

## Lithium rechallenge after renal transplant

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**How to cite:** Beasley AK, Larson CC, Garcia-Pittman EC. Lithium rechallenge after renal transplant. *Ment Health Clin* [Internet]. 2017;7(2):46-50. DOI: 10.9740/mhc.2017.03.046.

### Abstract

Mrs B is a 65-year-old, married, white woman with long-standing history of bipolar disorder type I who achieved mood stability with chronic lithium treatment. She developed end-stage renal disease, which was suspected to be the result of chronic lithium exposure in the context of medical comorbidity, and subsequently required renal transplantation. Following transplantation and discontinuation of lithium, Mrs B was unable to achieve mood stability with multiple medication trials and required more than 40 medical and psychiatric hospitalizations with eventual transition to skilled nursing care. After much discussion among the psychiatric treatment team, the patient, and her husband, primary care provider, nephrologist, and renal transplant surgeon, the decision was made to restart the patient on lithium given her previous treatment success. The purpose of this case report is to discuss the use of lithium following renal transplantation. In this case, a multidisciplinary approach was used to assist the patient in carefully weighing the risks and benefits of her treatment decisions. The consensus of the patient, her husband, and her providers was that the benefit of mood stabilization outweighed the potential risks of renal toxicity. Although treatment with lithium after renal transplant is not a first-line treatment option, this case illustrates that lithium could be considered in certain cases.

**Keywords:** lithium, end-stage renal disease, bipolar disorder, renal transplant

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**Disclosures:** Authors of this manuscript do not have any financial or personal relationships with commercial entities that may have direct or indirect interest in the subject matter of this manuscript.

### Background

Chronic kidney injury leading to end-stage renal disease (ESRD) is a known but rare complication of chronic lithium treatment.<sup>1</sup> End-stage renal disease requiring renal transplantation secondary to lithium treatment is even less common.<sup>2</sup> Data from available research<sup>3</sup> approximates that end-stage renal failure affects approximately

1% of patients who have taken lithium for more than 15 years. Psychiatric patients in the geriatric age group often have decreased renal functioning due to age-related changes and medications among other factors. Rej et al<sup>4</sup> found a decrease in the estimated glomerular filtration rate (eGFR) in nearly half of the geriatric psychiatric population they studied. They also found duration on lithium was independently associated with adverse renal outcome in those with impaired eGFR (<60 mL/min). Kirkham et al<sup>5</sup> demonstrated that a single exposure to a lithium level >1.0 mmol/L is associated with an increased risk of renal impairment in the first 3 months after exposure. These findings suggest that use of lithium should be given careful consideration in all geriatric patients as all will have some degree of functional decline that is likely to impact drug level and GFR.

Prevalence of ESRD in the lithium user population is estimated to be 1.5% with a relative risk of 7.8 for ESRD in



the lithium user population compared with the general population.<sup>6</sup> Presne et al<sup>7</sup> reported a 2% prevalence of lithium-induced ESRD among dialysis patients. Bendz et al<sup>1</sup> found a 6-fold increase in incidence of ESRD among lithium-treated patients compared to the general population with length of treatment as a risk factor for ESRD. Aiff et al<sup>8</sup> postulated that the risk of ESRD associated with lithium treatment reflected previous treatment/dosing standards. Stricter lithium treatment monitoring (to include individually adjusting lithium levels and frequent monitoring of renal functioning) has reduced the risk of lithium-associated ESRD. Levy<sup>9</sup> suggested that 25% to 50% of usual lithium dosage should be used in patients with ESRD with frequent monitoring of blood levels. According to the UK National Institute for Health and Clinical Excellence guidelines, as cited by Bora, the recommended monitoring of lithium levels is every 3 months, and monitoring of thyroid and kidney function is every 6 months.<sup>2,10</sup>

The literature contains only 1 case report<sup>11</sup> of a patient being treated with lithium following renal transplantation. This report focused on concerns for lithium toxicity due to comorbidities and complications of transplantation including ischemia reperfusion, toxic effects of calcineurin inhibitors, and BK virus nephropathy as well as unpredictable lithium clearance (rapid changes in graft function, diuretic use, and electrolyte imbalances). Discontinuation of lithium was recommended with transition to mood-stabilizing anticonvulsants and/or atypical antipsychotics. This illustrates the paucity of information about lithium use after renal transplant to date. It is unlikely that many providers have considered rechallenge with lithium in these medically complicated cases. Our case proposes lithium as a treatment option that may be used after renal transplantation in patients that are excellent lithium responders.

## Case Report

Mrs B is a 65-year-old, married, white woman with a long-standing history of bipolar disorder type I, who was transferred to our inpatient psychiatric hospital from a general medical hospital in May 2012. She had been treated in the emergency department for mania with psychosis as well as hypertension, hyponatremia, urinary retention with urinary tract infection (UTI), and resulting delirium. Psychosomatic medicine was consulted, and once medically stabilized, she was transferred to an inpatient psychiatric hospital.

Mrs B reported a history of mood symptoms beginning at age 12. Since that time, she noted discrete periods of mania with 4 to 5 days of elevated mood, decreased sleep, racing thoughts, pressured speech, impulsivity, spending

sprees, and reckless behavior. She also had previous major depressive episodes but endorsed more periods of mania than depressive episodes. She had multiple psychiatric hospitalizations, typically during times of mania. Her first hospitalization was at age 12, and she required multiple hospitalizations until she began treatment with lithium in her late teenage years.

Her medical history is significant for type 2 diabetes mellitus, hypertension, dyslipidemia, cataracts, history of secondary hyperparathyroidism, and history of anemia. She had a remote history of alcohol abuse but no current substance use. Family psychiatric history was notable for alcohol use disorder and mood disorders in her brother and both parents.

Mrs B's renal transplant was performed in August 2010 after several decades of lithium treatment. Her renal failure was suspected to be due to lithium nephrotoxicity in the setting of long-standing hypertension and diabetes. At the time of transplant, lithium was discontinued, and she was started on quetiapine 150 mg daily.

Between September 2010 and June 2012, she was hospitalized more than 40 times for medical and psychiatric reasons, including medication nonadherence, hypertensive crisis, and multiple episodes of mania with psychosis. The patient was admitted to multiple hospitals during this time, so not all records were available for review. Data from hospitalizations within our system are included in this report. In between hospitalizations, she required nursing home care as her husband was unable to safely care for her at home. A brief account of medication trials, including relative dates are detailed through May 2012 (Table).

Her final hospitalization was in May 2012. She was hospitalized from her nursing home for a UTI, elevated blood pressure, urinary retention, mania with psychosis, and delirium. She was treated with fluphenazine decanoate but developed QTc prolongation while medically hospitalized. She was then transitioned back to aripiprazole 15 mg twice daily. Her delirium improved after treatment of her UTI. However, she continued to demonstrate significant symptoms of agitation, violence, flight of ideas, word salad, and clang speech. She then required psychiatric hospitalization. Divalproex sodium delayed release (DR) 750 mg once daily was added without resolution of her mania. She continued to experience functional impairments not consistent with her previous baseline and was not considered safe for discharge by her husband or treatment team.

The decision to restart lithium was made in June 2012 by the primary inpatient team after discussion with the patient, husband, primary care physician, renal transplant

**TABLE:** Posttransplant summary of known hospitalizations and treatment between September 2010 and May 2012

Hospitalization	Medication Regimen	As Needed/Rescue Medications	Discontinued Medications	Medical Complications
September 2010	Quetiapine 200 mg at bedtime	Olanzapine, haloperidol, and chlorpromazine		
November 2010	Quetiapine 300 mg at bedtime + olanzapine 5 mg twice daily			
December 2010	Fluphenazine decanoate 37.5 mg monthly + quetiapine 400 mg twice daily	Fluphenazine	Olanzapine	QTc prolongation
January 2011	Aripiprazole + carbamazepine 300 mg 3 times daily	Fluphenazine	Quetiapine, fluphenazine, decanoate	
March 2011	Aripiprazole <sup>a</sup> + carbamazepine 300 mg in the morning and 900 mg in the evening	Fluphenazine		
April 2011	Aripiprazole <sup>a</sup> + carbamazepine <sup>a</sup>		Fluphenazine	UTI with urinary retention
January 2012	Aripiprazole <sup>a</sup> + carbamazepine <sup>a</sup>			Hyponatremia
February 2012	Fluphenazine decanoate 37.5 mg monthly + quetiapine 200 mg 3 times daily		Carbamazepine	Hyponatremia with delirium and vital sign instability
May 2012	Aripiprazole 15 mg twice daily + divalproex sodium DR 750 mg daily		Quetiapine, fluphenazine, decanoate	UTI with urinary retention and associated delirium, QTc prolongation

DR = delayed release; UTI = urinary tract infection.

<sup>a</sup>Medication dosages unavailable on electronic chart review.

surgeon, and nephrologist. This decision was based on the patient's previous history of long-standing mood stability with lithium and failed trials of multiple other medications as well as the patient and husband's desire to subvert nursing home placement. Lithium carbonate immediate release (IR) was started at 300 mg daily at bedtime. Within 24 hours, the patient was noted to have improvement in her symptoms. Her dose of lithium carbonate IR was later increased to 600 mg daily, and within 2 days, she had returned to her previous baseline. Prior to discharge, her serum lithium level was 1.0 mEq/L, and her serum creatinine value was 1.0 mg/dL. The discharge plan included follow-up with her primary care provider, geriatric psychiatry clinic, nephrology, and home health care. Complete blood cell count, basic metabolic panel, lithium, and valproic acid level were planned to be drawn 1 week after discharge.

In August 2012, Mrs B presented to the geriatric psychiatry clinic for hospital follow-up and intake assessment. Mrs B and her husband expressed the dramatic positive changes noticed since lithium carbonate IR was restarted, which she described as "a night and day of difference." She felt she had regained her independence in carrying out daily activities with improved clarity of thought and alertness. She progressively required less assistance, which enabled her to live at home with her

husband. At that time, she had no significant mood symptoms or psychosis. Her husband felt she was 50% back to her baseline mental status, and the patient felt she was closer to 80%.

Lithium level at that time was 1.2 mEq/L. There was some concern that this lithium level was exacerbating the cognitive impairment, which had previously developed with her ESRD. The lithium carbonate IR dose was reduced to 450 mg daily at that appointment. She was continued on divalproex sodium DR 750 mg twice daily and aripiprazole 30 mg once daily.

She was seen frequently over the next several months with ongoing continued stability of mood and denial of any symptoms consistent with psychosis or depression. However, she continued to have complaints of cognitive impairment, and lithium carbonate IR was further decreased to 300 mg daily.

Mrs B was able to reach remission of her symptoms on this medication regimen with minimal cognitive symptoms after the final lithium carbonate IR dose decrease. Her renal function continued to be carefully monitored but was stable over time on this medication regimen.

## Discussion

Lithium is one of the most effective medications used in the long-term treatment of bipolar disorder. It decreases both the frequency and severity of relapses, but it does carry the risk of renal compromise. Although renal failure leading to dialysis and transplantation is rare, a subtle decline in renal function with long-term use and increasing age is common and should be included in this informed consent discussion.

Since reinitiation of lithium carbonate IR in 2012, Mrs B has continued to demonstrate mood stability with improved cognition (initial Montreal Cognitive Assessment [MoCA] score was incomplete, followed by MoCA scores of 22/30 in February 2013 and 28/30 in March 2015) and functioning.<sup>12</sup> The outpatient team continued to monitor her lithium level every 3 months and regularly coordinated care with nephrology. Given her previous treatment success with lithium monotherapy prior to ESRD/renal transplantation, the outpatient treatment team was hopeful to simplify her medication regimen. In 2014, Mrs B began a successful dose reduction of aripiprazole 30 mg (reducing by 5 mg every 3-6 months). This dose reduction was continued until she suffered a brief period of mania requiring psychiatric hospitalization in August 2015 in the context of nonadherence to lithium, aripiprazole, and divalproex sodium DR. Mrs B resumed her previous medication regimen with resolution of mania by November 2015. She required use of zolpidem 2.5 to 5 mg at bedtime to assist with sleep immediately following hospitalization, and this was discontinued in December 2015 without difficulty. She is currently treated with lithium carbonate extended release 450 mg daily, aripiprazole 15 mg daily, and divalproex sodium DR 750 mg twice daily without ill effects. She continues close follow-up with nephrology, and they voice no acute concerns regarding lithium treatment—now 6 years post renal transplantation.

This case required multidisciplinary collaboration to provide initial as well as ongoing informed consent to the patient and her caregiver. This collaborative approach was essential to ensure continued well-being and monitoring of her health status. The *team* in her case included her family medicine doctor, nephrologist, renal transplant surgeon, and endocrinologist and the geriatric psychiatry team, which included a psychiatric clinical pharmacist. Such complex decision making and monitoring could not have been accomplished without the expertise of multiple specialties. In this particular patient, the benefits of lithium treatment were felt to outweigh the risk. This patient's euthymia was made possible by an understanding of the complexities of her medical conditions and careful surveillance by a team of care providers and supportive caregivers.

## Conclusion

This case was selected because it highlights the importance of a multidisciplinary approach and illustrates the successful use of lithium after renal transplant.

Given improvements in health care and increasing life spans, we will more commonly provide treatment to patients with severe mental illness as they enter senior adulthood. In the older population, medical comorbidities and polypharmacy complicate the picture and reiterate the importance of using a multidisciplinary approach when formulating a treatment plan. A case such as this mandates the understanding of the interplay between a patient's age-related physiologic changes, long-term risks of psychopharmacologic treatment as well as potential age-related cognitive and functional impairments, including those associated with primary psychiatric disorders. Although treatment with lithium after renal transplant is not a first-line option, this case illustrates that lithium may be considered as an option in certain scenarios.

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