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Managing bipolar affective disorder in chronic kidney disease when lithium is no longer an option

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SUMMARY

The therapeutic benefits of lithium use in bipolar affective disorder (BPAD) are well established; however, it can cause adverse side effects including chronic kidney disease and progression to end-stage renal disease (ESRD). We describe the cases of two patients with BPAD stable on lithium for many years. In both cases, kidney function declined towards ESRD, prompting cessation of lithium therapy and precipitating a period of mental instability. Concurrent lithium and haemodialysis treatment was successfully trialled in case 2. There is a dearth of guidance on managing those on lithium therapy with kidney disease progressing towards ESRD. We describe the management and outcomes of two such patients attending a community mental health team.

BACKGROUND

Lithium therapy is established as the gold-standard treatment for bipolar affective disorder (BPAD) and it is indicated in the management of acute mania and prevention of affective relapse.[1] Furthermore, lithium has been shown to decrease suicide risk in patients with BPAD.[2]

Clinical use of lithium can be problematic due to its narrow therapeutic index and concerns for its toxicity in various organ systems,[3] in particular renal function.[4] Lithium therapy is associated with nephrotoxicity including nephrogenic diabetes insipidus, chronic tubulointerstitial nephropathy, and acute tubular necrosis with risk of progression to chronic kidney disease (CKD).[5] Those who develop progressive CKD need cross-speciality input from nephrology and psychiatry services to weigh the risks and benefits of continuing lithium therapy as kidney function deteriorates. End-stage renal disease (ESRD) is the final stage of CKD where the kidneys stop functioning, and either dialysis or kidney transplant is typically required. There is a dearth of guidance on managing patients with BPAD on lithium approaching ESRD.

This case series examines the care of two patients attending a community mental health team (CMHT) with established diagnoses of BPAD type 1 who were stable for many years on maintenance lithium therapy. In both cases, kidney function deteriorated towards ESRD, prompting cessation of lithium, both subsequently suffering affective relapses of their BPAD. In case 1, alternative mood stabilisers were introduced, and increased intervention and support were required from the CMHT to achieve affective stability. In case 2, maintenance lithium therapy was reintroduced to the patient on haemodialysis to good effect with stabilisation of mental state.

CASE PRESENTATION

Case 1

This man in his 70s was diagnosed with BPAD in the 1970s and commenced on lithium following several episodes of acute mania. He was stable in mental health for decades on maintenance lithium 600 mg daily. He developed medical comorbidities including cardiovascular disease, hypertension, sleep apnoea, nephrogenic diabetes insipidus and declining kidney function. He was diagnosed with CKD stage 3B (estimate of glomerular function rate (eGFR) of 33, creatinine of 175 and urea of 9.6), prompting referral to nephrology and re-evaluation of lithium therapy. His lithium was discontinued with alternative mood stabilisers quetiapine and sodium valproate introduced.

Unfortunately, after many years of stability and symptom control, his mental state deteriorated on cessation of lithium. He developed significant health anxiety and was admitted to the acute psychiatric unit on three occasions for prolonged stays with mania and depressive relapses. Between admissions, he required intensive additional support from the CMHT to manage his symptoms including weekly reviews by a psychiatrist and intensive support from the community psychiatric nurses. Given his complex medical history, he has been advised by nephrology that his kidney function will likely continue to deteriorate and progress to ESRD irrespective of lithium discontinuation.

Case 2

This is the case of a woman in her 70s on lithium maintenance therapy for BPAD while on haemodialysis for ESRD. Similar to case 1, she experienced multiple inpatient admissions for manic episodes in her twenties and then remained stable in mental state for many years on maintenance lithium therapy. She was diagnosed with CKD stage 3B (eGFR 30, creatinine 164, urea 13.5) while maintaining lithium levels ranging from 0.84 to 0.94. She was referred to nephrology, and her lithium dose was reduced with continued decline in renal function.

Due to continued kidney function decline, lithium was discontinued with olanzapine and carbamazepine commenced as alternative mood stabilising agents. Her mental health then deteriorated, which led to a prolonged inpatient admission for manic relapse necessitating a combination of olanzapine, carbamazepine and clonazepam to stabilise her mental state. Following discharge home, her mental

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state failed to return to baseline, and she experienced significant anxiety symptoms and subjective memory impairment.

As she was approaching ESRD, she was referred for consideration of renal transplant. She was initially listed for transplantation; however, her mental state remained anxious with depressive symptoms. Following protracted assessment and support from nephrology, psychiatry, transplant services and her family, she was deemed no longer suitable, and she was delisted for transplant. Renal decline progressed, and she was commenced on haemodialysis. She continues to experience significant depressive symptoms, and following extensive collaboration with specialist services, the patient and her family, she was recommenced on lithium while concurrently receiving haemodialysis. The proposed titration and monitoring were discussed at length with the renal team prior to commencement. It was decided that the approach would include slow titration of lithium, regular monitoring of mental state and biweekly lithium levels. Lithium was initially commenced at 100 mg daily, with biweekly, predialysis lithium levels taken (as this was the frequency of the patient's dialysis). While taking 100 mg daily, her lithium levels remained within the range of 0.13–0.22. Her dose was increased to 200 mg 1 month later, remaining in a range between 0.3 and 0.45. This was finally increased to 300 mg, at which time her mental state stabilised. This allowed for the gradual withdrawal of other neuroleptics. The patient has declined referral back to the transplant team for reconsideration of renal transplant.

OUTCOME AND FOLLOW-UP

These two cases highlight the balancing act that is lithium use in BPAD with declining kidney function. In case 1, cessation of lithium was associated with deterioration in mental state, which to the present date has remained difficult to treat and poorly responsive to alternative mood stabilisers. In case 2, cessation of lithium was also associated with a deterioration in mental state that did not respond adequately to alternative agents. This highlights the superiority of lithium in maintaining remission in BPAD in both patients. In case 2, lithium was recommenced while the patient was established on haemodialysis after other agents had been unsuccessful. The reinstatement of lithium rapidly stabilised the patient's mental state, and she has since remained relapse-free. Her lithium levels have fluctuated significantly, with a range of 0.43–1.22 over a period of 2 years. Her mental state has remained stable in this period, with no clinical evidence of lithium toxicity.

DISCUSSION

Lithium has a narrow therapeutic window, and all patients prescribed it should have individualised medication dosing and frequent serum lithium levels during acute titration, with levels 1 week after each dose change and weekly until levels are stable.[6] Serum lithium concentrations and renal function monitoring should occur at a minimum of every 3–6 months in stable patients, with goal serum lithium trough concentrations between 0.6 and 1.2 mmol/L.[6] Enhanced frequency of monitoring is recommended if kidney function is declining; however, these guidelines do not advise for those approaching ESRD or on haemodialysis.

National Institute for Health and Care Excellence (NICE) guidelines for CKD state that serum creatinine and eGFR are used as markers of CKD.[7] As per these guidelines, an eGFR <60 mL/min in/1.73 m2 in an adult with no history of kidney function impairment should have the test repeated in 2 weeks. In those with a confirmed eGFR <60 mL/min in/1.73 m2, proteinuria should be assessed for with urinary albumin-creatinine ratio (ACR).

CKD is classified using a combination of ACR and eGFR categories which together indicate risk of adverse outcomes including CKD progression and cardiovascular disease. A renal ultrasound is indicated if eGFR <30 mL/min in/1.73 m2. It is essential to address other risk factors which may contribute to the progression of CKD including lifestyle factors (NSAID use, smoking) and comorbidities (hypertension, diabetes). Referral to a specialist service is indicated if there is accelerated CKD progression, defined as a sustained decrease in eGFR of 25% or more and a change in eGFR category within 12 months or a sustained decrease in eGFR of 15 mL/min/1.73 m2 or more per year. It is reasonable to discuss management with a renal specialist if there are concerns around CKD prior to formal referral. In those with progressive CKD, there is no strict cut-off point in eGFR when lithium should be discontinued. The risk of declining kidney function and progression to dialysis must be balanced with the therapeutic benefits of lithium.

Should a decision to continue lithium and 'watch and wait' be made, a shared care plan between nephrology, psychiatry, the patient, their carer and their General Practitioner is useful in guiding management. A decision to stop lithium can be made following discussion with relevant parties and consideration for the physical health risks vs the risk of major relapse. Factors which may affect this decision include the rate of deterioration in renal function, other physical health comorbidities, the patient's previous response to alternative agents, and the patient's typical course of illness.[8]

There are many alternative agents to lithium, which can be considered for the treatment of acute relapse or maintenance. These include anticonvulsants and antipsychotic medications.[9] Sodium valproate was commonly used, either as an alternative to, or in conjunction with lithium for many years.[10] However, the use of valproate has fallen significantly in recent years due to international guidelines, introduced to mitigate the risk of teratogenic effects.[11] Carbamazepine can be considered an alternative to lithium for management of mania but is considered second line due to tolerability.[12] In terms of atypical antipsychotics, risperidone, haloperidol and olanzapine are highly efficacious alternatives as monotherapy. Benzodiazepines are often used to manage acute episodes and may be used as polytherapy for maintenance, but longer-term use carries significant risk of dependence.[13] While monotherapy is associated with improved tolerability and compliance, polytherapy has been shown to be more efficacious.[8]

When a patient's renal function deteriorates to the point of requiring dialysis, dialysis effectively eliminates lithium and can be an effective pharmacotherapy in lithium toxicity. There is a dearth of guidelines on prescribing lithium to patients on haemodialysis. Multiple case reports, however, have demonstrated the efficacy and safety of prescribing lithium in this cohort.[14–17] There are challenges to prescribing lithium in haemodialysis, including variability of dosing, lack of consensus for therapeutic drug monitoring and the potential for rebound in lithium concentrations post-dialysis.[18] In one review of 15 case reports of patients receiving lithium while on dialysis, there was no uniform lithium dosing procedure in dialysis identified.[19] These patients generally had lower than recommended lithium serum level concentrations. However, standard target trough concentrations have been described.[18]

In those concurrently receiving lithium and haemodialysis, the frequency of lithium concentration monitoring has been suggested to be performed daily during the first 2 weeks of

treatment and reduced to thrice weekly pre-dialysis after three consecutive concentrations have been stable on the same dose. Following this period, monitoring frequency may be extended to everyone to 3 months, as clinically indicated.

With longevity of use, the clinical risks and benefits of lithium are clearly described. Adverse effects including impact on glomerular function and end-stage renal disease are considerations for the psychiatrist when commencing lithium in a younger patient. Clarity of diagnosis where there is a risk of suicide and recurrence of an acute manic or depressive episode must be confirmed before lithium is commenced. Ceasing lithium therapy as renal function declines and cross-titrating to other mood stabilisers is an option. In both of our cases, alternative mood stabilisers were appropriately trialled when CKD stage 3b was reached but were not sufficient to maintain stability of mental state.

The mortality gap between individuals with BPAD and the general population is widening. Psychiatrists should take a proactive approach to physical health monitoring with intervention when abnormalities are detected.

This case series highlights the challenges of managing BPAD in those with lithium-induced kidney disease approaching ESRD. Collaboration between specialties is essential in managing these patients. Recommencing lithium in haemodialysis with careful monitoring of lithium levels and dosing regimens in coordination with the patient's haemodialysis schedule was a successful option in case 2. With advances in medical management and life expectancy in ESRD, this clinical scenario will likely become more prevalent. Regular monitoring of laboratory parameters including creatinine and eGFR is essential, as is personal follow-up. Further research in this area, including clear guidance on prescribing lithium in haemodialysis, would be valuable to clinicians and patients.

Learning points

- Lithium is a highly effective mood stabiliser in bipolar affective disorder; however, damage to organ systems including the kidneys is a recognised risk of treatment.
- All patients on lithium must have close monitoring of physical health including renal function with intervention and onward referral to nephrology if indicated.
- There is no clear cut-off in renal function when lithium should be discontinued. Seek specialist nephrology input early if kidney function is declining and involve the patient in treatment decisions. Alternative mood stabilisers may be trialled.
- In those with end-stage renal disease on haemodialysis with refractory affective symptoms, lithium may be a therapeutic option. Pre-dialysis lithium serum concentrations can be measured with a serum lithium target lower than the conventional range.

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