793FM.3.1 LITHIUM FOR USE IN PSYCHIATRIC SERVICES - Shared Care Protocol

This protocol provides prescribing and monitoring guidance for lithium therapy. It should be read in conjunction with the Shared Care Responsibilities Document, the Summary of Product Characteristics (SPC) available on www.medicines.org.uk/emc and the BNF.

Contents

Background for use

1. Lithium is predominantly used in the following situations:
   a. The acute treatment of mania or hypomania
   b. Prophylaxis in bipolar disorders
   c. The control of aggressive behaviour or intentional self-harm
   d. Treatment and prophylaxis of recurrent depression where treatment with other antidepressants has been unsuccessful

   Its use is supported by the NICE guidelines for depression (NG90) and bipolar disorder (NG185).
2. For most patients, lithium is a long-term treatment. For example, it is recommended that patients with bipolar disorder take lithium for at least 2 - 5 years depending on number of episodes.
3. The aim of treatment is to control symptoms and prevent relapse in patients with conditions described above. Lithium should be initiated by or on the advice of a psychiatrist.
4. Lithium has a narrow therapeutic index – the usual therapeutic range is between 0.4 and 1.0 mmol/L. Levels below 0.4 mmol/L are subtherapeutic whilst those above 1.2 mol/L are toxic in most patients. See table in Monitoring section for details on managing low/high levels. Toxicity is serious and clinical consequences include seizures and irreversible renal damage.
5. Even when lithium levels are within range the risk of long term side effects which include, hypothyroidism, weight gain and renal impairment remain.
6. Changes in renal function, fluid balance and electrolyte levels can lead to lithium toxicity.
7. Significant alterations in lithium levels can occur with commonly prescribed and over the counter medication such as non-steroidal anti-inflammatory drugs (NSAIDs).
8. Due to the above it is important that patient's blood tests are monitored regularly in accordance with NICE and local guidance.
9. Information about side effects and signs of toxicity should be given to patients prescribed long-term lithium. They should be warned of the urgency of immediate action should symptoms appear, and of the need for a constant and adequate salt and water intake. Treatment should be discontinued on the first signs of toxicity.

10. Treatment with lithium is usually initiated and stabilised by psychiatrists. However, general medical practitioners who participate in shared care are responsible for prescribing and routine monitoring of results obtained from monitoring. Community pharmacists are responsible for dispensing lithium to patients treated in primary care and they should ensure that the required monitoring has been carried out when dispensing lithium.
11. According to the manufacturers, it takes 6 - 12 months before the full prophylactic effect occurs.

Responsibilities and roles

Shared care assumes communication between the specialist, GP and patient. The intention to share care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss medication therapy.

Specialist:

- Confirm diagnosis and assess need for and suitability of lithium treatment.
- Provide verbal and written patient information including a completed lithium booklet which includes the record book and alert card.
- Inform patients of signs of toxicity and, for women of child bearing age, about the possible lithium teratogenic effects.
- Arrange baseline monitoring in secondary care as indicated and record the results in the electronic patient record.
- Prescribe until the patient is on a stable dose of lithium and is mentally well and until the GP formally agrees to shared care.
- Carry out serum lithium monitoring during initial titration and after dose changes.
- Consider the potential for drug interactions (see Drug interactions for more information).
- Monitor benefits of treatment, side effects, treatment adherence and lithium monitoring details at clinic appointments (frequency indicated by clinical condition) and inform GP of progress.
- Evaluate any adverse events noted by the patient/carer or GP.
- Send a letter to the GP to request shared care once the dose of lithium is stable and the patient is well, outlining the shared care protocol criteria. If shared care is agreed, request that the GP prescribes lithium by brand name and carries out the necessary blood tests (see below and Monitoring section), recording them in the record book before issuing a repeat prescription.
- Ask GPs to carry out maintenance monitoring – lithium levels 3 monthly or 6 monthly as advised, 6 monthly urea and electrolytes (U&Es), estimated glomerular filtration rate (eGFR), calcium levels and thyroid function tests (TFTs), and yearly weight monitoring. Review results (view on ICE) and lithium record book entries at outpatient appointments.
- Advise on target lithium level and any recommended change of therapy.
- Provide a clear plan for lithium treatment to the GP, including anticipated duration of treatment.
- Be available to give advice to the GP and patient throughout treatment.
- Document all communication with the GP in the patient's electronic health record.
- When a patient is considered to have been stable mentally and functionally for a suitable period of time and it is intended that treatment with lithium will be lifelong, liaise with the GP about the possibility of fully discharging the patient back to the care of the GP. The specialist must advise of ongoing monitoring requirements. The GP must be able to access a fast track referral back to a secondary care specialist if needed at any point.

GP:

- Prescribe lithium once the dose is stable and shared care has been agreed.
- Prescribe and change the dose of treatment as advised by the hospital specialist team – ensuring the relevant tests have been carried out before issuing further prescriptions.
- Consider potential drug interactions with items prescribed for the patient and communicate and take account of possible changes in lithium levels when interacting medicines are identified.
- Check serum lithium levels every 3 months or 6 months as advised by hospital specialist (also see Monitoring section) once stable and take appropriate actions as indicated above, informing patients of lithium results.

- Check U&Es, eGFR, calcium and TFTs 6 monthly and monitor weight yearly (or per NICE CG189 Obesity: identification, assessment and management) and record in lithium book provided by the Community Mental Health Team.
- In addition to the lithium-specific monitoring, carry out a yearly physical health check to include the following, as per NICE CG185 Bipolar disorder: assessment and management recommendations:
    - weight or body mass index (BMI), diet, nutritional status and level of physical activity
    - cardiovascular status, including pulse and blood pressure
    - metabolic status, including glycosylated haemoglobin (HbA1c), and blood lipid profile
    - liver function
- Advise hospital specialist if there are concerns about adverse effects or concerns about lack of ongoing therapeutic benefit.
- Respond to a specialist's request for the discharge of patients who have been stable mentally and functionally for a suitable period of time.
- Where a patient, who will be on lithium lifelong, is discharged from secondary care, prescribe, monitor and review lithium as per consultant advice (see also NICE and NPSA guidelines).
- If there are any concerns about a discharged patient, seek advice from a secondary care specialist and refer the patient back for assessment as appropriate.

Community pharmacist:

- Ensure the patient has appropriate ongoing oral and written information and a record book to track lithium blood levels and the relevant clinical tests.
- Consider the potential significant drug interactions with any items prescribed for the patient using the patient medical record (PMR) and refer to the GP where necessary or contact Oxford Health NHS Foundation Trust (OHNHS FT) Medicines Advice Service on medicines.advice@oxfordhealth.nhs.uk or 01865 904365 if further information is needed.
- Check blood tests are monitored regularly and that it is safe to dispense the prescribed lithium.
- Inform the GP or the patient's community mental health team if the patient does not have a completed record card and it is not possible to ascertain compliance with monitoring.

Patient:

- Agree to treatment and monitoring after making an informed decision.
- Agree to being under the shared care of the GP and specialist.
- Request verbal or written information as needed.
- Ensure lithium is taken as prescribed – notifying GP or specialist of any adverse effects or concerns about medication.
- Ensure attendance for relevant blood monitoring as indicated by prescriber and information booklet and request that these be written in the lithium record book and bring it to all appointments.
- Attend GP and outpatient appointments as necessary and discuss any information needs or concerns as relevant.
- Inform healthcare professionals that lithium is being taken when seeking medical or pharmacy advice.

Supporting information

Lithium has a narrow therapeutic range necessitating blood levels between 0.4 - 1.0 mmol/L; NICE guidance states that when initiating long-term treatment, clinicians should aim for levels of 0.6 - 0.8 mmol/L normally and 0.8 - 1.0 mmol/L in patients who have relapsed previously on lithium or have sub-syndromal symptoms.

Lithium should be prescribed by brand name as there are two different salts of lithium available (lithium carbonate and lithium citrate) and preparations vary widely in bioavailability.

Available preparations

LITHIUM CARBONATE TABLETS		
Trade Name	**Tablet Strength Available**	**Amount of Lithium (Li^+) ion**
Priadel® - OHNHS FT preferred brand	200 mg m/r (scored) 400 mg m/r (scored)	5.4 mmol/200 mg 10.8 mmol/400 mg
Lithium carbonate (Essential Pharma)	250 mg m/r (scored)	6.8 mmol/250 mg
Camcolit 400®	400 mg m/r (scored)	10.8 mmol/400 mg
Liskonum®	450 mg m/r (scored)	12.2 mmol/450 mg
LITHIUM CITRATE LIQUID		
Trade Name	**Liquid Strength Available**	**Amount of Lithium (Li^+) ion**
Priadel®	520 mg/5 ml	5.4 mmol/5 ml
Li-liquid®	509 mg/5 ml	5.4 mmol/5 ml
Li-liquid®	1018 mg/5 ml	10.8 mmol/5 ml

Dosing frequency depends on preparation prescribed. Liquid preparations and Liskonum® tablets should be prescribed twice daily. Other lithium preparations are usually prescribed as a single dose at night (Camcolit® is usually administered twice daily until levels are stabilised).

Modified release tablets should not be crushed or chewed.

If lithium is to be discontinued, particularly in cases of high doses, the dose should be reduced slowly over a minimum of 4 weeks as abrupt withdrawal can cause relapse. Lithium should be stopped 24 hours before major surgery, but the normal dose can be continued for minor surgery if fluids and electrolytes are carefully monitored.

Adverse effects

Side effects are usually related to serum lithium concentrations and will usually respond to a temporary reduction or discontinuation of lithium.

TYPE OF ADVERSE EFFECT	INCIDENCE and MANAGEMENT
GI disturbances e.g. nausea, diarrhoea, excessive sweating, gastritis, taste disorder, abdominal discomfort.	**Uncommon:** Ensure patient is aware of the need for fluid replacement. As symptoms may lead to excessive salt or water depletion, monitor dosage and make dose adjustments as necessary.
Weight gain	**Common:** Monitor – advise to avoid crash diets and sugary drinks.
Oedema (swelling of the ankles)	**Rare:** Monitor – may respond to dose reduction.
Fine tremor	**Common** on treatment initiation. If persistent, consider dose reduction.
Polyuria (frequent urination) **Polydipsia** (frequent thirst)	**Common** on initiation of therapy. Maintain fluid intake. If persistent monitor renal function and consider dose reduction.
Hypothyroidism	**Uncommon:** Lithium treatment increases the risk of clinical hypothyroidism up to 5-fold (risk particularly high in women who are 40 - 59 years old). Consider thyroid replacement if clinically indicated.
Renal damage	**Rare:** If significant renal impairment, avoid if possible/reduce dose and monitor serum lithium carefully and discuss with psychiatrist.
Cardiovascular e.g. ventricular ectopics, bradycardia; **electrocardiogram (ECG) changes and conduction disturbances** e.g. sinus node dysfunction	**Rare:** Usually benign cardiovascular side effects may occur in 20 - 30% patients. If any clinical signs of cardiovascular problems carry out ECG and review.
Hypercalcaemia	**Rare:** Overall risk of clinically important calcium/parathyroid abnormalities is low. Seek advice from endocrinologist if appropriate.
Leucocytosis	**Common:** Not significant and no action necessary.
Signs of toxicity: Blurred vision, muscle weakness, drowsiness, coarse tremor, dysarthria, ataxia, nausea and vomiting, confusion, convulsions, ECG changes (flat or inverted T waves, QT prolongation)	**Rare:** Stop lithium immediately, measure serum lithium, creatinine, U&Es. **Refer to hospital if clinical condition warrants.**

Contraindications/precautions

Cardiac disease - cardiac failure, sick sinus syndrome and cardiac insufficiency	**Avoid**
Clinically significant renal impairment: 1. GFR <10 mL/min 2. GFR 11 – 50 mL/min	According to The Renal Drug Database 2017: Contraindicated in renal impairment GFR (mL/min): 20 - 50 - Avoid if possible, or reduce dose to 50 - 75% and monitor plasma concentration carefully. GFR (mL/min): 10 - 20 - Avoid if possible, or reduce dose to 50 - 75% and monitor plasma concentration carefully. GFR (mL/min): <10 - Avoid if possible, or reduce dose to 25 - 50% and monitor plasma concentration carefully.
Untreated hypothyroidism	Stabilise thyroid disease before initiation of lithium.
Patients with low body sodium levels e.g. dehydrated patients or those on low sodium diets	Rehydrate before starting lithium.
Addison's disease, Brugada Syndrome or family history of it	Avoid
Breastfeeding/pregnancy	**Women taking lithium should be clearly informed of the possible risks of teratogenicity**. If they are planning a pregnancy or become pregnant they should be referred to psychiatric services for advice. Lithium is excreted in breast milk with resultant risk of toxicity in the infant. Manufacturers advise to avoid.
Hypersensitivity to lithium or excipients	Avoid. Excipients vary according to the preparation being used. Tablets might include glycerol monostearate, glycerol distearate, mannitol, acacia, sodium lauril sulfate, magnesium stearate, maize starch, sodium starch glycolate, gelatin, lactose. Liquid preparations contain ethanol.

Drug interactions *(refer also to BNF - Appendix 1 or relevant SPC)*
Serum lithium levels may be increased if one of the following drugs is co-administered. When appropriate, either lithium dosage should be adjusted or concomitant treatment stopped.

Diuretics (mainly thiazides), NSAIDs, ACE inhibitors, angiotensin II antagonists	Significant risk of toxicity as affect renal function and lithium excretion. May result in **significantly increased lithium levels.** *Unless lithium levels monitored and dose adjusted, concomitant use should be avoided if possible.*
Metronidazole, tetracycline and drugs affecting electrolyte balance	**Use with caution as may increase lithium levels.**
Theophylline, and marked consumption of caffeine or sodium containing preparations e.g. non-prescription antacids/urinary alkalinising agents	May cause a **reduction in lithium levels** and potential for relapse of symptoms.
Steroids	May alter lithium excretion and should be avoided.
Selective serotonin reuptake inhibitors (SSRIs)	Although commonly prescribed together, consider serotonergic syndrome if increased agitation/ autonomic changes, rigidity occur and consider reducing/stopping SSRI dose.

Although isolated reports of increased neurotoxicity with some antipsychotics, antidepressants, antiepileptic medicines, calcium channel blockers – combinations are generally not a cause of concern.

Monitoring*
Lithium has a half-life (t½) of 12 - 27 hours increasing to 36 in the elderly due to decreased renal function, it is necessary that blood levels are **taken at least 12 hours after the last dose**. Normally lithium is prescribed as a night time dose and levels should be carried out between 12 - 14 hours post-dose. Where dosing is twice a day, the morning dose should be withheld until after the sample for levels is taken.

Baseline Tests	Maintenance Monitoring
a. **U&Es** including calcium (Ca) and eGFR b. **TFTs** c. **Full blood count** (FBC) d. **Weight or BMI** or waist circumference e. **Consider ECG** in people who are at high risk of cardiovascular disease	a. **Serum lithium level** 1 week after initiation and 1 week after each dose change, then weekly until levels are stable and then every 3 months **for the first year**. After the first year, measure plasma lithium levels every 6 months, except in the following patients, where 3 monthly monitoring is recommended: • Older people • People taking drugs that interact with lithium • People who are at risk of impaired renal or thyroid function, raised calcium levels, or other complications • People who have poor symptom control • People with poor adherence • People whose last plasma lithium level was 0.8 mmol/L or higher. b. **U&Es including eGFR and Ca, and TFTs** every 6 months (more often if evidence of renal impairment, raised calcium levels or an increase in mood symptoms that might be related to impaired thyroid function). c. Monitor lithium dose and plasma lithium levels more frequently if urea levels and creatinine levels become elevated, or eGFR falls over 2 or more tests, and assess the rate of deterioration of renal function. d. **Weight or BMI** or waist circumference during the last year. e. **Consider ECG** if clinical signs of cardiovascular disease or increased risk. f. **Yearly health check** for people with bipolar disorder should include weight or BMI, diet, nutritional status and level of physical activity, cardiovascular status (including pulse and blood pressure), metabolic status (including HbA1c and lipids, and liver function.

Additional measurements should be made following: Development of intercurrent disease; signs of manic or depressive relapse; significant change in sodium/fluid intake (e.g. due to gastrointestinal upsets); concerns about non-adherence or if signs of lithium toxicity occur. Advice can be sought from secondary care via the Community Mental Health Teams or from the OHNHS FT Medicines Advice Service on medicines.advice@oxfordhealth.nhs.uk.

Plasma levels and recommended action to be taken

Level and Action to be Taken[+]	
Levels <0.4 mmol/L – in keeping with level agreed with specialist team and patient well	Do not alter dose.
Levels <0.4 mmol/L and patient unwell	If lower than level specified by specialist team review compliance, consider other factors e.g. drug interactions, excess fluid intake and recheck level/consult specialist team.
>1.0 mmol/L with no signs of toxicity	If there is an explanation for the high level e.g. dehydration, timing of level, i.e. not 12 hours post dose, interacting medicines, correct where possible and recheck level.
>1.0 mmol/L with no signs of toxicity and the trend is for high end of range	If level is consistent with range specified by specialist team do not alter dose. If not, decrease the dose, encourage fluids and recheck in 1 week.
>1.0 mmol/L with no signs of toxicity and no explanation for high level	Recheck level, investigate renal function and if repeat level is higher than original target level specified refer back to specialist for advice.
If patient shows signs of toxicity - blurred vision, muscle weakness, drowsiness, coarse tremor, dysarthria, ataxia, confusion, convulsions, nausea and vomiting, ECG changes	Stop lithium immediately, measure lithium level, urea and electrolytes, creatinine and eGFR. **Refer to hospital if clinical condition warrants.**

Patient information

All patients should be supplied with the NPSA lithium information pack, which includes the information booklet, lithium alert card and lithium monitoring record book, by the specialist initiating treatment. The written information for patients informs them that healthcare professionals like community pharmacists will ask them for their record book to confirm that it is safe to dispense further supplies of their medicine. Monitoring results should be recorded in the books by the specialist or GP prescriber team.

Back-up information and advice

Consultant/prescriber:	Contact details:
Older Adult Community Mental Health Teams	• North Bucks Older Adult CMHT, based at The Whiteleaf Centre, Aylesbury – 01865 901048 • South Bucks Older Adult CMHT, based at Shrublands, High Wycombe – 01865 901309
Adult Community Mental Health Teams	• Aylesbury Vale AMHT Fact 1&2, based at the Whiteleaf Centre, Aylesbury – 01865 901287 • Chiltern AMHT Fact 1&2 (previously Wycombe area), based at Valley Centre, High Wycombe – 01865 901344 • Chiltern AMHT Fact 3&4 (previously Amersham area), based at Valley Centre, High Wycombe – 01865 901880
Oxford Health NHS Foundation Trust Medicines Advice Service 9am – 5pm Monday to Friday	01865 904365 or medicines.advice@oxfordhealth.nhs.uk (emailed enquiries are given a 2 week deadline unless indicated otherwise)

Shared Care Agreement Form

Available on DocGen. When not available, use the Word version linked here.

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- National Institute for Health and Care Excellence. Depression in adults: recognition and management, Clinical Guideline 90, 2016. https://bnf.nice.org.uk
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