Specialised Medication – Lithium (Adult Patients) Guideline

1. Guiding Principles

This document provides guidance for the prescription and administration of lithium in adult patients, and should be used in conjunction with appropriate references e.g. Therapeutic Guidelines, Australian Medicines Handbook.

For paediatric patients, refer to the Perth Children's Hospital (PCH) document – Lithium -Paediatric.

2. Guideline

2.1 Presentation

- 250mg lithium **carbonate** *immediate release* tablet (Lithicarb®)
- 450mg lithium **carbonate** *slow release* tablet (Quilonum®)
- 127mg lithium **citrate** BP per 1mL oral solution. (Auspman®)
  - Equivalent to 50mg lithium **carbonate** per 1mL oral solution
  - not available in all regions – hospital use only.

  127mg Lithium **citrate** = 50mg Lithium **carbonate**

2.2 Indication(s)[1]

- Prevention of manic or depressive episodes in bipolar disorder.
- Treatment and prophylaxis of acute mania.
- Schizoaffective disorder and chronic schizophrenia (rarely used)
- Accepted – augmentation for treatment-resistant depression.

2.3 Contraindications[2]

- Hypersensitivity to lithium or any component of the formulation.
- Severe or significant cardiovascular disease as lithium may cause ECG changes and/or arrhythmias, such as sick sinus syndrome.
- Severe or significant renal disease.
- Severe sodium depletion and conditions associated with hyponatraemia e.g. Addison's disease, dehydration, severely debilitated patients and patients on low sodium diets.
- Frank hypothyroidism.
- Concurrent use of lithium and diuretics without dose adjustment.

2.4 Precautions

- **Pregnancy**[3] – Australian Category D. The decision to continue lithium treatment should be made between the specialist and the patient. Further information available from King Edward Memorial Hospital Drug Information Centre (Ph: 08 9340 2723) or Pregnancy and Breastfeeding Medicines Guide, The Royal Women's Hospital Victoria (available from WACHS Library).

- **Lactation**[3] – Lithium is excreted in breast milk with the potential to cause lithium toxicity in the neonate. Breastfeeding an infant should only occur under the supervision of a perinatal psychiatrist who can monitor serum lithium concentration, thyroid function, electrolytes.[4] Seek specialist advice. Further information available from King Edward Memorial Hospital Drug Information Centre (Ph: 08 9340 2723) or Pregnancy and Breastfeeding Medicines Guide, The Royal Women's Hospital Victoria (available from WACHS Library).
- **Elderly** – Use with care in the elderly as excretion may be reduced, therefore requiring lower dosages and more frequent monitoring to avoid toxicity.[1]
- **Surgery** – Interruption of therapy perioperatively (approximately 24hrs pre-surgery) and postoperatively should be considered as fasting and fluid/physiological changes can effect serum lithium levels.[1]
- **Renal** – Lithium should be used with caution in patients with renal impairment as it is primarily excreted by the kidneys.[1] Where possible, the use of lithium is to be avoided in patients with severe renal impairment.[1] Doses should be reduced and lithium levels aimed at the lower end of the therapeutic range and more frequently monitored in renal impairment and unstable kidney function.[4]
- **Hyponatraemia** – Depleted sodium levels increase serum lithium levels and therefore increase toxicity.[1]
- **Hypothyroidism** – Lithium can cause thyroid dysfunction therefore use with caution in patients with existing thyroid disease.[4]
- **Serotonin toxicity** – Lithium can contribute to serotonin toxicity when used in combination with other drugs that may cause serotonin toxicity.[1]
- **Post-acute mania phase** – patients may tolerate higher doses of lithium while acutely manic, however, signs of toxicity should be monitored after this stage has passed as tolerances may be reduced.[5]

2.5 Drug interactions[1,2,5,6,7]

The following drug interactions are limited to those which occur most commonly in practice. Drug interactions with lithium are extensive therefore a comprehensive list is beyond the scope of this document. Multiple references should be consulted including the Approved Product Information (available via MIMs), AMH, and specialised drug interaction texts; Specialist and/or Clinical Pharmacist advice should be considered.[1,2,5,6,7]

- **Angiotensin Converting Enzyme (ACE) inhibitors**: decrease lithium excretion and therefore may increase lithium levels and the risk of toxicity.
- **Angiotensin II Receptor antagonists**: decrease lithium excretion and therefore may increase lithium levels and the risk of toxicity.
- **Loop diuretics e.g. frusemide**: may increase lithium levels and the risk of toxicity.
- **NSAIDs e.g. ibuprofen**: decrease lithium excretion and therefore may increase lithium levels and the risk of toxicity. Avoid the combination where possible. Low dose aspirin is safe to use.

- **Thiazide diuretics e.g. hydrochlorothiazide**: may increase lithium levels and the risk of toxicity. Avoid the combination where possible.
- **Drugs that can cause serotonin toxicity e.g. fentanyl**: Lithium can contribute to serotonin toxicity therefore patients who are prescribed a combination of these drugs should be closely monitored.
- **Antipsychotics**: Rapid dose increases of lithium and antipsychotics together may cause neurotoxicity.

· Concomitant use lithium with any of the above agents will require monitoring of lithium concentration, renal function and clinical effects for extended periods. Use an alternative agent where possible. Adjust the dose of lithium when necessary.

2.6 Dosage (as lithium carbonate)

Lithium monotherapy is one of a number of treatment options for both acute mania and prophylaxis of bipolar disorder. The recommendations below outline maximum doses that may be used and are not a standardised dosing schedule.

Combination therapies and slower titrations may be used according to practitioner preferences and clinical factors.

Patient doses should be individualised and titrated based on serum lithium levels (see therapeutic drug monitoring). Doses of lithium are not recommended to exceed 2500mg daily.

· **Acute Mania**[(1)]:
Immediate release product: Initially no more than 500mg bd. Increase by 250mg-500mg increments, based on serum lithium levels (see 2.7), until symptoms resolve.

· **Slow release product**: Begin with a maximum of 450mg daily and titrate according to lithium levels (see 2.7) and patient response.

· **Prophylaxis of bipolar disorder**[(1)]: 125mg - 500mg bd for two weeks. Then adjust dose to serum lithium levels (see 2.7).

· After a patient's dose has been stabilised, single nightly doses should be prescribed, where possible, to facilitate morning blood tests and improve compliance.[(4)]

· Twice daily doses of the slow release product should be spaced by 12 hours.[(1)]

· Reduce doses and monitor closely in the elderly and in patients with renal impairment.[(1)]

· It may take up to three weeks to observe therapeutic effect.[(9)]

2.7 Therapeutic Drug Monitoring

· Blood taken to determine serum lithium levels should be taken 10-14 hours (ideally 12 hours) after the last dose.[(4)] Doses that would be given prior to blood being drawn should be held until after blood has been taken. Unless requested by the medical officer, continue with usual dose until the results are available.

- Steady state concentration is achieved after 5-7 days.[1] This may be longer, between 7 to 10 days, in the elderly or those with renal impairment.[1]
- Levels should be assessed 5-7 days after starting treatment, after each dose change and every three months.[1] More frequent monitoring is required in certain situations such as illness (particularly if febrile or vomiting), acute mania or depression, changes in diet, pregnancy, concurrent use of other medication (e.g. diuretics) or when there are signs of toxicity.[1]
- Target ranges are as follows:

  Prophylaxis of bipolar disorder[4]*:* 0.4-1.0 mmol/L

  Acute Mania[8]*:* 0.8-1.2 mmol/L (bd or tds dosing)
- Target concentrations in the upper end of the therapeutic range should be aimed for if the patient is prescribed a single night time dose of lithium. For example, in patients prescribed lithium for prophylaxis of bipolar disorder, the target range for a single nightly dose may be 0.7mmol/L to 1mmol/L compared to more frequent daily dosing (0.6mmol/L to 0.8mmol/L).[8]
- If a patient is taking lithium on admission to hospital, it is recommended a level be taken to ensure a current level is available to guide clinical decisions.

2.8 Clinical Monitoring

- Baseline tests which should be conducted prior to treatment commencement include: full blood picture, electrolytes, creatinine, fasting blood sugar levels, body mass index, thyroid function tests, calcium and phosphate, ECG and pregnancy test (if appropriate).[1]
- A personal and family medical history of thyroid function, previous cardiac disease, renal disease and medication should be established.[9]
- These baseline measurements should then be repeated at the intervals shown in the table below[9]:

Lithium level	Establish lithium level 5-7 days after commencement and after any dose change Repeat 3 monthly after establishing stable dose
Full blood picture, thyroid function tests	Repeat 3 months after establishing stable dose and then 6 monthly
Creatinine, renal function* and electrolytes	Repeat every 3 to 6 months
Fasting blood sugar levels and body mass index	Repeat every 6 to 12 months
Calcium and phosphate	Repeat every 1 to 2 years
ECG	Repeat every 5 years
Pregnancy test	Ensure adequate contraception

*Renal function tests may need to be conducted more frequently if the patient has renal instability.[1]

- Monitor for clinical signs and symptoms of thyroid dysfunction and toxicity.

2.9 Adverse effects

2.9.1 The following adverse effects relate specifically to **lithium toxicity** and serve as indications of possible overdose.

Mild to moderate toxicity[1]: blurred vision, increasing diarrhoea, nausea, vomiting, anorexia, muscle weakness, drowsiness, apathy, ataxia, flu-like illness.

Severe toxicity[1]: increased muscle tone, hyper-reflexia, myoclonic jerks, coarse tremor, dysarthria, disorientation, psychosis, seizures, coma, death.

Symptoms of toxicity are common at serum lithium levels above 1.5 mmol/L.[1] This may be lower in elderly patients, even occurring within the therapeutic range at 1.2 mmol/L.[1]

Chronic poisoning (also known as Syndrome of Irreversible Lithium Effectuated Neurotoxicity or SILENT) may also occur and this is associated with significant morbidity and mortality.[8] It has an insidious onset and a toxicologist should be consulted if poisoning is suspected.

2.9.2 **Other adverse effects** include:

Common adverse effects (>1% of patients) [1]:
metallic taste, nausea, diarrhoea, epigastric discomfort, weight gain, fatigue, headache, vertigo, tremor, acne, psoriasis, leucocytosis, nephrotoxicity, hypothyroidism (usually asymptomatic), benign T wave changes on ECG.

Infrequent adverse effects (0.1-1% of patients) [1]:
memory impairment, hair loss, hyperparathyroidism.

Rare adverse effects (<0.1% of patients) [1]:
Arrhythmias, hyperthyroidism, nystagmus.

2.9.3 Lithium can cause a number of nephrotoxic effects including nephrogenic diabetes insipidus (with polydipsia and polyuria), reduced glomerular filtration rate leading to end-stage renal disease, tubular atrophy, focal interstitial nephropathy and, rarely, nephrotic syndrome.[1] Some renal insult may be reversible upon cessation of lithium.[1]

The long term use of lithium is associated with an increased risk chronic kidney disease with an insidious onset in **15-20% of patients**.
Risk factors for kidney injury include duration of lithium exposure, cumulative dose and advanced age.[10]

The other effects mentioned in 2.9.2 are generally dose-related, and therefore can potentially be prevented by ensuring lithium levels remain in the therapeutic range.[6]

2.10 Patient Counselling (1)

- Due to the potentially serious nature of high serum lithium levels, it is vital that the patient understands how to avoid lithium toxicity.
  - Ensure the patient understands the need for regular blood tests and monitoring.
  - Emphasise the need for the patient to record all blood tests, levels and dose changes. This information should be shared with all relevant health professionals including, but not limited to, the patient's general practitioner, community pharmacist, hospital doctor and mental health case worker.
  - Provide information regarding signs and symptoms of lithium toxicity, i.e. extreme thirst, frequent urination, nausea, vomiting and worsening diarrhoea.
  - Inform the patient of circumstances which may affect lithium levels e.g. illness (such as vomiting and diarrhoea), exercise, changes in diet, dehydration, medications and drug use and excessive heat and sun exposure.
  - Encourage seeking advice from health professionals in these situations.
  - Discuss the importance of maintaining a normal diet without excessive salt, alcohol or low fluid intake.
  - Take tablets with food to minimise aggravation on the stomach.
  - Swallow slow release tablets whole – do not crush/chew.
  - Avoid over the counter medications such as anti-inflammatories, indigestion medications and urinary alkalisers, unless in consultation with a health professional. Impress the need for compliance to ensure effect.
  - If lithium is to be withdrawn, it should be withdrawn slowly to avoid relapse.

Provide a copy of the Department of Health Lithium Medicine information leaflet to the patient (available from the Choice and Medication internet site).[7]

3. Roles and Responsibilities

The **Medical Officer** is responsible for:

- completing orders on the WA Hospital Medication Chart
- ensuring lithium therapy remains suitable for the patient throughout their admission
- timely, ongoing assessment of required monitoring parameters
- documenting blood test results and the reason for therapy changes
- devising a monitoring plan to ensure the patient's ongoing care is comprehensively understood by the entire care team
- handing over of important information to future carers to ensure continuity of care. It is the responsibility of the Health Service Team (inpatient or community) to ensure routine monitoring is completed until care has been formally handed over to a GP service
- reviewing recorded observations regularly and alter treatment where required.

- educating the patient about medication, lifestyle management and risks and benefits of therapy
- completing all treatment and duties within scope of practice.

The **Registered Nurse / Midwife / Enrolled Nurse** is responsible for:

- recording observations as directed and notify the medical officer of any abnormal reading
- monitoring the patient for any concerning trends which may indicate lithium toxicity and report these to the medical officer
- accurately recording the time of administration of each dose to ensure that blood drawn for therapeutic drug monitoring occurs at the appropriate time
- liaising with the patient's carer/case worker/GP to arrange required follow up appointments or blood tests to ensure continuity of care
- completing all nursing duties for the patient within scope of practice
- completing all required documentation.

4. Appendices

Appendix 1 - Clinical Handover for Patient Prescribed Lithium
This clinical handover provides information on the recommended monitoring parameters and intervals for patients being treated with lithium. It may be used as a tool to transfer information between points of care.

Appendix 2 - Environmental Hazards of Prescribing in the Kimberley and Pilbara Regions of Western Australia
Written and provided by Dr David Gaskell and Dr Siva Bala giving recommendations on prescribing considerations and precautions unique to the environmental factors in the tropical regions of Western Australia.

5. Evaluation

Clinical incidents relating to the prescribing and monitoring of lithium are to be zero (0).

6. Standards

National Safety and Quality Health Service Standards (Second edition 2017) – 4.1, 4.15

7. Related Policy Documents

MR170A WA Hospital Medication Chart – Adult Short Stay
MR171 WA Hospital Medication Chart – Adult Long Stay

8. Related WA Health System Policies

Medication Chart Policy - MP 0078/18

9. Policy Framework

Clinical Governance, Safety and Quality Policy Framework

10. Acknowledgment

1. Farr J. Draft - Guideline for Prescribing and Monitoring of Inpatient Lithium Therapy. 2014
2. Farr J. Draft - Project Brief: The Implementation of Monitoring and Prescribing Guidelines for Lithium in the Mental Health Setting. 2014.

11. References

1. AMH [Internet]. Australian Medicines Handbook Pty. Ltd. 2015 [cited 30th June, 2015].
2. Lithicarb (Approved Product Information) [database on the Internet]. MIMS Australia. [cited 30th June, 2015].
3. Lithium. In: Loke YC, In M, Ismail H, Leung L, Nguyen C, Rogers J, Wong S, editors. Pregnancy and Breastfeeding Medicines Guide. Melbourne: The Royal Women's Hospital, Pharmacy Department; 2010.
4. Taylor D, Paton, C, Kapur S. Chapter 3 - Bipolar affective disorder. In: The Maudsley Prescribing Guidelines in Psychiatry. 12th ed. Great Britain. John Wiley & Sons, Ltd; 2015.
5. UpToDate [database on the Internet]. Wolters Kluwer Health. 2015 [cited 30th June, 2015]
6. Bazire S. Psychotropic Drug Directory 2014. Norfolk, UK: Page Bros Ltd; 2014
7. Bazire S, Bolton G, Bleakley S, Feetam C, Walker H. (UK). Choice and Medication [Internet]. Mistura Enterprise Ltd. [Updated March 2015, cited 30th June 2015]
8. eTG [database on the Internet]. Therapeutic Guidelines Ltd. 2011 [cited 30th June, 2015]
9. Guideline: Lithium Therapy – Initiation and Continuation. Perth: Fiona Stanley Hospital; 2015.
10. Lerma EV. Renal toxicity of lithium: literature review. [Internet]. Aug 2015 [cited 2015 Sep 15. Available from: UpToDate
11. Policy: Lithium: Prescribing Guidelines. Perth: North Metropolitan Mental Health Service; 2013.
12. Close H, Reilly J, Mason JM, Kripalani M, Wilson D, Main J, et al. (2014) Renal Failure in Lithium-Treated Bipolar Disorder: A Retrospective Cohort Study. PLoS ONE 9(3): e90169.
13. Lepkifker E. et al. Renal insufficiency in long-term lithium treatment. J Clin Psychiatry 2004; 65:850-856
14. State Government Victoria Department of Health (AU). Perinatal Psychotropic Medicines Information Service - Lithium [Internet]. VIC (Australia): The Royal Women's Hospital 2015 [cited 2015 Sept 24].

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Contact:	WACHS Chief Pharmacist (M.Clay)		
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