NHS South of Tyne and Wear

serving Gateshead Primary Care Trust, South Tyneside Primary Care Trust and Sunderland Teaching Primary Care Trust

SHARED CARE GUIDELINE

For

Lithium therapy

Implementation Date: 21.6.2011

Review Date: 21.3.2013

This guidance has been prepared and approved for use within Gateshead, South Tyneside and Sunderland in consultation with Primary and Secondary Care Trusts and Local Medical Committees.
The guideline sets out the details of the transfer of prescribing and respective responsibilities of GPs and specialist services within shared care prescribing arrangements. It is intended to provide sufficient information to allow GPs to prescribe these treatments within a shared care setting

Further copies are available from

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Approved by:

Committee	Date
NHS South of Tyne & Wear	21.6.2011

Lithium Preparations:

Lithium should be prescribed by brand and form because of the differences in bioavailability between the products. Not all preparations are bioequivalent; care must be taken to make sure that the patient receives the same preparation each time a new prescription is supplied. Changing the preparation requires the same precautions as initiation of treatment.

Lithium Carbonate Tablets			Lithium Citrate Liquid		
Brand name	Tablet Strength	Amount of lithium	Brand name	Liquid strength	Amount of lithium
Priadel	200mg MR (scored) 400mg MR (scored)	5.4mmol/200mg 10.8mmol/400mg	**Priadel**	520mg/5ml	5.4mmol/5ml
Camcolit 250 **Camcolit 400**	250mg (scored) 400mg MR (scored)	6.8mmol/250mg 10.8mmol/400mg	**Li-liquid**	509mg/5ml 1.018g/5ml	5.4mmol/5ml 10.8mmol/5ml
Liskonum	450mg MR (scored)				

Lithium citrate liquid should be given TWICE DAILY.

Note differences in amount of lithium (mmol lithium) between tablets and liquid. i.e. between lithium carbonate and lithium citrate; lithium carbonate 200mg ≡ lithium citrate 509mg

Conditions(s) to be treated	Aim of treatment
prophylaxis in bipolar disorder **treatment-resistant depression** (lithium used in addition to an antidepressant) **management of acute manic or hypomanic episodes** **control of aggressive behaviour or intentional self harm**	To show a positive response to the patient's mental health. This will be achieved by maintaining lithium levels within the therapeutic range and monitoring therapy to minimise potential harm.

Patients excluded from shared care	**Unstable disease state. Patients who refuse to accept the NPSA lithium information pack.**
Eligibility criteria for shared care	**Dose stable and optimal serum lithium range determined.**
Initiation	The specialist team will initiate, monitor and regularly review the patient's therapy until the optimum dose and serum lithium concentration have been determined
Duration of treatment	For as long as benefit is maintained. The specialist team will be responsible for treatment discontinuation.
Dosage and lithium levels.	Patients are usually started on lithium carbonate MR at a dose of 400-800mg daily. For elderly patients half to a quarter of this dose is often used. **The dose is titrated to achieve a therapeutic serum level, usually 0.4 – 1.0mmol/L.** In bipolar disorder aim for 0.6 – 0.8mmol/l normally, or 0.8 – 1.0mmol/l if the patient has relapsed previously on lithium or has sub-syndromal symptoms. Sometimes lower levels of the range are used for resistant depression and

	occasionally below the lower therapeutic level are used for elderly patients. It is important to determine the optimum range for each patient. Initially lithium levels need to be measured weekly until a stable therapeutic level is achieved then every one to two months for 6 months and every three months thereafter**.** **Blood levels should be taken 12 hours post dose although in practice 10-14 hours (preferably 12-14hours) between the dosage and the sample is acceptable as long as the interval is specified for each measurement and is consistent.**
Usual Dose Range	200mg – 1200mg at night
Maximum Dose	Guided by serum lithium concentration
Cost (Drug Tariff January 2011)	The brands of lithium tablets range from around £2.30 to £4.80 per 100 tablets The brands of lithium liquid are approximately £5.80 for 150ml
Adverse effects (Side effects may be short term and are often dose dependent. They may be prevented or relieved by a moderate reduction in dose.) **Signs of serious toxicity** ⁎NB May occur at normal levels **Conditions that affect Lithium Levels**	For full prescribing information on Lithium, please refer to the Summary of Product Characteristics available from the electronic medicines compendium at: www.emc.medicines.org.uk/ Mild gastrointestinal effects, particularly nausea, vertigo, muscle weakness can occur initially but frequently disappear after stabilisation. Fine hand tremors, polyuria and mild thirst may persist. Refer back to the hospital if severe. Oedema can occur but should not be treated with diuretics. If severe or persistent, refer back to the hospital specialist. Hypercalcaemia, hypothyroidism and abnormal renal function tests arise more commonly in patients taking lithium. Weight gain and skin conditions such as acne and rashes and exacerbation of psoriasis can occur. Memory Impairment/ slowing and fatigue. **Nausea, vomiting, blurred vision, coarse tremor, slurred speech, muscle weakness, confusion, ECG changes, ataxia, convulsions, and drowsiness are signs of lithium toxicity.** If these occur, contact the initiating specialist urgently and consider stopping the lithium. If symptoms are severe, consider referring patient to acute hospital A&E department. **Persistent vomiting or diarrhoea** can lead to salt and water depletion and lithium toxicity: **Drastic changes in diet:** can affect fluid balance and cause serum lithium levels to change.
Contra-indications	Known hypersensitivity to lithium, clinically significant renal disease, untreated hypothyroidism, cardiac disease, Addison's disease or breast feeding
Renal impairment and liver disease	Lithium is contra-indicated in clinically significant renal disease. No dosage adjustment is required in liver disease.
Pregnancy and breast feeding	Contact specialist team for advice. Lithium should only be used during pregnancy when it is considered essential. 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.
Monitoring	Lithium has a narrow therapeutic range and regular monitoring (serum lithium levels every 3 months, thyroid and renal function every 6 months) as described below is essential to ensure patient safety.

Specialist Responsibilities:

- To assess the patient, establish the diagnosis, perform baseline tests (where recent results are not provided by the patient's GP) before lithium initiation and determine an individual patient management strategy.
- To initiate, monitor and regularly review the patient's therapy until the optimum dose and serum lithium concentration have been determined.
- New patients must be provided with the NPSA lithium information pack. Care must be taken that the patient is fully informed about their treatment, drawing specific attention to the signs of lithium toxicity (page 18 "important information for patients"). The patient must understand what they should do if they experience signs of toxicity.
- Particular emphasis should also be placed on "what can make the level of lithium in my blood too high" (page 19 – 20 "important information for patients"). The section on "taking some other medicines" mentions "before buying a medicine to treat pain, you should check that it is safe to take with lithium." It does not specifically mention the interaction with ibuprofen and this should be verbally re-enforced to the patient.
- All relevant information in the lithium therapy record book, "important information for patients", and lithium alert card must be completed by the initiating prescriber.
- If the patient refuses to accept the NPSA lithium information pack, the benefits of the pack should be reiterated to the patient. If the patient still declines to use the pack, this fact should be communicated to the GP and documented in the patient's clinical notes. Patients who refuse to accept the NPSA information pack are not candidates for shared care.
- To request that the patient's GP takes over prescribing when appropriate.
- To provide the GP with details of the patient's management plan including:
    - Indication for prescribing.
    - The proposed therapeutic range of serum lithium levels for that patient.
    - The last recorded lithium, renal and thyroid results.
    - Timing of the next outpatient visit and / or frequency of subsequent follow-up.
    - Details of the patient's care manager.
    - The brand of lithium used, the strength and dose
    - When the patient received the last supply of treatment
    - When he/she will require the next supply.
    - Details of any potentially interacting medication that the patient is currently prescribed, with further advice if necessary.

- To be available for advice if the patient's condition changes
- To ensure that procedures are in place for re-assessment.
- To review the overall management of the patient as necessary and notify the GP of any changes in therapy that may arise in future.
- Notification to the GP if the patient does not attend appointments for specialist review within 1 month, plus specific information on the planned course of action. If the patient refuses to attend their reviews the specialist will contact the GP to dissolve the shared care arrangement. At this point the GP will no longer prescribe lithium for the patient and care for this indication will revert fully to the specialist.

GP Responsibilities
To contact the specialist immediately and discuss exceptional cases if he/she is unwilling to accept shared care prescribing.

To invite all patients with a history of enduring serious mental illness to be included on the practice SMI register.

For patients on SMI registers, to offer a check of general physical health and the accuracy of prescribed medication, including a medication review, at least every 12 months.

Existing patients must be provided with the NPSA lithium information pack and any necessary information updated. Care must be taken that the patient is fully informed about their treatment.

To prescribe a length of supply suitable for the patient, this will usually be up to **monthly** repeat prescriptions. In certain circumstances it may be justifiable to consider longer prescription lengths provided it is clinically appropriate and safe to do so. Prescribers should check that blood tests are being monitored and that it is safe to issue a repeat prescription.

To monitor serum lithium levels every 3 months.

Blood levels should be taken 12 hours post dose although in practice 10-14 hours between the dosage and the sample is acceptable as long as the interval is specified for each measurement and is consistent.

It is recommended that before routine monitoring, the ICE system is checked so that tests are not unnecessarily duplicated.

Where it is anticipated the level may be in the toxic range (i.e. patients showing signs of toxicity), mark the sample as urgent. Any levels above 1.0mmol/l should be telephoned through to the prescriber and any appropriate action taken within 24 hours of the sample being taken from the patient.

Non-urgent lithium levels which are subsequently found to be in the toxic range should be telephoned through to the prescriber and any appropriate action taken within 24 hours of the result being analysed / phoned through.

To monitor thyroid, renal function (U & Es and serum creatinine and eGFR) every 6 months and obtain appropriate advice if necessary.

All lithium results and any other appropriate test results should be made available to the relevant specialist if still under their care. NB. All results must also be entered in the lithium therapy record book.

It is recommended that bloods for routine lithium monitoring should normally be taken on Monday to Thursday mornings. This will give the best chance of contact with the appropriate specialist during normal working hours in the event of abnormal results.
A robust recall system must be in place for anyone who fails to attend lithium monitoring.

If there are any signs of serious lithium toxicity (which can occur at therapeutic levels), to stop lithium immediately (following consultation with the specialist if possible) and measure lithium levels, urea and electrolytes, and eGFR

To monitor medication concordance

To be vigilant for adverse effects, performing additional tests where clinically relevant (see enclosed lithium information sheet)

To communicate copies of relevant non-psychiatric secondary and tertiary care referrals and correspondence to the Psychiatrist if still under their care.

To contact secondary care when necessary including:
-Any spontaneous deterioration in mental state that cannot be managed by the GP.
-Patient experiencing intolerable adverse effects.
-Patient has signs of toxicity or deterioration in renal / thyroid function.
-Concerns about apparent non-concordance or lack of efficacy.
-Unusual prescribing circumstances e.g. pregnancy, initiation of potentially interacting medication.
-Requests to stop lithium.
-When considering dose changes
-High lithium levels

<table>
<tr><td rowspan="2">Communications</td><td>Specialist to GP</td><td>▪ To request that the patient's GP takes over prescribing when appropriate.
▪ To provide the GP with details of the patient's management plan including:

o Indication for prescribing.
o The proposed therapeutic range of serum lithium levels for that patient.
o The last recorded lithium, renal and thyroid results.
o Timing of the next outpatient visit and / or frequency of subsequent follow-up.
o Details of the patient's care manager.
o The brand of lithium used, the strength and dose
o When the patient received the last supply of treatment
o When he/she will require the next supply
o Details of any potentially interacting medication that the patient is currently, with further advice if necessary.

▪ To notify the GP of any changes in therapy that may arise in future.
● Notification to the GP if the patient does not attend appointments for specialist review within 1 month, plus specific information on the planned course of action
▪ If the patient declines to use the NPSA lithium information pack, this fact should be communicated to the GP and documented in the patient's clinical notes. Both the specialist and the GP must ensure that systems are in place to ensure the safe prescribing and monitoring of lithium in such cases.</td></tr>
<tr><td>GP to Specialist</td><td>▪ If unwilling to accept shared care prescribing.
▪ lithium results and any other appropriate test results should be made available to the relevant specialist if still under their care.
▪ To communicate copies of relevant non-psychiatric secondary and tertiary care referrals and correspondence to the Psychiatrist if still under their care.

To contact secondary care when necessary including:

-Any spontaneous deterioration in mental state that cannot be managed by the GP.
-Patient experiencing intolerable adverse effects.
-Patient has signs of toxicity or deterioration in renal / thyroid function.
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<tr><td>Contact details</td><td colspan="2">Specialist:</td></tr>
<tr><td>Agreed Date
21.6.2011</td><td colspan="2">Expiry date
21.6.2013</td></tr>
</table>

For full prescribing information on lithium, please refer to the Summary of Product Characteristics available from the electronic medicines compendium at: www.emc.medicines.org.uk

Prescribing Notes

Preparations

Lithium should be prescribed by brand and form because of the differences in bioavailability between the products. **The brand should be stated in both the lithium therapy record book and on the lithium alert card**. Not all preparations are bioequivalent, care must be taken to make sure that the patient receives the same preparation each time a new prescription is supplied. The manufacturers' recommendations vary slightly for each brand however the information in this guideline is considered to be best practice.

Pharmacology

The mechanism of action of lithium is unknown. It is thought that lithium may affect ionic channels or the serotinergic system.

Serum Levels

The dose is titrated to achieve a therapeutic serum level, usually 0.4 – 1.0mmol/L. In bipolar disorder aim for 0.6 – 0.8mmol/l normally, or 0.8 – 1.0mmol/l if the patient has relapsed previously on lithium or has sub-syndromal symptoms. Sometimes lower levels of the range are used for resistant depression and occasionally below the lower therapeutic level are used for elderly patients. Initially lithium levels need to be measured weekly until a stable therapeutic level is achieved then every one to two months for 6 months and every three months thereafter**. Blood levels should be taken 12 hours post dose although in practice 10-14 hours between the dosage and the sample is acceptable as long as the interval is specified for each measurement and is consistent.**

Thyroid Function

Long-term lithium therapy can cause hypothyroidism or hyperthyroidism. Hypothyroidism is the most common and can be treated with levothyroxine (women are at a greater risk). Thyroid function should be checked every 6 months. If hyper or hypothyroidism is suspected then TFTs need to be monitored more frequently as the thyroid dysfunction can resolve spontaneously.

Managing Serum Lithium Levels

(always check that the time at which the blood sample was taken is appropriate.)

- **If the level is low (typically < 0.4 mmol/l)**
    - Patient is well and levels are consistently low but within the desired specified range for that patient ***do not alter dose.***
    - If the patient's condition is not well controlled and the pattern of lithium levels has been bordering on the lower end of the range
        - ***Assess medication concordance***
        - ***Increase dose if appropriate, but only after discussion with specialist.***
        - ***Recheck levels in 5 days***
    - If the low level is inconsistent with the trend i.e. a one off :
        - ***Assess concordance***

        - ***Consider other factors e.g. drug interactions, excess fluid intake, brand change***
        - ***Recheck the level***

- **If the level is within therapeutic range (typically 0.4 – 1 mmol/l)**
    - If the patient is well and tolerating lithium ***do nothing***
    - If the patient is well but complaining of side effects e.g. polydipsia, polyuria, ***liaise with the psychiatrist to consider reducing the dose and check if there has been:-***
        - ***A change in diet e.g. salt restriction or crash diets can cause blood lithium to rise.***
        - ***Initiation of interacting medicines by doctor or use of OTC products***
    - If the patient is clinically unwell liaise further with psychiatrist.

- **If the level is high (> 1.00 mmol/l), but with no signs of toxicity, same day action is required.**
    - If there is an explanation for the high level e.g. dehydration, timing blood sampling for lithium levels, interacting medication, brand change; ***correct where possible and recheck level****.*
    - If the level is part of a pattern of levels which have bordered on being too high:
        - ***Decrease the dose, after discussion with specialist***
        - ***Encourage fluids***
        - ***Recheck level in 5 days***
    - If there is no clear explanation for high levels, ***liaise with the psychiatrist to consider temporary discontinuation/rechecking the lithium level and investigation of renal function***
    - If the patient is elderly, *liaison with the psychiatrist should be considered to discuss temporarily discontinuing lithium and reducing the maintenance dosage.*
- **Signs of Toxicity can occur at normal levels. *Consider stopping lithium immediately. It is important to consult with the specialist as soon as possible, check lithium, serum creatinine U&Es.***

High Risk Patients

Certain high-risk patients may require more frequent monitoring. These include those:

- Over 65 years old
- On interacting medication (see enclosed information sheet)
- With or at risk of renal / thyroid / cardiac disease.

Lithium interactions with other medicines

1.1 Because of lithium's relatively narrow therapeutic range, interactions with other drugs can be very important. Prescribers must have a system for checking, identifying and acting on any concurrent medications that may interact with lithium. It is good practice to check the BNF for interaction potential when a new medicine is commenced for a patient stabilised on lithium.

1.2 In order to minimise potential toxic effects of lithium interactions prescribers should ensure that patients are aware of possible signs and symptoms indicating a toxic lithium level.

1.3 The most problematic interactions with other medicines include

- Thiazide diuretics
- ACE inhibitors eg ramipril, lisinopril
- Non-steroidal anti-inflammatory drugs (NSAIDs)

Up to 4 fold increases in lithium plasma level may occur. However the effect is variable and cannot be predicted. Ideally combinations of lithium with these medications should be avoided. However if this is not possible then lithium levels should be closely monitored. The lithium dose in patients stabilised on lithium may need to be reduced in anticipation of an interaction however this will depend on individual patients: their clinical condition and whether lithium levels are already near or at the top of the desired therapeutic range. NSAIDs are of particular concern because these may be obtained by the patient without prescription (eg ibuprofen). Patients should be advised to choose alternative painkillers (paracetamol is a suitable first line alternative); and that the interaction risk can still occur with occasional use of NSAIDs.

1.4 Other medicines may increase lithium levels. Evidence of interaction is restricted to case reports. Increased lithium level monitoring is recommended for:

- Angiotensin II receptor antagonists eg candesartan, losartan
- Antibacterials eg metronidazole, tetracyclines, co-trimoxazole
- Diuretics eg loop, triamterene, spironolactone
- Methyldopa

1.5 Medicines may also lower lithium levels the most important ones being:

- Xanthines eg aminophylline, theophylline
- Sodium containing drugs eg antacids, urinary alkalinisers
- Acetazolamide

lithium levels should be closely monitored. The lithium dose may need to be increased

1.6 Medications may interact by increasing the toxic effects of lithium without a change in plasma level. These include

- Amiodarone
- Antiepileptics eg carbamazepine, phenytoin, topiramate
- Antipsychotics eg clozapine, flupentixol, olanzapine, haloperidol, phenothiazines, sulpiride, zuclopenthixol
- Calcium channel blockers eg verapamil, diltiazem, nifedipine
- Antidepressants eg SSRIs, venlafaxine, tricyclics

1.7 A detailed summary of possible interactions which may occur with lithium are listed in the following table:

These medicines can cause clinically significant increases in lithium levels. Evidence of interaction is well documented. Concurrent use is not recommended.

Drug	Importance	Comment
ACE inhibitors	• Not clinically important in every patient • Can get up to 4-fold increases in plasma lithium levels. • Increase in lithium level can occur over several weeks	• Concurrent use only with caution and close monitoring. Avoid if possible.
Thiazide diuretics	• Not clinically important in every patient • Can get up to 4-fold increases in plasma lithium levels • Increase in lithium level usually apparent in the first 10 days	• This is an established well-documented and potentially serious interaction. Avoid if possible. Other diuretics may be safer. • Consider a lithium dose reduction
Non-steroidal anti-inflammatory drugs NSAIDs	• Not clinically important in every patient • Increase in lithium level may develop after a few days or up to several months • Resulting effect can vary from 10% to > 4-fold increase in plasma lithium level.	• Patients taking lithium should be warned not to take over-the-counter NSAIDs (eg ibuprofen). • Prescribing NSAIDs should be avoided if possible

These medicines can cause clinically significant interactions with lithium in some patients. Caution and close monitoring is recommended.

Drug	Importance	Comment
Amiodarone	• Increased risk of hypothyroidism	• Increased monitoring of thyroid function.
Aminophylline /theophylline	• Reduced plasma concentration of lithium by approx. 20 – 30%	• Increased monitoring of plasma levels with concurrent use
Angiotensin II receptor antagonists	• Case reports of increase in plasma levels.	• Increased monitoring of plasma levels with concurrent use, particularly during the first couple of months.
Antibacterials: (Metronidazole/ tetracyclines/ co-trimoxazole)	• Case reports of increase in plasma levels +/or lithium toxicity	• Increased monitoring with concurrent use • In some cases other factors associated with infection eg fever, poor fluid intake may have contributed to toxicity.
Antiepileptics: (carbamazepine, phenytoin topiramate)	• Case reports of neurotoxicity (without increase in lithium plasma level). Interaction less well established with phenytoin & topiramate.	• Monitor concurrent use for signs of neurotoxicity.
Antipsychotics: (clozapine, flupentixol, olanzapine, haloperidol, phenothiazines, sulpiride, zuclopenthixol)	• Case reports of increased risk of EPSEs and possibly neurotoxicity	• Monitor concurrent use for signs of neurotoxicity
Ca channel blockers: (verapamil, diltiazem, nifedipine)	• Case reports of neurotoxicity (without increase in lithium plasma level).	• Monitor concurrent use for signs of neurotoxicity
Diuretics: (loop, triamterene, acetazolamide spirononolactone)	• Case reports of decrease in plasma levels with acetazolamide • Case reports of increased plasma levels and toxicity with loop diurestics, triamterene and spironolactone	• Considered to be safer in combination with lithium than thiazide diuretics (see table above) however increased monitoring of plasma levels is advised with concurrent use
Antidepressants: (SSRIs, venlafaxine, tricyclics)	• Case reports of symptoms of serotonin syndrome with SSRIs and venlafaxine • Case reports of neurotoxicity, serotonin syndrome and neuroleptic malignant syndrome with tricyclics	• Monitor concurrent use for signs of neurotoxicity
Methyldopa	• Case reports of increase in plasma levels +/or lithium toxicity	• Increased monitoring with concurrent use
Sodium containing medicines: (antacids, urinary alkalinisers)	• Excessive sodium intake associated with reduced plasma concentration of lithium	• Antacids containing aluminium/magnesium hydroxide are a safer alternative

References:
British National Formulary 59 March 2010
Stockley's Drug Interactions [online] Pharmaceutical Press (medicinescomplete.com accessed 08.3.10)

Appendix 2 Shared Care Request Form

- **Consultant to complete FIRST SECTION of form**
- **GP to complete SECOND section and RETURN to Secondary Care Trust Clinician Team**

Section 1

Consultant	
Hospital address	
Contact Phone Number	

Patient's name	
Address	
This patient is stabilised on	
Dose	
Prescription for 28 days supply given on	

Compliance aid	YES/NO
Monitored by	
Designated community pharmacy	

Their treatment has been explained to them and a review has been arranged for

…… ……..

Appointments to continue every …… months

Section 2

Patient's name	
Address	

I **ACCEPT** the proposed Shared Care Agreement for this patient

to start ……

I do **NOT ACCEPT** the proposed Shared-Care Agreement for this patient

My reasons for not accepting: Please complete this section

Signed ……date……..

Please return to the Secondary Care Trust Clinician team at :

_____

_____

_____