Lithium

Shared Care Protocol

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

Shared Care Responsibilities

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 drug therapy.

Specialist:

- Confirm diagnosis and assess need for and suitability of lithium treatment
- Proviside 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- possible lithium teratogenetic effects
- Arrange baseline monitoring as indicated above in secondary care or by arrangement with the GP 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.
- Ensure that serum lithium monitoring is carried out during initial titration and after dose changes either in secondary care or by arrangement with the GP.
- Jointly consider potential drug interactions with the GP (see above 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 above), 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 U&Es, eGFR and Ca levels, and TFTs, yearly weight monitoring. Request monitoring results to be communicated to Specialist Team and review lithium record book entries at outpatient appointments.
- Advise on target lithium level and 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, liaise with the GP about the possibility of fully discharging the patient back to the care of the GP. 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.
- Carry out baseline monitoring as agreed with Hospital team during initial titration and after dose

changes and communicate results to the Specialist team

- Check serum lithium levels every 3 months or 6 months as advised by hospital specialist once stable & take appropriate actions as indicated above, informing patients of lithium results.
- Check U&Es, eGFR, Calcium, & TFTs 6 monthly & monitor weight yearly, or according to NICE obesity guidelines) and record in lithium book provided by community mental health team.
- Carry out yearly health check as per NICE recommendation.
- Advise hospital specialist if there are concerns about adverse effects or ongoing therapeutic benefit
- Discuss with the specialist when it may be suitable for patients who have been stable mentally and functionally for a suitable period of time to be fully discharged back to the care of the GP.
- Where a patient is discharged from secondary care, prescribe, monitor & review lithium as per 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 patient using PMR & refer to GP where necessary or contact Oxford Health NHS FT Medicines Information Service on med.info@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.

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 and bipolar disorder.
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 yrs 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. Levels below 0.4mmol/L are sub therapeutic whilst those above 1.2mol/L are toxic in most patients. 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 NSAIDs.
8. Due to the above it is important that patients blood tests are monitored regularly in accordance with NICE 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 Consultant Psychiatrists. However, General Medical Practitioners who participate in shared care are responsible for prescribing, routine monitoring and initiating action, on results obtained from monitoring. Community Pharmacists are mostly responsible for dispensing lithium and should ensure required monitoring has been carried out when dispensing lithium.
11. According to the BNF it takes 6-12 months before the full prophylactic effect occurs.

Supporting information

Lithium has a narrow therapeutic range necessitating blood levels between 0.4-1.0mmol/L; The NICE guidance states that when initiating long-term treatment, clinicians should aim for levels of 0.6-0.8mmol/L normally and 0.8-1.0mmol/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.

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

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 gradually 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	**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 & 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 yrs old) Consider thyroid replacement if clinically indicated
Renal damage	**Rare** If significant renal impairment, avoid if possible/reduce dose & monitor serum-lithium carefully & discuss with Psychiatrist

Cardiovascular e.g. Ventricular ectopics, bradycardia, ECG changes & 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 & vomiting, confusion, convulsions, ECG changes (flat or inverted T waves, QT prolongation)	**Rare** Stop Lithium immediately, measure serum lithium, creatinine, urea & electrolytes. **Refer to hospital if clinical condition warrants**

CONTRA-INDICATION/CAUTIONS

Cardiac disease - Cardiac failure, sick sinus syndrome and cardiac insufficiency	**avoid**
Clinically significant renal impairment: 1. GFR<10ml/min 2. GFR 11-50ml/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
Breast-feeding/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 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	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) **Urea and electrolytes** (U&Es) including eGFR b) **Thyroid function tests** (TFTs) c) **Full blood count** c) **Weight or BMI** or waist circumference d) **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 0.8mmol/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 gastro intestinal 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 Oxford Health Medicines Information team on med.info@oxfordhealth.nhs.uk

Level and Action to be Taken[+] patient's specialist team should advise the lithium target levels on initiation of lithium	
Levels < 0.4 mmol/L – level in keeping with that agreed with specialist team and patient is well	Do not alter dose
Levels < 0.4 mmol/L and lower than the range specified by the consultant **OR** if the 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 12hrs 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 & vomiting, ECG changes	Stop lithium immediately, measure lithium level, urea and electrolytes, creatinine and eGFR. **Refer to hospital if clinical condition warrants**

Patient information leaflet

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:**
Oxford Health NHS Foundation Trust Medicines Information Service	01865 904365 med.info@oxfordhealth.nhs.uk

References:

- National Institute for Health and Care Excellence. Depression in adults: recognition and management, Clinical Guideline 90, 2016. www.nice.org.uk
- National Institute for Health and Care Excellence. Bipolar disorder: assessment and management, Clinical Guideline 185, 2016. www.nice.org.uk
- Goodwin GM. Recurrence of mania after lithium withdrawal. Implications for the use of lithium in the bipolar affective disorder. *BJPsych* 1994;164:149-52.
- National Patient Safety Agency. Safer Lithium therapy Patient Safety Alert NPSA 2009/PSA005. December 2009. www.nrls.npsa.nhs.uk/
- Rosemont Pharmaceuticals Limited. Li-Liquid 509 mg/5ml Oral Syrup. Summary of Product Characteristics. Last Updated on eMC 09-Mar-2017
- Sanofi. Priadel 200mg prolonged release tablets Summary of Product Characteristics. Last Updated on eMC 25-Jun-2015
- Sanofi. Priadel Liquid Summary of Product Characteristics. Last Updated on eMC 25-Jun-2015.
- Essential Pharma. Camcolit 400mg, controlled release Lithium Carbonate Summary of Product Characteristics. Date of revision of the text: 07/04/2015 (accessed at www.mhra.gov.uk)
- Teofarma. Liskonum tablets Summary of Product Characteristics. Date of revision of the text: 03/06/2016 (accessed at www.mhra.gov.uk)