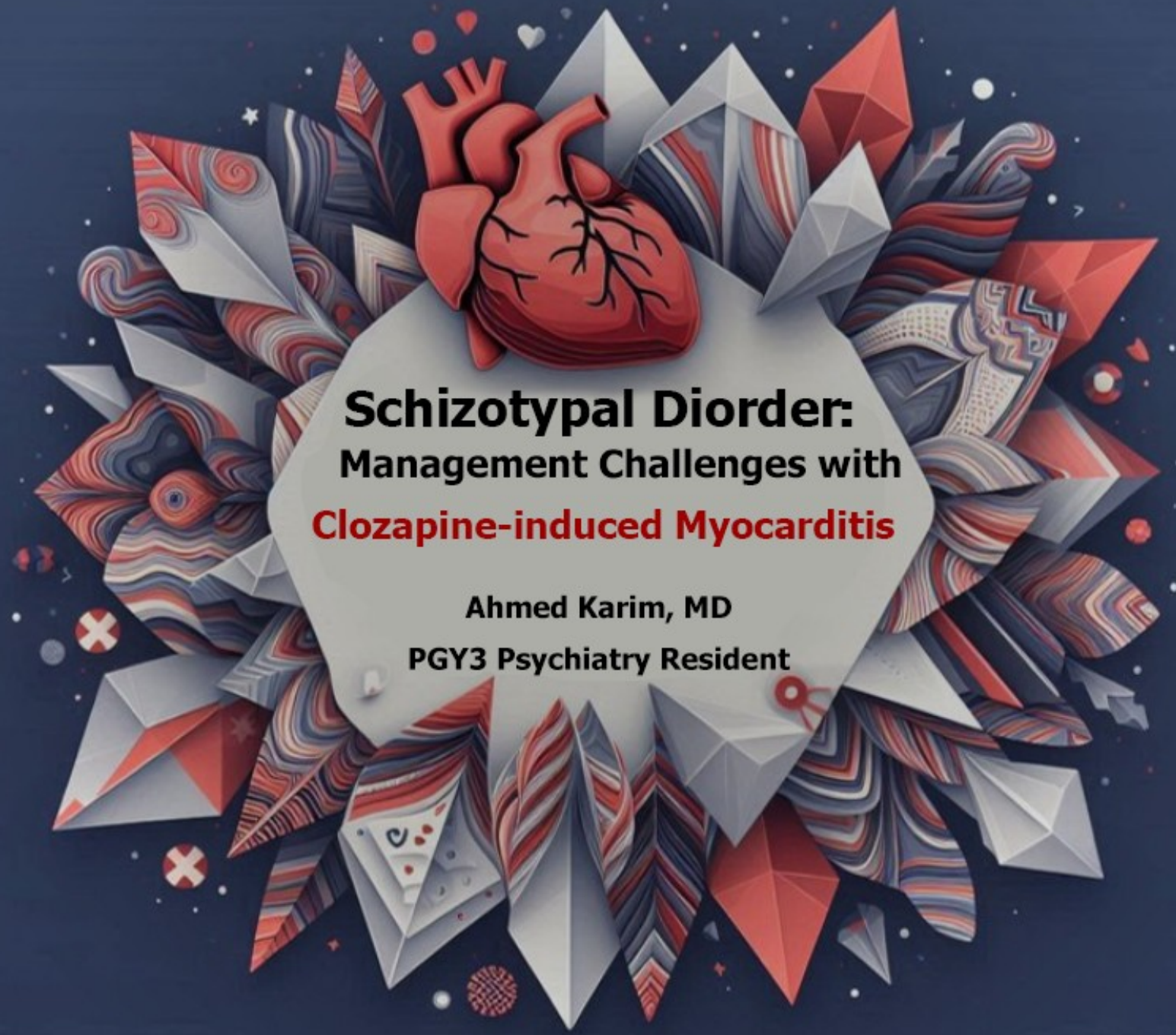

Schizotypal Diorder:
Management Challenges with
Clozapine-induced Myocarditis

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PGY3 Psychiatry Resident

Disclosure

I currently have no relationships of any kind with any company whose products or services in any way relate to the practice of medicine, medical education or research.

Goals of Presentation

- Introduction to Personality Disorders
- Differentiate between Schizophrenia and Schizotypal Personality Disorder SPD.
- Roles of Antipsychotics in Schizotypal Personality Disorder.
- Exploring Diagnostic Criteria and Etiologies for Clozapine-Induced Myocarditis (CIM).

Patient Demographics/Identifying Data:

- **Age:** Late twenties
- **Gender:** Male
- **Psychiatric History:** Schizotypal Personality Disorder
- **Legal:** A first-degree relative is the guardian. He was in a detention center and was referred for a forensic evaluation. He was opined competent to stand trial (CST) and released in October 2022.

Substance Use History

- **Past Use:** Cannabis, LSD, mushrooms
- **Last Use:** 2017 (episodes started in 2017 after heavy use of LSD and mushrooms.)
- **Connection to Symptoms:** Patient attributes telepathic voices to LSD

Social History

- **Living Situation:** With mother (guardian; History of witnessing domestic violence.
- **Relationships:** None, due to mental illness
- **Employment:** Unemployed
- **Education:** High school graduate

Past Psychiatric History

- **Multiple Admissions:** August 2022, April 2023, August 2023, March 2024 and April 2024
- **Forensic Admission:** Competency restoration; diagnosed with Schizotypal Personality Disorder, Unspecified Psychotic Disorder, and Cannabis Use Disorder.
- **Treatment History:** Trials of various antipsychotics with limited efficacy. Patient showed improvement on diazepam and sertraline. Participated in Dialectical Behavior Therapy (DBT).
- **Clinical Concerns:** Multiple admissions related to self-harm and aggression.
- **Diagnosis:** Schizotypal Personality Disorder, Unspecified Psychosis, Cannabis Use Disorder
- **Behavioral History:** History of impulsivity, anger outbursts, and self-injurious behavior.
- **Medications Trials:** Paliperidone, Divalproex, Aripiprazole, And Naltrexone — all with limited response.
- **Effective Regimen:** Stabilized on Diazepam and Sertraline

Forensic psychiatric evaluation for competency to stand trial in Jan 2022

- **Primary Discharge Diagnosis: Schizotypal Personality Disorder.**
  - **Secondary Diagnoses:** Unspecified Psychosis & Cannabis Use Disorder.
- **Symptomology:**
  - Odd beliefs or magical thinking that influence behavior.
  - Overelaborate, vague, or metaphorical speech.
  - Odd or eccentric behaviors.
  - Social isolation.
  - Odd affect.
- **Behavioral Patterns During Hospitalization:**
  - Impulsivity, anger, and self-injurious behavior (e.g., hitting himself in the head)
  - Emotional dysregulation characterized by screaming and verbal aggression toward staff
  - Frequent use of Lorazepam 2 mg PRN for emotional outbursts.

- **Effective Medication Regimen:**
  - **Diazepam 5 mg BID:** Reduced self-harming behaviors and emotional outbursts.
  - **Sertraline (up to 200 mg/day):** Improved isolation, anxiety, and depression.
  - **Melatonin 6 mg QHS:** Managed insomnia.
  - **Therapy:** Participated in Dialectical Behavior Therapy (DBT).
  - **Competency Status:** Opined competent to stand trial August 2022. Discharged to the County Detention Center.
- **Discharge Medications:**
  - Diazepam 5 mg BID (scheduled) for impulsivity, severe anxiety, and self-harm.
  - Sertraline 200 mg for anxiety and depression.
  - Melatonin 6 mg QHS for insomnia.

(Oct 2022)

- **Initial Presentation/Reason for admission:**
  - Nonadherent to medications
  - After 3 days, he was discharged on parole to the care of his mother. But, he was not given a 30-day supply
  - Self-injurious behavior post-release from detention. He felt others were provoking him, leading to frustration and scratching his face.
  - Involuntary admission (96-hour hold)
- **Key Symptoms:**
  - Self-harm (scratching face, hitting head), fixated on vaccine indications, intervals, and pathophysiology.
- **Mental Status Exam:** Coherent, cooperative
  - Denies SI/HI/AVH
  - Talked to himself and exhibited odd behaviors (e.g., screaming at the mirror, yelling in his room).

(Oct 2022)

- **Legal:** relative (1st Degree) was seeking guardianship
- **Length of stay:** 41 days
- **Outcome:**
  - Consistently denied SI, HI and AVH.
  - No aggressive or self-injurious behaviors observed.
  - Restarted on Diazepam 5 mg BID, Sertraline 200 mg daily, and slept well with Trazodone.
  - QMHP worked on level 2 placement; mother decided to bring him home.

(Summer 2023)

- **Reason for admission:**
  - Admitted after assaulting his mother and pets.
  - Patient requested to be taken to hospital
  - Prior to that admission, he spent 2-3 days in jail following incident.
  - His body being controlled from outside by multiple people

- **Psychological Assessment:**
  - Schizotypal Personality Disorder based on testing: Minnesota Multiphasic Personality Inventory-3
- **Incident:**
  - Aggressive episode – he requested Lorazepam, became agitated, attempted to kick and spit on staff. Manual hold applied.
- **Length of stay:** 101 days
- **Medication Adjustments:**
  - Transitioned from Olanzapine to Loxapine 10 mg twice daily (increased to 10 mg AM and 30 mg PM).

Treatment Plan:

- Initially prescribed **Olanzapine** 10 mg twice daily for psychosis and aggression
- Also taking **Sertraline** 200 mg daily for mood and anxiety management
- **Loxapine** was increased from 10 mg to 20 mg twice daily to better target psychotic symptoms
- Patient was gradually tapered off olanzapine and transitioned to **Loxapine** 10 mg in the morning and 30 mg at bedtime
- Reported no longer experiencing auditory hallucinations; described remaining telepathic experiences as more pleasant and less distressing

On Discharge:

- He was observed smiling to himself
- Discharge to the mother

(March 2024)

- Self-harm, aggression towards mother and the dogs
- Similar to previous presentations with linear thought process and calm demeanor
- Continues to endorse telepathic communications and mind control
- A possible Exacerbated anxiety? moving, mother's job loss, and leaving a friend

- **Diagnoses:**
  - *Schizotypal personality disorder*
  - *Unspecified psychotic disorder*
  - *History of cannabis use disorder*
- **Treatment plan:**
  - *Start Clozapine titration*

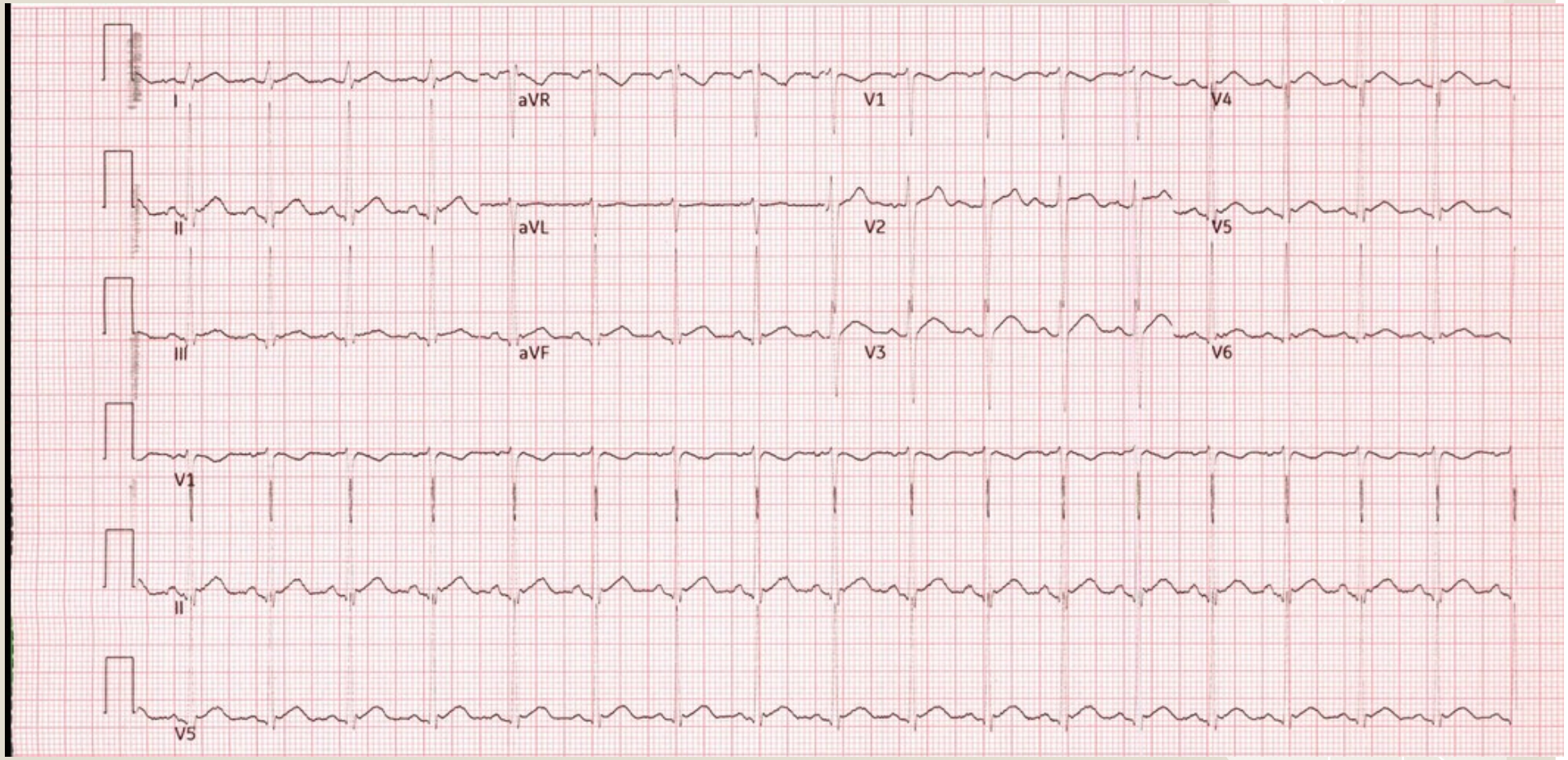
Treatment Course and Test Results

- 1st week since admission: Clozapine started on of March and titrated up to 50mg AM and 100mg PM
- 2nd week since admission: He experienced low grade fever with T 100.1°F, with headache, nausea, and myalgias. He reports that this has completely resolved.
  - CBC, CRP, troponin and EKG (QTC 283/423)
  - Slightly elevated troponin of 5.3.
  - Denied chest pain, shortness of breath, irregular heartbeat, dizziness, or headache.
  - Received a COVID vaccine on 03/13/24.
- Troponin levels at **15.8** (greater than twice the upper limit of normal-Normal high 4.9) , which was trending upward from **5.3** to **14.1,** alongside normal CRP levels (12.1).

- In the ED:
  - Negative Sed rate, downtrending CRP (9.8), and troponin (6.5).

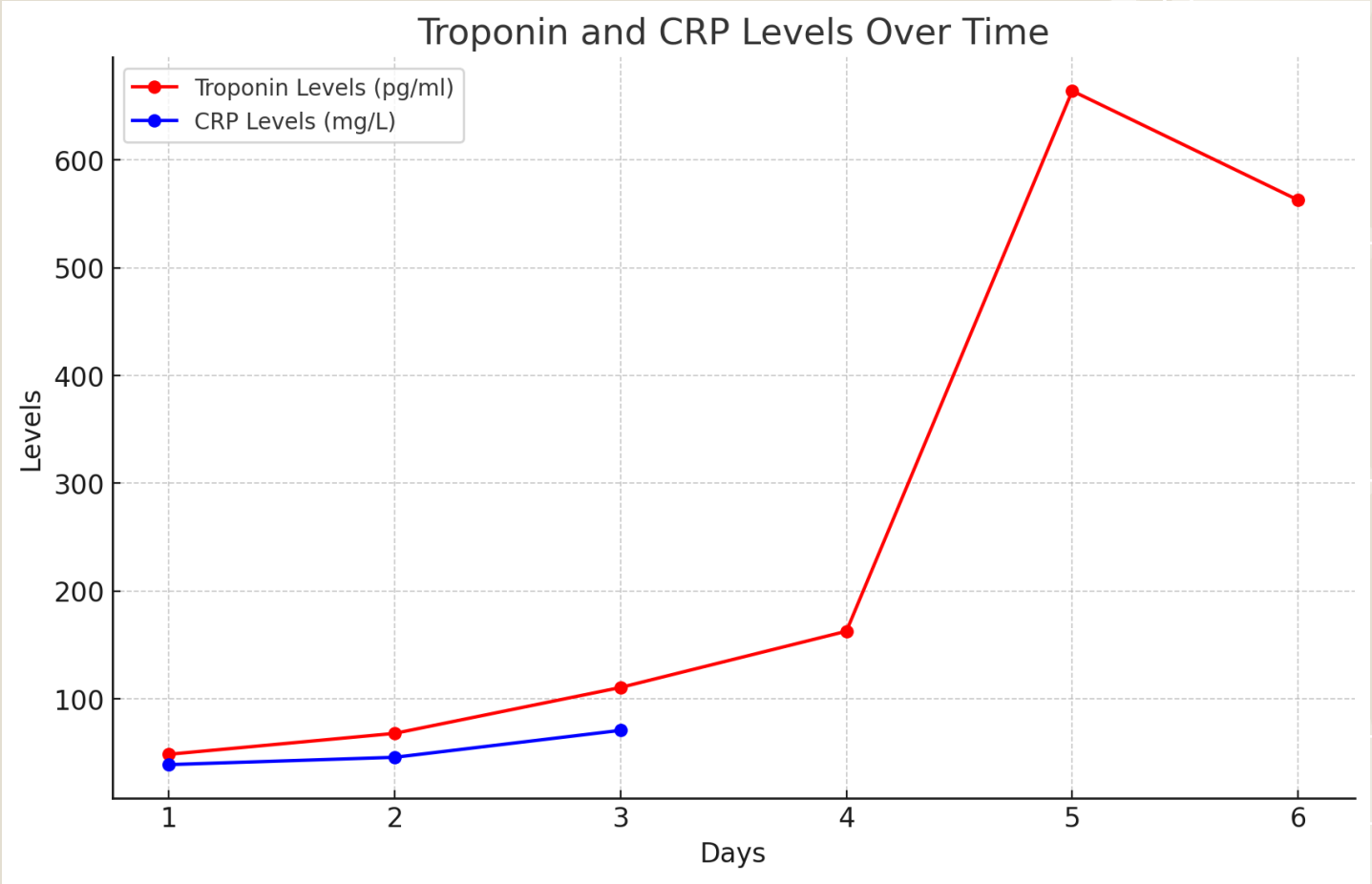
EKG

- Vent. Rate : 110 BPM
- Atrial Rate : 110 BPM
- P-R Int : 130 ms
- QRS Dur : 078 ms
- QT Int : 330 ms
- P-R-T Axes : 067 088 066 degrees
- QTc Int : 446 ms



Cardiac Enzymes Trends:

- 3rd week since admission:
  - 2nd ED admission
  - Troponin levels in 2 days:
    - **48.5 pg/ml**
    - **67.9 pg/ml**
    - **110.5 pg/ml**
    - **162.7 pg/ml**
    - **664.1 pg/ml**
    - **562.8 pg/ml**
  - CRP 2 days:
    - **38.9**
    - **45.7**
    - **70.7**



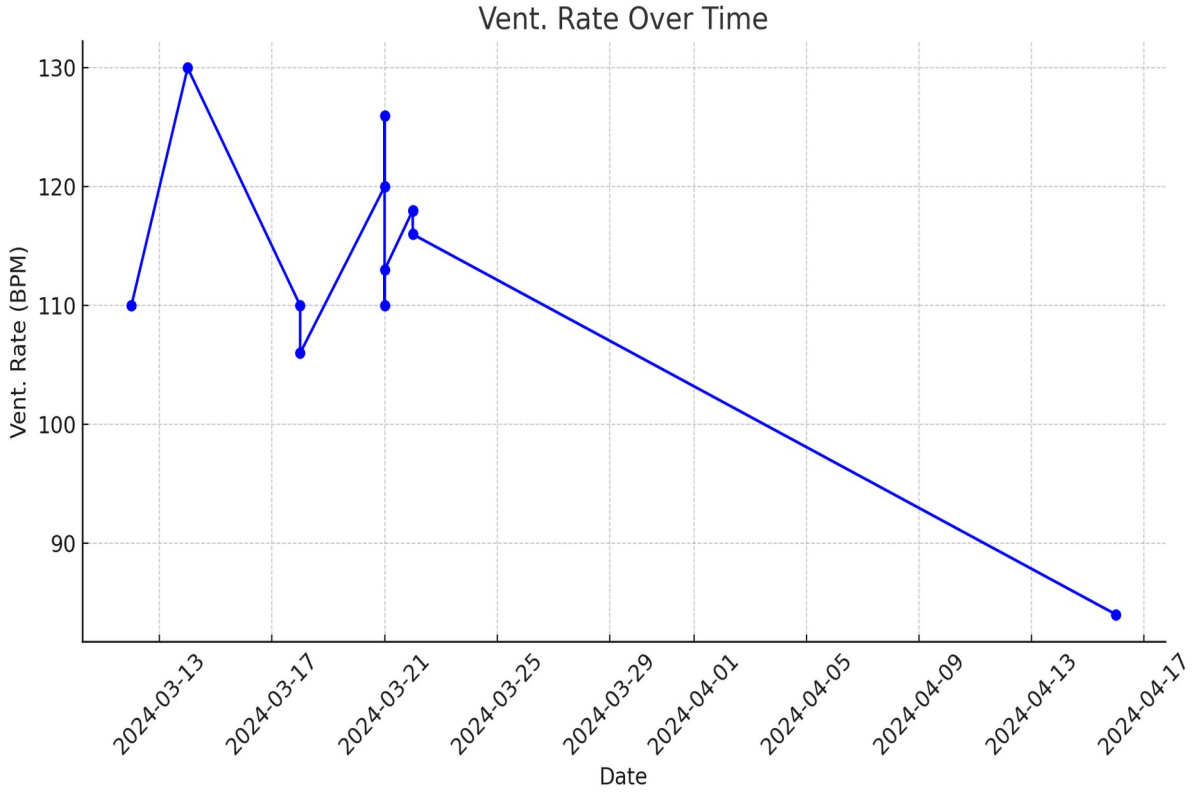
Cardiac Workup

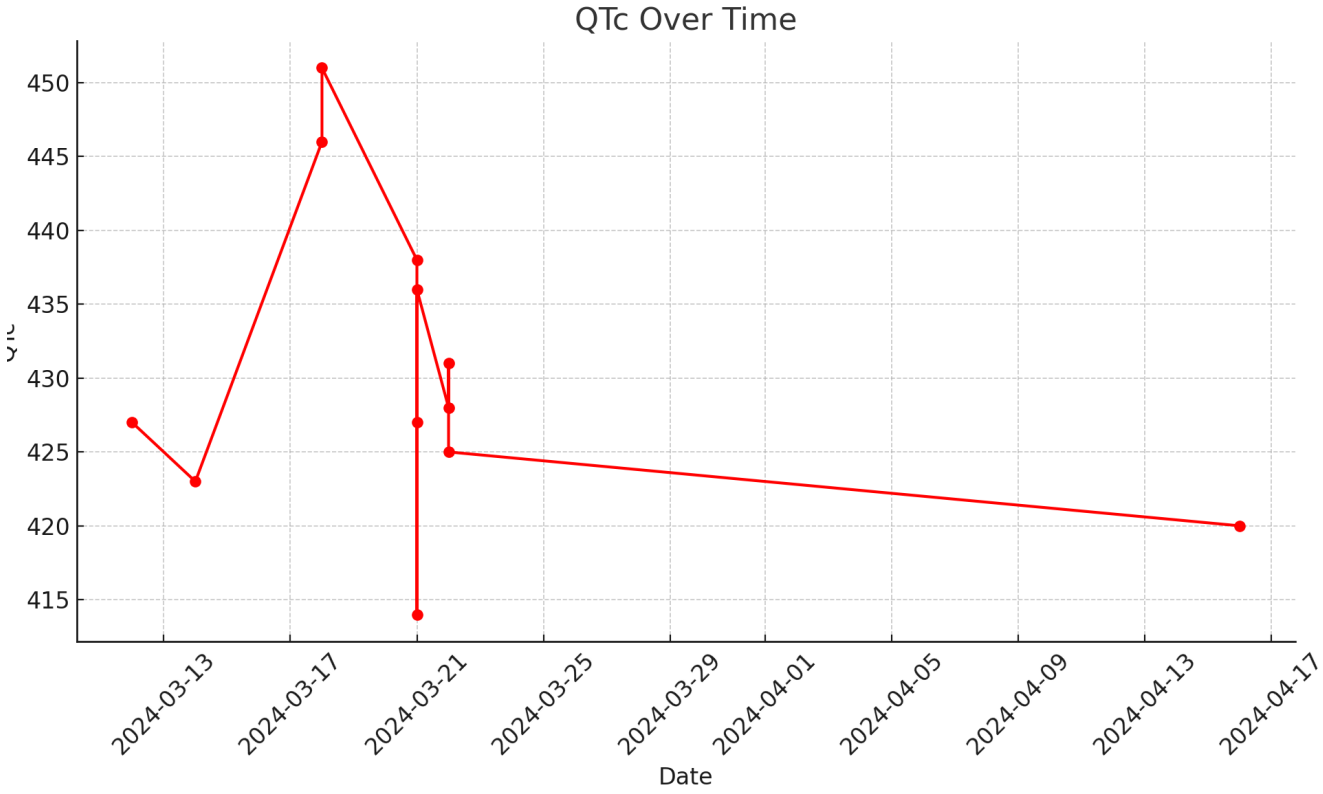
- Serial of EKG
- US Echocardiogram –
  - Left ventricular systolic function is mildly reduced, estimate is 45-50%.
  - View suggested distal anterior and apical hypokinesis
  - Diastolic function could not be accurately assessed due to tachycardia.
  - The right ventricle is normal
- 3 days after the echo, Cardiac Nuclear Stress Test performed:
  - Myocardial perfusion imaging is normal. There is no evidence of ischemia.
  - LVEF is 64%. Post stress wall motion is normal.
- Patient hemodynamically stable and asymptomatic
- Negative sed rate, downtrending CRP and troponin
- No indication for further workup or monitoring at that time
- Plan to schedule for outpatient cardiac MRI to further investigate possible myocarditis

EKG trends (Vent. Rate and QTC)

Normal Vent Rate: 60 - 100 bpm

Normal range of the QT/QTc: 350 – 470 ms





(April 2024)

- Self-harm, aggression towards mother and dogs.
- Continues to discuss telepathic communications and mind control.
- Open about stressors: moving, mother's job loss, and leaving a friend.

<u>Mental Status Exam:</u>

- Appearance: Large bruise over right eye with notable swelling
- Attitude: calm and cooperative
- Speech: normal rate, mono tone, volume
- Affect: Blunted, minimally reactive, mood congruent, and Calm demeanor
- Thought process: Linear, goal-oriented
- Thought content: Denies SI, HI, discusses mind control

(April 2024)

Medications course:

- Loxapine, titrated up to 100 mg PO daily → discontinued due to (EPS).
- Added Cariprazine 1.5 mg PO QD as dual therapy → increased to 6 mg PO daily. → discontinued at 6 mg QD after 3 weeks, due to a lack of symptom improvement.

New Treatment Plan:

- Patient reported previous improvement on Risperidone monotherapy.
- Risperidone was started and titrated to 3 mg PO daily, which is the discharge dose.

Additional Medications:

- While on Cariprazine monotherapy, the patient requested PRN Lorazepam (generic name for Ativan) 1-2 times per day, reporting that it helped quiet telepathic communication.
- After switching to Risperidone, the patient reduced PRN Lorazepam usage and has not requested it for 5 days prior to discharge.

Treatment for PTSD Symptoms:

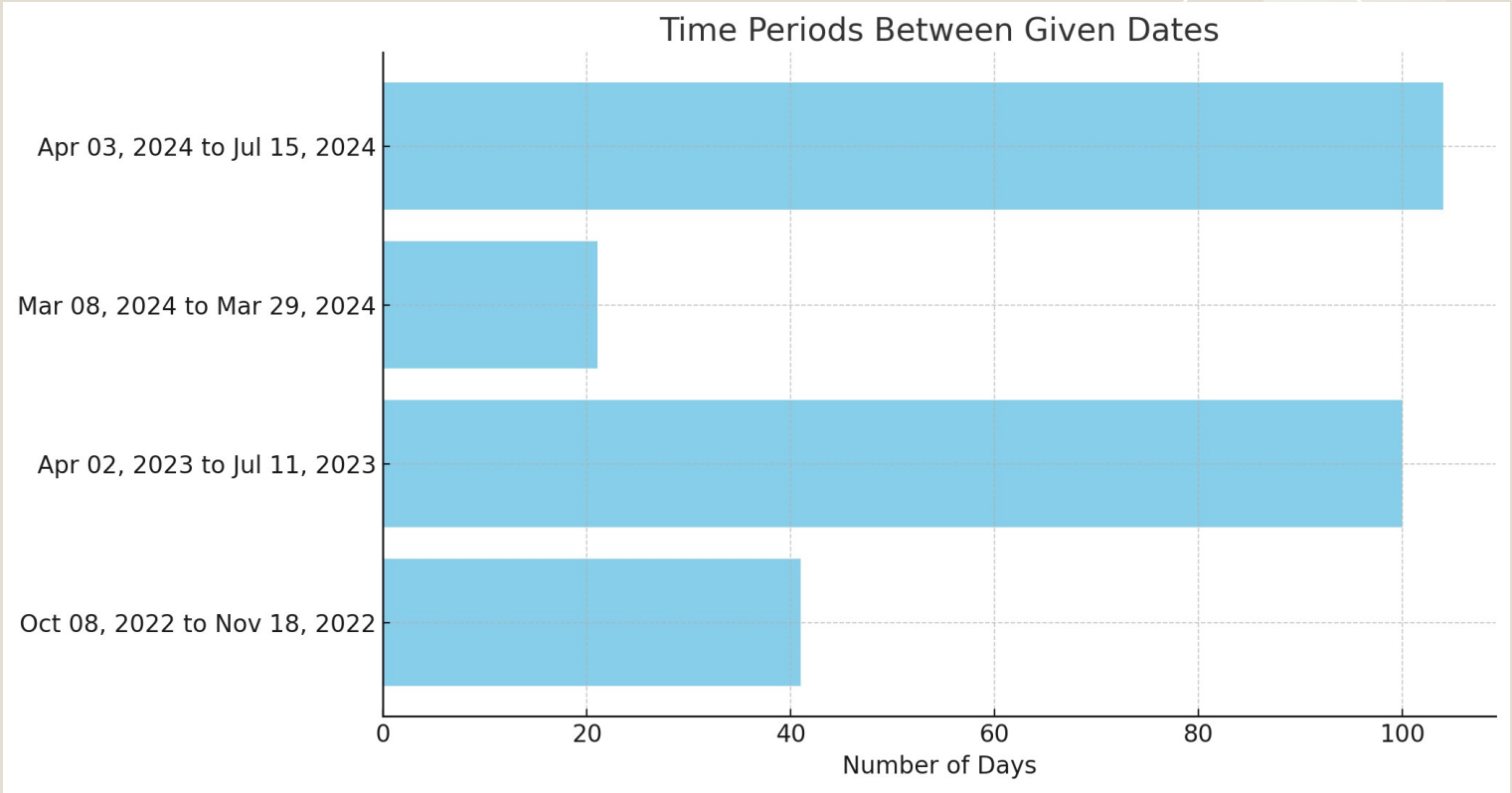
- Sertraline 50 mg PO QD then increased to 150 mg PO daily.

Brain Imaging:

- Two brain images were available
- During April 2022, admission (forensic admission):
  - Had CT Head w/o Contrast: No acute intracranial abnormality.
  - Indications: self-inflicted blunt trauma
- During April, 2024 admission:
  - Had head CT w/o Contrast: Right cheek soft tissue swelling/hematoma.
  - Indications: self-inflicted blunt trauma

Length of Stay Chart (Number of days)

Start Date	End Date	Number of Days
3-Apr-24	15-Jul-24	103
8-Mar-24	29-Mar-24	21
2-Apr-23	11-Jul-23	100
8-Oct-22	18-Nov-22	41



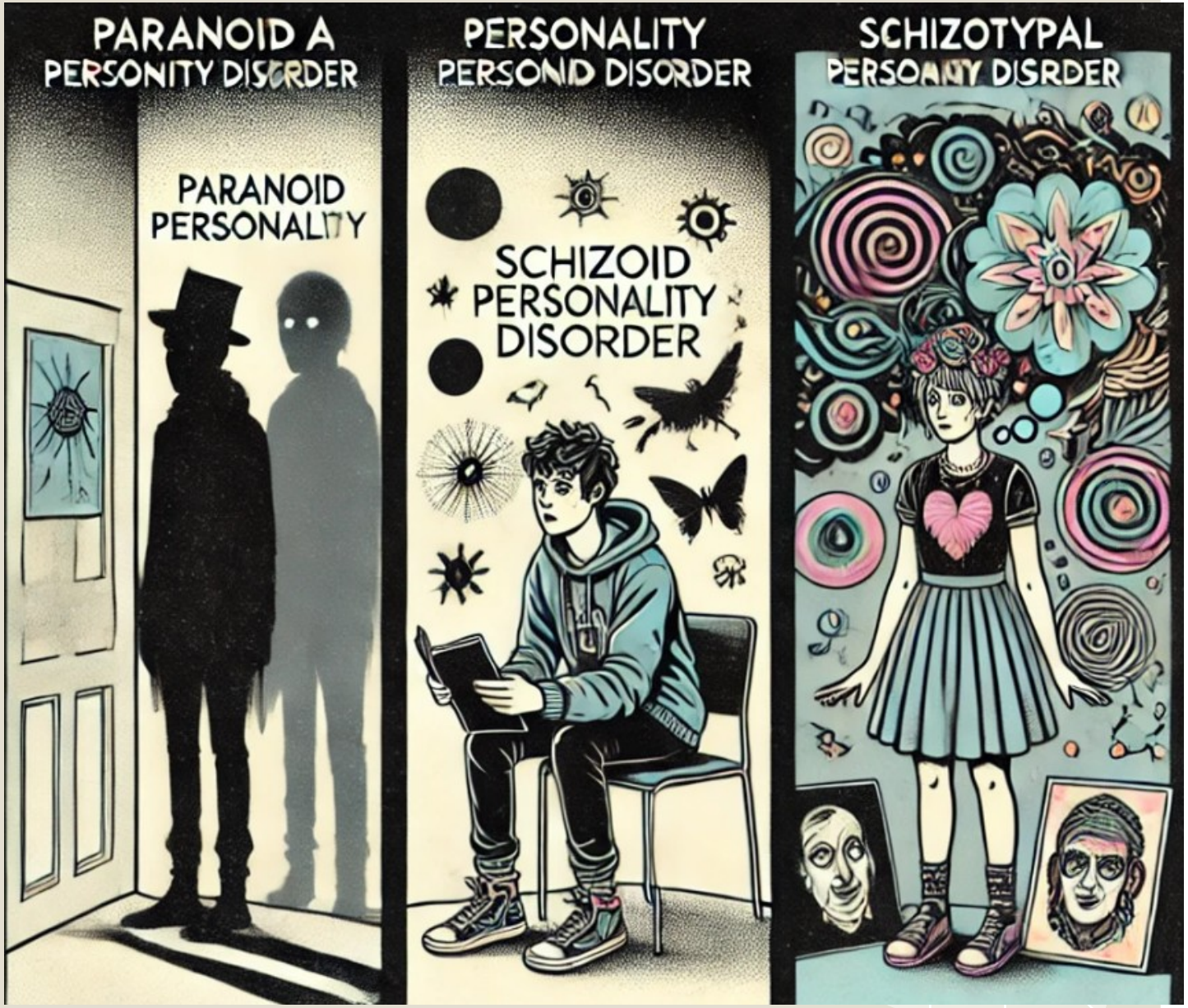
Personality disorders

- **Definition**: Inflexible, maladaptive, and pervasive behavior patterns causing distress or impaired functioning.
  - Typically egosyntonic (feels okay to me!) and present by early adulthood.

Clusters:

Cluster A ("Weird"): Odd or eccentric behaviors; difficulty forming social relationships. Linked with schizophrenia.

- Paranoid: Pervasive distrust, suspicion, and hypervigilance. Individuals often have a cynical view of the world.
- Schizoid: socially withdrawn and solitary activities. Displays limited emotional expression and indifference to others' opinions.
- Schizotypal: Marked by eccentric appearance, odd beliefs, and interpersonal awkwardness. Associated with the schizophrenia spectrum.



(Le et al., 2024, p. 582)

Personality disorders

Cluster B ("Wild"): Dramatic, emotional, or erratic behaviors. Associated with mood disorders and substance use.

- Antisocial: Disregard for others, criminality, impulsivity, no remorse; linked to conduct disorder before age 15; more common in males.
- Borderline: Unstable mood, relationships, self-image; fear of abandonment, impulsivity, self-harm; dialectical behavior therapy often used.
- Histrionic: Attention-seeking, dramatic, shallow emotions, provocative behavior; often uses appearance to gain attention.
- Narcissistic: Grandiosity, need for admiration, lack of empathy; reacts defensively to criticism, envious of others.

(Le et al., 2024, p. 582)

Personality disorders

Cluster C ("Worried"): Anxious or fearful behaviors. Associated with anxiety disorders

- Avoidant: Very sensitive to rejection and criticism, avoids social situations, but still wants relationships despite feeling inadequate.
- Obsessive-Compulsive: Focuses on order, perfection, and control; actions match their beliefs.
- Dependent: Needs constant support and reassurance, lacks self-confidence, may stay in harmful relationships.

(Le et al., 2024, p. 582)

SPD vs Sychosis

Feature	Schizotypal Personality Disorder (SPD)	Schizophrenia/Psychosis
Main Traits	Odd beliefs, strange thinking, and social anxiety	Delusions, hallucinations, and jumbled thinking
When It Starts	Teenage years or early adulthood	Late teenage years to early adulthood
How Long It Lasts	Long-term, relatively steady symptoms	Long-term, with sudden intense episodes of psychosis
Thinking Ability	Mildly affected; thoughts may be odd or unusual	Often seriously affected; thinking can be confused or slow
Social Life	Ongoing "**intense**" social anxiety, not many close friends	Major problems in social and work life
Medication Response	Medication may **NOT** be very effective; usually not needed unless psychotic episodes happen	Antipsychotic medications are the **main treatment**
Paranoia	Mild to moderate; often linked to social anxiety	Can be severe; paranoid thoughts are common

(Francois & Torrico, 2024)

Beliefs Comparison

Feature	Odd Beliefs	Delusions
What It Is	Unusual beliefs that seem strange but could be possible.	Strongly held false beliefs that aren't true, even with proof.
Connection to Reality	Usually aware that others don't share the belief.	Firmly believe it's true, even when proven wrong.
Examples	Believing in lucky charms or strange superstitions.	Thinking the government is spying on you without any evidence.
Cultural Influence	Influenced by culture, religion, or community.	May start from cultural ideas but become extreme and irrational.
Flexibility	Can change or be dropped if proven wrong.	Hard to change; belief stays strong even with evidence against it.

(Chaudhury & Kiran, 2009)

Presenting features of adverse reactions to clozapine and of biopsy-proven idiopathic myocarditis

Clozapine adverse drug reactions cited by researchers, in order of frequency[6]	Presenting features in patients with biopsy-proven idiopathic myocarditis[13]
Electro- or echocardiographic abnormality (66%)	Abnormal ECG in all patients (prolonged QT interval in 90%)
Fever (49%)	Dyspnoea (90%)
Tachycardia (46%)	Palpitations/arrhythmia (70%)
Elevated troponin level (36%)	Elevated levels of cardiac biomarkers (70%)
Chest pain (32%)	Influenza-type illness/viral prodrome (including fever) (50%)
Elevated creatine kinase level (31%)	Tachycardia (40%)
Leucocytosis (28%)	Leucocytosis (35%)
Dyspnoea (27%)	Chest pain (25%)

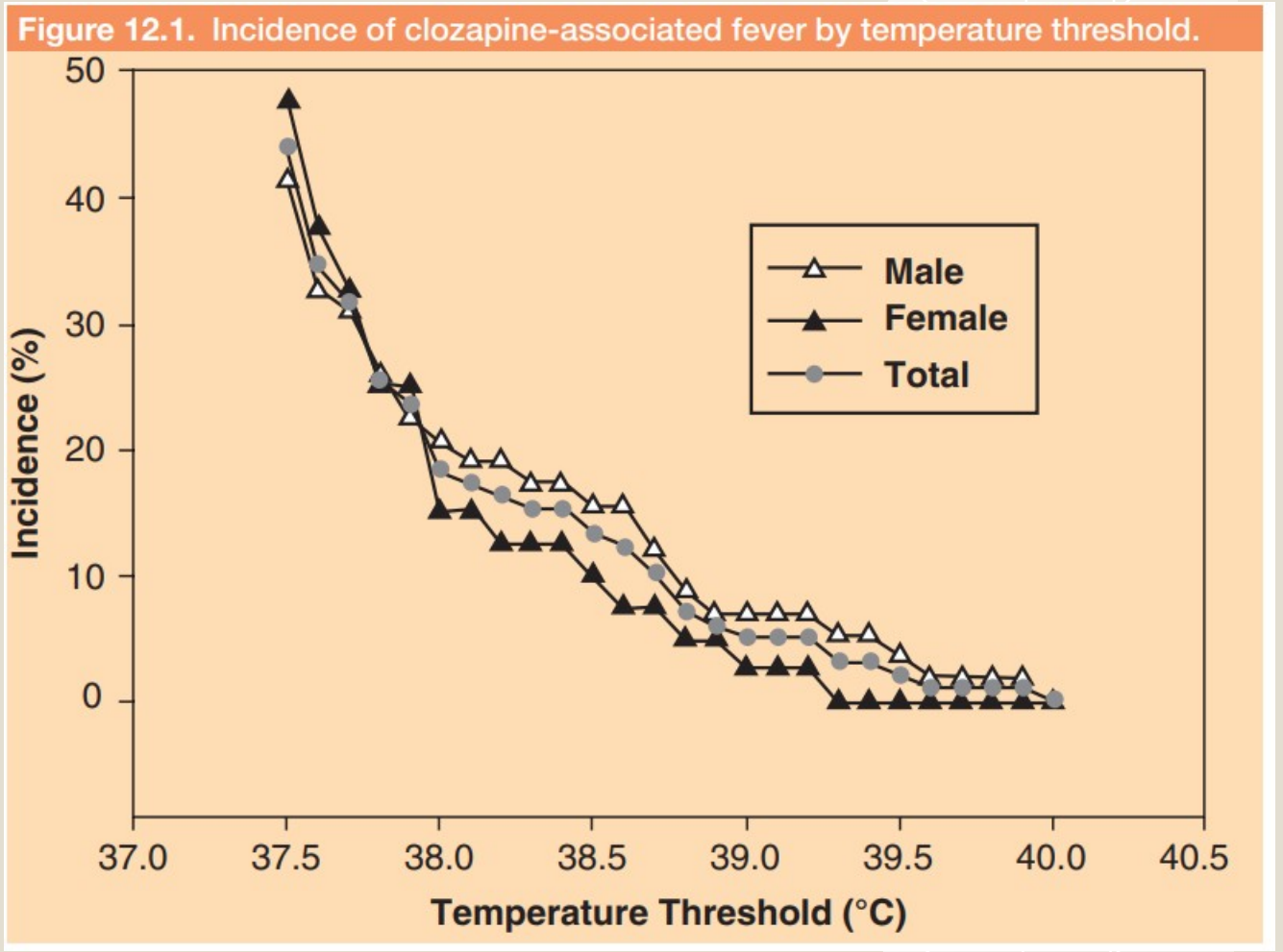
ECG = electrocardiogram.

(Ramamurthy et al., 1993)

Signs and symptoms in literature:

- 87% of patients develop symptoms within the first month of treatment.
- The median age of patients and dose of clozapine at presentation was 30years and 250mg/day respectively
- Clinical presentation included:
  - Shortness of breath (67%)
  - Fever (67%)
  - Tachycardia (58%).
  - Cardiac markers are elevated in 87% of the 54 cases that reported these markers.
  - Global ventricular dysfunction was the predominant echocardiogram finding (57%).

(Bellissima, Tingle et al. 2018)



(Adapted from: Jeong, S. H., Ahn, Y. M., Koo, Y. J., et al. (2002). The characteristics of clozapine-induced fever. *Schizophrenia Research*, 56, 191–193

Etiologies:

- The exact mechanisms remain unclear. (Layland et al., 2009)
- leading hypothesis is that of an IgE-mediated hypersensitivity reaction.
  - Supported by peripheral eosinophilia and eosinophilic inclusions within endomyocardial biopsy sample. (Kilian et al., 1999)

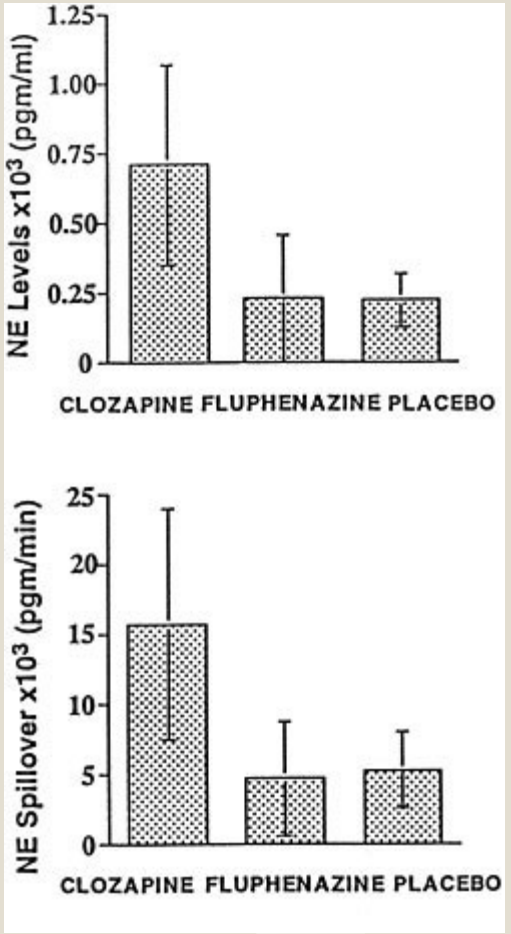
- The odds of clozapine-induced myocarditis increased with concurrent sodium valproate use (Ronaldson et al., 2012)
  - (k = 6, n = 903, pooled OR 3.58, 95% CI 1.81–7.06)

Etiologies:

Rule of catecholamines in CIM?

- Patient treated with Clozapine had higher noradrenaline which may lead to left ventricular (LV) dysfunction. (Elman et al., 1999)
    - For example, increased plasma catecholamine levels have been implicated in Takotsubo cardiomyopathy (reversible form of LV dysfunction. Thus it is plausible that increased catecholamine levels could be a contributing factor in the development of myocarditis and/or cardiomyopathy among affected patients. (Novak et al., 2007)

- However, high catecholamines doesn't explain the inflammatory process.



NE plasma level, NE spillover, and NE clearance in schizophrenic patients treated with clozapine (Elman et al., 1999)

Other Etiologies:

Other unproven mechanisms:

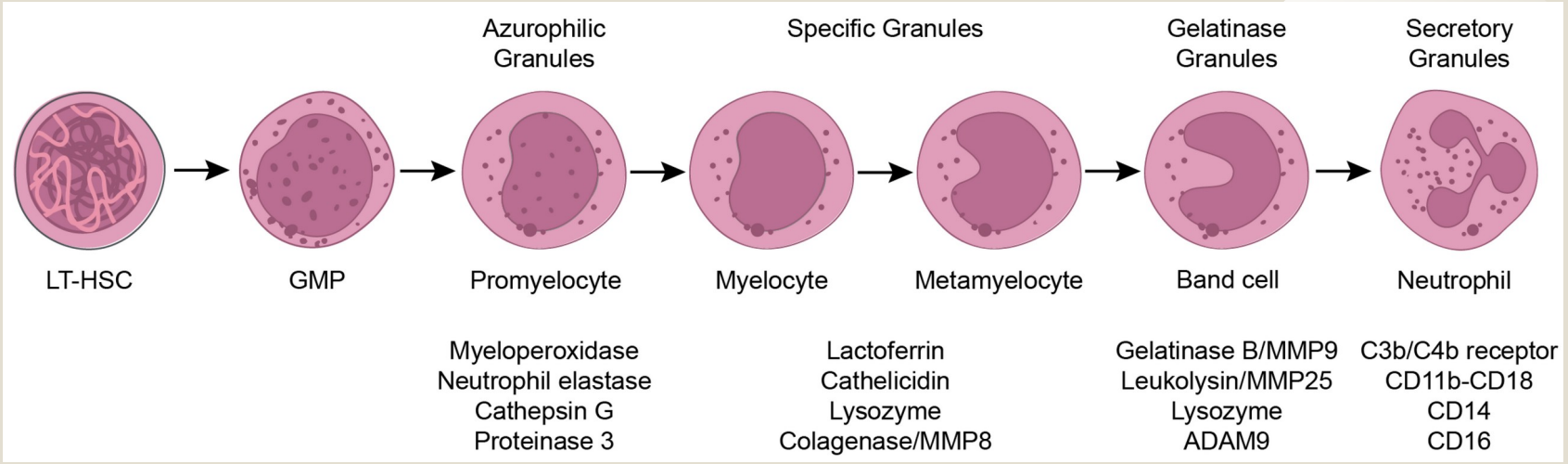
- Lack of Clozapine metabolism, due to Cytochrome P450 1A2/1A3 enzyme deficiencies (Devarajan et al., 2000)

- Low serum selenium levels: According to some studies, clozapine (Clozaril) can lower blood levels of selenium
  - Selenium concentrations in plasma and red cells → significantly lower in schizophrenic patients treated with clozapine as compared with all other groups. (Vaddadi, E. Soosai, and G. Vaddadi 2003)
  - "The reactive metabolite (nitrenium)of clozapine reacts with glutathione, and therefore, it is likely that it also binds to selenocysteine-containing proteins, such as glutathione peroxidase, thioredoxin reductase, and protein disulfide isomerase." (Ip & Uetrecht, 2008)

Other Etiologies:

Low Selenium- Continued

- The highest Selenium levels can be found in myelocyte stage (Possibly neutrophil myelocytes?)
- Clozapine is activated to free radical metabolites; activated neutrophils may metabolize clozapine to a reactive nitrenium ion, thereby producing agranulocytosis by either direct toxicity or an immune-mediated mechanism. (Linday et al., 1995)



(Tsioumpekou et al., 2023)

Anti-psychotic medication role in SPD?

- Minimal evidence regarding pharmacotherapy (Koch et al., (2016) 6 (2): 75–81.)
  - Olanzapine, risperidone, haloperidol, fluoxetine, and thiothixene showed benefits, but such agents should be considered on a case-by-case basis. (Koch et al., (2016) 6 (2): 75–81.)
- Risperidone was the most often studied drug class and were described as beneficial. Studies on the longitudinal course described a moderate remission rate and possible conversion rates to other schizophrenia spectrum disorders. (Kirchner et al., 2018)
- Risperidone appears to be effective in reducing symptom severity in SPD and is generally well tolerated. (Koenigsberg et al., 2003)

Mortality sequelae:

- The mortality rate associated with clozapine-induced myocarditis varies across studies, with reported rates generally ranging from around 10% to as high as 50%.
  - **24%** and **64%** (Kilian et al., 1999; Remington et al., 2017). In a **6** year long prospective cohort study with 503 patients on clozapine in Australia, 3% developed myocarditis and 2% had sudden death with 90% of the deaths attributed to cardiac etiologies including myocarditis, cardiomyopathy, and idiopathic arrhythmias (Khan et al., 2017).
  - **10% to 46%** (Sackey et al. 2018)
  - **10%** - Ronaldson, K. J., et al. (2010). "Rapid clozapine titration and increased risk of clozapine-induced myocarditis." The Journal of Clinical Psychiatry, 71(11), 1566-1571 .
  - **10% to 20%** - Bellissima, B. L., et al. (2018). "The incidence of clozapine-induced myocarditis: A systematic review and meta-analysis." Journal of Clinical Psychopharmacology, 38(5), 451-458 .
  - Around **20%** - Killick, S. K., et al. (2018). "Clozapine-induced myocarditis: A case series and literature review." General Hospital Psychiatry, 54, 45-49 .
  - **12-13% -** Reinders, J., et al. (2020). "Clozapine-induced myocarditis: An analysis of 38 cases." Australian & New Zealand Journal of Psychiatry, 44(1), 63-67 .

(Li, Gurrera, and Delisi 2018)

Take home points

1. Diagnosing SPD can be challenging and requires a multidisciplinary team approach.
2. Consider managing anxiety as a key component of treatment.
3. Monitor vitals closely, especially during the first weeks.
4. Troponin and CK levels are sensitive indicators for detecting CIM.
5. Therapy and behavioral interventions are crucial alongside pharmacotherapy.

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