



## Clozapine-Induced Myocarditis

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### INTRODUCTION

Clozapine, the first atypical antipsychotic, is recognized as the most effective therapeutic option in schizophrenia cases resistant to other treatments (1-3). Studies have confirmed the superiority of clozapine compared to alternative atypical antipsychotics in various aspects such as compliance to treatment, patient satisfaction, mortality, suicidality and drug response (4). Clinicians are more likely to prefer clozapine owing to the high efficacy of this agent and the low likelihood of causing extrapyramidal side effects. The side effects of clozapine mainly include agranulocytosis, hepatitis, ileus, epileptic seizure, cardiovascular effects, sedation, hypotension, metabolic syndrome, hypersalivation, and these side effects are the reason clozapine is not positioned as a firstline treatment for psychotic disorders (2-4). The concerning cardiovascular side effects of clozapine, which can be fatal, are myocarditis and cardiomyopathy (5). Typically, myocarditis is acute and occurs within thirty days of initiation of clozapine, while cardiomyopathy tends to be more chronic and occurs months to years later (5-7). Our limited knowledge of the etiology and epidemiology of clozapine-induced myocarditis causes challenges in the monitoring, diagnosis and treatment of this serious side effect, which may lead to fatal outcomes.

### CLOZAPINE-INDUCED MYOCARDITIS

Development of clozapine as a potential pharmacological therapy for schizophrenia dates back to over 5 decades ago (8). Clozapine is known to offer higher

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## REFERENCES

1. Kanniah G, Kumar S. Clozapine associated cardiotoxicity: Issues, challenges and way forward. *Asian Journal of Psychiatry*. 2020 Apr; 50: 101950. doi: 10.1016/j.ajp.2020.101950
2. Meltzer HY. Suicide and schizophrenia: clozapine and the InterSePT study. *Journal of Clinical Psychiatry*. 1999, 60.12: 47.
3. Tiihonen J, Lönnqvist J, Wahlbeck K, et al. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *The Lancet*. 2009 Aug 22;374(9690):620-7. doi: 10.1016/S0140-6736(09)60742-X.
4. McEvoy JP, Lieberman JA, Stroup TS, et al. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. *American Journal of Psychiatry*. 2006 Apr;163(4):600-10. doi: 10.1176/ajp.2006.163.4.600.
5. Bellissima BL, Tingle MD, Cicović A, et al. A systematic review of clozapine-induced myocarditis. *International journal of cardiology*. 2018 May 15;259:122-129. doi: 10.1016/j.ijcard.2017.12.102.
6. Alawami M, Wasylwich C, Cicovic A, et al. A systematic review of clozapine induced cardiomyopathy. *International journal of cardiology*. 2014 Sep 20;176(2):315-20. doi: 10.1016/j.ijcard.2014.07.103.
7. Siskind D, Sidhu A, Cross J, et al. Systematic review and meta-analysis of rates of clozapine-associated myocarditis and cardiomyopathy. *Australian & New Zealand Journal of Psychiatry*. 2020 May;54(5):467-481. doi: 10.1177/0004867419898760.
8. Wagner E, Sifaris S, Fernando P, et al. Efficacy and safety of clozapine in psychotic disorders: a systematic quantitative meta-review. *Translational psychiatry*. 2021 Sep 22;11(1):487. doi: 10.1038/s41398-021-01613-2.
9. Huhn M, Nikolakopoulou A, Schneider-Thoma J, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *The Lancet*. 2019 Sep 14;394(10202):939-951. doi: 10.1016/S0140-6736(19)31135-3.
10. Leucht S, Corves C, Arbter D, et al. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *The Lancet*. 2009 Jan 3;373(9657):31-41. doi: 10.1016/S0140-6736(08)61764-X.
11. Krause M, Zhu Y, Huhn M, et al. Antipsychotic drugs for patients with schizophrenia and predominant or prominent negative symptoms: a systematic review and meta-analysis. *European archives of psychiatry and clinical neuroscience*. 2018 Oct;268(7):625-639. doi: 10.1007/s00406-018-0869-3.
12. Torrisi SA, Laudani S, Contarini G, et al. Dopamine, cognitive impairments and second-generation antipsychotics: from mechanistic advances to more personalized treatments. *Pharmaceuticals*. 2020 Nov 5;13(11):365. doi: 10.3390/ph13110365.
13. Meltzer HY. Update on typical and atypical antipsychotic drugs. *Annual review of medicine*. 2013;64:393-406. doi: 10.1146/annurev-med-050911-161504.
14. Schimmelmann BG, Schmidt SJ, Carbon M, et al. Treatment of adolescents with early-onset schizophrenia spectrum disorders: in search of a rational, evidence-informed approach. *Current opinion in psychiatry*. 2013 Mar;26(2):219-30. doi: 10.1097/YCO.0b013e32835dcc2a.
15. Taipale H, Lähteenvirta M, Tanskanen A, et al. Comparative effectiveness of antipsychotics for risk of attempted or completed suicide among persons with schizophrenia. *Schizophrenia bulletin*. 2021 Jan 23;47(1):23-30. doi: 10.1093/schbul/sbaa111.
16. Abou-Saleh MT. Psychopharmacology of substance misuse and comorbid psychiatric disorders. *Acta Neuropsychiatrica*. 2004 Feb;16(1):19-25. doi: 10.1111/j.1601-5215.2004.0061.x.

17. Lally J, MacCabe JH. Antipsychotic medication in schizophrenia: a review. *British medical bulletin*. 2015 Jun;114(1):169-79. doi: 10.1093/bmb/ldv017.
18. Jensen VE, Gøtzsche O. Allergic myocarditis in clozapine treatment. *Ugeskrift for laeger*. 1994 Jul 11;156(28):4151-2.
19. Ronaldson KJ, Fitzgerald PB, McNeil JJ. Clozapine-induced myocarditis, a widely overlooked adverse reaction. *Acta Psychiatrica Scandinavica*. 2015 Oct;132(4):231-40. doi: 10.1111/acps.12416.
20. Citrome L, McEvoy JP, Saklad SR. Guide to the management of clozapine-related tolerability and safety concerns. *Clinical schizophrenia & related psychoses*. 2016 Jul 25. doi: 10.3371/CSRP.SACI.070816.
21. Haas SJ, Hill R, Krum H, et al. Clozapine-associated myocarditis: a review of 116 cases of suspected myocarditis associated with the use of clozapine in Australia during 1993–2003. *Drug Safety*. 2007;30(1):47-57. doi: 10.2165/00002018-200730010-00005.
22. Munshi TA, Volochniouk D, Hassan T, et al. Clozapine-induced myocarditis: is mandatory monitoring warranted for its early recognition?. *Case reports in psychiatry*. 2014;2014:513108. doi: 10.1155/2014/513108.
23. Segev A, Iqbal E, McDonagh TA, et al. Clozapine-induced myocarditis: electronic health register analysis of incidence, timing, clinical markers and diagnostic accuracy. *The British journal of psychiatry*. 2021 Dec;219(6):644-651. doi: 10.1192/bjp.2021.58.
24. Feldman AM, McNamara D. *Myocarditis*. *N Engl J Med*. 2000 Nov 9;343(19):1388-98. doi: 10.1056/NEJM200011093431908.
25. Merrill DB, Dec GW, Goff DC. Adverse cardiac effects associated with clozapine. *Journal of clinical psychopharmacology*. 2005 Feb;25(1):32-41. doi: 10.1097/01.jcp.0000150217.51433.9f.
26. Kilian JG, Kerr K, Lawrence C, et al. Myocarditis and cardiomyopathy associated with clozapine. *The Lancet*. 1999 Nov 27;354(9193):1841-5. doi: 10.1016/s0140-6736(99)10385-4.
27. Pollmächer T, Schuld A, Kraus T, et al. On the clinical relevance of clozapine-triggered release of cytokines and soluble cytokine-receptors. *Fortschritte der Neurologie-psychiatrie*. 2001 Sep;69 Suppl 2:S65-74. German. doi: 10.1055/s-2001-16533.
28. Wang JF, Min JY, Hampton TG, et al. Clozapine-induced myocarditis: role of catecholamines in a murine model. *European journal of pharmacology*. 2008 Sep 11;592(1-3):123-7. doi: 10.1016/j.ejphar.2008.06.088.
29. Nair GM, Skaria DS, James T, et al. Clozapine disrupts endothelial nitric oxide signaling and antioxidant system for its cardiovascular complications. *Drug Research*. 2019 Dec;69(12):695-698. doi: 10.1055/a-0991-7684.
30. Burian J. Myocarditis: the immunologists view on pathogenesis and treatment. *Swiss medical weekly*. 2005 Jun 25;135(25-26):359-64. doi: 10.4414/smw.2005.10940.
31. Ronaldson KJ, Fitzgerald PB, Taylor AJ, et al. Rapid clozapine dose titration and concomitant sodium valproate increase the risk of myocarditis with clozapine: a case-control study. *Schizophrenia research*. 2012 Nov;141(2-3):173-8. doi: 10.1016/j.schres.2012.08.018.
32. Ronaldson KJ, Fitzgerald PB, Taylor AJ, et al. Clinical course and analysis of ten fatal cases of clozapine-induced myocarditis and comparison with 66 surviving cases. *Schizophrenia research*. 2011 May;128(1-3):161-5. doi: 10.1016/j.schres.2011.01.017.
33. Serrano A, Rangel N, Carrizo E, et al. Safety of long-term clozapine administration. Frequency of cardiomyopathy and hyponatraemia: two cross-sectional, naturalistic studies. *Australian & New Zealand Journal of Psychiatry*. 2014 Feb;48(2):183-92. doi: 10.1177/0004867413502089.
34. Cook SC, Ferguson BA, Cotes RO, et al. Clozapine-induced myocarditis: prevention and considerations in rechallenge. *Psychosomatics*. . 2015 Nov-Dec;56(6):685-90. doi: 10.1016/j.psym.2015.07.002.

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35. Fineschi V, Neri M, Riezzo I, et al. Sudden cardiac death due to hypersensitivity myocarditis during clozapine treatment. *International journal of legal medicine*. 2004 Oct;118(5):307-9. doi: 10.1007/s00414-004-0464-1.
36. Vickers M, Ramineni V, Malacova E, et al. Risk factors for clozapine-induced myocarditis and cardiomyopathy: A systematic review and meta-analysis. *Acta Psychiatrica Scandinavica*. 2022 May;145(5):442-455. doi: 10.1111/acps.13398.
37. Nguyen B, Du C, Bastiampillai T, et al. Successful clozapine re-challenge following myocarditis. *Australasian Psychiatry*. 2017 Aug;25(4):385-386. doi: 10.1177/1039856217707394.
38. Ronaldson KJ, Fitzgerald PB, Taylor AJ, et al. Observations from 8 cases of clozapine rechallenge after development of myocarditis. *The Journal of clinical psychiatry*. 2012 Feb;73(2):252-4. doi: 10.4088/JCP.11l07467.
39. Ronaldson KJ. Cardiovascular disease in clozapine-treated patients: evidence, mechanisms and management. *CNS drugs*. 2017 Sep;31(9):777-795. doi: 10.1007/s40263-017-0461-9.