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Clozapine and COVID-19

Initiation, continuation and special precautions

Clozapine initiation

Clozapine is the only effective therapy for treatment-resistant schizophrenia. For these patients no other antipsychotic treatment is likely to provide symptom relief. 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.

The most frequently reported symptoms of COVID-19 infection are fever, cough, myalgia, fatigue and shortness of breath. Patients with concurrent coronary heart disease, hypertension or diabetes tend to a more severe prognosis. Acute cardiac injury, acute kidney injury and secondary infection may follow.

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:

- Need for regular monitoring of vital signs and mental state necessitates increased contact with staff, increasing the risk of virus spreading
- Reduced ability to perform twice daily vital sign monitoring, so risking missing signs of rare but serious complications (myocarditis, sepsis secondary to agranulocytosis)
- Overlap between symptoms of COVID-19, benign side effects of clozapine and serious adverse effects of clozapine risks leading to diagnostic confusion.
- 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 along with the difficulties of caring for acutely mentally unwell patients in the context of reduced staffing and inpatient bed availability.

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 (1). Clozapine is particularly associated with pneumonia compared with other antipsychotics (2,3). Higher doses and antipsychotic polypharmacy confer even greater risk (3). Some studies have also found the risk to be highest in the period immediately following antipsychotic initiation (4). Other medications that increase the risk of pneumonia include inhaled corticosteroids and sedative drugs (5), 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, COPD, bronchitis, asthma, cardiovascular disease, heart failure, cerebrovascular disease, stroke, Parkinson's disease, multiple sclerosis, diabetes, cancer, chronic hepatic or renal disease and dysphagia (6). Many of these are common comorbidities in people with schizophrenia or may be exacerbated by the side effects of antipsychotic drugs, including clozapine.

Whether there is a causal link between antipsychotics and pneumonia, or independent factors associated with serious mental illness that increase the risk, or a combination of both is unclear. The risk of aspiration may be increased by several factors such as agitation, and by antipsychotics themselves (through hypersalivation, sedation, impairment of swallowing and cough reflexes or EPSEs). Poor self-care may result in delays in seeking help for respiratory symptoms (4), and smoking is well known to increase the risk of acute pneumonia (7).

There are currently no data exploring any relationship between antipsychotics or schizophrenia and the risk of contracting COVID-19 or developing severe symptoms to the infection. In the absence of data it should be assumed that patients taking antipsychotics, especially clozapine and particularly where co-morbities exist may be at particular risk from COVID-19 and associated pneumonia. Early recent research from one group has found a reduction in immunoglobulin levels in patients taking clozapine, with a greater effect in those taking long-term treatment (8–10). The significance of this requires further research before practical clinical advice can be given.

Myocarditis and cardiomyopathy

Clozapine is associated with the development of myocarditis and cardiomyopathy. Myocarditis, a hypersensitivity response to clozapine, is most likely to occur in the first 6–8 weeks of clozapine treatment. 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 (11). The symptoms of myocarditis include fever, flu-like symptoms, fatigue and dyspnoea – symptoms similar to COVID-19 infection.

It is not yet clear whether COVID-19 infection causes myocarditis or cardiomyopathy, but previous coronavirus outbreaks have been associated with cardiovascular complications, including myocarditis (12). Higher levels of troponin-I have been seen in severe COVID-19 illness (13,14), and patients with chronic cardiovascular disease (especially hypertension and coronary heart disease) may be more likely to become infected and develop more severe symptoms (15).

It is not known whether the potential for clozapine to cause myocarditis increases the risk of developing viral myocarditis in patients taking clozapine who have COVID-19 infection. Patients with underlying cardiac disease, including clozapine-related cardiovascular disease, should be assumed to be at higher risk.

Diabetes

Clozapine is linked to hyperglycaemia, impaired glucose tolerance and diabetic ketoacidosis (11). The risk appears to be higher than with other antipsychotics, and is further compounded by lifestyle factors (obesity, poor diet and exercise) and a family history. Clozapine directly induces insulin resistance and increases insulin plasma levels in a dose-dependent fashion (11).

Diabetes, in addition to cerebrovascular and cardiovascular disease, is one of the comorbidities found in patients who die from or suffer severe symptoms of COVID-19 (16). Patients with COVID-19, in common with other infections, are likely to experience fluctuations in blood glucose levels. There are as yet no data describing blood glucose levels in patients taking clozapine who have COVID-19 infection, but it should be assumed that glucose levels are likely to fluctuate.

Recommendations

- Low levels of **vitamin D** are commonly found in patients with schizophrenia (17). This is associated with an increased risk of cardiovascular disease, metabolic syndrome and respiratory tract infections (18). Take vitamin D levels and replace where required.
- The risk and severity of the majority of clozapine-induced side effects can be minimised 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.
- 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.
- 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 accordingly and review as the clinical picture changes, informed by plasma concentrations.
- **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.

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