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CADTH Reference List

Monitoring Patients With Psychotic Disorders for Clozapine-Induced Myocarditis or Cardiomyopathy

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Key Messages

- No literature was identified regarding the diagnostic accuracy of high-sensitivity troponin I testing versus troponin T testing for detecting myocarditis or cardiomyopathy in patients receiving clozapine for psychotic disorders.
- Four evidence-based guidelines were identified regarding the use of clozapine for patients with psychotic disorders.

Research Questions

1. What is the diagnostic accuracy of high-sensitivity troponin I testing versus troponin T testing for detecting myocarditis or cardiomyopathy in patients receiving clozapine for psychotic disorders?
2. What are the evidence-based guidelines on the use of clozapine for patients with psychotic disorders?

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, the Cochrane Database of Systematic Reviews, the international HTA database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Troponin I (cTn-I) testing and clozapine. No filters were applied to limit the retrieval by study type for question 1. CADTH-developed search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, or network meta-analyses, and guidelines for question 2. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2016 and May 17, 2021. Internet links were provided, where available.

Selection Criteria

One reviewer screened literature search results (titles and abstracts) and selected publications according to the inclusion criteria presented in Table 1. Full texts of study publications were not reviewed. Open access full-text versions of evidence-based guidelines were reviewed when abstracts were not available.

Results

Four evidence-based guidelines were identified regarding the use of clozapine for patients with psychotic disorders.[1-4] No health technology assessments, systematic reviews, randomized controlled trials, or non-randomized studies were identified regarding the diagnostic accuracy of high-sensitivity troponin I testing versus troponin T

Table 1: Selection Criteria

Criteria	Description
Population	Patients with psychotic disorders (e.g., delusional disorder, schizophrenia [including treatment-resistant], schizoaffective disorder, and bipolar disorder) in any setting (e.g., acute, tertiary, or outpatient/community settings)
Intervention	Q1: High-sensitivity troponin I test (index test) Q2: Clozapine (trade name: Clozaril)
Comparator	Q1: Troponin T test (comparator test); reference standard (biopsy or diagnosis by a cardiologist) Q2: Not applicable
Outcomes	Q1: Diagnostic accuracy for myocarditis or cardiomyopathy (e.g., sensitivity, specificity, negative predictive value, positive predictive value) Q2: Recommendations regarding: • monitoring of clozapine-induced cardiomyopathy or clozapine-induced myocarditis (e.g., what physical symptoms to identify; what type and magnitude of vital sign changes) • guidance for the frequency and timing of assessing the following tests: ECG, ECHO, CRP, and troponin • any other biomarkers that should be assessed (e.g., BNP, CBC) • guidance on actions to take in the case of test abnormalities • clozapine dosing • clozapine titration • guidance on clozapine management in patients with co-prescriptions (e.g., divalproex or valproic acid).
Study designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies, evidence-based guidelines

BNP = B-type natriuretic peptide; CBC = complete blood count; CRP = C-reactive protein; ECG = electrocardiogram; ECHO = echocardiogram.

testing for detecting myocarditis or cardiomyopathy in patients receiving clozapine for psychotic disorders.

Additional references of potential interest that did not meet the inclusion criteria are provided in Appendix 1.

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References

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses

No literature identified.

Randomized Controlled Trials

No literature identified.

Non-Randomized Studies

No literature identified.

Guidelines and Recommendations

1.The American Psychiatric Association. Practice guideline for the treatment of patients with schizophrenia. 3rd ed. Washington, DC: American Psychiatric Association; 2021: https://psychiatryonline.org/doi/pdf/10.1176/appi.books.9780890424841. Accessed 2021 May 20.
See: Table 3. Antipsychotic medications: available oral and short-acting intramuscular formulations and dosing considerations – Clozapine (p.37); Initiation of Treatment With an Antipsychotic Medication (p.64-65); Monitoring During Treatment With an Antipsychotic Medication (p.66-67); Myocarditis and Cardiomyopathy (p.69); Statement 7: Clozapine in Treatment-Resistant Schizophrenia (p.88-96)

2.National Institute for Health and Care Excellence. Rehabilitation for adults with complex psychosis *(NICE guideline NG181)* 2020; https://www.nice.org.uk/guidance/ng181/resources/rehabilitation-for-adults-with-complex-psychosis-pdf-66142016643013. Accessed 2021 May 20.
See: Pharmacological Treatments (p.32-35); Pharmacological treatments (recommendations 1.9.9 to 1.9.19) (p.68-69)

3.German Association for Psychiatry, Psychotherapy and Psychosomatics, DGPPN. S3 Guideline for schizophrenia. 2019 https://www.dgppn.de/_Resources/Persistent/b794e84f9cbdf0d761b26cb1bd323b65188cb9e6/038-009e_S3_Schizophrenie_2019-03.pdf Accessed 2021 May 20.
See: 5.3 Therapeutic Drug Monitoring (TDM) – Recommendation 20, 21 (p.25); Table 7: Recommended oral doses of various antipsychotics in acute treatment (p.27); 5.4 – Dose, determining the lowest possible dose, treatment frequency and discontinuation (p.29-30); Table 9 (p.40)

4.Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord.* 2018;20(2):97-170. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5947163/pdf/BDI-20-97.pdf Accessed 2021 May 20. PubMed
See: 8.3.4 – Haematological effects (p.144)

Appendix 1: References of Potential Interest

Previous CADTH Reports

5.Clozapine initiation for schizophrenia: a review of clinical effectiveness and guidelines. *(CADTH Rapid response report: summary with critical appraisal)*. Ottawa (ON): CADTH; 2020: https://cadth.ca/sites/default/files/pdf/htis/2020/RC1229%20Clozapine%20Initiation%20Final.pdf. Accessed 2021 May 20.

Systematic Reviews and Meta-analyses

Monitoring for Clozapine-Induced Myocarditis or Cardiomyopathy — Troponin Test Not Specified

6.Bellissima BL, Tingle MD, Cicovic A, Alawami M, Kenedi C. A systematic review of clozapine-induced myocarditis. *Int J Cardiol*. 2018 05 15;259:122-129. PubMed

7.Curto M, Girardi N, Lionetto L, Ciavarella GM, Ferracuti S, Baldessarini RJ. Systematic review of clozapine cardiotoxicity. *Curr Psychiatry Rep*. 2016 07;18(7):68. PubMed

Alternative Population – Patients with Psychotic Disorders Not Specified

8.Knoph KN, Morgan RJ, 3rd, Palmer BA, et al. Clozapine-induced cardiomyopathy and myocarditis monitoring: a systematic review. *Schizophr Res*. 2018 09;199:17-30. PubMed

Systematic Review of Guidelines

9.Keating D, McWilliams S, Schneider I, et al. Pharmacological guidelines for schizophrenia: a systematic review and comparison of recommendations for the first episode. *BMJ Open*. 2017 01 06;7(1):e013881. PubMed

Non-Randomized Studies

Accuracy of High-Sensitivity Troponin I Testing for Alternative Cardiac Conditions — Not Specific to Patients with Psychotic Disorders

10. Boeddinghaus J, Nestelberger T, Koechlin L, et al. Early diagnosis of myocardial infarction with point-of-care high-sensitivity cardiac troponin I. *J Am Coll Cardiol*. 2020 03 17;75(10):1111-1124. PubMed

11. Zhou P, Liu H, Gong L, et al. A faster detection method for high-sensitivity cardiac troponin-POCT quantum dot fluorescence immunoassay. *J Thorac Dis*. 2019 Apr;11(4):1506-1513. PubMed

12. Suh D, Keller DI, Hof D, von Eckardstein A, Gawinecka J. Rule-out of non-ST elevation myocardial infarction by five point of care cardiac troponin assays according to the 0 h/3 h algorithm of the European Society of Cardiology. *Clin Chem Lab Med*. 2018 03 28;56(4):649-657. PubMed

13. Walter JE, Honegger U, Puelacher C, et al. Prospective validation of a biomarker-based rule out strategy for functionally relevant coronary artery disease. *Clin Chem*. 2018 02;64(2):386-395. PubMed

Guidelines and Recommendations

Alternative Methodology — Chart Reviews

14. Ballon JS, Ashfaq H, Noordsy DL. Clozapine titration for people in early psychosis: a chart review and treatment guideline. *J Clin Psychopharmacol*. 2018 Jun;38(3):234-238. PubMed

15. Manu P, Lapitskaya Y, Shaikh A, Nielsen J. Clozapine rechallenge after major adverse effects: clinical guidelines based on 259 cases. *Am J Ther*. 2018 Mar/Apr;25(2):e218-e223. PubMed

Alternative Methodology — Based on Other Guidelines

16. Remington G, Addington D, Honer W, Ismail Z, Raedler T, Teehan M. Guidelines for the pharmacotherapy of schizophrenia in adults. *Can J Psychiatry*. 2017 09;62(9):604-616. PubMed

Alternative Methodology — Expert Opinion

17. Wagner E, Kane JM, Correll CU, et al. Clozapine combination and augmentation strategies in patients with schizophrenia -recommendations from an International Expert Survey Among the Treatment Response and Resistance in Psychosis (TRRIP) Working Group. *Schizophr Bull*. 2020 12 01;46(6):1459-1470. PubMed

Unclear Methodology

18. Griffin JM, Woznica E, Gilotra NA, Nucifora FC, Jr. Clozapine-associated myocarditis: a protocol for monitoring upon clozapine initiation and recommendations for how to conduct a clozapine rechallenge. *J Clin Psychopharmacol*. 2021 Mar-Apr 01;41(2):180-185. PubMed

19. Flanagan RJ, Lally J, Gee S, Lyon R, Every-Palmer S. Clozapine in the treatment of refractory schizophrenia: a practical guide for healthcare professionals. *Br Med Bull.* 2020;135(1):73-89. https://academic.oup.com/bmb/article/135/1/73/5897754. Accessed 2021 May 20. PubMed
See: Initiating clozapine; Plasma clozapine and norclozapine monitoring; Drug-drug interactions; Age, sex, body weight, and clozapine dose requirement; Myocarditis and cardiomyopathy

20. Sweeney M, Whiskey E, Patel RK, Tracy DK, Shergill SS, Plymen CM. Understanding and managing cardiac side-effects of second-generation antipsychotics in the treatment of schizophrenia. *Br J Psych Advances.* 2020;26:26-40. https://www.cambridge.org/core/services/aop-cambridge-core/content/view/B2B19AA8ADD041AC735603A442A052E3/S2056467819000495a.pdf/understanding-and-managing-cardiac-side-effects-of-second-generation-antipsychotics-in-the-treatment-of-schizophrenia.pdf Accessed 2021 May 20.
See: Myocarditis (p.31-35)

21. Clozapine Guidelines (including clozapine initiation both inpatient and community, long term monitoring and treatment, actions following a red result and GP reference guide). Southampton (United Kingdom): NHS Southern Health. 2018 https://www.southernhealth.nhs.uk/EasysiteWeb/getresource.axd?AssetID=77706&type=full&servicetype=Inline Accessed 2021 May 20.

22. BPAC NZ. Clozapine: safe prescribing. 2017 https://bpac.org.nz/2017/docs/clozapine.pdf Accessed 2021 May 20.
See: Initiating clozapine for treatment-resistant schizophrenia (p.1-2); Monitoring and managing the adverse effects of clozapine (p.2); Monitoring patients for cardiac toxicity (p.3-4); Table 2: Recommended schedule for managing patients treated with clozapine (p.6)

23. Clozapine management clinical guideline. *(Policy No: CG260)*. Adelaide (Australia): Government of South Australia, SA Health; 2017: https://www.sahealth.sa.gov.au/wps/wcm/connect/059961804298b3078c77be80c298878e/Clozapine+Management+Clinical+Guideline_13092017.pdf?MOD=AJPERES&CACHEID=ROOTWORKSPACE-059961804298b3078c77be80c298878e-nzp2rc3. Accessed 2021 May 20.
See: Protocols – Commencing Clozapine, Ongoing Participant Monitoring (p.5-17)

24. Queensland Psychotropic Medication Advisory Committee. Safe and quality use of clozapine therapy in mental health services. *(Document number # QH-GDL-437:2016)*. Brisbane (Australia): State of Queensland (Queensland Health); 2016: https://www.health.qld.gov.au/__data/assets/pdf_file/0025/625354/qh-gdl-437.pdf. Accessed 2021 May 20.
See: 5. The administration, monitoring and prescribing of clozapine therapy (p.5-19), Appendix 1 - Protocol for monitoring patients commenced on clozapine for clozapine-induced myocarditis (p.22)

Diagnostic Accuracy of High-Sensitivity Troponin I Testing for Ruling Out Myocardial Infarction – Not Specific to Patients with Psychosis Disorders

25. National Institute for Health and Care Excellence. High-sensitivity troponin tests for the early rule out of NSTEMI. *(Diagnostic guidance DG40)* 2020; https://www.nice.org.uk/guidance/dg40/resources/highsensitivity-troponin-tests-for-the-early-rule-out-of-nstemi-pdf-1053804469957 Accessed 2021 May 20.
See: Comparative diagnostic accuracy for more than 1 test (p.20-21)

Review Articles

Clozapine-Induced Myocardiopathy and Myocarditis

26. American College of Cardiology. Clozapine-induced pericarditis: outweighing risks versus benefits. 2020: https://www.acc.org/latest-in-cardiology/articles/2020/06/08/09/23/clozapine-induced-pericarditis Accessed 2021 May 20.
See: Figure 1: Proposed protocol for monitoring patients commenced on clozapine for clozapine-related cardiomyopathy, myocarditis and pericarditis

27. Patel RK, Moore AM, Piper S, et al. Clozapine and cardiotoxicity - A guide for psychiatrists written by cardiologists. *Psychiatry Res.* 2019;282:112491 PubMed

28. Citrome L, McEvoy JP, Saklad SR. Guide to the management of clozapine-related tolerability and safety concerns. *Clin Schizophr Relat Psychoses*. 2016 2016;10(3):163-177. PubMed

Additional References

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