Clozapine and the corona virus

Many healthcare professionals may have questions concerning the effect of the current corona virus pandemic on the use of Zaponex® (clozapine), and especially the mandatory blood tests. The measures taken against the COVID-19 outbreak have significant consequences for both clozapine patients and their caretakers.
Our official statement regarding COVID-19 can be found on the ZTAS website since March 12th 2020. This information letter aims to give updated information as well as include new advice from health authorities and HCP groups. Please note that the following is only meant as a guideline rather than a definite treatment strategy, as all treatment choices are ultimately clinical decisions.

COVID-19 infection and clozapine use

From our official statement:
"There is currently no data that suggests that clozapine patients should not continue to take their clozapine if they are confirmed or suspected to have contracted COVID-19, as this is not a contraindication. Although specific information is lacking, we refer to our standard information with regards to clozapine use in patients with influenza or other airway infections.

Please note that bacterial or viral infections have been reported to increase clozapine plasma levels. In patients who develop clozapine overdose symptoms such as drowsiness, sedation, lethargy, confusion, agitation, tachycardia, hypotension, respiratory depression and seizures, high plasma levels should be suspected and a plasma level assay should be done to confirm or exclude this. In positive cases, the clozapine dose may need to be temporarily reduced until the infection resolves. Since the results of these assays can take some days to come in, it may be necessary to do an anticipatory dose reduction in patients who display symptoms of both infection and overdose."

Current observations

NHS England regularly updates their statements on their public website (see link in References[1]), and as per their guidance, they consider any patient "*on immunosuppression therapy sufficient to significantly increase risk of infection*" as extremely vulnerable. Leyden Delta (manufacturer of Zaponex/Leydex clozapine) is of the opinion that although clozapine is not an immunosuppressant, clozapine use may be regarded a risk when patients experience clozapine-induced leukopenia or neutropenia. Clozapine patients often have comorbidities (e.g. diabetes) that could make them more vulnerable, and there is also limited evidence that clozapine may have immunomodulatory effects (e.g. affecting immunoglobulin levels), which could also contribute to an increased risk of infection.

The Dutch Clozapine Plus Collaboration Group (CPCG) has noted that due to the current pandemic, it is impossible to distinguish between an infection from clozapine-induced agranulocytosis and a corona infection. Several UK-based blood sampling points are only operational for the most urgent cases, which severely limits the options for blood monitoring. Patients are understandably worried to have their blood checked at hospitals where staff members may have been infected. Conversely, patients who display infectious symptoms such as fever should only have their bloods checked when isolated from non-infected people (preferably avoiding clinics), and if the person doing the test can take the necessary precautions to prevent becoming infected themselves.

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Continuity of regular blood monitoring frequency

We concur with the NHS advice to have patients come over to PoCHI clinics or sampling points only when they do not have symptoms. To go to clinicals during the UK lockdown, patients can get special waivers that explain their medical urgency.

To avoid having suspected COVID-19-positive patients come to the clinic as much as possible, we would suggest to consider the possibility of drawing blood at home, or only allow a visit to the clinic if there is no alternative. This would involve taking appropriate measures for self-protection of HCPs (gloves, protective glasses, face mask, frequent handwashing and respiratory hygiene) and subsequent testing of the blood sample on the PoCHI machine. A community nurse or the patient's GP could possibly execute or arrange the blood sampling at home.

We are aware that it is getting increasingly difficult to get blood from patients due to home isolation or risk of spreading the corona infection. Our initial suggestion would be to use the extended validity in blood tests to limit the number of tests for the upcoming period wherever possible. Patients are allowed a clozapine supply that lasts as long as the maximum validity of their current blood test. As per the ZTAS Manual, those validities are as follows:

Monitoring frequency	**Maximum validity of blood**	**Maximum clozapine supply**
Weekly	7 + 7 days	14 days
Fortnightly	14 + 7 days	21 days
Monthly	28 + 14 days	42 days

Current observations suggest that mild cases of COVID-19 seem to last a few weeks at most, so if clinically acceptable, this would be an in-license option that allows clinicians some manoeuvrability around testing, and make them less frequent.

Extenuating circumstances

Although there is no waiver for blood monitoring, we understand that in certain circumstances, the periodic blood tests can place both patients and caregivers at unacceptable risks. For patients who have been on *long-term clozapine treatment with stable blood counts*, the risk of contracting the corona infection during a regular blood check may far outweigh the risk of an undetected agranulocytosis. This may be a particular issue in frail or elderly patients with comorbidities. The CPCG, the Journal of Psychiatry & Neuroscience (*J Psychiatry Neurosci*)[2] and The Royal College of Psychiatrists (*RCPsych*)[3] have therefore issued the following recommendations:

1. Clozapine patients in the first 18 weeks of clozapine use: ***continue the weekly bloods***. Despite all the practical limitations, this is the period in which patients are at the highest risk of neutropenia and agranulocytosis, so it is important to keep checking the blood for possibly life-threatening abnormalities.

2. Clozapine patients in weeks 19 to 52: there is an advice to temporarily lower to ***monthly bloods*** (which would be ***off-license***).

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3. Clozapine patients after more than 1 year of use and without a history of clozapine-induced neutropenia (**ANC<1.5 x 10^9/L**, or **<1.0** with a history of benign ethnic neutropenia): temporary suspension of monthly blood tests; suggested to lower to ***once every 8-12 weeks*** (which would be ***off-license***).

4. Clozapine patients who have confirmed neutropenia or agranulocytosis: ***discontinue clozapine and start daily testing*** until two blood results have been obtained with normal blood counts (as per our regular SmPC warning).

5. Clozapine patients with fever: ***immediately test for both agranulocytosis and the corona virus***; especially when they also suffer from ***coughing, sore throat, shortness of breath and a runny nose***.

Concerning scenario 3: please note that both *J Psychiatry Neurosci* and *RCPsych* are more conservative, stating that ANC cannot have been below 2.0 (1.5 for BEN patients) for a year to qualify for suspension of monthly blood tests.

In case of scenario 5, we also strongly recommend to ***immediately cut the clozapine dose in half*** to prevent clozapine toxicity (not awaiting plasma level assay results), or by **25%** in case of patients with a **high risk of psychotic relapse**. Infections inhibit clozapine metabolism and can quickly lead to high clozapine plasma levels. This is even more important in patients who are hospitalised and ***forced to stop smoking***, as this can cause a further rise in plasma levels (factor 2 to 10). Seizure and constipation prophylaxis may also be necessary.
If plasma levels from around the time that the patient started to display signs of infection are known, the clozapine dose can be increased as soon as these signs have resolved. If no plasma levels are known, wait for three days following the resolution of infection signs before re-starting clozapine.

Practical arrangements

As previously mentioned, the decision to deviate from the mandatory frequency for blood monitoring would be at the treating physician's discretion, based on a benefit-risk assessment. However, as stated above, this would constitute unlicensed use of our product, so please inform us if Zaponex will be used under off-license conditions. An off-license agreement form can be requested from ZTAS or Medical Information, and returned to ZTAS (info@ztas.co.uk) after signing.

In case of multiple patients needed to be treated off-license quickly, an email notifying us which patients will be treated off-license will suffice, as the paperwork can be dealt with later. Alternatively, consultant psychiatrists can also send us an email with a list of patients to whom this might apply, alongside *a single signed off-license agreement*. A formally signed off-license agreement per patient can be omitted in such cases. If the consultant psychiatrist is not able to write this email, their proxy or non-medical prescriber (NMP) could take over. The consultant psychiatrist would still continue to have the overall responsibility for the patient's treatment.

In case that doctors (consultant psychiatrists) cannot write repeat prescriptions because they are self-isolating or have become ill themselves, but their patients have valid blood results, again a

proxy/NMP could issue those repeat prescriptions, and treatment can continue within license. Any treatment decision is at the discretion of the responsible physician.

In case of off-license treatment due to the COVID pandemic, we will add the moniker " OL COVID" to the patient's name and move them to "status interrupted" for 6 weeks (in case of regular 4-weekly monitoring) after the last full blood count, so that they do not show up as "prohibited". We request that new blood results are send to us by email. Subsequently, patients will briefly revert to active treatment to enter the blood results, and will then be moved back to status interrupted for another 6 weeks. This will not show up as a treatment break on their records. Patients can go back to their original monitoring scheme after having been transferred to in-license treatment again.

Please be aware that if we are not informed, patients will eventually show up as "Late" on ZTAS, and clozapine dispensing might become prohibited by the pharmacy.

References

1. NHS Guidance on shielding and protecting people defined on medical grounds as extremely vulnerable from COVID-19.
2. J Psychiatry Neurosci: Consensus statement on the use of clozapine during the COVID-19 pandemic.
3. Royal College of Psychiatrists/COVID-19: Providing medication/Clozapine treatment.

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