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# Potentially fatal outcomes associated with clozapine

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ABSTRACT

Clozapine has been shown to be the most efficacious therapy for treatment resistant schizophrenia, estimated at one third of all schizophrenia cases. There is significant morbidity and mortality associated with clozapine including risk of agranulocytosis, aspiration pneumonia, bowel ischemia, myocarditis, seizures, and weight gain. Here we present a case of a 62-year-old man with chronic paranoid schizophrenia refractory to numerous antipsychotics who was started on clozapine therapy during an acute inpatient psychiatric admission. Within three weeks of starting clozapine, the patient developed flu-like symptoms, pleuritic chest pain, and was sent to a medical hospital for evaluation. After transfer, the patient had a rapidly deteriorating course with newly developed congestive heart failure, acute respiratory failure requiring intubation, and cardiovascular collapse requiring vasopressors. The patient expired within two days of transfer and four days after initial symptoms developed. The underlying etiology in this case is likely clozapine induced myocarditis leading to rapid cardiovascular collapse and death. Mortality with clozapine induced myocarditis has been estimated up to 24%. Given that 90% of clozapine cardiotoxic sequelae are seen in the first month post-initiation, more rigorous post-initiation surveillance is recommended for the first four weeks of clozapine with weekly cardiac enzymes (troponins, creatinine kinase-MB), EKG, and acute inflammatory markers (C-reactive protein, and erythrocyte sedimentation rate).

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## 1. Introduction

Treatment resistant schizophrenia (TRS - lack of response to at least 2 antipsychotic medications) accounts for roughly one-third of all schizophrenia cases (Kane, 1996; Siskind et al., 2017). Clozapine, an atypical antipsychotic medication and dibenzodiazepine, has been shown to be the most efficacious therapy for TRS in terms of quality of life, mortality, self-harm and suicidality, boasting greater than a 50% clinical response rate (Chakos et al., 2001; Kane, 1996; Nielsen et al., 2012; Rohde et al., 2017; Tiihonen et al., 2009; Tiihonen et al., 2017; Wimberley et al., 2017). Although it's exact molecular mechanism is unknown, clozapine has high dopamine receptor 4 (D4) blockade, muscarinic receptor 4 (M4) agonism, as well as antagonist activity at serotonin (5HT) 2A, 5HT2C, dopamine receptor 2 (D2), muscarinic receptor 2 (M2), and histamine receptor 1 (H1) (Leung et al., 2017). Despite its well documented efficacy in TRS, clozapine has a multitude of serious possibly fatal adverse effects, such as arrhythmias from myocarditis or cardiomyopathy, aspiration pneumonia from hypersialorrhea, or bowel ischemia from constipation. Herein, we present a case of a 62-year-old male patient with chronic paranoid schizophrenia, who unexpectedly passed away from sepsis in the context of recent clozapine initiation for TRS.

## 2. Methods

Complete chart review of the patient's file, including outside hospital and out of state records, was completed. Systematic review of the literature in the last 20 years through Pubmed, EMBASE, and EBSCO databases consisting of PsycInfo, Psychology and Behavioral Sciences, PsychARTICLES, PsycBOOKS with the MESH/keyword clozapine and Boolean combination with the following terms: mortality, death, "sudden death", pneumon*, constipation, ileus, ischemia, myo*, necrosis, hypomotility, aspiration, sialorrhea, "pulmonary embolism", "venous thromboembolism", and "bowel ischemia". 594 articles were found. 165 were found to be duplicates and removed. 31 articles were found to be written in languages other than English or related to child and adolescent populations were excluded. 398 articles were reviewed and 254 articles were excluded for not being relevant. Of the remaining articles, 23 are directly related and 121 are indirectly related. These articles were closely examined and incorporated into the literature review.

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## 3. Case presentation

In the setting of medication non-adherence, Mr. C, a 62-year-old man, was initially brought in to a local emergency room (ER) by police after being found wandering several miles from his group home and yelling religious epithets. In the ER, there was evidence of disorganized thought process and severe paranoid delusions, leading to physical assault of healthcare staff. The patient was then transferred to an acute inpatient psychiatric unit where his outpatient medications were restarted - fluphenazine deconate 100 mg intramuscularly every 3 weeks, fluphenazine 5 mg orally twice daily, and alprazolam 1 mg twice daily as needed for anxiety. Upon admission, severe extrapyramidal symptoms (EPS) with an abnormal involuntary movement scale (AIMS) score of 11, was noted.

The patient's relevant past medical history includes chronic paranoid schizophrenia, poorly controlled non-insulin dependent type 2 diabetes, acid reflux, and long-standing daily cannabis and tobacco use. Developmental, academic, and family history were non-contributory. The natural history of Mr. C's schizophrenia followed a relapsing and remitting course with inpatient psychiatric hospitalizations intermittently over the 30–40 years of his illness. Mr. C had numerous multi-year trials of antipsychotics, including risperidone, paliperidone (both intramuscular and oral), quetiapine, olanzepine, haloperidol (both intramuscular and oral).

After two weeks without symptom improvement and several episodes of agitation (including taking a running dive onto the floor), clozapine was considered given recurrent antipsychotic treatment failures, severe extrapyramidal symptoms, and tardive dyskinesia. Pre-initiation work-up with 12 lead EKG (normal sinus rhythm with Bazett QTC of 451 ms), internal medicine consultation, and routine blood work revealed no concerning medical considerations to clozapine. Clozapine was started at 12.5 mg daily and titrated to 75 mg daily over 3 weeks, showing dramatic reduction of psychotic and EPS. However, notable side effects, hypersialorrhea, constipation, and orthostasis, developed. Symptomatic treatment was started with glycopyrrolate, pro-motility agents, and compression stockings. During the 4th week of clozapine, the patient reported upper respiratory symptoms with nasal congestion, non-productive cough, abdominal pain, and reduced oral intake. At that time, vitals revealed mild tachycardia of 109 beats/min. Blood work revealed serum clozapine level of 93 μg/L, norclozapine level of 24 μg/L, normal CBC and BMP. Four days after initial flu-like symptoms, Mr. C reported sharp chest pain worsened with inspiration and palpation, generalized discomfort, non-productive cough, and dyspnea. Vitals revealed a fever of 102.2 F and tachypnea up to 30 breaths/min. After the internal medicine consultant discovered a high D-dimer of 663 ng/mL, the patient was immediately transferred to the emergency room to rule out a pulmonary embolism (PE). Labs just prior to transfer showed a complete blood count, cardiac enzymes including troponin and CKMB, BMP, liver panel, and urinalysis within normal limits with negative blood and urine cultures.

CT angiogram showed no primary filling defects, but could not rule out secondary and tertiary branch filling defects. Chest x-ray showed no acute pathology. CT head showed mild age-related cerebral volume loss and microvascular ischemic changes. Lower extremity ultrasound, chest x-ray, and respiratory panel were negative. Broad spectrum antibiotics, IV vancomycin and piperacillin/tazobactam, were started. Twelve hours after transfer to the medical floor, Mr. C started having worsening dyspnea, increasing oxygen requirement, and destabilized vitals. Labs showed leukocytosis of 19.44 K/cm, elevated troponin of 13.33 ng/mL, and metabolic acidosis. Portable chest x-ray showed right patchy opacities and pulmonary vascular congestion suggesting layering pleural effusion, but unable to rule out pneumonia. Arterial blood gas suggested acute respiratory failure and the patient was emergently intubated, transferred to the intensive care unit, and started on vasopressin drip. Cardiology recommended transesophageal echocardiogram showed novel systolic congestive heart failure with an ejection fraction of 10–15%, dilated atria, and global hypokinesis. At this point, a family meeting with the patient's brother, his healthcare proxy, and his sister concluded with a decision to switch to comfort care measures only. Soon after, the patient expired. His family declined an autopsy.

## 4. Literature review

### 4.1. Fatal cardiac sequelae

Initially reported in 1999 by Kilian et al., clozapine induced myocarditis and cardiomyopathy have high rates of mortality, 24% and 64% respectively (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). Clozapine has a direct binding effect on $K_v11.1$, a myocardial potassium channel. (Hill et al., 2014; Lee et al., 2006; Sangoi et al., 2017). $K_v11.1$, the human ether *a-go-go*-related gene myocardial potassium channel, acts as a gate control to ensure proper ventricular repolarization and prevent premature ventricular beats (Hill et al., 2014). This pathway is a possible explanation for clozapine related ventricular tachyarrhythmias. Clozapine induced autonomic dysfunction, sympathetic hyperactivity, and parasympathetic hypoactivity have also been suggested to contribute to the reduced threshold for ventricular tachyarrhythmias through unknown mechanisms (Cohen et al., 2001). Clozapine has been shown to reduce heart rate variability, which is partly regulated by the autonomic nervous system (Buckley and Sanders, 2000). Alternative hypothesis focus on cardiac damage arising from an allergic hypersensitivity reaction and associated eosinophilia (Katta et al., 2016).

### 4.2. Fatal gastrointestinal sequelae

Clozapine induced gastrointestinal hypomotility (CIGH) is a common adverse effect estimated at 50–80%, resulting in death of 0.07–0.33% of all clozapine patients(Every-Palmer and Ellis, 2017; Every-Palmer et al., 2017; West et al., 2017). Clozapine patients have been found to have a dose-dependent prolongation of their colonic transit time (CTT), up to 4 times longer than non-clozapine patients (Every-Palmer et al., 2016). CIGH is likely the result of the combined effects of clozapine's strong anti-muscarinic (decreasing peristalsis) and anti-adrenergic effects (reducing intestinal perfusion) (West et al., 2017). Decreased peristalsis increases intraluminal pressure by retention of intraluminal contents. Increased intraluminal pressure results in mucosal strain eventually causing mucosal breakdown and possible intraluminal bleeding. The antiadrenergic effects of clozapine also reduces intestinal perfusion which in conjunction with the aforementioned antimuscarinic effects can lead to intestinal ischemia (West et al., 2017).

### 4.3. Fatal hematological sequelae

Clozapine can cause a variety of blood dyscrasias including eosinophilia, thrombocytopenia, leukocytosis, and agranulocytosis, the most well-known adverse effect (Fabrazzo et al., 2017). Clozapine's hematological effects, similar to other adverse effects, have significantly higher prevalence within the first year of clozapine treatment (Fabrazzo et al., 2017). Clozapine induced agranulocytosis (CIA), first reported in 1974, has two phenotypes on a spectrum of severity starting from benign neutropenia (estimated prevalence 2–3%) with absolute neutrophil count (ANC) <1500 to possibly fatal agranulocytosis with ANC <500 (estimated prevalence at 0.7%) (de With et al., 2017; Lally et al., 2017). Although not completely understood, the mechanism of clozapine induced agranulocytosis is hypothesized to be two-fold including 1 – an immunologic component whereby clozapine metabolites induce an

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