Nottinghamshire Area Prescribing Committee

Lithium Prescribing Guideline for Mental Health Indications

Amber 2

Lithium initiated by Secondary Care (Mental Health)

Prescribe by Brand Name (usually Priadel®)

Indications include mania, prophylaxis of bipolar disorder, treatment-resistant depression

Check patient has been given a copy of the NPSA Lithium Therapy Information Pack[11]

Monitoring Required (Secondary Care (Mental Health))

Baseline

eGFR, LFTs, thyroid function (TSH) tests, calcium, bodyweight, height. Assess physical health, especially metabolic status (fasting blood glucose, HbA1c, lipid profile) and cardiac function (pulse, blood pressure and **ECG if indicated**). Full blood count. Exclude pregnancy. Discuss effective contraception, if relevant.

Lithium serum levels: check 7 days after initiation and repeat weekly until stable (sample to be taken 12 hours post dose, prior to the next dose if twice daily dosing). Once stable, monitor levels every 3 months for the first year. Re-check levels 7 days after dose changes.

Patients with bipolar disorder should be advised that erratic compliance / rapid discontinuation of lithium may increase the risk of relapse.

Transfer to Primary Care

*The psychiatrist will send the GP a copy of this guideline and a copy of the patients' care plan including diagnosis, current test results, list of concomitant medication and professional healthcare contact details. The **brand, form, strength, and dosage** of lithium must be clearly stated in any correspondence.*

To ensure both the GP and psychiatrist receive a copy of any blood test results the name and address of both parties should be specified on the sample forms.

Monitoring Required (Primary Care)

Add patients with a diagnosis of bipolar disorder or depression with psychotic symptoms to the Severe Mental Illness (SMI) register.

All patients to have lithium serum levels every 3 months for the first year[1].

Thereafter **check lithium levels at least every 3 months in high-risk patients. This includes older people (age ≥65years), people taking medicines that interact with lithium, people who have poor symptom control, people with poor adherence, people whose last plasma lithium level was ≥0.8mmol/L and people who are at risk of impaired renal or thyroid function, raised calcium levels or other complications[1].**

Check lithium serum levels more frequently if patient is physically unwell, if urea and creatinine levels become elevated or if eGFR falls over 2 or more tests.

Check lithium serum levels at least every 6 months in stable patients who are not in a high-risk category as outlined above[1].

Check eGFR, TSH, calcium, weight every 6 months (more frequently, if clinically indicated)[1].

Check FBC and assess cardiac function if clinically indicated.

An annual health check for people on the SMI register should also include metabolic status (fasting blood glucose HbA1C, blood lipid profile), cardiovascular status (pulse and blood pressure), liver function, diet, level of physical activity, nutritional status, smoking/alcohol, and contraceptive advice (if relevant).

Lithium doses may need to be altered to maintain a level within the range 0.4-1.0mmol/l (based on sample taken 12 hours post dose). Individual patients may have a narrower target level within this range (refer to guideline). Re-check levels 7 days after dose changes.

If the level is 1.0 – 1.5 mmol/L, but with no signs of toxicity – CHECK possible reasons for the high level (e.g. dehydration, sample taken less than 12 hours post dose, new interacting medicines, brand change, incorrect dose taken). Correct where possible and recheck the level. If there are no identified correctable reasons for the level being high – DECREASE the dose, check renal function, encourage fluids, and recheck the level after 5-7 days.

If lithium toxicity suspected or level >1.5mmol/l – STOP lithium immediately and assess patient. Repeat serum lithium, U&Es and creatinine levels and seek hospital advice. Levels >2.0mmol/l consider referral to A&E.

Circumstances in which patients may be referred back to secondary care or advice sought

- Problematic side-effects, including signs of toxicity (ataxia, tremor, cognitive impairment)
- Clinically significant deterioration in renal function
- Clinically significant deterioration in thyroid function despite treatment in primary care
- Hypercalcaemia with other causes excluded
- Deterioration of mental state, or where level of risk to self or others is increased
- Pregnancy
- Erratic/non-compliance
- Advice on drug interactions
- To consider the appropriateness of discontinuing lithium for any reason (patients may not wish to be referred; discontinuation may be possible in primary care on a case by case basis following discussion with the specialist). Only in exceptional clinical circumstances (e.g. palliative care) should lithium be discontinued in primary care without specialist input.

Introduction

Lithium has been classified as an 'Amber 2' drug on the Nottinghamshire joint formulary. As such, lithium must be initiated by a specialist (e.g. consultant psychiatrist, speciality doctor or appropriately qualified non-medical prescriber) in secondary care for all indications. Once treatment is stabilised (after a period of 3-6 months), prescribing and monitoring responsibilities may be transferred to primary care, in line with this guidance.

Licensed Indications

1. The management of acute manic or hypomanic episodes.
2. Prophylaxis of bipolar disorders.
3. Augmentation of antidepressant medication in the management of episodes of recurrent or resistant depressive disorders where treatment with antidepressant alone has been unsuccessful.
4. Control of aggressive behaviour or intentional self harm.

Place in Therapy

Lithium is the most effective long-term treatment for bipolar disorder[1]. It reduces the frequency, duration, and severity of bipolar disorder relapses, and reduces suicidal acts, suicide, and overall mortality. Poor adherence or abrupt discontinuation of lithium may increase the risk of relapse.

The decision to give prophylactic lithium for bipolar disorder is based on a careful consideration of the potential benefits weighed against the likelihood of illness recurrence, patient compliance, and the risks in the individual patient, including physical risk factors. Lithium should only be offered to patients with bipolar disorder, who are motivated to take it regularly for at least one year, otherwise the benefits of taking it may be outweighed by the costs of an increased relapse rate on abrupt discontinuation.

Lithium augmentation (the addition of lithium to antidepressant treatment) is a treatment option for patients whose depression has failed to respond to several antidepressants (NICE CG 91 and NICE Guideline 222)[2,3].

Other medicines used in bipolar disorder include antipsychotics, valproate, and lamotrigine. There are NAPC Amber 2 prescribing guidelines for antipsychotics and lamotrigine.

Dose and Lithium Levels

The initial dose of lithium (as the carbonate salt) is usually Priadel MR 200-600mg at night (100-250mg in the frail or elderly)[12]. Once daily dosing at night may reduce kidney damage compared to multiple daily dosing, improve adherence and facilitates daytime blood tests 12 hours post dose[4]. Lithium citrate liquid preparations are prescribed twice daily; they are not modified release[1]. Doses are adjusted according to patient response and serum lithium level results.

For treatment and prophylaxis of bipolar disorder in lithium-naïve patients, the recommended target initial lithium levels should be between 0.6–0.8mmol/l. For treatment and prophylaxis of recurrent major depressive disorder (unipolar depression) the target is between 0.4–0.6mmol/l. Some patients may need higher lithium levels of 0.8–1 mmol/litre in bipolar disorder and 0.6–0.8mmol/l in unipolar depression to gain control of their symptoms[12]. This decision should be made by the specialist.

Levels at the lower end of the therapeutic range are recommended for older people and those with risk factors such as heart disease, renal impairment, and those taking interacting concomitant medications. A lower target level may also be indicated for those on longer-term maintenance therapy[2].

Different preparations of lithium are not bioequivalent. **Once stabilised the patient must be kept on the same brand and formulation.** Lithium should be prescribed by brand name (normally **Priadel**). Lithium liquid is better prescribed twice daily whereas all modified-release tablets can be taken once daily, preferably at bedtime.

Lithium levels should be checked 7 days after any change in brand or formulation. Care needs to be taken if changing from a lithium carbonate to a lithium citrate preparation to ensure that the **molar dose** (mmol lithium) remains the same. For example: Priadel 200mg tablets contain lithium carbonate 200mg or **5.4mmol lithium/tablet;** and Li-Liquid 509mg/5ml contains lithium citrate 509mg/5ml or **5.4mmol lithium/5ml** (see BNF)**.**

When reviewing lithium levels, check the level was taken at the correct time (12 hours post dose, prior to the next dose if on twice daily dosing).

Duration of treatment and discontinuation

Duration of treatment will be determined by the indication, the individual's previous history, clinical efficacy, and other patient specific risk factors.

The decision to discontinue lithium therapy should be a shared decision between the patient, the specialist, and the GP. Depending on individual patient circumstances, the discontinuation might be managed in primary care with specialist advice. Only in exceptional clinical circumstances (e.g. palliative care) should lithium be discontinued in primary care without specialist input.

When used as prophylaxis for bipolar disorder, treatment can sometimes be indicated for many years. Unless toxicity or adverse effects dictate otherwise, lithium should be discontinued gradually over at least 4 weeks, preferably up to 3 months even if the person has started taking another mood stabiliser. During dose reduction and for 3 months after lithium treatment is stopped, monitor the person closely for early signs of relapse. Thereafter, actively monitor symptoms, mood, and mental state for 2 years (this may be undertaken in primary care)[1].

People who have had a good response to treatment with an antidepressant and lithium augmentation, should remain on this combination after remission if they find the side effects tolerable and acceptable[2]. If one medication is stopped, it should usually be the augmenting lithium first. Lithium should not be used as a sole agent to prevent recurrence of depression[2]. For people continuing medication to prevent relapse of depression, review at least every 12 months in primary care. This review should monitor mood, side effects, and review any personal, social, or environmental factors that may impact on risk of relapse.

Contra-indications

Severe kidney disease, serious heart disease, Addison's disease, untreated hypothyroidism and personal or family history of Brugada syndrome are all **relative** contra-indications to lithium. Specialist advice should always be sought.

Monitoring (see Algorithm)

It is important to note that the toxic effects of lithium may appear before symptoms of acute toxicity, renal or thyroid disease.
An abnormal estimated Glomerular Filtration Rate (eGFR) i.e. below 60ml/min is often found in patients taking lithium, and is not indicative of renal damage, unless there is a fall of >4ml/min per year. Thus it is important to monitor serial eGFRs[5]. If the eGFR falls over 2 or more tests then lithium levels should be monitored more frequently.

Patients with a declining eGFR over time (below 60ml/min), or any eGFR below 30ml/min without acute dehydration, require further assessment for proteinuria, haematuria and cardiovascular status, and referral to a renal specialist[5].

eGFR may be less reliable in certain situations (for example: acute kidney injury, pregnancy, oedematous states, muscle wasting disorders, and in adults who are malnourished, have higher muscle mass or use protein supplements, or who have had an amputation). eGFR has not been well validated in certain ethnic groups (for example, black, Asian, and other minority ethnic groups with chronic kidney disease living in the UK)[6].

With regards to thyroid function, a raised TSH, with normal free T3 or T4, may be clinically important, as it is often associated with worsening control of mood symptoms. A reduction in the lithium dose, or the addition of levothyroxine may be indicated after consultation with a specialist[5].

ECG monitoring should be considered in people at high risk of cardiovascular disease.

An annual physical health check for patients on the SMI register should include a review of all test results and focus on blood (plasma) glucose, HbA1C, blood lipid profile, liver function, cardiovascular status (BP and pulse), weight, diet, nutritional status, level of physical activity, smoking/alcohol and contraceptive advice (if relevant)[1].

Adverse Effects

Adverse effects that occur early on in treatment and are generally minor and transient. They include nausea, loose stools, dyspepsia, metallic taste, fine hand tremor, polyuria, and polydipsia.

Please note that with regards to polyuria and polydipsia, these are important symptoms that may indicate the development of nephrogenic diabetes insipidus, so tests of urine osmolality are indicated[3].

Long-term adverse effects include weight gain. A small percentage of patients (exact incidence is unknown; women are at greater risk) develop hypothyroidism and/or goitre (see above).

Other adverse effects are hyperparathyroidism and hypercalcaemia (hence rationale for 6-monthly calcium level checks), oedema and leucocytosis,

Please note that side-effects can often be relieved by a slight reduction in dose.

Signs of Lithium Toxicity

Lithium toxicity occurs at serum lithium concentrations of approximately 1.5 mmol/L and above but may occur despite an apparently normal lithium level. Signs suggestive of lithium toxicity include severe diarrhoea, vomiting or anorexia, coarse hand tremor, muscle twitching, dehydration, drowsiness, confusion, cognitive impairment, muscle weakness, slurred speech, ataxia, paraesthesia, nystagmus, vertigo, tinnitus, restlessness, and blurred vision. Patients may look ashen/grey.

The central nervous system is most affected in chronic lithium toxicity, with an altered level of consciousness being the most common sign[7]. Chronic lithium toxicity is usually secondary to longer term therapy as a result of febrile illness, dehydration, new interacting medicines, deteriorating renal function and acute or chronic overdose (e.g. switching lithium salts with no dose adjustment)[8].

Patients with acute toxicity (e.g. overdose) may be asymptomatic initially, although gastrointestinal effects such as diarrhoea and vomiting may develop[8].

Severe poisoning (level >2.0mmol/l) is associated with convulsions, renal failure, electrolyte imbalance, hypotension and clouding of consciousness. Coma and death may occur.

Risk factors for lithium toxicity include older age, higher lithium levels, alcohol use, female gender, thyroid dysfunction, and long term conditions such as Addison's disease, hypertension, diabetes, congestive heart failure, chronic renal disease and schizophrenia[7,9].

Management of Lithium Toxicity

If a patient's lithium level is 1.0 - 1.5 mmol/L, but there are no signs of toxicity, check for possible reasons for the high level. Note that there may be a delay of 1 - 2 days before maximum toxicity occurs, so check the level again after 24 hours. Possible reasons for high levels include dehydration, acute illness, sample taken too close to the last dose, new interacting medicines, recent lithium salt change, incorrect dose taken, significant reductions in dietary sodium. Correct the reason where possible and recheck the level. If no correctable reason for the high level can be identified then consult with the specialist to decrease the lithium dose, check renal function, encourage fluids, and recheck the level after 5 - 7 days.

If lithium toxicity is suspected, or if the level is greater than 1.5mmol/L, withhold lithium immediately and assess the patient. Repeat serum lithium, U&Es and creatinine levels and seek hospital advice. Consider referral to A&E depending on the severity of symptoms[10]. Medical assessment is also advised in the following situations: Accidental ingestion of ≥50mg/kg lithium carbonate or ≥100mg/kg lithium citrate; patients known to have renal impairment; those taking interacting medicines that may cause lithium accumulation; patients aged ≥65 years; cases of intentional lithium overdose[8].

Patients with a level over 2.0mmol/L are likely to show signs of serious toxicity and urgent hospital advice should be sought and referral to A&E considered.

Hospital treatment for lithium toxicity includes hydration to increase urine output, and correction of electrolyte imbalances. Haemodialysis may be recommended for more severe cases[8].

Preventing Lithium Toxicity

In order to avoid developing lithium toxicity, patients should be encouraged to maintain a good intake of fluids and to avoid sudden changes in dietary salt intake (e.g. low salt diet, slimming diet), as lack of salt can result in lithium toxicity. Patient information is covered in the NPSA Lithium Therapy Information Pack[11] given to patients by the specialist at the start of treatment and should also be provided verbally throughout treatment. Patients must be educated on the signs and symptoms of lithium toxicity, risk factors, prevention of lithium toxicity and when to seek medical attention. Lithium patient information leaflets are available in multiple languages and easy-read formats from mental health services. Regular blood tests to check lithium levels also serve to prevent lithium toxicity from developing.

Primary care can order the NPSA Lithium Therapy Information Pack via Primary Care Support England (PCSE). See the SPS resource page on high risk medicines for further details.

Drug Interactions with Lithium

Diuretics (particularly thiazide)	-	All may cause lithium toxicity
NSAIDs (including COX-2 selective inhibitors)	-	as they reduce renal excretion
ACEIs (including Angiotensin II Antagonists)	-	of lithium. Serum lithium levels
Metronidazole, tetracyclines		can be increased by up to 60%.

Patients should be advised not to take over the counter NSAID analgesics such as ibuprofen (e.g. Nurofen, Advil, Cuprofen) and naproxen (e.g. Feminax Ultra). Paracetamol and aspirin are safe alternatives.

The use of products containing significant amounts of sodium as chloride or bicarbonate (e.g. some antacids, urinary alkalinisers and effervescent analgesics) can lower previously stable lithium levels and should be used under medical supervision.

The following brands of iodine dressing are contraindicated in patients receiving lithium: Iodoflex®, Iodosorb®, Iodozyme® and Oxyzyme®.

If interacting drugs are co-prescribed, they should be prescribed on a regular rather than PRN basis. Check lithium levels more frequently and adjust the lithium dose accordingly. Other drug interactions are listed in the BNF/eBNF.

Pregnancy and breast-feeding

Women of child-bearing age should be strongly advised to use a robust method of contraception. Lithium is associated with an increased risk of fetal abnormalities (e.g. fetal heart defects, Ebstein's anomaly). Should pregnancy occur whilst taking lithium, the GP should immediately inform the specialist looking after the patient. In addition, it is good practice to involve the Perinatal Psychiatry Team and specialists in Feto-Maternal Medicine early as the patient will need access to specialised services in pregnancy and post-partum.

Most patients will wish to have early ultrasound scans to look for foetal anomalies, and as many will choose to continue with their pregnancies, they will require frequent monitoring by Psychiatry and Obstetric Services to ensure there are adequate reviews and treatment plans with regards to their medication and follow-up antenatally, peri- and post-partum.

Lithium is excreted into breast milk, so breast-feeding is not advised.

Further information can be obtained from the Perinatal Psychiatry Service based at Hopewood by email on perinatalcommunityreferrals@nottshc.nhs.uk (For urgent advice only, Tel: 0115 952 9477).

Cost of Treatment (28 days)

Priadel brand – lithium carbonate modified-release tablets 400mg-800mg/day, **£3.95 - £7.91** (Drug Tariff October 2024).

CRITERIA FOR TRANSFERRING CARE TO PRIMARY CARE/GP

- **The patient is tolerating and taking a maintenance dose of lithium.**
- **Suitable support arrangements for community care are in place.**
- **An agreed care plan is in place with respect to monitoring the patients' mental and physical health, assessing the effects and side-effects of medication, and actions required if the patient shows signs of relapse or lithium toxicity.**
- **It should be clearly documented in correspondence who will be responsible for prescribing and carrying out routine monitoring tests and who will be acting upon the results of these tests**.

SPECIALIST RESPONSIBILITIES

- **To assess the patient, establish the diagnosis, determine a management strategy and devise a care plan in conjunction with the GP, other healthcare professionals and appropriate support agencies.**
- **To initiate lithium, monitor response, assess/manage initial side-effects.**
- **To provide verbal and written information about the illness and lithium treatment. This will include provision of an individualised NPSA Lithium Therapy Information Pack[11], with Record Book updated when necessary.**
- **To provide the GP with a copy of the agreed care plan and these guidelines.**
- **The care plan should state who is responsible for undertaking and acting on the results of lithium levels, eGFR, TSH, calcium and bodyweight taken at the appropriate time intervals.**
- **To be available for advice and agree an action plan if the GP reports signs of relapse, side-effects, unexpected blood results, compliance problems or level of risk to self or others is increased.**
- **To have procedures in place for rapid referral by the GP where appropriate.**
- **To prescribe lithium for at least 3-6 months until the GP agrees to take over care.**
- **To notify the GP as soon as practical of any test results and changes to drug treatment or care plan.**
- **To ensure the GP and specialist receive a copy of any blood test results from Pathology, the name and address of BOTH parties should be specified on the blood sample forms. The clinician who requests the tests is responsible for reviewing the results and taking appropriate action.**
- **To advise on dose adjustments and when, and how to stop lithium.**
- **To discharge the patient when appropriate, following agreement with the GP.**

GP RESPONSIBILITIES

- **To check that the patient has had the necessary blood tests and to interpret the results, seeking advice where necessary. It would be sensible to not routinely issue repeat prescriptions for lithium without first confirming that appropriate tests have been carried out at the suggested intervals.**
- **To check the patient has a copy of the NPSA Lithium Therapy Record Book[6] and encourage them to update this when necessary.**
- **To monitor at regular intervals the mental health, general health and wellbeing of the patient, assess compliance, adjust dose in consultation with a specialist, monitor and manage adverse effects, in liaison with the specialist if necessary.**
- **When prescribing lithium to specify the brand, form, strength, and dose.**
- **To notify the specialist as soon as practical of any test results or changes to drug treatment, if appropriate.**
- **To ensure the GP and specialist receive a copy of any blood test results from Pathology, the name and address of BOTH parties should be specified on the blood sample forms. The clinician who requests the tests is responsible for reviewing the results and taking appropriate action.**
- **To place patient on the practice SMI (Severe Mental Illness) register and undertake an annual health check focusing on cardiovascular disease, diabetes, obesity, respiratory disease and level of physical activity.**

PHARMACIST RESPONSIBILITIES

- **Pharmacy staff will follow an agreed standard operating procedure (SOP) for supplying lithium, as recommended in the NPSA Patient Safety Alert[11].**
- **As a principle, lithium therapy will not be withheld unless professional judgement prevails.**
- **Pharmacy staff will not dispense a prescription for lithium without first confirming the brand and formulation required, checking for lithium-drug interactions, and asking to see the patient's Lithium Therapy Record Book to check if relevant blood tests have been taken.**
- **Where pharmacy staff identify that the patients Record Book needs updating (or replacing) the patient will be asked to raise this with their prescriber.**
- **The pharmacist will contact the prescriber to discuss or highlight any clinically relevant issues which make lithium therapy safer.**

PATIENT RESPONSIBILITIES

- **Your specialist will give you an Information Pack on lithium therapy when you first start taking lithium. This will be completed with basic information about you and your lithium treatment. You can use the Record Book to record the results of your blood tests (e.g. lithium blood level, kidney checks, thyroid checks, and weight), and when your next blood tests are due.**
- **Keep this information in a safe place.**
- **Take your Record Book with you each time you see your GP, attend a clinic, visit a community pharmacy, request a new prescription, or have a prescription dispensed.**
- **If you misplace your Information Booklet or Record Book please ask your specialist for another one. Alternatively, the booklets can be downloaded online here.**

References

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For further information, please refer to the current British National Formulary and SPC.