A young man's affair of the heart

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After several failed antipsychotic trials, clozapine resolves Mr. Z's delusions and hallucinations, but sudden chest pain, fatigue, and shortness of breath spell trouble. What next?

CASE You're a 'freak'

A local mental health agency refers Mr. Z, age 23, to our inpatient psychiatry service because of increasing suicidality and psychosis. He began receiving care from the mental health agency 3 years ago, after a psychiatrist diagnosed paranoid schizophrenia.

At presentation, Mr. Z is delusionally preoccupied with a brief relationship he had with a young woman at college 2 years ago. He feels embarrassed about his conduct toward her during a psychotic episode and her subsequent response. He believes strangers are ridiculing him, and he hears voices calling him a "freak" and making crude references to the encounter. He is also contemplating suicide and endorses a suicide plan.

Mr. Z was hospitalized for 1 month last year with schizophrenia symptoms. He is medically healthy and does not abuse alcohol or drugs.

We admit Mr. Z because of his suicidality. Four weeks later, he remains suicidal and hears voices telling him to "rape" and "kill." Successive 2-week trials of risperidone, 1 mg/d titrated to 5 mg/d, and quetiapine, 200 mg/d titrated to 700 mg/d, cause intolerable akathisia. We try adding propranolol, 20 mg every 8 hours, to alleviate akathisia, but to no avail. Previous trials of olanzapine, 30 mg/d, and haloperidol, dosage unknown, were unsuccessful or caused akathisia.

What medication(s) would you try for Mr. Z's paranoid schizophrenia?

a) combination antipsychotics
b) clozapine
c) an antidepressant
d) an adjunctive mood stabilizer with existing antipsychotics

The authors' observations

Substantial evidence supports clozapine's efficacy in treatment-resistant schizophrenia, and this second-generation antipsychotic (SGA) also might reduce suicidality.[1,2] Clinicians often combine antipsychotics, switch to an antidepressant, or add a mood stabilizer for treatment-resistant schizophrenia,[3] but little evidence supports these options.

Mr. Z had failed at least 4 antipsychotic trials. We consider clozapine for patients with severe psychosis who have failed 2 or 3 antipsychotic trials or cannot tolerate these medications. Severity of psychosis and presence of suicidality warrant use of clozapine in treatment-resistant cases.

If Mr. Z had tolerated risperidone or quetiapine, we would have waited as long as 8 weeks before switching to clozapine. In inpatients, improvement should be seen 2 to 4 weeks after starting an antipsychotic.

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continued

How would you handle this case?

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Box 1

How clozapine might cause myocarditis

Myocarditis is a potentially fatal inflammation of the myocardium that can result from a viral infection, toxins, medications, or hypersensitive immune reactions.

Data on myocarditis prevalence are scarce because no relatively noninvasive assessment tools exist. Among 2,200 patients with unexplained heart failure occurring over <2 years, myocarditis was found in 10% after endomyocardial biopsy.[5]

An FDA-mandated "black box" in clozapine's package insert describes an "increased risk of fatal myocarditis, especially during—but not limited to—the first month of therapy."[6] Proposed explanations of how clozapine causes myocarditis include:

- direct toxic effect on cardiac myocytes related to impaired clozapine metabolism in some patients[7,8]
- myocardial damage mediated by clozapine blockade of a muscarinic M_2 receptor subtype[9]
- selenium deficiency or presence of reactive clozapine nitrenium metabolites contributing to myocardial toxicity.[10,11]

The common presence of peripheral eosinophilia on autopsy—including diffuse eosinophilic infiltrates in myocardial and perivascular areas—might suggest a hypereosinophilic syndrome or a type II hypersensitive immune reaction mediated by clozapine.[7,12] Similar immune-mediated conditions of acute, progressive myocarditis have been noted after exposure to other medications such as penicillin or sulfonamides.[13]

Noting that clozapine increases inflammatory cytokines, some authors believe TNF-alpha and other inflammatory cytokines contribute to myocarditis.[14]

Clinical Point

Clozapine side effects can occur anytime, but risk is especially high in the first year of therapy

Thoroughly discuss clozapine's risks and benefits with the patient and caregiver(s) before prescribing. Clozapine can cause a range of side effects, including sedation, weight gain, sialorrhea, seizures, diabetes, pulmonary emboli, and—most notoriously—agranulocytosis. These effects can occur anytime, but the risk is especially high within 1 year of starting the medication.[4]

Perform blood tests weekly during the first 6 months of clozapine therapy and biweekly thereafter to check for abnormally low white blood cell counts that might suggest agranulocytosis.

TREATMENT New regimen

After discussing clozapine's risks and benefits with Mr. Z and his parents, we start the medication at 25 mg/d to gauge tolerability, then titrate to 300 mg/d over 10 days. Mr. Z tolerates clozapine well, with some sedation and sialorrhea. A blood test taken 7 days after we start clozapine shows a normal white blood cell count.

After 10 days on clozapine, Mr. Z's delusions and hallucinations are considerably less intense. He is no longer suicidal and visits his former college with his parents without thinking about his past acquaintance. We discharge him on clozapine, 300 mg/d, and refer him to the local mental health agency.

Two days later, Mr. Z's parents report that since discharge their son has had extreme fatigue, shortness of breath, leg edema, and chest pain. We advise them to immediately take their son to the ER for cardiac workup.

Mr. Z's sudden symptom onset suggests:

a) time-limited viral syndrome
b) benign clozapine side effects
c) agranulocytosis
d) another serious clozapine side effect

The authors' observations

Mr. Z's sudden-onset physical symptoms suggest myocarditis, a rare but potentially fatal side effect of clozapine whose specific cause is unclear (***Box 1***).[5-14] Myocarditis has been reported in 0.02% to 0.18% of patients

exposed to clozapine,[15-18] with incidence as high as 1.3% per 235 patients.[19]

Affected patients typically have been taking clozapine at therapeutic dosages (100 to 450 mg/d).[7] Clozapine use is most prevalent among men ages 20 to 40, who tend to have more severe schizophrenia and lower cardiac risk than other populations. Correspondingly, clozapine-induced myocarditis is most prevalent in younger men,[20] although what specifically causes this susceptibility is unknown.

Nonspecific symptoms such as dyspnea, tachycardia, chest pain, or fever can signal myocarditis (***Table***)[7,21] and can surface within 4 to 8 weeks of starting clozapine.[22] Haas et al[20] reported other symptoms—such as leukocytosis—in young (median age 30), predominantly male patients with clozapine-induced myocarditis. Symptoms that typically occur during clozapine titration—such as fever and tachycardia—can mask "subclinical" myocarditis.[22]

Mr. Z's nonspecific symptoms could signal clozapine-induced agranulocytosis or a viral syndrome, or could be delusional. The patient's acute, sudden symptom onset strongly suggests a cardiac cause. Also, his delusions subsided, and normal blood readings helped us rule out agranulocytosis.

Coulter et al[23] associated myocarditis and cardiomyopathy, a noninflammatory heart muscle disease, with several antipsychotics—including clozapine, chlorpromazine, fluphenazine, haloperidol, and risperidone—as well as lithium. More research is needed to confirm this association.

Emergency medical intervention is critical because mortality rates for myocarditis induced by clozapine have been estimated at 50%.[20] Myocarditis could progress to dilated cardiomyopathy,[24] with similarly high mortality rates across 5 years.[7]

Order a cardiology consult and workup including:

- serum electrolytes
- complete blood count
- ECG[21]
- tests for myocardial damage including creatine kinase with MB fractionation (CK-MB) and testing for serum troponin I,[25] lactic dehydrogenase, and aspartate transaminase (SGOT)[21]
- assessment for immune activation and peripheral eosinophilia.[25]

Findings on ECG are wide-ranging and might include sinus tachycardia, atrial or ventricular arrhythmias, left ventricular hypertrophy, nonspecific ST segment and T-wave abnormalities, and intraventricular conduction defects. Assess cardiac function with echocardiography to monitor for dilated cardiomyopathy. Stop clozapine immediately if findings suggest myocarditis.[19]

Table

Symptoms that could signal myocarditis in patients taking clozapine

• Chest pain
• Confusion/mental status changes
• Dyspnea
• Edema
• Fatigue/weakness
• Fever
• Prolonged tachycardia

Source: Reference 7

TESTING 'Is this necessary?'

We contact the ER physician to request the above-mentioned tests, but he questions the need for such extensive and costly testing in a psychiatric patient with nonspecific symptoms.

After several phone conversations to review our recommendations, the emergency physician suggests sending Mr. Z home on a watch-and-wait protocol. We politely but firmly emphasize that Mr. Z needs a full cardiac workup, after which the physician consents to the tests (*Box 2, page 91*).

continued

Clinical Point

Nonspecific symptoms during clozapine therapy could be delusional or signal agranulocytosis or a more serious problem

Clinical Point

Monitor for myocarditis early in clozapine therapy. At minimum, order ECG at baseline and 2 and 4 weeks after starting clozapine

FINDINGS Suspicious readings

Mr. Z's cardiac imaging results suggest a cardiopathy:

- echocardiogram shows mild ventricular enlargement with a decreased ejection fraction of 45% (normal reading, 55% to 60%)
- ECG shows normal sinus rhythm with low-voltage diffuse T-wave flattening throughout all leads without ST elevation
- creatine phosphokinase (CPK) and CK-MB are within normal ranges
- troponin I is 0.33 ng/mL, a high-normal reading.

Mr. Z had no past cardiac abnormality, but an aunt had died in her 30s of viral myocarditis.

Based on these readings, the cardiology service admits Mr. Z with a presumptive diagnosis of clozapine-induced cardiomyopathy. The attending cardiologist stops clozapine and starts the angiotensin-converting enzyme inhibitor enalapril, 2.5 mg bid, for ventricular remodeling. Medical workup includes cytologic testing to rule out immunologic or viral disease.

Five days later, Mr. Z's cardiac symptoms have resolved. The cardiology unit discharges him on enalapril, 2.5 mg bid, and schedules a cardiac ultrasound for 2 weeks after discharge to confirm progress.

The authors' observations

Maintain high clinical suspicion while using clozapine. Similar to other patients with a clozapine-induced cardiopathy,[16] Mr. Z showed rapid symptomatic changes after a benign initial course and experienced fairly vague symptoms that raised limited clinical concern at first.

Before starting clozapine therapy, screen all patients for pre-existing cardiac disease, which contraindicates this medication. Alert patients and caregivers to the risks and symptoms that require close monitoring early in treatment.

Many researchers suggest monitoring for myocarditis during the first month of therapy and ordering ECG at baseline and 2 and 4 weeks after starting clozapine.[21,22] Berk et al[26] suggest more aggressive monitoring, including:

- baseline ECG
- transthoracic echocardiogram
- baseline troponin/CK-MB
- ECG and troponin/CK-MB at 7 and 14 days
- echocardiogram at 6 and 12 months and then annually.

RELAPSE Return of the 'freak'

Immediately after Mr. Z's discharge from the cardiology unit, we readmit him to inpatient psychiatry. His parents and case manager say he is again becoming preoccupied with his brief college relationship. He has been off clozapine for 5 days.

How would you treat Mr. Z now?

a) Rechallenge with clozapine
b) Start a different SGA
c) Start a different SGA with another medication
d) Avoid antipsychotics altogether

The authors' observations

The American Psychiatric Association[27] recommends maximizing 1 medication for at least 2 to 4 weeks to assess schizophrenia symptom response and urges clinicians to consider adverse effects, medical comorbidities, and patient preference before continuing the medication.

These recommendations highlight the challenges of treating medication-resistant schizophrenia. Relapse is common after a serious reaction to clozapine, and combining 2 or more other antipsychotics could lead to significantly greater side effects. A time-limited trial with an antipsychotic and an adjunctive agent might be attempted while carefully weighing the combination's risks and benefits.[27]

Clozapine reduced Mr. Z's psychosis, but rechallenge would likely cause his potentially fatal cardiomyopathy to re-emerge. His sensitivity to adverse antipsychotic

Box 2

'These tests are needed': How to convince other specialists

Many physicians are reluctant to pursue additional tests or procedures—and risk a confrontation with a consultant, insurer, or ER physician—especially when the risk of abnormality is extremely low. Advocating for cardiac workup in patients with vague symptoms is challenging, particularly if the suspected side effect is rare.

Taking the path of least resistance can increase the risk of a serious—albeit rare—adverse event. Failure to test could prolong a potentially harmful treatment, and the test results—even if negative—could be critical to planning care.

Calmly but firmly spell out the risks of missing a suspected cardiac problem (death, proceeding with potentially harmful treatment). Tell the ER manager or consultant, "I realize this is a very rare side effect, but not catching it could be life-threatening."

Be circumspect when pleading your case—an overaggressive approach might cause the ER doctor to "dig in his heels" and reject your request. Use a medically focused response such as, "This is a known complication of this medicine with this common time course and presentation."

effects discourages polypharmacy and further complicates our decision.

Because our therapeutic options are limited, we consider an agent chemically similar to clozapine with pharmacologic overlap—such as olanzapine,[6] which had improved Mr. Z's psychotic symptoms during his hospitalization 1 year ago but caused akathisia. We hope to avoid this adverse effect by limiting the dosage to 30 mg/d and adding the antidepressant bupropion, which Mr. Z says had helped him previously.

TREATMENT Another trial

We start olanzapine, 5 mg/d, and titrate to 20 mg/d over 1 week. We add sustained-release bupropion, 200 mg bid, for associated dysphoria.

Mr. Z's symptoms and paranoia gradually decline, and he tolerates off-unit passes with friends and family before discharge. Staff works closely with him to develop cognitive-behavioral strategies to manage residual paranoia and hallucinations, such as assessing evidence for his delusional beliefs and developing tools to distract him from remaining "voices." He reports no cardiac symptoms and continues taking enalapril, 2.5 mg bid.

We discharge Mr. Z after 1 week, at which point he shows no suicidal or homicidal thoughts. Follow-up echocardiogram 2 weeks later shows ejection fraction has improved to 60%, suggesting absence of cardiomyopathy.

When last contacted 3 months ago, Mr. Z was stable and living with his parents. He was continuing outpatient psychiatric care and hoped to find an apartment and transition to independent living.

Clinical Point

After a serious reaction to clozapine, try a different antipsychotic and an adjunctive agent; carefully weigh the risks and benefits

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continued

Related Resource

- Clozapine safety information. www.clozaril.com/info/tools/product.jsp.

Drug Brand Names

Bupropion • Wellbutrin
Chlorpromazine • Thorazine
Clozapine • Clozaril
Enalapril • Vasotec
Fluphenazine • Prolixin, Permitil
Haloperidol • Haldol
Lithium • Eskalith, others
Olanzapine • Zyprexa
Propranolol • Inderal
Quetiapine • Seroquel
Risperidone • Risperdal

Disclosure

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

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Clinical Point

Cognitive-behavioral strategies, such as assessing evidence for delusional beliefs, can help patients manage residual paranoia

Bottom Line

Rare, potentially fatal cardiac effects of psychotropics require rapid clinical response and evaluation. Educate patients and caregivers to watch for symptoms that could suggest a cardiopathy. Be wary when symptoms develop during therapy, and be prepared to convince other specialists of the need to test aggressively.