Management of the renal adverse effects of lithium: an audit cycle

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Lithium is a standard first-line treatment for bipolar disorder and one of the recommended augmenting agents for treatment-resistant depression. However, concerns remain about the long-term organ toxicity of this drug, mainly renal adverse effects. Here, Dr Gupta and colleagues discuss their local audit of administering lithium in CKD patients and how the results were used to inform trust policy and improve clinical practice.

Since the early 2000s, research evidence has increasingly suggested the superiority of lithium over other mood stabilising drugs but renal adverse effects have been known since the 1970s. Tubular adverse effects (presenting as polyuria and polydipsia) are the most common adverse effects, usually identified by patient complaints. In contrast, glomerular adverse effects (presenting as chronic kidney disease (CKD) or renal failure) are less common and identified by blood tests. For several decades, regular monitoring of renal function by blood testing for the early identification and management of such adverse effects has been the norm.

Over the years, the regular monitoring of renal function by mental health services has improved, as evidenced by Prescribing Observatory of Mental Health (POMH) audits. However, concerns continued to be raised about poor identification and management of these adverse effects. Possible reasons are a lack of:

i. guidance for clinicians (especially in the psychiatric literature)

ii. research evidence, and

iii. clinical emphasis on adverse effects.

On a positive note, these adverse effects have been increasingly recognised in psychiatric guidelines and medical literature over the past few years. A gradual deterioration in renal function, as measured by either serum creatinine levels or the estimated glomerular filtration rate (eGFR), is seen in up to 20% of patients exposed to lithium. Furthermore, a few patients can develop renal failure or end stage renal disease. For these patients, the risk is not restricted to progression to renal failure: CKD patients are also more likely to suffer from cardiovascular disorders. Clinicians have the responsibility to manage the condition, as well as to discuss the risks and benefits of lithium continuation or discontinuation with patients, help them to make informed decisions.

To address the issue of how to safely continue administering lithium therapy in CKD patients, we searched the available evidence and discovered a dearth of guidance for psychiatrists on how to monitor renal function and when to intervene. Moreover, practice varied significantly among psychiatrists. Therefore, we audited the current prevailing practices and compared these with the available standards from relevant guidelines.

Table 1. Compliance with audit standards in the initial audit and re-audit

<table>
<thead>
<tr>
<th>No.</th>
<th>Audit standard</th>
<th>Audit 1</th>
<th>Audit 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Did the patient have renal function testing at least every six months during the audit period?</td>
<td>87.7% (575/656)</td>
<td>98.5% (637/647)</td>
</tr>
<tr>
<td>2</td>
<td>Did the patient have CKD?</td>
<td>10.8% (71/656)</td>
<td>10.0% (65/647)</td>
</tr>
<tr>
<td>3</td>
<td>If the patient had CKD, was s/he informed?</td>
<td>40.8% (29/71)</td>
<td>72.3% (47/65)</td>
</tr>
<tr>
<td>4</td>
<td>If the patient had CKD, was there evidence that the risks and benefits of lithium continuation/discontinuation had been assessed and discussed with the patient?</td>
<td>26.7% (19/71)</td>
<td>61.5% (40/65)</td>
</tr>
<tr>
<td>5</td>
<td>If the patient had CKD, was there evidence that additional tests (for proteinuria) were done?</td>
<td>18.3% (13/71)</td>
<td>32.3% (21/65)</td>
</tr>
<tr>
<td>6</td>
<td>If the patient had CKD, was there evidence of enhanced monitoring of renal function?</td>
<td>21.1% (15/71)</td>
<td>47.6% (31/65)</td>
</tr>
<tr>
<td>7</td>
<td>If the patient had CKD, was there evidence that the dosage of lithium was reduced?</td>
<td>21.1% (15/71)</td>
<td>48% (31/65)</td>
</tr>
<tr>
<td>8</td>
<td>Did the patient have CKD stage IV?</td>
<td>0.3% (2/656)</td>
<td>0.3% (1/1)</td>
</tr>
<tr>
<td>9</td>
<td>If the patient had CKD, have they been referred to nephrology?</td>
<td>0% (0/2)</td>
<td>100% (1/1)</td>
</tr>
</tbody>
</table>
Methods
The initial audit was undertaken in August 2013. Patients on lithium therapy were identified from a lithium register, containing records of blood test results for all patients on lithium therapy in secondary mental health services. The lithium register is maintained by the Tees, Esk and Wear Valleys NHS Foundation Trust’s pharmacy team. The audit focussed on patients receiving treatment from the adult community mental health team (656 patients).

The audit standards were developed from NICE guidelines on bipolar disorder and CKD, along with a published guideline,\(^1^,\(^5^,\(^7\) and were focussed on:
- whether patients receiving lithium therapy had regular blood tests
- whether, for patients who developed CKD (eGFR of less than 60mL/min for three consecutive months), the clinician informed them about CKD, discussed the risks and benefits of continuation/discontinuation of lithium therapy, and
- how CKD was managed.

In the initial audit, patients who fulfilled the criteria for having CKD were identified from the lithium register. We subsequently reviewed their medical records to find out how their CKD had been managed. Data were collected using a standardised audit tool. The audit report was submitted to the trust and discussed by the trust’s drug and therapeutic committee. Based on the audit’s recommendations, the trust’s policy on lithium therapy was amended to reflect good clinical practice and the audit report was disseminated to all clinicians.

The re-audit was undertaken in October 2016. Although NICE guidelines for CKD were revised in 2014 and the terminology used to describe CKD had been changed, we used the same terminology as in the first audit to ensure consistency and comparability.\(^4\) The first audit included patients who had discontinued lithium therapy between January 2011 and August 2013. Data were also included on patients receiving adult services, mental health services for older people, learning disability services and forensic mental health services. We reviewed the patients’ medical notes to identify the reason(s) for lithium discontinuation. Additionally, we also recorded the management of CKD, if this was the reason for the discontinuation.

Results
The initial audit identified 656 patients receiving lithium therapy. Of these, 575 patients (87.6%) had undergone renal function monitoring at least every six months during the audit period. A total of 71 patients (10.8%) fulfilled the diagnostic criteria for CKD. Of these, only 29 patients (40.8%) had been informed about CKD and only 19 (26.7%) had discussed the risks and benefits of lithium continuation/discontinuation with clinicians. In 23 patients (32.3%), renal function was monitored more frequently, while 13 patients (18.3%) had been tested for proteinuria. In 15 patients (21.1%), the lithium dosage of was reduced. Two patients (2.8%) suffered from CKD stage IV but had not been referred to nephrology.

We also found significant variability among different community mental health teams. For example, of the 14 community mental health teams, only four teams (28.5%) had performed additional proteinuria tests. Similarly, in one team most patients with CKD were advised to stop lithium therapy. The medical notes showed that a few clinicians did not interpret abnormal blood results, especially eGFR, appropriately. For example, on a few occasions one low value was given undue significance or one clinician preferred serum creatinine level over eGFR.

Between 2011 and 2013, 284 patients stopped lithium therapy for various reasons, including 15.1% (43/284) owing to renal impairment. In addition, only 32.5% of patient records (14/43) contained evidence of a risk–benefit analysis. A significant proportion of patients (13/43; 26.2%) relapsed and a few of these needed inpatient treatment. The medical records of only a small proportion (4/43; 9.3%) showed follow-up monitoring of renal function. The re-audit found some improvement. Almost all patients had six-monthly blood tests for renal function (98% vs 88%). Although a similar proportion of patients suffered from CKD, significantly more of these were identified and managed appropriately (Table 1). However, these improvements related to only a few community mental health teams and clinicians.

Discussion
Both audits found that about 10% of patients suffered from CKD, mainly stage III. As expected, CKD IV was not very common, as lithium is usually discontinued before progression to this stage. The reason for the slightly low CKD prevalence may be that we did not include those patients receiving mental health services for older people.

Renal adverse effects of lithium therapy are common, but progression to renal failure is not common. Despite this, early recognition of CKD is very important. Firstly, we need to ensure that lithium therapy can be continued safely. Some evidence indicates that impaired renal function might be associated with high serum levels of lithium and lithium toxicity, caused by reduced elimination of lithium. Secondly, and most importantly, CKD patients are more likely to develop cardiovascular disorders, which can lead to higher mortality rates.

Recent years have seen growing evidence that lithium discontinuation might not reverse renal impairment.\(^2\) In...
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addition, significant research evidence shows that discontinuation is associated with a high risk of relapse and can make bipolar disorder more refractory to treatment. Therefore, some authors suggest that risk–benefit analysis would favour continuation of lithium therapy for most patients. As lithium remains the first-line treatment for bipolar disorder and a standard augmenting agent for treatment-resistant depression, lithium therapy is here to stay. We must ensure it is used safely and effectively. Over the years, POMH audits on lithium have confirmed that most patients have regular blood tests for renal function monitoring. However, these audits did not focus on the actions taken by professionals in response to abnormal blood results. Recent years have seen increased research, with an emphasis on managing the adverse effects of lithium, including the renal adverse effects. However, clinical guidelines have not given due emphasis to managing these adverse effects.

There is currently a lack of evidence on whether impaired renal function is reversible or irreversible. If lithium therapy is discontinued, follow-up monitoring to assess the impact of lithium discontinuation is expected, to assess the impact of the intervention. However, the first audit found that only a small proportion of patient records (four; <10%) showed follow-up monitoring of renal function.

CKD diagnosis and management has improved significantly in the past few decades. Increased use of eGFR testing and routine proteinuria monitoring have improved the management of CKD in primary care and by nephrologists. However, there is still a lack of awareness of these tests amongst psychiatrists. In a recent survey of patients who had developed renal failure due to lithium therapy, patients reported they were not given enough information about the renal adverse effects of lithium and that they were not adequately involved in the decision making. Clearly, monitoring of the renal adverse effects of lithium and involving patients in shared decision making is unsatisfactory at present. CKD is a common function and, with increased life expectancy, secondary mental health teams are likely to see more patients with CKD. Hence, psychiatrists are expected to make efforts to become familiar with the basic principles of interpreting eGFR/proteinuria tests and CKD management.

These audits had the benefit of including all patients receiving care from adult mental health teams. In this audit, we focussed on the glomerular adverse effects of lithium therapy. The renal adverse effects of lithium are an under-researched area. We need more longitudinal studies to find out the prevalence and predictors of these adverse effects and, most importantly, to discover the renal and psychiatric consequences of lithium continuation/discontinuation for patients.

Conclusion
Recent improvements in physical health monitoring by mental health services include blood tests for monitoring renal functions in patients on lithium therapy. However, we still need to improve the way we deal with abnormal blood results. Audits are an effective way to ensure continuous improvement of services. Our re-audit found improvements in the identification and management of renal adverse effects of lithium, but these were restricted to a few teams/clinicians. Regular audits and feedback to clinicians are therefore needed to expand and sustain these improved practices. Therefore, we have disseminated the audit findings to clinicians and will endeavour to conduct another audit in the future. Similarly, we recommend the inclusion of audit standards on management of renal adverse effects in future POMH audits on lithium.

Declaration of interest
No conflicts of interest were declared.

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References