The pattern of serum lithium test requesting across three UK regions: a service evaluation of adherence to monitoring guidelines.

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Abstract

Background Bipolar disorder is the fourth most common mental health condition, affecting ~1% of UK adults. Lithium is an effective treatment for prevention of relapse and hospital admission, and is widely recommended as a first-line treatment. We previously showed in other areas that laboratory testing patterns are variable with sub-optimal conformity to guidance. We therefore examined lithium results and requesting patterns relative to monitoring recommendations.

Methods Data on lithium levels and intervals between requests were extracted from Clinical Biochemistry laboratory information systems at the University Hospitals of North Midlands, Salford Royal Foundation Trust and Pennine Acute Hospitals from 2012-2018 (46,555 requests; 3,371 individuals). Data were examined with respect to region/source of request, age and sex.

Results Lithium levels on many requests were outside the recommended UK therapeutic range (0.4-0.99 mmol/L); 19.2% below the range and 6.1% above the range (median [Li]: 0.60 mmol/L). A small percentage were found at the extremes (3.2% at <0.1mmol/L, 1.0% at >1.4mmol/L). These findings were comparable across all sites. Most requests were from general practice (56.3%) or mental health units (34.4%), though those in the toxic range (≥1.4 mmol/L) were more likely to be from acute care or other secondary care units (63.9%). For requesting interval, there was a distinct peak at 12 weeks, consistent with guidance for those stabilised on lithium therapy. There was no peak evident at 6 months, as recommended for those aged <65 years on unchanging therapy. There was a peak at 0-7 days, reflecting those requiring closer monitoring (e.g. treatment initiation or for toxicity). However, for those with initial lithium concentrations within the BNF range (0.4-0.99 mmol/L), 69.4% of tests were requested outside expected testing frequencies.

Conclusions Our data showed: (a) lithium levels are often maintained at the lower end of the recommended therapeutic range, (b) patterns of lithium results and testing frequency were comparable across three UK sites with differing models of care and, (c) re-test intervals demonstrate a noticeable peak at the recommended 3-monthly, but not at 6-monthly intervals. Many tests were repeated outside expected frequencies, indicating the need for additional work to minimise inappropriate testing.

Introduction

Bipolar disorder is the 4th most common mental health condition, affecting approximately 1% of adults [1]. Individuals with bipolar disorder typically have recurrent episodes of elevated mood (mania) and periods of depressed mood, which may last for several weeks. A combination of therapies is often required to manage different aspects of bipolar disorder, including pharmacological treatments, psychological therapies and lifestyle advice.

Lithium is the most effective treatment for prevention of relapse and hospital admission in people with bipolar disorder, and is recommended by The National Institute for Health and Care Excellence (NICE) in the UK as a first line long-term treatment [2], as well as in clinical practice guidelines in the USA, Canada, Japan, the Netherlands, and Australia and New Zealand, and in the International Society for Bipolar Disorders [3–5]. Lithium is also used to treat other conditions such as recurrent depression [6].

However, lithium treatment is associated with both short-term and long-term risks. Insufficient dose, poor adherence or sudden discontinuation of lithium can result in relapse. In contrast, acute lithium toxicity can presents with a variety of clinical manifestations including renal, neurological, gastrointestinal, cardiac and endocrine abnormalities [7].

Because of these factors, maintaining blood lithium concentration within a relatively narrow therapeutic index is desirable. NICE guidelines currently advise maintaining serum lithium concentration between 0.6 and 0.8 mmol/L, or between 0.8 and 1.0 mmol/L in people who have relapsed whilst taking lithium, or people who have sub-threshold symptoms with functional impairment [2]. The British National Formulary recommends that serum lithium is maintained within the range 0.4-1.0 mmol/L, focusing on the lower end of this range for those on maintenance therapy and in elderly patients [6].

Recommended monitoring intervals for lithium vary according to individual status. For people initiating lithium therapy, NICE guidelines recommend weekly monitoring until a stable baseline is established [2]. Subsequently, it is suggested that serum lithium be monitored on a three-monthly basis for the first year of treatment, increasing to six-monthly for people under 65 years of age with

no changes affecting lithium concentration. More frequent monitoring may be initiated for a variety of reasons, including dose and formulation changes, changing other medications or intercurrent illness. In particular, individuals with potentially toxic serum lithium concentrations (> 1.4 mmol/L) should have serial daily lithium measurements taken to ensure elimination and avoid rebound toxicity [8]. We have shown in other areas that laboratory testing patterns are highly variable and that conformity to guidance in sub-optimal [9–11]. This study therefore aims to assess lithium results and patterns of requesting, and compare these findings to current guidance on lithium requesting. We examined these using clinical laboratory data collected from three large UK centres, where the approach to managing patients with bipolar disorder and ordering lithium testing varies.

Materials And Methods

Data collection

All lithium requests received by the Clinical Biochemistry Departments at the University Hospitals of North Midlands (UHNM), Salford Royal Foundation Trust (SRFT) and Pennine Acute Hospitals NHS Trust (PAT) between 2012 and 2018 were extracted from the respective Laboratory Information and Management Systems (49,584 requests). People with a single lithium request, those initiating lithium therapy in the final year of data collection and those under the age of 18 were excluded, leaving a data set of 46,555 requests from 3,371 individuals.

Data categorisation

Sources of request were categorised as GP practices, Mental Health Units (MHUs; including inpatient and outpatient requests), Acute Care (including Emergency Departments, acute medical & surgical units, etc.), Secondary Care (all acute hospital inpatient and outpatient, excluding Acute Care sources) and Other (including unknown sources). The demographics of this data set are shown in Table 1.

Table 1

Study demographics.

		PAT	%	SRFT	%	UHNM	%	Total	%
Number of patients	Total	1613		1162		596		3371	
Sex	Male	670	41.5	469	40.4	238	39.9	1377	40.8
	Female	943	58.5	690	59.4	358	60.1	1991	59.1
Age (years)	Median (IQR)	50 (39–62)		53 (41–68)		54 (42–67)		52 (40–65)	
Number of requests	GP	17118	73.4	5890	44.7	3215	32.0	26223	56.3
	MHU	3938	16.9	6101	46.3	5996	59.6	16035	34.4
	Secondary Care	1658	7.1	642	4.9	559	5.6	2859	6.1
	Acute Care	461	2.0	470	3.6	177	1.8	1108	2.4
	Other	144	0.6	71	0.5	115	1.1	330	0.7
	Total	23319	50.1	13174	28.3	10062	21.6	46555	
Requests per patient		14.5		11.3		16.9		13.8	

Abbreviations and definitions: PAT: Pennine Acute Trust; SRFT: Salford Royal Foundation Trust; UHNM: University Hospitals of North Midlands; GP: General Practice; MHU: Mental Health Unit (including inpatient and outpatient), Secondary Care: Acute hospital inpatient and outpatient, excluding Acute Care sources; Acute Care: Acute hospital Emergency Departments and acute medical/surgical units; Other: all other sources of requests, including unknown sources; IQR: Inter-quartile range.

Lithium concentrations were grouped into categories: <0.10 mmol/L; 0.10–0.39 mmol/L; 0.4–0.59 mmol/L; 0.60–0.79 mmol/L; 0.8–0.99 mmol/L; 1.0-1.39 mmol/L and ≥ 1.4 mmol/L.

Intervals between lithium tests were calculated as number of days until the next lithium result was requested for each person.

Data analysis

As this study represented a service evaluation and audit of practice, limited statistical analysis has been performed (using Stata, version 14; College Station, TX). This study therefore did not require ethical committee approval. Were statistical analyses was performed, we used the Kruskal-Wallis test for comparisons of median lithium concentrations across sites and Mann-Whitney U test for comparisons between males and females. Linear regression was used to assess the association between lithium concentration with age.

Results

Demographics

Table 1 shows a demographic summary of people included in the study. At all three trusts, the majority of requests came from either GP practices or Mental Health Units (MHUs), with a minority from acute care units, secondary care, or other sources. However, the proportion of requests from GP practices compared to MHUs varied between Trusts. At PAT, GP requests comprised 73.4% of total

requests, whereas at UHNM, most requests originated from MHU (59.6%; GP practice requests comprised 32.0%). At SRFT, GP and MHU requests were evenly split (44.7% and 46.3%, respectively).

Lithium concentrations

Overall, the median lithium concentrations were at the lower limit of the therapeutic range (0.60 mmol/L; IQR 0.44–0.76) (Table 2). The median lithium concentrations were generally lowest in samples from the SRFT and highest from UHNM ($p < 0.001$, Kruskal-Wallis test) and were slightly higher in females (0.60 mmol/L; IQR 0.45–0.76) than males (0.59 mmol/L; IQR 0.43–0.75; $p < 0.001$, Mann-Whitney U test). There was also a statistically significant positive correlation between lithium concentration and age ($p < 0.001$, linear regression), though the strength of this association was not clinically meaningful ($r = 0.07$).

Table 2

Detailed breakdown of serum lithium concentration profile by site and source of requests.

	Lithium concentration (mmol/L)								Median (IQR) lithium concentration (mmol/L)
	< 0.1	0.1–0.39	0.4–0.59	0.6–0.79	0.8–0.99	1.0-1.39	≥ 1.4	Total	
Site									
PAT	3.5%	16.0%	29.9%	30.2%	14.3%	5.1%	1.1%	100.0%	0.60 (0.44–0.76)
SRFT	3.3%	17.5%	32.6%	29.9%	12.0%	3.9%	0.8%	100.0%	0.58 (0.43–0.73)
UHNM	2.6%	14.0%	27.4%	30.5%	17.9%	6.4%	1.2%	100.0%	0.63 (0.47–0.80)
Total	3.2%	16.0%	30.1%	30.2%	14.4%	5.1%	1.0%	100.0%	0.60 (0.44–0.76)
Source									
GP	53.7%	47.7%	57.2%	60.0%	60.6%	53.7%	24.4%	56.4%	0.61 (0.46–0.76)
MHU	31.3%	39.1%	35.6%	33.9%	32.4%	28.3%	11.1%	34.4%	0.58 (0.42–0.74)
Acute care	4.5%	3.0%	1.5%	1.1%	1.8%	6.0%	38.0%	2.4%	0.66 (0.38–1.10)
Secondary care	9.3%	9.2%	5.0%	4.3%	4.7%	11.3%	25.9%	6.1%	0.53 (0.34–0.75)
Other	1.3%	1.0%	0.6%	0.7%	0.5%	0.7%	0.6%	0.7%	0.57 (0.38–0.68)
Total	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	

The categories within the NICE- and BNF-recommended therapeutic range are highlighted in bold: 0.4–0.59 mmol/L for BNF extension to the NICE-recommended range, 0.6–0.79 mmol/L for NICE-recommended range for people receiving routine lithium treatment; 0.8–0.99 mmol/L for NICE-recommended range for people who have relapsed whilst taking lithium, or people who have sub-threshold symptoms with functional impairment.

The proportion of lithium tests in the key categories referred to in guidance showed that, in the

overall dataset, 74.7% of results were within the 0.4–0.99 mmol/L range, with the majority of these in the lower part of this range. Approximately 30% of lithium results fell into 0.4–0.59 mmol/L range (within the BNF recommended range).

The distribution of lithium concentrations from requests across the three Trusts (Figure Legends Figure 1) showed that the lithium concentration profile for each of the Trusts were broadly similar, with a peak at approximately 0.6 mmol/L. This indicated that almost half of results (49.3%) were below the NICE recommended therapeutic window, while only 6% were above the window. A large peak was noted at < 0.1 mmol/L; reflecting results below the detectable range of the assay. When examined in terms of proportions within the lithium concentration categories (Table 2), these were broadly similar between sites, though a slightly higher proportion of results from UHNM were within the range 0.8–0.99 mmol/L. This was reflected in the higher overall median lithium concentration for UHNM. A small percentage of results were found at the extremes - less than 4% at < 0.1 mmol/L and less than 2% at > 1.4 mmol/L – across all three sites.

Similarly, lithium requests falling into each category were split by source (Table 2). For those cases were tests were within the range 0.4–0.99 mmol/L, most tests were requested by GPs or MHUs. There was little difference between the therapeutic range (0.6–0.99 mmol/L) and the 0.4–0.59 mmol/L categories in the proportion requested by GPs and MHUs. For results in the two toxic ranges (1.0-1.39 and ≥ 1.4 mmol/L), a greater proportion were requested from acute and, to a lesser extent, secondary care when compared with non-toxic levels. This was reflected in the higher median lithium concentration for requests from acute care sources.

Requesting intervals

Figure 2 shows the relative frequencies of intervals between pairs of requests for the total group (Fig. 2A) and for each category of lithium concentration (Fig. 2B-H). Overall, there was a distinct peak at 12 weeks, as suggested in NICE and BNF guidance for those stabilised on lithium therapy. There was no peak evident at 6 months as suggested in NICE guidance for those less than 65 years old on unchanging therapy. As 22732 requests were from the 15514 people aged < 65 years of age whose initial lithium concentration was in the range 0.4–0.99 mmol/L, we would have expected a distinct

peak of test requests at 6 months. Moving these cases from 3- to 6-monthly testing would reduce the number of lithium request by up to 6644 per year across the regions serviced by these three laboratories.

There was a peak at 0–7 days, reflecting those requiring closer monitoring (e.g. at treatment initiation or with results in the toxic range). It was also noted that there were spikes of tests requested at weekly intervals throughout, suggesting that there may be a weekly recurring clinic at which samples were collected. There were no noticeable differences in overall pattern when stratified by site (data not shown).

We also examined the pattern of requesting intervals based on initial lithium result. This showed distinct patterns of request interval for each category of lithium result (Fig. 2B-H). For results within the NICE and BNF recommended range categories (0.4–0.59 mmol/L, 0.6–0.79 mmol/L and 0.8–0.99 mmol/L), the modal interval was 84 days (12 weeks). In contrast, peaks are noted at much earlier intervals for other categories: at 7 days for < 0.1 mmol/L and 0.1–0.39 mmol/L concentrations; and at 1 day for 1.0-1.39 mmol/L and > 1.4 mmol/L concentrations.

Table 3 shows the proportion of cases within defined interval categories, split by initial lithium concentration. This illustrates the large proportion of tests requested outside recommended retesting intervals. For example, for those with initial lithium concentrations within the range 0.4–0.99 mmol/L where the recommended intervals (with the exceptions defined in the Introduction) is generally 12 weeks or 26 weeks, a large proportion were requested either before this time (< 11 weeks; 36.7%), in the gap between these two recommended intervals (weeks 14–22; 22.5%) or later than recommended > 27 weeks (10.2%). In those cases in the toxic range > 1 mmol/L, there were a number that were requested later than recommended: 64.6% were re-tested later than 7 days in those with an initial lithium level of 1.0-1.39 mmol/L and 39.5% were retested later than 1 day in those with initial lithium concentrations of > 1.4 mmol/L. Similarly, those in the < 0.4 mmol/L category might be expected to be re-checked at 1–2 weeks during lithium dose up-titration, for example. However, 40.3% were re-tested outside the 2–7 days and 8–76 days categories.

Table 3

Intervals between lithium requests stratified by initial lithium concentrations.

	Lithium concentration (mmol/L)*						
Interval between requests	< 0.1	0.1–0.39	0.4–0.59	0.6–0.79	0.8–0.99	1.0-1.39	> 1.4
0–1 days	2.6%	2.2%	1.0%	1.0%	1.6%	9.8%	60.5%
2–7 days	14.1%	16.2%	6.5%	4.3%	7.4%	25.6%	26.6%
8–76 days (weeks 2 to 10)	45.6%	46.4%	30.4%	27.8%	33.0%	46.0%	9.9%
77–98 days (weeks 11 to 13)	7.6%	13.1%	24.53%	27.0%	23.0%	6.1%	0.2%
99–160 days (weeks 14 to 22)	11.7%	12.6%	22.0%	23.7%	21.1%	7.3%	1.3%
161–189 days (weeks 23 to 26)	3.4%	2.7%	5.2%	5.9%	4.9%	1.5%	0.4%
190–365 (weeks 27 to 51)	8.8%	5.0%	8.5%	8.6%	7.5%	2.9%	0.6%
> 365 (weeks 52 and above)	6.1%	1.7%	2.0%	1.8%	1.5%	0.8%	0.4%
Total	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Categories where the majority of tests would be expected based on guidelines are highlighted in bold.							
*lithium concentration was based on the result of the first lithium of each pair of tests that define an interval							

Discussion

The use of lithium as a treatment for bipolar disorder has been established for over forty years. In the UK, USA, Canada, Japan, the Netherlands and Australia and New Zealand, lithium is currently recommended as a first line treatment for bipolar disorder [1–5]. Lithium has a low therapeutic index, with a narrow interval between therapeutic and toxic doses; ensuring people taking lithium are receiving sufficient dosage for clinical effect, but are minimising risk of side effects and toxicity. If tolerated, lithium has been shown to be an effective treatment for bipolar disorder. Improper dosing may lead to non-adherence, prescription of additional or alternative medication, or failure of therapy, leading to relapse.

Lithium levels

In our study, the mean plasma lithium concentration was found to be around 0.6 mmol/L across all three centres. This is at the lower end of the NICE recommended range [2], but within that recommended by the BNF [6]. Indeed, the overall pattern of lithium concentrations was very similar across the three centres suggesting that, despite differences in proportion of tests requested by general practices and mental health units, there is consensus on target levels. Approximately 30% of results were between 0.6 and 0.8 mmol/L and a further 30% between 0.4 and 0.6 mmol/L. The finding

that around 45% of results fall into the range recommended by NICE for the majority of our patient population (0.6-1.0 mmol/L) is in keeping with the findings of Nikolova et al [4] who found that serum levels were within this range in 50.7% of cases.

Although it may appear concerning that such a large proportion of lithium test results are outside the NICE recommended therapeutic range, this may be indicative of widespread use of the BNF ranges in local guidelines, or pragmatic prescribing by clinicians or inconsistencies between individual recommendations, as summarised by Nederlof et al [3]. Local Shared Care Agreements covering the three centres in this manuscript appear to refer to the BNF quoted range of 0.4-1.0 mmol/L [12–14]. A lack of relevant, well-designed studies in determining the optimal concentration has been noted [5]. Several reviews quoted by Nolen et al [5] suggest the minimum effective serum lithium concentrations may be as low as 0.4 mmol/L. In the UK, NICE guidance published in 2018 [2], recommends clinicians consider maintaining plasma lithium level at a relatively conservative range of 0.6–0.80 mmol/L, or 0.8-1.0 mmol/L in people who have relapsed whilst taking lithium, or people who have sub-threshold symptoms with functional impairment. More recently, Nolen et al [5], as part of the ISBD/IGSLI Task Force on treatment with lithium, concluded that serum lithium concentration should be maintained at 0.6–0.8 mmol/L, with the option to reduce to 0.4–0.6 mmol/L in cases of good response but poor tolerance; or an increased concentration of 0.8-1.0 mmol/L in cases of insufficient response but good tolerance. A controlled study by Gelenberg et al [15] found that patients randomly assigned to a “low” lithium level (0.4–0.6 mEq/L) had fewer side effects but more illness episodes than patients in the “standard” lithium group (0.8–1.0 mEq/L). However, the lithium levels of some of the patients in the low-lithium group decreased relatively rapidly from their previous treatment levels, a decrease that could have increased their risk of relapse. It must be noted that lithium monitoring is an individualised process, and clinical team must be confident to tailor dosages as best suits the person taking lithium. A number of individuals in our cohorts may be achieving therapeutic benefit at a lower plasma lithium concentration, and the prescribing clinician may have chosen to maintain this, rather than risk additional side effects with an increased dose. This may therefore be reflected in both our findings and those of Nikolova et al [4], who also identified a large proportion (42.4%) of cases

with levels below the recommended 0.6-1.0 mmol/L.

Those patients with lower blood lithium concentrations (< 0.4 mmol/L) comprised 19.2% of cases overall. This is higher than that described by Parton et al [16] who identified that, in a study of 2776 patients with affective disorders from 35 UK MHUs, lithium levels were below 0.4 mmol/L in approximately 10% of patients. This difference is unlikely to be due to the source of the requests as out equivalent data for MHUs was similar to the overall figure at 21.1%. Those with undetectable levels may reflect lack of adherence to medication, while those with low but detectable levels (0.1–0.39 mmol/L) may indicate partial adherence or other scenarios such as up-titration of lithium following initiation of treatment or monitoring after a phase of lithium toxicity. Whilst the majority of these appear to be managed in GPs or MHUs, a larger proportion of these tests were requested in acute or secondary care than those with results within the therapeutic range.

Approximately 5% of results could be defined as over-treated (range 1-1.39 mmol/L). However, this may reflect people who have not yet stabilised their dosage or, for those requested in acute or secondary care, monitoring those experiencing toxicity-associated symptoms. In addition, this group of results may include people who have had samples taken less than 12 hours post previous dose.

These proportions are again in keeping with the findings of Nikolova et al [4], who identified levels above 1 mmol/L in 6.9% of cases. Reassuringly, only a small proportion of results (1%) were within the toxic range (> 1.4 mmol/L), and a large proportion of these results were requested by either in acute (38.0%) or secondary (25.9%) care, suggesting an appropriate response to potential toxic side-effects.

Requesting intervals

Examining the overall patterns of testing frequency (Fig. 1A); we noted that there were multiple spikes of requesting it weekly intervals. This would indicate a tendency for attendance and phlebotomy at clinics on the same day each week within GP practices and MHUs. This has been seen elsewhere where regular testing is required, both by us [9] and others [17].

According to clinical guidance, monitoring serum lithium concentration at regular intervals is necessary, depending on individual status. More frequent monitoring is recommended for those

beginning or changing lithium dosage, changing other medications or experiencing intercurrent illness (1 week intervals); and less frequent monitoring is recommended for people who are stable (3–6 months) [2]. Given this advice, it might be expected that frequency plots would show three major peaks, corresponding to populations of unstable therapy (1 week) and at stable therapy (at 3 and 6 months), with a further peak at 1 day for those with lithium levels in the toxic range. Our data indicates that this is broadly true. However, there was a large number of tests performed at non-recommended intervals that are outwith guidance, and there was no evidence of any defined peak at 6 months. In some cases, these tests will be appropriate: for example, people unable to attend their 3-monthly appointment may attend one shortly before or after; or those who become unwell.

NICE guidelines recommend maintaining plasma lithium concentration between 0.6 and 0.8 mmol/L for most people taking lithium, with a higher concentration of 0.8 to 1.0 mmol/L for individuals who have had previous relapse. In the absence of other factors affecting lithium, these patients could be expected to adhere to a 3-monthly monitoring regimen. Although it can be seen that the peak representing the most common interval until next test for these results was around 12 weeks, with a smaller peak at 7 days, it is clear that the majority of results are not being repeated within an appropriate time frame; either too early or too late. Further analysis shows that, for those with these lithium concentrations of 0.4–0.99 mmol/L, 36.7% of tests were requested before 11 weeks, 22.5% between 14 and 22 weeks and 10.2% after 27 weeks.

The absence of a significant peak of testing at 6 months likely relates to the logistics of testing; most lithium clinics in the UK are configured to test at 3 month intervals and local shared care agreements for the centres covered made no mention of 6 monthly monitoring for lithium [12–14]. A significant number of tests (22732) were performed in those aged < 65 years of age whose lithium concentration was in the range 0.4–0.99 mmol/L, where 6-monthly lithium testing is indicated, so we would have expected to see a clear peak at this time point if NICE recommendations were being followed. Following the guidance regarding 6-monthly testing would save up to 6644 lithium tests per year, which, if extrapolated to a UK population would equate to around 200,000 fewer tests per year (equivalent to approximately £250,000 per year). Clearly, a number of these patients will have more

frequent tests for other reasons, though it does appear that the 6-monthly guidance is largely not being followed, leading to excessive inappropriate testing.

Conversely, there some people for whom the interval between tests was more than 12 months, perhaps indicating challenges with attendance in this patient group [18].

Reassuringly, for results outside the NICE and BNF recommended lithium concentrations, the repeat intervals were generally shorter. The toxic limit for lithium is usually taken as > 1.4 mmol/L, and for results at this level and above, the majority (60.5%) were repeated either same day or next day and over 87% within 7 days. However, a significant minority (12.9%) were repeated more than 1 week later. As discussed previously, results at this level are usually managed in acute or secondary care, and likely represent active monitoring of lithium overdose. Those requests with lithium levels in the range 1.0-1.39 mmol/L also showed a shorter re-testing frequency, but with a generally longer interval than those with toxic levels. However, again, there were a significant number that were not re-checked within 1 week (n = 1462; 64.6% of requests). Overall, these may represent those with previously toxic levels under closer monitoring, or those patients who are more disengaged from the service.

Strengths and Limitations

Compared with some studies [19, 20], we were not able to determine from clinical laboratory records the reason for each lithium test request or the primary diagnosis. Our data is also based on the presence of at least one lithium test and may therefore underestimate those who are on lithium treatment, but who are not tested. However, our data does agree with those of other studies in terms of tests per year. However, in addition, our study examines each result and its follow-up interval on a patient-by-patient basis, thereby giving a more detailed view of intervals between requests. Furthermore, our data is based on a large number of patients and is consistent across three sites over 6 years with differing models of distribution of care between general practice and mental health units. Whilst specific information on reason for requesting each test was unavailable as were details of underlying psychiatric diagnosis, the recommendations for lithium monitoring within national and international guidance are consistent regardless of indication.

Conclusions

In summary, our findings indicate that; (a) there is a tendency to manage patients at levels at the lower end of the NICE-recommended therapeutic range, (b) those with elevated levels are frequently managed in acute or secondary care, (c) patterns of lithium results and testing frequency are comparable across three UK sites with differing models of care, (d) intervals between tests demonstrate a noticeable peak at the recommended 3-monthly interval, but there was no evidence of any noticeable peak of testing at 6-monthly intervals, (e) a very large proportion of patients are being monitored outside the recommended intervals and (f) a significant minority with toxic levels are not being monitored adequately. These observations support the need for a review of the recommendations regarding the therapeutic window for lithium and indicate that more needs to be done to improve adherence to the associated guidance on long-term monitoring of lithium levels.

Declarations

Ethics approval and consent to participate: This study represented an evaluation of the current service on lithium testing and hence ethical approval was not required.

Consent for publication: Not applicable

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests

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Authors' contributions: AAF, CJD, DH and AAH conceived the original idea, CJD, JS and LG performed the initial data extraction from each of the three sites and CP performed the data clean-up and drafted the initial version of the paper. AAF and DH performed the data analysis. AAF, AAH and JS crafted the final version of the manuscript which was then reviewed and approved by all authors prior to submission of the final version.

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Authors' information: CP, CJD, JS, LG and AAF are all Clinical Biochemists at the three sites and have

access to all lithium testing data from the acute hospital trusts, general practices and mental health units across three UK regions covering approximately 3% of the UK population. AHH is a dual trained Consultant Endocrinologist and Psychiatrist, and has experience of working across the three sites. DH is the Programmes Lead for the Benchmarking Partnership, which provides benchmarking services for NHS clinical laboratories including assessing links between laboratory testing and clinical outcomes.

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Figures

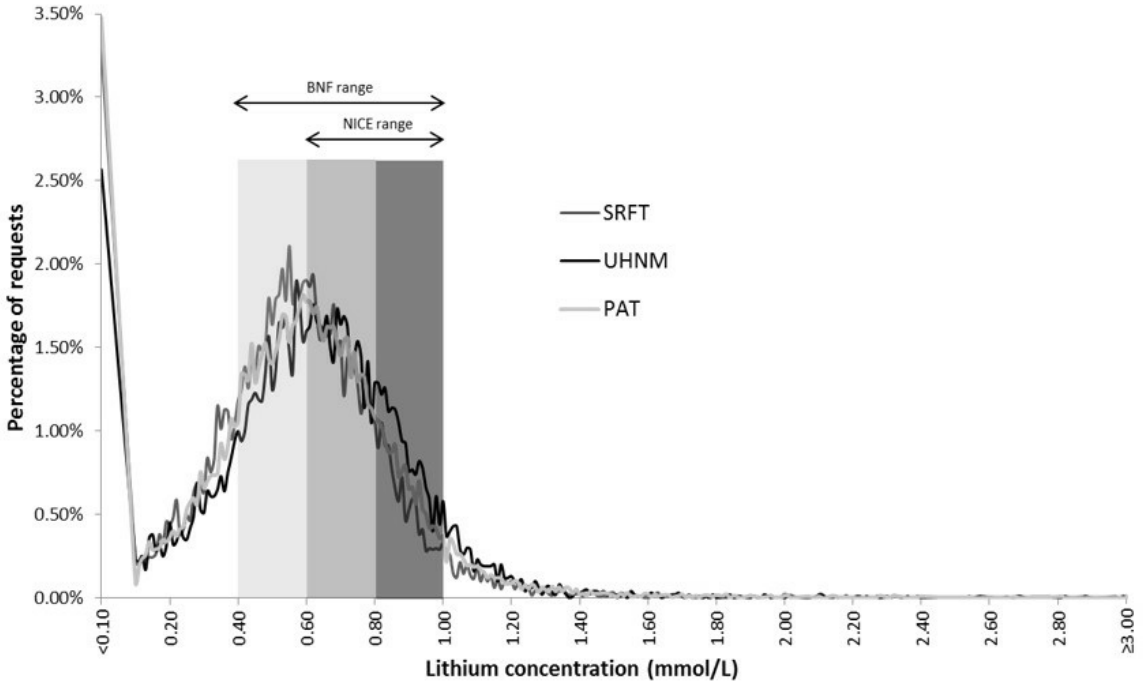

Figure 1

Serum lithium concentration profile for each site. The categories within the NICE- and BNF-recommended therapeutic range is indicated by shading: light grey for BNF extension to the NICE-recommended range (0.4-0.59 mmol/L), mid grey for NICE-recommended range for people receiving routine lithium treatment (0.6-0.79 mmol/L); dark grey for NICE-recommended range for people who have relapsed whilst taking lithium, or people who have sub-threshold symptoms with functional impairment (0.8-0.99 mmol/L).

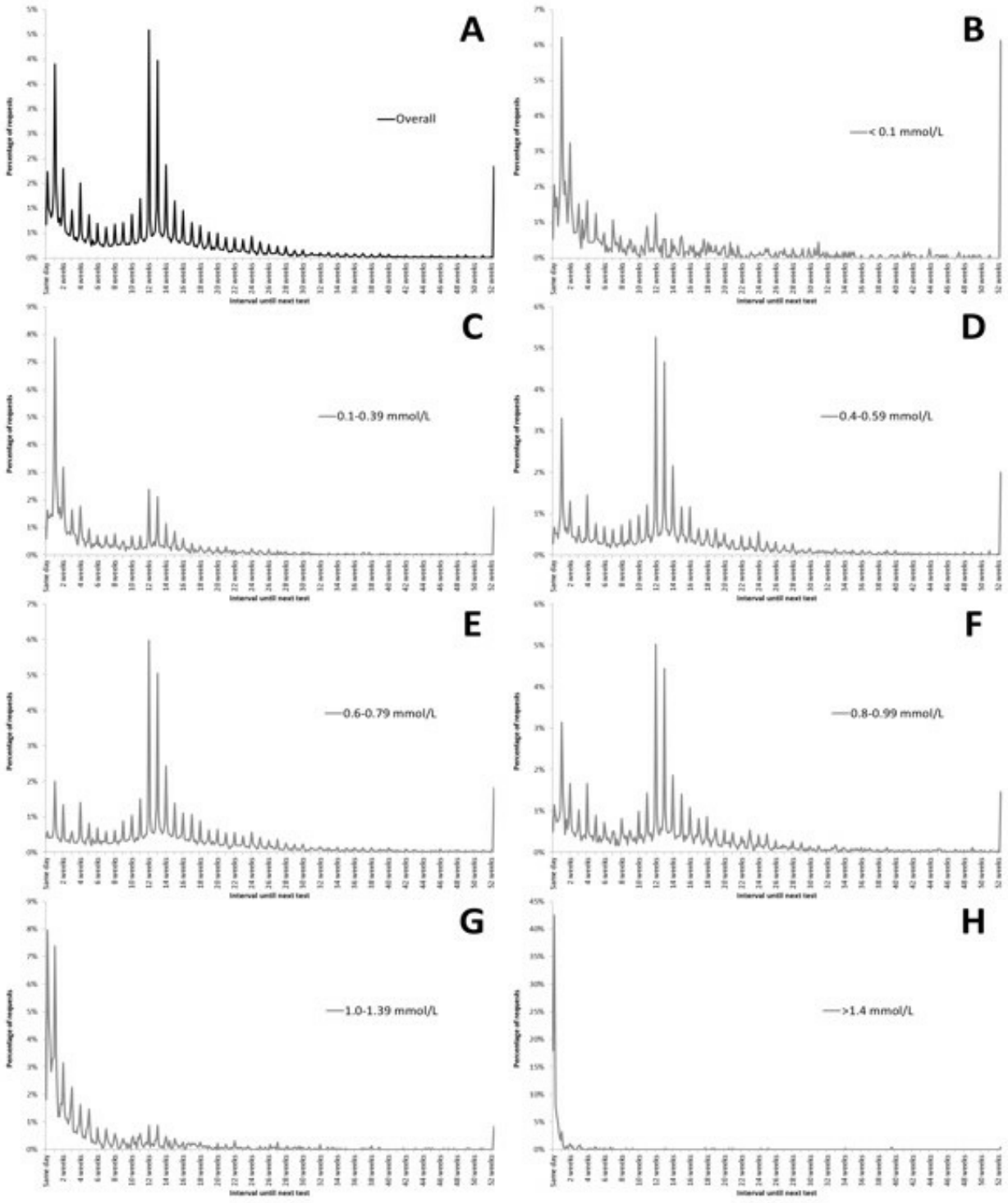

Figure 2

Frequency of intervals between consecutive lithium requests (truncated at 1 year).

Percentages of requests reflect daily requests and are show for the total number of requests (panel A) and categorised by initial lithium concentration (panels B-H).