NIHR | Oxford Health Biomedical Research Centre

PRECISION PSYCHIATRY LAB

UNIVERSITY OF OXFORD

Clozapine treatment – How to manage patients on clozapine during the COVID-19 pandemic.

Please note all questions within each section are linked to each other and should be read in conjunction. Below each question are the weblinks to the sources of evidence to support the guidance recommendation.

Clinical question	Guidance
Starting clozapine	
Can I start my patient on clozapine? [link1] [link5]	**It is highly unlikely that during this period it will be possible to start patients on clozapine treatment safely** unless normal haematological monitoring can be assured. There may be some rare clinical situations in inpatient settings where this is the right thing to do, supported by advice from the relevant clozapine patient monitoring service (see our Inpatient wards table for further advice on inpatient settings). For patients being initiated on clozapine, adherence to current country-specific protocols for ANC monitoring is suggested for the first 6 months of treatment.
Measuring white cell count (WCC) and assessing its significance in the presence of possible COVID-19	
What should I do if a patient on clozapine describes symptoms suggestive of infection or of COVID-19? [link1] [link2] [link5] [link8] [link9]	Be aware that **similar symptoms to COVID-19 can arise from incidental (non-COVID-19) infections** associated with neutropenia. For people on clozapine with symptoms of infection, including fever, sore throat and flu-like symptoms, an **urgent neutrophil count is strongly recommended** (this is a requirement within the product licence in the UK. Patients may be asked to omit clozapine until the results of this blood test are received. Continuing clozapine without this blood test would be outside of its licensed use). **Refer to local guidance** (see an example of the guidance for clinicians in Oxford Health NHS Trust). An urgent physician assessment could take place either in person or by telehealth based on local protocols. If patients on clozapine become symptomatic with fever and flu-like symptoms, the emergence of signs and symptoms of clozapine toxicity may require clinicians to reduce the dose of clozapine by as much as a half. Continue the lower dose until 3 days after the fever has subsided, then increase clozapine in a stepwise manner to the pre-fever dose. Where available, clozapine levels help facilitate clinical decision-making, particularly after substantial dosage change, inadequate response or unexpected adverse effects. Any decisions about changes to clozapine dose and monitoring should be made as part of a well-documented, informed consultation with patients and family/caregivers. Ensure that **patients are fully informed and have access to information** (see an example).

	If the patient is suspected of having a serious clozapine-related AE then stop clozapine and investigate appropriately. Symptoms of COVID-19 can mimic clozapine related AEs: notably, myocarditis and neutropenic sepsis. Clozapine related myocarditis is more likely to occur within the first 6 weeks of treatment. Therefore, after the initial period, the likelihood of any myocarditis being clozapine related reduces.
How do I assess WCC when this may also be affected by COVID-19 infection? [link3] [link11]	Coronavirus infection **may depress lymphocytes. Emerging data shows that it also may transiently reduce neutrophils**. It appears likely that patients with COVID-19 infection will have a low WCC. This seems to be largely due to reduced lymphocytes. As the monitoring parameters for clozapine include total WCC, a reduction may result in patients registering results that, under normal circumstances, require interruption of clozapine treatment. **However, the purpose of interrupting clozapine treatment is to protect patients from neutropenia and agranulocytosis. Where a low WCC count occurs in the presence of a normal or non-dangerous neutrophil level in the context of COVID-19 infection, it is reasoned that clozapine can be safely continued**.
Should I discontinue clozapine if WCC is low in a COVID-19 patient? [link3] [link11]	Emerging data shows a reduction in WCC, neutrophils and lymphocytes in patients taking clozapine who become infected with COVID-19. This reduction is small (mean of around 1x109/L) and transient, recovering within 2 weeks. For some patients, this temporary reduction in WCC and neutrophils may be sufficient to cause their blood tests to be classified as 'amber' or even 'red' by ZTAS. If clozapine-related neutropenia can be ruled out, it is not always necessary to stop clozapine for these patients. Confirmed cases of COVID should be reported to the clozapine monitoring service and they may give further advice about continuing treatment. It is important to consider the **risk of discontinuing an effective antipsychotic treatment such as clozapine** at a time when uncontrolled psychotic symptoms (which are unlikely to be treated by other drugs) may present challenges in safely managing an infected patient.
How do I manage difficulties in keeping to the recommended frequency of blood testing?	
Can I change the frequency of blood monitoring? [link1] [link2] [link5] [link10]	As always, '**Centralised monitoring of leucocyte and neutrophil counts for patients taking clozapine is mandatory**. The frequency of blood testing and duration for which a blood test is 'valid', is based on the risk of clozapine-induced neutropenia and agranulocytosis. **Dispensing or administering clozapine outside these durations (i.e. without a valid full blood count, FBC) is unlicensed**.' However, the following guidance may be considered during the pandemic: **For patients on monthly monitoring:** **If clozapine patients meet the following criteria:** • have been on clozapine continuously **for more than one year**, and • have not had an ANC <2000/µl (or <1500/µl if they have a history of benign ethnic neutropenia), and there is no safe or practical access to neutrophil testing, and • there is a high risk of deterioration if interruption of clozapine therapy were to occur, **then clozapine may be dispensed in the absence of a recent (within 42 days) neutrophil count.** In effect, the validity of the FBC would be extended to 12 weeks, allowing a maximum supply of 12 weeks from the date of the last 'green' FBC result.

	Please note, dispensing of clozapine in the absence of an FBC from the past 42 days is outside the limits of clozapine's product licence. Decisions about ANC monitoring for patients on continuous clozapine treatment **for 6–12 months** may be made on a **case-by-case basis**. Irrespective of ANC monitoring, patients on clozapine should **continue to receive regular clinical assessments of mental state and review of potential adverse drug reactions**, either face-to-face or through telehealth consultations. In the UK, **monitoring blood concentrations of clozapine for toxicity** is now advised in the following clinical situations: • a patient stops smoking or switches to an e-cigarette; • concomitant medicines may interact to increase blood clozapine levels; • a patient has pneumonia or other serious infection; • poor (reduced) clozapine metabolism is suspected; • toxicity is suspected.
What should I do if normal monitoring for FBC is disrupted? [link1] [link6]	**Clinicians can request permission to extend blood test validity** for individual patients in circumstances where clozapine might normally be withheld pending the results of an FBC. A local expert in clozapine use will review the request and respond with 48 hours. **Local services must identify the local expert with responsibility for reviewing requests** (see an example of a clozapine prescribing variation request). (Local guidelines may ask clinicians to fill in an off-licence form prior to extending the validity of blood tests, instead of the clozapine prescribing variation request (please refer to your local guidance for more details)). **The decision to supply clozapine outside the licensed duration of a valid blood test may be taken to meet the needs of a specific patient.** The reasons for recommending and supplying clozapine should be **fully explained to the patient and documented in the patient notes**. Where it is anticipated that a **patient will be unable to attend a blood test** on time and they are likely to **run out of medication** this should be communicated with their supplying Pharmacy as soon as possible to arrange for an interim supply. Note that this will often be a hospital pharmacy, not their usual community pharmacy. Pharmacy staff may have to assist patients to obtain the medication e.g. by arranging delivery to the patient directly or to a nominated person. Posting medication may also be considered in some circumstances.
What about blood tests if a patient is self-isolating? [link4]	Community mental health and community learning disability teams will need to consider how to continue to deliver critical aspects of care: e.g., blood tests for patients on clozapine, lithium or ADHD medication. Where patients are self-isolating, or unable to attend clinics for testing, **alternative arrangements will need to be made** to ensure people can access their usual medications and monitoring. **This may include home visits** to undertake mandatory testing to keep patients safe (depending on local policy and advice).
Do I need to consider any changes to staff training? [link4]	**Refresher training and upskilling staff on key aspects of physical healthcare** to ensure a sufficient pool of staff is available to undertake mandatory blood testing: e.g. for patients on clozapine, lithium, or ADHD medication, this may include pharmacy staff undertaking phlebotomy training and refreshing knowledge, skills and practice in infection control (please refer to local and national advice).

Where can I find information about specific brands of clozapine? [link1]	**The three companies who supply clozapine in the UK have issued guidance about their brand of clozapine and COVID-19 virus**. This information has been sent directly from each company to those pharmacies who supply their respective brand of clozapine. More details are available from info@ztas.co.uk (zaponex), Denzapine@britannia-pharm.com (denzapine) and CPMS@mylan.co.uk (cloraril).
General advice for patients/carers on managing medications and prescriptions during COVID-19 [link7]	In the UK, PHE advises patients as follows: • Keep taking your medication. • You might be able to order repeat prescriptions by phone, or online using an app or website if your doctor's surgery offers this. • Ask your pharmacy about getting your medication delivered or think about who you could ask to collect it for you if you are self-isolating or shielding. The NHS website has more information about getting prescriptions for someone else and checking if you have to pay for prescriptions. • Continue to order your repeat prescriptions in your usual timeframe. There is no need to order for a longer duration or larger quantities. • Your GP practice (or clinical team) may move your prescriptions to repeat dispensing arrangements, so you only have to contact your pharmacy to get a repeat of your medicine rather than your practice. • Be careful about buying medication online. You should only buy from registered pharmacies. You can check if a pharmacy is registered on the General Pharmaceutical Council website. • You can contact NHS 111 in England if you're worried about accessing medication.
Are there any additional risks of clozapine and COVID-19?	
Can COVID-19 infection alter clozapine blood levels? [link3] [link5]	**Serious infection is sometimes associated with an increase in clozapine blood levels**, either because of a direct effect on metabolism or because smoking cessation reverses hepatic enzyme induction (or both). If patients on clozapine become symptomatic with fever and flu-like symptoms, the emergence of signs and symptoms of clozapine toxicity may require clinicians to reduce the dose of clozapine by as much as a half. Continue the lower dose until 3 days after the fever has subsided, then increase clozapine in a stepwise manner to the pre-fever dose. Where available, clozapine levels help facilitate clinical decision-making, particularly after substantial dosage change, inadequate response, or unexpected adverse effects.
Are clozapine treated patients at greater risk of COVID-19? [link12] [link13]	**No clear data are available**. A retrospective study on 6309 patients with a schizophrenia-spectrum diagnosis (102 tested positive for COVID-19) found that individuals who were on clozapine had increased risk of COVID-19 infection compared with those who were on other antipsychotic medication (unadjusted hazard ratio HR = 2.62, 95% CI 1.73–3.96), which was attenuated after adjusting for potential confounders, including clinical contact (adjusted HR = 1.76, 95% CI 1.14–2.72). See the attached papers for discussion points.