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REVIEW ARTICLE

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# Clozapine associated pulmonary embolism: systematic review

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**ABSTRACT**

**Background**: Clozapine is a second-generation antipsychotic used in refractory schizophrenia. Clozapine can lead to pulmonary embolism (PE) by various mechanisms including immobility, weight gain and increased platelet aggregation.

**Objectives**: We performed a systematic review on published cases of PE associated with clozapine.

**Methods**: Comprehensive search of Medline, Embase and Cochrane library was done for relevant articles from inception until June 2017

**Results**: Total of 34 cases from 24 articles were included in the analysis. The mean age was 43.2 years with male predominance (63.6%). The mean dosage of clozapine was 281.4 mg daily. Duration of intake ranged from few days to many years. Nearly half of patients (47.82%) had no other co-morbidities for PE other than clozapine. For those reporting treatment, anticoagulation was chosen in 80%, thrombolysis in 10% and inferior vena cava filter placement in 5%. Mortality was 36.36% with three dying on presentation and an additional 9 dying during the follow-up period. Of the 18 patients in which follow-up data of clozapine were available, the drug was discontinued in 14 patients.

**Conclusion**: PE can occur at doses lower than usual dose of clozapine (300 mg daily). It is important to consider this association especially in patients with no other risk factors for PE.

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**KEYWORDS**
Clozapine; pulmonary embolism; anticoagulation; schizophrenia

## 1. Introduction

Clozapine, a tricyclic dibenzodiazepine, is a newer atypical antipsychotic efficacious in the management of treatment-resistant schizophrenia [1]. Clozapine does not cause extrapyramidal side effects like the typical antipsychotics [2]. Common side effects of clozapine include agranulocytosis, sedation, tachycardia, orthostatic hypotension, seizures, myocarditis, diabetes mellitus and weight gain [2]. In addition to these side effects, the prescribing information contains a precaution regarding risk of pulmonary embolism (PE) in patients receiving clozapine [3]. Over the years, multiple case reports and case series of PE associated with clozapine have been reported in medical literature. In this article, we expand the understanding of this association by systematic review of all published cases in the current literature.

## 2. Materials and methods

### 2.1. Search strategy

We searched Medline, Embase, Cochrane and clinical trials.gov from inception until June 2017. We used search terms 'Clozapine' and 'Clozaril' for clozapine and 'pulmonary embolism', 'pulmonary thromboembolism' and 'PE' for pulmonary embolism and combined them by using Boolean operator 'AND'. We also performed a hand search of references of included articles to identify additional publications.

### 2.2. Eligibility criteria

(1) Articles in English language
(2) Patient was on clozapine therapy when he/she was diagnosed with PE
(3) Diagnosis of PE via imaging (computerized tomography chest, ventilation/perfusion scan) or on autopsy

### 2.3. Data collection and analysis

Saroj Lohani (SL) screened the articles for eligibility. Screening, inclusion and elimination of articles were performed as per PRISMA guidelines (see Figure 1). Authors-SL and RP extracted data from included articles. Data extracted included demographic variables, clinical presentation, treatment, outcome and fate of clozapine after PE. Data analysis was performed by Rakshya Poudyal (RP). Statistical analysis was performed using Microsoft Excel 2010 (Microsoft Corporation, Richmond, VA

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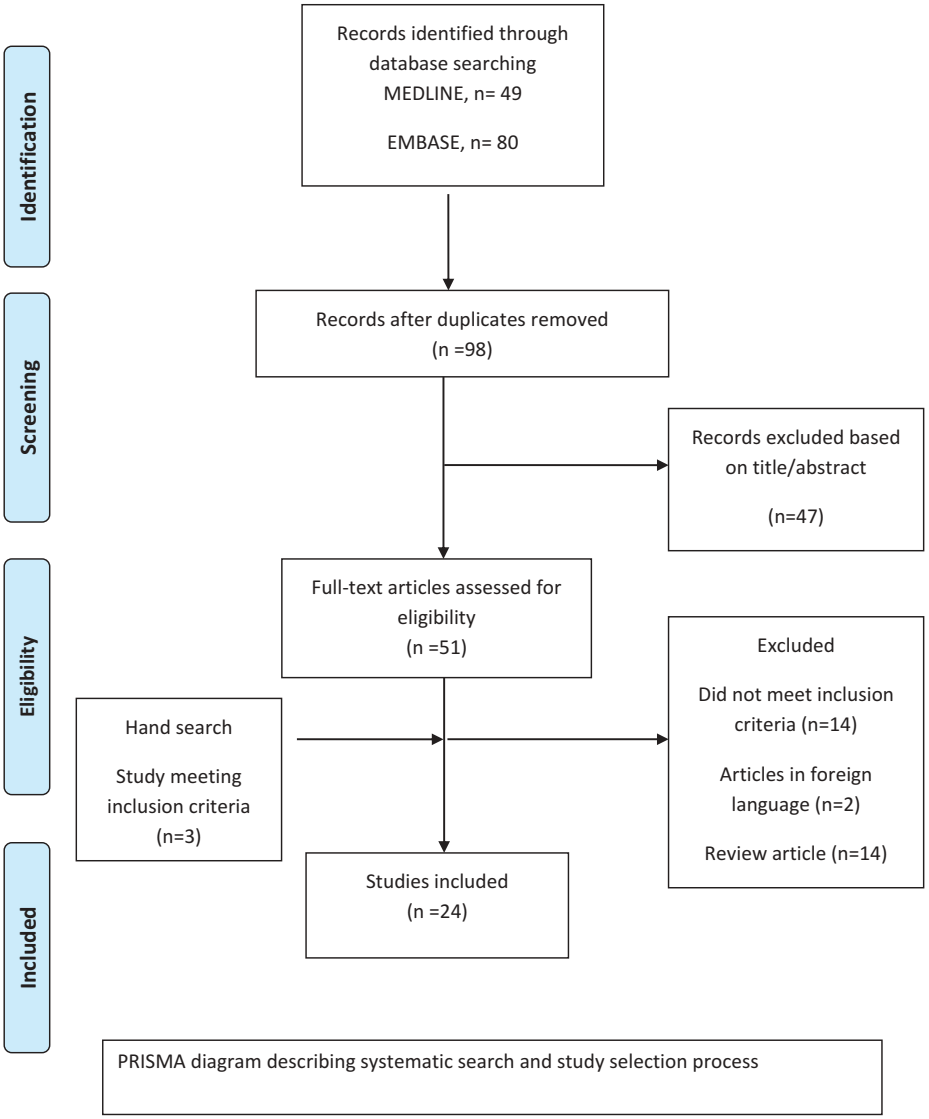


Figure 1. PRISMA diagram describing systematic search and study selection process.

## 3. Results

A total of 34 cases of PE associated with clozapine from 24 articles were included in the final analysis (see Table 1). The mean age of patients was 43.21 years with male predominance (63.63%, n = 21/33). The mean dosage of clozapine was 281.45 mg per day. There was a large variation in data on duration of clozapine use and development of PE. Duration ranged from few days to many years. Respiratory distress was the most common presenting complaint (55.55%, n = 15/27) followed by concurrent respiratory distress and chest pain both in five patients. Three patients presented with syncope while one presented with worsening of somatic symptoms and was diagnosed with PE. Three patients presented with sudden death, and PE was diagnosed on autopsy. In article by Hagg et al [4] PE was diagnosed in five patients on autopsy and one patient on CT of chest. No additional details on clinical presentation were available. Treatment of PE was mentioned in 20 patients. Anticoagulation was the mainstay of treatment in 80% (n = 16/20). Two patients were treated with Tissue plasminogen activator (TPA), and one patient was treated with only Inferior Vena Cava filter placement. In a case reported by Yang et al [5] patient developed massive PE. TPA therapy was refused by family, and the patient died. Mortality rate in our review was 36.36% (n = 12/33). Fate of clozapine after PE episode in patients who survived was available in 18 patients. Clozapine was discontinued in 14 patients. In four patients clozapine was continued. The details of the four patients in which clozapine was continued are discussed below.

## 4. Discussion

Venous thromboembolism (VTE) is a rare side effect of clozapine. In a study of the WHO international database of adverse drug reactions, 754 suspected cases of VTE related to treatment with antipsychotics were mentioned [6]. Clozapine was one of the second-generation antipsychotics having a disproportionately high number of VTE reports [6]. In a US record linkage study [7], mortality rates and causes of death

Table 1. Demographic features,medication characteristics, management and outcomes of cases of pulmonary embolism associated with clozapine.

| Author/year | Age/Sex | Dose mg/day | Duration | Treatment | Outcome | Fate of clozapine |
|---|---|---|---|---|---|---|
| Marinkovic/2015 [23] | 26/F | NA | 370 days | Sudden death | Death | - |
| Joksovic/2011 [24] | 52/M | 300 | 17 days | Anticoagulation | Survived | Discontinued |
| Yeh/2009 [25] | 51/F | 300 | 15 days | Anticoagulation | Survived | Discontinued |
| O Luanaigh/2006 [26] | 52/M | 400 | 270 days | Anticoagulation | Survived | Discontinued |
| Chate/2013 [27] | 39/M | 150 | 240 days | TPA | Survived | Discontinued |
| Coodin/2000 [28] | 30/M | 150 | 12 days | Anticoagulation | Survived | Discontinued |
| Munoli/2013 [29] | 34/M | 50 | 7 years | TPA | Survived | Discontinued |
| Pan/2003 [30] | 58/M | 250 | 5 days | Anticoagulation | Survived | Discontinued |
| Hagg/2000 [4] | 59/M | 300 | 14 days | NA | Death | - |
| Hagg/2000 [4] | 26/M | 500 | 20 months | NA | Death | - |
| Hagg/2000 [4] | 38/F | 150 | 14 days | NA | Death | - |
| Hagg/2000 [4] | 53/M | 100 | NA | NA | Death | - |
| Hagg/2000 [4] | 33/M | 200 | 90 days | NA | Death | - |
| Hagg/2000 [4] | 36/M | 200 | 60 days | NA | Survived | NA |
| Hagg/2000 [4] | 29/M | 400 | 21 days | NA | Survived | NA |
| Modai/1998 [31] | NA | NA | NA | Sudden death | Death | - |
| Sulejmanpasic/2012 [32] | 56/F | 400 | NA | NA | NA | NA |
| Schmidinger/2014 [33] | 63/M | 50 | 14 days | Anticoagulation | Survived | Discontinued |
| Farah/2004 [34] | 47/F | 300 | 730 days | Anticoagulation | Death | - |
| Gami/2016 [13] | 40/M | 350 | 180 days | Sudden death | Death | - |
| Goh/2016 [19] | 31/F | 300 | 18 days | Anticoagulation | Survived | Continued |
| Lacika/1999 [35] | 71/F | 200 | 4 years | IVC filter | Survived | Discontinued |
| Selten/2003 [20] | 28/M | 400 | 10 days | Anticoagulation | Survived | Continued |
| Scholl/2001 [36] | 29/M | 300 | 42 days | NA | Death | - |
| Tripp/2011 [21] | 58/F | 175 | 42 days | Anticoagulation | Survived | NA |
| Tripp/2011 [21] | 30/M | 700 | 90 days | Anticoagulation | Survived | Continued |
| Tripp/2011 [21] | 63/F | 200 | 22 days | NA | Survived | Continued |
| Yang/2003 [5] | 31/M | 100 | 60 days | TPA declined by family, patient died | Death | - |
| Suttman/2000 [37] | 33/F | 250 | 12 days | Anticoagulation | Survived | Discontinued |
| Ul-Haq/2009 [38] | 41/F | 450 | 5 months | NA | Death | - |
| Ul-Haq/2009 [38] | 64/F | 200 | 21 days | Anticoagulation | Survived | Discontinued |
| Ul-Haq/2009 [38] | 50/M | 500 | 4 months | Anticoagulation | Survived | Discontinued |
| Maynes/2000 [39] | 30/M | 400 | 5 months | Anticoagulation | Survived | Discontinued |
| Srihari/2008 [40] | 45/M | NA | 6 months | Anticoagulation | Survived | Discontinued |

Abbreviations: M Male; F Female; NA Not Available; HTN Hypertension; HDL Hyperlipidemia; NIDDM Non Insulin Dependant Diabetes Mellitus; PE Pulmonary Embolism; CT scan Compueterized Tomography scan; TPA Tissue Plasminogen Activator

in clozapine users was investigated. PE was found to be the second most common cause of death after external causes such as suicide and accidents.

Various risk factors such as age, obesity, smoking, increased risk of cardiovascular diseases in schizophrenic patients [8] also contribute to development of PE in clozapine users. Multiple mechanisms have been proposed for increased risk of VTE in clozapine users. One of them is immobility. Sedation is a common side effect of clozapine [9] which can lead to immobility and predispose patients to sedentary lifestyle and venous stasis. Clozapine can cause significant weight gain [10], which increases the risk of PE. Raised levels of antiphospholipid antibodies is established risk factors for PE and has been observed in patients on clozapine [11].In a study by Axelsson et al. [12] clozapine was found to increase platelet adhesion and aggregation which can lead to PE.

### 4.1. Demographic variables

In our review of 34 patients from 24 articles, mean age was 43.21 years with male predominance (63.64% 21/33 patients). This finding was similar to other published reviews on PE associated with clozapine use [4,13]. Mean clozapine dose was 281.45 mg per day which is less than defined dose of 300 mg daily. Similar finding was reported by Hagg et al. [4]. There was a large variation in duration of clozapine use (few days to years) and development of PE.

### 4.2. Co-morbidities

PE is associated with risk factors such as obesity, smoking, immobilization, trauma, pregnancy, use of oral contraceptives, malignancy and certain cardiovascular and hematological disorders such as Factor V Leiden mutation. In our review, presence or absence of additional co-morbidities was mentioned in only 23 patients. There were no additional co-morbidities besides clozapine use in 11 patients (47.82%). Obesity was present in seven patients, and five patients were smokers. Other co-morbidities reported included history of immobilization in one patient, sickle cell disease in one patient and Factor V Leiden mutation in one patient.

We also reviewed whether the patient was on other medications which increased the risk of PE. Haloperidol use was reported in four patients, risperidol use in three patients and escitalopram use in two patients. Meanwhile one patient each used olanzapine, carbamazepine and chlorpromazine.

In article published by Parkin et al. [14] use of antidepressants which included tricyclic antidepressants, selective serotonin reuptake inhibitors was associated with increased risk of VTE.

Similarly in articles published by Zornberg et al. [15] and Parkin et al. [16], there was an increased risk of VTE associated with use of psychotropic drugs which included phenothiazines, thioxanthene, haloperidol.

### 4.3. Clinical presentation

In article published by Stein et al. [17] dyspnea/tachypnea was the main presenting complaint in 90% of patients with PE which is similar to the findings in our review article - respiratory distress in 55.57% of patients. Similarly, syncope is the presenting complaint for PE in 10% of patients which is similar to the findings of our review [18].

### 4.4. Treatment and prognosis

Anticoagulation was the mainstay of treatment in majority of patients diagnosed with PE (80% 16/20 patients). Mortality rate was 36.36%, with three dying on presentation and an additional nine dying during the follow-up period. Out of nine patients, six patients had PE on necropsy and no treatment details were available. One patient died after therapy. One patient presented with cardiac arrest and died before treatment could be administered. In one patient, treatment was declined by family and died. Fate of clozapine after pulmonary embolus was reported in 18 patients. Clozapine was discontinued in 14 patients (77.78%) and continued in four patients.

In the article by Goh et al. [19], clozapine was continued as hematology consultation suggested clozapine was unlikely direct contributing factor and the patient had additional risk factors like obesity, poor mobility and smoking. She did not have any further episodes of PE until 3 months. Anticoagulation was continued for 6 months. No additional follow-up data were available.

In the article by Selten et al. [20] clozapine was continued after first episode of PE, and oral anticoagulation was stopped after 9 months. Twenty-six months after discontinuation of his anticoagulant, he developed another episode of PE. Patient was advised to discontinue clozapine however he refused citing the reason that there is no guarantee other drugs will be as effective. He had no further episodes of PE on 2-year follow-up.

In the second patient reported by Tripp et al. [21], no reason was mentioned for continuation of clozapine. Patient was continued on warfarin for 2 years, and no further PE episodes were reported. No further follow-up data were available.

In the third patient reported by Tripp et al [21] no reason was mentioned for continuing clozapine. No follow-up data was available for further episodes of PE.

In recent years, review articles have been published on association between clozapine and PE. The notable article is one published by Sarvaiya et al. [22]. This article is the review of 23 cases identified by Medline search. Our article includes 34 cases identified by Medline, Embase, Cochrane and Clinical trials.gov. Our article includes all cases included by Sarvaiya et al. and additional cases from Embase.

The findings of our article are consistent to findings from review article by Sarvaiya, et al. In this article, 9 cases were associated with low dose of clozapine (200 mg/day or less) and 11 cases with high dose (300 mg/day or more). In our review, 13 cases were associated with low dose and 16 cases were associated with high dose. The ratio of cases associated with high dose versus low dose is comparable (1.22 in article by Sarvaiya et al. and 1.23 in our review). Similarly the incidence of early onset PE (within 6 months) associated with clozapine was 0.86 (20/23) in the article by Sarvaiya et al. and 0.77 (24/31) in our article. The mortality rate of PE associated with clozapine was 26.08 in the article by Sarvaiya et al. (6/23) and 36.36 (12/33) in our article.

## 5. Limitations of our study

The quality of the synthesis of data was dependent on each study uniformly reporting study parameters and outcomes and was therefore limited by missing and incomplete data. Publication bias could not be excluded. Course of illness was not mentioned in many cases. Additional co-morbidities for PE were not mentioned in many cases. We included articles only in English language, so there may be a substantial population whose literature we have not included. Only limited follow-up data were available on patients who were continued on clozapine after episode of PE.

PE is a rare side effect associated with clozapine. The Clozaril National Registry performs monitoring of white blood cell count of patients on clozapine for detection of agranulocytosis associated with clozapine. Next steps could be the addition of thromboembolic events to REMS registery.

## 6. Conclusion

Clozapine is a second generation antipsychotic highly effective in resistant schizophrenia. PE is a rare side effect of clozapine. It is not a dose-dependent side effect and can occur from a few days to many years after initiation of therapy. PE in many cases can be fatal. It is not entirely clear whether patients who have PE on clozapine can be restarted on clozapine. It should take into account risks and benefits of drug continuation and further studies are needed in this matter. Further steps would be inclusion of thromboembolic events in REMS registry for clozapine.

## Disclosure statement

No potential conflict of interest was reported by the authors.

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