King's Research Portal

DOI:

[10.1177/0269881118760663](https://doi.org/10.1177/0269881118760663)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Nikolova, V. L., Pattanaseri, K., Hidalgo-Mazzei, D., Taylor, D., & Young, A. H. (2018). Is lithium monitoring NICE? Lithium monitoring in a UK secondary care setting. *Journal of Psychopharmacology*, 32(4), 408-415. <https://doi.org/10.1177/0269881118760663>

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Original Paper

Corresponding author:

Viktoriya L. Nikolova, Centre for Affective Disorders, Department of Psychological Medicine, Institute of Psychiatry, Psychology & Neuroscience, King's College, Denmark Hill, London, UK, SE5 8AF.

Email: viktoriya.nikolova@kcl.ac.uk

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

Viktoriya L Nikolova*1, Keerati Pattanaseri*2, Diego Hidalgo-Mazzei³, David Taylor⁴ and Allan H Young¹

*co-first authors

1 Centre for Affective Disorders, Institute of Psychiatry, Psychology & Neuroscience, King's College London; South London and Maudsley NHS Foundation Trust, UK

2 Department of Psychiatry, Thammasat University Hospital, Thailand

3 Bipolar disorders program, Department of Psychiatry and Psychology, Institute of Neuroscience, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Spain

4 Department of Pharmacy, South London and Maudsley NHS Foundation Trust, UK

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 1: Summary of the major international guidelines for lithium use as treatment of bipolar disorder

Guideline	Year	Phase	Lithium range (mmol/l)	Toxic level (mmol/l)	Frequency of monitoring	
					Lithium level	Renal & Thyroid function
BAP	2016	Acute Maintenance	1.0-1.5 0.6-0.8	1.5	5 days after titration, then every 3 months in the first year and then every 6 months	Every 12 months
CANMAT	2013	Acute Maintenance	0.8-1.1 0.8-1.1	not specified	5 days after titration until 2 consecutive levels are stable then every 3-6 months	4 weeks after initial dose and then every 12 months
Maudsley	2015	Acute Maintenance	1.0-1.2 0.6-1.0	1.5	7 days after dose change and every 6 months	At baseline and then every 6 months
NICE	2014	Acute (first use) Acute (relapse) Maintenance	0.6-0.8 0.8-1.0 0.6-0.8	not specified not specified not specified	7 days after dose change then weekly until stable; then every 3 months in the first year and every 6 months thereafter	At baseline and then every 6 months
RANZCP	2015	Acute Maintenance	0.8-1.2 0.6-0.8	not specified not specified	At baseline; every 6 months in the first year and then every 12 months	At baseline; every 6 months in the first year and then every 12 months
WFSBP	2013 2009	Acute mania Maintenance	0.8-1.3 0.6-1.2	not specified not specified	Frequently until stable, then every 3-6 months	Every 6-12 months

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 Bissarbe, 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, methyl dopa, 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 $\pm$ 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 ($\pm$ 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

Key characteristics		Full sample (n=412)	Sub-sample* (n=123)
Gender	Female (%)	210 (51)	59 (48)
Age	Mean age in years (SD)	40.1 (14.4)	41.1 (14.3)
	Median age, years (IQR)	37 (18)	38 (17)
	Age range in years	18 - 89	18-84
	Elderly (>65 years) (%)	32 (7.7)	10 (8.1)
Ethnicity	Asian (%)	29 (7.0)	12 (8.1)

	Black (%)	105 (25.5)	31 (25.2)
	White (%)	241 (58.5)	69 (56.1)
	Mixed or other (%)	37 (9.0)	13 (10.6)
Primary Diagnosis	Bipolar disorder (%)	279 (67.7)	83 (67.5)
	Other (%)	128 (31.1)	40 (32.5)
Chronic comorbidity	Any (%)	129 (31.3)	45 (36.6)
	Hypertension (%)	30 (7.3)	8 (6.5)
	Diabetes (%)	28 (6.8)	9 (7.3)
	Thyroid disorder (%)	20 (4.9)	7 (5.7)
On medication interacting with lithium** (%)		251 (60.9)	74 (60.2)

*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.

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

*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 & Denning (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 of 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.

Acknowledgements

CRIS is supported by the NIHR Biomedical Research Centre for Mental Health BRC Nucleus at the South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, Psychology and Neuroscience, King's College London jointly funded by the Guy's and St Thomas' Trustees and the South London and Maudsley Trustees.

Funding

The authors received no specific financial support for the research, authorship, and/or publication of this article. Professor Young's research is funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. Dr Mazzei was indirectly supported by a Río Hortega grant (CM15/00127) from Instituto de Salud Carlos III, Spain. Professor Taylor's research is funded by the NHS and King's College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

Declaration of conflicting interest

Professor Allan Young: paid lectures and advisory boards for the following companies: AstraZeneca, Eli Lilly, Janssen, Lundbeck, Sunovion, Servier, Livanova; Investigator initiated studies from AstraZeneca, Eli Lilly, Lundbeck, Wyeth. Professor David Taylor:

advisory board member of Allergan; research funding from Janssen, Lundbeck, Sunovion; lectures for Janssen, Otsuka, Servier, Lundbeck, Sunovion.

References

- Aubry RE, Scott L and Cassidy E. (2017) Lithium monitoring patterns in the United Kingdom and Ireland: Can shared care agreements play a role in improving monitoring quality? A systematic review. *Irish Journal of Psychological Medicine* 34: 127-140.
- Baird-Gunning J, Lea-Henry T, Hoegberg LCG, et al. (2016) Lithium poisoning. *J Intensive Care Med*.
- Bauer M, Dell'osso L, Kasper S, et al. (2013) Extended-release quetiapine fumarate (quetiapine XR) monotherapy and quetiapine XR or lithium as add-on to antidepressants in patients with treatment-resistant major depressive disorder. *J Affect Disord* 151: 209-219.
- Butler and Taylor. (2000) A survey of monitoring and prescribing patterns. *International Journal of Psychiatry in Clinical Practice*: 135-138.
- Cade JF. (1949) Lithium salts in the treatment of psychotic excitement. *Med J Aust*: 349-352.
- Cleare A, Pariante CM, Young AH, et al. (2015) Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines. *J Psychopharmacol* 29: 459-525.
- Collins N, Barnes TR, Shingleton-Smith A, et al. (2010) Standards of lithium monitoring in mental health trusts in the UK. *BMC Psychiatry*: 80. doi 10.1186/1471-1244X-1110-1180.
- Crossley NA and Bauer M. (2007) Acceleration and augmentation of antidepressants with lithium for depressive disorders: two meta-analyses of randomized, placebo-controlled trials. *J Clin Psychiatry*: 935-940.
- Eagles JM, McCann I, MacLeod TN, et al. (2000) Lithium monitoring before and after the distribution of clinical practice guidelines. *Acta Psychiatr Scand* 101: 349-353.

- Gerrett D, Lamont T. , Paton C. , et al. (2010) Prescribing and monitoring lithium therapy: summary of a safety report from the National Patient Safety Agency. *Bmj*: c6258.
- Ghaemi SN, Ostacher MM, El-Mallakh RS, et al. (2010) Antidepressant discontinuation in bipolar depression: a Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) randomized clinical trial of long-term effectiveness and safety. *J Clin Psychiatry* 71: 372-380.
- Gitlin M. (2016) Lithium side effects and toxicity: prevalence and management strategies. *International Journal of Bipolar Disorders* 4: 27.
- Glover KJ and Lawley D. (2005) How safe is lithium prescribing? Audit of a local prescribing framework and patient survey. *Psychiatric Bulletin* 29: 98-100.
- Goodwin GM, Haddad P. M., Ferrier I. N. , et al. (2016) Evidence-based guidelines for treating bipolar disorder: Revised third edition recommendations from the British Association for Psychopharmacology.
- Grunze H, Vieta E. , Goodwin G. M., et al. (2009) The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2009 on the treatment of acute mania. *The World Journal of Biological Psychiatry*: 85-116.
- Grunze H, Vieta E. , Goodwin G. M. , et al. (2013) The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2012 on the long-term treatment of bipolar disorder. *The World Journal of Biological Psychiatry*: 154-219.
- Hawley CJ, Loughlin PJ, Quick SJ, et al. (2000) Efficacy, safety and tolerability of combined administration of lithium and selective serotonin reuptake inhibitors: a review of the current evidence. Hertfordshire Neuroscience Research Group. *Int Clin Psychopharmacol* 15: 197-206.
- Hayes JF, Marston L, Walters K, et al. (2016a) Adverse Renal, Endocrine, Hepatic, and Metabolic Events during Maintenance Mood Stabilizer Treatment for Bipolar Disorder: A Population-Based Cohort Study. *PLOS Medicine* 13: e1002058.
- Hayes JF, Pitman A, Marston L, et al. (2016b) Self-harm, Unintentional Injury, and Suicide in Bipolar Disorder During Maintenance Mood Stabilizer Treatment: A UK Population-Based Electronic Health Records Study. *JAMA Psychiatry* 73: 630-637.
- 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.
- Joint Formulary C. (2015) *British national formulary 70*, London: BMJ Publishing and the Royal Pharmaceutical Society.
- Kehoe RF and Mander AJ. (1992) Lithium treatment: prescribing and monitoring habits in hospital and general practice. *British Medical Journal* 304: 552-554.
- Kirkham E, Bazire S, Anderson T, et al. (2013) Impact of active monitoring on lithium management in Norfolk. *Therapeutic Advances in Psychopharmacology* 3: 260-265.
- Kraszewska A, Abramowicz M., Chlopocka-Wozniak M. , et al. (2014) The effect of lithium on thyroid function in patients with bipolar disorder. *Psychiatr Pol*: 417-428.
- Malhi GS, Bassett D., Boyce P., et al. (2015) Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. *Aust N Z J Psychiatry*: 1087-1206.
- Malhi GS, Gessler D and Outhred T. (2017) The use of lithium for the treatment of bipolar disorder: Recommendations from clinical practice guidelines. *J Affect Disord* 217: 266-280.
- Malhi GS and Outhred T. (2016) Therapeutic Mechanisms of Lithium in Bipolar Disorder: Recent Advances and Current Understanding. *CNS Drugs* 30: 931-949.
- McKean A and Vella-Brincat J. (2012) Is it NICE to monitor lithium routinely. *N Z Med J*: 50-54.
- McKnight RF, Adida M., Budge K., et al. (2012) Lithium toxicity profile: a systematic review and meta-analysis. *Lancet*: 721-728.
- Meyer JS and Quenzer LF. (2013) *Psychopharmacology: drugs, the brain, and behavior (2nd ed.)*, Sunderland, Mass.: Sinauer Associates.
- Mitchell AJ and Selmes T. (2007) Why don't patients take their medicine? Reasons and solutions in psychiatry. *Advances in Psychiatric Treatment* 13: 336-346.
- Miura T, Noma H, Furukawa TA, et al. (2014) Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis. *The Lancet Psychiatry* 1: 351-359.
- Mowry JB, Spyker DA, Cantilena LR, et al. (2013) 2012 Annual report of the American association of poison control centers' national poison data system (NPDS): 30th annual report. *Clin Toxicol.* 51.
- NICE. (2014a) *Bipolar disorder: assessment and management*. Available at: Retrieved from <https://www.nice.org.uk/guidance/cg185>.

- NICE. (2014b) *Psychosis and schizophrenia in adults: prevention and management*. Available at: <https://www.nice.org.uk/guidance/cg178>.
- NIHR-BRC. (2015) *What is CRIS*. Available at: Retrieved July, 2, 2016, from <http://www.maudsleybrc.nihr.ac.uk/about-us/core-facilities/clinical-record-interactive-search-cris/what-is-cris/>.
- Oruch R, Elderbi MA, Khattab HA, et al. (2014) Lithium: A review of pharmacology, clinical uses, and toxicity. *European Journal of Pharmacology* 740: 464-473.
- Pacchiarotti I, Bond DJ, Baldessarini RJ, et al. (2013) The International Society for Bipolar Disorders (ISBD) task force report on antidepressant use in bipolar disorders. *Am J Psychiatry* 170: 1249-1262.
- Paterniti S and Bisslerbe JC. (2013) Pharmacotherapy for bipolar disorder and concordance with treatment guidelines: survey of a general population sample referred to a tertiary care service. *BMC Psychiatry*: 211. doi 10.1186/1471-1244X-1113-1211.
- Paton C, Adroer R. and Barnes TR. (2013) Monitoring lithium therapy: the impact of a quality improvement programme in the UK. *Bipolar Disord*: 865-875.
- Paton C, Barnes T. R., Shingleton-Smith A. , et al. (2010) Lithium in bipolar and other affective disorders: prescribing practice in the UK. *J Psychopharmacol*: 1739-1746.
- Perera G, Broadbent M, Callard F, et al. (2016) Cohort profile of the South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLaM BRC) Case Register: current status and recent enhancement of an Electronic Mental Health Record-derived data resource. *BMJ Open* 6: e008721.
- Perlis RH. (2007) Use of treatment guidelines in clinical decision making in bipolar disorder: a pilot survey of clinicians. *Curr Med Res Opin*: 467-475.
- Sajatovic M, Bauer MS, Kilbourne AM, et al. (2006) Self-reported medication treatment adherence among veterans with bipolar disorder. *Psychiatr Serv* 57: 56-62.
- Samalin L, Guillaume S., Auclair C., et al. (2011) Adherence to guidelines by French psychiatrists in their real world of clinical practice. *J Nerv Ment Dis*: 239-243.
- Samanta ASJ and Gunn M. (2003) Legal considerations of clinical guidelines: will NICE make a difference. *J R Soc Med*: 133-138.
- Song J, Sjölander A, Joas E, et al. (2017) Suicidal Behavior During Lithium and Valproate Treatment: A Within-Individual 8-Year Prospective Study of 50,000 Patients With Bipolar Disorder. *The American Journal of Psychiatry*: appiajp201716050542.

- Stahl SM. (2013) *Stahl's essential psychopharmacology: neuroscientific basis and practical application (4th ed.)*, Cambridge: Cambridge University Press.
- Stewart R, Soremekun M, Perera G, et al. (2009) The South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLAM BRC) case register: development and descriptive data. *BMC Psychiatry* 9: 51.
- Storosum JG, Wohlfarth T, Schene A, et al. (2007) Magnitude of effect of lithium in short-term efficacy studies of moderate to severe manic episode. *Bipolar Disord* 9: 793-798.
- Taylor D, Paton C. and Kapur S. (2015) *The Maudsley Prescribing Guidelines in Psychiatry, 12th Edition*: Wiley-Blackwell.
- Tohen M, Greil W., Calabrese J. R, et al. (2005) Olanzapine versus lithium in the maintenance treatment of bipolar disorder: a 12-month, randomized, double-blind, controlled clinical trial. *Am J Psychiatry*: 1281-1290.
- Udumaga E and Mannion L. (2010) An audit in general adult psychiatry service. *Ir Med J* 103: 123-124.
- Waring WS, Laing WJ, Good AM, et al. (2007) Pattern of lithium exposure predicts poisoning severity: evaluation of referrals to a regional poisons unit. *Qjm* 100: 271-276.
- Yatham LN, Kennedy S. H. , Parikh S. V. , et al. (2013) Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. *Bipolar Disord*: 1-44.