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# Impact of active monitoring on lithium management in Norfolk

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***Abstract***

**Background:** Lithium has been used in the fields of rheumatology and psychiatry since the 1800s and it is now generally considered to be a gold standard treatment for bipolar disorders. However, lithium is known to have significant side effects and requires close serum level monitoring to ensure levels remain within the therapeutic range to minimize the risk of serious adverse effects or toxicity. This article reviews the monitoring of lithium and reports on the implementation of a regional lithium register and database within Norfolk.

**Methods:** Recorded blood results from the Norfolk lithium database were extracted for the first full year of operation across the region, 2005/6, and from the most recent full year 2011/12. The number of lithium monitoring tests, U&Es and thyroid function tests conducted on all people registered on the database were compared between the two sample years.

**Results:** In 2005/6 there were a significant number of people not receiving the recommended number of four or more serum lithium test per year (68.3%) and the majority of people had two or three tests (62%). By 2011/12 this had noticeably increased with the majority of patients having four or more tests per year (68.5%) and the number having only two or three tests reducing dramatically (26.4%).

**Conclusion:** Improved rates of lithium testing and monitoring have been demonstrated since the introduction of the Norfolk database helping to achieve national targets. Consequently, the chances of adverse events from insufficient monitoring have been minimized.

***Keywords:*** bipolar disorder, databases, drug monitoring, factual, lithium, psychiatry

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## History of lithium

Although as an element lithium had been discovered in the 1800s and used in the fields of rheumatology and psychiatry since this time, it was not until 1949 that the first academic work on lithium in psychiatry appeared. This work showed that lithium had a significant effect in a case series of 10 patients with mania presenting with 'psychotic excitement' [Garrod, 1859; Lange, 1886; Cade, 1949; Schioldann, 2011]. By 1950 a hospital-based trial had led to the development of indicators for safe lithium doses and initial signs of toxicity, including gastric disturbances, muscular weakness, ataxia and slurred speech [Ashburner, 1950; Noack and Trautner, 1951; Malhi and Gershon, 2009]. However, by 1951 lithium's use in medicine had been somewhat discredited by reports of deaths in the USA and Australia after the widespread use of lithium salts as a table salt substitute [Corcoran and Taylor, 1949].

Despite being somewhat discredited by the early 1970s, lithium was first registered by the US Food and Drug Administration (FDA) for long-term prophylactic use in bipolar disorder with approval in the UK occurring by 1985 [FDA, 2012]. Lithium has since been licensed in the UK for the treatment and prophylaxis of mania and hypomania, prophylactic treatment of recurrent affective disorders, treatment of recurrent bipolar depression when the use of alternative antidepressants has been ineffective, and the treatment of aggressive or self-mutilating behaviour [Norgine Ltd, 2011; Rosemont Pharmaceuticals Ltd, 2011; Sanofi-Aventis, 2012].

Renal function is import for the elimination of lithium, as it is primarily renally excreted, and a declining estimated glomerular filtration rate (eGFR) will increase any risks of lithium intoxication due to accumulation. Although a little

evidence supports the theory that lithium is responsible for progressive glomerular damage, there are still conflicting opinions of the effect of long-term lithium use on eGFR [Waller and Edwards, 1985; Tredget *et al.* 2010]. Most evidence suggests that although there is not a definitive correlation between lithium therapy and glomerular function decline leading to renal failure, there does appear to be some association between lithium therapy and urinary concentrating ability [McKnight *et al.* 2012]. Only a small number of patients on long-term lithium therapy go on to develop renal insufficiency or end-stage renal disease caused by lithium [Coşkunol *et al.* 1997; Markowitz *et al.* 2000; Tredget *et al.* 2010].

## Lithium monitoring in the UK

Until 2003 with the publication of the British Association of Psychopharmacology (BAP) guidelines and later in 2006 with the National Institute for Health and Clinical Excellence (NICE) bipolar guidance there were no nationally recognized guidelines covering lithium monitoring outside of the recommendations in the BNF [NICE, 2006; BAP, 2009]. In the 1980s these recommendations were limited to adjusting the dose to achieve plasma concentrations between 0.6 and 1.2mmol/liter [BNF, 1988].

In 2004 the Quality and Outcomes Framework (QOF) was initiated as part of the General Medical Services Contract. The QOF is a voluntary incentive scheme for primary care. It contains groups of indicators against which practices are scored according to their level of achievement [The Information Centre for Health and Social Care, 2012]. Within the QOF section on mental health, practices are scored for the percentage of patients on lithium with a record of serum creatinine and thyroid stimulating hormone (TSH) within the preceding 9 months, a record of lithium levels in the therapeutic range within the previous 4 months and a body mass index (BMI) recorded in the past 15 months [The Information Centre for Health and Social Care, 2012]. NICE bipolar guidance states that, during maintenance treatment with lithium, a serum lithium level should be taken every 3 months, renal and thyroid function tests should be completed every 6 months (more often if there is evidence of impaired renal function), and weight, BMI or waist circumference should be measured annually [NICE, 2006]. The BAP guideline recommends that renal and thyroid function are tested every 12 months, with lithium levels checked every 3–6 months in people on a stable dose [BAP, 2009].

In December 2009 the National Patient Safety Agency (NPSA) released a patient safety alert to improve the safety of lithium therapy [NPSA, 2009]. This focused on regular monitoring in line with NICE guidance; reliable communication systems for blood test results; appropriate verbal and written information provided to patients and systems are in place to identify and deal with potential interactions with lithium therapy [NPSA, 2009].

## Lithium management in Norfolk

Following a series of clinical incidents in primary care regarding lithium toxicity, concerns were raised at Norwich Primary Care Trust that there was not a consistent approach to lithium monitoring across Norfolk. Data were extracted from the Norfolk and Norwich University Hospital pathology system from October 1999 to October 2000. From a total of 1457 people with lithium levels recorded within this year, 32.6% had only one level, 54.3% had one or two levels, 45.6% had three or more levels, and 29.4% had four or more levels [Holmes, 2005]. By May 2000 a pharmacy-led prescribing group had conceived the idea of a Norfolk-wide lithium register and database to help minimize the potential for future clinical incidents relating to lithium prescribing and monitoring. The lithium database was first implemented in May 2002 and complete rollout across Norfolk occurred by 2004 [Holmes, 2005].

For the successful implementation of this database there were two issues surrounding lithium prescribing and monitoring which needed to be addressed. First there was some conflict as to who would retain overall responsibility for the individual patient and the ongoing monitoring and prescribing of lithium, so a shared-care agreement was created [Holmes, 2005]. In this guideline secondary care remains responsible for the individual's lithium monitoring for the 4 months following initiation or until the person is stable, at which point responsibility for monitoring as well as the prescribing passes to primary care. The second issue identified was variations in therapeutic plasma levels quoted by the pathology laboratories used in Norfolk: 0–1.0 mmol/liter and 0.5–0.8 mmol/liter. Consensus agreement was reached that the ranges quoted by both

**Table 1.** Norfolk database: lithium monitoring tests or measures conducted on all people registered between June 2005 and June 2006 ($n$ = 946) and between June 2011 and June 2012 ($n$ = 1385).

| Number of tests in past year | Serum lithium $n$ (%) | |
|---|---|---|
| | 2005/6 | 2011/12 |
| 0 | 0 (0%) | 0 (0%) |
| 1 | 60 (6.3%) | 71 (5.1%) |
| 2 | 205 (21.7%) | 124 (9.0%) |
| 3* | 381 (40.3%) | 241 (17.4%) |
| 4[$] | 220 (23.3%) | 617 (44.5%) |
| 5 or more[$] | 80 (8.5%) | 332 (24.0%) |

*Meets Quality and Outcomes Framework targets.
[$]Meets National Institute for Health and Clinical Excellence standards.

laboratories would be changed to 0.4–0.8 mmol/liter. The pathology laboratories used in Norfolk automatically send all lithium level results to the database administration team who import results for registered patients. For patients registered on the database, other monitoring parameters such as renal and thyroid function are also automatically reported. Cooperation exists with these local laboratories for electronic data transmission of all lithium results to the database administrators on an agreed schedule. At present this process is not automated and relies on cooperation between the NHS Trust and the local pathology laboratories.

The main objectives of the database are to ensure that all patients on lithium have access to adequate information, education and specialist advice, and receive regular blood tests following an agreed protocol. Patient consent to being included in the database should be taken at the time of the prescribing decision in secondary care. If a lithium result is received for a patient who has not been registered on the database, the pharmacy team alert the doctor associated with that patient to the database and the process of registration. Once registered, patients receive an information pack and the initial blood test recall system is put in place. Blood test reminders are automatically sent for 12-weekly monitoring, with the option for this to be adjusted if more frequent monitoring is needed. If no blood test results are received 5 weeks after they are due, a follow-up letter is sent; if the blood test becomes 2 months overdue, a further letter is sent and a telephone call made to the patient if possible. At this point, a GP alert is also activated [Holmes, 2005].

## Impact of the Norfolk database on rates of testing

By May 2012 the database had been in existence for almost 10 years across Norfolk, allowing the ongoing effect of the database on testing rates to be assessed compared with the first full year of the database in 2005.

Table 1 shows that in 2005/6 there were a significant number of people not receiving the recommended number of four or more serum lithium tests per year (68.3%) and the majority of people had two or three tests (62%). However, this has noticeably increased by 2011/12, with the majority of people having four or more lithium tests per year (68.5%) and the number having only two or three tests dramatically reducing (26.4%). Similar rates of improvement can be seen with renal and thyroid function tests (Tables 2 and 3).

At the time of writing, the only national audit on lithium monitoring occurred in 2009 by the Prescribing Observatory for Mental Health on data from 38 mental health trusts, excluding Norfolk, who submitted results for a total of 3373 individuals (2976 results for patients who were receiving maintenance treatment, in that lithium was initiated at least 1 year ago) [Collins *et al.* 2010] (Table 4).

One limitation for the generalizability of the data is the lack of variation in the population in Norfolk. Compared with 16.5% of the population in England who were aged 65 or over in 2010, in Norfolk this was 21.4% [ONS, 2011a]. Between 2001 and 2008 in Norfolk, 94.8% of the population were recorded as white British/Irish/Other

**Table 2.** Norfolk database: creatinine tests conducted on all people registered between June 2005 and June 2006 (*n* = 946) and between June 2011 and June 2012 (*n* = 1385).

| Number of tests in past year | Creatinine *n* (%) | |
|---|---|---|
| | 2005/6 | 2011/12 |
| 0 | 84 (8.9%) | 7 (0.5%) |
| 1* | 695 (73.5%) | 134 (9.7%) |
| 2$ | 113 (11.9%) | 590 (42.6%) |
| 3$ | 31 (3.3%) | 389 (28.1%) |
| 4$ | 18 (1.9%) | 175 (12.6%) |
| 5 or more$ | 5 (0.5%) | 90 (6.5%) |

*Meets Quality and Outcomes Framework targets.
$Meets National Institute for Health and Clinical Excellence standards.

**Table 3.** Norfolk database: thyroid function tests conducted on all people registered between June 2005 and June 2006 (*n* = 946) and between June 2011 and June 2012 (*n* = 1385).

| Number of tests in past year | Thyroid function tests *n* (%) | | | |
|---|---|---|---|---|
| | T4 | | TSH | |
| | 2005/6 | 2011/12 | 2005/6 | 2011/12 |
| 0 | 800 (84.6%) | 435 (31.4%) | 536 (56.7%) | 16 (1.2%) |
| 1* | 111 (11.7%) | 199 (14.4%) | 262 (27.7%) | 176 (12.7%) |
| 2$ | 23 (2.4%) | 412 (29.8%) | 92 (9.7%) | 583 (42.1%) |
| 3$ | 8 (0.8%) | 219 (15.8%) | 25 (2.6%) | 409 (29.5%) |
| 4$ | 4 (0.4%) | 91 (6.6%) | 24 (2.5%) | 149 (10.8%) |
| 5 or more$ | 0 (0%) | 28 (2.0%) | 7 (0.7%) | 51 (3.7%) |

*Meets Quality and Outcomes Framework targets.
$Meets National Institute for Health and Clinical Excellence standards.
TSH, thyroid stimulating hormone; T4, thyroxine.

white background, compared with 87.7% for England as a whole [ONS, 2011b].

## Outcomes

We believe that by aiding communication between primary and secondary care, the database and shared care policy have facilitated good practice and helped to create an environment of partnership working. As well as impacting on rates of testing in the 5 years prior to the NPSA alert, there were no reported incidents relating to lithium therapy in Norfolk compared with the 560 patient safety incidents reported to the NPSA. A key theme in these incidents was a lack of patient monitoring. This suggests that the database has had a direct impact on improving patient safety [NPSA, 2009; Cree, 2011].

## Opportunities for future research

In August 2012 the database started to expand into Suffolk. Within this catchment area there are a group of people who had not been on an active management database but who had been subject to guidelines and the NPSA alert. This cohort can be analysed to see if there is any further impact of the database in addition to national guidelines on the rates of lithium testing and associated monitoring, as well as the impact the database and resources sent with the registration pack have on patients' knowledge about and involvement with their lithium therapy. As the database has the potential to expand into other NHS Trusts with more variable patient populations, more specific effects of lithium on these patient groups could be studied. There is also the potential for a longitudinal review of the data to identify relationships

**Table 4.** POMH-UK data: lithium monitoring tests or measures conducted during maintenance treatment (*n* = 2976).

| Number of tests in past year | U&Es with creatinine | Thyroid function tests | Serum lithium |
|---|---|---|---|
| 0 | 553 (19%) | 524 (18%) | 273 (9%) |
| 1 | 795 (27%)* | 976 (33%)* | 668 (22%) |
| 2 | 592 (20%)$ | 693 (23%)$ | 572 (19%)* |
| 3 | 466 (16%)$ | 453 (15%)$ | 561 (19%)* |
| 4 | 313 (11%)$ | 208 (7%)$ | 503 (17%)$ |
| 5 or more | 257 (9%)$ | 122 (4%)$ | 399 (13%)$ |

*Meets Quality and Outcomes Framework targets.
$Meets National Institute for Health and Clinical Excellence standards.
POMH-UK, Prescribing Observatory for Mental Health; U&Es, urea and electrolytes test.

between lithium levels, monitoring parameters and toxicity.

## Conclusion

Regular blood tests for lithium are important. Lithium is known to have significant side effects and requires close serum level monitoring to ensure levels remain within the therapeutic range to minimize the risk of serious adverse effects or toxicity. Ensuring that these monitoring tests occur as well as supplying information to patients prescribed lithium is a priority for all healthcare organizations where lithium therapy is initiated, prescribed, dispensed and monitored [NPSA, 2009]. Since the database was started in Norfolk there has been a steady increase in the number of people receiving the lithium, renal and thyroid function tests recommended by NICE [NICE, 2006]. There have also been no incident reports in Norfolk since the initiation of the database, suggesting safe prescribing of lithium.

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## Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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