Lithium in Affective Disorders in Adults: Prescribing Support Document

Executive summary

- Please refer to the Cambridgeshire and Peterborough Joint Formulary for links to local and national guidance.
- Lithium requires **specialist initiation** with three monthly monitoring of lithium levels for first year, which may be reduced to six monthly thereafter unless in a specified risk group.
- Six monthly monitoring of: weight/BMI, urea and electrolytes, eGFR and calcium, and thyroid function is required.
- **As well as responding to absolute values in laboratory tests, a rapid change or a consistent trend in any value should prompt caution and extra vigilance.**
- Patients should be monitored for adverse effects.
- Lithium should be **prescribed by brand** to assure consistent bioavailability.
- A **lithium treatment pack** should be given to patients on initiation of lithium treatment by the specialist.

Advice and Support

The Cambridgeshire and Peterborough NHS Foundation Trust (CPFT) 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 CPFT pharmacy teams, 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 Advice and Guidance.

Please see **Appendix 1 Guidance for Routine Monitoring** for advice of handling out-of-range lithium level and when toxicity is suspected.

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

Patients prescribed lithium should be given a purple lithium treatment pack 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. Apps are free to download from Apple and Android app stores via NHS Physical Health Monitor App or supplies of the booklets can be ordered from 3M directly by telephone via 0845 610 111 or via email.

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. The specialist is responsible for discussing potential risks and benefits of lithium therapy with the patient, and providing a purple lithium booklet 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

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 and overseen by the patient's specialist (via Advice & Guidance), with close monitoring of plasma lithium levels with support from specialist.

Dosage and plasma lithium level

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 200mg Priadel tablet 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).

The specialist should specify the appropriate target range for lithium level, and record this in the patient's purple book. The usual target range in bipolar disorder is between 0.4- 1.0mmol/L for adults and more specific ranges may be recommended depending on other factors such as indication and age

(see appendix 1). In unipolar depression where lithium is prescribed to prevent recurrence or relapse, the plasma lithium level should be between 0.4-0.6mmol/L in all ages.

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.

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 as per BNF guidance, 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 and elderly patients.

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

For further information please consult the latest edition of the BNF or Summary of Product Characteristics (SPC) for full details.

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.

Drug/Therapeutic group	**Interaction**
ACE inhibitors	ACE inhibitors can raise lithium levels, and in some individuals two- to fourfold increases have been recorded.
Thiazide diuretics	Thiazide and related diuretics can cause a rapid rise in lithium levels, leading to toxicity.
NSAIDS	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).
Angiotensin II receptor antagonists	Lithium toxicity
Sodium compounds	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.
Theophylline	Lithium levels are reduced by 20 to 30% by the concurrent use of theophylline.
SGLT2 inhibitors	SGLT2 inhibitors may decrease serum lithium concentrations.

Adverse effects

Prescribers should consult the latest edition of the British National Formulary or Summary of Product Characteristics (SPC) for full details.

Type	Adverse effect
Side-effects at 'therapeutic' lithium levels	Mild gastro-intestinal disturbance (nausea, diarrhoea) especially at the start of treatment, fine tremor, dry mouth, metallic taste, oedema, polydipsia, polyuria, weight gain
Longer term effects	Hypothyroidism, renal impairment, hypercalcaemia
Toxicity	Signs include blurred vision, increased gastrointestinal disturbance, coarse tremor, muscle weakness, ataxia, confusion, drowsiness

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 Accident & Emergency

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, paternal exposure 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.

For patients of childbearing potential taking lithium who are planning a pregnancy or who are pregnant refer to perinatal mental health service.

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 patient continues taking lithium during pregnancy:

- check plasma lithium levels every four weeks, then weekly from the 36th week.

- adjust the dose to keep plasma lithium levels in the patient's therapeutic range.
- ensure the patient maintains an adequate fluid balance.
- ensure the patient 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 the patient's last dose.

Animal studies have reported spermatogenesis abnormalities that may lead to impairment of fertility. It is unknown if this risk applies to humans. There is currently no evidence that lithium used by those who can biologically father a child, around the time of conception can harm the baby.

Patients of child-bearing potential should be advised to use a reliable form of contraception, preferably a highly effective user independent form such as an intra-uterine device or implant or two complementary forms of contraception including a barrier method. It is the responsibility of the specialist to provide advice on the need for contraception to male and female patients on initiation and at each review, but the ongoing responsibility for providing this advice rests with both primary care prescriber and the specialist.

Information for healthcare professionals can be found via the UK Teratology Information Service and information for patients and carers via Medicines in Pregnancy.

Breastfeeding

Lithium is secreted in breast milk and there have been case reports of neonates showing signs of lithium toxicity. Breastfeeding should be avoided during treatment with lithium.

Information for healthcare professionals can be found via the Specialist Pharmacy Service.

Monitoring Specialist responsibility

Please refer to previous section on Dosage and plasma lithium level.

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
- Exclude pregnancy and breastfeeding

Additional baseline investigations should be included when lithium is indicated for bipolar disorder:

- Diet, nutritional status and level of physical activity
- Cardiovascular status including pulse and blood pressure (BP)
- Metabolic status including fasting blood glucose/glycosylated haemoglobin (HbA_{1c}) and blood lipid profile.
- Liver function tests (LFTs)

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. 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.

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.

When prescribing and/or monitoring responsibilities are transferred to the GP, the following information should be provided by the specialist to the GP:

- Prescription details (Including name, brand and form of medication; dose and frequency)
- Results of most recent blood results including:
    - o Lithium level
    - o Urea and electrolytes (including serum creatinine and eGFR calculation)
    - o Thyroid function
    - o Calcium level
- Target lithium level range
- Date of next blood test
- Required frequency of blood tests
- Details of whether a lithium booklet have been provided

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. It is the specialist's responsibility to specify the required frequency of lithium level monitoring.

- 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, calcium and eGFR - To be monitored more frequently if there is any evidence of impaired renal function.
- Thyroid function - To be monitored more frequently if there is any evidence of impaired thyroid function.

The following should be monitored annually as part of physical health check:

- Diet, nutritional status and level of physical activity
- Cardiovascular status including pulse and blood pressure (BP)
- Metabolic status including glycosylated haemoglobin (HbA_{1c}) and blood lipid profile.
- Liver function tests (LFTs)

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.

Advice and Support

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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:

- Treatment or prophylaxis in bipolar disorder is 0.4-1.0mmol/L in adults aged 18-64.
    - 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.
- Older people (adults aged 65 or above) are more sensitive to lithium levels and side effects. In bipolar disorder a maintenance level of 0.4-0.8mmol/L is generally recommended and for people aged 80 or above, the top range should not exceed 0.7mmol/L.
- Prophylaxis In unipolar depression, target range should be between 0.4-0.6mmol/L in all ages.

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

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, >0.8 mmol/l for older people) 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.

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