Good Practice Standards

Safe Lithium Treatment

Scope

This document is intended to support the safe use of lithium in mental health services including Forensic and Learning Disability services across NHS Greater Glasgow & Clyde.

Key Documents/bibliography

NICE; Bipolar in Adults (QS95), July 2015

NICE; Bipolar disorder: assessment and management (CG185), September 2015

NHS GG&C; Mental Health Service – Physical Healthcare Policy

Maudsley Prescribing Guidelines, 12th Edition 2015

Psychotropic Drug Directory 2018

National guidance for monitoring lithium – SGHD/CMO (2019)4

Introduction

Lithium is a useful drug, particularly in the maintenance treatment of bipolar affective disorder, recurrent depression and self-injurious behaviour. It is widely used and most patients prescribed lithium are in the community. It has a narrow therapeutic index, with a high potential for toxicity and therefore careful monitoring is required for safe use. This document replaces previous guidance that was developed within the Mental Health Partnership in response to problems and potential problems in managing lithium treatment.

The narrow therapeutic index of lithium and the potential for acute and chronic side effects place an absolute requirement to establish clear systems of work that protect patient safety. This should include robust systems in place to ensure monitoring is carried out irrespective of setting.

The document contains the following sections

1. Treatment initiation
2. Maintenance treatment and routine monitoring
3. Early identification and management of lithium toxicity
4. Patient and staff education
5. Stopping lithium
6. Use in special populations
7. Appendices

Some sections will contain detailed procedural information whereas others are more general guidelines.

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Care planning

Each patient prescribed lithium will have lithium treatment identified as a need/risk within their care plan. The care plan will ensure all the clinical and safety aspects are identified and managed for each patient.

1. Treatment initiation

Baseline pre-treatment tests

When initiating lithium treatment it is important to ensure that appropriate baseline physical health checks are undertaken to ensure treatment can be safely established. It is often useful to undertake a full physical assessment before starting lithium. The following table describes the baseline checks that must be undertaken before initiating treatment.

Baseline Parameter/checks	Comments
ECG	For patients with known cardiac disorders or cardiac risk factors including those on medications known to prolong QTc e.g. antipsychotics, citalopram
U&Es	Include Sodium, Potassium, Urea, Creatinine & eGFR. Patients must have adequate renal function (eGFR>60ml/min) before commencing lithium. Note in some populations the eGFR may over estimate renal function and therefore calculation of creatinine clearance would be more appropriate. For further advice see impaired renal function section.
Thyroid function	
Calcium	Request via bone profile from biochemistry
Weight	Lithium can cause significant weight gain. Baseline weight is useful to support on-going physical health monitoring
Review for potential drug interactions	NSAIDs including COX-2 inhibitors, diuretics, ACE inhibitors and other drugs that may adversely affect renal function or increase lithium levels. **Note** there is an increased risk of neurotoxicity when lithium is combined with antipsychotics.

Initial patient education

Patients will be provided with appropriate education prior to commencing lithium treatment. This should focus on

- The indication – i.e. what it is for
- What to expect in terms of outcome
- Risk of relapse or worsening outcome with poor compliance
- Likely dose
- The need for, and rationale of, regular monitoring including blood tests
- Side effects which occur within the normal blood levels
- Signs of toxicity
- Drug interactions especially with regards to ‘over the counter’ medications
- Need for adequate and consistent hydration and consistent dietary salt intake

The Choice and Medication website is recommended, www.choiceandmedication.org/nhs24/

Initial prescribing

Priadel, as either lithium carbonate (tablets) or lithium citrate (liquid) is the recommended lithium preparation in NHS Greater Glasgow & Clyde. Different preparations may vary in bioavailability.

The recommended starting dose is 200 – 400mg* once daily (100 – 200mg daily in older adults) in the case of the tablets or in divided doses in the case of the liquid preparation. **Note:** 5ml (520mg) of Priadel liquid is considered equivalent to 200mg of Priadel tablets.

Lithium tablets should be prescribed once daily at night to enable morning trough plasma levels to be conveniently taken (see below). Lithium liquid is usually prescribed twice daily.

*Note the SPC for Priadel and the BNF entry make reference to dosing by patient weight and allow a starting dose range of 0.2 – 1.2g daily. However accepted practice is to start low for all patients and titrate the dose upwards depending on response, level measurements and adverse effects.

Initial monitoring

A lithium level should be taken no earlier than 5-7 days after starting treatment. The level should be a 12 hour trough i.e. taken approximately 12 hours after the last dose of lithium (In twice daily dosing the morning dose should be withheld until the level has been taken.)

Subsequent levels should then be taken no earlier than 5-7 days after every dose change until the patient is stable and the target level is achieved.

The target level for new lithium patients is between 0.6 – 0.8mmol/L.

Please note some patients will respond adequately at levels below the target range, therefore the full clinical situation should always be considered. For people who have relapsed previously while taking lithium or who still have sub-threshold symptoms with functional impairment while receiving lithium, a trial of at least 6 months with lithium levels between 0.8 – 1mmol/L should be considered.

The lower end of the range is usually target for treatment and maintenance therapy of older adults and special populations.

2. Maintenance treatment and routine monitoring

Once a stable dose has been achieved a programme of routine monitoring of levels, side effects and physical health monitoring should be established. The table below summarises the appropriate schedule;

Test or measurement	Frequency	Comments
Lithium levels	3 monthly	Additional levels should be taken 5-7 days after any dose change or if there is a suspicion of toxicity[a]
Thyroid function	6 monthly	Monitor more frequently if evidence of deterioration
Renal function (including urea & electrolytes, creatinine and calcium)	6 monthly	Monitor more frequently e.g. monthly if evidence of deterioration or if patient starts taking drugs known to affect renal function[b]. If eGFR falls rapidly to <45ml/min review lithium treatment and refer to renal medicine. Investigate & correct for hyponatraemia or hypernatraemia.
Routine side effect monitoring [c]	At every blood test	See appendix for side effect rating scale
Weight	6 monthly minimum and as necessary	Monitor pro-actively if patient gains weight rapidly
Drug interactions	Every clinical contact.	Review and discontinue if possible drugs that may induce lithium toxicity.

a. Toxic effects may develop within the normal range especially in older people. Toxicity should be considered if there are signs of suggestive of dehydration, any change in mental or physical state e.g. confusion, falls or increased tremor.

Symptoms of toxicity include; coarse tremor, muscle twitches, gastric upset including diarrhoea, muscle weakness, unsteady gait/falls, slurred speech, blurred vision, drowsiness and confusion

Services should have a low threshold of suspicion for toxicity and undertake additional levels to confirm or discount toxicity as a matter of urgency.

b. Drugs that may affect renal function and/or lithium clearance and potentially result in toxicity if used with lithium include;

- NSAIDs e.g. ibuprofen, naproxen, celecoxib
- ACE inhibitors e.g. ramipril, enalapril
- Angiotensin 2 antagonists e.g. losartan
- Diuretics, especially thiazides (bendroflumethiazide)

Avoid the use of these drugs if possible and monitor lithium levels more frequently if use is unavoidable.

c. Common side effects seen within normal therapeutic dosing include
    - polyuria,
    - polydipsia,
    - nocturia,
    - diabetes insipidus,
    - metallic taste
    - fine tremor.

3. Early identification and management of lithium toxicity

Services should adopt a pro-active systematic approach to the early identification and management of lithium toxicity. Patient, carer and staff education are key.

In community settings patients and/or their carers should be provided with education that gives advice on the signs and symptoms of toxicity and details of situations and issues that might lead to toxicity.

Patients and carers should be advised to see a doctor as soon as possible if any of the signs and symptoms in Note a. above emerge. They should also be advised to avoid purchasing any over the counter medicines without seeking the advice of a pharmacist in order to avoid potential drug interactions. They should also be advised to maintain adequate hydration especially if on holiday in a hot climate and to seek medical advice if they develop diarrhoea or vomiting that lasts more than 24 hours.

In hospital setting the pre-administration factors to consider, which are part of the Lithium Bundle (appendix 1), will be adopted to support early detection and management of lithium toxicity.

If lithium toxicity develops, stop lithium immediately and provide supportive medical treatment as necessary. Moderate and severe cases (levels 1.5mmol or higher) would be considered a medical emergency and admission to an Acute hospital may be required. **Be aware that lithium levels may continue to rise for 24 to 48 hours after stopping lithium**.

Lithium treatment can only be re-introduced once toxicity has resolved and if restoration is then deemed clinically appropriate.

4. Patient, carer and staff education

All patients and where appropriate their carers will be given education tailored to their needs to support the safe and effective use of lithium. This should include both verbal and written information. Details of the information provided should be documented. Educational messages will be reinforced at appropriate intervals e.g. during physical health monitoring or during routine out-patient appointments. A record of consent by the patient or designated other should be documented following agreement to initiate treatment.

Education should cover

- The purpose and potential outcomes of treatment
- Preparation and dose
- The potential side effects and risks

- Signs and symptoms of toxicity and what to do about them
- Common drug interactions and how to avoid them
- The importance of ongoing compliance
- The need for adequate hydration
- The need for and purpose of regular blood tests
- The need to inform healthcare professionals that they take lithium
- How to get help if problems occur

The following resources are recommended

www.choiceandmedication.org/nhs24/

http://www.rcpsych.ac.uk/mentalhealthinfo/problems/bipolardisorder/bipolardisorder.aspx

http://www.rcpsych.ac.uk/pdf/Lithium%20ld%20final.pdf

http://www.birmingham.ac.uk/research/activity/ld-medication-guide/index.aspx -provides easy read information for people with cognitive deficits.

All staff involved in the prescribing, dispensing or administration of lithium will receive appropriate lithium training. This will include the Key Facts from the Lithium Bundle and where appropriate the face to face Lithium Training Package (a presentation has been developed).

5. Stopping lithium

A lithium trial should continue for at least 6 months to establish effectiveness. If stopping lithium, reduce the dose gradually over at least 4 weeks, and preferably up to 3 months, even if the person has started taking another anti-manic agent. Continue monitoring whilst reducing the dose. Abrupt discontinuation of lithium increases the risk of relapse.

6. Use in special populations

Pregnancy

For all women of childbearing potential undertake a discussion of childbearing intentions and contraception status. This must include, advice on risks and benefits in relation to childbearing and advice/signposting on contraception (incl. LARC). Informed consent must be recorded in writing. The 'BUMPS' website should be used to reinforce verbal information. www.medicinesinpregnancy.org.

Ideally lithium should be avoided in pregnancy due to known risk of teratogenic effects.

If a woman on lithium is planning a pregnancy they should be fully advised of the risks of remaining on or coming off lithium. A treatment plan should be developed to support the patient and their consent to that should be recorded.

If a patient on lithium becomes pregnant consider the following steps

- Confirm the pregnancy as early as possible.
- Seek advice on management from the Peri-natal Service (see appendix 3).

- If pregnancy is confirmed in the first trimester and the woman is stable, consider stopping lithium gradually over 4 weeks and inform the woman that this may not remove the risk of cardiac defects in the foetus.
- If lithium treatment is to continue, check lithium levels every 4 weeks, then weekly from the 36th week and less than 24 hours after child birth. The dose should be adjusted to keep levels within the therapeutic range. The woman should maintain adequate fluid intake.
- Consider offering an antipsychotic as prophylactic medication
- Offer appropriate screening and counselling about the continuation of pregnancy, the need for additional monitoring and the risk to the foetus if the woman stays on medication. Record details of all advice given and the woman's consent to the treatment plan developed.
- The newborn baby should have a full paediatric assessment and social and medical help should be provided for the mother and child.

More information on the use of lithium in pregnancy is available in appendix 3.

Breastfeeding

Women on lithium who wish to breast feed should

- Be given advice on the risks and benefits of breast feeding
- Should be advised not to if taking lithium and an alternative prophylactic agent should be offered.

Impaired renal function

Lithium is nephrotoxic and contraindicated in severe renal impairment. It may only be considered in renal impairment with extreme care, close monitoring, reduced dosing and following consultation with renal medicine and biochemistry. In all cases of renal impairment a full discussion of the additional risks must be undertaken with the patient and ongoing consent obtained and documented. If lithium is used in renal impairment, toxicity is more likely. In addition, the following renal markers should prompt a referral to renal medicine during lithium treatment;

- eGFR falling rapidly to <45ml/min
- Significant proteinuria (identified by albumin creatinine ratio)
- A steady or persistent fall in eGFR
- Stages 4 or 5 of chronic kidney disease

Lithium levels and renal function should be monitored more frequently and at least monthly for patients with altered renal function.

Prescribing Management Group – Mental Health
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Appendix 1

Lithium Ward Bundle

A Lithium Ward Bundle has been developed to help ward based staff implement the standards for patients prescribed lithium.

It contains the following elements

- Key facts document for staff
- Principles for safe lithium use – to support effective care planning
- Multi-disciplinary Team check list which will be used at ward MDT meetings to ensure the standards are being met.
- Clinical factors to consider before administering a dose of lithium. This is intended to flag up early signs of lithium toxicity.
- Educational tool for staff using lithium.

The full bundle is available here.

Lithium Side Effect Checklist (LiSEC) Appendix 2

Patient name		CHI number	
Date of Assessment		**Name of assessor**	

	Over the past week, have you experienced any of the following possible side effects and if so, to what extent?	Never	Mild	Moderate	Severe	Tick if this is distressing
1.	I have been very thirsty and/or passing urine more frequently					
2.	I have woken during the night because I needed to pass urine					
3.	I have felt more hungry than usual or have gained weight					
4.	I have a metallic taste in my mouth					
5.	My mouth has been dry					
6.	I have felt like I am going to be sick					
7.	My ankles have been swollen					
8.	I have had difficulty remembering things and/or concentrating					
9.	I have developed a rash/ skin problem or an existing skin problem has got worse					
10.	I am tired *					
11.	My skin/ hair is drier than usual *					
12.	I have had problems opening my bowels (constipation) *					
13.	**My hands or arms have been shaky *[1]**					
14.	**My vision has been blurry**					
15.	**My speech is slurred**					
16.	**I have felt very sleepy during the day**					
17.	**I have vomited and/or had diarrhoea**					
18.	**My muscles have felt weak and/or my muscles have been twitching**					
19.	**I have been unsteady on my feet**					
20.	**I feel confused**					

Actions taken:

Notes for staff:

Side effects in bold indicate the possibility of lithium toxicity, an urgent lithium level should be obtained if any of these symptoms are reported.

* these side effects may indicate hypothyroidism. Check TFTs if not done in past month.

*[1] a coarse hand tremor is potentially indicative of lithium toxicity, where as a fine tremor can be reported at therapeutic levels.

Further questioning may be required to ascertain significance and /or severity of a reported side effect and whether this is new problem related to lithium therapy.

Discussion of the results of the checklist should provide an opportunity to remind patients of key points of safe lithium therapy e.g.

- importance of keeping well hydrated especially if there is any evidence of dehydration (vomiting, diarrhoea, perspiration)
- importance of regular blood monitoring
- avoiding interacting medicines
- what to do in the event of experiencing side effects including toxic side effects

All side effects identified must be reported to the patient's Responsible Medical Officer (RMO) as soon as possible and discussed at the next multi-disciplinary team meeting.

If potential toxic effects are identified report these immediately to medical staff.

Appendix 3

Glasgow Perinatal Mental Health Service

Lithium in pregnancy – information for healthcare staff

Lithium is a mood stabilising drug used in the management of bipolar affective disorder, mania and recurrent depression. It is rarely used in pregnancy because of teratogenicity and neonatal complications. However, it may be prescribed under specialist supervision.

It has a narrow therapeutic to toxic ratio and must be monitored regularly by blood sampling,. Dose range to achieve therapeutic blood levels is usually between 400mg – 1200mg/d, but this is less important than the blood level. The dose required to achieve therapeutic levels may increase from mid-pregnancy, but high levels at delivery can be associated with toxicity in the mother and neonate. For this reason, the dose is usually reduced in advance of delivery. Lithium should not be administered once labour has commenced.

Any woman taking lithium in pregnancy should have an individualised psychiatric care plan for lithium management throughout pregnancy and the peripartum.

Lithium levels

- Routine Lithium levels should be taken 12 hours after last dose and no sooner than 5-7 days after a dose change (unless there are concerns about toxicity)

- **Therapeutic levels** are usually within the range **0.6 – 0.8 mmol/l**

- **Toxicity** is usually evident **above 1.5 mmol/l**

Toxicity

Symptoms of lithium toxicity include:

- Early - restlessness, apathy, nausea, coarse tremor
- Later - vomiting, diarrhoea, ataxia, dysarthria, confusion
- Leading to - convulsions, renal failure, coma, death

If lithium toxicity is suspected:

- Immediately take a blood sample for urgent lithium level. Do not use a lithium heparinised blood tube. Note the time when the sample was taken and the time and amount of the last dose.
- Seek medical/psychiatric advice.
- Withhold further lithium until a satisfactory blood result is obtained.
- Moderate-severe toxicity (levels 1.5mmol or higher) would be considered a medical emergency and medical admission may be required.

Toxicity can be precipitated by:

- Dehydration
- Impaired renal function
- Sodium-restricted diet
- Overdose
- Drug interactions

Drugs that interact with lithium to cause toxicity include:

- NSAIDs e.g. ibuprofen, naproxen, celecoxib
- ACE inhibitors e.g. ramipril, enalapril
- Angiotensin 2 antagonists e.g. losartan
- Diuretics, especially thiazides e.g. bendroflumethiazide

  Avoid the use of these drugs if possible and monitor lithium levels more frequently if use is unavoidable.

Pregnancy-related conditions that increase the risk of lithium toxicity include:

- Fluid loss at delivery
- Hyperemesis
- Pre-eclampsia

(Note: Lithium levels may be reduced in later pregnancy due to increased clearance)

Risk of lithium use in pregnancy

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 in some studies. 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).

There is no compelling evidence of increased rates of spontaneous abortion, intrauterine death, or adverse neurodevelopmental outcome, following lithium exposure in utero, however the data are currently too limited to completely exclude an increased risk of these outcomes.

An increased risk of preterm delivery and neonatal complications (which is likely related to infant blood levels and may include reduced Apgar scores, hypotonia, CNS and neuromuscular complications) has been identified.

NICE clinical guideline 192 - Antenatal and postnatal mental health: clinical management and service guidance

Do not offer lithium to women who are planning a pregnancy or pregnant, unless antipsychotic medication has not been effective.

Preconception advice	If antipsychotic medication has not been effective and lithium is offered to a woman who is planning a pregnancy or pregnant, ensure: • the woman knows that there is a risk of fetal heart malformations when lithium is taken in the first trimester, but the size of the risk is uncertain • the woman knows that lithium levels may be high in breast milk with a risk of toxicity for the baby • lithium levels are monitored more frequently throughout pregnancy and the postnatal period.
On Lithium → becomes pregnant + is well	If a woman taking lithium becomes pregnant, consider stopping the drug gradually over 4 weeks if she is well. Explain to her that: • stopping medication may not remove the risk of fetal heart malformations • there is a risk of relapse, particularly in the postnatal period, if she has bipolar disorder.
On Lithium → becomes pregnant + is unwell or high risk of relapse	If a woman taking lithium becomes pregnant and is not well or is at high risk of relapse, consider: • switching gradually to an antipsychotic or • stopping lithium and restarting it in the second trimester (if the woman is not planning to breastfeed and her symptoms have responded better to lithium than to other drugs in the past) or • continuing with lithium if she is at high risk of relapse and an antipsychotic is unlikely to be effective.

Taking Lithium in pregnancy

If a woman continues taking lithium during pregnancy:

- check plasma lithium levels every 4 weeks, then weekly from the 36th week
- adjust the dose to keep plasma lithium levels in the woman's therapeutic range
- ensure the woman maintains an adequate fluid balance to avoid dehydration
- ensure the woman gives birth in hospital
- detailed ultrasound anomaly scanning by obstetricians

Labour and postnatal management

- Due to the risk of neonatal lithium toxicity and the need for monitoring during labour, delivery in hospital is advised.

- Once labour has started, lithium should be stopped and plasma lithium levels (12hr post dose) and fluid balance should be checked regularly until baby has been delivered, due to the risk of dehydration and toxicity in mother and child.

- Consider the option of induction of labour with suspension of lithium administration 24-48 hours beforehand (similar guidance on lithium management if having planned caesarean section).

- Recommence maternal lithium postnatally (usually at pre-conception dose) once heamodynamically stable.

- All neonates exposed to lithium in utero should have their serum lithium level measured shortly after delivery.

- Follow the management plan of the PEPP (Pregnancy and early postnatal mental health care plan)

Breastfeeding

- As general guidance, breastfeeding is usually not recommended when on lithium therapy.

- Caution is advised, particularly when infant elimination is impaired, or in newborn or premature infants.

- It is estimated that a fully breastfed infant would receive approximately 26% (range 11 to 42%) of the weight-adjusted maternal dose of lithium.

- Case reports have identified lithium toxicity in breastfed infants of women on lithium therapy.

- The long-term effects of lithium on infants are not known but limited data indicate no obvious problems in growth and development.