

Factsheet

Lithium Preparations

LITHIUM CARBONATE: Camcolit[®], Priadel[®], Liskonum[®]

LITHIUM CITRATE: Priadel[®] Liquid, Li-Liquid[®]

Prophylaxis of bipolar illness, adjunctive treatment in resistant depression

Start date: November 2016

Review date: November 2019

Document Control		
Date	Version	Action
May 2016	V1	Factsheet produced by Camden and Islington NHS Foundation Trust Agreed by NCL Medicines Optimisation Network: 24/11/16 (Chair's action) Ratified by NCL Joint Formulary Committee: 24/11/16
December 2016	V1.1	Typographical update regarding renal function monitoring. Annual calcium monitoring changed to 6-monthly corrected calcium. Typographical update under <i>Interactions</i> section Ratified by NCL Medicines Optimisation Network: 19/12/16

FACTSHEET TO FACILITATE PRESCRIBING

PLEASE NOTE THIS IS NOT A SHARED CARE GUIDELINE, NOR IS IT A FULL SUMMARY OF DRUG INFORMATION. ALWAYS REFER TO THE MOST RECENT BNF AND/OR SUMMARY OF PRODUCT CHARACTERISTICS.

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NCL JFC is funded by and provides advice to Acute Trusts and Clinical Commissioning Groups in NCL.

*Prophylaxis of bipolar illness
Adjunctive treatment in resistant depression*

Lithium preparations should only be initiated by a consultant psychiatrist. The consultant psychiatrist 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 consultant psychiatrist with indication for use, likely duration of treatment and evidence that the specialist has counselled the patient on lithium (side 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 a consultant psychiatrist 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 mental health 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 consultant psychiatrist if the patient:
 - Relapses
 - Is intolerant of side 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):
 - Check thyroid and renal function (U&Es, creatinine, eGFR) every six months
 - Measure plasma lithium level 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: QOF indicators for monitoring patients on lithium therapy are slightly different to NICE recommendations. QOF indicators for monitoring patients on lithium therapy are for a record of lithium levels in the therapeutic range in the preceding 4 months and a record of plasma creatinine and thyroid stimulation hormone in the preceding 9 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.

Dose and Administration

- **Lithium must be prescribed by brand as bioavailability may vary between brands.**
- 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).
- Liquid preparation: should be divided into two doses. 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. A target lithium plasma level of 0.4 - 0.8 mmol/L is recommended for maintenance therapy and older people. 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)

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 from Priadel® liquid to 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 via the renal route, 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 in this population. 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 consultant psychiatrist.* 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 stopped or is to be discontinued abruptly, consider changing therapy to an atypical antipsychotic or valproate. The consultant psychiatrist will communicate recommendations regarding prescribing to the GP.

Adverse Effects

Most common side 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 consultant psychiatrist. 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 consultant psychiatrist and /or dermatologist
Sexual dysfunction (decreased libido, erectile dysfunction, priapism and decreased sperm motility)	Uncommon	Refer to consultant psychiatrist
Fine tremor	Uncommon	Check lithium level, may be a sign of toxicity. Consider other drug causes. Refer to consultant
<p>*In appropriate maintenance therapy these adverse effects are uncommon. If they persist, refer the patient back to consultant psychiatrist. 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</p>		

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. Drugs likely to upset electrolyte balance such as diuretics should also be reported. Indeed, 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 epileptic threshold, or in epileptic patients

Benign intracranial hypertension

There have been case reports of benign intracranial hypertension. Patients should be warned to report persistent headache and/or visual disturbances.

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 disease in renal function.

Children

The use in children is not recommended.

Performance

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

Pregnancy and Breastfeeding:

Lithium is a human teratogen. Women of child bearing age should be advised to use a reliable form of contraception.

The patient should talk to their psychiatry 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 a Consultant psychiatrist. If lithium is continued during pregnancy the prescribing can be continued by the GP with the advice from the consultant psychiatrist.

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, losinopril)	
Angiotensin-II antagonists (E.g. losartan, candesartan, irbesartan)	
Diuretics (Thiazide, loop and potassium sparing diuretics)	
Antipsychotics (clozapine, flupentixol, haloperidole, phenothiazines, risperidone, zuclopentixol, olanzapine, sulphiride)	Increased risk of EPSEs 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.

For a full list of interactions, please refer to the Summary of Product Characteristics.

Clinical Monitoring

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

Parameter	Baseline	Follow up
Lithium levels	N/A	1 week after initiation and 1 week after every dose change until levels 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. In the event of a twice daily dosing regimen, the morning dose should be omitted until after the blood sample has been taken. 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 consultant psychiatrist.

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.

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 consultant psychiatrist 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.

Blood Test	Normal Range*	Action	
		Action if below normal range	Action if above normal range
Lithium level (12 hrs post dose)	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)	Discuss with patient/carer. Check compliance. Assess whether a dose increase is clinically indicated. Contact consultant psychiatrist for further advice.	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 consultant psychiatrist for further advice.
eGFR	>90ml/min/1.73m ² is considered normal	Action if eGFR ≤90ml/min/1.73m² & ≥60ml/min/1.73m²	Action if eGFR < 60 ml/min/1.73 m²
		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.	SAME DAY CONTACT with patient and consultant psychiatrist. 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 consultant psychiatrist. Lithium is contra-indicated in severe renal insufficiency (eGFR <30ml/min/1.73 m ²)
Plasma Creatinine	40-120 micromol/L	Action if above normal range	
		Refer to consultant psychiatrist. Increase frequency of plasma creatinine monitoring and lithium monitoring.	
Thyroid Function	TSH 0.3-5.5 mU/L Free Thyroxine (FT4) 9-23 pmol/L	Hypothyroidism	Hyperthyroidism
		Refer to consultant psychiatrist. Treat with thyroxine. Monitor thyroid function tests	If substantially raised make SAME DAY CONTACT with patient and consultant psychiatrist. Referral to an endocrinologist must be considered.

*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 team and an appropriate treatment plan is in place.

Contact Details

Camden and Islington NHS Foundation Trust

Mental Health Advice and Assessment Team

Address: 4 St Pancras Way, St Pancras Hospital, London, NW1 0PE, United Kingdom

Phone number: 020 3317 7300

Email: cim-tr.aat-referrals@nhs.net

Opening hours Monday - Friday 9.00am - 5.00pm

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/>

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

Appendix One: Additional Background and Clinical Information

Background¹

Lithium is an element that the body handles in a similar way to 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, has made it extremely difficult to ascertain the key mechanism(s) of action of lithium in regulating mood. For example, there is some evidence that people with bipolar illness have higher intracellular concentrations of sodium and calcium than controls, and that lithium can reduce these. Reduced activity of sodium-dependent intracellular second messenger systems has been demonstrated, as have modulation of dopamine and serotonin neurotransmitter pathways, reduced activity of protein kinase C and reduced turnover of arachidonic acid. Lithium may also have neuroprotective effects, possibly mediated through its effects on N-methyl-D-aspartate (NMDA) pathways. For a review see Marmol (2008).² It is notable that, with the exception of a database study linking lithium use with a reduced risk of developing dementia,³ literature pertaining to the possible neuroprotective effect of lithium reports largely on either in vitro or animal studies. The clinical literature is rather more dominated by reports of neurotoxicity.⁴

Indications¹

Lithium is effective in the treatment of moderate to severe mania with a number needed to treat (NNT) of 6.⁵ Its use for this indication is limited by the fact that it usually takes at least a week to achieve a response⁶ and that the co-administration of antipsychotics may increase the risk of neurological side-effects. It can also be difficult to achieve therapeutic plasma levels rapidly and monitoring can be problematic if the patient is uncooperative.

The main indication for lithium is in the prophylaxis of bipolar affective disorder where it reduces both the number and the severity of relapses.⁷ Lithium is more effective at preventing manic than depressive relapse;⁸ the NNT to prevent relapse into mania or depression has been calculated to be 10 and 14 respectively.⁸ Lithium also offers some protection against antidepressant-induced hypomania. It is generally clinically appropriate to initiate prophylactic treatment: (1) after a single manic episode that was associated with significant risk and adverse consequences; (2) in the case of bipolar I illness, two or more acute episodes; or (3) in the case of bipolar II illness, significant functional impairment, frequent episodes or significant risk of suicide.⁹

NICE supports the use of lithium as a first-line mood stabiliser; lithium alone is probably more effective than valproate alone,¹⁰ with the combination being better still.¹¹ The earlier in the course of the illness that lithium treatment is started, the better the response is likely to be.¹² Lithium augmentation of an antidepressant in patients with unipolar depression is recommended by NICE as a next-step treatment in patients who have not responded to standard antidepressant drugs.¹³ A recent meta-analysis found lithium to be three times as effective as placebo for this indication with a NNT of 5,¹⁴ although the response rate in STAR-D was more modest. The effectiveness of lithium in treating mood disorders does not go unchallenged. For a review, see Moncrieff.¹⁵ Lithium is also used to treat aggressive¹⁶ and self-mutilating behaviour, to both prevent and treat steroid-induced psychosis,¹⁷ and to raise the white blood cell count in patients receiving clozapine.

Adverse Effects¹

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 side 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.

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