



# Best Practice Guidelines for Prescribing and Monitoring of Lithium Therapy

**This document is intended as a “best practice” guideline and is not to be regarded as a document offering definitive legal advice in relation to the subject matter.**

Publication Date: May 2012

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## About the IMSN

The Irish Medication Safety Network (IMSN) is an independent group of pharmacists and other specialists working in the acute sector, whose principal aim is to improve patient safety with regard to the use of medicines through collaboration, shared learning and action.

The following document is based on best practice as of March 6th, 2012.

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## Introduction

### Background

Lithium is indicated for the prophylaxis and treatment of mania, in the prophylaxis of bipolar disorder and as an augmentation strategy for patients with treatment-resistant depression. It is a potentially toxic medicine with a narrow therapeutic index, with recognised adverse effects on renal and thyroid function<sup>1</sup>. Clinical guidelines published by the National Institute for Health and Clinical Excellence in the UK (NICE) recommend renal and thyroid function checks before lithium is prescribed, as well as ongoing monitoring of renal function, thyroid function and serum lithium levels<sup>2</sup>.

Analysis of errors reported to the UK's National Patient Safety Agency (NPSA) suggests lithium therapy is an error-prone process, and monitoring of therapy is a specific issue<sup>3</sup>. The Prescribing Observatory for Mental Health in the UK (POMH-UK) recently invited all UK Mental Health Trusts to participate in a benchmarking audit of lithium monitoring against recommended standards. The results demonstrated less than optimal monitoring of lithium and a failure to adequately prepare patients to recognise therapy-induced side effects or toxicity<sup>4</sup>.

In 2009 the NPSA issued a patient safety alert on lithium therapy, requiring action by all UK healthcare organisations where lithium therapy is initiated, prescribed, dispensed and monitored<sup>3</sup>. This alert came about partly because of the results of the POMH-UK audit, and partly in response to a number of deaths, severe harms and a substantial number of reported events relating to lithium therapy.

### Evidence of Harm

In the UK over 5 years of incident reporting (2003 to 2008) there were 567 reports of incidents relating to lithium use. Two of these were of severe harm<sup>3</sup>. The NHS Litigation Authority dealt with 2 fatal and 12 severe harm incidents involving lithium between 1995 and 2004, and the UK Medical Defence Union has been involved with 15 incidents since 1996<sup>3</sup>.

In Ireland over 7 years of incident reporting (2004 to 2010), a total of 1,106 reports relating to medication incidents in mental health were submitted to the Clinical Indemnity Scheme via the STARSWeb system<sup>5</sup>. Although the total number of reports submitted via STARSWeb is relatively small (reflecting significant under-reporting), a sizeable proportion of these (7.7%) related to lithium.

There are no national guidelines in place for prescribing or monitoring of lithium therapy in Ireland, and national statistics are not available for adherence with accepted monitoring standards. However in light of lithium's potential for toxicity and serious adverse effects, it is clear that there is an important potential for harm and/or litigation if accepted procedures are not followed. Extrapolation of UK data would suggest that problems with adherence to accepted standards could also be expected in Ireland. Anecdotal reports from Irish hospitals suggest that monitoring of lithium is less than optimal, highlighting the need to standardise practice regarding lithium prescribing and monitoring, and the provision of information to patients and carers.

### Examples of medication safety incidents which have occurred with lithium

- Patient on lithium for many years. Discharged on diuretic but lithium dose not reduced. Readmitted three weeks later with life-threatening lithium toxicity. [Lithium levels are increased when diuretics are introduced<sup>6</sup>]. (NPSA)
- Patient on lithium. Prescribed NSAID during admission. No adjustment in lithium dose. Patient felt unwell so lithium was held and level sent. [NSAIDs may increase lithium levels. The extent of the increase is unpredictable and can vary from 10% to over 400%<sup>6</sup>]. (Irish Acute General Hospital)
- Emergency admission of patient for lithium toxicity in a critical condition. Lithium levels were out of date. The most recent level, taken 5 months previously, was within the therapeutic range so his lithium was re-authorized. At the time of the report the patient was being ventilated (NPSA).
- Patient on lithium with a history of difficulty in maintaining therapeutic lithium levels required high doses of diuretics for co-morbidity. Dose of furosemide was substantially increased during admission (from 80mg daily to 180mg daily) but lithium dose/level was not considered. No patient harm resulted as the interaction was noted by a pharmacist and raised with the medical team (Irish Acute General Hospital).

### The key recommendations of the IMSN are as follows:

- ✓ Patients prescribed lithium are monitored in accordance with best practice guidance.
- ✓ Prescribers check that blood tests are carried out and monitored regularly and that it is safe to issue a repeat prescription. The responsibility for ensuring that monitoring takes place lies with the prescriber.
- ✓ Pharmacists, where feasible, check that blood tests are monitored regularly and that it is safe to dispense the prescribed lithium.
- ✓ There are reliable systems to ensure that blood test results are communicated between laboratories and prescribers.
- ✓ Prescribers, pharmacists and patients are aware of medicines that might adversely interact with lithium therapy.
- ✓ At the start of lithium therapy and throughout their treatment patients receive appropriate ongoing verbal and written information, and a record book to track lithium blood levels and relevant clinical tests. To facilitate implementation of this recommendation, information on ordering patient information booklets, patient-held record books and lithium alert cards will be made available on the IMSN website, [www.imsn.ie](http://www.imsn.ie).

## Best Practice Guidance

As very comprehensive guidance relating to the safe use of lithium has previously been published in the UK by the National Institute for Clinical Excellence (NICE) and the NPSA, the Irish Medication Safety Network has decided to re-focus attention on key practice points from these published recommendations.

### 1. Initial Workup

When initiating lithium as long-term treatment, prescribers should:

1. Provide verbal and written information to the patient and/or carer on lithium, its adverse effects, symptoms of toxicity and drug/diet interactions, in order to assure safe use<sup>3</sup>. Discuss pregnancy and contraception with women of childbearing age<sup>2, 7</sup>. A patient information booklet and record book for lithium therapy should be provided to all patients being initiated on lithium and the information therein should be reinforced verbally.
2. Measure height, weight and arrange tests for urea and electrolytes, serum creatinine and thyroid function<sup>2</sup>. Calculate body mass index (BMI). Arrange a full blood count if clinically indicated<sup>2</sup>.
3. Measure kidney function<sup>3, 8</sup> by calculating the eGFR using the MDRD formula<sup>8, 9, 10</sup> \*. In extremes of weight (BMI less than 18.5 kg/m<sup>2</sup> or greater than 30kg/m<sup>2</sup>) and in the very old, the GFR as calculated from the Cockcroft & Gault formula is the preferred measurement of renal function<sup>1</sup>.
4. Arrange an ECG for patients with cardiovascular disease or risk factors for it<sup>2</sup>.
5. Advise patients that erratic compliance or rapid discontinuation may increase the risk of manic relapse<sup>2</sup>. Treatment should not be started unless there is a clear intention to continue it for at least 3 years, as intermittent treatment with lithium may worsen the natural course of bipolar illness<sup>3, 6</sup>. Note that to establish its effectiveness as a long term treatment, it should be taken for at least 6 months<sup>2</sup>.

\* Estimated calculations of Glomerular Filtration Rate (GFR) are the best overall indices of the level of kidney function. GFR is usually estimated using either the Modification of Diet in Renal Disease (MDRD) or the Cockcroft & Gault formula. The MDRD formula provides a rigorously developed equation for estimating GFR, which may allow for improved and more accurate prediction of GFR, when compared with the Cockcroft & Gault formula, and may be used to measure renal function during lithium use. In extremes of weight (BMI less than 18.5 kg/m<sup>2</sup> or greater than 30kg/m<sup>2</sup>) and in the very old, the GFR as calculated from the Cockcroft & Gault formula is the preferred measurement of renal function. eGFR (MDRD formula) is increasingly routinely reported on samples sent for creatinine measurement, or may be easily calculated using an eGFR calculator such as that available at [www.renal.org/eGFRcalc/](http://www.renal.org/eGFRcalc/).

## 2. Prescribing Lithium

1. The usual starting dose in adults is 200 - 400mg of lithium carbonate at night<sup>3</sup>.
2. The recommended starting dose in the elderly is 200mg of lithium carbonate at night<sup>6</sup>. Lithium clearance is reduced in the elderly through reduced renal function and increased volume of distribution; the elderly may develop symptoms of lithium toxicity at standard therapeutic blood levels. Doses may need to be reduced by as much as 50%, but with close and frequent monitoring lithium can be safely used<sup>11</sup>.
3. Always prescribe lithium by proprietary (brand) name (i.e. Priadel<sup>®</sup> or Camcolit<sup>®</sup>). Although there is no clinically significant difference in the pharmacokinetics of the two brands of lithium available in Ireland<sup>6</sup>, patients should be maintained on the same brand (unless toxicity is suspected or proven). If it is necessary to change brand or formulation (e.g. to liquid form), lithium levels must be monitored weekly, until the desired level is established on the new regime.
4. Liquid formulations of lithium contain lithium citrate; tablet formulations contain lithium carbonate. When prescribing lithium liquid, remember that the strength is expressed in terms of the citrate salt. Lithium carbonate 204mg is equivalent to lithium citrate 520mg. Priadel<sup>®</sup> liquid contains 520mg lithium citrate in 5mL, so 5mL is approximately equivalent to 200mg lithium carbonate<sup>12</sup>. Priadel<sup>®</sup> liquid should be prescribed in divided doses twice daily; in the morning and at night.
5. When initiating lithium, arrange for serum lithium levels to be checked one week after starting and one week after every dose change until the levels are stable<sup>2</sup>. Steady state levels are likely to be reached approximately five days after a dosage adjustment.
6. When arranging sampling of serum lithium levels, remember that sample should routinely be taken 12 hours post dose<sup>3</sup>. Most patients take lithium in the evening; therefore samples should usually be taken in the morning (i.e. if a patient takes lithium at 22.00, levels can be checked at 10.00 the following morning). For patients on lithium liquid, sampling should be done before the morning dose is administered<sup>12</sup>.
7. Aim to maintain serum levels between 0.6 - 0.8 mmol/L in people being prescribed lithium for the first time<sup>2</sup>. The minimum effective plasma level for prophylaxis is 0.4mmol/L with the optimal range being 0.6-0.75 mmol/L<sup>6</sup>. Lower plasma levels of lithium may be better at preventing relapse of bipolar depression and higher levels to prevent mania<sup>11</sup>. Adequate lithium levels (0.4mmol/L or more) seem necessary when lithium is used in combination with antidepressants for the treatment of depression<sup>11</sup>. Toxic effects reliably occur at levels >1.5mmol/L<sup>6</sup>. The optimal maintenance level is the highest dose tolerated without significant side effects and will vary from patient to patient. Lower levels may be required in the elderly, as they may experience toxicity at standard therapeutic blood levels<sup>2</sup>.
8. If lithium therapy is to be stopped, the dose should be reduced gradually over at least 4 weeks and preferably over up to 3 months, particularly if the patient has a history of manic relapse (unless toxicity is suspected or proven)<sup>2</sup>.

### 3. Monitoring of Lithium Therapy

Monitoring of serum lithium levels is necessary to ensure maintenance within the appropriate therapeutic margins. This requires scheduled monitoring; patient harm is possible when patients taking lithium do not have their dosage adjusted based on serum lithium levels and other laboratory parameters as determined from regular blood tests<sup>3</sup>. Clinically significant alterations in lithium blood levels may occur with commonly prescribed and over-the-counter medicines, with changes in salt or fluid intake, or with dehydration due to physical illness (e.g. vomiting, diarrhoea) or exercise<sup>2, 6</sup>. Monitoring of tolerability by regular discussion of side effects and symptoms of toxicity is also advised during long-term treatment<sup>3</sup>.

1. Check serum lithium levels every 3 months routinely<sup>2, 3</sup>.
2. Initiate closer monitoring of lithium dose, serum levels and eGFR if there is evidence of deteriorating renal function. The decision whether to continue lithium depends on clinical efficacy and degree of renal impairment. Lithium is contraindicated in severe renal impairment and the Renal Drug Handbook advises that if glomerular filtration rate is less than 50mL/min it should be avoided if possible, or the dose reduced and plasma level monitored carefully<sup>13</sup>. Consider seeking advice from a renal specialist if there is evidence of deteriorating renal function<sup>2</sup>.
3. Monitor lithium plasma levels closely if a patient is being initiated on medications which have the potential to interact with lithium, particularly
  - a. Thiazides (and related diuretics);
  - b. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-II receptor antagonists;
  - c. Non-steroidal anti-inflammatory drugs (NSAIDs);

These medicines may affect kidney function and lithium excretion<sup>3, 6</sup>. Concomitant use may cause lithium toxicity unless lithium levels are monitored and the dose adjusted<sup>3</sup>. The timescale of effect is variable, from a few days to several months<sup>6</sup>, so more frequent monitoring during the first three months of concomitant use is suggested by IMSN. Note that some NSAIDs are available over the counter, e.g. Nurofen<sup>®</sup> (ibuprofen) and Disprin<sup>®</sup> (aspirin). Advise patients to avoid these and use paracetamol instead where simple analgesia is required. Patients and carers should also be advised to consult their community pharmacist when purchasing any over the counter medication, to ensure that it is safe to take with lithium.

4. Other indications for checking serum lithium levels include<sup>2</sup>:
  - a. Clinical deterioration
  - b. Abnormal results
  - c. Change in sodium or fluid intake
  - d. Symptoms suggestive of abnormal renal or thyroid function.

Lithium toxicity is made worse by sodium depletion. Sodium imbalance (e.g. from diarrhea, vomiting, infection or from disease such as Addison's) requires correction – dose reduction or discontinuation of lithium may be required<sup>1</sup>.

5. Ask routinely at each visit whether the patient is experiencing any side effects or signs of lithium toxicity. Monitor particularly for symptoms of neurotoxicity (tremor, paraesthesia, ataxia, cognitive impairment) which can occur at therapeutic levels<sup>2</sup>; and gastrointestinal symptoms (anorexia, nausea, diarrhoea) which can be signs of lithium toxicity<sup>6</sup>.
6. Ensure that there is a reliable system in place to allow timely communication of the results of blood tests between laboratories and prescribers, to inform both initial and repeat prescribing. This will require that patients' bloods are taken in advance of clinical assessment. For consistent interpretation and reliability, blood samples should be taken as close as possible to 12 hours after the last dose<sup>3</sup>.

#### 4. Monitoring of Physical Health

Plasma levels of lithium are dependent on renal function and lithium has the potential to interfere with renal and thyroid functions<sup>3</sup>. Lithium may cause weight gain and bipolar patients appear to be at risk of more physical comorbidity and mortality than the general population<sup>2</sup>. Monitoring of renal function, thyroid function, weight, and general health is necessary.

1. Check renal function (eGFR) and thyroid function every 6 months and whenever the clinical status changes<sup>2,3</sup>.
2. Check weight/BMI annually and more often if there is rapid weight gain<sup>2</sup>.
3. Check blood pressure and plasma glucose annually<sup>2</sup>.
4. Check the lipid profile annually for patients over the age of 40<sup>2</sup>.

#### 5. Lithium and Surgery

Lithium is probably safe in minor surgery, but is usually discontinued before major procedures and re-started once electrolytes normalise<sup>6</sup>. The following points should be considered when deciding whether or not to continue lithium during surgery and the perioperative period.

**5.1** Lithium prolongs the action of both depolarizing and non-depolarising muscle relaxants<sup>6</sup>.

**5.2** Surgery-related electrolyte disturbance and reduced renal function may precipitate lithium toxicity<sup>6</sup>.

**5.3** Adequate hydration must be ensured, as dehydration may precipitate lithium toxicity<sup>6</sup>.

**5.4** NSAIDs should be avoided due to their effects on renal function and lithium excretion<sup>6</sup>.

**5.5** There is a possible increased risk of arrhythmia associated with lithium use in surgery<sup>6</sup>.

**5.6** If stopping lithium prior to surgery, slow discontinuation is desirable to reduce the risk of relapse<sup>6</sup>. If this is not possible, ensure that the patient's mental state is closely monitored, and that lithium treatment is reinstated as soon as it is safe to do so.



## Safe Use of Lithium: Implementation of Recommendations

Individual healthcare organisations should compare local practices with the recommendations above. The aim is to identify any system weaknesses which might be addressed by implementing new safety initiatives or strengthening existing ones. An annual audit system should be put in place to monitor adherence to these recommendations.

### The following safety strategies address the key recommendations:

- Local clinical policies and procedures should include a requirement to follow current monitoring guidelines for lithium therapy, as described in section 3 above.
- Plans or systems should be put in place to effectively communicate blood test results between laboratory services and prescribers<sup>3</sup>.
- Local policies and procedures should specify the requirement to issue and support the use of a lithium booklet, alert card and record book<sup>3</sup>.
- Local policies and procedures should direct prescribers, pharmacists and nurses to check the scheduling of blood tests, and to reassure themselves where feasible before prescribing, dispensing or administering that, given the test results, no patient harm will result<sup>3</sup>.
- Local policies and procedures direct healthcare practitioners to communicate and take account of possible changes in lithium levels when interacting medicines are identified<sup>3</sup>.
- Active promotion of key recommendations should be undertaken at suitable educational opportunities e.g. nursing in-services, intern orientation, junior doctor education sessions.
- Passive promotion of recommendations should be undertaken by means of in-house publications, where available e.g. Prescribers' Guides, medication safety bulletins, medication safety intranet sites.

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