CLOZAPINE INDUCED PERICARDITIS: A SYSTEMATIC REVIEW

Aliu Opeyemi Yakubu*,[a] Olorungbami Kolade Anifalaje,[b] Moses Gregory Effiong,[c] Maryam Abubakar,[d] Francess Oluwaferanmi Adeyemi,[e] Oluwakemi Eunice Olalude[f]

a) General Adult Psychiatry, NHS Lanarkshire, Wishaw, Scotland, United Kingdom.
b) Emergency Medicine, NHS Dumfries and Galloway, Scotland, United Kingdom.
c) Public Health Department, Glasgow Caledonian University, Glasgow, Scotland, United Kingdom.
d) Old Age Psychiatry, NHS Lanarkshire, Wishaw, Scotland, United Kingdom.
e) Afe Babalola University, Ado Ekiti, Nigeria.
f) Department of Internal Medicine, Lagos State University Teaching Hospital, Ikeja, Lagos, Nigeria.

Background:

Clozapine is an atypical antipsychotic for treatment-resistant schizophrenia. Despite its efficacy, there are potential life-threatening side effects, including pericarditis, which has limited its usage. Clozapine-induced pericarditis may range from mild symptoms to life-threatening complications. Despite increasing case reports, a comprehensive synthesis is lacking, necessitating a systematic review.

Aims and Hypothesis

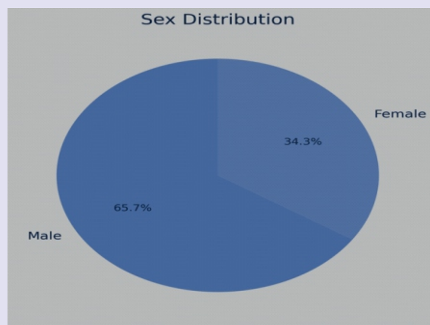
This systematic review aims to synthesize evidence on clozapine-induced pericarditis, exploring its incidence, clinical features, diagnostic criteria, management strategies, and outcomes. This will provide clinicians with actionable insights to enhance risk stratification, early detection, and decision-making for patients on clozapine therapy.

Methods

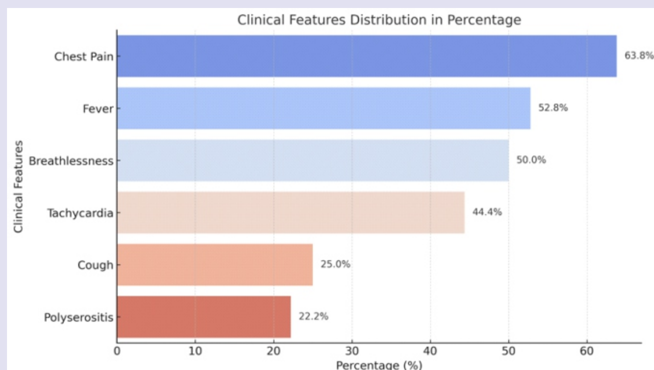
A systematic review was conducted following PRISMA 2020 guidelines and registered in PROSPERO. Eight databases, including PubMed, Embase, and PsycINFO, were searched, identifying case reports published between 1980 and 2024. Inclusion criteria focused on English-language case reports diagnosing clozapine-induced pericarditis. Exclusion criteria included non-clozapine-induced pericarditis and mixed etiologies without clozapine-specific data. Data extraction captured demographics, clinical presentation, diagnostic findings, management, and outcomes. Results were synthesized qualitatively.

Results

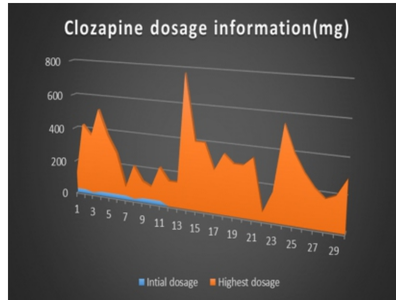
A total of 941 articles were identified, of which 36 met the inclusion criteria. The mean patient age was 33.56 years (SD: 15.56), with males comprising 63.9% (Figure 1).



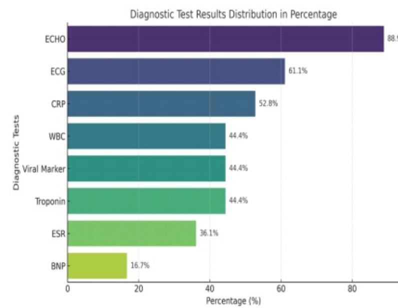
Clinical features such as chest pain (63.8%) and fever (52.8%) were the most commonly reported symptoms (Figure 2).



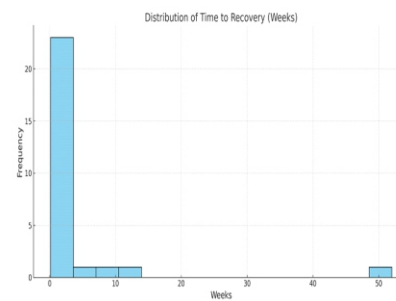
Clozapine dosage represented in figure 3



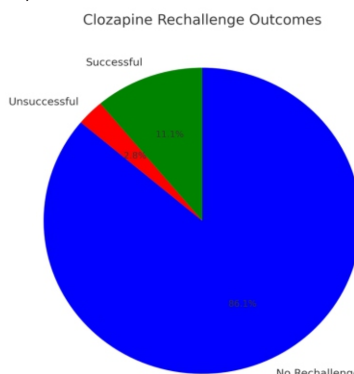
Diagnostic findings highlighted consistently elevated inflammatory markers, including CRP (mean: 88.13 mg/dL) and ESR (mean: 72.72 mm/hr), with pericardial effusion confirmed by echocardiograms in 88.9% of cases (Figure 4).



Time to recovery averaged 3.73 weeks (SD: 9.8), and all but one case achieved full cardiac recovery. (figure 5)



Clozapine rechallenge was attempted in 16.7% of cases, with successful outcomes reported in 83.3% (Figure 6)



Management strategies varied, with colchicine used in 16.7% of cases and analgesics in 19.4%.Psychiatric stability was generally maintained through substitution with alternative antipsychotics, predominantly olanzapine and risperidone (Table 1)

Treatment and Medication Overview

Medication	Number of Cases	Percentage (%)
Colchicine	6	16.7%
Analgesia	7	19.4%
Substituted Medications	22	61.1%
- Olanzapine	7	-
- Risperidone	5	-

Discussion

Clozapine-induced pericarditis represents a critical yet poorly understood adverse event. The mean age of affected patients aligns with the typical onset of schizophrenia, suggesting that the timing of clozapine initiation during early adulthood could explain the higher prevalence in younger populations. While pericarditis is often described as an early complication of clozapine therapy, this review found cases presenting decades after initiation, emphasizing the need for long-term vigilance.

Rapid dose titration and higher clozapine doses have been implicated in inflammatory syndromes like DRESS, potentially contributing to pericarditis. However, this review found that the mean maximum clozapine dose was relatively low, suggesting that factors beyond dosage, such as genetic variations in drug metabolism or inflammatory predispositions, may play a significant role.

The symptom profile highlights both general inflammatory markers (fever, tachycardia) and more specific cardiac manifestations (chest pain, breathlessness). While elevated inflammatory markers such as CRP and ESR are consistently observed, they are non-specific and necessitate confirmatory imaging. The findings reinforce the diagnostic value of echocardiography, which frequently reveals pericardial effusion and aids in distinguishing pericarditis from other cardiac complications. Although electrocardiographic changes can support the diagnosis, their absence does not exclude pericarditis, necessitating a comprehensive diagnostic approach.

Rechallenging with clozapine, although attempted in only 16.7% of cases, was successful in the majority, indicating that this option should be considered on a case-by-case basis with careful monitoring. The efficacy of colchicine in managing inflammation highlights its potential utility in future treatment protocols for clozapine-induced pericarditis.

Conclusions

This review underscores the need for heightened clinician awareness and standardized protocols to optimize care for patients requiring clozapine therapy.