North Central London
Joint Formulary Committee

Factsheet

Lithium Preparations

LITHIUM CARBONATE: Camcolit®, Priadel®, Liskonum®
LITHIUM CITRATE: Priadel® Liquid, Li-Liquid®

Prophylaxis of bipolar illness, adjunctive treatment in resistant depression and prophylaxis of cluster headache

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September 2022	V3.0	Included indication of prophylaxis of cluster headache Approved by NCL Shared Care Group: October 2022

Disclaimer

Factsheets support GPs in taking ongoing responsibility for continuing a medicine initiated in secondary care. It differs from a shared care agreement where secondary cares retain a proportion of responsibility for ongoing care.

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Factsheet – LITHIUM CARBONATE: Camcolit®, Priadel®, Liskonum®
LITHIUM CITRATE: Priadel® Liquid, Li-Liquid®

Prophylaxis of bipolar illness (licensed)
Adjunctive treatment in resistant depression (licensed)
Prophylaxis of cluster headache (unlicensed)
Other licensed indications for treatment with lithium are outside the scope of this factsheet

Where lithium is being initiated for bipolar illness or in resistant depression, preparations should only be initiated by a specialist†, or under the supervision of a specialist† where support from a community mental health team is available.
In all indications, the specialist† will be responsible for monitoring (including checking blood results) until the patient is stabilised on lithium therapy. Once the patient is stabilised on lithium therapy responsibility for ongoing monitoring can be transferred to the GP. The patient will be stabilised on lithium therapy when blood tests are within optimal range and predictable.

Check list and actions for GP:

- Ensure documented communication has been received from a specialist† with indication for use, likely duration of treatment and evidence that the specialist† has counselled the patient on lithium (adverse effects/risks/pregnancy) and has given the patient a completed lithium pack*.
- Before continuation in primary care ensure that the patient meets criteria for continuation of treatment (i.e., lithium treatment is initiated by the specialist†, or under the supervision of the specialist† (including in mental health indications, where support from a community mental health team is available), and the patient is stabilised on lithium treatment)
- Conduct necessary blood test monitoring at agreed schedule (see **Clinical Monitoring section**) and communicate results to the relevant team.
- Prescribe routine supplies of lithium (specifying the brand and formulation on the prescription) once confirmed that blood tests have been monitored regularly and that it is safe to issue a repeat prescription.
- Monitor the patient's overall physical health and well-being.
- Refer the patient back to the initiating specialist† (ideally with a new or recent serum lithium level) if the patient:
    - Relapses
    - Is intolerant of adverse effects
    - Is non-compliant with medicines (or this is suspected)
    - Experiences adverse events
    - Has a change in circumstances affecting lithium (e.g. pregnancy)
- Ensure monitoring is carried out according to NICE clinical guidelines (CG185) and monitor by Quality and Outcomes Framework (QOF): *(see monitoring section for further information)*
    - Check thyroid and renal function (U&Es including calcium, creatinine, eGFR) every six months
    - Measure plasma lithium level (12 hours post-dose) every three months for the first year
    - After the first year, measure plasma lithium levels every six months, or every three months for people in any of the following groups:
        1. Older people
        2. People taking drugs that interact with lithium
        3. People who are at risk of impaired renal or thyroid function, raised calcium levels (corrected calcium) or other complications
        4. People who have poor symptom control
        5. People with poor adherence
        6. People whose last plasma lithium level was 0.8 mmol per litre or higher

Note: For mental health indications, QOF indicators for monitoring patients on lithium therapy align with NICE. For the QOF indicators a record should be kept of patients on lithium therapy. All practices should undertake an audit of the current quality of their prescribing in relation to patients receiving lithium and being monitored in primary care who have not had a recorded check of their lithium concentrations, estimated glomerular filtration rate, urea and electrolytes, serum calcium and thyroid function in the previous 6 months.

*The lithium pack includes information booklet, lithium alert card and record book for tracking blood tests. The lithium pack is provided by mental health services and completed when issued to the patient. The patient should be advised to bring the Lithium record book to appointments. The lithium record book is now available as a digital application and as an alternative to the paper record book can be downloaded on a digital device:

- Android device
- Apple device

Lithium record booklet PDF

Lithium information booklet PDF

Dose and Administration

- **Lithium must be prescribed by brand as bioavailability may vary between brands.**
- **Brands of lithium carbonate(tablets) include Priadel®, Camcolit®, Liskonum®**
- **Brands of lithium citrate (liquid) include Priadel® Liquid, and Li-Liquid®**
- **Priadel® is the brand of lithium most widely prescribed.**
- Priadel® Initiation: 400mg daily (200mg in the elderly). Dose is then adjusted according to plasma lithium levels. The slow release tablets can be administered as a single daily dose (usually at night).
- Priadel® Liquid preparation: should be divided into two doses initially, but once daily administration is preferred when serum lithium concentration stabilised. Care is needed when changing from lithium carbonate to lithium citrate to ensure that the dose remains equivalent.
- The **usual range for plasma lithium levels is between 0.4 - 1.0 mmol/L,** but reference ranges may vary between centres. Aim to maintain plasma lithium level between 0.6 and 0.8 mmol per litre in people being prescribed lithium for the first time. The minimum effective plasma level for prophylaxis is 0.4 mmol/L. A target lithium plasma level of 0.8 – 1 mmol/L is recommended for acute episodes of mania, and for patients who have previously relapsed or who have sub-syndromal symptoms.

For dosing with specific preparations see BNF.

- **Priadel® Liquid:** Lithium citrate tetrahydrate 520 mg is equivalent to lithium carbonate 204 mg.
- **Li-Liquid®:** Lithium citrate tetrahydrate 509 mg is equivalent to lithium carbonate 200 mg.

Changing from lithium tablets (lithium carbonate) to lithium liquid (lithium citrate) or vice versa
When changing between lithium formulations, plasma lithium levels should be checked prior to switching and then measured 4 to 7 days after switching formulations, once plasma lithium levels have reached steady state. *The mental health team or a pharmacist can be contacted to confirm the conversion.*

Worked example: changing between Priadel® liquid and Priadel® tablets

For a patient taking 25 mL (2600 mg) **lithium citrate** liquid = 5 x 5 mL of 520 mg/5 mL = 5 x 204 mg lithium carbonate = 1020 mg = Approx. 1000 mg of **lithium carbonate** tablets
(E.g. Priadel tablets 2 x 400 mg and 1 x 200 mg)

520mg/5ml Lithium citrate liquid = 204 mg Lithium carbonate tablet

***Renal impairment**:* Since lithium is primarily excreted renally, significant accumulation of lithium may occur in patients with renal insufficiency. Therefore, if patients with mild or moderate renal impairment are being treated with lithium, plasma lithium levels should be closely monitored and the dose should be adjusted accordingly. If very regular and close monitoring of plasma lithium levels and plasma creatinine levels is not possible, lithium should not be prescribed. Lithium is contraindicated in patients with severe renal insufficiency

***Hepatic impairment**:* Lithium is not metabolised in the liver. Dose adjustment not required.

***Discontinuing treatment:** Review / discontinuation of therapy should be carried out by a specialist[†].* While there is no clear evidence of withdrawal or rebound psychosis, abrupt discontinuation of lithium increases the risk of relapse. If lithium is to be discontinued, the dose should be reduced gradually over a period of at least 4 weeks (preferably over a period of up to 3 months). Patients and their carers should be warned of the risk of relapse if lithium is discontinued abruptly. If lithium is discontinued or stopped abruptly, it may be appropriate to consider alternative treatment. The specialist[†] will communicate recommendations regarding prescribing to the GP.

Adverse Effects

Most common adverse effects reported for Lithium preparations are weight gain and hypothyroidism (common), followed by polyuria and polydipsia, diarrhoea, nausea/vomiting, dermatological effects (including exacerbation of existing dermatological conditions), sexual dysfunction (decreased libido, erectile dysfunction, priapism and decreased sperm motility), fine tremor (uncommon).

Adverse effect	**Frequency (in maintenance therapy)**	**Management**
Weight gain	Common	Give advice on diet and exercise.
Hypothyroidism	Common	Refer to specialist[†]. Treat with thyroxine. Monitor thyroid function tests.
Polyuria and polydipsia	*Uncommon	Transient following initiation. Try reducing dose. May occur more frequently with twice-daily dosing. If persists, check creatinine and U&Es. Advise patient drinks fluid in moderation to avoid changes in fluid balance.
Diarrhoea	*Uncommon	**May be a sign of toxicity.** Give advice on fluid and salt replacement. If toxicity is suspected stop Lithium and refer to A&E. See clinical monitoring below for additional information on lithium toxicity.
Nausea/vomiting	*Uncommon	Give after food. Use a slow-release preparation.
Dermatological effects (including exacerbation of existing dermatological conditions)	Uncommon	Refer to specialist[†] and /or dermatologist
Sexual dysfunction (decreased libido, erectile dysfunction, priapism and decreased sperm motility)	Uncommon	Refer to specialist[†]
Fine tremor	Uncommon	Check lithium level, may be a sign of toxicity. Consider other drug causes. Refer to consultant
*In appropriate maintenance therapy these adverse effects are uncommon. If they persist, refer the patient back to specialist[†]. Common: between 1 in 10 and 1 in 100 people are affected Uncommon: between 1 in 100 and 1 in 1,000 people are affected		

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard

Contraindications
- Hypersensitivity to lithium or to any of the excipients.
- Cardiac disease.
- Cardiac insufficiency.
- Severe renal impairment.
- Untreated hypothyroidism.
- 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.

Special Warnings and Precautions for Use

Fluid/electrolyte balance
If episodes of nausea, vomiting, diarrhoea, excessive sweating, and/or other conditions leading to salt/water depletion (including severe dieting) occur, lithium dosage should be closely monitored and dosage adjustments made as necessary. Initiation of drugs likely to upset electrolyte balance, may lead to sodium depletion increases the lithium plasma concentration (due to competitive reabsorption at the renal level). In these cases, lithium dosage should be closely monitored and reduction of dosage may be necessary.

Caution should be exercised to ensure that diet and fluid intake are normal in order to maintain a stable electrolyte balance. This may be of special importance in very hot weather or work environment. Infectious diseases including colds, influenza, gastro-enteritis and urinary infections may alter fluid balance and thus affect plasma lithium levels.

Risk of convulsions
The risk of convulsions may be increased in case of co-administration of lithium with drugs that lower the seizure threshold, or in epileptic patients

Benign intracranial hypertension
There have been case reports of benign intracranial hypertension with lithium. Patients should be warned to report any visual disturbance and attend their optician or eye clinic.
In the case of patients using lithium for bipolar illness or resistant depression, patients should be warned to report persistent headache; in the case of patients taking lithium for cluster headache, they should report any change in the nature of their headache with their specialist.

QT prolongation
As a precautionary measure, lithium should be avoided in patients with congenital long QT syndrome, and caution should be exercised in patients with risk factors such as QT interval prolongation (e.g. uncorrected hypokalaemia, bradycardia), and in patients concomitantly treated with drugs that are known to prolong the QT interval.

Brugada syndrome
Lithium may unmask or aggravate Brugada syndrome, a hereditary disease of the cardiac sodium channel with characteristic electrocardiographic changes (right bundle branch block and ST segment elevation in right precordial leads), which may lead to cardiac arrest or sudden death. Lithium should not be administered to patients with Brugada Syndrome or a family history of Brugada Syndrome. Caution is advised in patients with a family history of cardiac arrest or sudden death.

Older people
Older people are particularly liable to lithium toxicity and may exhibit adverse reactions at plasma levels ordinarily tolerated by younger patients. Caution is also advised since lithium excretion may be reduced in older people due to age related decline in renal function.

Children
The use in children is not recommended.

Performance

Lithium may impair performance of skilled tasks for example driving, operating machinery.

Patients must inform the DVLA if they have:

- Bipolar disorder (see DVLA website)
- Depression if the condition affects their ability to drive safely (see DVLA website)
- Medication(s) cause side effects likely to affect safe driving
- A medical professional has advised the patient to inform the DVLA

If a clinician feels the patient's driving may be impaired to a significant degree due to their condition or lithium, they should be advised to inform the DVLA.

Pregnancy and Breastfeeding:
Women of child bearing age should be advised to use a reliable form of contraception. There is epidemiological evidence that it may be harmful to the foetus in human pregnancy.

The patient should talk to their psychiatry/neurology team, care co-ordinator or GP as soon as possible if planning pregnancy or if she might be pregnant. The patient must be referred back to the specialist[†] (and the mental health peri-natal service, if applicable; see contacts). The patient should not abruptly stop lithium treatment until specialist advice is available. If lithium is continued during pregnancy the prescribing can be continued by the GP with the advice from the specialist[†].

The majority of studies have not suggested an overall increased risk of congenital malformation, although a possible increased risk of cardiac defects has been found. An early retrospective study suggested an association between in utero lithium exposure and Ebstein's anomaly. This has not been replicated by other studies, and as the expected background rate of Ebstein's anomaly is 1 in 20,000, even with the hypothesized increased risk following lithium exposure, the estimated absolute risk to an exposed fetus remains very low (1 in 1,500).

If lithium is continued, lithium levels need to be monitored more frequently throughout pregnancy and the postnatal period. Lithium use in pregnancy is complicated by its fluctuating pharmacokinetics and narrow therapeutic index, which together present a risk of both suboptimal maternal treatment and maternal/neonatal lithium toxicity.

Lithium is secreted in breast milk and there have been case reports of neonates showing signs of lithium toxicity. Therefore, lithium should not be used during breast-feeding. A decision should be made whether to discontinue lithium therapy or to discontinue breast-feeding, taking into account the importance of the drug to the mother and the importance of breast-feeding to the infant.

Drug Interactions

Drug group	Description of interaction
NSAIDs (e.g. Ibuprofen, diclofenac)	Increase in lithium plasma level
ACE inhibitors (e.g. captopril, enalapril, lisinopril)	
Angiotensin-II antagonists (e.g. losartan, candesartan, irbesartan)	
Diuretics (thiazide, loop and potassium sparing diuretics)	
Antipsychotics (clozapine, flupentixol, haloperidol, phenothiazines, risperidone, zuclopentixol, olanzapine, sulpiride)	Increased risk of extra pyramidal side effects and possibly neurotoxicity when lithium given with certain antipsychotics
Methyldopa	Neurotoxicity may occur
Antidepressants	Increased risk of serotonergic and CNS effects with SSRIs and lithium toxicity with tricyclics
Anti-arrhythmics	Risk of ventricular arrhythmias with amiodarone – avoid.
Sodium bicarbonate (E.g. sodium bicarbonate containing, non-prescription antacids or urinary alkalinising agents)	May reduce lithium plasma level.

This list is not exhaustive; please consult the BNF or SPC for a full list of potential interactions.

QT prolongation: As a precautionary measure, lithium should be avoided in patients concomitantly treated with drugs that are known to prolong the QT interval. ECG should be performed after initiation of treatment and at any point where the patient becomes symptomatic or when there are changes in disease or treatment which may increase the risk of interaction or arrhythmia.

Clinical Monitoring (as per NICE clinical guidelines (CG185)); monitoring is the same for mental health and non-mental health indications.

Outpatient appointments are organised every 1 to 6 months based on clinical need.

Parameter	Baseline	Follow up
Lithium levels (12 hours post dose) * In the event of a twice daily dosing regimen, the morning dose should be omitted until after the blood sample has been taken.	N/A	Measure plasma lithium levels 1 week after starting lithium and 1 week after every dose change, and weekly until the levels are stable, then every 3 months. After the first year, measure plasma lithium levels every 6 months, or every 3 months for people at higher risk (See below)
Renal function - U&Es, creatinine, and eGFR	✓	Every 6 months; more often if evidence of deterioration or the patient starts taking drugs such as ACE inhibitors, diuretics or NSAIDs
Thyroid Function Tests	✓	Every 6 months; more often if evidence of deterioration
ECG monitoring where necessary	**If there is a cardiovascular disease or associated risk factors**	The need for further monitoring should be assessed on an individual basis.
FBC	✓	Annually
Corrected Calcium	✓	Every 6 months
Weight (or BMI)	✓	Annually or more frequently if patient gains weight rapidly

Lithium levels should be taken 12 hours post dose and checked a week after each dose change. Plasma concentrations should then be measured weekly until dosage has remained constant for four consecutive weeks and then every three months thereafter for the first year. After the first year, measure plasma lithium levels every 6 months, or **every 3 months for people in any of the following higher risk groups** according to NICE clinical guidelines (CG185):

1. Older people
2. People taking drugs that interact with lithium
3. People who are at risk of impaired renal or thyroid function, raised calcium levels or other complications,
4. People who have poor symptom control
5. People with poor adherence
6. People whose last plasma lithium level was 0.8 mmol per litre or higher

If more frequent monitoring is required due to multiple risk factors a monitoring plan should be formulated with the initiating specialist[†].

Older people need to be monitored carefully for symptoms of lithium toxicity because they may develop high plasma levels of lithium at doses in the normal range and lithium toxicity is possible at moderate plasma levels.

Lithium Toxicity: Usually levels above 1.5 mmol/l includes increasing diarrhoea, vomiting, nausea, anorexia, muscle weakness, lethargy, giddiness, ataxia (failure of muscular coordination), lack of coordination, blurred vision, coarse tremor, choreoathetoid (abnormal movements of hands and legs), drowsiness. Above 2.0mmol/l, increased disorientation and seizures usually occur which can progress to coma and ultimately death

Toxicity may occur in people with reduced fluid and sodium intake or in cases of diarrhoea and vomiting.

If toxicity is suspected refer the patient to A&E for an urgent blood plasma level and renal function. Withhold lithium treatment. Ensure a specialist[†] is informed and an appropriate treatment plan is in place.

Management of abnormal lithium level, renal & thyroid function

The following table outlines the normal ranges for blood tests and outlines the required action if the blood test result falls outside this range. Reference ranges are the same for mental health and non-mental health conditions.

<table>
<tr><th>Blood Test</th><th>Normal Range*</th><th colspan="2">Action</th></tr>
<tr><td rowspan="2">Lithium level (12 hrs post dose)</td><td rowspan="2">Once daily dosing:
0.4-1.0 mmol/l

Twice daily dosing:
0.5-0.8 mmol/l

(lower end of range for elderly patients)</td><td>Action if below normal range</td><td>Action if above normal range</td></tr>
<tr><td>Discuss with patient/carer. Check adherence. Assess whether a dose increase is clinically indicated. Contact the initiating specialist[†] for further advice.</td><td>SAME DAY CONTACT with patient. Assess for symptoms of toxicity. Depending on level may need to omit some doses. Regular dose will need reducing and plasma level repeated after 7 days. Renal function will need to be assessed. Review use of OTC medication and if any medicines recently initiated. Admission to hospital for supportive measures may be required in some cases. Contact the initiating specialist[†] for further advice.</td></tr>
<tr><td rowspan="2">eGFR</td><td rowspan="2">>90ml/min/1.73m2 is considered normal</td><td>Action if eGFR ≤90ml/min/1.73m2 & ≥60ml/min/1.73m2 (CKD 2)</td><td>Action if eGFR < 60 ml/min/1.73 m2 (< CKD3 a)</td></tr>
<tr><td>Increase frequency of eGFR monitoring and frequency of lithium levels. Adjustment of dosing may be necessary to maintain plasma lithium levels within normal therapeutic range.</td><td>If significant deterioration SAME DAY CONTACT with patient and initiating specialist[†]. Increase frequency of eGFR monitoring and lithium monitoring. The decision whether to continue lithium depends on clinical efficacy, and degree of renal impairment; prescribers must consider seeking advice from a renal specialist and psychiatry specialist[†].

Lithium is contra-indicated in severe renal insufficiency (eGFR <30ml/min/1.73 m2)</td></tr>
<tr><td rowspan="2">Plasma Creatinine</td><td rowspan="2">40-120 micromol/L</td><td colspan="2">Action if above normal range</td></tr>
<tr><td colspan="2">Refer to the initiating specialist[†]. Increase frequency of plasma creatinine monitoring and lithium monitoring (see actions for eGFR)</td></tr>
<tr><td rowspan="2">Thyroid Function</td><td rowspan="2">TSH 0.3-5.5 mU/L

Free Thyroxine (fT4) 9-23 pmol/L</td><td>Hypothyroidism</td><td>Hyperthyroidism</td></tr>
<tr><td>Refer to initiating specialist[†]. Treat with thyroxine. Monitor thyroid function tests</td><td>If substantially raised make SAME DAY CONTACT with patient and specialist[†]. Referral to an endocrinologist must be considered.</td></tr>
</table>

*****May differ according to laboratory. There have been reports from the national patient safety agency of patients having lithium levels within normal range but developing symptoms of lithium toxicity. If toxicity is suspected despite levels being within range refer the patient to A&E for an urgent blood plasma level and renal function. Withhold lithium treatment. Ensure there is communication with the appropriate mental health/neurology team and an appropriate treatment plan is in place.

Contact Details

Camden and Islington NHS Foundation Trust

Primary Care Mental Health Teams
Islington CORE/ Practice Based Mental Health Team
Email: islington.MHCT@Candi.nhs.uk Phone number: 020 3317 7513
Camden CORE/ Primary Care Mental Health Team
Email: camden.MHCT@Candi.nhs.uk Phone number: 020 3317 6806

Other specialist contact – Crisis Resolution Team: Phone number 020 3317 6333
This number is available 24 hours a day, 7 days a week.

Barnet, Enfield and Haringey Mental Health NHS Trust

Crisis Resolution and Home Treatment Team (CRHT) service
Urgent outreach service, assessing service users 24 hours a day, 7 days a week.

Borough	Address	Telephone	Fax
Barnet	1st floor, Dennis Scott Unit, Edgware	0208 702 4040	0208 702 4202
Enfield	Ivy House, Chase Farm Hospital	0208 702 3800	0208 702 5062
Haringey	Lea Unit, St. Ann's Hospital	0208 702 6700	0208 442 5890

GP Advice Line
An advice line is available for GPs who would like to speak to a consultant about any mental health issue.
Telephone number: 0208 702 3997
Phone line operational 9am – 5pm
Calls received by 12.45pm will be responded to by a consultant between 1pm and 2pm on the same day. Calls taken after 12.45pm will result in a call back the following day.

http://www.beh-mht.nhs.uk/gps-and-referrers/

North London Partners Specialist Perinatal Mental Health Service

Mondays to Fridays 9am-5pm
Email: *NCL.perinatal@candi.nhs.uk*
Phone number: 020 3317 7114

To find a Summary Product Characteristics: https://www.medicines.org.uk/emc/

NCL headache services

NHNN headache service
Headache CNS: uclh.enquiry.headacheservicecns@nhs.net
Secretaries for the headache consultants: uclh.headache.secretary@nhs.net
Phone number: 0203 448 3664

RFL headache service
Email: rf.headache@nhs.net
Switchboard: 020 7794 0500
Headache CNS: Ext 39575
Clinical Pathway Administrator: Ext 38245

Appendix One: Additional Background and Clinical Information

Background

1. Lithium is an element in the same group of the periodic table as sodium. The ubiquitous nature of sodium in the human body, its involvement in a wide range of biological processes and the potential for lithium to alter these processes (and lithium's multiplicity of other effects) have made it extremely difficult to ascertain the key mechanism(s) of action of lithium in regulating mood and behaviour. For example, there is some older evidence that people with bipolar illness have higher intracellular concentrations of sodium and calcium than controls and that lithium can reduce these. Glycogen synthase kinase 3 (GSK3), cAMP response element-binding protein (CREB) and Na+/K+- ATPase related mechanisms may be important for lithium's effects. For a recent review of lithium's potential mechanism(s) of action see Alda.[1] Lithium may have neuroprotective effects that preserve the function of neurones and neuronal circuits.[2] Lithium also promotes the creation of new neurones (neurogenesis) in the hippocampus, which is potentially important for learning, memory and stress responses.3 Although the older literature pertaining to the possible neuroprotective effect of lithium consisted largely of either *in vitro* or animal studies, a recent meta-analysis suggests lithium may prevent transition to dementia.4 Notably, however, both reversible and irreversible neurotoxicity related to lithium are recognised adverse effects.[5,6]

Indications

Acute treatment of mania

Lithium is effective for the treatment of mania, at a plasma level of 0.8–1.0 mmol/L.[7] If a faster action is needed an adjunctive or single-agent antipsychotic with an evidence base for treating mania is recommended.7 It can be difficult to achieve therapeutic plasma lithium levels rapidly and monitoring may be problematic if the patient is uncooperative.

Treatment of acute mania in patients already on long-term lithium

British Association for Psychopharmacology (BAP) guidelines[7] suggest that in the event of relapse an urgent plasma lithium level should be obtained to indicate the level of adherence with lithium therapy and inform possible dose adjustment. If lithium level measurement indicates non-adherence, the reason should be ascertained. If the lithium level is confirmed to be optimal, but the control of mania is inadequate, then addition of a dopamine antagonist, dopamine partial agonist or valproate is recommended.[7]

Maintenance treatment of bipolar disorder

Aim for the highest tolerable lithium plasma level in the range 0.6–0.8 mmol/L[7] with the aim of complete remission of both manic and depressive episodes.8 Lithium may be the best performing medicine for bipolar disorder in practice: Hayes et al.[9] prospectively analysed the progress of 5089 bipolar patients prescribed monotherapy maintenance treatment: lithium (n = 1505), olanzapine (n = 1366), valproate (n = 1173) and quetiapine (n = 1075). It was found that monotherapy failure in 75% of each cohort occurred by 2.05 years for lithium monotherapy, 1.13 years for olanzapine monotherapy, 0.98 years for valproate monotherapy, and 0.76 years for quetiapine monotherapy.[9]

Augmentation of antidepressants in unipolar depression

Approximately 30–50% of patients fail to respond to trials of first- or second-line antidepressants, and outcomes from 'treatment-resistant depression' are poor.[10] Providing evidence-based guidelines for treating depressive orders with antidepressants, Cleare et al.11 suggest that either lithium or quetiapine are agents of first choice for augmenting the existing antidepressant and that lithium augmentation of selective serotonin reuptake inhibitors (SSRIs) or venlafaxine is most effective at a lithium plasma level of 0.6–1.0 mmol/L. To help determine which, if either, is the better of these two augmenting agents over a follow-up period of one year, a head-to-head, parallel group, openlabel, multisite randomised pragmatic trial of lithium versus quetiapine augmentation in treatment-resistant depression (LQD) was initiated in England in 2017.[12] Clinical predictors associated with a better outcome in lithium augmentation for treatment resistant depression included: more severe depressive symptomatology, psychomotor retardation, significant weight loss, a family history of

major depression, and a personal experience of more than three episodes.[13] Of course, adherence with lithium augmentation should also be added to this list.

Prophylaxis of unipolar depression

The use of lithium for long-term treatment of unipolar depression has recently been reviewed.14 Cipriani et al. (2006)[15] analysed eight randomised controlled trials (n = 475) and found lithium was significantly superior to antidepressants in preventing relapses that required hospitalisation with a relative risk of 0.34. Abou-Saleh et al. (2017)[16] proposed lithium prophylaxis in unipolar depression if a patient has suffered two depressive episodes in 5 years, or after one episode if the episode is severe and there is a strong suicide risk, with indefinite treatment if there is adherence and adverse events are not problematic, particularly if a bipolar background is suspected.

Prophylaxis of cluster headache

Lithium for cluster headache was approved by the NCL Joint Formulary Committee in September 2021 in patients who did not respond to verapamil. The evidence of efficacy, safety and cost-effectiveness, as well as the Committee discussion, can be found in the meeting minutes (available here).

*Other uses of lithium (**outside the scope of this factsheet)***

Lithium is also used to treat aggressive and self-mutilating behaviour, and recent studies have confirmed benefits[17] to both prevent and treat steroid-induced psychosis[18] and to raise the white blood cell count in patients receiving clozapine.[19]
The information above is taken from The Maudsley Prescribing Guidelines in Psychiatry[20]

Adverse Effects[20]

1. **Thyroid function monitoring:** Lithium may inhibit thyroxine release leading to the development of goitre. Both goitre and hypothyroidism may be reversible; some patients however may not recover or else have a delayed recovery of their thyroid when lithium is discontinued. Hyperthyroidism has also been reported with no clear mechanism.

2. **Renal Function Monitoring:** (U&Es, creatinine, eGFR): Lithium can reduce urinary concentrating capacity – nephrogenic diabetes insipidus - hence the occurrence of polydipsia and polyuria, via an effect on cAMP & vasopressin. This change is generally reversible during the first 5-6 yrs but may be irreversible after long-term treatment (greater than 15 yrs). Lithium treatment can also lead to a reduction in the glomerular filtration rate.

3. **ECG monitoring:** Lithium rarely causes clinical problems although cardiac failure and sick sinus syndrome are contraindications. Usually benign cardiovascular adverse effects may occur in 20-30% patients. The main problems with lithium can be T-wave flattening (or possibly inversion), ventricular ectopics, congestive myopathy, bradycardia, ECG changes & conduction disturbances e.g. sinus node dysfunction.

4. **Calcium monitoring (corrected calcium):** Lithium use is sometimes associated with mild hypercalcaemia and elevated parathyroid hormone levels. The overall risk of clinically important calcium/parathyroid abnormalities is low.

5. **FBC monitoring:** A mild, benign leucocytosis is commonly seen during the course of lithium therapy due to a bone marrow-stimulating effect of lithium on leucocyte production.

6. **Weight and BMI monitoring:** Weight increase occurs predominantly during the first two years of treatment, more often in people already overweight and maybe more common in women than men. Increased thirst has been strongly correlated with weight gain although increased in hunger/food intake has not been shown so the predominant mechanism may be increased intake of high-calorie drinks. Thyroid status could also be a contributory cause. Lithium also increases insulin secretion, which may lead to more adipose tissue being produced, contributing to BMI gain.

References

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† Clinical decision to initiate/discontinue treatment must involve a consultant (in the case of mental health indications, this would be a consultant psychiatrist)