WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL RESEARCH

Research Article

2025
Volume: 02
Issue: 03
Page: 01-17

LITHIUM: UNDERSTANDING ITS THERAPEUTIC BENEFITS AND BLACK BOX WARNING RISKS AMONG PHARMACY STUDENTS

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Received: 22 January 2025 **Revised: 12 February 2025** **Accepted: 02 March 2025**

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ABSTRACT

This study takes a focused look at lithium's role in treating psychiatric disorders, especially bipolar disorder, and the extent of pharmacy students' understanding of its clinical use. Through a survey of professional pharmacy students, we evaluated both their knowledge of lithium's therapeutic effects and safety concerns. The survey results show that while students understand the importance of patient education regarding lithium, there are clear gaps in their knowledge, particularly around how dehydration impacts lithium levels. These findings point to the need for targeted education that deepens future healthcare providers' understanding of lithium's risks and benefits, equipping them with the skills needed to ensure patient safety.

KEYWORDS: Survey, lithium, black box warning, therapeutic index, toxicity.

INTRODUCTION

Lithium is a mood stabilizer and antimanic agent, also recognized as an anticonvulsant. Its therapeutic use began in the 1940’s and gained traction in the late 1950’s for treating manic episodes in bipolar disorder. The FDA approved lithium carbonate for this purpose in 1970, and it is primarily used to prevent both manic and depressive episodes in bipolar disorder, with off-label uses for conditions like schizoaffective disorder and severe aggression. While its exact mechanism of action is not fully understood, lithium is thought to modulate neurotransmitter levels, particularly serotonin and norepinephrine, and inhibit inositol monophosphatase, contributing to its mood-stabilizing and neuroprotective effects.[1]

Black box warnings for lithium include severe neurological and renal complications. This warning stems from its narrow therapeutic index, where the margin between effective and toxic doses is narrow, necessitating careful monitoring. Risk factors for toxicity include dehydration, renal impairment, and drug interactions. Vulnerable populations, such as children, the elderly, and individuals with pre-existing conditions like renal or cardiovascular issues, are at heightened risk due to varying metabolic rates and compromised physiological responses. Consequently, vigilant monitoring and dosage adjustments are essential for these groups.[1]

The effectiveness of lithium in treating bipolar disorder and other mood disorders is well-established through clinical trials, observational studies, and real-world evidence. A meta-analysis indicates that lithium significantly reduces the risk of suicide in patients with bipolar disorders, with a prevalence rate of about 30-40% among those receiving treatment. Case reports also demonstrate variability in responses to lithium, underscoring the importance of personalized treatment. A review of literature from databases like PubMed and PsycINFO supports these findings, including the studies by Tondo et al.[2] on long-term lithium treatment and Lewitzka et al.[3] on its suicide prevention effects.

When prescribing lithium, it is important to monitor specific parameters to ensure patient safety and therapeutic effectiveness. Key monitoring areas include serum lithium levels, renal function tests (serum creatinine and estimated glomerular filtration rate), and thyroid function tests, as lithium can impact thyroid hormone levels. Serum lithium levels are typically checked every 1-3 months during the initial treatment phase and every 6 to 12 months, once the patient is stable. Dehydration can lower lithium levels. Lithium serum concentration is recommended to be in the 0.4-1.2 mmol/l range.[4] Early signs of lithium toxicity, such as gastrointestinal disturbances, tremors, confusion, and ataxia, should be closely observed. Regular monitoring allows for timely identification of these symptoms and necessary treatment adjustments to prevent severe toxicity.[1]

Common side effects of lithium include nausea, vomiting, dizziness, and tremors.[5] Patients should be advised on lifestyle modifications to mitigate these effects, such as avoiding alcohol and caffeine and making appropriate dietary changes. Additionally, they should be informed about when and what symptoms to report to their healthcare providers to ensure timely intervention.[1] Maintaining consistent fluid and sodium intake is essential, as lithium

levels can be affected by dehydration or excessive sodium loss. Adverse effects of lithium include weight gain, somnolence, and tremor and should be discussed with the patient beforehand. Lithium should not be taken with antidepressants, since the interactions can increase adverse events.[4]

One study has demonstrated that healthcare providers have an average to low knowledge level on treatment practices with lithium. Knowledge was adequate in the general aspects of treatment, but deficient in monitoring side effects of lithium. Educational interventions proved beneficial in enhancing knowledge of healthcare providers with lithium treatment for psychiatric disorders.[6] The main objectives of this paper was to determine the efficacy of lithium for treatment of bipolar disorder and depression, assess student knowledge on lithium treatment practices. and obtain students' opinion related to the black box warnings of lithium.

METHODS

A survey was conducted to obtain data on the opinions and knowledge of first year pharmacy students. A total of 44 students took part in the survey. Students were required to input their demographic information including gender, work experience, prior knowledge of or experience with black box warnings, and their level of education. A total of 10 questions were administered, with five assessing student knowledge on treatment practices of lithium and five focusing on the opinion questions to determine any trends amongst the students. Before conducting the survey, the questions were reviewed a Drug Informatics professor, and a licensed pharmacist to ensure clarity, relevance, and alignment with the research objectives. The survey was administered online during class, where students were asked to use their phone or laptop and record their answers. The survey responses were compiled by the same professor who reviewed the survey questions. A descriptive statistical data analysis, such as means, standard deviation and variance was conducted. A Likert scale was used to collect data and record opinions: 1=strongly agree; 2=agree; 3=disagree; 4=strongly disagree. A two-tailed Fisher Exact Test was utilized to evaluate the significance of differences in the knowledge-based questions.

RESULTS

Demographic Data

The demographic data of the class is presented in Table 1. The class of pharmacy consists of a majority female student population at 72.7%. About half of the students (48.8%) worked or

are currently working for more than 3 years. The table also shows that most students have worked in a pharmacy-related setting prior to taking this survey. Additionally, it provides a summary of the participants' educational history, indicating that the majority of students attended a four-year college and majored in basic science or health science.

Table 1. Demographic data of the participants (*n*=44).

Demographic characteristics		***n* (%)**
Gender	Male	12 (27.3)
	Female	32 (72.7)
Work experience*	In healthcare-related job	7 (15.9)
	Pharmacy-related job	27 (61.4)
	In non-health related job	9 (20.4)
If worked, for how many years?	< 1 years	6 (14.0)
	1-3 Years	16 (37.2)
	>3 years	21 (48.8)
Education (highest level attended)	2-year college	2 (4.5)
	4 years (BSc/BA)	28 (68.2)
	MSc or higher	8 (18.2)
	Other	4 (9.1)
What was your major as an undergraduate student?	Basic or health sciences	28 (63.6)
	Social Science	1 (2.3)
	Business	1 (2.3
	Other	14 (3.2)

*One respondent never worked.

The data in Table 2 shows that a little over half of the student population has relative familiarity with Black Box Warnings and has either experienced or knows someone who has experienced the Black Box Warning effects prior to taking this survey.

Table 2: Participants familiarity and experience with Black Box Warning.

Question posed	**Response**	**Number of respondents[*n* (%)]**
Have you heard of black box warning before joining the pharmacy program?	Yes	23 (52.3)
	No	16 (36.3)
	Maybe	5 (11.4)
Have you or any member of your family or friends experienced related adverse drug reactions in the past? *	Definitely yes	10 (23.3)
	Probably yes	25 (58.1)
	Definitely not	8 (18.6)

*One participant did not provide an answer.

Opinion-Based Questions

The results of the opinion-based survey questions (Table 3) show a range of agreement and disagreement regarding the education of lithium, its uses and black box warnings. The majority lean towards agreement at a combined rate of 82.7% ("aggregate strongly agree and agree" data points). The surveyed students agree that education is an important part in lithium therapy; however, there is a split that suggests that some participants (18.2%) feel training may be lacking or inconsistent.

Table 3: Opinion-based questions (Reponses of survey participants; *n* = 44).

Question	SA (*n*, %)	A (*n*, %)	DA (*n*, %)	SA (*n*, %)	Mean LK ± SD	Variance
How would you rate the importance of patient education regarding lithium's black box warning and the potential side effects?	27 (61.4)	12 (27.3)	5 (11.4)	0 (0.0)	1.5±0.6908	0.4773
Do you believe that heath care providers receive sufficient training on monitoring lithium therapy to prevent adverse outcomes?	13 (29.5)	23 (52.3)	8 (18.2)	0 (0.0)	1.8864±0.6814	0.4644
How confident are you in lithium as a long-term treatment for bipolar disorder, considering its neurological and renal complication risks?	18 (40.9)	16 (36.4)	8 (18.2)	2 (4.5)	1.8636±0.8684	0.7541
In your opinion, do the benefits of lithium in preventing manic depressive episodes outweigh the risks associated with its black box warnings?	14 (31.8)	21 (47.7)	6 (13.6)	3 (6.8)	1.9545±0.8516	0.7252
How concerned are you about the potential for lithium toxicity, given its therapeutic index and the need for careful monitoring?	20 (45.5)	18 (40.9)	5 (11.4)	1 (2.3)	1.7045±0.7562	0.5718
Average (%)	41.8	40.9	14.6	2.7	1.7818 ± 0.7697	0.5986

Abbreviations: SA=Strongly agree; A=Agree; DA=Disagree; SD=Strongly disagree; LK=Likert Score; SD=Standard deviation

Knowledge-Based Questions

Based on the knowledge-based question data shown in Table 4, participants appear to have a moderate understanding of lithium therapy practices, as the overall average was calculated to be 56.8%. There is, however, a severe gap in knowledge of dehydration and its effects on lithium levels in the body.

Table 4: The results of the knowledge-based questions (participants, *n*=44).

Questions	Correct Answer	True (*n*)	False (*n*)	Participants with correct answers: *n* (%) *	Mean correct answer rate out of 1 (±SD)	Variance
1. Dehydration can influence lithium levels making them appear lower during testing	False	35	9	9 (20.5)	0.2045±0.4034	0.1627
2. Lithium is a wide therapeutic index drug	False	22	22	22 (50)	0.5±0.5	0.25
3. It is safe to combine lithium with antidepressants as they do not significantly increase the risk of adverse events	False	19	25	25 (56.8)	0.5618±0.4953	0.2454
4. Early signs of lithium toxicity include gastrointestinal disturbances, tremors, confusion and ataxia	True	40	4	40 (90.9)	0.9091±0.2875	0.0826
5. The recommended therapeutic range of serum lithium concentration is 0.4-1.2 mmol/L	True	29	15	29 (65.9)	0.6591±0.4740	0.2247
Average correct answer				56.8%	0.5669±0.4320	0.1931

Participants with Correct*P values for correct a SD=Standard deviation. *P values for correct answers: 4 vs 1 (p=0.0001); 4 vs 2 (p=0.0001); 4 vs (p=0.0005); 4 vs 5 (p=0.0011); 3 vs 1 (p=0.0009); 3 vs 2 (p=0.6694); 3 vs 5 (p=0.5116); 5 vs 1 (p=0.0001); 5 vs 2 (p=0.1948) and 5 vs 3 (p=0.5116)

DISCUSSION

Lithium, known as a mood stabilizer and antimanic agent, has been used in treating bipolar disorder since the 1940s, with FDA approval coming in 1970. Though its exact mechanism remains unclear, lithium is thought to regulate neurotransmitters such as serotonin and norepinephrine, the key chemicals which stabilize mood. Lithium is widely used to prevent both manic and depressive episodes in bipolar patients, and it is also prescribed off-label for other conditions such as schizoaffective disorder and severe aggression. Lithium has a narrow therapeutic range which leads to a black box warning for neurological and renal complications, especially in vulnerable groups like the elderly and those with pre-existing conditions. Dehydration, kidney issues, and certain medications can increase the risk of toxicity, prompting the need for regular monitoring of lithium levels, kidney function, and thyroid function. Early signs of toxicity, such as tremors, confusion, and gastrointestinal issues, need to be recognized quickly to avoid serious complications. Studies consistently back lithium's effectiveness in reducing symptoms of bipolar disorder and preventing suicide, although patient responses may vary. Healthcare providers often need more knowledge about lithium's side effects and monitoring requirements, and educational programs have been shown to improve their understanding. This paper aimed to review the literature about lithium's effectiveness in treating bipolar disorder, assess pharmacy students' knowledge on aspects of lithium therapy, and gather their opinions on its black box warnings.

In a randomized, double-blind study of lithium compared with placebo, it was shown that lithium significantly improved increased activity and motor hyperactivity compared with placebo.[7] Lithium was shown to not only improve the motor activity in bipolar patients, but also the efficacy also lasts for maintenance treatment for the disorder. When bipolar patients were randomized to groups of higher serum-lithium levels (0.8-1.0 mEq/L) or lower levels (0.4-0.6 mEq/L), the higher levels were shown to be more effective in the prevention of manic/mixed episodes.[8]

An investigation looking into adherence to black box warnings indicated the importance of education of healthcare providers. In a study of 324 548 outpatients who received medications in 2002, 2354 (0.7%) received a prescription with black box warnings. The number of medications taken, the number of medical problems, and the site of care were also associated with overlooking black box warnings. As a result, less than 1% of patients who received a drug in violation of a black box warning had an obvious adverse drug event.[9]

Educating providers on the risks associated with high-alert medications and the specific circumstances may decrease the likelihood of adverse events, a consideration which is important for patient safety. When providers are well-informed about black box warnings, they are better equipped to make safe prescribing decisions, manage complex medication regimens, and recognize situations where extra caution is needed.

The survey results in this study reveal both strengths and gaps in participants' understanding and attitudes toward lithium therapy. Opinion-based responses indicate that most participants recognize the importance of patient education on lithium, with strong support for informing patients about its risks and benefits. However, a considerable portion of participants expressed uncertainty about whether healthcare providers receive adequate training on lithium, suggesting a perceived need for further education in this area. Knowledge-based responses show a varied understanding of lithium's clinical aspects. While 90.5% of participants correctly identified early signs of lithium toxicity, only 20.5% understood how dehydration affects lithium levels. This discrepancy highlights specific areas of targeted education such as the impact of dehydration on lithium levels..

A significant number of the respondents had correct answer rate (90.5%) when compared, respectively, to the correct answer rate regarding how dehydration affects lithium's drug concentration (20.5%, p=0.0001), lithium's therapeutic index (50%, p=0.0001), the safety of combining lithium with antidepressants (56.8%, p=0.0001), and therapeutic range of serum lithium concentration (65.9%, p=0.0011). Regarding the safety of combining lithium with antidepressants, a significantly higher percentage (56.8%) of the respondents answered correctly compared with the low 20.5% correct answer rate for respondents who recognized that dehydration increases serum lithium level (p=0.0009). Compared to the latter 20.5%, a significantly higher (65.9%) answered correctly the question on the recommended therapeutic range of serum lithium concentration (p=0.0001). The average correct knowledge rate of 56.8% is comparable with similar rates in our earlier surveys in other areas of pharmacy.[10-12] Overall, the results of the current survey suggest a foundational knowledge of lithium among participants, coupled with certain misconceptions and concerns that could benefit from additional training and clarification.

Some limitations to this study include the lack of diversity among participants, and the small sample size which does not allow for generalizability. These limitations could be corrected with a larger population.

CONCLUSION

This study emphasizes lithium's essential role in managing mood disorders and the responsibility of healthcare providers to grasp its complex nature. Its narrow therapeutic range requires careful attention to dosing, patient education, and symptom monitoring. The pharmacy students surveyed in this study showed an average knowledge level (56.8%) of understanding lithium's benefits and its role in managing bipolar disorder, but the gaps in their knowledge, particularly concerning factors like dehydration, reveal an opportunity for growth. Addressing these areas could enhance patient safety and treatment outcomes by equipping providers with a thorough understanding of lithium's pharmacology and monitoring requirements. Future research should continue to explore educational strategies that effectively convey both the therapeutic benefits and risks associated with lithium treatment. As future healthcare providers, the surveyed students carry the responsibility to navigate the delicate balance between lithium's promise and its perils, guided by a commitment to patient safety and well-being.

Compliance with ethical standards

ACKNOWLEDGEMENT

All first-year pharmacy students at Howard University College of Pharmacy who participated in this survey are acknowledged.

Disclosure of Conflict of Interest

The authors declare no conflict of interest.

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