Lithium handbook			
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Contents

1.0 Introduction

Lithium has been in clinical use for over 70 years and is recommended by NICE as the first line treatment for bipolar disorder. It has proven anti-manic, antidepressant and prophylactic effects in bipolar disorder, and is also effective as an adjunctive treatment for refractory depression.

Lithium, however, has a narrow therapeutic index and has the potential to be toxic in overdose. Careful consideration must be given to patient selection, initiation and long-term management with Lithium.

2.0 Lithium initiation and monitoring

The prescriber should discuss the nature of the treatment with the patient and their likelihood of compliance needs to be considered. Patients should be aware of benefits, adverse effects and causes and signs of toxicity.

Appropriate advice should be given to women of childbearing age on the risks of lithium in pregnancy and advice should be given on contraception (although the risks to the foetus of lithium exposure in-utero are much less than previously thought.)

Patient's medications, including non-prescribed medications, should be reviewed for potential interactions (e.g., NSAIDs, ACE inhibitors and diuretics). Where possible, consideration should be given to a reduced dose or switching to an alternative.

2.1 Contraindications to lithium therapy

- Severe renal impairment
- Untreated hypothyroidism
- Hyponatraemic states and low-sodium diets
- Addison's disease
- Brugada Syndrome (absolute contraindication). Patients with 1st degree relatives known to have Brugada syndrome should undergo formal testing.

2.2 Baseline tests prior to starting lithium

- Weight and BMI
- Urea and electrolytes, an estimated Glomerular Filtration Rate (eGFR)
- Serum calcium
- Thyroid function
- ECG (for patients with cardiovascular disease or risks factors)
- Pregnancy test to exclude pregnancy

- Urine Albumin: Creatinine ratio (uACR)

Note that uACR provides a useful baseline for distinguishing incidental proteinuria from proteinuria that results from initiating lithium treatment. Therefore, it is often useful to obtain this with baseline investigations or within the first few months of commencing lithium. It also assists with assessing the risk of progressive CKD.

2.3 Preparations

There are a variety of lithium preparations available. The common formulary choice in NHS Lothian is Priadel prolonged-release tablets. Switching between liquid and tablets requires careful consideration – see BNF for details. Lithium must be prescribed by brand as advised by the specialist team. The salt of lithium (carbonate or citrate) and the formulation (MR tablets, tablets or liquid) should be included in all prescriptions. Different preparations of lithium may vary widely in bioavailability.

- The preferred brand of lithium carbonate is Priadel MR tablets.
- The preferred brand of lithium citrate is Priadel 520mg/5ml liquid. Patient should continue on same brand of lithium. If changing between brands or between tablets and liquid, more frequent monitoring may be required initially as the change may result in alterations in lithium levels.

Particular care should be taken when changing from tablets to liquid or vice versa: lithium carbonate tablet 200mg (Li + 5.4 mmol) is approx. equal to lithium citrate liquid 5ml (Li + 5.4 mmol) i.e. lithium carbonate tablet 200mg does not equal lithium citrate liquid 200mg.

Seek advice from pharmacy when switching between lithium formulations.

Dosage and administration

Refer to current Summary of Product Characteristics (SmPC): www.medicines.org.uk

Suggested starting doses:

- Adults: 400mg at night
- Elderly: 200mg at night

For those recently stopped on lithium, higher starting doses may be used based on previous maintenance dose. The relationship with dose and plasma levels is linear, and this should be considered when making adjustments.

2.4 Patient counselling

On commencing lithium therapy, patients must receive ongoing verbal and written information about the symptoms of toxicity. They should also be provided with information about minimizing the risks of toxicity. This should cover:

- The importance of having regular blood tests, as well as the importance of levels being taken 12 hours post dose.
- The importance of maintaining an adequate fluid intake, particularly during periods of hot weather or during an acute illness e.g. vomiting/diarrhoea/when febrile.
- The importance of compliance. They should also be advised not to double a dose if one is inadvertently omitted.
- The importance of taking the same brand of lithium.
- They should aim to avoid large changes in dietary salt intake and be alert for signs of toxicity when dehydrated for any reason.
- Women of childbearing age should be advised to use contraception. They should seek advice from their GP/specialist if there are concerns regarding pregnancy.

3.0 Lithium monitoring

3.1 Initiation phase

Regular monitoring ensures adequate serum levels are achieved and minimises risk of toxicity.

Lithium has a distribution half-life of 18-30 hours. Serum lithium levels should be checked between 5 to 7 days following initiation and any subsequent dose adjustments and should be repeated weekly until concentrations are stable.

Once concentrations are stable, serum lithium levels should be tested at 3 monthly intervals for the first year. Consider more frequent blood samples if there is a clinical concern or potential interaction.

Samples testing serum lithium levels should be taken approximately 12 hours post-dose.

The specialist should always provide target serum levels to primary care. Examples are provided below.

DOSAGE FREQUENCY	12 HOURS POST DOSE	24 HOURS POST DOSE
Once daily	0.7 – 1.0 mmol/L	0.5-0.8 mmol/L
Twice daily	0.5 – 0.8 mmol/L	

Older people are more sensitive to lithium and its side effects. Consideration should be given to maintaining these patients on the lower end of the therapeutic range. The agreed therapeutic range in NHS Lothian for patients over 65 years is provided below.

DOSAGE FREQUENCY	12 HOURS POST DOSE
Once daily	0.4 – 0.8 mmol/L

The optimal serum lithium levels when used to augment antidepressant therapy is unclear. NICE recommends that the dose should be titrated to response and tolerability, and that plasma lithium levels should not exceed 1.0mmol/L

If the decision is made to initiate lithium in patients with altered renal function, start lithium at low doses, in 1 to 2 daily divided doses and titrate slowly based on clinical response and tolerability. Levels should be monitored frequently.

3.2 Maintenance phase

Serum lithium levels should be checked every three months. Serum lithium levels should also be checked if there is significant change to the patient's sodium and fluid intake.

At every clinical contact:

- Patients should be screened for signs of lithium toxicity (see section 6).
- Patients should be routinely asked about thirst, urine output and nocturia. If diabetes insipidus is suspected, endocrinology/nephrology advice should be sought.

Other tests should be carried out as follows:

• Weight and BMI	annually
• Blood pressure	annually
• uACR	annually
• Renal function + serum electrolytes	6 monthly
• Calcium levels	6 monthly
• Serum electrolytes	6 monthly
• Thyroid function	6 monthly

Women of reproductive age should have the following annually:

- Advice on risks and benefits in relation to childbearing
- Advice/signposting on contraception
- Informed consent provided in writing.
- For women who become pregnant on lithium: Do not stop abruptly. Review risks and benefits of continuing or stopping treatment.

If calcium 2.7 mmol/L or above, check PTH and refer to endocrinology. For lower-level elevations (<2.7 mmol/L) – monitor and check PTH if persistently elevated (two or more readings).

3.3 Renal impairment

Monitoring should be altered in the setting of deteriorating renal function. Should renal function decline at a rapid rate, nephrology input should be sought.

Stage of chronic kidney disease	eGFR (ml/min/1.73m 2 body surface)	Proteinuria	Action
Normal kidney function or Stage 1 or 2	>60	Test urine for ACR prior to, or within 3 months of starting lithium; thereafter, urine ACR should be checked annually. If no previous ratio is available, check initially.	If heavy proteinuria is present, refer to nephrology, otherwise monitor uACR annually

Moderately reduced eGFR (Stages 3a and 3b)	45-59 (stage 3a) 30-44 (stage 3b)	Test urine for ACR; Do reagent strip test for haematuria if proteinuria is present	Check eGFR every 3 months. Frequency of monitoring can be reduced once eGFR determined to be stable. Monitor uACR annually Refer to nephrology, and discuss discontinuation, if eGFR is declining rapidly (see thresholds below) or has fallen below 30 ml/min, if uACR rising progressively or is persistently above 70 mg/mmol, or if proteinuria and haematuria are present.
Severely reduced eGFR (Stages 4 and 5)	15-29 (stage 4) <15 (stage 5)	As for stages 3a and 3b	Refer to nephrology Lithium is normally contraindicated
ACR: albumin:creatinine ratio eGFR: estimated glomerular filtration rate PCR: protein:creatinine ratio			
• Heavy proteinuria corresponds to an albumin:creatinine ratio of 70 mg/mmol, protein:creatinine ratio of ≥ 100mg/mmol or urinary protein excretion ≥ 1g/24h. • Proteinuria corresponds to an albumin:creatinine ratio of 30 mg/mmol. • Rapid Decline in eGFR: >5 ml/min over 1 year or >10 ml/min over 5 years. For further details around the interpretation of urinary protein tests see: https://edren.org/ren/handbook/unithdbk/ckd/proteinuria/ For more information on referring patients with Lithium-induced CKD to the Renal Medicine service, see: https://apps.nhslothian.scot/refhelp/guidelines/renalmedicine/lithiuminducedckd/			

3.4 Adverse effects of lithium

There are several adverse effects that can occur despite appropriate therapeutic use of lithium.

Short-term (days or weeks)	Nausea, diarrhoea, abdominal discomfort
	Metallic taste
	Tremor, ataxia
	Polyuria, polydipsia
	Dry mouth
Intermediate to long-term (weeks or months)	Persistent mild diarrhoea
	Polyuria, Nephrogenic diabetes insipidus
	Leucocytosis

	Tremor, ataxia
	T-wave inversion on ECG
	Worsening of skin conditions e.g. psoriasis
	Thyroid and parathyroid abnormalities
Long-term (months or years)	Weight gain
	Acne, alopecia
	Tremor, myopathy, ataxia
	Renal impairment

It is worth noting that nephrogenic diabetes insipidus may be irreversible after prolonged treatment. This is despite withdrawal of lithium.

Lithium-associated hypothyroidism is reversible in most patients once lithium has been discontinued.

4.0 Acute lithium toxicity

Risk factors for acute toxicity are increased by dehydration, altered sodium intake, diarrhoea, vomiting, diuretics, NSAIDs and other medications.

4.1 Signs and symptoms of acute lithium toxicity

Mild	• Nausea, vomiting • Diarrhoea • Fine resting tremor • Blurred vision • Polyuria Muscular weakness
Moderate	• Confusion • Increased deep tendon reflexes
Severe	• Truncal ataxia, ataxic gait, incoordination • Scanning speech • Hypotension that does not resolve with intravenous fluid administration • Cardiac dysrhythmias (including bradycardia and sinoatrial block) • Rigidity, hypertonicity, myoclonus • Seizures • Stupor, coma, nonconvulsive status epilepticus

Symptoms do not correlate with serum lithium levels, however it is important to determine the chronicity of exposure

- Acute – levels are expected to rise rapidly as the bolus of lithium is absorbed
- Chronic – levels are not expected to rise rapidly
- Acute on chronic – levels are expected to rise rapidly. However, symptoms of neurotoxicity are usually seen at lower serum lithium levels when compared to acute toxicity.

4.2 Management of lithium toxicity

If a patient on Lithium becomes unwell (regardless of the cause), their serum lithium levels should be measured.

In patients with any suspicion of lithium toxicity, an immediate serum lithium level should be measured. This is to be interpreted in conjunction with the signs and symptoms as described above.

Specialist toxicology +/- renal advice should be sought when managing lithium toxicity. However, the following points may be useful:

- Activated charcoal does not prevent the absorption of lithium
- There is no specific antidote to lithium
- Serial Lithium concentrations should be obtained since absorption and distribution is slow.

In patients with clinical features of Lithium toxicity, intravenous fluids should be administered to increase renal Lithium elimination (even when euvolemic).

Extracorporeal removal / haemodialysis should be considered if there are severe symptoms of toxicity (see above), irrespective of the lithium concentration or if serum lithium concentration >5 mmol/L. It should also be considered if serum Lithium >4mmol/L in patients with impaired kidney function, in older adults or patients with a low muscle mass, or patients who show a doubling of baseline serum creatinine.

4.3 Useful resources for management of lithium toxicity
https://www.extrip-workgroup.org/lithium
https://www.toxbase.org/

5.0 Drug interactions

Thiazide diuretics, ACE inhibitors, Angiotensin II receptor blockers, NSAIDs and Cyclo-oxygenase inhibitors can considerably increase lithium levels and should be avoided where possible.

Co-administration of some antipsychotics, antidepressants and carbamazepine may increase the risk of neurotoxicity.

Refer to current Summary of Product Characteristics (SmPC): www.medicines.org.uk for details.

6.0 Information Sources

Chief Medical Officer - The Scottish Government. (2019, 03 27). *NATIONAL GUIDANCE FOR MONITORING LITHIUM*. Retrieved from https://www.sehd.scot.nhs.uk/cmo/CMO(2019)04.pdf

Decker, B., Goldfarb, D., & Dargan, P. (2015). Extracorporeal Treatment for Lithium Poisoning: Systematic Review and Recommendations from the. *Journal of the American Society of Nephrology*.

Joint Formulary Committee. (n.d.). *Lithium Carbonate*. Retrieved from British National Formulary: https://bnf.nice.org.uk/drugs/lithium-carbonate/#indications-and-dose

Kripalani, M., Shawcross, J., Reilly, J., & Main, J. (2009). Lithium and Chronic Kitney Disease. *BMJ*, 166-172.

National Poisons Information Service. (2020, 11). *TOXBASE*. Retrieved from https://www.toxbase.org/poisons-index-a-z/l-products/lithium/

NICE. (2023, 12 21). *Bipolar Disorder: assessment and management.* Retrieved from https://www.nice.org.uk/guidance/cg185

7.0 Stakeholder consultation

Dr Robert Hunter, Consultant Physician, Renal medicine
Prof Daniel Smith, Consultant Psychiatrist, REH
Dr Rong Bing, Dr Neil Grubb, Cardiology at RIE
Dr Nicola Zammitt, Consultant Physician

8.0 Version Control

Date	Authors	Version/Page	Reason for change
06/12/2023	Dr Rayard Ramlogan Dr Robert Hunter Paulina Mlawa Dr Sharon Smith	1.0	- Creation of updated guidance - Merging Initiation and maintenance guidelines - Introduction of uACR monitoring
30/04/24	REAS Drugs and Therapeutics Committee	1.1 Technical Update	Amendment to section 2.3 The deletion of the statement " Consider seeking advice from pharmacy " as this is different from the final sentence in the section Add "The salt of lithium (carbonate or citrate) and the formulation (MR tablets, tablets or liquid) should be included in all prescriptions". Addition of NHS Lothian logo