SHARED CARE GUIDELINES FOR PRESCRIBING LITHIUM

INDICATION

Lithium is used in primary and secondary care for the:

- Management of mania and hypomania - NICE CG185
- Management of bipolar depression- NICE CG185
- Long term management of bipolar disorder – NICE CG 185
- Management of recurrent depression as augmentation of antidepressants - NICE CG90

The decision to give prophylactic lithium requires specialist advice and must be based on careful consideration of the likelihood of recurrence in the individual patient and the benefit weighed against the risks. Long term treatment should be undertaken with careful assessment and the need for continued therapy should be assessed regularly and maintained only if benefit persists.

Lithium salts have a narrow therapeutic/toxicity ratio and regular monitoring is required. Target lithium plasma levels are provided in table 2. Facilities for monitoring serum lithium concentrations must be available whenever it is prescribed. Communication of the results of tests between primary and secondary care is essential for safe and effective patient care.

Lithium is an inorganic metal usually prescribed as lithium carbonate but is also available as the citrate salt. Lithium is not metabolised and is almost entirely renally excreted. Renal function should, therefore, be assessed before and at regular intervals during treatment (see Table 1). All patients should be encouraged to maintain a good intake of fluids and to avoid sudden changes in dietary intake of salt.

It should be noted that the preferred brand of lithium may vary between Trusts. However, where a brand of lithium is not specified on initiation of treatment in Dorset 'Priadel®' is the brand that is always supplied. When prescribing liquid (as lithium citrate), 10.8mmol/5ml is the preferred strength to reduce errors or the risk of accidental overdose.

Adults with learning disabilities should only be started on lithium in consultation with a specialist in these fields.

Lithium is not suitable for less than 12 years of age.

AREAS OF RESPONSIBILITY FOR SHARED CARE

This shared care agreement outlines suggested ways in which the responsibilities for managing the prescribing of lithium can be shared between the specialist and general practitioner (GP). GPs are invited to participate. If the GP is not confident to undertake these roles, then he or she is under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. If a specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as practicable.

Sharing of care assumes communication between the specialist, GP and patient. The intention to share care is usually explained to the patient by the doctor initiating treatment. It is important that patients are consulted about treatment and are in agreement with it. This shared care agreement highlights the boundaries of responsibilities between healthcare professionals.

The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.

REFERRAL AND INITIATION

Shared Care is only appropriate if it provides the optimum solution for the patient.

- Patients will only be referred to the GP once the GP has agreed in each individual case

SPECIALIST RESPONSIBILITIES	
1	To assess the patient and establish the diagnosis, determine a management strategy and ensure appropriate follow-up in conjunction with the GP.
2	Where appropriate: • Assess suitability of the patient for treatment and perform baseline tests (see Table 1) • Advise patients that erratic compliance or rapid discontinuation may increase the risk of manic relapse • Advise patients that treatment with lithium is a commitment of at least 3 years (? – 2 years BAP) to derive the best outcome • Advise patient and carer of risks associated with lithium and provide any information both written and verbal to facilitate concordance • Advise the patient to always obtain medicines including OTC products from their regular pharmacist and to remind their pharmacist and any prescriber that they are taking lithium. In particular, to avoid ibuprofen unless discussed with their GP and advise them of the reasons for this • Advise the patient to contact their GP should they become physically or mentally unwell. To avoid becoming dehydrated, overheated, salt deficient • To advise the patient and their carer of the signs of toxicity, such as increasing tremor, increasing GI symptoms such as nausea, vomiting and diarrhea, cognitive impairment and what to do should these occur • To ensure the patient has given informed consent to their treatment
3	Initiate and supply the first 3 months of treatment to establish response and efficacy. Measure serum lithium levels 7 days after initiation and 7 days after subsequent dose increments. The frequency of long term monitoring once stabilised is not well defined. NICE CG185 & BAP recommend measurement of levels every 3 months for the 1st year then every 6 months thereafter but remaining on a 3 monthly monitoring schedule if clinically indicated (see table 1). NICE CG90 & the BNF recommend measurement of levels every 3 months including beyond the 1st year for all patients. The Summary of Product Characteristics (SPC) for Priadel® recommends routine long term monitoring of lithium levels every 2-3 months.
4	Reassess the patient after 3 months to check that: • The illness has stabilised • The side effects of the medication are manageable • The target serum level has been achieved • Concordance to the regime is established
5	Obtain consent from the patients GP to continue prescribing once treatment has been stabilised.
6	Where urea and creatinine levels become elevated, closer monitoring of lithium levels and dose will be undertaken and an assessment made of the rate of deterioration of renal function. Prescribers will consider seeking advice from a renal specialist regarding ongoing treatment.
7	Patients must be issued with the following documents: • Lithium booklet card • Lithium patient information booklet • Lithium alert card. Lithium therapy packs can be obtained from NHS stationery suppliers. Copies of the documents for reference can be found at www.nrls.npsa.nhs.uk/alerts/?entryid45=65426 The patient's details, service provider details, current lithium therapy, current blood level, intended range and healthcare test results should be completed in the relevant documents

	before issue (NPSA/2009/PSA005). Patients should be advised to carry their lithium alert card at all times. Amend blood range in documentation to reflect current clinical expectation for safe and effective therapy.
8	Ensure that patients know what to do and who to contact if they experience adverse events or an exacerbation of their condition.
9	To provide the GP with appropriate prescribing information and any additional information requested, including intended levels if different from normal treatment range.
10	To be available for advice if the patient's condition changes.
11	To ensure that procedures are in place for the rapid re-referral of the patient by the GP.
12	To liaise with the GP on any suggested changes in prescribed therapy.
13	To discontinue treatment gradually if no longer thought to be beneficial.
14	To be aware that renal function may be expected to deteriorate with ageing and that a long standing effective dose of lithium may need to be revised down if accumulation and toxicity are to be avoided in the older patient.

General Practitioner Responsibilities	
1	Initially, to refer the patient for specialist advice.
2	Where appropriate to continue to prescribe lithium and undertake monitoring.
3	To continue to deal with general health issues of the patient and carry out annual physical health check including screening for metabolic risk factors - BAP.
4	To liaise with the consultant regarding any complications of treatment or changes in mental state. Should a change of mental state be seen, the GP should take blood for an urgent lithium sample and refer urgently to the consultant.
5	To take serum lithium levels at recommended intervals and after any dose changes, change of preparation, during an acute illness, or changes in other medication which may affect lithium levels and take appropriate action if these tests are abnormal. The frequency of long term monitoring once stabilised is not well defined. NICE CG185 & BAP recommend measurement of levels every 3 months for the 1st year then every 6 months thereafter but remaining on a 3 monthly monitoring schedule if clinically indicated (see table 1). NICE CG90 & the BNF recommend measurement of levels every 3 months including beyond the 1st year for all patients. The Summary of Product Characteristics (SPC) for Priadel® recommends routine long term monitoring of lithium levels every 2-3 months.
6	To liaise with the consultant psychiatrist regarding lithium dose changes which may be required in the event of certain drugs being considered, such as NSAIDs for chronic use, ACE inhibitors, thiazide diuretics etc.
7	To be aware that age related changes in renal function may lead to slowly occurring lithium toxicity. Consider routinely requesting lithium levels each time renal function is checked.
8	To monitor patients for side effects and signs of lithium toxicity at each appointment.
9	To inform the consultant psychiatrist of any anomalous test results.
10	To reduce the dose or discontinue treatment in serious diarrhoea, vomiting or concurrent infection (especially if sweating profusely). Consideration should be given to stopping lithium for up to seven days if the patient becomes acutely and severely ill with a metabolic or respiratory disturbance of any cause.
11	To stop lithium if signs of toxicity occur and liaise with the consultant psychiatrist for advice on treatment and future management.
12	Refer back to secondary care for specialist advice if the treatment is ineffective.
13	To discontinue treatment if advised.
14	If the patient becomes pregnant, the situation should be discussed urgently with the specialist or perinatal service.

Patient's role (or that of carer)	
1	Report to the specialist or GP if he or she does not have a clear understanding of the treatment.
2	Attend appropriate consultant, GP and blood test appointments.
3	Share any concerns in relation to treatment with lithium.
4	Use the purple lithium therapy packs and other written information on the medication.
5	Seek help urgently if suspect side effects, or otherwise unwell.
6.	To be aware of the risks of some interacting drugs, the signs of impending toxicity and general principles of personal care whilst on lithium.
7	To inform the community pharmacy that they are taking lithium when purchasing medication.
8	Advise the GP immediately if pregnancy suspected.

Pharmacist's role	
1	Provide patient information as appropriate and encourage the use of the purple lithium therapy packs.
2	Check blood results are monitored regularly and that it is safe to dispense the prescribed lithium.
3	Encourage patients to return to the same community pharmacy for their prescriptions and any OTC medication to reduce the risk of interactions.

SUPPORTING INFORMATION

Dosage and Administration

Please Note Preparations can vary widely in bioavailability

Lithium Carbonate 200mg = Lithium Citrate 509mg
The different preparations of lithium are not bioequivalent although a switch between Camcolit® and Priadel® is unlikely to require dosage adjustment. However, serum lithium levels should be checked 1 week after any change in brand or formulation. Particular care needs to be taken if changing from a lithium carbonate to a lithium citrate (salt used in liquid formulation) preparation to ensure that the molar dose remains the same.

Lithium carbonate:
Priadel®

Adults (body weight up to 49kg)
Initially 200 - 400mg daily.

Adults (body weight 50kg and above)
Initially 400 – 1200mg once daily

Older Adults
Initially 200 - 400mg daily

The dosage of lithium should be adjusted to produce the required plasma lithium level 12 hours after the last dose. Target lithium plasma levels are provided in Table 2.

Use in children: Not recommended

Twice daily, versus once daily dosing of lithium gives sustained higher minimum concentrations & this has been linked to more pathological renal changes on biopsy. Once daily dosing also has advantages for adherence and monitoring. As a result, once daily, nighttime dosing is recommended with the exception of those patients prescribed a liquid formulation, who should be prescribed a twice daily regime.

Maintenance Monitoring

Independent of routine monitoring, patients should be seen at least once every 6 months to maintain rapport and encourage compliance, as well as monitor physical and biochemical status
Table 1. Lithium Monitoring

Requirement	Test	Person Responsible	Frequency
Baseline tests	U&Es FBC Creatinine (including calculation of GFR) Pulse and BP(?) TFTs Calcium ECG (if indicated by co-morbid risk factors and family history of cardiac disease) BMI	Initiating specialist	Once prior to initiation
Initiation tests	Lithium plasma level	Initiating specialist	1 week after initiation
Attaining required dose	Lithium level following dose changes	Initiating specialist	Weekly until stable
Long term maintenance tests	BMI urea and electrolytes including calcium, estimated glomerular filtration rate (eGFR) and thyroid function	GP	6 monthly more often if there is evidence of impaired renal or thyroid function, raised calcium levels or an increase in mood symptoms that might be related to impaired thyroid function
	Lithium level	GP	Every 3 months for the first year. After the first year, every 6 months, or every 3 months for people in any of the following groups: • Older people • People taking drugs that interact with lithium* *on initiation of interacting drugs, ensure prescription is regular (not prn) and monitor levels monthly until stable, then every 3 months • 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 monitor lithium dose and plasma lithium levels more frequently if urea levels and creatinine levels become elevated, or eGFR falls over 2 or

	Screening for metabolic risk factors	GP	more tests, and assess the rate of deterioration of renal function. Seek advice from renal specialist & psychiatrist. (NICE CG185) Annually (even in the absence of dopamine antagonists) - BAP
	Ask about side effects	GP	At every appointment. Symptoms of neurotoxicity, including paraesthesia, ataxia, tremor and cognitive impairment can occur at therapeutic levels of lithium
	ECG	GP	For people with cardiovascular disease or risk factors.
Dose reduction or stopping	During dose reduction and for 3 months after lithium treatment is stopped	GP	Monitor the person closely for early signs of mania and depression.

Table 2. Recommended target plasma levels

Patient Group	Target Lithium Plasma Level (mmol/L)
Patients prescribed Lithium for the 1st time	0.6 – 0.8 NICE CG185
Patients taking lithium who have relapsed	0.8 – 1.0 (for a trial of at least 6 months) NICE CG185
Patients taking lithium with subthreshold symptoms with functional impairment	0.8 – 1.0 (for a trial of at least 6 months) NICE CG185
Acute mania	0.8 – 1.2 (until symptoms controlled then reduce to maintenance level) – Priadel® SPC
Long term treatment	0.6 – 0.8 for patients using lithium for the first time (NICE 185)
Twice daily dosing	0.5 – 0.8 Priadel® Liquid SPC
Older Adults	0.4 – 0.8 (maintenance dose)

Contraindications

- 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.

Side Effects

For a full list of side effect including symptoms of toxicity, please refer to the manufacturers summary of product characteristics.

Acute, generally self limiting adverse effects include nausea, other gastro-intestinal disturbances and fine tremor. Chronic adverse effects include polyuria and polydipsia, weight gain, hypothyroidism and occasional histological and functional changes in the kidney. Mild cognitive impairment may occur during long term use. Diabetes insipidus can occur in the first few months of treatment which can be irreversible. The condition could be suspected if symptoms of thirst and polyuria occur.

Hypercalcaemia, hypermagnesaemia and hyperparathyroidism have also been reported. Exacerbation of psoriasis may occur. Oedema with weight gain can occur and may lead to an increased risk of lithium toxicity if treated incautiously with diuretic drugs.

Signs of Lithium Toxicity
Lithium levels should be checked in any patient complaining of: severe thirst, severe diarrhoea, poor oral intake, vomiting or anorexia, fever, loss of weight, muscle twitching, shaking of hands or legs, drowsiness, confusion, muscle weakness, slurred speech, ataxia, blurred vision or any serious current medical illness.
Older adults need to be monitored carefully for symptoms of lithium toxicity because they may develop high serum levels of lithium, due to a reduction in renal function, at doses in the normal range and lithium toxicity may occur at moderate serum levels.

Management of Lithium Intoxication
In cases of suspected lithium toxicity, lithium should be stopped and an urgent serum lithium level taken. In all cases of lithium toxicity advice should be obtained from a specialist. For levels between 1.0-1.5mmol/L reduce dose and review treatment.
In mild cases of toxicity (levels between 1.5 and 2.0mmol/L), withdrawal of lithium and administration of copious fluids and sodium will often alleviate the problem. Patients with levels over 2.0mmol/L will require hospital admission for appropriate management. When toxic concentrations are reached there may be a delay of 1-2 days before maximum toxicity occurs.

Discontinuation
Lithium should be stopped wherever possible over at least 4 weeks, but preferably over a period of three months particularly if the patient has a history of manic relapse. For 3 months after lithium treatment is stopped, monitor the person closely for early signs of mania and depression.

Drug Interactions

Diuretics, especially thiazides, non-steroidal anti-inflammatory drugs (NSAIDs) and angiotensin converting enzyme (ACE) inhibitors may all cause lithium toxicity as they reduce renal excretion of lithium. If they are used lithium dosage should be reduced and levels should be checked more frequently. The patient should be assessed regularly for signs and symptoms of lithium toxicity. Symptoms of nephrogenic diabetes insipidus are particularly prevalent in patients receiving concurrent treatment with tricyclic or tetracyclic anti-depressants. Use with concomitant QT prolonging drugs (e.g. Class IA and III antiarrhythmics, arsenic trioxide, dolasetron mesylate, mefloquine, IV erythromycin) is not recommended. Use with drugs causing electrolyte imbalance is not recommended.

This list is not exhaustive. The manufacturer's summary of product characteristics (SPC) and the most current edition of the British National Formulary should be consulted for full information on contra-indications, warnings, side-effects and drug interactions.

Drug Costs

At current prices (BNF online June 2017):

Lithium carbonate 400mg tabs (Camcolit®) x 100 = £4.02
Lithium carbonate 450mg tabs (Liskonum®) x 60 = £2.88
Lithium carbonate 200mg tabs MR (Priadel®) x 100 = £2.76
Lithium carbonate 400mg tabs MR (Priadel®) x 100 = £4.02
Lithium citrate 509mg/5ml (Li-Liquid®) x 150ml = £5.79
Lithium citrate 1.018g/5ml (Li-Liquid®) x 150ml = £11.58
Lithium citrate 520g/5ml (Priadel®) x 150ml = £6.73

When initiating treatment, Priadel® is the preferred brand. If a liquid is required, the higher strength lithium citrate Li-Liquid 1.018g/5ml (10.8mmol/5ml) is the preferred strength to reduce the risk of accidental overdose.

References

1. Camcolit® 400mg tabs (Norgine Ltd) Summary of Product Characteristics. July 2015
2. Praidel® 200 & 400mg prolonged release tablets (Sanofi Aventis) Summary of Product Characteristics. July 2015
3. NICE Clinical Guidance CG185. Bipolar disorder: the assessment and management of bipolar disorder in adults, children and young people in primary and secondary care. September 2014.
4. NICE Clinical Guideline CG90 Depression in Adults: the treatment of depression in Adults. October 2009
5. Evidence-based guidelines for treating bipolar disorder: Revised third edition recommendations from the British Association of Psychopharmacology. Journal of Psychopharmacology 2016

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