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Clozapine-induced cardiomyopathy and myocarditis monitoring: A systematic review

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ABSTRACT

The use of clozapine requires monitoring the absolute neutrophil count because of the risk of agranulocytosis, but other potentially fatal adverse events associated with clozapine (specifically, myocarditis and cardiomyopathy) do not have mandatory procedures. We performed a systematic review of English-language articles to synthesize an evidence-based approach for myocarditis and cardiomyopathy monitoring. Articles published from January 1988 through February 2017 were identified through a search of Ovid MEDLINE, Ovid Embase, Ovid Cochrane Database of Systematic Reviews, Web of Science, Scopus, and Google Scholar. Selected articles were required to relate to myocarditis or cardiomyopathy in humans from exposure to clozapine. A total of 144 articles were included. Recommendations varied widely. Some authors recommended baseline laboratory monitoring, with or without follow-up testing, for C-reactive protein, creatine kinase MB, and troponin. Electrocardiography was commonly recommended, and echocardiography was less commonly recommended. The expense of monitoring was a consideration. A unanimous recommendation was to stop the use of clozapine and seek a cardiovascular consultation if myocarditis or cardiomyopathy is suspected. Although there is general agreement on which tests to perform for confirming myocarditis and cardiomyopathy, preemptive screening for these clozapine-induced conditions is controversial, and cost and barriers for the use of clozapine are concerns. For asymptomatic patients receiving clozapine, testing could include baseline electrocardiography, echocardiography as part of a cardiac consultation if patients have cardiac disease or risk factors, and monitoring of C-reactive protein and troponin as indicated.

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1. Introduction

Clozapine is associated with the risk of potentially fatal agranulocytosis and its use requires monitoring the absolute neutrophil count (ANC) through the US Food and Drug Administration (FDA) Risk Evaluation and Mitigation Strategy (REMS) program. ANC monitoring improves the hematologic safety of clozapine, but other potentially fatal adverse events associated with clozapine do not have mandatory procedures. Specifically, clozapine is associated with myocarditis and cardiomyopathy with an estimated absolute risk of 0.01% to 0.19% (Citrome et al., 2016). This is lower than the risk of agranulocytosis (1.3%), but mortality rate estimates for myocarditis and cardiomyopathy (10%–46%) are clinically significant (Citrome et al., 2016). In the United States, the clozapine package insert (2017) mentions common laboratory and radiologic findings in myocarditis and cardiomyopathy, but it lacks specific monitoring recommendations.

Compared to patients in other areas of the world, Australian patients have a higher incidence of myocarditis and cardiomyopathy (Haas et al., 2007; Kilian et al., 1999), which has led to multiple investigations on the topic in that region. For example, Ronaldson et al. (2011a) proposed a myocarditis screening protocol for all patients beginning treatment with clozapine. This protocol, which includes a baseline echocardiogram, has been criticized for not being cost-effective and, if made mandatory, for possibly introducing a barrier to initiating clozapine therapy in areas with limited resources (Freudenreich, 2015; Murch et al., 2013b). Despite the protocol proposed by Ronaldson and colleagues, consensus is still lacking in the medical literature on the most appropriate monitoring for patients in the absence of clinical suspicion for myocarditis or cardiomyopathy. We conducted a systematic review to

Abbreviations: ANC, absolute neutrophil count; CK-MB, creatine kinase MB; CRP, C-reactive protein; ECG, electrocardiography; ESR, erythrocyte sedimentation rate; FDA, US Food and Drug Administration; NT-proBNP, *N*-terminal pro-brain natriuretic peptide; REMS, Risk Evaluation and Mitigation Strategy.

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collate all available information and synthesize an evidence-based approach for the preemptive monitoring of clozapine-induced myocarditis and cardiomyopathy.

2. Methods

2.1. Literature search

A search of English-language articles published from January 1988 through February 2017 was designed in Ovid MEDLINE, Ovid Embase, Ovid Cochrane Database of Systematic Reviews, Web of Science, and Scopus. The strategy included the following keywords: ("Clozapine"[MAJR] OR clozapine[TIAB]) AND ("Cardiomyopathies"[MAJR] OR myocarditis[TIAB] OR cardiomyopath* [TIAB] OR pericarditis [TIAB]) AND ("diagnosis"[Subheading] OR "Diagnosis"[Mesh] OR "Drug Monitoring"[Mesh] OR monitor* or detect* or diagnos* or screen* or examin* or inspect* or identif*). As a final search for relevant articles, references of gathered publications were reviewed and a Google Scholar search was conducted using search terms "clozapine and myocarditis" and "clozapine and cardiomyopathy."

2.2. Screening

Articles were included if they related to myocarditis or cardiomyopathy from exposure or reexposure to clozapine. Articles were excluded if they were duplicates, discussed animal models, or were overdose reports or conference abstracts. The full texts of articles were reviewed by 3 authors (K.N.K., A.C.O., and J.G.L.) who determined inclusion and reviewed and summarized the articles.

3. Results

The search produced 153 articles after removing duplicates, with an additional 30 articles found by searching references and Google Scholar. After screening, 39 articles were eliminated. A total of 144 publications related to clozapine-associated myocarditis and cardiomyopathy were included (Fig. 1).

3.1. Review articles

In the 27 identified review articles (Table 1), consistent recommendations included obtaining a thorough medical history, family history, and social history and performing a complete physical examination before prescribing clozapine. Cardiology consultation was recommended for any relevant findings from the history or physical examination (Citrome et al., 2016; Marder et al., 2004; Merrill et al., 2005; Raja and Raja, 2014; Wooltorton, 2002), including arrhythmias, chest pain, coronary artery disease, heart failure, myocardial infarction, alcohol abuse, syncope, uncontrolled hypertension, and family history of dilated cardiomyopathy. A need to detect nonspecific signs and symptoms of physical illness was widely emphasized as these may represent the early manifestations of cardiac adverse events (Ronaldson et al., 2015a; Wehmeier et al., 2005). Authors' recommendations varied in support of routine laboratory monitoring, if any, and clinical monitoring alone (Citrome et al., 2016; Cohen et al., 2012; Layland et al., 2009).

Eosinophilia was considered nonspecific or delayed and thus less helpful for the detection of early myocarditis (Roge et al., 2012). Other recommendations for baseline laboratory monitoring included obtaining baseline and weekly levels of C-reactive protein (CRP), creatine kinase MB (CK-MB), and troponin (singly or in combination) within the first 3 to 4 weeks of therapy. *N*-terminal pro-brain natriuretic peptide (NT-proBNP) was discussed as having a role in detecting early cardiac dysfunction, but more data are needed to support its use (Alawami et al., 2014; Curto et al., 2016; Rostagno et al., 2011a). Erythrocyte sedimentation rate (ESR), which may be elevated in acute myocarditis, was less commonly recommended, and its role in routine monitoring is unclear. The articles did not suggest that serum clozapine levels are useful in predicting myocarditis (Remington et al., 2013). Low selenium levels may be associated with cardiomyopathy (Berk et al., 2007). One author cautioned that because myocarditis has a rapid onset, laboratory monitoring protocols may provide a false sense of security, highlighting the ongoing need for concurrent clinical monitoring (Berk et al., 2007).

Electrocardiography (ECG) was commonly recommended at baseline and at various routine intervals early in therapy to assess the QT interval rather than to specifically assess for myocarditis (Abidi and

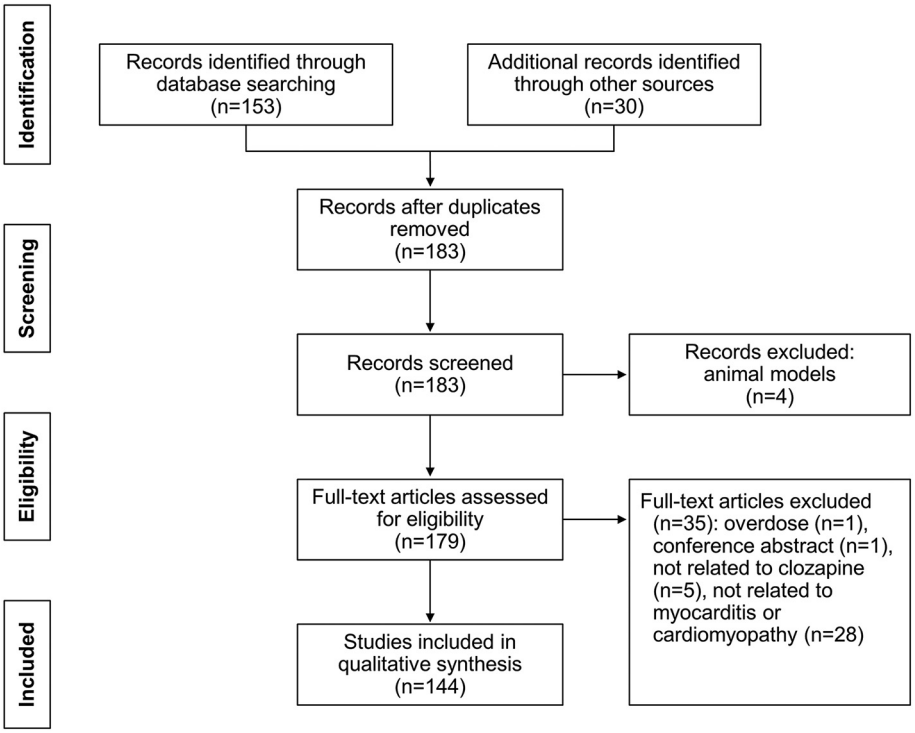

Fig. 1. Flow diagram of included studies.

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