Don’t Go Breaking My Heart: Re-Initiation Following Clozapine-Induced Myocarditis

Learning Objectives

1. Review the definition, pathophysiology, and treatments of schizophrenia, as well as how it can lead to treatment-resistant schizophrenia (TRS)
2. Describe the role of clozapine in the management of TRS
3. Recognize the pathophysiology and common clinical markers of clozapine-induced myocarditis
4. Formulate an opinion regarding re-initiation of clozapine therapy following clozapine-induced myocarditis
Introduction to Schizophrenia

I. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) definition of schizophrenia
   a. Thought disorder involving a complex mix of symptoms
   b. Diagnostic criteria
      i. Two (or more) of the following, each present for a significant portion of time during a one-month period (or less if successfully treated); with one of the symptoms including delusions, hallucinations, or disorganized speech
         1. Delusions
         2. Hallucinations
         3. Disorganized speech
         4. Grossly disorganized or catatonic behavior
         5. Negative symptoms

Table 1: Categories of Schizophrenia-Associated Symptoms

<table>
<thead>
<tr>
<th>Positive</th>
<th>Negative</th>
<th>Cognitive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hallucinations</td>
<td>Blunted or flat affect</td>
<td>Poor executive function</td>
</tr>
<tr>
<td>Delusions</td>
<td>Social withdrawal (passive-apathetic)</td>
<td>Impaired attention</td>
</tr>
<tr>
<td>Paranoia or suspiciousness</td>
<td>Lack of personal hygiene</td>
<td>Impaired memory</td>
</tr>
<tr>
<td>Conceptual disorganization</td>
<td>Prolonged time to respond</td>
<td></td>
</tr>
<tr>
<td>Hostility</td>
<td>Poor rapport</td>
<td></td>
</tr>
<tr>
<td>Grandiosity</td>
<td>Poor abstract thinking</td>
<td></td>
</tr>
<tr>
<td>Excitement</td>
<td>Poverty of speech</td>
<td></td>
</tr>
<tr>
<td>Loose associations</td>
<td>Emotional withdrawal</td>
<td></td>
</tr>
<tr>
<td>Thought broadcasting</td>
<td>Alogia</td>
<td></td>
</tr>
<tr>
<td>Thought insertion</td>
<td>Ambivalence; prevents decision making</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Autism (internally directed)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amotivation (avolition)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anhedonia</td>
<td></td>
</tr>
</tbody>
</table>

 ii. Level of functioning is markedly below the level achieved prior to the onset of symptoms
 iii. Continuous signs of the disturbance persist for at least six months, including one month of active symptoms
 iv. Minimal or lack of mood symptoms
 v. The disturbances are not attributable to the physiological effects of a substance or another medical condition

II. Epidemiology
   a. Incidence
      i. Affects 21 million people worldwide
      ii. Occurs in 1% of the general population
      iii. Most common age of onset:
1. Men – early to mid-20s  
2. Women – late 20s

**Figure 1. Natural Course of Illness in Schizophrenia**

b. Risk factors  
i. Genetic  
   1. Family history  
      a. Heritable component accounts for nearly 70% of schizophrenia cases  
      b. People which schizophrenia tend to have higher rates of rare genetic mutations  
         i. Hundreds of different genes may be disrupted  
         ii. Mutations may impact brain development  
   2. Older age of the father  
ii. Environmental  
   1. Early life  
      a. Obstetric complications, including infections  
      b. Season of birth  
      c. Maternal malnutrition or stress  
   2. Childhood  
      a. Child abuse  
      b. Head injury  
   3. Late life  
      a. Drug abuse  
      b. Urbanization  
      c. Immigration  
      d. Social adversity  
iii. Autoimmune  

III. Pathophysiology[7-12]  
   a. Neurotransmitter involvement (**Figure 2**)  
      i. The Dopamine Hypothesis  
         1. Schizophrenia is caused by dysregulation of dopamine  
            a. Increased dopamine levels
i. Occurs in the mesolimbic tract
ii. Excess dopamine is hypothesized to cause the positive symptoms of schizophrenia

b. Decreased dopamine levels
i. Occurs in the nigrostriatal and mesocortical pathways
ii. Contributes to extrapyramidal symptoms (EPS), negative symptoms, and cognitive defects

2. Flaws in this theory
a. Blockade of dopaminergic neurotransmission does not fully alleviate symptoms
b. Role of dopamine is very complex

ii. Glutamate
1. Major central nervous system (CNS) excitatory neurotransmitter
2. Hypofunction of the NMDA glutamate receptor has been hypothesized to contribute to cognitive symptoms of schizophrenia

iii. Gamma-aminobutyric acid (GABA)
1. Major CNS inhibitory neurotransmitter
2. GABAergic interneurons are important for regulation of prefrontal cortical function, through their modulation of glutamatergic pyramidal cells
3. Interneuron dysfunction in schizophrenia
   a. Decrease in their overall number
   b. Diminished expression of the enzymes that synthesize GABA
   c. Diminished expression of neuropeptides that are released during neurotransmission

Table 2. Summary of Neurotransmitter Changes in Schizophrenia

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Brain pathway</th>
<th>Effect in patients without schizophrenia</th>
<th>Change</th>
<th>Effect in patients with schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>Mesolimbic tract (ventral tegmental area)</td>
<td>Motivation</td>
<td>↑</td>
<td>Positive symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pleasure</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reward</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
|                  | Substantia nigra and mesocortical areas | Substantia nigra – motor movements | ↓ | Extrapyr
|                  |              | Mesocortical tract – cognition, executive function, emotion, affect | | amidal, negative, and cognitive symptoms |
| Glutamate        | Prefrontal cortex | Decision making capabilities | | Cognitive symptoms; may cause positive symptoms via interaction with dopamine neurons |
|                  |               | NMDA receptor hypofunction | | |
| GABA             | Prefrontal cortex | Decision making capabilities | Alterations in GABA interneurons | Positive symptoms via interaction with glutamate and dopamine |
b. Multiple brain regions dysfunction
   i. Enlarged ventricles
   ii. Less gray matter
   iii. Decreased number of neurons in various brain regions

IV. Treatment
   a. Antipsychotics are the mainstay of treatment for schizophrenia (Appendix A)
   b. Selection based on efficacy, side effects, and available formulations
Treatment-Resistant Schizophrenia

I. Based on meta-analyses, 10% to 30% of patients with schizophrenia do not respond adequately to treatment

II. Definition
   a. Various psychiatric guidelines and algorithms have developed differing definitions of treatment-resistant schizophrenia (TRS)
   b. Overall, no consensus exists for how to appropriately define TRS, but commonalities between guidelines suggest the following:
      i. A history of failure of at least 2 antipsychotic trials (one of them with an atypical antipsychotic) with adequate doses, with 4 to 6 weeks’ duration, and without satisfactory response, particularly in terms of persistence of psychotic symptoms
      ii. High levels of psychopathology, particularly the presence of psychotic symptoms that have an impact on the patient’s conduct and functionality
      iii. Presence of suicidality, violence, and substance abuse

III. Evaluation and management
   a. “Pseudoresistance”
      i. Re-evaluate primary diagnosis
      ii. Co-occurring conditions
      iii. Side effects
      iv. Nonadherence
   b. Non-pharmacologic modalities
      i. Cognitive-behavioral therapy for persistent delusions or hallucinations
      ii. Family psychoeducational interventions for those with significant family involvement
      iii. Social skills training to improve independent skills for daily functioning
      iv. Assertive community treatment for those with repetitive hospitalizations or homelessness
      v. Crisis intervention for patients whose symptoms are exacerbated by emotional crises or other psychosocial stressors
   c. Optimizing current therapies

IV. Treatments
   a. Antipsychotic augmentation
      i. Electroconvulsive therapy (ECT)
      ii. Transcranial magnetic stimulation
      iii. Antidepressants
      iv. N-acetylcysteine
      v. Topiramate
   b. Clozapine
      i. Background
         1. Initially developed in the 1958 and withdrawn from the market due to fatal agranulocytosis
         2. Re-introduced in 1990 as a third-line agent for patients with TRS
         3. Considered the “gold standard” in TRS
4. Tricyclic dibenzodiazepine derivative

![Clozapine chemical structure](image)

**Figure 3.** Clozapine chemical structure\(^{37}\)

5. Receptor activity
   a. Broad-spectrum antagonistic properties at the following receptors:
      i. Dopamine
         1. Antagonist at the D\(_1\), D\(_2\), D\(_3\), and D\(_5\) receptors
         2. High affinity for the D\(_4\) receptor
         3. Relatively weak D\(_2\)-receptor affinity
      ii. Serotonin – 5HT\(_2\), 5HT\(_3\), 5HT\(_6\), and 5HT\(_7\) subtypes
      iii. Norepinephrine
      iv. Histamine
      v. Acetylcholine – muscarinic A1 and A2 receptors
   b. Significant effects on GABAergic and glutamatergic systems

![Clozapine receptor activity](image)

**Figure 4.** Clozapine receptor activity\(^{12}\)

ii. Efficacy
   1. In 1988, clozapine was initially compared to chlorpromazine in a double-blind comparison lasting 6 weeks
      a. Up to 900 mg/day of clozapine vs up to 1800 mg/day of chlorpromazine
      b. 30% of clozapine-treated patients were categorized as responders compared to 4% of chlorpromazine-treated patients
c. Clozapine produced significantly greater improvement in the BPRS, CGI, and NOSIE scales; with improvements in both positive and negative symptoms

2. More recently, in 2013, clozapine was shown to be more effective in TRS than olanzapine
   a. Systematic review comparing clozapine with olanzapine in patients with TRS
      i. Seven RCTs were included in the analysis
      ii. Over 600 patients involved
   b. Clozapine was superior to olanzapine for PANSS positive and negative subscales

3. Along with symptom improvement, clozapine has been associated with decreased rates of mortality, suicide, and aggression
   iii. Prescribing
      1. Supplied as a 25 mg or 100 mg tablet
      2. Dosing
         a. Initial:
            i. 12.5 mg orally 1 to 2 times daily and continue with daily increases in increments of 25 to 50 mg/day, as tolerated
            ii. Target dose of 300 to 450 mg/day (in 2 to 3 divided doses) by the end of 2 weeks
         b. Maintenance:
            i. Dosage adjustments should be made no more than 1 to 2 times per week in increments not to exceed 100 mg
            ii. Max daily maintenance dose of 900 mg

3. REMS Program
   a. Established due to the severe neutropenia associated with clozapine (ANC < 500/µL)
   b. Required by the FDA for clozapine to ensure that the benefits of the drug outweigh the risk of severe neutropenia
   c. Required of clozapine prescribers, dispensing pharmacies, and patients
   d. Available at: https://www.clozapinerems.com

iv. Monitoring
   1. Boxed warnings
      a. Agranulocytosis
      b. Seizures
      c. Myocarditis and cardiomyopathy
      d. Other adverse effects
         i. Orthostatic hypotension
         ii. Bradycardia
         iii. Syncope
         iv. Cardiac arrest
      e. Increased mortality in elderly patients with dementia-related psychosis
2. Additional adverse effects
   a. Weight gain
   b. Sedation
   c. Hypersalivation
   d. Rapid heart rate
   e. Fever

Clozapine-Induced Myocarditis

I. Myocarditis
   a. Defined as an inflammatory disease of the myocardium
   b. Clinical presentation
      i. Variable presentation
      ii. May include the following:
         1. Fatigue or exercise intolerance
         2. Chest pain
         3. Heart failure
         4. Cardiogenic shock
         5. Arrhythmias
         6. Respiratory distress/tachypnea
   c. Etiology
      i. Infections – viral, bacterial, spirochetal, mycotic, protozoal, helminthic, rickettsial
      ii. Cardiotoxins
      iii. Hypersensitivity reaction
      iv. Systemic disorders
   d. Diagnostic and laboratory changes (Table 3)

Table 3. Diagnostic and Laboratory Abnormalities in Myocarditis

<table>
<thead>
<tr>
<th>Diagnostic or Laboratory Test</th>
<th>Observations in Myocarditis</th>
</tr>
</thead>
<tbody>
<tr>
<td>EKG</td>
<td>May be normal</td>
</tr>
<tr>
<td></td>
<td>ST changes similar to an acute MI</td>
</tr>
<tr>
<td></td>
<td>Atrial or ventricular ectopic beats</td>
</tr>
<tr>
<td></td>
<td>Ventricular arrhythmias</td>
</tr>
<tr>
<td>Cardiac biomarkers</td>
<td>Serum cardiac troponins</td>
</tr>
<tr>
<td></td>
<td>BNP or NT-proBNP</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td>Enlarged heart</td>
</tr>
<tr>
<td></td>
<td>May or may not involve pleural effusions</td>
</tr>
<tr>
<td>Cardiovascular magnetic resonance</td>
<td>Edema</td>
</tr>
<tr>
<td></td>
<td>Myocyte necrosis and scar tissue</td>
</tr>
<tr>
<td></td>
<td>Changes in ventricular size and geometry</td>
</tr>
<tr>
<td></td>
<td>Pericardial effusion</td>
</tr>
</tbody>
</table>

e. Diagnosis
   i. Endomyocardial biopsy (EMB) is required for a definitive diagnosis of myocarditis
ii. Diagnosis is supported with histology, immunohistochemical staining, and detection of viral genomes by polymerase chain reaction (PCR)

II. Epidemiology\(^{24, 40-47}\)
   a. Incidence
      i. Approximately 1.2% of patients on clozapine have been reported to develop myocarditis
         1. Incidence varies in the literature
         2. Could be under-reported due to nonspecific initial symptoms
      ii. Most cases occur early in treatment
         1. More than 85% of cases occur in the first 2 months
         2. Up to 75% of cases are reported within 3-4 weeks of starting clozapine therapy
         3. Average time to onset approximates 15 days (± 7 days)
   b. Prognosis
      i. Mortality rate has been reported to approach 50%
      ii. Death from clozapine-induced myocarditis may be independent of coronary artery disease (CAD), except in cases where CAD is severe
   c. Risk factors
      i. Thought to be related to rapid dose titration
      ii. Medication interactions
         1. Antibacterials – sulfonamides and beta-lactams
         2. Thyroxine – levothyroxine sodium
         3. Ranitidine
         4. Cyclophosphamide
         5. Lithium
         6. Phenothiazines
         7. Certain antidepressants – sertraline and TCAs (amitriptyline, imipramine, desipramine)

III. Pathophysiology\(^{35, 48-51}\)
   a. Inflammation
      i. Clozapine increases the release of inflammatory cytokines
      ii. Primarily focused around elevations in TNF-α
   b. Allergy
      i. IgE-mediated hypersensitivity reaction
      ii. Hypereosinophilic syndrome
         1. Eosinophils block cholinergic M2 receptors
            a. Leads directly to cardiotoxicity
            b. Infiltrates in myocardial and perivascular areas
         2. Evidence of peripheral eosinophilia on autopsy
         3. Dose-independent
   c. Hypothesized mechanisms
      i. Elevation in norepinephrine
         1. Elevated plasma norepinephrine levels in clozapine-treated patients compared to those treated with other antipsychotics
         2. Increased noradrenergic tone may lead to myocarditis in select patients
ii. Clozapine accumulation
   1. Possibly due to cytochrome P450 1A2/1A3 deficiency
   2. Decreased metabolism leads to toxicity

IV. Clinical Presentation\textsuperscript{24}
   a. Presentation may be highly variable (Table 4)
   b. Initial symptoms may mimic common side effects seen when initiating clozapine titration, including mild fever, tachycardia, and fatigue
   c. Prodromal syndrome may present preceding the onset of myocarditis by several days to a few weeks
      i. Fever
      ii. Rash
      iii. Myalgias and arthralgias
      iv. Fatigue
      v. Respiratory or gastrointestinal symptoms
   d. Myocarditis may also present without accompanying symptoms

Table 4. Signs and Symptoms that may be Associated with Clozapine-Related Myocarditis\textsuperscript{24}

<table>
<thead>
<tr>
<th>More Common Signs and Symptoms</th>
<th>Less Common Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flu-like symptoms, such as fever, myalgias, dizziness or faintness, arthralgias, nasal congestion, sensations of “scratchy throat”</td>
<td>Dysuria</td>
</tr>
<tr>
<td>Fatigue or decreased exercise tolerance</td>
<td>Left-shoulder pain on inspiration</td>
</tr>
<tr>
<td>Respiratory symptoms such as dyspnea, cough, subjective sensations of chest discomfort, orthopnea</td>
<td>Rash</td>
</tr>
<tr>
<td>Cardiovascular symptoms such as persistent resting tachycardia, increased heart rate, palpitations, chest pain, syncope, arrhythmias, hypotension</td>
<td>Cyanosis</td>
</tr>
<tr>
<td>Gastrointestinal symptoms such as diarrhea, vomiting, abdominal pain</td>
<td>Seizures</td>
</tr>
<tr>
<td>Acute mental status change and delirium</td>
<td>Dysarthria</td>
</tr>
</tbody>
</table>

V. Monitoring and diagnosis\textsuperscript{24, 38, 49}
   a. Monitoring
      i. No established guidelines surrounding monitoring of clozapine-induced myocarditis
      ii. According to the package insert, patients should be monitored for other signs of myocarditis if they develop tachycardia within the first month of starting clozapine therapy
      iii. Monitoring protocols have been proposed for patients starting on clozapine (Appendix B)
   b. Diagnosis
      i. No consensus of diagnostic criteria
      ii. May consider myocarditis in patients who present with unexplained fatigue, dyspnea, tachypnea, fever, chest pain, palpitations, other signs of symptoms of heart failure, or electrocardiographic abnormalities (Table 5)
      iii. Hypereosinophilia may be present in clozapine-induced myocarditis, but is not a predictive marker of the condition
Table 5. Laboratory and Instrumental Data that may Assist in the Diagnosis of Clozapine-Related Myocarditis

<table>
<thead>
<tr>
<th>Lab Techniques</th>
<th>Diagnosis of Clozapine-Related Myocarditis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood count</td>
<td>Hypereosinophilia, leukocytosis, neutrophilia</td>
</tr>
<tr>
<td>Cardiac biomarkers</td>
<td>↑ troponin I or T</td>
</tr>
<tr>
<td></td>
<td>↑ CK or CK-MB levels</td>
</tr>
<tr>
<td></td>
<td>↑ BNP levels</td>
</tr>
<tr>
<td>Inflammatory biomarkers</td>
<td>↑ CRP levels</td>
</tr>
<tr>
<td></td>
<td>↑ ESR</td>
</tr>
<tr>
<td>Transthoracic Echocardiography</td>
<td>Left ventricular systolic dysfunction</td>
</tr>
<tr>
<td></td>
<td>Global systolic dysfunction</td>
</tr>
<tr>
<td></td>
<td>Right ventricular systolic dysfunction</td>
</tr>
<tr>
<td></td>
<td>Reduced ejection fraction</td>
</tr>
<tr>
<td></td>
<td>Abnormal diastolic filling patterns</td>
</tr>
<tr>
<td></td>
<td>Pericardial effusion</td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td>Sinus tachycardia</td>
</tr>
<tr>
<td></td>
<td>Nonspecific T-wave abnormalities</td>
</tr>
<tr>
<td></td>
<td>ST-segment elevation or depression</td>
</tr>
<tr>
<td></td>
<td>PR depression</td>
</tr>
<tr>
<td></td>
<td>Pathologic Q waves</td>
</tr>
<tr>
<td></td>
<td>Supraventricular or ventricular arrhythmias</td>
</tr>
<tr>
<td>Chest radiograph changes</td>
<td>Cardiomegaly; pericardial effusion; pulmonary venous congestion</td>
</tr>
<tr>
<td>Cardiovascular magnetic resonance</td>
<td>Subepicardial enhancement; myocardial inflammation and edema; pericardial effusion</td>
</tr>
<tr>
<td>Myocardial biopsy</td>
<td>Extensive inflammatory infiltrates, mainly represented by eosinophils and lymphocytes</td>
</tr>
</tbody>
</table>

VI. Treatment

a. Discontinue clozapine treatment immediately
   i. Cardiac abnormalities may be reversible
   ii. Cardiac function may improve over time once clozapine therapy is ceased

b. Supportive care based on symptoms, including standard heart failure therapies, until clinically stable
   i. Diuretics
   ii. ACEIs or ARBs
   iii. Beta-blockers

VII. Some clinicians may choose to continue clozapine in mild cases of myocarditis

Clinical Question

Should clozapine be reinitiated in patients with TRS who have experienced clozapine-induced myocarditis?
Literature Review

Jayathilake I, Singh AK: Clozapine rechallenge after myocarditis. Australas Psychiatr 2009; 17(5):421-422.53

<table>
<thead>
<tr>
<th>Year published</th>
<th>2009</th>
</tr>
</thead>
</table>
| Patient characteristics | • 42 year old male  
• Paranoid schizophrenic  
• Poor response to antipsychotic therapy for 25 years  
• No previous history of cardiac disease  
• Risk factor of smoking |
| Clozapine dosing upon discontinuation | 175 mg daily |
| Time until onset of symptoms | 15 days |
| Myocarditis symptoms | Subjective  
• Chest pain lasting 15 minutes in duration  
• Heart palpitations  
Objective  
• HR 120 BPM  
• BP 120/90 mmHg  
• Troponin 0.06 μg/L  
• EKG showed inferolateral T wave inversions |
| Time to resolution of symptoms | 2 days |
| Time until rechallenge | Unclear, ~2 weeks |
| Monitoring parameters | Daily – physical exam  
Every other day - troponin levels, CRP, and CBC  
Weekly – EKG |
| Titration | 12.5mg initially, followed by 12.5mg dose increases every 3rd day |
| Clozapine dose following rechallenge | 50 mg daily |
| Additional comments | No eosinophilia, normal CXR noted |
| Outcome | On Day 12 of clozapine re-initiation, patient experienced chest pain with palpitations, elevated troponin (0.05 μg/L), elevated HR (112 BPM), and abnormal EKG; clozapine discontinued |


<table>
<thead>
<tr>
<th>Year published</th>
<th>2011</th>
</tr>
</thead>
</table>
| Patient characteristics | • Male in his early 30s  
• Paranoid schizophrenic; would carry weapons on his person when experiencing paranoid delusions  
• Poor response to antipsychotic therapy for 5 years  
• No previous history of cardiac disease |
| Clozapine dosing upon discontinuation | 225 mg |
| Time until onset of symptoms | 19 days |
| Myocarditis symptoms | Subjective  
• Intermittent chest pain  
Objective  
• Troponin I was 1.7 μg/L |
<p>| Time to resolution of symptoms | Unclear |
| Time until rechallenge | 25 months |</p>
<table>
<thead>
<tr>
<th>Monitoring parameters</th>
<th>Baseline EKG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Daily – nursing physical observations</td>
</tr>
<tr>
<td></td>
<td>Twice weekly – full blood examination, serum troponin, CK, CRP, EKG</td>
</tr>
<tr>
<td></td>
<td>Routine EKG on day six following initiation, and approximately every month for the first six months</td>
</tr>
<tr>
<td></td>
<td>Urgent EKG in the setting of troponin elevation or other suspicious cardiac anomalies</td>
</tr>
<tr>
<td>Titration</td>
<td>6.25 mg daily initially, with an increase of 12.5 mg every two days</td>
</tr>
<tr>
<td>Clozapine dose following rechallenge</td>
<td>400 mg</td>
</tr>
<tr>
<td>Additional comments</td>
<td>Troponin peaked again at 0.17 μg/L with mild CRP elevation of 16.2 mg/L when clozapine dose reached 137.5 mg daily on day 26 of post-rechallenge; no changes to therapy documented</td>
</tr>
<tr>
<td>Outcome</td>
<td>Patient discharged to a less restrictive setting. EKG monitoring every six months along with annual outpatient cardiology review.</td>
</tr>
</tbody>
</table>

Bray A, Reid R: Successful clozapine rechallenge after acute myocarditis. Aust N Z J Psychiatry 2011; 45(1):90.55

<table>
<thead>
<tr>
<th>Year published</th>
<th>2011</th>
</tr>
</thead>
</table>
| Patient characteristics | • 43 year old male  
• Resistant to non-clozapine antipsychotics, alone or in combination, over 20 year history of schizophrenia  
• No previous history of cardiac disease, family history, or cardiac risk factors |
| Clozapine dosing upon discontinuation | Not published |
| Time until onset of symptoms | 15 days |
| Myocarditis symptoms | Subjective  
• Fainting  
Objective  
• Troponin 0.89 μg/L  
• Sinus tachycardia noted on EKG |
| Time to resolution of symptoms | 3 days |
| Time until rechallenge | Not published |
| Monitoring parameters | Serum troponin three times weekly for the first six weeks, then weekly for four months, then monthly  
EKG at months 1, 3, 6 and 12 |
| Titration | 12.5 mg daily and increased daily |
| Clozapine dose following rechallenge | Not published |
| Additional comments | When clozapine was discontinued, patient decompensated and experienced catatonia requiring ECT three times weekly |
| Outcome | Successful rechallenge – patient able to return home 8 weeks following clozapine re-initiation, free of delusions and no longer catatonic |
Summary

<table>
<thead>
<tr>
<th>Authors</th>
<th>Monitoring</th>
<th>Slow Titration</th>
<th>Comments</th>
<th>Successful? Cardiac</th>
<th>Successful? Psych</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jayathilake and Singh (2009)</td>
<td>√</td>
<td>√</td>
<td>CBC monitored</td>
<td>X</td>
<td>X</td>
<td>Unknown EKG results</td>
</tr>
<tr>
<td>Hassan et al. (2011)</td>
<td>√</td>
<td>√</td>
<td>Approached max dose</td>
<td>√/X</td>
<td>√</td>
<td>No discussion about decision to continue therapy following cardiac abnormalities Markedly elevated troponins compared to Case #1</td>
</tr>
</tbody>
</table>

Recommendations

I. Re-initiation of clozapine may be beneficial in patients with treatment-resistant schizophrenia, in light of suspected myocarditis
   a. Depends on the severity of myocarditis
   b. Clozapine may allow for improved functioning and quality of life in patients

II. Clinicians must weigh potential risks vs. benefits for individual patients when considering whether to re-initiate clozapine

III. Monitoring
   a. Daily for the first two months, then weekly for two months, then biweekly indefinitely
      i. Blood pressure
      ii. Heart and respiratory rates
      iii. Temperature
      iv. Subjective assessment – chest pain, flu-like symptoms, palpitations
   b. Weekly for the first month, then every other week for one month, then once monthly for the first year, and as needed clinically
      i. CRP
      ii. Troponins
      iii. EKG
      iv. CBC

IV. Re-initiation should occur under strict medical supervision and close follow-up

Future Considerations

I. Greater published literature of rechallenging attempts, irrespective of outcome, to allow for more informed risk-benefit analyses

II. Screening protocol for patients initiated on clozapine and those deemed to be at risk for developing clozapine-induced myocarditis

III. Defined monitoring parameters for clozapine-induced myocarditis need to be established for consistency among clinicians
References

37. Clozapine Risk Evaluation and Mitigation Strategy (REMS) Program. Available at
Appendix A. TMAP Antipsychotic Algorithm

Stage 1: First-Episode Schizophrenia

Trial of a single SGA (aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone)

Partial or nonresponse

Stage 2

Trial of a single SGA or FGA (not SGA tried in Stage 1)

Partial or nonresponse

Stage 3

Clozapine

Partial or nonresponse

Stage 4

Clozapine + (FGA, SGA, or ECT)

Inconsistent results in RCTs

Nonresponse

Stage 5

Trial of a single agent FGA or SGA (not tried in Stages 1 or 2)

Value in clozapine failures not established

Stage 6

Combination therapy eg, SGA + FGA, combination of SGAs, FGA or SGA + ECT, FGA or SGA + other agent (eg, mood stabilizer)

Case reports; no controlled studies of combinations in long-term treatment of schizophrenia
Appendix B. Proposed monitoring protocol for clozapine-induced myocarditis in clozapine naïve patients\textsuperscript{52}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{protocol_diagram.png}
\caption{Proposed monitoring protocol for clozapine-induced myocarditis in clozapine naïve patients.}
\end{figure}

- **Patient starting clozapine**
  - Baseline:
    - Troponin I or T
    - CRP
    - Echocardiography

- **At least every second day for the first 28 days**
  - BP
  - Pulse
  - Body temperature
  - Respiration rate

- **On Days 7, 14, 21 & 28**
  - Troponin I or T

- **Ask patients (and advise carers if outpatients) to report feeling unwell and any symptoms of illness including**
  - Fever, cough, chest pain, shortness of breath, diarrhoea, vomiting, nausea, sore throat, myalgia, headache, sweatiness, and urinary discomfort or frequency

- **If the patient develops**
  - Signs or symptoms of unidentified illness OR
  - HR \( \geq 120 \) bpm or increased by \( >30 \) bpm OR
  - CRP 50-100 mg/L OR
  - Mild elevation in troponin (\( \leq 2 \) ULN)

  - **Continue clozapine with increased monitoring**
    - Check troponin and CRP daily and monitor patient for developing illness until features normalize

  - **Troponin \( > 2 \) ULN OR
    - CRP > 100 mg/L

  - **Cease clozapine**
    - Repeat echocardiography
    - Consult a cardiologist
## Appendix C. Abbreviations used

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full name</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI</td>
<td>Angiotensin-converting enzyme inhibitor</td>
</tr>
<tr>
<td>ANC</td>
<td>Absolute neutrophil count</td>
</tr>
<tr>
<td>ARB</td>
<td>Aldosterone receptor blocker</td>
</tr>
<tr>
<td>BNP/NT-proBNP</td>
<td>Brain-type natriuretic peptide</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>BPM</td>
<td>Beats per minute</td>
</tr>
<tr>
<td>BPRS</td>
<td>Brief Psychiatric Rating Scale</td>
</tr>
<tr>
<td>CAD</td>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>CBC</td>
<td>Complete blood count</td>
</tr>
<tr>
<td>CGI</td>
<td>Clinical Global Impression Scale</td>
</tr>
<tr>
<td>CK/CK-MB</td>
<td>Creatine kinase</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CXR</td>
<td>Chest X-ray</td>
</tr>
<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>ECT</td>
<td>Electroconvulsive therapy</td>
</tr>
<tr>
<td>EMB</td>
<td>Endomyocardial biopsy</td>
</tr>
<tr>
<td>EPS</td>
<td>Extrapyramidal symptoms</td>
</tr>
<tr>
<td>ESR</td>
<td>Erythrocyte sedimentation rate</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FGA</td>
<td>First-generation antipsychotic</td>
</tr>
<tr>
<td>GABA</td>
<td>Gamma-aminobutyric acid</td>
</tr>
<tr>
<td>HR</td>
<td>Heart rate</td>
</tr>
<tr>
<td>IgE</td>
<td>Immunoglobulin E</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>NMDA</td>
<td>N-methyl-D-aspartate</td>
</tr>
<tr>
<td>NOSIE</td>
<td>Nurses’ Observation Scale for Inpatient Evaluation</td>
</tr>
<tr>
<td>PANSS</td>
<td>Positive and Negative Syndrome Scale</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized control trial</td>
</tr>
<tr>
<td>REMS</td>
<td>Risk Evaluation and Mitigation Strategy</td>
</tr>
<tr>
<td>SGA</td>
<td>Second-generation antipsychotic</td>
</tr>
<tr>
<td>TCA</td>
<td>Tricyclic antidepressant</td>
</tr>
<tr>
<td>TMAP</td>
<td>Texas Medication Algorithm Project</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Tissue necrosis factor-alpha</td>
</tr>
<tr>
<td>TRS</td>
<td>Treatment-resistant schizophrenia</td>
</tr>
</tbody>
</table>