LITHIUM Prescribing Support in Affective disorders in Adults
(June 2018)

- Please refer to the CCG formulary for links to local and national guidance: https://www.cambridgeshireandpeterboroughccg.nhs.uk/health-professionals/prescribing-information/formulary-and-drug-classification/
- Lithium requires specialist initiation.
- 3 monthly monitoring of lithium levels for first year, maybe reduced to 6 monthly thereafter unless in a specified risk group.
- 6 monthly monitoring of: Weight/BMI, Urea and electrolytes, eGFR and calcium, Thyroid function.
- Monitor for adverse effects.
- Prescribe by brand to assure consistent bioavailability.
- A lithium treatment pack should be given to patients on initiation of lithium treatment.

Further information regarding specialist prescribing is available in the Cambridgeshire and Peterborough NHS Foundation Trust (CPFT) Lithium Prescribing and Monitoring Guidelines http://www.cpft.nhs.uk/help/documents-that-guide-practice.htm

Advice and Support

The Cambridgeshire and Peterborough NHSFT Pharmacy Departments are available, Monday-Friday 9am-5pm, to provide general advice and support on the prescribing and monitoring of lithium.

For urgent specialist advice about individual patients, please contact pharmacy, in the first instance, and they will facilitate access to the patient’s consultant if necessary.

For routine specialist advice about individual patients, contact the patient’s consultant via your PRISM practitioner.

Pharmacy contact numbers

Peterborough, Huntingdonshire and Fenland localities: (01733) 776006
Cambridge, South and East Cambridgeshire localities: (01223) 219523

Licensed indications and prescribing good practice
Lithium is licensed for the treatment of:

- Treatment of acute manic or hypomanic episodes
- Treatment of recurrent depression where other antidepressants have failed
- Prophylaxis in bipolar affective disorder
- Control of aggressive behaviour or intentional self-harm
Please refer to the CCG formulary for links to local guidance:
https://www.cambridgeshireandpeterboroughccg.nhs.uk/health-professionals/prescribing-information/formulary-and-drug-classification/

Patients prescribed lithium should be offered a purple lithium booklet, in which they can record the results of lithium levels, renal/thyroid function tests, and dates for next test. The patient should be encouraged to bring the booklet to any appointment with the prescriber or specialist. They should also be asked for it when a supply of lithium is dispensed by a pharmacy. Supplies of the booklets can be ordered from nhsforms@mmm.com, alternatively apps are available for apple and android, respectively, at:

Lithium should be initiated by a specialist. Patients should be involved in the decision to initiate lithium and be provided with information to make an informed choice. Printable leaflets including handy charts for comparing all the treatments available can be found at the CPFT choice and medication website: http://www.choiceandmedication.org/cambridgeshire-and-peterborough/. The specialist is responsible for discussing potential risks and benefits of lithium therapy with the patient, and providing a purple NPSA lithium pack.

Lithium should never be stopped abruptly, except in cases of toxicity; abrupt discontinuation is associated with significant risk of relapse. If the patient wishes to discontinue lithium, the GP should refer back to the specialist.

Preparations and Dosage
The specialist should specify the appropriate target range for lithium level, and record this in the patient’s purple book. The usual target ranges will be between 0.4-1.0mmol/L, more specific ranges may be recommended depending on a number of factors including indication and age (see appendix 1).

Lithium should be prescribed by brand name, because of its narrow therapeutic range and differences in bioavailability between products.

Within CPFT, the preferred brand is Priadel®; this is available as:

- Priadel MR tablets (lithium carbonate) 200mg – scored tablet, can be split in two. Usually given as a single daily dose
- Priadel MR tablets (lithium carbonate) 400mg – scored tablet, can be split in two. Usually given as a single daily dose
- Priadel liquid (lithium citrate) 520mg/5mL. Usually given as a twice-daily dose

5mL of Priadel liquid is equivalent in lithium content (5.4mmol Li⁺) to a Priadel 200mg tablet.

Other brands of lithium preparation include Camcolit® and Liskonium® tablets, and Li-Liquid® in two different strengths. Any switch between preparations should be managed cautiously, with close monitoring of plasma lithium levels.

The recommended starting dose is 400mg Priadel tablet (200mg for elderly), taken at night. A lithium level should be taken after 5-7 days, and the dose adjusted if necessary. An appropriate dose increment for community initiation would be an increase in the daily dose by 400mg Priadel tablet (200mg for elderly) until the lithium level approaches target range, then smaller increments if needed.

Dose should be adjusted to maintain the plasma lithium level within the target range specified for the patient. Lithium exhibits linear pharmacokinetics, so the steady-state plasma level will be proportional to the dose (i.e. doubling the dose will approximately double the lithium level).

Contraindications and cautions
Lithium is contraindicated in patients with hypersensitivity to lithium or to any of the excipients, Cardiac disease, Cardiac insufficiency, Severe renal impairment, Untreated hypothyroidism, Breast-feeding, Patients with low body sodium levels, including for example dehydrated patients or those on low sodium diets, Addison's disease, Brugada syndrome or family history of Brugada syndrome.
Lithium is cautioned in mild or moderate renal Impairment, patients with disturbed fluid/electrolyte balance (e.g. patients with nausea, vomiting, diarrhoea, excessive sweating, severe dieting, very hot weather or work environment), infectious diseases (including colds, influenza, gastro-enteritis and urinary infections) and/or other conditions leading to salt/water depletion, epilepsy, QT prolongation, elderly patients

There have been case reports of benign intracranial hypertension. Patients should be warned to report persistent headache and/or visual disturbances.


Drug interactions
Below are some general drug interactions with lithium but prescribers must consult the Summary of Product characteristics for more detailed information on each specific drug. This is not an exhaustive list.

<table>
<thead>
<tr>
<th>Drug/Therapeutic group</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>ACE inhibitors can raise lithium levels, and in some individuals two- to fourfold increases have been recorded.</td>
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<tr>
<td>Thiazide diuretics</td>
<td>Thiazide and related diuretics can cause a rapid rise in lithium levels, leading to toxicity.</td>
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<tr>
<td>NSAIDS</td>
<td>NSAIDs can increase lithium levels leading to toxicity, especially risky if used on PRN basis (e.g. high-dose for several days/weeks for acute injury).</td>
</tr>
<tr>
<td>Angiotensin II receptor antagonists</td>
<td>Lithium toxicity</td>
</tr>
<tr>
<td>Sodium compounds</td>
<td>The ingestion of marked amounts of sodium can prevent the establishment or maintenance of adequate lithium levels. Conversely, dietary salt restriction can cause lithium levels to rise to toxic concentrations if the lithium dose is not reduced appropriately.</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Lithium levels are reduced by 20 to 30% by the concurrent use of theophylline.</td>
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</tbody>
</table>

Adverse effects

<table>
<thead>
<tr>
<th>Type</th>
<th>Adverse effect</th>
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<tbody>
<tr>
<td>Side-effects at ‘therapeutic’ lithium levels</td>
<td>Mild gastro-intestinal disturbance (nausea, diarrhoea) especially at the start of treatment, Fine tremor, Dry mouth, metallic taste, Oedema, Polydipsia, polyuria, Weight gain</td>
</tr>
<tr>
<td>Longer term effects</td>
<td>Hypothyroidism, Renal impairment, Hypercalcaemia</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Signs include: Blurred vision, Increased gastrointestinal disturbance, Coarse tremor, Muscle weakness, Ataxia, Confusion, Drowsiness</td>
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Toxicity may develop as a result of dehydration (including fever, stomach ‘bugs’), drug interaction, changes in sodium intake, or decline in renal function.

If the patient exhibits signs of lithium toxicity:

- STOP LITHIUM IMMEDIATELY
- Check lithium level, eGFR and U&Es
- Ensure an adequate fluid intake
- Consider transfer to A&E
A patient’s lithium level may be high (typically > 1.0 mmol/l) but with no signs of toxicity. In this circumstance if there is an identifiable cause (e.g. dehydration, timing of level, interacting medicines, brand change), where possible, correct the cause and recheck the level. If it is not possible to correct the cause, or if there is no explanation, seek specialist advice.

Toxic effects reliably occur at levels >1.5mmol/l but may occur at lower levels, including therapeutic levels. Levels of 2mmol/l or more will require urgent transfer and treatment at an acute hospital.

**Pregnancy and contraception**

The majority of studies have not suggested that taking lithium in pregnancy increases the overall risk of birth defects. An increased risk of foetal heart defects has been suggested but not confirmed. Any risk that exists to the foetus needs to be balanced with the importance of maintaining mental health in pregnancy.

Seek specialist advice for women taking lithium who are planning a pregnancy or who are pregnant.

If a decision to stop lithium is taken, slow discontinuation before conception is the preferred course of action because abrupt discontinuation is suspected of worsening the risk of relapse.

If a woman continues taking lithium during pregnancy:

- check plasma lithium levels every 4 weeks, then weekly from the 36th week
- adjust the dose to keep plasma lithium levels in the woman’s therapeutic range
- ensure the woman maintains an adequate fluid balance
- ensure the woman gives birth in hospital
- ensure monitoring by the obstetric team when labour starts, including checking plasma lithium levels and fluid balance because of the risk of dehydration and lithium toxicity
- stop lithium during labour and check plasma lithium levels 12 hours after her last dose

**Monitoring**

**Specialist responsibility**

Before treatment is started, the following should be checked:

- Urea and electrolytes, calcium, and eGFR
- Thyroid function
- Full blood count
- Baseline weight/BMI
- Baseline ECG if patient has cardiac disease or known risk factors

During the initial stages of treatment, weekly lithium levels should be taken and the dosage adjusted accordingly. It is the specialist’s responsibility to ensure the patient is prescribed lithium and monitored appropriately until the dose is stable.

This may be done by:

- Blood sampling, monitoring and prescribing remaining within secondary care until a stable dose is reached. This option may be difficult to achieve in some locations, and can be inconvenient for the patient.
- Blood sampling done in primary care, with results communicated to secondary care, and specialist prescribing (or specialist advising GP on prescribing). This option relies on good two-way communication between GP and specialist.
- Blood sampling, monitoring and prescribing done within primary care. This can be achieved if the specialist gives clear advice to the GP on the target level and dose increments.

If a GP practice does not agree to make individual arrangements for patients, the prescribing and monitoring until stable must be undertaken in secondary care.
Samples for plasma lithium level should be taken approximately 12 hours after the last dose (range 10-14 hours). Once-daily dosing at night will allow the sample to be taken at a convenient time in the morning. If lithium is taken twice a day, it may be necessary to delay the morning dose on the day of sampling.

Once the lithium level is within the target range, the blood test should be repeated after another week to ensure it is stable on that dose. Continue to repeat weekly testing if the level is significantly different.

**GP and Primary care responsibility**
Routine ongoing prescribing and monitoring of lithium will usually be the responsibility of the GP (see Appendix 1 for further guidance). Advice or referral back to the specialist should be considered if lithium levels, renal function, calcium levels and/or thyroid function are outside of normal range for that patient.

Once a stable dose has been reached, lithium levels should be checked every 3 months for the first year. After that, levels should be checked *as a minimum* once every 6 months.

NICE guidance recommends checking lithium levels every 3 months for people in any of the following groups:

- Older people
- Those taking medicines that interact with lithium
- Those at risk of impaired renal function or thyroid function, raised calcium levels, or other complication
- Those with poor symptom control
- Those with poor adherence
- Those whose last plasma level was 0.8 mmol/L or higher.

In addition, the following should be monitored every 6 months:

- Weight/BMI
- Urea and electrolytes, eGFR and calcium
- Thyroid function

Advice or referral back to the specialist will also be required if the patient wishes to discontinue lithium or their condition deteriorates to warrant a referral to secondary care.

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**References**

Appendix 1
Guidance for Routine Monitoring

Lithium level
Always check that the timing of the blood sample has been appropriate. It is important to determine the optimum range for each individual patient. The desired level depends on what indication lithium has been prescribed for, age and past clinical response:

- Target range for preventing relapse in mania and depression is 0.4-1.0mmol/L
- Older people are more sensitive to lithium levels and side effects, aim for lower end of range.
- 0.6-0.8 mmol/L for people being prescribed lithium for the first time.
- 0.8-1.0 mmol/L may be considered for people who have had a relapse whilst previously taking lithium or are taking lithium and have subthreshold symptoms with functional impairment.

If the level is low (typically <0.4mmol/l)
1) If the patient is well and the levels are consistently low but within the desired specified range for that patient, do not alter dose.
2) If the patient is unwell and pattern of levels have been bordering on the lower end of the range:
   a) assess compliance
   b) increase the dose if appropriate
   c) recheck the level in 5 days
3) If the low level is inconsistent with the trend:
   a) assess compliance
   b) consider other factors, e.g. drug interactions, excess intake of fluid, brand change.
   c) recheck level in 5 days

If the level is within therapeutic range (typically 0.4 – 1.0 mmol/l)
1) If the patient is well and tolerating lithium, do not alter dose.
2) If the patient is well but complaining of side-effects e.g. polyuria, polydipsia, reduce the dose and check:
   a) If change in diet e.g. dietary salt restriction.
   b) Initiation of interacting medicines by doctor or use of OTC products.
3) If the patient is clinically unwell, liaise further with CPN / psychiatrist

If the level is high (typically >1.0 mmol/l) but with no signs of toxicity
1) Consider whether there is an explanation for the high level e.g. dehydration, timing of level, interacting medicines or brand change. Correct where possible and recheck level.
2) If the level is part of a pattern of levels which have bordered on being too high:
   a) Decrease the dose by 200-400mg
   b) Encourage fluids
   c) Recheck level in 5 days
3) If there is no clear explanation for high level:
   a) Recheck level
   b) Investigate renal function
Toxic effects reliably occur at levels >1.5mmol/l but may occur at lower levels, including therapeutic levels. Levels of 2mmol/l or more will require urgent transfer and treatment at an acute hospital.