

Management of clozapine treatment during the COVID-19 pandemic

Siobhan Gee , Fiona Gaughran, James MacCabe, Sukhi Shergill, Eromona Whiskey  and David Taylor 

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Abstract: Clozapine is the only available treatment for refractory schizophrenia but its use involves frequent physical contact with healthcare workers for the purpose of mandatory blood monitoring. During the COVID-19 pandemic, patients taking clozapine will be self-isolating to reduce the risk of infection, not least because these patients are at high risk of serious illness and fatality because of high rates of diabetes, obesity and pulmonary disease and an increased risk of pneumonia. Problems may also arise because both clozapine-induced myocarditis and neutropenic sepsis share signs and symptoms with COVID-19 (fever, chest pain, dyspnoea, etc.). We recommend decreasing the frequency of physical contacts by extending the blood monitoring interval to 12 weeks in those patients taking clozapine for more than 1 year. To distinguish COVID-19 from clozapine-related physical adverse effects, we suggest an urgent antigen test alongside a full blood count. In those taking clozapine who develop COVID-19, we suggest continuing with clozapine whenever possible (even during ventilation), reducing the dose if necessary in line with blood assay results. Blood monitoring should continue but clozapine should only cease if there is a significant fall in neutrophils (COVID-19 is linked to lymphopenia but not neutropenia). To protect against the likelihood and severity of respiratory infection, we recommend the use of vitamin D in all clozapine patients. Initiation of clozapine is likely to remain problematic while the risk of infection remains, given the degree of physical contact required to assure safety.

Keywords: agranulocytosis, clozapine, coronavirus, COVID-19, schizophrenia, vitamin D

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Introduction

COVID-19 is the infectious disease caused by the recently discovered coronavirus, SARS-CoV-2. First identified in Wuhan, China, in December 2019, it was characterised as a pandemic by the World Health Organisation (WHO) 3 months later. The most frequently reported symptoms of COVID-19 infection are fever, cough, myalgia, fatigue and shortness of breath. The majority of infected people experience a mild illness and recover with no medical treatment, but about 1 in 6 become seriously ill and develop respiratory distress.¹ Patients with concurrent coronary heart disease, hypertension or diabetes are at greater risk of this more severe disease. Acute cardiac injury, acute kidney injury and secondary infection may follow.

Patients with serious mental health disorders often have physical health comorbidities,² which likely increase their risk of both contracting the infection and developing complications. Psychotropic medication may further increase risk, through side effects or comorbid physical conditions. Patients with serious mental illness may have greater viral exposure due to frequent contact with health services or an inability to comply with social distancing. Mental health may, in addition, be directly affected by the stress of living under social distancing conditions, a reduction in support available from health services as resources are depleted or redeployed, or treatments available to them being restricted for reasons of safety or resource management.

Correspondence to:

David Taylor
Pharmacy Department,
South London and
Maudsley NHS Foundation
Trust, Maudsley Hospital,
Denmark Hill, London
SE5 8AZ, UK

Institute of Pharmaceutical
Science, King's College
London, London, UK
**David.Taylor@slam.
nhs.uk**

Siobhan Gee
Pharmacy Department,
South London and
Maudsley NHS Foundation
Trust, Maudsley Hospital,
London, UK

Institute of Pharmaceutical
Science, King's College
London, London, UK

Fiona Gaughran
James MacCabe
Sukhi Shergill
Eromona Whiskey
Pharmacy Department,
South London and
Maudsley NHS Foundation
Trust, Maudsley Hospital,
London, UK

Institute of Psychiatry,
Psychology and
Neuroscience, King's
College London, London,
UK



People of black, Asian or minority ethnic (BAME) heritage are particularly severely affected by COVID-19,³ and certain ethnic groups, such as South Asians, have higher rates of comorbidities including diabetes, hypertension and cardiovascular disease.⁴ People of BAME backgrounds also have an enhanced risk for psychotic illnesses,⁵ compounding this inequity, and may require lower clozapine doses than Caucasians.⁶

Clozapine is the only effective therapy for treatment-resistant schizophrenia.⁷ For these patients no other antipsychotic treatment is likely to provide symptom relief. A viral pandemic presents particular challenges for safe management of clozapine treatment because of the need for clozapine to be continued despite the regulatory necessity for close physical monitoring and despite the association of clozapine with numerous factors that complicate the diagnosis and management of COVID-19. There are currently no published data on the use of clozapine in patients with COVID-19 infections. This article outlines the relevant evidence currently available and applies it to practical management of patients established on clozapine treatment or considering starting clozapine. Pragmatic suggestions based on clinical experience are made where no evidence to guide decisions exists.

Blood dyscrasia

Monitoring of white cell counts

Clozapine has known haematological side effects. The most common (2.7% of patients)⁸ is neutropenia, which can sometimes portend life-threatening agranulocytosis (0.4% of patients).⁹ For this reason, monitoring of the white cell count (WCC) [including absolute neutrophil count (ANC)] is mandatory in many countries.¹⁰ Over 80% of cases of agranulocytosis occur in the first 18 weeks of treatment.¹¹ By the end of the first year of treatment, the risk of agranulocytosis is comparable to that of other antipsychotics.¹² Neutrophil counts of $0.5\text{--}1.5 \times 10^9/\text{l}$ (mild-to-moderate neutropenia) are not associated with a significantly increased risk of infection.¹³ Agranulocytosis in this context is defined as neutrophil counts of $<0.5 \times 10^9/\text{l}$, where the case fatality rate is between 2% and 4%.¹⁴

Current data suggest that COVID-19 infection results in a lowered ($<4.0 \times 10^9/\text{l}$) WCC for 9–45% of patients.^{15–19} Lymphocytopenia (lymphocytes

$<1.5 \times 10^9/\text{l}$) is especially common, being reported in 33–83% of patients.^{15–20} More severe abnormalities correlate with severity of the disease. Studies have found neutrophils to be in the normal range ($3.0\text{--}7.5 \times 10^9/\text{l}$).^{15,16,20}

It appears likely that patients with COVID-19 infection will have low WCC.^{15,18,20} This seems to be due largely to reduced lymphocytes. Where the monitoring parameters for clozapine include total WCC, a reduction in WCC caused by COVID-19 may result in patients registering results that might, under normal circumstances, mandate interruption of clozapine treatment. However, the purpose of interrupting clozapine treatment is to protect patients from neutropenia.

It is important to consider the considerable risk of discontinuing an effective antipsychotic treatment at a time when uncontrolled psychotic symptoms (unlikely to be treatable by other drugs) potentially present a greater challenge in safely managing an infected or vulnerable patient, or in reducing an individual's ability to protect themselves from infection. In this case, we suggest that clinicians use neutrophil levels rather than the total WCC to monitor for clozapine-induced neutropenia. This is the approach taken in routine practice by countries including the United States (US),²¹ but may constitute unlicensed prescribing in countries such as the United Kingdom (UK) and most of the European Union (EU), where total WCC monitoring is currently mandatory. As such, communication about local policy with manufacturers of clozapine will be of crucial importance.

Frequency of blood monitoring

The risk of a clozapine-induced neutropenic event occurring after the first 18 weeks of treatment is minimal, and comparable to that of other medicines that are not subject to the same blood testing requirements.¹² In addition, bi-weekly or monthly monitoring have a low likelihood of picking up the rapid fall in neutrophil counts that leads to agranulocytosis.^{22,23}

During the viral pandemic, taking blood tests (in hospital settings but especially in the community) is a resource-heavy and potentially risky procedure, increasing physical contact between staff and patients. Patients may be unable to or discouraged from attending centralised phlebotomy services. The availability of staff to take blood tests at

patients' homes may be limited. Given the balance of risks and benefits in measuring the WCC of patients stabilised on clozapine, and the increased exposure to infection in society and the burden to healthcare providers of attempting to do so, we suggest reducing the frequency of WCC monitoring to 3 monthly for patients who have been haematologically stable on clozapine for 12 months or longer and cannot safely or practically access blood test monitoring.²⁴

It is vital that any reduction in the amount of physical contact patients have with staff is compensated by increased contact by telephone or other means, so that the amount of monitoring patients receive is not compromised. Clinicians must continue to monitor patients for signs of, for example, constipation (one of the leading causes of death in patients taking clozapine) and any cardio-respiratory compromise.²⁵ Alternative methods of supporting patients must be implemented.

COVID-19 versus neutropenic sepsis

The most frequently reported symptoms of COVID-19 infection are fever, cough, myalgia, fatigue and shortness of breath.¹⁵ Signs and symptoms of clozapine-associated neutropenic sepsis include a fever, 'flu-like' symptoms, rigors and malaise.²⁶ The overlap of the symptom of fever between these two conditions means that rapid differential diagnosis is essential. We therefore remind prescribers that all patients who take clozapine and present with fever and 'flu-like' symptoms should have a blood sample taken immediately for WCC and ANC, alongside a coronavirus antigen swab test where available.

Recommendations

- Use ANC to monitor for clozapine-induced neutropenia. Where a low WCC count occurs without severe neutropenia ($<2.0 \times 10^9/l$), clozapine could reasonably be safely continued with ongoing close monitoring.
- Order an urgent ANC and antigen test for patients presenting with symptoms of COVID-19 in order to differentiate from neutropenic sepsis, taking into account the reduced likelihood of the latter diagnosis after the first 18 weeks of treatment and the practical risks and difficulties with obtaining blood samples.
- Reduce the frequency of WCC monitoring to 3-monthly for patients who have been

taking clozapine for >1 year, are haematologically stable and who cannot safely or practically access blood testing (discuss with clozapine monitoring agency where required).²⁴

- Clinicians are reminded to continue to monitor patients for clozapine-induced side effects whilst adhering to social distancing guidelines.

Cardiac side effects

Clozapine is rarely associated with the development of myocarditis and cardiomyopathy.²⁷ Myocarditis, a hypersensitivity response to clozapine, is most likely to occur in the first 6–8 weeks of clozapine treatment.⁸ Cardiomyopathy is usually seen later in treatment (median 9 months) and is linked to previous myocarditis, concurrent medical conditions (obesity, tachycardia, diabetes) or previous personal or familial cardiac events. Both may occur at any time.⁸ The symptoms of myocarditis include fever, flu-like symptoms, fatigue and dyspnoea – symptoms similar to COVID-19 infection.

Previous coronavirus outbreaks have been associated with cardiovascular complications, including myocarditis,²⁸ and this also appears to be the case for COVID-19.^{29–31} Higher levels of troponin-I have been seen in severe COVID-19 illness,^{15,17} and patients with chronic cardiovascular disease (especially hypertension and coronary heart disease) may be more likely to develop more severe symptoms.³²

It is not known whether clozapine increases the risk of developing viral myocarditis in COVID-19 infection. Patients with underlying cardiac disease, including clozapine-related cardiovascular disease, should be assumed to be at higher risk of adverse outcomes if they contract COVID-19.

Recommendations

- Promptly investigate all patients in the first 2 months of treatment with clozapine presenting with flu-like symptoms and chest pain to rule out a diagnosis of myocarditis [take C-reactive protein (CRP) and troponin levels; do an antigen test].
- Consider the likelihood of myocarditis in all other patients presenting with 'flu-like' symptoms; ensure that the possibility of a diagnosis of COVID-19 does not prevent investigation for other diagnoses.

Diabetes

Clozapine treatment is associated with increased risk of hyperglycaemia, impaired glucose tolerance and diabetic ketoacidosis.⁸ The risk appears to be higher than with other antipsychotics, and is further compounded by lifestyle factors (obesity, poor diet and exercise) and family history. Clozapine directly induces insulin resistance and increases insulin plasma levels in a dose-dependent fashion.⁸

Diabetes, alongside cerebrovascular and cardiovascular disease, is one of the comorbidities more often found in patients who die from or suffer severe symptoms of COVID-19.³³ Patients with COVID-19, in common with other infections, are likely to experience poor glycaemic control. There are as yet no data describing blood glucose levels in patients taking clozapine who have COVID-19 infection, but it is likely that these will increase.

Recommendations

- Patients taking clozapine who have COVID-19 and a comorbid diagnosis of diabetes and who usually monitor their blood glucose at home should do so more frequently.³⁴
- Consider the risk of blood glucose fluctuations in all patients taking clozapine who have COVID-19; advise patients of signs of hyper- and hypo-glycaemia

Pneumonia

Almost 1 in 5 deaths in schizophrenia are attributable to respiratory disease, with mortality from pneumonia 3.8 times that of the general population.³⁵ Clozapine is particularly associated with pneumonia compared with other antipsychotics.^{36,37} Higher doses and antipsychotic polypharmacy confer even greater risk.³⁷ Some studies have also found the risk to be highest in the period immediately following antipsychotic initiation.³⁸ Other medications that increase the risk of pneumonia include inhaled corticosteroids and sedative drugs,³⁹ the latter of which may be particularly likely to be co-prescribed to those with serious mental illness.

Comorbid medical conditions that also increase the risk of pneumonia include dementia, chronic obstructive pulmonary disease (COPD), bronchitis, asthma, cardiovascular disease, heart failure, cerebrovascular disease, stroke, Parkinson's disease, multiple sclerosis, diabetes, cancer, chronic

hepatic or renal disease and dysphagia.⁴⁰ Many of these are common comorbidities in people with schizophrenia or may be exacerbated by the side-effects of antipsychotic drugs, including clozapine.

Whether or not clozapine has a direct effect on the risk of pneumonia, or whether the association is confounded by other factors, is unclear. It has been suggested that some of the increased risk could be driven by aspiration pneumonia secondary to hypersalivation.

There are currently no data exploring any relationship between antipsychotics or schizophrenia and the risk of contracting COVID-19 or developing severe symptoms of the infection. In the absence of data it should be assumed that patients taking antipsychotics, especially clozapine and particularly where comorbidities exist, may be at particular risk from COVID-19 and associated pneumonia.

Early recent research from one research group has found a reduction in immunoglobulin levels in patients taking clozapine, with a greater effect in those taking long-term treatment.⁴¹⁻⁴³ These studies found clinically significant panhypogammaglobulinaemia and impaired vaccine responses in patients taking clozapine that were not fully explained by smoking or concurrent medication.⁴¹ Reductions in pneumococcal-specific IgA and IgM were also observed.⁴³ A longer duration of clozapine use was associated with a higher risk of hypogammaglobulinaemia (annual decline of 0.15 g/l).⁴² The magnitude of the reduction was larger than that caused by rituximab and methotrexate immunosuppressant therapy in rheumatoid arthritis.⁴² There is a linear correlation between a fall in immunoglobulin level and rate of infections,⁴² although the implication of this for COVID-19 infection is not known. Secondary immune response (IgA/IgM production) may be impaired but it is not clear how this might affect COVID-19 outcome. Immunoglobulins are not routinely measured in clozapine patients. In the absence of immunoglobulin serum levels, reviewing the number of antibiotic prescriptions received in the previous 6 months may provide a proxy marker for immunosuppression. The significance of this requires further research before practical clinical advice can be given.

There is evidence that vitamin D supplementation enhances the function of the immune system and reduces the risk of developing acute

respiratory infection, with a number needed to treat in the general population of 33.⁴⁴ The protective effects are strongest in those with profound vitamin D deficiency where the risk of acute respiratory infection reduced from 60% to 32% and the number needed to treat drops to eight.⁴⁴ As well as this, it appears that high levels of vitamin D reduce the severity of respiratory infection.^{45–47} People with psychosis are at particularly high risk of vitamin D deficiency. In one study in England, about half the community dwelling patients with established psychotic illness were vitamin D deficient, and only 14% of patients had sufficient levels, defined conservatively as >20 ng/ml.⁴⁸ People experiencing their first episode of psychosis are three times as likely to have vitamin D deficiency as their age-, sex- and ethnicity-matched peers.⁴⁹ The precise mechanism by which vitamin D exerts its protective effect against infection is unknown. Vitamin-D is nonetheless known to play a role in the immune system where it influences antigen presentation, innate immunity and T-cell function.⁵⁰ Vitamin D also affects the expression of angiotensin converting enzyme 2 (ACE2), the functional receptor for the SARS-CoV-2.⁵¹ Unless patients have hypercalcaemia, renal stones, sarcoidosis or renal impairment (where a different form of vitamin D may be required), we recommend that all patients with schizophrenia receive vitamin D replacement therapy. Vitamin D plasma concentrations should be measured first but, as discussed, the difficulties of doing so during the pandemic may make this impractical.

Recommendations

- All patients should receive vitamin D supplementation, ideally guided by plasma concentrations.
- The risk and severity of the majority of clozapine-induced side effects can be ameliorated by maintaining the lowest possible dose. This may additionally reduce the risk of the development of pneumonia and diabetes, and therefore the risk of complications of COVID-19 infection. Use plasma levels to optimise dose.
- Ensure hypersalivation is treated effectively to reduce the risk of aspiration pneumonia, which could cause a secondary bacterial or chemical pneumonia.⁵²
- Patients who have cerebrovascular disease, cardiovascular disease, diabetes, or who have had multiple respiratory infections

requiring antibiotic treatment in the previous 6–12 months are assumed to be at higher risk of severe complications of COVID-19. Optimise management of these conditions.

- Patients who have not received the annual influenza or pneumococcal vaccine may be at increased risk of superimposed infections. Patients with chronic respiratory, heart, kidney or liver disease or diabetes are at particular risk. If possible, consider vaccinating these patients.

Plasma concentrations

Fever and rises in CRP, indicative of systemic inflammation, can cause a reduction in the metabolism of clozapine *via* CYP1A2 liver enzymes.⁵³ This results in a rise in clozapine plasma concentrations. It is possible that infection with COVID-19 will have this effect. Patients with respiratory infections may also be likely to stop smoking or, if they continue to do so, then at a reduced frequency or with less efficient inhalation. Polycyclic aromatic hydrocarbons in cigarette smoke induce CYP1A2 enzymes, so stopping or reducing smoking can have a marked effect on clozapine plasma concentrations (an increase of up to 50%, possibly more in those also taking sodium valproate). Normalisation of enzyme activity occurs over the course of a week or so. Note that nicotine replacement therapy, including e-cigarettes, has no effect on hepatic enzymes – switching from tobacco smoking to other forms of nicotine has the same effect as stopping smoking.

Some guidelines recommend stopping clozapine in the presence of a severe respiratory infection. This approach guards against the potential for clozapine toxicity but has the disadvantage of increasing the risk of a psychotic relapse. We suggest that clinicians should take a patient-centred approach, taking into account previous relapse speed and severity, physical comorbidities or concurrent drugs that would make a high clozapine plasma concentration more likely or hazardous, and the frequency of plasma concentration monitoring that is achievable. In patients for whom stopping clozapine entirely is undesirable, a dose reduction of 30–50% may be considered whilst awaiting guidance from plasma concentrations. Remember that if smoking is likely to restart on recovery from the respiratory illness, clozapine

doses should be gradually increased to maintain therapeutic response.

Surprisingly low levels of smoking have been observed in published Chinese COVID-19 positive cohorts (around 10%).^{15,18} It has been suggested that the nicotinic-acetylcholinesterase receptor may be involved in the hyperinflammatory response seen in some patients with COVID-19 infection, and that nicotine would prevent this.⁵³ Smoking cigarettes causes significant harm to health, largely due to the inhalation of tar and other chemicals. Drugs targeting nicotinic receptors may play a future role in COVID-19 treatment or prevention, but cigarette smoking should still be discouraged.

Recommendations

- Patients who smoke should be strongly encouraged to stop. Remember that a reduction in smoking will increase clozapine plasma levels. Reduce doses accordingly.
- Plasma levels of clozapine rise in patients with concurrent infections. Reduce doses by 30–50% and review as the clinical picture changes, informed by plasma concentrations.

Clozapine initiation

The most common adverse effects associated with initiation of clozapine are hypotension, tachycardia, fever and sedation. These side effects are usually benign and do not necessitate stopping treatment. They can be managed through gradual dose titration, dose adjustment and (if required), symptom-targeted medications (e.g. beta-blockers, paracetamol). Patients who are restarting clozapine after a treatment break are subject to the same side effects on re-initiation, and these are likely to follow a similar pattern to any they experienced on previous titrations.

Starting clozapine in a patient who has, or is at risk of contracting, COVID-19 is therefore potentially complicated by an overlap of COVID-19 symptoms and clozapine side-effects. It is not known whether clozapine itself affects the risk of contracting or developing complications of COVID-19. Particular difficulties with initiating clozapine (especially for the first time and particularly in community settings) during the COVID-19 pandemic include:

- The need for regular monitoring of vital signs necessitates increased contact with staff, increasing the risk of viral spreading
- Reduced ability to perform daily vital sign monitoring due to staffing restrictions risks missing signs of rare but serious complications (myocarditis, sepsis secondary to agranulocytosis)
- An overlap between the symptoms of COVID-19, benign side effects of clozapine and serious adverse effects of clozapine leading to diagnostic confusion
- An increased risk of developing pneumonia in general on clozapine treatment and specifically in the initial stages of treatment may increase the risks associated with contracting COVID-19, although no specific evidence is yet available.

It is recommended that clinicians carefully evaluate the risks and benefits of clozapine initiation. The potential benefit to patients and families should be considered, acknowledging that no other drug treatment is likely to be as effective for symptom relief as clozapine could be. Further, failure to effectively treat psychosis may cause particular problems with managing mentally unwell patients during times of social distancing, added pressure on acute and mental health services, reduced staffing capacity and restricted inpatient bed availability.

Recommendations

- Avoid prescribing paracetamol for (the common and benign) clozapine-induced fever during initiation. This may mask symptoms of COVID-19.
- Consider carefully the risks *versus* the benefits of initiating clozapine, particularly for the first time and in community settings.

Clozapine in sedated or intubated patients

Of patients hospitalised with COVID-19 infections, data from China show that about a quarter to a third require admission to intensive care units (ICU).^{15,20} The vast majority (>80%) of these patients receive ventilation.²⁰ It is usual practice in intensive care settings, particularly where patients are sedated, to discontinue all 'non-essential' prescriptions. This is particularly important for some medicines; there is a risk of serotonin syndrome when serotonergic medicines (not limited to SSRIs)

Table 1. Management of clozapine treatment during the COVID-19 pandemic.

Patients who are COVID-19 negative	Patients who have symptoms of, or are shown to be COVID-19 positive
<ul style="list-style-type: none"> • Reduce the frequency of WCC monitoring for patients who have been stable on clozapine for >1 year • Continue to monitor for clozapine-induced side effects and treat these effectively • Provide vitamin D supplementation • Ensure influenza and pneumococcal vaccination • Encourage smoking cessation 	<ul style="list-style-type: none"> • Take an urgent FBC to rule out neutropaenic sepsis • Use ANC to monitor for clozapine-induced neutropaenia • Take CRP and troponin to rule out myocarditis • Monitor blood glucose levels in patients with comorbid diabetes, advise patients of signs of hyper- and hypo-glycaemia • Reduce clozapine doses, preferably guided by plasma concentration monitoring
All patients: aim for continuation of clozapine	
ANC, absolute neutrophil count; CRP, C-reactive protein; FBC, full blood count; WCC, white cell count.	

are continued where patients are also receiving drugs such as fentanyl. Plasma levels and/or metabolic clearance of drugs may radically alter, risking direct toxicity from drugs with a narrow therapeutic index (clozapine, lithium) or increasing the risk of dose-related side effects to which patients are already particularly vulnerable when sedated (constipation, gastrointestinal ulceration, thrombus). Experience in previous coronavirus outbreaks and emerging evidence from COVID-19 has suggested severely affected patients to be in a hyperinflammatory state, which may increase the permeability of the blood–brain barrier to medication, increasing the risk of neurotoxicity.

There are disadvantages of stopping psychotropic medications during sedation. There is a risk of developing withdrawal symptoms. Patients who are sedated in intensive care settings are at high risk of developing delirium; it is usually considered preferable to minimise the number of changes in neuroleptics to reduce this risk, especially those that are part of established therapy. Finally, and probably at the forefront of most clinicians' concerns, there is the risk of a relapse of the psychiatric condition when sedation is weaned. This can cause myriad problems on the ICU, including difficulties with ventilator weaning and the challenge of safely dealing with very agitated patients in high-intensity medical settings.

Clozapine is a particular problem in this regard, since restarting after a treatment break almost always requires a slow titration and often weeks to achieve therapeutic plasma concentrations. The delay that this can cause to being able to reduce sedation and discharge patients from intensive

care may be unacceptably long, and possibly dangerous for patients who are sedated for long periods of time. It may therefore be reasonable to continue clozapine during ventilation and/or sedation, or to restart titration after an initial break whilst patients are still sedated. The decision to do so should consider the risks of relapse, examining previous relapse patterns and consequences, as well as the physical stability of the patient. Plasma levels should be used to guide dosing.

Recommendations

- Clozapine can probably be safely continued during periods of sedation with careful consideration of individual patient factors. Dose reduction may be required.

Summary

Clozapine is a uniquely effective medication for treatment-resistant schizophrenia. Use during the viral pandemic is particularly challenging, with overlapping clozapine-induced adverse effects and symptoms and sequelae of COVID-19, as well as practical difficulties with blood count monitoring. Given the clear benefits to patients, carers and health services of treating serious mental illness as effectively as possible at all times and including during this global crisis, every effort should be made to facilitate continued use of clozapine. These efforts should be carefully considered so as to avoid jeopardising patient safety, in terms of COVID-19 specific considerations (Table 1) and also the well-known adverse effects of clozapine that continue during this time and must not be forgotten.

Conflict of interest statement

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ORCID iDs

Siobhan Gee  <https://orcid.org/0000-0003-1020-6777>

Eromona Whiskey  <https://orcid.org/0000-0002-6146-0073>

David Taylor  <https://orcid.org/0000-0002-2557-1710>

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