Is lithium monitoring NICE?: Lithium monitoring in a UK secondary care setting

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Abstract

**Background:** Lithium is widely used for the treatment of bipolar disorder. Due to its narrow therapeutic index and side-effect profile, regular monitoring of serum levels, renal and thyroid function has been recommended by all major guidelines on lithium use. **Objectives:** We investigated whether lithium monitoring during maintenance phase treatment in clinical practice meets the latest recommendation by the National Institute for Health and Clinical excellence (i.e. lithium levels between 0.6-1.0mmol/l and lithium level, thyroid and renal function tests every six months; NICE, 2014) in one of the largest mental health organisations in Europe, the South London and Maudsley (SLaM) NHS Foundation Trust. **Methods:** Retrospective data were extracted from SLaM’s Clinical Record Interactive Search (CRIS) system. Adult patients with a psychiatric disorder who were on lithium at any point during the period January 2012-January 2016 and had at least one lithium level test result in the system were included in the analyses. **Results:** 2639 lithium level tests results were retrieved for 412 patients. Overall, serum level was within the recommended range in 50.7% of all tests, below the range in 42.4% and above in 6.9%. Lithium level, renal and thyroid function tests were performed at the recommended frequency of 6 months (or less) in 76.2%, 72.7% and 60.2% of patients, respectively. **Conclusion:** These data demonstrate that there is a gap between the NICE 2014 recommendation and lithium monitoring practice in secondary care, with a high number of lithium level results below the therapeutic minimum. Reminder strategies for secondary care practitioners, shared care agreements or a central registry for lithium users could improve monitoring performance.

**Keywords**

lithium, bipolar disorder, affective disorder, monitoring
Background

Lithium has been widely used in clinical practice as a mood stabiliser after John Cade first observed its therapeutic effects for manic episodes (Cade, 1949). Since then, lithium has been licensed for the acute treatment of mania, for maintenance treatment in bipolar disorder and as augmentation to antidepressants for treatment resistant depression. There is ample evidence for its efficacy, tolerability and cost-effectiveness for all these indications (Storosum et al., 2007; Crossley and Bauer, 2007; Miura et al., 2014). All major international and UK treatment guidelines support the use of lithium for these indications. In the context of bipolar disorder, lithium is considered the most effective treatment to date (Malhi and Outhred, 2016). In addition, large recent studies have shown that bipolar disorder patients taking lithium have a significantly reduced rate of self-harm and suicide-related events compared to patients on other treatments or no treatment (Hayes et al., 2016b; Song et al., 2017).

Lithium has a narrow therapeutic index as serum levels below 0.4 mmol/l have no therapeutic benefit, levels ranging between 0.4-1.2 mmol/l are considered therapeutic (depending on the patient group), and toxicity can occur at 1.5 mmol/l. Table 1 summarizes the recommendations put forward by the major international guidelines regarding optimal and toxic serum lithium levels. Of particular relevance to the UK are the National Institute for Health and Clinical excellence (NICE) and British
association for Psychopharmacology (BAP) guidelines for bipolar disorder, most recently updated in 2014 (NICE, 2014a) and 2016 (Goodwin et al., 2016), respectively. NICE recommends the optimal level for first use as an acute treatment to be between 0.6-0.8 mmol/l, for the acute treatment of relapse between 0.8-1.0 mmol/l and for maintenance treatment 0.6-0.8 mmol/l, with toxicity level unspecified. The BAP 2016 guideline recommends the same range for maintenance treatment as NICE (2014), with the optimal dose considered “the highest tolerated without significant adverse reactions”, and a higher recommended range for acute treatment of 1.0-1.5 mmol/l, advised only for “unusual circumstances where alternative treatments have failed” (Goodwin et al., 2016). In BAP 2016 guideline for bipolar disorder toxic effects are considered to occur above 1.5 mmol/l, with life-threatening toxicity at 2.0 mmol/l and above. Toxicity side-effects may present to multiple systems including gastrointestinal, renal, endocrine, cardiac and neuropsychiatric (Stahl, 2013). At high levels lithium may precipitate seizure, coma and death (Meyer and Quenzer, 2013). Nevertheless, recent data from various countries have shown that mortality rates from lithium intoxication are low: between 0-1% (Baird-Gunning et al., 2016; Mowry et al., 2013), with reports from the UK indicating 0% (Waring et al., 2007).

Of particular concern with lithium toxicity or long-term lithium therapy (even if the levels are within the recommended range) are the potential adverse effects to the
kidney and thyroid. As lithium is almost entirely excreted in urine, conditions that influence kidney function or fluid balance can increase lithium accumulation (Paton et al., 2010). Lithium toxicity can affect glomerular and tubular renal function, induce nephrogenic diabetes insipidus and, in most severe cases, cause end-stage renal failure. The absolute risk of renal failure, however, has been calculated to be low at approximately 0.5% (McKnight et al., 2012). In the case of thyroid dysfunction, lithium accumulates in thyroid glands and inhibits the release of thyroid hormones, hence it can cause goitre, hypothyroidism and hyperthyroidism (Kraszewska et al., 2014; Hayes et al., 2016a). A meta-analysis by McKnight et al. (2012) reported that the rate of hypothyroidism is increased almost six-fold in patients receiving lithium therapy compared to the general population. In addition, the risk of developing renal and thyroid side-effects from lithium is increased in patients who: (i) have comorbid conditions that affect these systems (Baird-Gunning et al., 2016); (ii) have a genetic predisposition (Gitlin, 2016); (iii) are taking drugs that interact with lithium (Joint Formulary, 2015); and (iv) are older than 50 years (Baird-Gunning et al., 2016). Therefore, testing of renal and thyroid function before the initiation of lithium treatment and regular monitoring thereafter, especially in groups at a high risk of toxicity, is warranted.
<table>
<thead>
<tr>
<th>Guideline</th>
<th>Year</th>
<th>Phase</th>
<th>Lithium range (mmol/l)</th>
<th>Toxic level (mmol/l)</th>
<th>Frequency of monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lithium level</td>
</tr>
<tr>
<td>BAP</td>
<td>2016</td>
<td>Acute</td>
<td>1.0-1.5</td>
<td>1.5</td>
<td>5 days after titration, then every 3 months in the first year and then every 6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maintenance</td>
<td>0.6-0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7 days after dose change and every 6 months</td>
</tr>
<tr>
<td>CANMAT</td>
<td>2013</td>
<td>Acute</td>
<td>0.8-1.1</td>
<td>not specified</td>
<td>5 days after titration until 2 consecutive levels are stable then every 3-6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maintenance</td>
<td>0.8-1.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maudsley</td>
<td>2015</td>
<td>Acute</td>
<td>1.0-1.2</td>
<td>1.5</td>
<td>7 days after dose change and every 6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maintenance</td>
<td>0.6-1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NICE</td>
<td>2014</td>
<td>Acute (first use)</td>
<td>0.6-0.8</td>
<td>not specified</td>
<td>7 days after dose change then weekly until stable; then every 3 months in the first year and every 6 months thereafter</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acute (relapse)</td>
<td>0.8-1.0</td>
<td>not specified</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maintenance</td>
<td>0.6-0.8</td>
<td>not specified</td>
<td></td>
</tr>
<tr>
<td>RANZCP</td>
<td>2015</td>
<td>Acute</td>
<td>0.8-1.2</td>
<td>not specified</td>
<td>At baseline; every 6 months in the first year and then every 12 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maintenance</td>
<td>0.6-0.8</td>
<td>not specified</td>
<td></td>
</tr>
<tr>
<td>WFSBP</td>
<td>2013</td>
<td>Acute mania</td>
<td>0.8-1.3</td>
<td>not specified</td>
<td>Frequently until stable, then every 3-6 months</td>
</tr>
<tr>
<td></td>
<td>2009</td>
<td>Maintenance</td>
<td>0.6-1.2</td>
<td>not specified</td>
<td></td>
</tr>
</tbody>
</table>

BAP: British Association for Psychopharmacology; CANMAT: Canadian Network for Mood and Anxiety Treatment; Maudsley: The Maudsley Prescribing Guidelines in Psychiatry; NICE: UK National Institute for Health and Care Excellence; RANZCP: Royal Australian and New Zealand College of Psychiatrists; WFSBP: The World Federation of Societies of Biological Psychiatry.
All major guidelines have included a recommendation on how frequently these tests need to be performed and the recommended interval varies significantly (Table 1). For example, NICE (2014) recommends performing tests for urea and electrolytes, including calcium, eGFR and TSH at baseline and then every 6 months (NICE, 2014a), while BAP recommends similar tests to be performed once every 12 months (Goodwin et al., 2016). A detailed discussion of the recommendations from (and discrepancies between) all major international guidelines was recently published by Malhi et al. (2017). In the UK, the NICE guidelines are considered to be the ‘golden standard’ as they are based on the highest-quality evidence and are strongly supported by government policy (Samanta and Gunn, 2003). Therefore, NICE 2014 will be used as the reference standard for this study.

Recently, a systematic review was published identifying 7 audits of lithium monitoring in the UK and 1 audit in Ireland dating between 1992 and 2013 (Aubry et al., 2017). This review concluded that while lithium monitoring has improved through the years, gaps remain between standard recommendation and clinical practice. The largest attempt to date to improve lithium monitoring nationally was the Quality Improvement Programme (QIP) launched by the Prescribing Observatory for Mental Health (POMH) in response to the results of an audit conducted in 2008 (Paton et al., 2010) and alerts by the National
Patient Safety Agency (NPSA). Two audits (in 2010 and 2011) were performed to assess the programme’s impact, which showed that monitoring of lithium, renal and thyroid function had indeed improved since the baseline audit, however, significant gaps still remained between recommendation (NICE 2006 at the time) and clinical practice (Paton et al., 2013). Further, the co-prescription of drugs that interact with lithium had remained common (Paton et al., 2013). The audits performed to date have had varied limitations ranging from small sample sizes (Butler and Taylor, 2000; Glover and Lawley, 2005), sample selection bias (Paton et al., 2013) and failure to identify the guidelines which were used as a reference standard or the use only of local guidelines (Glover and Lawley, 2005; Kehoe and Mander, 1992; Udumaga and Mannion, 2010; Eagles et al., 2000).

The reasons for poor monitoring suggested by the audits performed so far include: (i) patient factors, including inadequate information given to patients regarding the importance of monitoring (Collins et al., 2010; Gerrett et al., 2010); (ii) clinician factors, including varying willingness to accept guidelines (McKean and Vella-Brincat, 2012; Paterniti and Bisserbe, 2013; Perlis, 2007; Samalin et al., 2011); (iii) procedural factors, including lack of systems to generate reminders and poor communication between primary and secondary care (Aubry et al., 2017; Gerrett et al., 2010); and (iv) the nature
of the disease itself, as it has been shown that a third of patients with bipolar disorder miss at least 30% of prescribed doses (Sajatovic et al., 2006).

The aims of this study were to determine whether routine lithium monitoring practice during maintenance phase treatment in one of the largest mental healthcare organisations in Europe - the South London and Maudsley (SLaM) NHS Trust (Jackson et al., 2017), reaches the standard set by the most recent NICE guideline (NICE, 2014a). The study benchmarks were as follows:

1. Serum lithium level should be between 0.6-1.0 mmol/l;
2. Serum lithium level needs to be measured every 6 months;
3. Renal function and thyroid function tests should be performed every 6 months;
4. Monitoring of lithium levels should be performed every 3 months for patients at an increased risk of toxicity.

Methods

The dataset
The Clinical Record Interactive Search system (CRIS) is a large, reliable and constantly updated research database established in 2008 that extracts information from the SLaM NHS Trust electronic clinical records system (NIHR-BRC, 2015). SLaM is among Europe’s largest mental health trusts, providing care for over 1.2 million people locally, in addition to national specialist services. According to recent estimates, the database contains the clinical records of more than 250,000 patients and over 3.5 million documents (Jackson et al., 2017) with identifiable information removed (e.g. names, address, NHS number; DOB restricted to month and year, etc.). Additionally, pathological laboratory results have been incorporated into CRIS since January 2012 from the largest hospital in the Trust (King’s College Hospital), with the aim to expand the integration to all laboratories in the area. A detailed description of the database has previously been published elsewhere (Stewart et al., 2009; Perera et al., 2016). Lithium monitoring practice has not been investigated in this area since this system was established.

**The sample**

Patients registered with the SLaM NHS Trust were selected for analysis if they met the following criteria: (i) aged 18 and above; (ii) had a mental disorder diagnosis (defined by
ICD-10 codes); (iii) were registered in the Trust and taking lithium anytime between January 2012 and January 2016; (iv) stayed in the service for at least 6 months; and (v) had at least one lithium level test during the observation period. The requirement for at least one test result in the system was necessary to indicate that monitoring was performed in this service. Patients fulfilling the above criteria were included regardless of whether they were inpatients, outpatients or both during the observed period.

Patient consent was not required for this study. Approval was obtained from the CRIS Oversight Committee and the Mood, Anxiety and Personality Disorder Clinical Academic Groups (MAP-CAG) of SLaM NHS Trust.

Data extraction and preparation

The following data were extracted for patients who met the selection criteria: age, gender, primary psychiatric diagnosis, chronic comorbid medical diagnoses, co-prescribed medications that interact with lithium as specified by the Joint Formulary Committee (i.e. ACE inhibitors, angiotensin II receptor antagonists, calcium channel blockers, carbamazepine, COX II inhibitors, SSRIs, loop diuretics, methyldopa, metronidazole, NSAIDs, potassium sparing, thiazide, topiramate, acetazolamide, aminophylline, sodium
bicarbonate and theophylline) (Joint Formulary, 2015), serum lithium test results, renal function and thyroid function test results. Diagnoses and medications data were extracted from both free text and fixed fields. Extraction from free text was done with the use of natural language processing applications that can recognise a diagnostic statement (not speculation over a diagnosis) and a diagnosis that is related to the patient only (not a friend/family member etc.). These applications have been previously described elsewhere and have demonstrated specificity and sensitivity (Perera et al., 2016). Lab test data were extracted from fixed fields only as these are automatically populated into CRIS from the lab’s record since 2012.

As it could not be estimated what phase of treatment bipolar patients were in (i.e. under which NICE recommendation category they fall under), for the purposes of this study a serum level between 0.6-1.0 mmol/l and a measurement taken every 6 months (within a ± 31 day window) was considered as in keeping with NICE 2014 guidelines. For the subgroups of patients at increased risk of toxicity, a test performed every 3 months (± 31 days) was considered as in keeping with NICE 2014 guidelines. Similarly to a previous audit conducted by Collins et al. (2010), multiple test that were conducted within 31 days of each other were counted as a single test and their values were removed from the
lithium level test result analysis, as these were considered to be performed for a purpose outside of routine maintenance monitoring. Additionally, these could have been performed as part of treatment initiation, which is not the focus of this study.

As data on end date of treatment cannot be reliably extracted from CRIS, for the purposes of these analyses we calculated the exposure period to lithium for each patient as ‘the time from the date of first lab test to the date of last lab test’ recorded in the system. This way we could most reliably estimate whether patients were monitored according to the schedule recommended by NICE, while they were monitored in SLaM NHS Trust.

Statistical analyses

Descriptive statistics were used to describe the sample and determine performance against the survey benchmarks in terms of serum lithium level and frequency of lithium, thyroid function and renal function testing. Regression analyses were performed to investigate whether co-prescription, age and comorbidity were associated with monitoring performance. All analyses were completed using statistical software (SPSS, version 23; IBM Corp, Armonk, NY, USA).
Results

A total of 412 patients who fulfilled the inclusion criteria were retrieved from CRIS. The mean age of the sample was 40 years, 210 (51%) were female, 279 (67.7%) had a primary diagnosis of (any) bipolar disorder, 129 (31.3%) had an additional chronic comorbidity and 251 (60.9%) were co-prescribed a medication interacting with lithium (Table 2). Of these, 289 patients only had one serum lithium test result recorded in the system. Consequently, these patients could only be included in the lithium level analyses and had to be excluded from the frequency of testing analyses. Frequency of lithium level, renal and thyroid function testing analyses were performed with the remaining sub-sample (n=123). The demographic characteristics of this sub-sample are also summarised in Table 2.

### Table 2: Demographic characteristics of the sample

<table>
<thead>
<tr>
<th>Key characteristics</th>
<th>Full sample (n=412)</th>
<th>Sub-sample* (n=123)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender Female (%)</td>
<td>210 (51)</td>
<td>59 (48)</td>
</tr>
<tr>
<td>Age Mean age in years (SD)</td>
<td>40.1 (14.4)</td>
<td>41.1 (14.3)</td>
</tr>
<tr>
<td>Median age, years (IQR)</td>
<td>37 (18)</td>
<td>38 (17)</td>
</tr>
<tr>
<td>Age range in years</td>
<td>18 - 89</td>
<td>18 - 84</td>
</tr>
<tr>
<td>Elderly (&gt;65 years) (%)</td>
<td>32 (7.7)</td>
<td>10 (8.1)</td>
</tr>
<tr>
<td>Ethnicity Asian (%)</td>
<td>29 (7.0)</td>
<td>12 (8.1)</td>
</tr>
<tr>
<td>Black (%)</td>
<td>105 (25.5)</td>
<td>31 (25.2)</td>
</tr>
<tr>
<td>-----------</td>
<td>------------</td>
<td>-----------</td>
</tr>
<tr>
<td>White (%)</td>
<td>241 (58.5)</td>
<td>69 (56.1)</td>
</tr>
<tr>
<td>Mixed or other (%)</td>
<td>37 (9.0)</td>
<td>13 (10.6)</td>
</tr>
<tr>
<td><strong>Primary Diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar disorder (%)</td>
<td>279 (67.7)</td>
<td>83 (67.5)</td>
</tr>
<tr>
<td>Other (%)</td>
<td>128 (31.1)</td>
<td>40 (32.5)</td>
</tr>
<tr>
<td><strong>Chronic comorbidity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any (%)</td>
<td>129 (31.3)</td>
<td>45 (36.6)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>30 (7.3)</td>
<td>8 (6.5)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>28 (6.8)</td>
<td>9 (7.3)</td>
</tr>
<tr>
<td>Thyroid disorder (%)</td>
<td>20 (4.9)</td>
<td>7 (5.7)</td>
</tr>
<tr>
<td><strong>On medication interacting with lithium</strong>** (%)</td>
<td>251 (60.9)</td>
<td>74 (60.2)</td>
</tr>
</tbody>
</table>

*with >1 lithium level test result; ** any specified in British National Formulary (BNF) (Joint Formulary, 2015)

**Serum lithium level**

For the 412 patients there were 2639 serum lithium level tests. Of these, there were 1337 (50.7%) within the therapeutic range of 0.6-1.0 mmol/l, 1119 (42.4%) below the range and 183 (6.9%) above the range. Numerical serum level result was present in the system for 2615 of these tests (see Figure 1 for distribution). The mean lithium level was $M=0.65$ ($SD=0.26$) and the range was between 0.04-2.01mmol/l. There were 324 (78.6%) patients who had a sub-optimal lithium level at least once and 73 (17.7%) patients who had at least one lithium level above the recommended range. Among those 73 patients, 58.9% were co-prescribed at least one medication interacting with lithium and 34.2% had at
least one chronic comorbidity (these rates are similar to those in Table 1). Only 0.5% of results (n=13, attributable to 10 patients) were above the toxicity cut-off of 1.5mmol/l.

[insert Figure 1.] *Figure 1. Distribution of lithium level test results (n=2615).*

**Frequency of serum lithium level tests and renal and thyroid function tests**

For those patients who had >1 test result in the database (n=123), the recommendation of at least one test every 6 months was met for 76.2% of cases for lithium level, 72.7% of cases for renal function and 60.2% of cases for thyroid function (Columns 1 & 2, Table 3). Among these patients, there were 85 patients that met NICE 2014 criteria for increased risk of toxicity (i.e. were elderly, had a chronic comorbidity and/or were co-prescribed at least one medication with a BNF-specified interaction with lithium) and have a recommended testing frequency for lithium levels of 3 months. The testing rates for this sub-group are presented in Table 3. Regression analyses were performed to investigate whether the risk factors co-prescription, age and comorbidity (diabetes, hypertension, thyroid disorders) were associated with monitoring performance. These were non-significant (P>0.05).
Table 3: Number of patients tested at each of the specified frequencies.

<table>
<thead>
<tr>
<th>Test</th>
<th>Frequency of testing</th>
<th>1-4 months</th>
<th>5-7 months</th>
<th>&gt; 7 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium level</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td>67 (54.9%)</td>
<td>26 (21.3%)</td>
<td>29 (23.8%)</td>
</tr>
<tr>
<td>&gt;65 years (n=10)</td>
<td></td>
<td>5 (50.0%)</td>
<td>3 (30.0%)</td>
<td>2 (20.0%)</td>
</tr>
<tr>
<td>On interacting drug* (n=74)</td>
<td></td>
<td>42 (56.8%)</td>
<td>20 (27.0%)</td>
<td>12 (16.2%)</td>
</tr>
<tr>
<td>With chronic comorbidity**</td>
<td>(n=23)</td>
<td>11 (47.8%)</td>
<td>5 (21.7%)</td>
<td>7 (30.4%)</td>
</tr>
<tr>
<td>Renal function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td>76 (62.8%)</td>
<td>12 (9.9%)</td>
<td>33 (27.3%)</td>
</tr>
<tr>
<td>Thyroid function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td>52 (42.3%)</td>
<td>22 (17.9%)</td>
<td>47 (38.8%)</td>
</tr>
</tbody>
</table>

*any medication interacting with lithium listed in the BNF; **hypertension, diabetes and/or any thyroid disorder;

Discussion

This study aimed to assess whether lithium monitoring during maintenance phase treatment in one of the largest mental health trusts in the UK is performed according to the standard set by the latest NICE guidelines for assessment and management of bipolar disorder (NICE, 2014a). This is the first study of this kind since the establishment of the Clinical Record Interactive Search system (CRIS) database in the South London and
Maudsley (SLaM) NHS Foundation Trust. Overall, we found that patients in SLaM have a mean serum lithium level of 0.65mmol/l, which closely resembles the level reported by other studies and audits in the UK (e.g. 0.63mmol/l in McKean & Vella-Brincat (2012) & Paton et al., (2010); and 0.64 mmol/l in Head & Dening (1998)). The main findings show that almost half of all serum lithium level tests results were outside of the optimal range. There were few lithium levels above range (6.9%). For some of these cases, it is possible that the target level was higher due to a more difficult-to-treat illness (Paton et al., 2010). There were very few test results above the toxicity level, which is a reassuring finding. The high number of tests in this study that were below the therapeutic threshold (42.4%) is worrying, as it indicates that these patients may not have been receiving the full therapeutic benefit of lithium, which could increase the risk of relapse and also contribute to the poor treatment adherence, which is common among this patient group (Mitchell and Selmes, 2007). However, due to the nature of the database, we could not investigate the potential relationship between sub-therapeutic levels and adverse outcomes (such as non-adherence or relapse). Alternatively, poor adherence itself could have contributed to the sub-optimal results; however, we had no adherence data available to investigate this possibility. The sub-therapeutic levels could also be reflective clinicians’ fear of toxicity,
despite the overwhelming evidence in the literature that first signs of toxicity manifest at plasma levels above 1.5mmol/l (Oruch et al., 2014).

The latest audit (the post-QIP POMH audit) reported that 86% of last recorded measurements for patients were within range (Paton et al., 2013). Reporting on the last observed value, however, only captures one time-point of patients’ treatment and is not necessarily reflective of a patient’s experience during long-term maintenance treatment. Further, this and other previous audits have set the therapeutic range to 0.4-1.0mmol/l. Almost 1 in 4 lithium levels in our study were between 0.4-0.6mmol/l which, according to the most up-to-date evidence and guidelines, is considered to be ineffective for bipolar disorder (Tohen et al., 2005) and also as augmentation for treatment resistant depression (Bauer et al., 2013; Cleare et al., 2015). Therefore, it is important that audits are re-evaluated after major guidelines are updated and Trust and laboratory policies are updated accordingly.

The high percentage of co-prescription of interacting drugs (60% of patients were on at least one such medication) could also be contributing to the high number of out-of-range results. In comparison, the post-QIP POMH audit reported only 9% of co-prescription of
such drugs, however, these included only NSAIDs, COX-2 inhibitors, ACE-inhibitors and angiotensin-2 receptor antagonists (Paton et al., 2013). In this study, we have included the full set of interacting drugs listed in the BNF, which also contains SSRIs (Joint Formulary, 2015). This could explain the large difference, as the post-QIP audit separately reported 41% co-prescription of an antidepressant in the bipolar patients and 85% in patients with other affective disorders (Paton et al., 2013). This is intriguing given the increasing evidence that antidepressants have limited effect in patient with bipolar disorder (Ghaemi et al., 2010; Pacchiarotti et al., 2013). Further studies are merited to investigate the high co-prescription observed in this survey and previous audits. While there is a theoretical reason to suppose an SSRI-lithium interaction, previous studies have demonstrated little potential for a toxic interaction; however, non-serious adverse events have been reported to arise frequently (Hawley et al., 2000). Better specificity in the NICE guidelines on which groups of interacting medications should be monitored more frequently would be useful in this patient group where lithium–SSRI co-prescription is common.

In terms of testing frequency, we found that for 76% of patients in this study the current NICE monitoring standard was met with lithium levels being measured every 6 months or
more frequently. For renal and thyroid tests, 73% and 60% of patients, respectively, were tested at the recommended frequency of 6 months or more often. In comparison with the most recent audits, monitoring performance is very similar to the post-QIP POMH audit (Paton et al., 2013) and poorer than in the Norfolk audit (following implementation of a regional lithium register and database) (Kirkham et al., 2013). Among the sub-groups at an increased risk of toxicity, there were too few patients over the age of 65 or with a chronic co-morbidity to draw meaningful conclusions. With regards to co-prescribed interacting medication, only 56.8% of patients on any such medication had lithium levels tested every 3 months, as indicated by NICE 2014. These, however, also include patients on SSRIs, the controversy of which was discussed above.

In this survey, there was a high number of patients (289 of 412) for whom there was only one serum lithium test recorded in the system. It is extremely unlikely that such a high proportion of patients were not monitored at all. A possible explanation is that for these patients routine monitoring was performed in other labs across the Trust (results from which are not integrated into CRIS), or more likely, in primary care. Such information was not available to us from the system. Indeed, some NICE guidelines (e.g. for the prevention and management of psychosis and schizophrenia; (NICE, 2014b) were recently
updated to regulate the responsibility of monitoring the physical health of patients with severe mental illness and to establish a role for primary care in monitoring particularly during maintenance phase treatment. Given that SLaM is one of the largest mental health Trusts in the UK, it should be clearer from patient electronic records where and by whom routine monitoring is being performed. This could be achieved through the development of Trust-wide shared-care agreements, an electronic reminder system for secondary/tertiary care or a central registry of all patients on lithium (e.g. similar to the clozapine system). Similar strategies have previously been attempted in smaller settings (Kirkham et al., 2013; Eagles et al., 2000) and have been shown to reduce the discrepancies between guideline recommendation and clinical practice (Aubry et al., 2017).

This study had several limitations, mainly stemming from the nature of the database used. First, as there are no dispensing records in the database, treatment adherence and any potential gaps in treatment could not be investigated. Second, initial start date of treatment and whether patients were first-time users could not be inferred with certainty. Third, as GP records are not integrated in the system, the role of primary care in the routine monitoring of patients in SLaM could not be assessed. Fourth, due to the
limitations of the database, there may be an inherent selection bias to the sample (e.g. the sample is limited to patients tested in one laboratory within the Trust), even if this was not intentionally imposed by the researchers. Further, this study did not look at parathyroid monitoring and future studies and audits should also examine frequency of calcium tests. Finally, a general limitation of retrospective observational analyses is that the reasons behind any observed non-adherence to the NICE guidelines cannot be determined with certainty. Conversely, the strengths of this study include: (i) clearly defined parameters based on the latest NICE guidelines; (ii) the use of a large, constantly updated and growing database of clinical records; (iii) diverse population of patients from one of the largest mental health trusts in the UK; (iv) the use of a retrospective observational cohort eliminates the recall bias that previous surveys have been criticised for.

**Conclusion**

Lithium monitoring remains sub-optimal with rates of serum lithium level, renal and thyroid function tests falling short from the current NICE recommendation. The high number of test results below the therapeutic minimum is concerning, as it can play a pivotal role in treatment non-adherence and relapse. Clinical practice should actively update to meet the most recent evidence-based guidelines which recommend that levels
above 0.6mmol/l should be maintained during maintenance phase treatment. Further, electronic reminder systems for secondary/tertiary care clinicians, shared care agreements or a central registry for lithium users should be implemented in order to improve monitoring performance in secondary care.

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References


Jackson RG, Patel R, Jayatilleke N, et al. (2017) Natural language processing to extract symptoms of severe mental illness from clinical text: the Clinical Record
Interactive Search Comprehensive Data Extraction (CRIS-CODE) project. *BMJ Open* 7.


