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CLINICAL ROUNDS

Clozapine-induced myocarditis and subsequent rechallenge: a narrative literature review and case report

Nadine Halawa PharmD, BCPS[1]; Mackenzie Armstrong MD, FRCPC[2]; Sarah Fancy, MD, FRCP[3]; Sabina Abidi MD, FRCPC[4]

Abstract

Clozapine is an antipsychotic medication that has been proven effective for the management of treatment-resistant schizophrenia (TRS). For some patients, it is the only medication that can improve disease burden and quality of life. Clozapine comes with various potentially serious adverse effects which may dissuade physicians from prescribing it despite its well-documented efficacy. One of these adverse effects is clozapine-induced myocarditis (CIM). Due to these risks, patients who undergo a clozapine rechallenge after CIM require close monitoring. Myocardial damage can be reversible if CIM is promptly identified, and clozapine is discontinued appropriately. The gold-standard for diagnosing myocarditis is an endomyocardial biopsy but there are no clear recommendations for how to use less invasive screening assessments to monitor for CIM during a clozapine rechallenge. This review article aims to increase awareness of CIM and provide guidance on monitoring and management. The accompanying case report presents a proposed strategy, including biomarkers that were used to identify inflammation and cardiac injury which guided the treatment of an adolescent patient who had a successful clozapine rechallenge. Further research is necessary to validate the proposed monitoring protocol and to further advance guidance for clinicians.

Key Words: *clozapine, clozapine-induced myocarditis, rechallenge, CIM, adolescents, protocol*

Résumé

La clozapine est une médication antipsychotique qui s'est révélée efficace pour la prise en charge de la schizophrénie résistante au traitement (SRT). Pour certains patients, c'est le seul médicament qui peut améliorer le fardeau de la maladie et la qualité de vie. La clozapine s'accompagne de divers effets secondaires potentiellement sérieux qui peuvent empêcher les médecins de la prescrire, malgré son efficacité bien documentée. L'un de ces effets indésirables est la myocardite induite par la clozapine (MIC). En raison de ces risques, les patients qui subissent une nouvelle provocation à la clozapine après une MIC demandent une surveillance étroite. Les lésions myocardiques peuvent être réversibles si la MIC est rapidement identifiée et que la clozapine est interrompue de façon appropriée. La référence en matière de diagnostic

[1]Adjunct Faculty and Lecturer, Department of Pharmacy, Dalhousie University; Clinical Pharmacy Specialist, IWK Child and Adolescent Mental Health and Addictions Program, Halifax, Nova Scotia
[2]Fifth-year Psychiatry Resident, Dalhousie University, Halifax, Nova Scotia
[3]Assistant Professor, Department of Psychiatry, Dalhousie University; Staff Psychiatrist, IWK Garron Centre for Child and Adolescent Mental Health, Halifax, Nova Scotia
[4]Associate Professor, Department of Psychiatry, Dalhousie University; Associate Chief, Division of Child and Adolescent Psychiatry IWK Mental Health and Addictions Program; Head, IWK Youth Psychosis Program, Halifax, Nova Scotia

Corresponding E-Mail: sarah.fancy@iwk.nshealth.ca

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de myocardite est une biopsie endomyocardique mais il n'y a pas de recommandations nettes sur la façon d'utiliser des évaluations de dépistage moins invasives pour surveiller la MIC durant une nouvelle provocation à la clozapine. Le présent article de revue vise à accroître la connaissance de la MIC et à offrir un guide de la surveillance et de la gestion. Le rapport de cas ci-joint présente une stratégie proposée, notamment des biomarqueurs qui ont servi à identifier l'inflammation et la blessure cardiaque qui a guidé le traitement d'un patient adolescent ayant subi une provocation à la clozapine réussie. Il faut plus de recherche pour valider le protocole de surveillance proposé et faire avancer le guide pour les cliniciens.

Mots clés: *clozapine, myocardite induite par la clozapine, provocation, MIC, adolescents, protocole*

Introduction

Schizophrenia is a mental disorder characterized by disturbances in thought, perception, and behavior (1). Roughly one-third of patients diagnosed with schizophrenia have treatment-resistant schizophrenia (TRS). TRS is defined when patients do not have adequate response to at least two trials of different antipsychotics, with sufficient dose and duration (2). Compared to individuals with treatment-responsive schizophrenia, those with TRS spend significantly more days per year in hospital (75 versus 5.3 days) and score 20% lower on quality-of-life scales (3). Patients with TRS also have higher rates of suicide (4). Clozapine is a second-generation antipsychotic that has proven efficacy for the treatment of TRS, including evidence for decreased suicidality and mood stabilization (5,6).

Approximately 5% of patients with schizophrenia are diagnosed before the age of 18 (7). Since early-onset schizophrenia (EOS) occurs during crucial years of neurodevelopment, it is a predictor of worse prognosis, with greater chronicity and clinical morbidity (1). Response rates to antipsychotics are lower in patients with EOS relative to other individuals (8). Hence, this population is more commonly treatment-resistant and eligible for clozapine treatment (7). In Canada, clozapine is recommended as first-line treatment in youth with TRS (9). Although the data are limited compared to adult populations, clozapine's superior efficacy in TRS has also been demonstrated in youth. Tolerability is comparable to adult populations, with low discontinuation rates (3-6%) (7).

Unfortunately, initiation is often delayed in youth who meet criteria for TRS despite availability of guidelines which may be due to prescriber discomfort and inherent risks (10,11). This may be particularly true in the pediatric population where literature is limited. Clozapine's restricted use in TRS is in part due to the risk for rare but severe adverse effects, some of which include agranulocytosis, seizures, and myocarditis (2).

In Canada, all patients that are on clozapine treatment are registered under a national network to monitor for agranulocytosis (12). The cumulative incidence of agranulocytosis associated with clozapine treatment was reported to be 0.8% over a one-year period (13). Myocarditis associated with clozapine has a estimated incidence, ranging from 0.7% to 1.2%, over a ten-year period (14) and laboratory monitoring is not mandated in Canada (12). Since myocarditis can be life-threatening, vigilance and close monitoring should be recommended with clozapine treatment where a history of clozapine-induced myocarditis (CIM) is present (15,16).

This article reviews the definition, rates, and pathophysiology of CIM, as well as recommendations for monitoring, diagnosing, and treating CIM. This is followed by a case report of a successful clozapine rechallenge in an adolescent who had a history of CIM, along with an accompanied proposed monitoring protocol that was implemented. This review and case presentation may serve to aid clinicians when considering clozapine rechallenge by providing a potential framework for monitoring in the context of a rechallenge.

Clozapine-Induced Myocarditis (CIM)

Myocarditis is an inflammatory disease of the cardiac muscle, which can be caused by infectious and non-infectious conditions (17). In adults, the absolute risk of CIM has been reported to be low at 0.01% to 0.19% (18) with true risk estimated to be higher than that given potential underreporting (17). The incidence of CIM ranged from 0.7% to 1.2% of treated patients in a 10-year period (14) with one inpatient study identifying 10 of 316 patients as meeting criteria for CIM during their hospitalization (19). CIM has been reported to occur primarily in the first two to eight weeks of clozapine treatment (17,20). The mortality rate of CIM ranged from 10 to 30%, with the highest risk occurring in the first month of treatment (19). In children and adolescents, the epidemiology of CIM is unknown given the small number of studies published.

The exact pathophysiology of CIM is unknown. Some hypothesize clozapine has a direct myotoxic effect (21) while others suspect it triggers a type I immunoglobulin E (IgE)-mediated hypersensitivity reaction (15). In the review of cases of CIM, the development of eosinophilia has been observed. This suggests an IgE mediated hypersensitivity reaction as far as mechanism (21,22). A rise in proinflammatory cytokines has been found to be dose-dependent and leads to increased oxidative stress and cardiotoxicity (23). Several pathways are involved including immune modulation and proinflammation including an IgE-mediated response, catecholamine activation, induction of free radicals and oxidative stress, and activation of cardiomyocyte cell death pathways (24). Furthermore, sympathetic hyperactivity and blockade of cholinergic and adrenergic receptors are also attributed to myocarditis (25). A full appreciation of the mechanisms remains unclear but observed to be multifactorial.

The course of CIM has been described in the literature (26). It involves a benign increase in heart rate (HR) of 10-20 beats per minute (bpm) around 10-19 days after clozapine initiation, followed by onset of respiratory, gastrointestinal, and urinary symptoms and/or a mild C-reactive protein (CRP) rise. This is then followed by further rise in HR of 20 to 30 bpm (higher than previous), with subsequent troponin-I elevation greater than two times the upper limit of normal, CRP greater than 100 mg/L, and abnormalities in left ventricular (LV) function on echocardiogram. Commonly, nonspecific symptoms are experienced including malaise, myalgia, pleuritic chest pain, tachypnea, low-grade fever, fatigue, and hypotension.

The onset of CIM typically occurs 10 to 30 days after clozapine is started, with 88% of cases occurring during the first three weeks (26). CIM that begins beyond three weeks could represent a delayed hypersensitivity reaction (type II or IV) where clozapine forms an antigen complex with cardiac myocytes (27). This complex attracts monocytes and promotes inflammation, resulting in myocardial damage. Hence, clozapine-induced cardiomyopathy can occur much later with a median onset of 9 months (28). Furthermore, the presentation of CIM overlaps with other types of myocarditis, other viral infections, and medical conditions therefore alternative causes must be excluded.

Five cases of suspected CIM in youth have been published (29,30,31,32). The cases range in age from 15-18 with multiple presenting symptoms suspicious for CIM including fever, chest pain, dyspnea, tachycardia, myalgias and lethargy as well as abnormalities on bloodwork. Four of the patients developed cardiac symptoms at daily clozapine doses between 125-200mg two weeks after starting treatment (30,31,31). All five patients stabilized following clozapine discontinuation (29,30,31,32).

A systematic review of reported CIM in youth as an adverse drug reaction (ADR) from the Word Health Organization (WHO) pharmacovigilance database was published by Les Cuevas and colleagues in 2022 (33). The authors identified 19 possible, and 22 probable cases of CIM based on symptom presentation and the ADR scale confirming that CIM does occur in youth. Roughly two thirds of patients were on clozapine monotherapy, and most cases of CIM occurred in the first month of treatment often associated with up-titration. Fatal outcomes were lower in children and increased by age in this sample. The characteristics observed in these cases was deemed similar to adults, including heterogeneity of symptom presentation.

Monitoring Recommendations for CIM

In Canada, the clozapine product monograph details signs and symptoms of myocarditis but only recommends discontinuation of clozapine and to obtain an urgent cardiac evaluation upon suspicion of CIM (12,34). A 2018 systematic review summarized clozapine monitoring recommendations from 27 studies (35). At baseline, a physical exam, history, and interval electrocardiograms (EKGs) are consistently suggested (17,36,37). If the patient has any cardiac risk factors, a cardiology consult is indicated (35). The recommendations for baseline echocardiograms are inconsistent, with some reviews cautioning against its use unless the patient has significant cardiac risk factors (17,38). Others recommend a baseline echocardiogram for all clozapine patients, with a repeat scan in either two or six months (37,39). Prolonged QTc (QT corrected for heart rate) on EKG may also be observed and should be monitored (40). Caution and vigilance should be observed for patients with a known history of cardiovascular or conduction abnormalities (12).

After clozapine is initiated, the recommendations include monitoring for clinical signs of myocarditis, including cardiac distress [i.e., chest pain, palpitations, dyspnea] and immune response [e.g., fever, fatigue, myalgia] (28). Recommendations for laboratory testing are varied, but several studies recommend baseline and weekly troponin-I, creatine kinase (CK), and CRP for the first three to four weeks of clozapine therapy (41,42,43). The evidence is mixed as to the role of measuring white blood cells (WBCs), erythrocyte sedimentation rate (ESR), B-type Natriuretic Peptide (BNP) and eosinophils to screen for myocarditis.

CIM may be difficult to detect based upon specific signs, symptoms, and echocardiogram alone. Left ventricular

impairment is observed in approximately two-thirds of patients and early symptoms are often nonspecific (19).

Diagnosing CIM

Endomyocardial biopsy is the gold standard for diagnosing myocarditis but in practice, it is more frequently diagnosed using a combination of less invasive assessments, including clinical, biochemical, electrocardiographic, and echocardiographic tests (19,31). Experts also suggest Cardiovascular Magnetic Resonance (CV-MRI) as part of the assessment (19,44).

An Australian team developed an evidence-based monitoring protocol for adults based on the analysis of 75 CIM cases, which details laboratory thresholds for when clozapine should be stopped (26). Their monitoring protocol recommends baseline troponin-I/T, CRP and echocardiography, and monitoring troponin-I/T and CRP on days 7, 14, 21 and 28 of treatment; hence, active monitoring for at least four weeks when reintroducing clozapine in cases with a history of CIM. They suggest that clozapine administration should cease if CRP is greater than 100 mg/L or if troponin-I/T is more than two times the upper limit of normal. If CRP is between 50-100 mg/L or if troponin-I/T is elevated but less than two times the upper limit of normal, they recommend continuing clozapine with increased monitoring. Elevated WBC, CK, ESR, and BNP would also be concerning and warrant further work-up. Investigating both CRP and troponin-I together was found to have a sensitivity of 100% for the detection of myocarditis in patients that are symptomatic. It is important to note that troponin I/T can be monitored and a high sensitivity troponin value above the 99th percentile upper reference limit at any time is also suggestive of early myocarditis (45), alongside other parameters such as N-terminal pro b-type natriuretic peptide (NT-proBNP) (19).

On EKG, no specific abnormality is pathognomonic for myocarditis, but concerning findings include ST elevation or depression, T wave inversions, arrhythmia, or bundle branch block (46,47). Approximately 25-50% of patients develop sinus tachycardia upon starting clozapine; it is one of the most common reasons for discontinuation (28,48). Although tachycardia with clozapine is typically transient and benign, it should prompt additional assessments (e.g., EKG, cardiovascular exam) to rule out underlying pathology, such as myocarditis (28). Clozapine-induced tachycardia is a result of direct effects on the sympathetic nervous system and clozapine's anticholinergic properties and likely resulting from rapid dose titration (48).

A systematic review identified 58 patients with diagnosed clozapine-induced myocarditis whose echocardiogram findings were published (49). Of these, 57% had at least mild ventricular dysfunction and dilatation, while 10% had "unremarkable" echocardiograms, presenting an argument for further research on diagnostic criteria.

Treatment of CIM

If CIM is identified and no other causes are found, clozapine should be stopped immediately, and cardiology should be consulted (47). The individual will require hospital admission and supportive care. If all other causes are ruled out, early clozapine discontinuation should lead to the relevant symptoms and abnormal investigations returning to normal (19,31) and myocardial damage is typically reversible (2). Beyond discontinuation, a cardiology consultant may start steroids or other medications to specifically manage heart failure, such as beta-blockers, angiotensin-converting enzyme inhibitors, and diuretics in addition to supportive care (19,49). Refraining from exercise during this period is critical given the increased risk of arrhythmias and sudden death in the acute phase (50). Other treatments and transfer to a critical care unit may also be warranted (19).

Clozapine Rechallenge Following CIM

There is no consensus for how to safely rechallenge patients with clozapine after it has been stopped due to CIM (51). In deciding to rechallenge, the potential psychiatric benefit must outweigh the potential risk involved. To better inform this decision, a 2012 case-control study looked at eight adult patients who underwent a clozapine rechallenge after CIM (52). Of the eight cases, four had successful rechallenges. Of the four unsuccessful rechallenges, only one was diagnosed with myocarditis. The other three failed rechallenges developed non-specific, non-cardiac adverse effects during the first two to seven days after restarting clozapine. Based on these cases, they were not able to make any firm conclusions, but the authors proposed that the severity index of the myocarditis episode and the speed of clozapine uptitration during the rechallenge are crucial factors for predicting a successful rechallenge.

With regards to the severity of an index myocarditis episode, levels of CRP and LV function on echocardiogram could be predictive (53). For the four individuals who had successful clozapine rechallenges, their average peak CRP was 120 mg/L during the index myocarditis episode. This contrasts with the four patients who had unsuccessful rechallenges, with an average peak CRP of 211 mg/L during the index myocarditis episode. With regards to echocardiogram, 75% of the successful rechallenge cases had normal LV function during the index myocarditis episode, whereas

100% of the unsuccessful rechallenge cases previously had LV dysfunction. Ronaldson and colleagues analyzed 10 fatal cases in comparison with 66 surviving cases and found no difference regarding age, gender, smoking status, dose at onset or concomitant valproate; however, obesity and duration of clozapine was significantly longer for fatal cases, in addition to elevated CK over 1000 U/L after excluding one outlier (54).

When considering titration speed, 75% of successful rechallenges had relatively slow up-titrations (52). The one patient who was diagnosed with myocarditis after the rechallenge had been given a one-time 400 mg dose of clozapine, without any preceding up-titration. The authors suggested that clozapine rechallenge should not be contraindicated in patients with a history of CIM, but that rechallenge should be done with the patient's informed consent, careful monitoring, and with slow up-titration in cases of mild-moderate CIM (53).

Shivakumar and colleagues also recommended slow up-titration to minimize the risk of cardiotoxicity, speculating that this approach gives the body more time to become "desensitized" to clozapine's hypothesized IgE-mediated hypersensitivity reaction (27). While no threshold of increase was provided, the authors recommend that if CRP is elevated, clozapine up-titration should be held, and bloodwork should be repeated twice over two days. If CRP normalizes, the up-titration can re-start, but if CRP remains elevated, other causes for the inflammation should be investigated. If troponin-I is elevated at any time, they recommend discontinuing clozapine and consulting cardiology to help guide next steps.

To evaluate the risk associated with clozapine rechallenge after CIM, a systematic review identified 19 patients who were rechallenged with clozapine (49). The start date of these rechallenges ranged between several weeks to 25 months after discontinuation of clozapine. There were no deaths and 63% of the rechallenges were successful.

There are only two case reports of patients under age 19 who underwent a clozapine rechallenge after CIM (29,31). One of these rechallenges was unsuccessful, where clozapine was stopped in a 15-year-old patient after they developed nausea and vomiting on clozapine 12.5 mg (4 to 5 days after starting), with an elevated troponin-I (29). No other details were provided in the report which limits the ability to interpret the findings. The other rechallenge was successful with slow up-titration, where clozapine was restarted in a 15-year-old patient, initially at 6.25 mg and gradually increased by 6.25 mg every two days (31). The up-titration was accompanied by regular medical monitoring, including clinical (e.g., heart rate, blood pressure, temperature), biochemical (e.g., CBC with differential, troponin-I, CRP, BNP) and EKG assessments. These evaluations were combined with follow-up cardiology appointments. At six months, a CV-MRI showed unchanged chronic scarring from the previous episode of myocarditis, with no new abnormalities. At twelve months, the patient was tolerating clozapine 325 mg twice daily with no further evidence of myocarditis.

Case report

An 18-year-old female with a history of TRS since the age of 15 was admitted to hospital with a relapse of psychotic symptoms. The patient presented in distress, expressing suicidal ideation secondary to command auditory hallucinations. The patient was well-known to the inpatient medical team, and her decline was deemed significant and observable. When considering precipitants for her deterioration, the team found no evidence of substance use or medication non-adherence.

The patient was admitted for a third trial of clozapine on the following medications: pimozide 10 mg total daily dose; quetiapine extended release 900 mg at bedtime; loxapine 40 mg total daily dose, divalproex sodium 1250 mg at bedtime, and metformin 750 mg. The patient has a past medical history of iron deficiency anemia, previously documented CIM (resolved), metabolic syndrome, sinus tachycardia, and mild sleep apnea.

The patient has a complex history, with multiple hospital admissions as well as medication trials with minimal sustained clinical response to antipsychotics apart from clozapine. Previous medication trials consisted of both monotherapy and combination therapy of various antipsychotics including olanzapine, aripiprazole, lurasidone, loxapine, quetiapine, asenapine, zuclopenthixol, divalproex sodium, pimozide, and clozapine.

During this admission, a third trial (second rechallenge) of clozapine was assessed and implemented given that the patient responded well previously but had developed suspected CIM. A comprehensive medication review of the previous two trials of clozapine was conducted. The cardiologist at The Clozapine Support and Assistance Network (CSAN) a national centralized monitoring system for clozapine in Canada, was consulted alongside the hospital cardiologist. A review of these two previous clozapine trials is summarized below.

Clozapine Trial # 1

Before clozapine was started, the patient's CRP and troponin-I were within normal limits. Baseline EKG and chest x-ray showed no abnormalities. Clozapine was initiated and titrated by 25-50 mg every one to two days. The patient was asymptomatic during the up-titration and had significant observable improvement in her psychiatric symptoms. CRP and troponin-I were not routinely ordered. On day 18, at a clozapine dose of 300mg daily, the patient reported general fatigue and had a low-grade fever but no other reported

Table 1. Timelines and associated laboratory and test results post clozapine discontinuation after Trial #1

Time Period	Dose of clozapine	CRP (mg/L)	Troponin-I (ug/L)[a]	EKG/ECHO/Chest X-Ray
Day 18	Clozapine discontinued (last administered dose was 300 mg at bedtime)		11:05 AM → 8.050 12:35 AM → 6.190	EKG - QTc 431 msec; normal
Day 19	No clozapine		08:25 AM → 1.510	EKG - QTc 425 msec; normal Chest X-ray – normal; lungs clear; no pneumonia
Day 20			07:58 AM → 0.570 10:40 AM → 0.420	ECHO - normal structures; mild hypokinesis but overall normal function; small pericardial fluid; no mitral valve regurgitation.
Day 22			07:41 AM → 0.119	EKG - QTc 427 msec; normal sinus rhythm; nonspecific T wave flattening
Day 23			08:08 AM → 0.103	EKG - QTc 422 msec; normal sinus rhythm
Day 24		3.5		
~ three months post discontinuation				EKG - QTc 448 msec; borderline sinus tachycardia; otherwise normal
~ three months post discontinuation				EKG - QTc 435 msec; sinus tachycardia; T wave abnormality; consider inferior ischemia [Abnormal]
~ four months post discontinuation				EKG - QTc – 454 msec; sinus tachycardia; T wave abnormality ECHO - limited imaging; function normal; no effusion

[a]Local laboratory limits: Troponin I - 0.034 ug/L upper limit; normal <0.012 ug/L
CRP = C-reactive protein; ECHO = Echocardiogram; EKG = Electrocardiogram

symptoms suggestive of myocarditis. A troponin-I was ordered and found to be significantly elevated at 8.05 ug/L. An EKG was also ordered and was found to show sinus tachycardia and non-specific T-wave flattening. The hospital cardiologists' impression was that this was probable CIM and recommended discontinuation. An echocardiogram performed 2 days later showed mild hypokinesis and a small pericardial effusion; overall function was normal, and the patient suffered no cardiac structural consequence. The troponin-I and CRP returned to normal within four days after clozapine discontinuation. Refer to Table 1 for details around timeline post up-titration. Troponin-I was used for this case; nevertheless, both high sensitivity Troponin I/T indicates myocardial injury when at least one value is above the 99th percentile of the upper reference limit (55).

Clozapine Trial # 2 (first rechallenge)

Six months later the patient was readmitted for ongoing psychotic symptoms and suboptimal response to interventions. The patients' medications were titrated down: loxapine was decreased to 20 mg once daily (admission dose of 40mg total daily), quetiapine XR was decreased to 800 mg total daily dose (admission dose of 1200 mg total daily dose), metformin continued. At baseline, notable findings included sinus tachycardia on EKG and trivial pericardial effusion on echocardiogram (LV ejection fraction of 79%).

Table 2. Timelines and Associated Laboratory and Test Results During and After Trial #2 (First Rechallenge)				
Time Period	**Dose of clozapine**	**CRP (mg/L)**	**Troponin-I (ug/L)[a]**	**EKG/ECHO/other**
Day 1	12.5 mg at bedtime			EKG baseline - QTc 452 msec; sinus tachycardia ECHO baseline - trivial pericardial effusion with an ejection fraction of 79%
Day 2	12.5 mg twice daily			
Day 3	12.5 mg twice daily			
Day 4	25 mg twice daily	8.2	< 0.012	
Day 5	25 mg twice daily			
Day 6	25 mg in the morning; then clozapine was discontinued	47.7	< 0.012	
Day 7		46.8		
Day 8		38.2	< 0.012	
Day 9		26.8	< 0.012	
Day 10		14.9	< 0.012	
Day 11				
Day 12		4.7	< 0.012	
Post discontinuation				EKG - QTc 417 msec; sinus tachycardia; no significant change from baseline EKG/holter monitoring - results normal
[a]Local laboratory limits: Troponin I - 0.034 ug/L upper limit; normal <0.012 ug/L CRP = C-reactive protein; ECHO = Echocardiogram; EKG = Electrocardiogram				

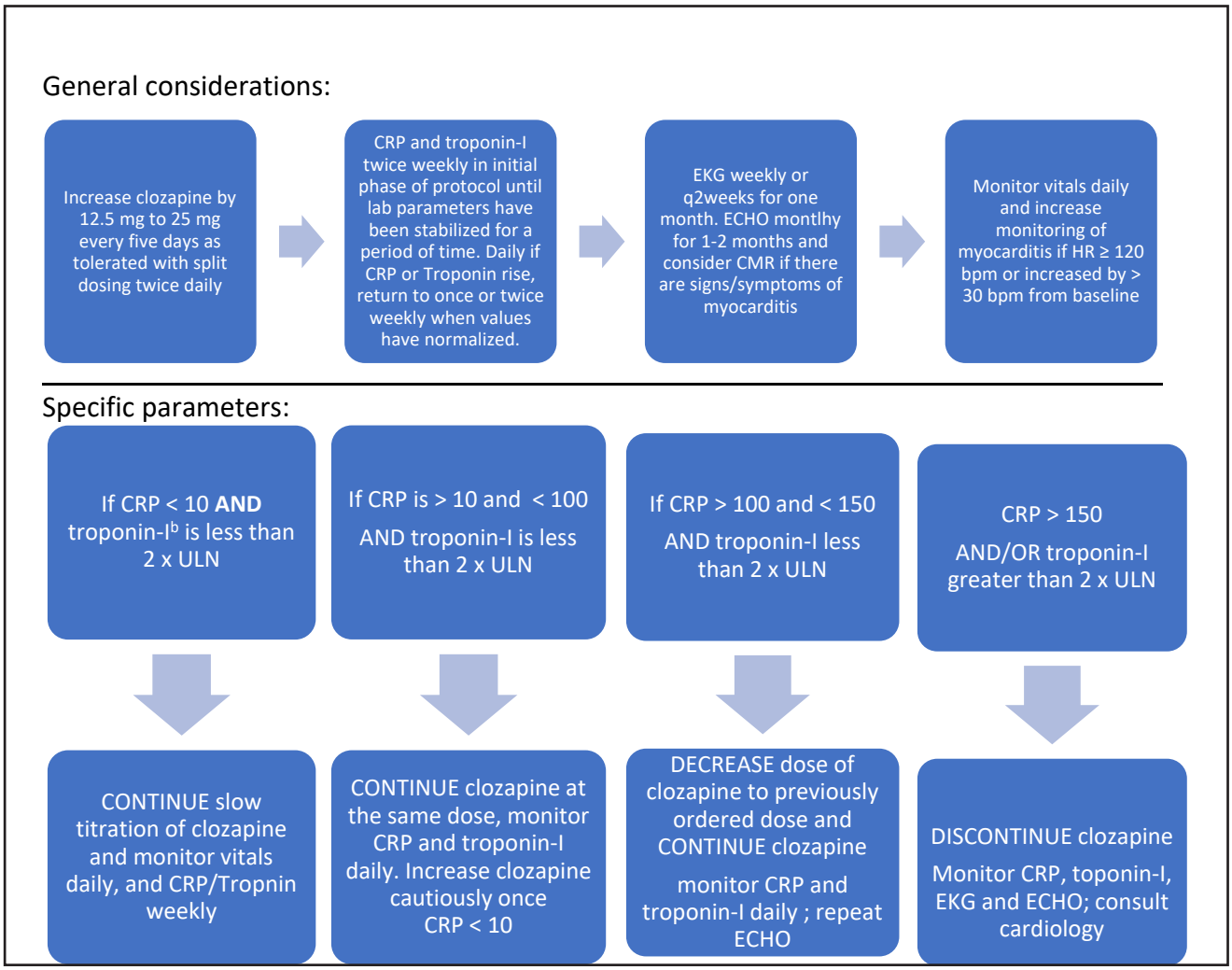
CRP was 6.9 mg/L and normal troponin-I (<0.012 ug/L). This first rechallenge involved a slower up-titration of clozapine by 25 mg per day every two days and a general split dosing of clozapine every 12 hours to minimize side effects. CRP and troponin-I were also monitored every one to two days. Troponin-I levels did not increase. By day six clozapine was 25 mg twice daily and CRP was elevated to 47.7 mg/L. The patient had no clinically significant physical complaints and troponin-I remained normal. Due to the elevated CRP within less than a week of clozapine exposure, the hospital cardiologist was consulted and again recommended discontinuation. Refer to Table 2 for more details around the timeline.

Clozapine Trial # 3 (second rechallenge)

During the most recent admission triggered once again by severe symptoms of the TRS and associated morbidity and risk, the course of the first and second trials of clozapine were thoroughly reviewed by the team along with the CSAN cardiologist. Since there was no elevation in troponin-I and no symptoms of clinical significance despite the elevated CRP, the team deemed the second trial (first rechallenge) an inadequate rechallenge of clozapine, with premature discontinuation.

In the effort to mitigate risk with the second clozapine rechallenge, all potential risk factors were minimized. The

Figure 1: Proposed Protocol for Mitigating Clozapine-Induced Myocarditis During a Rechallenge[a]



[a]This protocol was not otherwise validated.

[b]Troponin-I was used for this case per local laboratory requirements; however, high sensitivity Troponin I or T can be utilized.

CRP = C-reactive protein; CMR = Cardiovascular Magnetic Resonance; EKG = electrocardiogram; ECHO = echocardiogram; bpm = beats per minute; ULN= upper limit of normal

patient was titrated off all medications, including divalproex sodium, with exception of quetiapine extended release which was reduced to 600 mg daily and metformin which was continued and used to mitigate symptoms of metabolic syndrome. A strict protocol was set forth by the team based on literature review to inform the course of treatment. A cut-off of two times the upper limit of normal was chosen for troponin-I based upon Ronaldson and colleagues' findings to allow for flexibility in management (26). This protocol is presented in Figure 1.

The hospital Ethics Board was consulted regarding the risk and benefit of a second clozapine rechallenge. The benefits included it being the best chance for symptoms remission, improved quality of life for the patient and a potential decrease in physical risks associated with polypharmacy. The risks included the known potential for CIM and the possibility of treatment resistance to clozapine. The team and substitute decision maker felt that another clozapine challenge would give the patient the best possibility for positive life outcomes.

The third trial (second rechallenge) of clozapine occurred 1.5 years after the second trial. The baseline echocardiogram demonstrated normal LV and right ventricular (RV) function, a left ventricular ejection fraction (LVEF) of 79%, trivial pericardial effusion and mild septal hypokinesis. Baseline CBC, CRP, and troponin-I were within normal

Table 3. Timelines and Associated Laboratory and Test Results During Trial #3 (Second Rechallenge)

Time Period	Dose of clozapine	CRP (mg/L)	Troponin-I (ug/L)[a]	EKG/ECHO/HR
Day 1	12.5 mg at bedtime			
Day 2	12.5 mg twice daily	6.3	<0.012	
Day 3	12.5 mg twice daily	31.5	<0.012	
Day 4	12.5 mg twice daily			
Day 5	12.5 mg twice daily	48.8	<0.012	
Day 6	12.5 mg twice daily			HR 140 bpm
Day 7	12.5 mg twice daily	31.1	<0.012	
Day 8	12.5 mg twice daily	25.7	< 0.012	
Day 9	12.5 mg in the morning and 25 mg at bedtime			
Day 10	12.5 mg in the morning and 25 mg at bedtime	22.2	< 0.012	ECHO - Left ventricular function at 63%, septal wall hypokinesis HR 140 bpm
Day 11-13	12.5 mg in the morning and 25 mg at bedtime	Slowly decreased	<0.012	
Day 14	12.5 mg in the morning and 25 mg at bedtime	<10	< 0.012	ECHO - Left ventricular function increased to 69%, mild septal wall hypokinesis
Day 21	25mg in the morning and 37.5mg at bedtime	< remained below 10 for the rest of the titration	<0.012	ECHO - Left ventricular function increased to 73%, no septal wall hypokinesis HR - 110-120 bpm

[a]Local laboratory limits: Troponin I - 0.034 ug/L upper limit; normal <0.012 ug/L.
bpm = beats per minute; CRP = C-reactive protein; ECHO = Echocardiogram; EKG = Electrocardiogram; HR = heart rate

limits. The titration was slow, with a total weekly dose increase of 25 mg (divided into two 12.5 mg increases on subsequent days). Troponin-I and CRP were checked weekly, unless there was a rise, in which case they were checked every one to two days (with no clozapine dose change) until normalized. An echocardiogram was completed at the one-month mark.

By day 4 of the trial, the CRP peaked at 48.8 mg/L with no associated clinical symptoms; and then subsequently gradually decreased remaining under 10 mg/L from day 21 onwards. An echocardiogram was completed on day 10 (6 days post-CRP spike) which demonstrated a decrease in LVEF to 63% and the trivial pericardial effusion remained the same. On day 14, the LVEF improved to 67% with mild reduced septal motion. On day 18 the echocardiogram showed a spontaneously improved LVEF fraction of 73% and an exceedingly small anterior pericardial effusion. At that time, cardiology verbalized that given the improvements no further echocardiograms were required unless CRP spiked again. At no point during the trial did troponin I increase. The total length of the trial was a little over three months, with the clozapine dose reaching 300 mg daily and a dramatic clinical improvement in both positive and negative symptoms of schizophrenia. Table 3 includes the first 21 days of this trial where most major changes were experienced. One year later the patient continues clozapine with no evidence of cardiac compromise and positive clinical outcomes.

Discussion

With regards to the case presented, in the first clozapine trial, the up-titration of clozapine was 25 mg to 50 mg every one to two days, reaching 300 mg daily in 18 days; and the dose was not split twice daily. There was no scheduled

monitoring of CRP and troponin-I throughout the titration process. In retrospect, checking CRP and troponin-I may have better guided decision-making regarding up-titration of clozapine dose thereby reducing the risk of CIM. Specifically, when the initial rise in troponin-I began, holding the dose until troponin-I normalized may have allowed the trial to continue. Furthermore, a slower titration may have been beneficial given the patient's medical comorbidities. This first trial presents a probable case of CIM. A consideration of the severity of myocarditis was lacking, which could have better informed the rechallenge.

The second trial of clozapine was deemed an inadequate rechallenge upon review of the trial details. The CRP increased to 47.7 mg/L by day 6 at clozapine 25 mg twice daily and the hospital cardiologist recommended discontinuation out of caution given the history of CIM. A barrier to this trial continuing may have been lack of experience with clozapine and clozapine rechallenge amongst hospital cardiology and the psychiatric team. There was a lack of transparent agreement on thresholds for discontinuation prior to initiation of treatment. In hindsight, given the pathophysiology discussed previously, it would be expected to see an elevation in CRP with clozapine re-exposure, as was observed during this second trial. Having predetermined thresholds for how to manage dosing in the face of a rising CRP is valuable to consider.

In the third trial all efforts to mitigate risk of myocarditis were implemented including discontinuation of medications that can elevate risk, such as divalproex sodium (53). The up-titration of clozapine was slow, with a weekly 25 mg increase divided as two separate 12.5 mg increases, frequent monitoring of CRP and troponin-I, and monthly echocardiograms. The trial was considered successful as the patient's symptoms stabilized at clozapine 300 mg daily.

For this rechallenge it was most helpful to consult a cardiologist with more expertise in clozapine rechallenges, specifically the cardiologist that worked with CSAN. It was also helpful to have pre-determined protocols informed by existing literature for monitoring and titration thresholds for the team to consider. Throughout the trial, there was ongoing discussion and collaboration between psychiatry, pharmacy, cardiology, the patient, and the substitute decision maker to ensure consistency in approach and mitigation of risks.

The protocol set forth in Figure 1 is more rigorous than what has been previously described in the literature; however, this protocol is not validated. A review conducted by Knoph and colleagues suggested monitoring CRP and troponin twice weekly, slower re-titration of clozapine than the generally recommended increment of 25 mg per day and monitoring of echocardiography (35). The protocol we propose in Figure 1 based its thresholds for discontinuation on the Australian monitoring protocol previously described which focuses on monitoring during the first four weeks of treatment including CRP and Troponin I/T and echocardiography (26). In this monitoring protocol, clozapine is discontinued only when CRP is greater than 100 mg/L or when troponin-I or -T is two times the upper limit of the reference range. The protocol we present in this case report suggest monitoring CRP and troponin-I/T more frequently than once weekly, particularly after any dosage changes until the patient is stabilized, which is beyond the three-to-four-week monitoring period described in the literature (41,42,43). For this patient, the up-titration took a little over three months where monitoring of CRP and troponin I/T continued. Investigating both CRP and troponin-I/T together remains critical as it provides for more sensitive detection of myocarditis in symptomatic patients. In an analysis of 10 fatal cases of CIM, a CK greater than 1000 U/L was associated with death (p=0.0004) (55). Given this data, including CK monitoring as part of a monitoring protocol may be of additive value and consideration can be done in consult with cardiology.

Recommendations in the literature have been inconsistent regarding monitoring other indices outside of CRP and Troponin-I/T during clozapine rechallenge, thus routine monitoring of indices such as ESR, BNP or eosinophils (37) are not included in this protocol. Our protocol agrees with the continuation of clozapine in the presence of mild physical illness as described by Ronaldson and colleagues (26). Daily measurement of vitals including temperature, heart rate and blood pressure helps to identify any clinical symptoms of concern (37), and while they are not included in the proposed protocol, they were part of ongoing vital assessment for the patient during the inpatient admission. The protocol highlights measures outside of routine assessment.

While the proposed protocol reflects a successful rechallenge of clozapine following CIM, there are limitations. Identifying pathognomonic symptoms and laboratory investigations needed to confirm cases of CIM is challenging given the paucity of documented case reports and lack of guidance around managing CIM, especially in youth (33). Our protocol is guided by these few reports and specific to the patient in question. At this point given the heterogeneity of presentation of CIM, and without further published experiences, clozapine rechallenge protocols remain case specific. Furthermore, the decision to move forward with a clozapine rechallenge should be weighed against potential risks to the individual patient.

A further limitation of this work included a lack of incorporating patient and family goals in terms of quality of life. Outcome measurements along with self-report would allow for more valid determination of effectiveness of the intervention for the patient and family.

We report this case to raise awareness of CIM, emphasizing that developed protocols to mitigate risks can inform a decision towards clozapine rechallenge. Youth with TRS are vulnerable to poor outcomes without the option of clozapine. Approved protocols can assist in mitigating risks and optimizing options for rechallenge should risk occur. Future research directions should focus on the evaluation of such protocols. Validated protocols will enhance physician comfort in prescribing this potentially lifesaving intervention for young patients.

Conclusion

To increase prescriber and team comfort with clozapine-use and rechallenge, protocols are not only useful but essential. Without this guidance, treatment teams might avoid trials or a rechallenge of clozapine. Young patients with TRS may then suffer from psychiatric morbidity and mortality that could have been otherwise successfully treated with clozapine. Previously published literature has outlined how a clozapine rechallenge may be successful post-CIM. This review and case report builds upon the existing literature, providing a protocol developed from a successful experience with the intention of increasing clinician confidence in prescribing clozapine for adolescents with TRS and monitoring/mitigating the risk of CIM.

Conflict of Interest

The authors of this manuscript have no conflicts of interest to disclose.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. Vol. 5th ed. 2013.
2. Özaslan A, Kaya B. Clozapine-induced myocarditis : a case report. Klin Psikofarmakol Bul. 2019;29:135–136.
3. Kennedy JL, Altar CA, Taylor DL, Degtiar I, Hornberger JC. The social and economic burden of treatment-resistant schizophrenia: A systematic literature review. Int Clin Psychopharmacol. 2014;29(2):63–76.
4. Wimberley T, Støvring H, Sørensen HJ, Horsdal HT, MacCabe JH, Gasse C. Predictors of treatment resistance in patients with schizophrenia: A population-based cohort study. The Lancet Psychiatry. 2016;3(4):358–366.
5. Meyer JM, and Stahl SM. 2020. Stahl's Handbooks: The Clozapine Handbook. Cambridge University Press.
6. Meltzer Y, Thompson P. Reduction of Suicidality During of Neuroleptic-Resistant Impact on Risk-Benefit Clozapine Treatment Schizophrenia : Assessment. Psychiatry Interpers Biol Process. 1995;(February):183–190.
7. Schneider C, Corrigall R, Hayes D, Kyriakopoulos M, Frangou S. Systematic review of the efficacy and tolerability of Clozapine in the treatment of youth with early onset schizophrenia. Eur Psychiatry. 2014;29(1ecg):1–10.
8. Sikich L, Frazier JA, McClellan J, Findling RL, Vitiello B, Ritz L, et al. Double-blind comparison of first- and second-generation antipsychotics in early-onset schizophrenia and schizoaffective disorder: Findings from the treatment of early-onset schizophrenia spectrum disorders (TEOSS) study. Am J Psychiatry. 2008;165(11):1420–1431.
9. Abidi S, Mian I, Garcia-Ortega I, et al. Canadian guidelines for the pharmacological treatment of schizophrenia spectrum and other psychotic disorders in children and youth. Can J Psychiatry. 2017;62(9):635–647.
10. Howes OD, Vergunst F, Gee S, McGuire P, Kapur S, Taylor D. Adherence to treatment guidelines in clinical practice: Study of antipsychotic treatment prior to clozapine initiation. Br J Psychiatry. 2012;201(6):481–485.
11. Cirulli G. Clozapine prescribing in adolescent psychiatry: survey of prescribing practice in in-patient units. Psychiatric Bulletin. 2005;29(10):377-380.
12. CLOZARIL® Product Monograph. HLS Therapeutics Inc. April 17, 2023: Available from http://www.hlstherapeutics.com/wp-content/uploads/monograph_pdf/HLS-Clozaril-PM-E.pdf.
13. Mijovic A, MacCabe JH. Clozapine-induced agranulocytosis. Ann Hematol. 2020 Nov;99(11):2477-2482. doi: 10.1007/s00277-020-04215-y. Epub 2020 Aug 20. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7536144/
14. 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 Safe. 2007;30(1):47-57.
15. Kilian JG, Kerr K, Lawrence C, Celermajer DS. Myocarditis and cardiomyopathy associated with clozapine. Lancet. 1999;354(9193):1841–1845.
16. Ronaldson KJ, Fitzgerald PB, McNeil JJ. Clozapine-induced myocarditis, a widely overlooked adverse reaction. Acta Psychiatrica Scandinavica. 2015;132(4):231-240.
17. Merrill DB, Ahmari SE, Bradford JME, Lieberman JA. Myocarditis during clozapine treatment. Am J Psychiatry. 2006;163(2):204–208.
18. Citrome L, McEvoy JP, Saklad SR. Guide to the Management of Clozapine-Related Tolerability and Safety Concerns. Clin Schizophr Relat Psychoses. 2016 Fall;10(3):163-177.
19. Higgins JM, San C, Lagnado G et al. Incidence and management of clozapine-induced myocarditis in a large tertiary hospital. The Canadian Journal of Psychiatry. 2019;64(8):561-567.
20. Datta T, Solomon AJ. Clozapine-induced myocarditis. Oxf Med Case Reports. 2018;11–4.
21. Devarajan S, Kutcher S, Dursun S. Clozapine and sudden death. Lancet. 2000;355(9206):2000.
22. Ronaldson KJ, Taylor AJ, Fitzgerald PB, Topliss DJ, Elsik M, McNeil JJ. Diagnostic characteristics of clozapine-induced myocarditis identified by an analysis of 38 cases and 47 controls. J Clin Psychiatry. 2010;71:976–981.

23. Pollmächer T, Hinze-Selch D, Mullington J. Effects of clozapine on plasma cytokine and soluble cytokine receptor levels. J Clin Psychopharmacol. 1996;16(5):403–409.
24. Rabkin SW, Tang JKK. Clozapine-induced Myocarditis: Pathophysiologic Mechanisms and Implications for Therapeutic Approaches. Curr Mol Pharmacol. 2023;16(1):60-70.
25. Yuen JWY, Kim DD, Procyshyn RM, White RF, Honer WG, Barr AM. Clozapine-Induced Cardiovascular Side Effects and Autonomic Dysfunction: A Systematic Review. Front Neurosci. 2018;12:203. doi: 10.3389/fnins.2018.00203.
26. Ronaldson KJ, Fitzgerald PB, Taylor AJ, et al. A new monitoring protocol for clozapine-induced myocarditis based on an analysis of 75 cases and 94 controls. Aust NZ J of Psychiatry. 2011;45(6):458-465.
27. Shivakumar G, Thomas N, Sollychin M, Takács A, Kolamunna S, Melgar P, et al. Protocol for Clozapine Rechallenge in a Case of Clozapine-Induced Myocarditis. Can J Psychiatry. 2020;65(7):448–453.
28. Phansalkar S, Osser DN. Optimizing Clozapine Treatment: Part II. Psychopharm Rev. 2009;44(2):9–16.
29. Mudra S, Luedecke D, Grafmann M, Michael Schulte-Markwort. Myocarditis during treatment with clozapine in 2 adolescent cases. 2018;38(6):639–640.
30. Aboueid L, Toteja N. Clozapine-induced myocarditis: A case report of an adolescent boy with intellectual disability. Case Rep Psychiatry. 2015;2015:1–4.
31. Chow V, Feijo I, Trieu J, Starling J, Kritharides L. Successful rechallenge of clozapine therapy following previous clozapine-induced myocarditis confirmed on cardiac MRI. J Child Adolesc Psychopharmacol. 2014;24(2):99–101.
32. Kakar P, Millar-Craig M, Kamaruddin H, Burn S, Loganathan S. Clozapine induced myocarditis: A rare but fatal complication. Int J Cardiol. 2006;112(2):6–7.
33. De Las Cuevas C, Arrojo-Romero M, Ruan C-J, Schoretsanitis G, J. Sanz E, and de Leon J. Clozapine-induced myocarditis in children and adolescents: a pharmacovigilance study using VigiBase and a systematic literature review. Expert Opinion on Drug Metabolism & Toxicology. 2022;18(11):715-727.
34. Mylan Pharmaceuticals M. Clozapine [Product monograph]. Toxicology. 2020;1–55.
35. Knoph KN, Morgan RJ, Palmer BA, Schak KM, Owen AC, Leloux MR, et al. Clozapine-induced cardiomyopathy and myocarditis monitoring: A systematic review. Schizophr Res. 2018;199:17–
36. Abidi S, Bhaskara S. Adverse Effects and the Clinician's Dilemma. Can J Psychiatry. 2003;48(11).
37. Berk M, Fitzsimons J, Lambert T, Pantelis C, Kulkarni J, Castle D, et al. Monitoring the safe use of clozapine: A consensus view from Victoria, Australia. CNS Drugs. 2007;21:117-127. [cited 2020 Nov 11]
38. Manu P, Sarpal D, Muir O, Kane JM, Correll CU. When can patients with potentially life-threatening adverse effects be rechallenged with clozapine? A systematic review of the published literature. Schizophr Res. 2012;134(2–3):180–186.
39. Layland JJ, Liew D, Prior DL. Clozapine-induced cardiotoxicity: a clinical update. Med J Aust. 2009 Feb 16 [cited 2020 Nov 11];190(4):190–192.
40. Adetiloye AO, et al. Clozapine-Induced Myocarditis in a Young Man with Refractory Schizophrenia: Case Report of a Rare Adverse Event and Review of the Literature. Am J Case Rep. 2022 Jul 6;23:e936306. Doi: 10.12659/AJCR.936306.
41. Curto M, Girardi N, Lionetto L, Ciavarella GM, Ferracuti S, Baldessarini RJ. Systematic Review of Clozapine Cardiotoxicity. Curr Psychiatry Rep. 2016;18(7).
42. Rostagno C, Domenichetti S, Pastorelli F, Gensini GF. Usefulness of NT-Pro-BNP and echocardiography in the diagnosis of subclinical clozapine-related cardiotoxicity. J Clin Psychopharmacol. 2011;31(6):712–716.
43. Wehmeier PM, Schüler-Springorum M, Heiser P, Remschmidt H. Chart review for potential features of myocarditis, pericarditis, and cardiomyopathy in children and adolescents treated with clozapine. J Child Adolesc Psychopharmacol. 2004;14(2):267–271.
44. Ferreira VM, et al. Cardiovascular Magnetic Resonance in Nonischemic Myocardial Inflammation: Expert Recommendations. J Am Coll Cardiol. 2018;72(24):3158.
45. Mahajan V and Jarolim P. How to interpret elevated cardiac troponin levels. Circulation. 2011;124:2350-2354.
46. Marder SR, Essock SM, Miller AL, Buchanan RW, Casey DE, Davis JM, et al. Physical health monitoring of patients with schizophrenia. American Journal of Psychiatry. 2004; 161:1334–49.
47. Nielsen J, Correll CU, Manu P, Kane JM. Termination of Clozapine Treatment Due to Medical Reasons. J Clin Psychiatry [Internet]. 2013 Jun 15 [cited 2020 Nov 11];74(06):603–13. Available from: http://article.psychiatrist.com/?ContentType=START&ID=10008316.
48. Adeyemo S, Jegede O, Rabel P, Ahmed S, Tumenta T, Oladeji O, et al. Persistent Tachycardia in a Patient on Clozapine. Case Rep Psychiatry. Jul 6;2020:6352175. doi:10.1155/2020/6352175.
49. Bellissima BL, Tingle MD, Cicović A, Alawami M, Kenedi C. A systematic review of clozapine-induced myocarditis. Int J Cardiol. 2018;259:122–129.
50. Hurwitz B, Issa O. Management and Treatment of Myocarditis in Athletes. Curr Treat Options Cardiovasc Med. 2020;22(12):65.
51. Reinders J, Parsonage W, Lange D, Potter JM, Plever S. Clozapine-related myocarditis and cardiomyopathy in an Australian metropolitan psychiatric service. Aust N Z J Psychiatry. 2004;38(11–12):915–922.
52. Ronaldson KJ, Fitzgerald PB, Taylor AJ, McNeil JJ. Observations from 8 cases of clozapine rechallenge after development of myocarditis. J Clin Psychiatry. 2012;73(2):252–254.
53. Ronaldson KJ, Fitzgerald PB, Taylor AJ, Topliss DJ, Wolfe R, McNeil JJ. Rapid clozapine dose titration and concomitant sodium valproate increase the risk of myocarditis with clozapine: A case-control study. Schizophr Res. 2012;141(2–3):173–178.
54. Ronaldson KJ, Fitzgerald PB, Taylor AJ, Topliss DJ, McNeil JJ. Clinical course and analysis of ten fatal cases of clozapine-induced myocarditis and comparison with 66 surviving cases. Schizophr Res. 2011 May;128(1-3):161-5. doi: 10.1016/j.schres.2011.01.017.
55. Perrone MA, et al. Cardiac troponins: are there any differences between T and I? J Cardiovasc Med (Hagerstown). 2021;22(11):797-805.