levels within the therapeutic range after education increased from 57.1% to 100% in the intervention group, whereas they remained unchanged in the control group.
Peet and Harvey <sup>16</sup> (1991)	The study compared a total of 60 pts (29 study and 30 control) with BPAD in remission and on Li attending a Li clinic. The study group enrolled in the education program.	LKT, LAQ, LHS	An educational video and a written handout. At 6 wk the pts had a home visit where pt questions about Li were answered.	No	After the education program, the mean LKT in the education group was significantly higher than in the control group. The LHS scores significantly decreased in the education group; the LAQ scores also improved (but not statistically significant).

**TABLE 1: Studies assessing lithium (Li) knowledge after the provision of Li education program (continued)**

Study, y	Study Design and Population	Li Assessment Tool	Li Educational Strategy	Li Levels Assessed?	Findings
Rosa et al <sup>30</sup> (2006)	106 Adult pts with BPAD on Li treatment for at least 1 month, and regularly attending weekly visits at 2 psychiatric outpatient clinics in Brazil. This study tested the validity of the LKT in Portuguese.	LKT, LHS	The pts participated in psychoeducational groups about Li with a specialized nurse and support groups with psychiatrists to discuss topics related to the disease.	Yes	The Portuguese version of LKT showed good internal consistency, sensitivity, and specificity. Pts with higher LKT scores were more likely to have plasma Li levels within the therapeutic range. There was a significant negative correlation between age and LKT scores, and a significant positive correlation with LHS.
Rosa et al <sup>31</sup> (2007)	Face-to-face survey of 106 adult BPAD pts on Li treatment for at least 1 mo and regularly complying with weekly visits scheduled in 2 psychiatric outpatient services	LAQ, LKT, MARS, SEQ	Monthly psychoeducational groups.	Yes	There was a significant positive correlation between LKT with plasma Li levels, and a negative correlation between LKT and the associated hazard scores. A negative correlation of LKT and LAQ was also found.
Schaub et al <sup>20</sup> (2001)	Survey of 123 adult pts with unipolar, bipolar, and schizoaffective disorder attending an outpatient Li clinic.	German version of the LKT (with additional questions related to SEs and corresponding potential behavioral consequences).	At the Li clinic pts are provided with comprehensive information about Li at intake, and then knowledge is “refreshed” twice a year.	No	A consistent negative association between age and Li-related knowledge was obtained, including knowledge of behavioral adaptation, SEs and intoxication signs, and factors of importance for Li treatment (eg, nutritional precautions).

BPAD = bipolar affective disorder; LAQ = Lithium Attitudes Questionnaire; LHS = Lithium Knowledge Test Hazards Score; LKT = Lithium Knowledge Test; MARS = Medication Adherence Rating Scale; pt/pts = patient/patients; Q = Questionnaire, SE = side effect; SEQ = Side Effect Questionnaire.

outcomes in other chronic conditions, such as diabetes and chronic obstructive pulmonary disease.<sup>34,35</sup>

In one of the articles reviewed,<sup>24</sup> reinforcement of information and the use of more than 1 form of lithium educational strategy showed a positive correlation with lithium knowledge scores. These results are consistent with similar studies of educational strategies in other chronic diseases.<sup>36</sup> Additionally, studies<sup>14,16,20,27</sup> included in this review indicate that patient education strategies improve patients' knowledge of and attitudes toward lithium treatment and contribute to patients achieving more stable lithium levels. Another study, by Tillery,<sup>37</sup> showed improved lithium knowledge among health care providers after a lithium therapy education program was provided by clinical pharmacists. In this study, lithium levels were stable and maintained within the therapeutic range in the patients being cared for by these clinicians. This study was excluded from this review because the

lithium therapy education program was not aimed at patients and it did not assess patients' lithium knowledge. Pharmacist-run lithium clinics have been described in the literature, all of which highlight the important role of pharmacists in mental health, particularly with regard to patient education and therapeutic drug monitoring.<sup>27,38,39</sup>

The studies reviewed have also elucidated that increasing age appears to have a negative correlation with lithium knowledge. Some studies<sup>15,31</sup> have also demonstrated a positive correlation between age and hazard scores. These results are indicative that older patients may benefit from continuous reinforcement of information regarding lithium toxicity signs and ways to prevent toxicity.<sup>2,15,19,20,28,30,31</sup> This was also highlighted for patients with learning disabilities and their care providers, and for those receiving lithium maintenance treatment.<sup>15,25,31</sup> Future research should address whether more knowledge does, in fact, prevent adverse events and whether patient

**TABLE 2: Studies assessing lithium (Li) knowledge without the provision of a Li education program**

Study, y	Study Description	Li Assessment Tool	Li Levels Assessed?	Findings
Courtney et al <sup>27</sup> (1995)	15 pts attending a pharmacist-run outpatient Li clinic compared with 15 pts attending other consultant outpatient services.	LKT, LAQ, and a satisfaction questionnaire (developed for the purpose of this study).	Yes	There was a trend toward the pharmacy clinic pts scoring higher in the LKT than the outpatients followed up by the consultants. The LHS showed a significant difference in favor of the pharmacy group. There was no difference in the LAQ scores in the 2 groups. Serum Li level control was reported as “satisfactory” in pts attending the pharmacist-run Li clinic.
Delany <sup>28</sup> (1991)	50 of 250 pts on an Li registry who were clinically stable completed a questionnaire when attending an outpatient clinic for follow-up.	Q with open-ended questions about Li SEs, monitoring and management.	No	Pts on Li know dangerously little about their medication. Li knowledge scores were low, those older than 65 y did have a significantly lower score when compared with the younger group.
Dharmendra and Eagles <sup>29</sup> (2003)	A total of 742 BPAD pts known to be taking Li were surveyed postally, of whom 18% refused to participate.	LKT (including the LHS), LAQ; 67% of pts completed the LKT and 59% of pts completed the LAQ.	Yes	High scores on the LKT were associated with shorter duration of treatment, younger age, positive attitudes on the LAQ, and low LHS. Higher LHS (ie, potentially hazardous lack of knowledge) was associated with longer duration of treatment and with low knowledge scores. Positive attitudes toward Li on the LAQ were associated with higher serum Li levels and with continuing to take Li.
Enudi et al <sup>15</sup> (2014)	A total of 33 elderly pts who were established on Li treatment and attending the outpatient psychogeriatric services were surveyed.	LKT (including the LHS)	Yes	The mean score on the LKT was suggestive of poor knowledge of Li. The related LHS was indicative of a potentially hazardous lack of knowledge. There was a significant negative correlation between the LKT score and the LHS. There was a positive relationship between LKT score and Li level, albeit not a significant one.

BPAD = Bipolar affective disorder; LAQ = Lithium Attitudes Questionnaire; LHS = Lithium Knowledge Test Hazards Score; LKT = Lithium Knowledge Test; MDs = medical staff; pt/pts = patient/patients; Q = questionnaire; RNs = nursing staff; SE = side effect.

education can further improve knowledge, particularly in elderly patients, where other limitations (eg, cognitive impairment) might hamper educational efforts.<sup>20</sup>

## Conclusions and Recommendations

Lithium is an important medication for the treatment of serious mental illness. However, it is associated with potentially fatal toxicity because of its narrow therapeutic index, renal elimination, and multiple drug-drug interactions. The present review has identified several key areas for the safe and responsible monitoring of lithium treatment, including:

- Based on worldwide guidelines, good clinical management of patients with bipolar disorder involves an

appreciable educational component for both patients and their relatives.<sup>2,40</sup> Patients should receive written information reinforced with verbal advice before the first dose of lithium is taken.<sup>2,21,40</sup> It should be reinforced at the first lithium clinic appointment and, when necessary, throughout the course of their treatment.<sup>21</sup> Patients currently on lithium therapy should still receive this written and verbal advice.<sup>2,21,40</sup>

- In order to make lithium therapy safe, information must convey key messages, including:
  1. What lithium is and what it is used for
  2. Assessments needed before starting lithium
  3. How to take lithium
  4. Blood tests after a patient starts taking lithium
  5. What side effects lithium can cause
  6. What happens if the level of lithium is too high



7. What can make the lithium blood levels get too high
  8. Actions to be taken if lithium toxicity is suspected
- Lithium education is of particular importance in certain populations, such as the elderly, people with learning disabilities, patients on medications that can interact with lithium or increase the risk of dehydration, and those receiving lithium maintenance treatment.<sup>2,15,25,40</sup> Offering more regularly scheduled lithium education and refresher courses in these populations is advisable.
  - Educational strategies may best translate into improved knowledge and improved awareness of lithium toxicity by the use of a variety of interventions, written and verbal, imparted on a more regular basis (eg, at every 3-month follow-up), not just before commencing treatment.<sup>2,23,40</sup> Future directions should incorporate technology-based applications that can support and sustain the beneficial outcomes imparted by these educational strategies.
  - The knowledge imparted by educational strategies should be regularly tested to ensure they are effective in improving patients' knowledge of and attitudes toward treatments. The use of the LKT and LAQ are validated tools that can provide an adequate assessment of lithium education programs and to ensure that the necessary information has been retained by patients.
  - Pharmacists are valued members of the health care team with unique knowledge and skills in pharmacokinetic management who are available for consultation in most hospital settings, and who may provide education to other health care professionals not only in an inpatient psychiatric setting, but also in the community. Pharmacists working in outpatient settings are in a particularly good position to be educating on and assessing patients for lithium toxicity. Although educational material alone is unlikely to give rise to changes in clinical practice, lithium-monitoring standards may be improved through the involvement of a multidisciplinary team and a more detailed provider education system.

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