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Lithium and COVID-19

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With **all of us** in mind.

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Background

Lithium is a drug with a narrow therapeutic index and toxicity can develop quickly if levels are above the therapeutic range. Target lithium levels are 0.6-0.8 mmol/L (0.4mmol may be enough for some patients and indications).

In some patients, lithium may adversely affect renal or thyroid function. Lithium is exclusively excreted by the kidneys and can build up in the blood if kidney function is impaired. Lithium has been associated with a gradual decline in estimated glomerular filtration rate (eGFR) over time, particularly if levels are maintained near or above the maximum recommended level. Longer exposure to supra-therapeutic lithium levels is possibly more toxic than short exposure to high levels.

Patients on lithium therefore undergo blood testing routinely to ensure that their blood levels remain in range and that their kidney or thyroid function is not being adversely affected. Lithium levels should be taken after 5-7 days of stable dosing and as a trough i.e. 12 hours post dose.

Other monitoring includes Height, Weight, BMI, Thyroid function, ECG and Full Blood Count. Lithium monitoring is carried out at least every three months for the first year, but some patients may need to have lithium monitoring carried out more frequently (See at risk patients section below)

After the first year, patients in any of the at risk categories below should continue with monitoring at least three monthly however stable patients without risk factors can have blood testing every 6 months.

Signs of Lithium toxicity

Toxicity can occur with levels within the therapeutic range e.g. in the elderly, but is most likely to develop in patients with lithium plasma levels above 1mmol/L

- Symptoms include blurring of vision, anorexia, vomiting, diarrhoea, drowsiness, giddiness, ataxia, gross tremor and lack of co-ordination
- At very high levels, hyperreflexia, hyperextension of limbs, convulsions, toxic psychosis and oliguria may occur.
- Monitor for symptoms of neurotoxicity, including paraesthesia, ataxia, tremor and cognitive impairment, which can occur at therapeutic doses.

If any of the symptoms are experienced by the patient, then lithium therapy should be withheld and lithium levels checked urgently. Consider urgent medical referral and psychiatric advice.

Drug interactions are an important cause of increased lithium levels and subsequent decline in renal function. NSAIDs, diuretics and ACE inhibitors/ARBs are the most common drug causes of lithium toxicity. Dehydration or reduced fluid intake is another important cause of lithium toxicity.

In many cases of slowly developing lithium toxicity, symptoms can be relatively bland, non-specific or non-existent. Signs of moderate to severe lithium toxicity may include diarrhoea, vomiting, mental state changes, coarse tremor or falls due to ataxia.

Lithium and COVID-19

Recent reports from Wuhan, China suggested that "kidney disease on admission and acute kidney injury during hospitalisation was associated with an increased risk of in-hospital death" in patients with COVID-19 disease. Therefore, the possible effect of lithium on kidney function must be borne in mind when treating patients who develop the disease**.**

However there is no direct evidence that lithium itself increases the risk of developing infections such as respiratory tract infections or complications such as pneumonia. Where patients have developed an infection, they may be at an increased risk of developing lithium toxicity. Therefore vomiting, diarrhoea and infection (especially if sweating profusely due to fever) may require dose reduction or discontinuation.

Patients with COVID-19 frequently present with a fever and therefore may be at risk of dehydration. Patients who are isolated at home with limited supplies may significantly change their diet and therefore sodium intake which could also impact on lithium levels. (Note that NSAIDS and drugs acting on ACE may be withdrawn during COVID-19 infection, causing a resultant fall in lithium levels.)

Lithium patients with confirmed or suspected COVID-19

Where patients who are stable on lithium have symptoms of COVID-19, lithium use can be continued as usual and should continue to be monitored in line with usual monitoring advice. See Shared Care Guideline for Lithium (SCG)Calderdale, Kirklees and Wakefield. Shared Care guideline for Lithium Barnsley

Patients who develop moderate or severe symptoms of COVID-19, particularly those who are elderly or more likely to be at risk of lithium toxicity (as below) should have their lithium levels monitored as soon as possible. Where patients are at significant risk of dehydration or there any signs of lithium toxicity lithium should be withheld until lithium monitoring is carried out.

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Patients self-isolating without confirmed or suspected COVID-19

Patients self-isolating in line with government advice should continue to be monitored in line with usual monitoring advice. Unless they are in a "high-risk" group they can continue to attend clinics, phlebotomy clinics or GP surgeries to have their blood tests.

Decisions to extend monitoring should be managed on a case by case basis but may be considered for patients who have been stable for more than 1 year with no other risk factors.

Managing patients unable to attend for their blood test

Most patients prescribed lithium will be monitored in primary care and this should be continued as much as possible as per the SCG. If a patient is unable to attend their usual site for a blood test consideration should be given to alternative options e.g.

- Patient attends a GP practice (if phlebotomy service is available)
- Patient attends a blood test centre (e.g. hospital, note they will need a blood form)
- Patient attends a mental health team clinic/lithium clinic
- Nurse / doctor attend patient to take bloods *
- Consider if their Community Mental Health Team can attend to take bloods*

*For patients with symptomatic COVID-19, those at high risk, or those who are showing signs of lithium toxicity.

Wherever possible patients who are isolated with symptomatic COVID-19 or those who are isolated due to being in a "high-risk" group should have their blood samples taken at the place they are staying. Where staff are attending patients who have symptoms of COVID-19 they should wear full protective equipment in line with the Trust's infection control policy.

General guidelines and precautions

Remind all patients:-

- To seek medical attention if they develop diarrhoea or vomiting, or feel acutely unwell for any reason
- To ensure they maintain their fluid intake, particularly if they have a fever, if they are immobile for long periods or if they develop a chest infection or pneumonia
- To inform their care team of any changes to their drug treatment
- Not to take over-the-counter non-steroidal anti-inflammatory drugs (e.g. ibuprofen), but to take paracetamol instead.
- Not to stop lithium abruptly unless advised to do so by a specialist

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Patients without symptoms of COVID-19

Patients who are self-isolating should not attend the clinic or GP surgery for routine lithium monitoring tests. The appointment should be re-booked for a later date unless the patient falls under the high-risk group outlined below.

Patients with symptoms of COVID-19

Patients presenting with new cough and/or fever: ask the patient to continue taking lithium but take blood sample for lithium serum level and U&Es. Remind patient of need to maintain their fluid intake. If lithium levels are elevated or kidney function is compromised, seek urgent specialist advice.

If there is any delay in obtaining a lithium level, it may be reasonable to pause treatment and await the result of the lithium level. Blood levels should govern ongoing treatment and the dose used. Be aware that sudden discontinuation of lithium can be associated with a rapid relapse of symptoms, particularly mania. Use caution until the patient has regained physical health, with increased frequency of monitoring of lithium levels and renal function.

Patients presenting with flu-like/COVID-19 symptoms and symptoms of lithium toxicity (e.g. diarrhoea, vomiting, tremor, mental state changes, or falls): **WITHOLD lithium, take URGENT lithium serum level and U&Es.**

At-risk patients - People who require more frequent lithium monitoring

These patients MUST continue to have their regular lithium monitoring

- Elderly
- Initiating or stopping drugs that interact with lithium*
- Established chronic kidney disease
- Evidence of impaired thyroid function
- Raised calcium level
- Poor symptom control
- Poor adherence
- Has a lithium serum level > 0.8mmol/L

*NSAIDS, ACE inhibitors, ARBs, diuretics

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Standard tests for lithium monitoring

Parameter	Standard care	Special considerations
Serum lithium	Measure the person's plasma lithium level every 3 months for the first year. Then 6 monthly	• Older people (over 65s) • People taking drugs that interact with lithium (e.g. NSAIDS, diuretics, ACE inhibitors) • People who are at risk of impaired renal or thyroid function, raised calcium levels or other complications such as significant cardiac disease • People who have poor symptom control • People with poor adherence • People whose last plasma lithium level was 0.8 mmol per litre or higher at least 3 monthly
Serum creatinine and eGFR*	6 monthly	More frequently than 6 monthly if evidence of impaired renal function E.g. eGFR less than 60ml/min (do whenever a serum Lithium is done) or eGFR falls over 2 or more tests, and assess the rate of deterioration of renal function. Over 65s at least every 6 months
Serum calcium	6 monthly	Over 65yr or cardiac disorder; at least every 6 monthly More frequently if found that calcium level is raised.
Thyroid function test	6 monthly	More frequently than 6 monthly if there is evidence of impaired thyroid function or an increase in mood symptoms that might be related to impaired thyroid function. Over 65s at least every 6 months
U&Es	6 monthly	More frequently if urea levels and creatinine levels become elevated Over 65s at least every 6 months
BP	12 monthly	
ECG	Initially and if clinically indicated	
Weight	At start of therapy and every 6 months	
Where renal impairment is present, FBC is recommended. *if eGFR falls below 60ml/min, consider referring to Consultant Psychiatrist for review of the ongoing need for lithium		