Derbyshire Healthcare
NHS Foundation Trust

Clozapine, Antipsychotic Depot/Long-acting Injections, Other Psychotropics and COVID-19

Supply and Patient Treatment Advice

31 March 2020 (updated from original document issued on 17 March)

What's new

23/03/20: Added further detail about clozapine and managing antipsychotic long-acting/depot injections

31/03/20: Added section on lithium

General Advice about psychotropic medication and COVID-19

Patients should be reassured to continue to take their prescribed medication if stable and well as, with the exception of clozapine, they are not known to significantly affect the immune function. A relapse in mental illness could indirectly increase risk by affecting normal behaviours and lead to inpatient admission during a period of time when NHS capacity is significantly reduced.

Prescribers in all settings should not write prescriptions to cover longer periods than normal. Sudden surges in demand for medication will disrupt the medicines supply chain to the detriment of patients

Currently there are sufficient stocks of medicines, the supply chain is working normally and is routinely monitored.

What else is happening?

23/03/20: We have escalated questions about the following to NHS England using the pathways established for this and are also discussing them within Derbyshire:

- Clozapine blood testing
- Clozapine medication delivery
- Changes to supervised consumption in substance misuse
- The importance of everyone supporting current "shared care" agreements for medicines such as lithium and those for ADHD

NHS England has requested details from us and other Trusts about the number of clozapine patients we support and this was provided last week.

We are in regular contact with pharmacy networks at county, regional and national level so we can raise concerns and collate answers to pass back to clinical staff.

Clozapine

Several hundred of the Trust's patients are prescribed clozapine. The Trust is responsible for the supply of clozapine and the completion of required blood tests. For a small number of patients, supply and delivery of clozapine is via "Clozaril Homelife" however Homelife are not responsible for blood testing. Clozapine blood testing is a function currently shared between clozapine clinics, community hospitals and GP surgeries, but remains the responsibility of the trust. For the majority of patients, clozapine is sent to a pre-arranged "drop-off" point for collection by the patient or a carer. Some Derby patients collect their clozapine directly from our pharmacy department at Kingsway Hospital.

Patients prescribed clozapine will attend or be seen weekly, fortnightly or monthly and **clozapine can only be issued if the results of a blood test are satisfactory** ("green")

A quantity of clozapine can only be supplied to cover the time between required blood tests (one week, two weeks or four weeks).

Missing 48 hours of clozapine will mean that the patient will need to be re-titrated and this almost always requires inpatient admission to complete physical health monitoring to the required standard to assure patient safety. Business continuity plans therefore must prioritise the support of patients prescribed clozapine and the operation of the "clozapine clinics".

Clozapine Blood Testing

Local business continuity plans will need to ensure clozapine clinics and the need for patients to receive blood tests as scheduled are considered as part of contingency planning and prioritisation. At the time of writing regulatory authorities have made no announcements to change the current national regulatory recommendations (confirmed with Mylan, 23/03/2020).

Clozapine Clinics

It will be necessary to ensure sufficient staff are trained in how each clozapine clinic runs, phlebotomy, how clozapine supplies are quarantined, how to access POCHI and CPMS systems.

In the scenario where a clozapine clinic is cancelled, prioritise patients in order of blood test frequency (weekly first) as well as other clinical risks.

In the scenario where a patient is asked to self-isolate at home, phlebotomy-trained staff can visit the patient at home to take a blood sample (seeking Trust advice on personal protective equipment and its use in avoiding infection; and transporting blood samples). Pochi machines may be made available throughout the week for testing samples, or samples sent to local pathology laboratories.

In cases where the usual "one-stop" blood testing and clozapine supply cannot occur, there will need to be arrangements to deliver the clozapine to the patient.

We have received advice from Mylan about the safety of sampling blood samples via Pochi when a patient has been diagnosed with COVID-19. They say: "All samples analysed via Pochi should be considered high risk and therefore all clinic staff analysing samples should continue to follow normal procedure and wear correct PPE as instructed. Should there be a spillage of blood please follow your normal infection control procedures. No additional special considerations are necessary for a patient diagnosed with COVID-19."

Clozapine blood testing at community hospitals and GP surgeries

Local business continuity plans will need to ensure the need for patients to receive blood tests as scheduled (and if needed due to a clinical concern) are considered as part of contingency planning and prioritisation.

Clozapine Supply

The current method of supply for each patient should be confirmed and be available to clinical staff. Pharmacy can help with this and will be adding information to Paris records for clozapine patients in the coming days.

- Clozaril Homelife patients: delivery takes place to the patient's home or nominated site once a satisfactory blood test has been received. If there is disruption to the Homelife supply notify pharmacy at Kingsway Hospital on 01332 371037
- Outpatients who attend clozapine clinics: alert the pharmacy department to a patient's non-attendance and arrange blood testing and subsequent clozapine delivery once a satisfactory blood test result is confirmed
- Outpatients who collect from pharmacy at Kingsway Hospital: If not collected by lunchtime on each Friday as expected, the pharmacy department will contact the patient/carer to ensure they are intending to collect. If contact/assurance is not possible pharmacy will notify the relevant clinical team to follow-up the patient.
- Team bases: the team's business continuity planning will need to include patients to whom the team deliver clozapine and any patients who usually collect from the base but are unable to do so (e.g. due to self-isolation).
- Outpatients who collect from a Community Pharmacy, GP surgery or similar:
    - if the delivery of a patient's medication to a nominated site for subsequent collection is not possible (i.e. if the premises is shut due to loss of staff), the delivery will be returned to the pharmacy department at Kingsway Hospital who will then contact the patient and/or community team to discuss alternative arrangements.
    - Business continuity plans should include clozapine patients who cannot collect their clozapine as normal from their nominated site.

The Trust's Pharmacy team is aware of a small number of patients living in less central areas and also requiring more frequent supplies. Pharmacy will contact the relevant clinical teams in coming days to help refine plans for those people.

For patients presenting with an "amber" or "red" blood result follow the existing protocols and discuss with the patient's consultant (or covering consultant) as a matter of urgency. Be prepared to arrange additional blood tests as required.

Clinical considerations: clozapine and COVID-19

Fever and raised CRP, indicative of systemic inflammation, can cause a reduction in clozapine metabolism via CYP1A2 enzymes. This results in a rise in clozapine plasma levels with consequent increase in side effects and the risk of toxicity. It is possible that COVID-19 could cause this effect. The manufacturers of the clozapine brand used locally (Clozaril ®, Mylan) state in their FAQs that there is no contraindication to prescribing Clozaril® should the patient develop respiratory symptoms, but signs or symptoms of fever should be investigated for any potential neutropenia. As per the SmPC for Clozaril®: "Patients with fever should be carefully evaluated to rule out the possibility of an underlying infection or the development of agranulocytosis. In the presence of high fever, the possibility of neuroleptic malignant syndrome (NMS) must be considered. If the diagnosis of NMS is confirmed, Clozaril should be discontinued immediately and appropriate medical measures should be administered."

Our advice remains (in addition to the above):

- Patients presenting with **severe respiratory infection** should receive urgent medical review and specialist advice should be sought about the appropriateness of the current clozapine regimen.
- Patients presenting with **mild respiratory infection** should continue taking clozapine and be monitored for any change in efficacy or side-effects.
- Patients presenting with **flu-like symptoms** should continue taking clozapine. Make arrangements for an URGENT full blood count (FBC) blood test, suspect neutropenia and act on amber or red blood results in the usual manner.
- Patients presenting with **flu-like symptoms, chest pain and shortness of breath** should have their clozapine withheld, suspect myocarditis and investigate accordingly.

Note that the symptoms of COVID-19 infection overlap with those of a low white cell count such as neutropenia, as shown in the table collated by Mylan, the manufacturers of the Clozaril brand of clozapine, from information at www.nhs.uk/conditions :

COVID 19	Low White Cell Count
A high temperature of 38C or above	A high temperature of 38C or above
A new, continuous cough (coughing a lot for more than an hour, or three or more coughing episodes in 24 hours)	Flu-like symptoms (aches, lethargy, dry cough, headache, nausea, diarrhoea)
Breathing difficulties	Sore throat
	Chills and shivering

Patients who are unwell might reduce their **tobacco smoking** frequency and/or intensity. This will lead to a rise in clozapine plasma levels due to reduced inhibition of CYP1A2 enzymes. Clinicians should assume that smoking will reduce in patients with a respiratory infection. The use of nicotine replacement therapy (NRT) or e-cigarettes makes no difference to the effect on enzymes and clozapine levels will still rise.

Clinical Considerations: Other psychotropic drugs

As discussed above, there is an important and clinically relevant relationship between tobacco smoking and clozapine plasma levels. Olanzapine can also be affected to some extent and patients should be monitored for increased side effects, and dose adjusted if clinically appropriate.

Clinicians should also consider the effect of changed smoking habit due to respiratory infection, on other psychotropic medication with the potential for increased adverse effects.

Depot Injection Supply and Administration

Many Trust patients are prescribed antipsychotic depot/long-acting injections to prevent psychotic relapse. These medications are administered at intervals ranging from weekly or two-weekly to four-weekly or monthly. Some are administered in the community via “depot clinics”, others via home visits. Review of community team priority groups should include those on depots.

Supply of medication will occur to clinics and team bases via the usual routes.

Notify the pharmacy department at Kingsway Hospital if there are any interruptions in the normal supply of injections.

For self-isolating patients, staff can visit at home to administer, subject to following appropriate Trust advice in infection control and personal protective equipment.

In the scenario of a depot clinic being cancelled or staff not being able to visit a patient at home on the scheduled day, prioritise patients in order of depot administration frequency (i.e. weekly first, then two-weekly and so on) as well as geographical considerations.

For patients prescribed frequent doses of flupentixol decanoate, haloperidol decanoate or zuclopenthixol decanoate there may be opportunity to review their regimen in case a greater interval (up to four-weekly) is possible:

The first-generation depots can be given at a maximum interval of four weeks, subject to the following maximum doses at any one time per injection:

Depot	Maximum interval between injections	Maximum dose per injection
Flupentixol decanoate	Four weeks	400mg
Haloperidol decanoate	Four weeks	300mg
Zuclopenthixol decanoate	Four weeks	600mg

For more detail on individual products refer to www.medicines.org.uk and/or the British National Formulary (https://bnf.nice.org.uk/).

For patients on more frequent dosing (e.g. weekly or fortnightly) consider increasing the interval between doses and adjusting the dose given. Examples might be:

- Patient receives zuclopenthixol decanoate 300mg weekly, consider 600mg every two weeks
- Patient receives haloperidol decanoate 100mg every two weeks, consider 200mg every four weeks

Examples where it might not be appropriate to alter the regimen include:

- Patient receives zuclopenthixol decanoate 400mg weekly; cannot change to 800mg every two weeks as this exceeds the maximum dose for a single injection
- Patient is known to deteriorate around the time a depot is due; lengthening the interval might make this worse, even if a higher dose is given when injecting
- Patient has tried higher individual doses in the past but this has caused side-effects

Risperidone long-acting injection should continue to be given fortnightly and both paliperidone and aripiprazole injections should continue monthly

Other options are possible, however at this time we do not advocate switching patients from one type of depot to another in order to achieve a longer interval. The switching process itself creates a number of concerns including:

- Destabilising the supply chain for depot injections if the pattern of product use changes abruptly
- Increasing the need to monitor patients to ensure the new treatment is effective and does not cause problematic side effects; this requires many weeks of follow-up
- Increased risk of relapse
- Increased risk of side effects occurring that then need to be managed
- Need for clear communication between prescriber, patient, carer, nurse, supplying pharmacy, so that the change is understood by all; with all of these groups potentially affected by COVID-19 the risk of mis-communication is increased

In particular, a switch from depot to oral medication is very likely to increase the risk of relapse and the need for an inpatient bed.

Administering (or delaying) a depot injection to a patient showing signs of COVID-19 infection

It is not possible to give a single, definitive answer for these scenarios and a clinical judgement will need to be made in each case. The following points are offered as considerations within an informed decision-making process:

- Whether or not a depot is given the patient will still have a significant amount of that medication within their body anyway. The injection just "tops them up"
- Changing from the usual depot to an alternative (e.g. oral antipsychotics) carries significant risks of its own (see section above) including relapse at a time when inpatient capacity might be significantly reduced
- A depot can be given a day earlier or later than planned as it is highly unlikely to present a significant risk. This can be done safely without any alteration to the depot prescription. The risk of relapse increases the longer a depot is left ungiven. Contact the pharmacy team for further advice on a case-by-case basis about delays of more than a day and about whether future plans for administration should change or stay the same
- There is clear advice about paliperidone long-acting injection from its manufacturer, available at: https://www.medicines.org.uk/emc/product/7653/smpc
- There is also clear advice about aripiprazole long-acting injection from its manufacturer, available at: https://www.medicines.org.uk/emc/product/7965/smpc

Choice and medication

Don't forget that Choice and Medication is always available to provide you and your patients with information about mental health medicines and the conditions we treat with them. You can find this at https://www.choiceandmedication.org/derbyshcft/ . The site is constantly updated by experienced mental health pharmacists. A patient leaflet about clozapine and COVID-19 has recently been added: https://www.choiceandmedication.org/derbyshcft/generate/handyfactsheetclozapinecovid19.pdf

Lithium

The following advice about lithium has also been provided to our CCG and Primary Care colleagues

Lithium is a commonly used mood stabiliser indicated primarily for the management of bipolar affective disorder and unipolar depression and is often prescribed in primary care under a Shared Care Agreement. **There is a significant risk of rapid relapse of the underlying mental health condition if lithium treatment is abruptly stopped.**

Lithium has a narrow therapeutic window; therefore the dose required for treatment must be titrated and adjusted on the basis of regular monitoring of the serum concentration of lithium. The requirements for routine blood monitoring are set out in the Shared Care Agreement which reflects NICE guidance. The majority of patients require 3-monthly plasma lithium levels; however those with a stable level and not specified in the ongoing 3-monthly category may have them done at 6-monthly intervals instead.

In addition to lithium plasma monitoring renal function, thyroid function and weight should also be measured at regular intervals (usually 6-monthly) as per the Shared Care Agreement.

Unlike some antipsychotics such as clozapine there is no evidence that lithium increases the risk of developing infections such as respiratory tract infections or complications such as pneumonia. However where patients have developed an infection they may be at an increased risk of developing lithium toxicity. The manufacturer advises that additional measurements should be made if signs of lithium toxicity occur, on dosage alteration, development of significant intercurrent disease, signs of manic or depressive relapse and if significant change in sodium or fluid intake occurs.

Lithium blood testing during COVID-19 pandemic:

Management of routine monitoring

The current pandemic is putting a huge strain on the NHS as a whole including primary care and it is expected that access to blood monitoring will be significantly affected.

It may be possible to extend the interval between lithium plasma level monitoring and routine renal and thyroid function monitoring considering:

- Previous plasma levels
- Age
- Renal function
- Thyroid function
- Stability of dose
- Presence or absence of interacting medication
- Patient knowledge of signs of toxicity

This would need considered on a case by case basis and could only be safely managed as a short-term measure as some studies have shown that even one “high” plasma level can impact renal function up to a year afterwards and naturally declining renal function can raise lithium levels.

At risk patients who are unlikely to be appropriate for postponed monitoring include:

- 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 previous lithium serum level > 0.8mmol/L

* NSAIDS, ACE inhibitors, ARBs, diuretics

If postponing routine monitoring patients should be directly asked about side-effects, signs of toxicity and signs of hypothyroidism, hypercalcaemia & hyperparathyroidism.

Management of lithium patients with suspected or confirmed COVID-19:

The steps described above are likely to help reduce the overall burden on healthcare providers but unlikely to help with patients in self-isolation due to high-risk of COVID-19 or suspected or confirmed cases of COVID-19 as these patients are likely to be at higher risk of lithium toxicity. It would be inappropriate to delay routine monitoring for these people as it may cause more pressure on the healthcare system overall rather than relieving it.

Recent reports from Wuhan, China suggested that “kidney disease on admission and acute kidney injury (AKI) during hospitalization were associated with an increased risk of in-hospital death” in patients with COVID-19 disease. Therefore, adding weight to the need to continue routine monitoring in these patients wherever possible.

Where routine monitoring is required to continue provisions should be put in place proactively to manage this. In addition:

- Patients should be advised to maintain adequate sodium and fluid intake during any acute illness; including COVID-19
- Patients should be asked about any signs of toxicity and reminded of these signs (coarse tremor, nausea & vomiting, dysarthria, drowsiness, ataxia, blurred vision, muscle weakness, tinnitus, confusion and convulsions)
- Patients should be advised to inform their care team of any changes to their drug treatment and to not to take over-the-counter non-steroidal anti-inflammatory drugs (e.g. ibuprofen), but to take paracetamol instead
- Patients should be advised not to stop lithium abruptly unless directed to do so

Patients who develop a fever, moderate or severe symptoms of COVID-19 and patients who are unable to maintain adequate fluid intake during the course of the illness; particularly those who are elderly or more likely to be at risk of lithium toxicity (as above) should have their lithium levels and renal function monitored as soon as possible using local PPE equipment and consideration given to a proactive dose reduction or temporary omission. The patient's mental health team would need consulted in these circumstances as alteration of the lithium would depend on their history and risk of toxicity balanced against relapse risk.

If any signs of toxicity are present lithium should be immediately discontinued and plasma level and renal function monitoring arranged using local PPE equipment and procedures. The patient's mental health team should be contacted to advise of the actions taken.

Contacts

Clozaril Patient Monitoring Service:	www.clozaril.co.uk
Clozaril Homelife:	0800 587 0807
Clozapine queries (Kingsway):	01332 371037
General queries (Kingsway):	01332 623700 ext 33268

In emergencies the on-call pharmacist can be contacted via switchboard seven days a week for advice.

Acknowledgments

We would like to thank the following organisations for sharing their documents with us when compiling this advice:

- South London and Maudsley NHS Foundation Trust
- NELFT NHS Foundation Trust
- Pennine Care NHS Foundation Trust