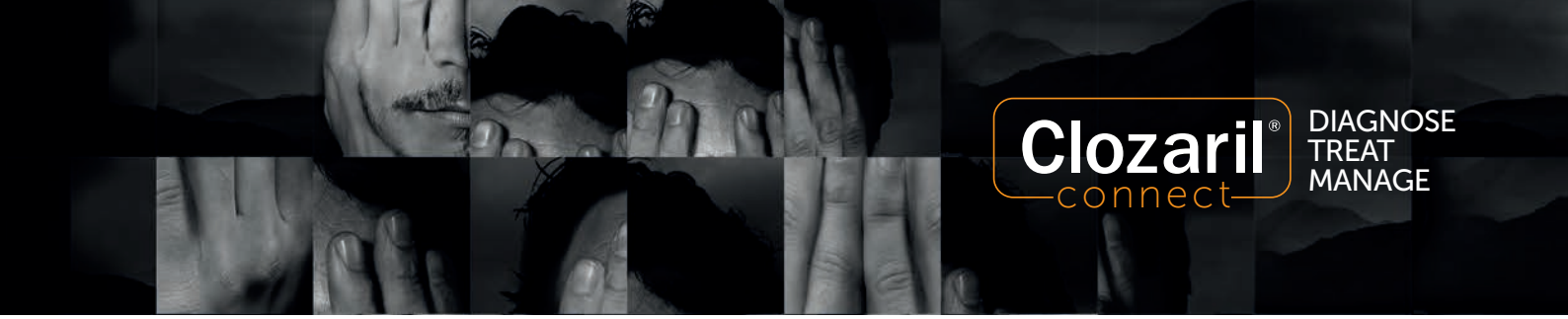


Clozapine and cardiovascular events

The information in this document is not intended as a definitive treatment strategy, but as a suggested approach for clinicians. It is based on previous successful experience. Each case should, of course, be considered individually.

This information is provided for healthcare professionals and should not be used as a patient information leaflet.

Before initiating clozapine the patient's history should be checked and a physical examination done.[1,2] If the patient has a history of cardiac illness or has abnormal cardiac findings on examination he/she should be referred to a specialist for other investigations (which might include an ECG).[1,2] Such patients should be treated only if expected benefits clearly outweigh the risks.[1,2]

With all patients, treating physicians should consider performing a pre-treatment ECG.[1,2]

Circulatory collapse and severe cardiac disorders (for example, myocarditis) are contraindications to Clozaril®.[1,2]

Tachycardia

The Summary of Product Characteristics (SmPC) for Clozaril® (clozapine) lists tachycardia as a very common (≥1/10) side-effect of Clozaril®.[1,2]

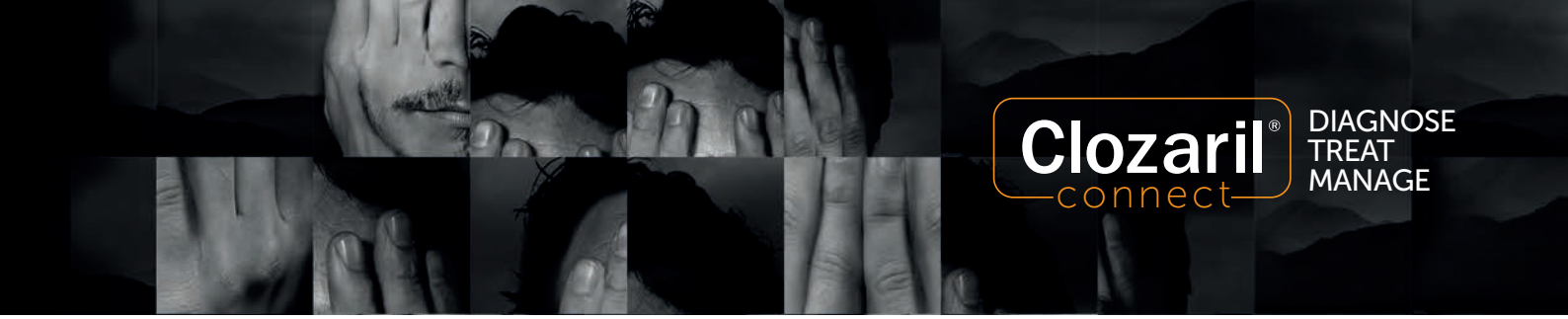
Tachycardia typically occurs in the first few weeks of treatment and it may persist in some patients. It is usually dose-related.[3]

To reduce the risk of tachycardia, the lowest possible dose of clozapine should be used. If it occurs, reducing the dose of clozapine is often effective. Decreasing smoking and caffeine intake may also be beneficial,[3] although this may affect clozapine plasma levels which should be considered. Please note, to obtain an accurate plasma levels the patient needs to have been on treatment at least a month and to have been on the same dose for at least a week.

Patients who develop tachycardia should have an ECG to exclude other arrhythmias or cardiac abnormalities. Checking the clozapine plasma level may be useful to exclude high levels. If clozapine-induced tachycardia does not improve following dose reduction then consultation with a medic or cardiologist is recommended. If tachycardia persists when the patient is at rest or if it is associated with other cardiac symptoms, myocarditis and cardiomyopathy should be excluded (see below).

Orthostatic hypotension, syncope, circulatory collapse and cardiac arrest

The SmPC for Clozaril® states that postural hypotension and syncope are common (≥1/100 but <1/10) side-effects of Clozaril® and circulatory collapse is listed as rare (≥1/10,000 but <1/1,000).[1,2] Cardiac arrest is listed as a very rare (<1/10,000) side effect of Clozaril®.[1,2]



Orthostatic hypotension can occur with clozapine treatment especially during the first few weeks of treatment.[1,2] Tolerance often develops, although it does persist in some patients.[3] The prevalence and severity of the hypotension has been found to be influenced by the rate and magnitude of clozapine dose titration.[1,2] Orthostatic hypotension can cause dizziness very commonly and syncope commonly.[1,2] Rarely, circulatory collapse can occur.[1,2] This can be profound and, very rarely, may be accompanied by cardiac and/or respiratory arrest.[1,2] On very rare occasions, circulatory collapse may occur after the first dose of clozapine hence, patients commencing clozapine require close medical supervision.[1,2] Circulatory collapse is more likely to occur during initial titration in association with aggressive dose escalation or with concurrent use of a benzodiazepine or other psychotropic agent.[1,2] Elderly patients and those with Parkinson's disease may be more susceptible to this.[1,2]

Patients starting clozapine treatment require close medical supervision. Monitoring of standing and supine blood pressure is necessary during the first weeks of treatment in patients with Parkinson's disease and those with increased risk of developing orthostatic hypotension.

To reduce the risk of orthostatic hypotension the lowest possible dose of clozapine should be used. If it occurs, a reduction in the clozapine dose should be considered and/or the rate of clozapine titration reduced.[3] Patients should be advised to stand up slowly and elastic stockings and increased hydration can be considered. If orthostatic hypotension persists clozapine plasma level monitoring may be useful to exclude high levels. Please note, to obtain an accurate plasma levels the patient needs to have been on treatment at least a month and to have been on the same dose for at least a week.

Hypertension

Hypertension is listed as a common (≥1/100 but <1/10) side-effect of Clozaril®[1,2] and it usually occurs in the first 4 weeks of treatment.[4]

If a patient develops hypertension during clozapine treatment they should be monitored closely and the dose increased slowly. Hypotensive therapy is required in some cases.[5]

ECG changes

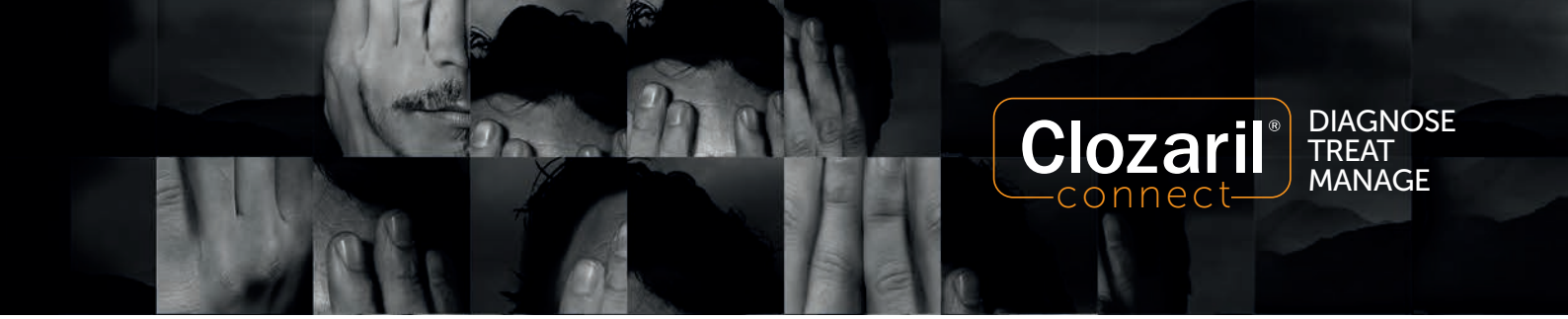
ECG changes, like those seen with other antipsychotics, are commonly seen in clozapine-treated patients.[1,2] They include S-T segment depression and flattening or inversion of T waves.[1,2] The clinical significance of these changes is unclear and they resolve when clozapine is stopped.[1,2] Such abnormalities have been seen in some cases of myocarditis and this diagnosis should be considered if ECG changes occur.[1,2]

ECG changes should be discussed with a cardiologist.

Cardiac arrhythmias

Cardiac arrhythmias occur rarely during clozapine treatment and some have been fatal.[1,2]

Cardiac arrhythmias should be discussed with a cardiologist and myocarditis and cardiomyopathy should be excluded. Plasma clozapine level monitoring may be useful to exclude high levels. Please note, to obtain an accurate plasma levels the patient needs to have been on treatment at least a month and to have been on the same dose for at least a week.



QT prolongation and Torsades de Pointes

Very rare cases of ventricular tachycardia and QT prolongation, which may be associated with Torsades De Pointes, have been observed with clozapine although there is no conclusive causal relationship to the use of the drug.[1,2] As with other antipsychotics, caution is advised in patients with known cardiovascular disease or family history of QT prolongation.[1,2] Caution should be exercised when clozapine is prescribed with medicines known to cause electrolyte imbalance or to increase the QTc interval.[1,2]

QT prolongation should be discussed with a cardiologist.

Myocarditis

The SmPC for Clozaril® lists myocarditis as a rare (≥1/10,000 but <1/1,000) side effect of Clozaril®.

The use of clozapine is associated with an increased risk of myocarditis which has, in rare cases, been fatal.[1,2] The increased risk of myocarditis is greatest in the first 2 months of treatment.[1,2]

Myocarditis or cardiomyopathy should be suspected in patients who experience persistent tachycardia at rest, especially in the first two months of treatment, and/or palpitations, arrhythmias, chest pain and other signs and symptoms of heart failure (for example, unexplained fatigue, dyspnoea, tachypnoea), or symptoms that mimic myocardial infarction.[1,2] Other symptoms which may be present in addition to the above include flu-like symptoms.[1,2]

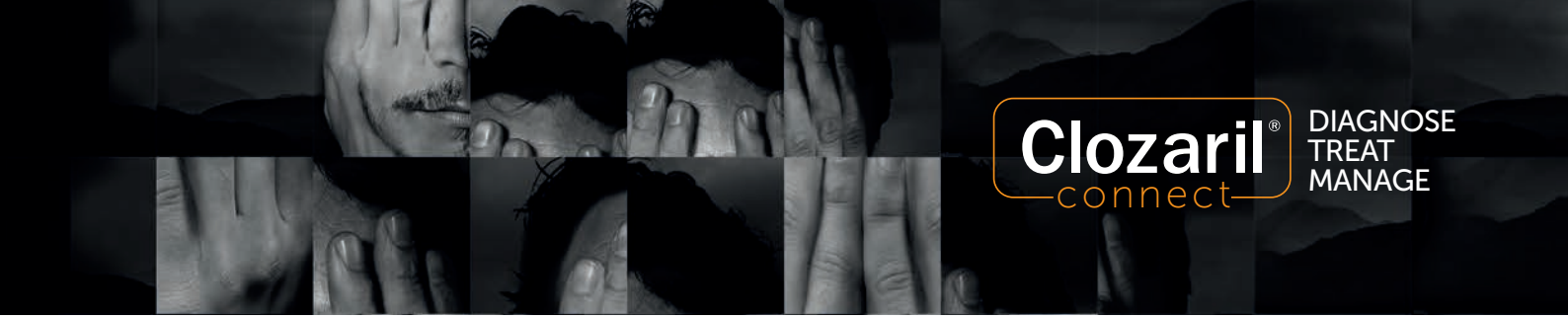
There is no classical presentation of clozapine-induced myocarditis and some patients may present with very few symptoms. If present, the clinical symptoms of myocarditis are highly variable and are non-specific in nature.[6] Also, the features may resemble symptoms of normal clozapine titration.[7] These factors make myocarditis a difficult condition to monitor and diagnose.

Progression to fulminant clozapine-induced myocarditis may be rapid, and the mortality rate, in the literature, has been reported to be up to 46%.[8]

Eosinophilia has been co-reported with some cases of myocarditis (approximately 14%) and pericarditis/pericardial effusion; it is not known, however, whether eosinophilia is a reliable predictor of carditis.[1,2] Discontinuation of Clozaril® is recommended if the eosinophil count rises above $3.0x10^9$/L and treatment should be restarted only after the eosinophil count has fallen below $1.0x10^9$/L.[1,2]

The Clozaril® SmPC does not specify monitoring for myocarditis in clozapine-treated patients other than to observe patients for the symptoms listed above. Many published articles have highlighted possible ways of diagnosing clozapine-induced myocarditis as early as possible and monitoring protocols have been suggested.[9,10] These focus on early recognition of symptoms, monitoring of vital signs and the active monitoring of troponins and C-reactive protein (CRP).

If myocarditis is suspected, clozapine should be discontinued and the patient referred to a cardiologist immediately. Patients who have had myocarditis should not be re-exposed to clozapine.



Cardiomyopathy

Very rarely patients receiving clozapine have developed cardiomyopathy and some cases have been fatal.[1,2] It generally occurs later in treatment than myocarditis and the length of treatment before the onset of symptoms has been reported from 2 weeks to 7 years and the reported mortality rate ranges between 15 and 25%.[11]

The mechanism of clozapine-induced cardiomyopathy is unclear.[12] There is a suggestion that undiagnosed clozapine-related myocarditis may progress to cardiomyopathy.[12]

Cardiomyopathy should be suspected if a patient develops persistent tachycardia at rest, palpitations, arrhythmias, chest pain, signs and symptoms of heart failure (unexplained fatigue, dyspnoea or tachypnoea), symptoms mimicking myocardial infarction.[1,2] Flu-like symptoms may be present in association with any of these symptoms.[1,2]

If cardiomyopathy is suspected, clozapine should be discontinued and the patient referred to a cardiologist immediately.[1,2] Patients who have had cardiomyopathy should not be re-exposed to clozapine.[1,2]

Pericarditis/pericardial effusion

Pericarditis and pericardial effusion have been reported rarely in clozapine-treated patients and some cases have been fatal.[1,2] Eosinophilia has been reported in association with some of these cases, but it is unclear whether eosinophilia is a reliable predictor of carditis.[1,2]

If pericarditis or pericardial effusion is suspected the patient should be referred to a cardiologist for confirmation of the diagnosis and further management.[1,2]

Thromboembolism

There have been rare cases of thromboembolism reported in association with clozapine treatment.[1,2]

Since patients treated with antipsychotics often present with acquired risk factors for thromboembolism, all possible risk factors should be identified before and during treatment with clozapine and preventive measures undertaken.[1,2]

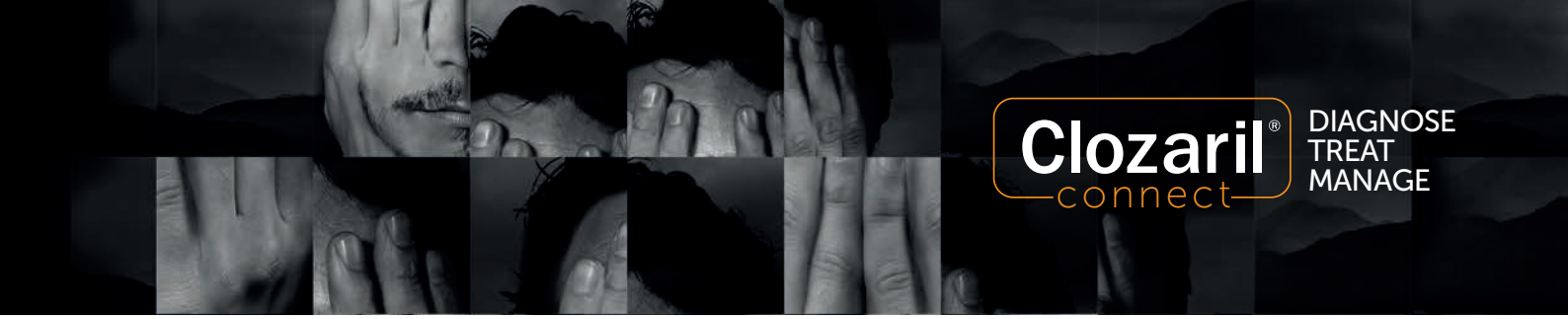
Risk factors for developing thromboembolism include heavy smoking, obesity, poor health, polypharmacy, sedation and low levels of exercise.

To reduce the risk of stroke immobilisation should be avoided and this may be especially relevant for sedated patients. Weight gain should be addressed and any other risk factors should be reduced if possible. Appropriate care should be taken with air travel.

If a thromboembolism occurs, it should be treated in the usual way.

Risk of stroke

An approximately 3-fold increased risk of cerebrovascular adverse events has been seen in randomised placebo controlled clinical trials in the dementia population with some atypical antipsychotics.[1,2] The mechanism for this increased risk is not known.[1,2] An increased risk cannot be excluded for other antipsychotics or other patient populations.[1,2] Clozapine should be used with caution in patients with risk factors for stroke.[1,2]



Myocardial Infarction, chest pain/angina pectoris

Myocardial infarction which may be fatal and chest pain/angina pectoris are listed as adverse effects to Clozaril® which have a frequency of 'not known'.[1,2]

There have been post marketing reports of myocardial infarction, in Clozaril®-treated patients, which may be fatal. In most of these cases, assessment of causality was difficult because of serious pre-existing cardiac disease and possible alternative causes.[1,2]

Metabolic changes

Atypical antipsychotic drugs, including clozapine, have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk.[1,2] These metabolic changes may include hyperglycaemia, dyslipidemia, and body weight gain.[1,2]

The SmPC for Clozaril® lists hypertriglyceridaemia and hypercholesterolaemia as a very rare (<1/10,000) side effects of Clozaril®.[1,2]

Dyslipidemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics, including clozapine.[1,2] Clinical monitoring, including baseline and periodic follow-up lipid evaluations in patients using clozapine, is recommended.[1,2]

Sudden unexplained death

Sudden unexplained death has been reported very rarely in patients receiving Clozaril®.[1,2] Such deaths are known to occur among psychiatric patients receiving antipsychotics and among untreated psychiatric patients.[1,2]

References

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Reporting of side effects
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:
UK: Reporting forms and information can be found at www.mhra.gov.uk/yellowcard
Ireland: HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517; Website: www.hpra.ie; E-mail: medsafety@hpra.ie.
Adverse events should also be reported to Mylan via cpms@mylan.co.uk

Clozaril® (clozapine)

CLOZARIL® Clozapine PATIENT MONITORING SERVICE

CLZ-2018-0130 Date of preparation: June 2018

Mylan
Better Health for a Better World