# Clozapine-induced cardiotoxicity: a clinical update

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## ABSTRACT

- Clozapine is a valuable drug for patients with treatment-resistant schizophrenia.
- Myocarditis is the most publicised cardiac complication of clozapine treatment, but cardiomyopathy and pericarditis have also been reported.
- Myocarditis has heterogeneous and non-specific presenting features, making it difficult to identify patients with clozapine-related myocarditis clinically. A high index of suspicion is required.
- The gold standard for diagnosis of myocarditis is an endomyocardial biopsy, but this is not a practical initial approach. Transthoracic echocardiography is a valuable, reproducible and widely available tool to assist in diagnosis of clozapine-induced cardiotoxicity.
- The level of B-type natriuretic peptide, a hormone secreted in response to ventricular wall stress, may be useful for evaluating patients with clozapine-induced cardiac dysfunction and may in the future be useful for screening asymptomatic patients.
- The mainstay of treatment of clozapine-induced cardiotoxicity is cessation of clozapine and provision of supportive care.


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Schizophrenia is a common disorder, with a lifetime prevalence of about 0.55% and an annual incidence of about 10–15 cases per 100 000 population.[1]

Clozapine, a tricyclic dibenzodiazepine derivative, is commonly classified as an atypical antipsychotic. It is distinguished from typical antipsychotics by its greater efficacy and reduced tendency to cause extrapyramidal movement disorders.[2,3] Often used for refractory schizophrenia, it can be life-changing for affected patients and has been shown to reduce overall mortality, largely through a reduction in suicide.[4] However, since its introduction in 1961, clozapine has been plagued by controversy because of its side-effect profile. Initial concerns were mainly related to agranulocytosis, but in recent years the focus has shifted to potentially fatal cardiotoxicity.

## Types of cardiotoxicity and incidence

The most publicised of the cardiotoxic adverse effects of clozapine is myocarditis, but dilated cardiomyopathy and pericarditis have also been reported. Furthermore, there is evidence that clozapine and other antipsychotics may predispose to development of the metabolic syndrome, itself a risk factor for diabetes and cardiovascular disease.[5]

### Myocarditis

Myocarditis is defined pathologically as an inflammatory disorder of the myocardium. Heterogeneous symptomatology may make diagnosis difficult and explain the lack of precise data on incidence and prevalence of the condition. Haas et al estimated the incidence of myocarditis in clozapine-treated patients to be between 0.7% and 1.2%.[6] With the estimated incidence of myocarditis at 1.8 per 10 000 000 in the general population,[7] the implication is that the risk of developing myocarditis is more than 10 000 times higher among users of clozapine. It is also compelling to note that patients who developed myocarditis in this cohort[6] were mostly taking standard doses of clozapine, implying a non-dose-dependent effect. Symptom onset was generally within the first 2 months, a key clinical observation with implications for the screening of patients commencing treatment.

### Cardiomyopathy

Cardiomyopathy, a more chronic disease of myocardial contractile dysfunction, has also been described in patients treated with clozapine, with the reported incidence varying from 0.02% in the United Kingdom[8] to 0.1% in Australia.[9] Symptom onset generally occurs later than clozapine-related myocarditis and usually after at least 8 weeks of treatment, but can occur at any stage.[9] Patients may be entirely asymptomatic, but may also present with progressive features of cardiac failure.

### Pericarditis

Clozapine-induced pericarditis is rare, with only a handful of cases documented in the literature. There is a range of clinical presentations from postural pleuritic chest pain (as part of a generalised polyserositic process) to cardiac tamponade. In most reported cases, clozapine treatment was discontinued, resulting in complete resolution of symptoms.

## Aetiology

The mechanisms by which clozapine causes cardiotoxicity remain unclear. The current leading hypothesis is that of an IgE-mediated hypersensitivity reaction. This is supported by common observations of peripheral eosinophilia and eosinophilic inclusions within endomyocardial biopsy samples of affected patients,[9] but these findings are inconsistent. Elman et al noted that patients treated with clozapine had higher noradrenaline levels than patients treated with other antipsychotics.[10] While increased plasma noradrenaline levels may reflect existing left ventricular (LV) dysfunction, recent evidence suggests that catecholamines may actually cause cardiac dysfunction. For example, increased plasma catecholamine levels have recently been implicated in takotsubo cardiomyopathy, a reversible form of LV dysfunction.[11] Thus it is plausible that increased catecholamine levels could be a contributing factor in the development of myocarditis and/or cardiomyopathy among affected patients. Other unproven mechanisms include cytochrome P450 1A2/1A3 enzyme deficiencies,[12] blockade of calcium-dependent ion channels, increased production of inflammatory cytokines, and low serum selenium levels.

**1 Presenting features of adverse reactions to clozapine and of biopsy-proven idiopathic myocarditis**

| Clozapine adverse drug reactions cited by researchers, in order of frequency[6] | Presenting features in patients with biopsy-proven idiopathic myocarditis[13] |
|---|---|
| Electro- or echocardiographic abnormality (66%) | Abnormal ECG in all patients (prolonged QT interval in 90%) |
| Fever (49%) | Dyspnoea (90%) |
| Tachycardia (46%) | Palpitations/arrhythmia (70%) |
| Elevated troponin level (36%) | Elevated levels of cardiac biomarkers (70%) |
| Chest pain (32%) | Influenza-type illness/viral prodrome (including fever) (50%) |
| Elevated creatine kinase level (31%) | Tachycardia (40%) |
| Leucocytosis (28%) | Leucocytosis (35%) |
| Dyspnoea (27%) | Chest pain (25%) |

ECG = electrocardiogram. ◆

## Clinical evaluation

There are no classical symptoms of clozapine-induced cardiotoxicity. Clinical presentations of myocarditis vary from no symptoms to mild symptoms (such as fever, myalgia and dyspnoea) to fulminant cardiogenic shock and death. A recent review of case reports of all adverse clozapine reactions submitted to the Australian Adverse Drug Reactions Unit sought to profile the clinical features of clozapine-induced cardiotoxicity.[6] The most common clinical features reported in adverse reactions to clozapine are compared with features of patients presenting with biopsy-proven viral myocarditis in Box 1.[13] There is a striking similarity between the two groups.

## Identification and screening

The current gold standard for diagnosis of myocarditis remains histological examination of an endomyocardial biopsy. However, the patchy nature of the disease and intra-observer variability in reporting can reduce the likelihood of a definitive diagnosis.[14] Furthermore, the procedure carries a small but definite risk of perforation and tamponade.[15] Leucocytosis and raised levels of inflammatory markers (such as erythrocyte sedimentation rate and C-reactive protein) are also observed in patients with myocarditis, but are non-specific.

Cardiac biomarkers, including creatine kinase and troponin, are routinely measured in patients with suspected myocarditis. Creatine kinase has been shown to be inferior to troponin for assessing myocardial injury, and is not useful for screening because of its low predictive value.[14] Although troponin appears to be a more useful marker, Lauer et al found that among 80 patients with suspected myocarditis only 35% had elevated troponin levels.[16] A similarly low level of sensitivity (34%) was noted in a substudy of the Myocarditis Treatment Trial.[17] The specificity, however, was 89%.

B-type natriuretic peptide (BNP) is released by the ventricular wall in response to increased wall stress[18] and reflects the haemodynamic status of the heart. BNP level is a highly accurate tool for diagnosis of congestive cardiac failure in patients presenting with dyspnoea.[19] Intuitively, we suspect it may represent a useful test for clozapine-induced cardiac dysfunction, but there have been very few studies testing its diagnostic value among patients with suspected myocarditis.

A small pilot study found that BNP levels increased significantly among clozapine-treated patients.[20] In a recent case series, three of five patients with myocarditis following clozapine treatment had elevated BNP levels, which fell after discontinuation of clozapine, in concert with alleviation of the patients' symptoms.[21] Measuring BNP level may therefore offer a means of monitoring patients taking clozapine to detect early and initially asymptomatic myocarditis, reducing the need for regular echocardiograms. However, until BNP testing has been validated in this patient cohort, its use should not replace careful history taking, physical examination and supplemental serial echocardiography.

There is currently no consensus recommendation on routine screening for LV dysfunction among patients receiving clozapine, and practices vary according to local protocol. Because of its widespread availability and because it does not involve radiation exposure, echocardiography is preferred over nuclear imaging for repeated screening. A common strategy employs echocardiography before starting therapy and 6- to 12-monthly thereafter. Ejection fraction as a measure of overall systolic function is usually assessed at echocardiography by the Simpson's biplane method, although there may be significant inter-observer variability. Furthermore, the fact that most cases of myocarditis present within 2 months of treatment initiation highlights the drawback of waiting 6 months before reassessing LV function.

## Treatment

Once clozapine-related myocarditis or cardiomyopathy has been diagnosed, the mainstay of acute management is to stop clozapine treatment and provide supportive care.[22] There is observational evidence that early cessation of clozapine treatment improves clinical outcomes.[21,23] The severity of presentation determines the degree of supportive care required. Patients with fulminant myocarditis or cardiac failure may require intensive haemodynamic support with inotropic agents. After initial haemodynamic stabilisation, management should focus on treating LV dysfunction with angiotensin-converting enzyme inhibitors, diuretics, β-blockers and possibly aldosterone antagonists. To a certain degree, LV dysfunction caused by clozapine treatment is reversible, with cardiac function improving over time providing clozapine therapy is discontinued.[18,23]

There have been case reports of favourable outcomes after use of corticosteroids to treat clozapine-related myocarditis, predominantly in patients with proven eosinophilic infiltrates on biopsy.[24,25] Corticosteroids have also been used successfully to treat non-clozapine-related eosinophilic myocarditis.[21,26] However, there have also been numerous reports of recovery of LV function without corticosteroid treatment. Limited trial data based on patients with biopsy-proven non-clozapine-related myocarditis suggest no benefit from routine treatment with immunosuppressive therapy.[27] Furthermore, corticosteroids may be associated with worsening of psychiatric symptoms. Therefore, based on current evidence, the routine use of corticosteroids to treat clozapine-induced cardiotoxicity cannot be recommended.

A difficult scenario arises when patients with treatment-resistant schizophrenia who respond only to clozapine develop clinical or echocardiographic evidence of cardiotoxicity. In some instances, clozapine treatment has been continued under close clinical and echocardiographic supervision (with appropriate consent). This

**2 Tips for clinicians**

- Clozapine can be a life-saving drug for patients with treatment-resistant schizophrenia, and cardiotoxicity is a rare complication.
- Screening for asymptomatic patients involves regular assessment of left ventricular function with transthoracic echocardiography, physical examination and perhaps, in the future, BNP assessment. (However, the lack of data on BNP measurement in this situation precludes its routine use.)
- All patients with suspected clozapine-induced cardiotoxicity require prompt medical assessment with a full blood count, measurement of cardiac biomarkers (including troponin and CRP) and an urgent transthoracic echocardiogram.
- Initial management of clozapine-induced cardiotoxicity involves cessation of the drug and provision of supportive care.
- Clozapine rechallenge is possible, but should only be attempted under close clinical supervision in a controlled environment.

BNP = B-type natriuretic peptide. CRP = C-reactive protein. ◆

approach is not routinely advocated, but may be an option of last resort for patients with severe psychosis.[9] Treating clinicians may also face a similar dilemma regarding whether or not to rechallenge patients with clozapine after previous cardiotoxicity. There are reported cases of successful clozapine rechallenge in patients with previous documented clozapine-induced myocarditis.[22,28] Needless to say, the decision should be made on an individual basis and the rechallenge administered in a well supervised, controlled environment.

## Conclusion (Box 2)

Clozapine is a useful drug for patients with disabling, treatment-resistant schizophrenia. The majority of patients taking clozapine do not experience side effects, but cardiotoxicity is a serious potential complication. Early detection of LV dysfunction is important, necessitating regular clinical review and echocardiographic assessment. In the future, simple and inexpensive cardiac biomarkers such as BNP may prove useful for screening, but further studies are needed to define their utility. Treatment of clozapine-related cardiotoxicity involves discontinuing clozapine treatment and providing supportive care. Active treatments such as corticosteroid therapy are not currently supported by evidence.

## Competing interests

None identified.

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