

IS CLOZAPINE SAFE TO REINITIATE IN A PATIENT WITH PREVIOUS COVID-19 VACCINE MYOCARDITIS? A CASE REVIEW

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Introduction

Clozapine-induced myocarditis (CIM) is a rare but potentially life-threatening adverse event seen to occur in approximately 7 in every 1000 cases of clozapine exposure¹, most commonly between 14-21 days after drug initiation². General prescribing guidelines recommend a degree of caution when initiating clozapine in patients with prior cardiovascular complaints.

COVID-19 mRNA vaccine-induced myocarditis (VIM) is a recently identified phenomenon seen to occur up to a rate of 3.2 per 100,000 in the high-risk subgroup of males aged 12-39 years of age, post-mRNA dose 2³. The demographics of this subgroup overlap considerably with the demographics of the average outpatient prescribed clozapine, found in one Canadian study to be males aged 39.5 ± 11.8⁴.

It is important to note that patients on clozapine are recognized to be at increased risk of COVID-19 infection and subsequent poor outcomes⁵, and there is a resounding consensus that the benefits of vaccination outweigh the risks. Complicating matters is the observation that COVID-19 vaccination can be associated with transient toxic clozapine levels, believed to potentially be driven by inflammation-mediated cytochrome P450 1A2 activity⁶.

Due to the overall uncertainty and differing hypotheses for the mechanisms behind both CIM and VIM, it is difficult to predict mechanistically if a diagnosis of one adverse reaction would be expected to predispose a patient to the other. Here, we present a case that highlights an approach to this uncertainty, and we review the paucity of literature discussing the relationship between these two rare adverse drug outcomes.

Literature Review

A focused systematic review was conducted to identify any prior studies or communications in the literature that specifically address a potential relationship between vaccine-induced myocarditis and clozapine-induced myocarditis. MEDLINE, PubMed, EMBASE, CENTRAL and PsycInfo were searched using the search strategy “(‘COVID-19’ OR ‘COVID-19 Vaccines’) AND ‘Clozapine’ AND ‘Myocarditis’”. Identified studies were screened and subsequently reviewed by two independent reviewers for relevancy; discrepancies were discussed (Figure 1). This search protocol ultimately yielded one relevant communication (Dawson et al., 2021)⁷, discussed here.

Clozapine was **safely reinitiated** and up-titrated in a patient with a history of probable vaccine-induced myocarditis.

Case Summary

A 21-year-old man with treatment-resistant schizophrenia, previously maintained on clozapine in the community for three years, was admitted to hospital for medication non-compliance and psychiatric decompensation. Aside from clozapine-induced tachycardia, for which he had been prescribed a beta blocker, he had no history of adverse reactions to clozapine. Four months prior to this admission he was seen by Cardiology and diagnosed with probable mild vaccine-induced myocarditis after he received a second dose of the Moderna COVID-19 mRNA vaccine.

Upon re-initiation of clozapine, a low but persistently elevated troponin T was observed (39 - 99 ng/L). He consistently showed no signs or symptoms of myocarditis however, and a repeat ECG was normal. As advised by Cardiology, up-titration was continued. Over the following two months the patient responded well to a maximum dose of 475 mg. The unexplained findings of persistently elevated troponin were ultimately determined to be a lab error due to assay antibody interference. Subsequent troponin I tests were normal.

Against medical advice, the patient received a third dose of COVID-19 mRNA vaccine while on a pass near the end of his admission. Aside from a briefly elevated CRP, no other clinical evidence of recurrent myocarditis was observed.

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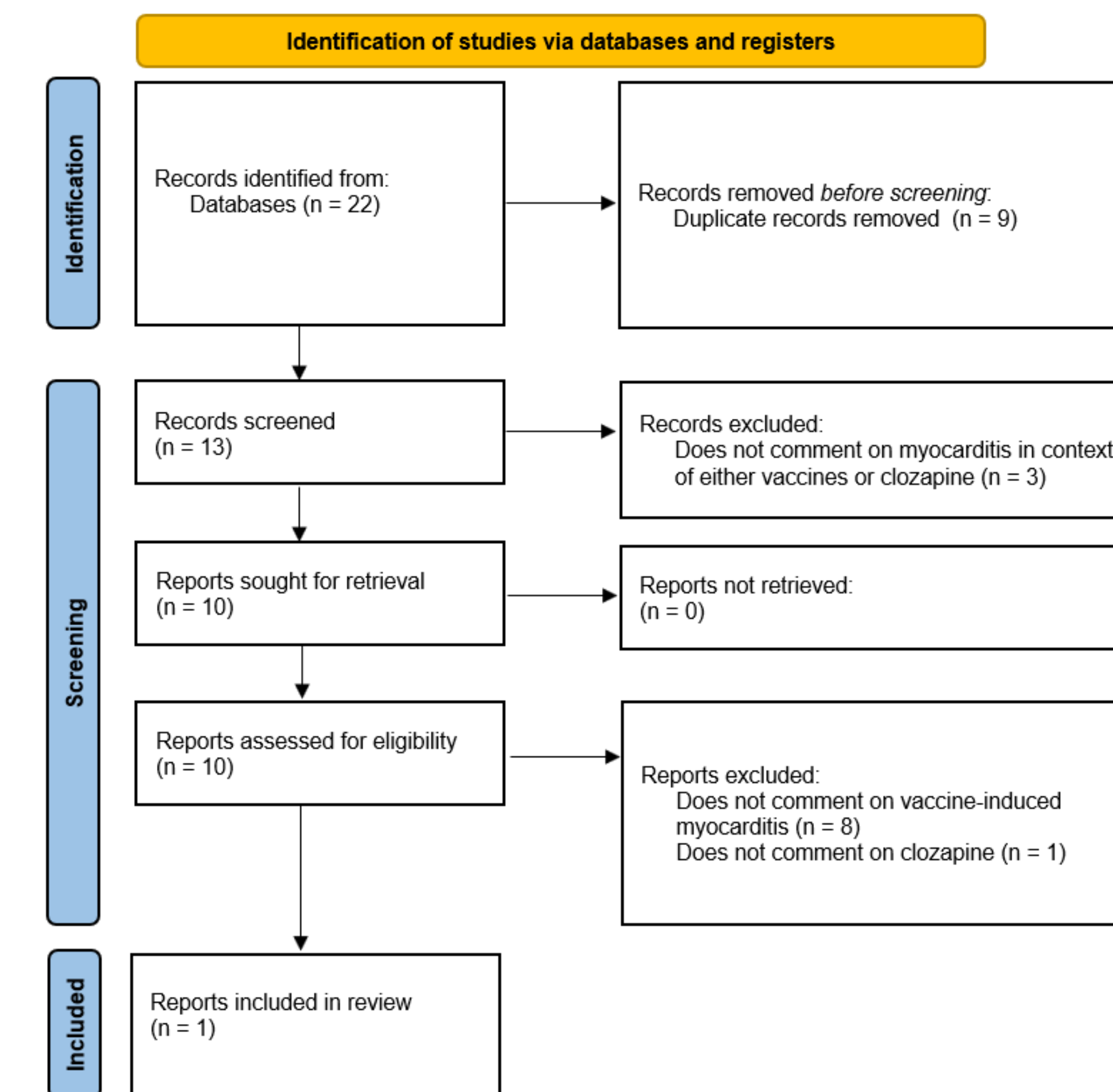


Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) 2020 Flow Diagram

Discussion

- This case should support clinicians in feeling comfortable initiating clozapine when encountering the rare patient with a history of prior vaccine-induced myocarditis.
- The importance of close monitoring for myocarditis and thoughtful interpretation of laboratory results is likewise highlighted.
- The results of this systematic review suggest that this is the first case in the literature to report on vaccine-associated myocarditis in patients on clozapine.
- The only paper identified in this systematic review, Dawson et al. (2021)⁷, describes a practice of avoiding overlaps between the first 14 days after COVID-19 mRNA vaccine administration and the first 28 days of clozapine treatment. This ensures that either agent is not mistakenly deemed contraindicated should symptoms of myocarditis arise.

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