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An Overview on Clozapine and Its Acute Toxicity

Manar Hamed Mostafa Arafa, Gehan Abdelaziz Zaki, Marwa Gabr Ahmed Abdallah, Shahenda Samy Abdelhamed Ashor

Forensic Medicine and clinical toxicology Department, Faculty of Medicine, Zagazig University, Egypt

***Corresponding author:** Shahenda Samy Abdelhamed Ashor

Email: drshahendasamy@gmail.com,

Abstract:

Antipsychotic drugs are the cornerstone of pharmacological treatment for schizophrenia and other psychotic disorders. Since their introduction in the mid-20th century, they have been widely used to manage positive symptoms such as hallucinations, delusions, and disorganized thinking. Antipsychotics are generally divided into two main categories: typical (first-generation) and atypical (second-generation). While typical antipsychotics (e.g., haloperidol, chlorpromazine) are effective in controlling positive symptoms, they are frequently associated with extrapyramidal side effects such as dystonia, parkinsonism, and tardive dyskinesia. Atypical antipsychotics (e.g., clozapine, risperidone, olanzapine) have a broader spectrum of activity, targeting both positive and negative symptoms, and are generally better tolerated, although they carry risks of metabolic side effects including weight gain, diabetes, and dyslipidemia. Understanding the pharmacology, therapeutic indications, and adverse effects of antipsychotic medications is crucial for optimizing patient care, improving adherence, and reducing the long-term complications associated with both the illness and the treatment.

Keywords: Antipsychotic drugs; Schizophrenia; Typical antipsychotics; Atypical antipsychotics; Extrapyramidal side effects; Metabolic syndrome; Clozapine; Dopamine antagonists.

Introduction:

Antipsychotic drugs are essential in the management of schizophrenia and other psychotic disorders. They primarily target positive symptoms such as hallucinations, delusions, and disorganized thought processes, and their use has significantly reduced the burden of untreated psychosis worldwide (1).

These medications are broadly classified into typical (first-generation) and atypical (second-generation) antipsychotics. Typical antipsychotics, such as haloperidol and chlorpromazine, are effective but often associated with extrapyramidal side effects. In contrast, atypical antipsychotics, such as risperidone and olanzapine, are better tolerated and provide broader efficacy, including effects on negative symptoms (2).

Clozapine remains the gold standard for treatment-resistant schizophrenia. Despite its superior efficacy, its use is limited by the risk of agranulocytosis and the need for frequent monitoring. Recent advances continue to highlight the role of clozapine in reducing both hospitalization rates and suicidality in high-risk patients (3).

The long-term use of antipsychotic medications is often complicated by metabolic side effects, including weight gain, diabetes mellitus, and dyslipidemia. These adverse outcomes contribute to increased cardiovascular morbidity and mortality among psychiatric patients (4).

Ongoing research is focused on developing new-generation antipsychotics with improved efficacy and reduced side effects. Advances in pharmacogenomics and personalized medicine are expected to shape the future of psychopharmacology by tailoring treatment to individual patient profiles (5).

History and Uses:

According to the World Health Organization, schizophrenia is one of the most debilitating and financially devastating diseases. It affects 26 million people worldwide, or 1% of the adult population. Because there is no known cause of schizophrenia, the goals of treatment are to alleviate disease-related symptoms and improve functioning . So, the cornerstone of the present treatment is antipsychotic medications. **(6).**

Antipsychotics are divided into conventional or first-generation medications and atypical or second-generation drugs. **(7).** The history of typical antipsychotics began in the 1950s, with the introduction of chlorpromazine. Chlorpromazine is known as the prototypical "typical" antipsychotic. It was followed by the introduction of numerous more typical antipsychotics, including haloperidol. Typical antipsychotic drugs were helpful in treating positive symptoms of schizophrenia (delusion, hallucination) and preventing relapses. **(8).**

In the 1970s, atypical or second-generation antipsychotics were introduced in response to the load of side effects associated with typical antipsychotics, particularly extrapyramidal side effects (EPSEs) **(9)**.

Because typical antipsychotics have high affinity for D2 receptors, they are associated with a significant risk of extrapyramidal symptoms, which include movement disorders like parkinson's disease. **(10).**

Compared to standard antipsychotics, atypical antipsychotics are more efficacious and less likely to cause extrapyramidal movement issues. **(11).**

Because of their potent antipsychotic effects, broader variety of treatment options for both positive(hallucination ,delusion) and negative symptoms(flat affect, anhedonia) and positive relapse prevention benefits, the newer atypical antipsychotic drugs were the preferred treatment for people with schizophrenia. **(12).**

Clozapine is useful for improving symptoms in patients who are resistant to treatment, lowering the risk of suicide, preventing tardive dyskinesia, and suppressing tardive dyskinesia that has already occurred. It also improves cognition, which helps people function better at work and in social situations. Additionally, it is linked to improved quality of life, longer duration of cessation, and fewer relapses. **(13).**

However, It is linked to a cardiovascular issue as myocarditis, agranulocytosis, and metabolic side effects like insulin resistance that raise the risk of type II diabetes. **(14).**

Nevertheless, the identification of these adverse effects led to efforts to create further novel medications, including quetiapine, olanzapine, and risperidone. however, 30% to 60% of individuals with resistant schizophrenia still receive clozapine as their preferred medication. **(15).**

Classifications of antipsychotics:

According to **Vasiliu (16)**, antipsychotics were classified into:

A- First generation antipsychotics, also named major tranquilizers, old, typical, conventional antipsychotics e.g Butyrophenones as Haloperidol and Phenothiazines as Chlorpromazine.

B- Second-generation antipsychotics, also named minor tranquilizers, new, recent, atypical antipsychotic e.g Benzopines as Clozapine, Olanzapine, and Benzisoxazole as Risperidone.

C- Third-generation antipsychotics used in clinical practice e.g Aripiprazole, Cariprazine, Brexpiprazole, and Lumateperone.

Clozapine

Background

Clozapine, a tricyclic dibenzodiazepine, is an atypical antipsychotic medication that has proven uniquely effective for individuals with treatment-resistant schizophrenia (**17**).

It is considered to be a cornerstone in psychiatric practice and is anticipated to remain irreplaceable in the future. Widely regarded as the "gold standard" among antipsychotics, clozapine is the most effective option for patients with schizophrenia who do not respond to or cannot tolerate other antipsychotic treatments (**18)**.

Clozapine effectively alleviates positive symptoms, such as delusions, hallucinations, and thought disorders, as well as negative symptoms, including emotional withdrawal, apathy and reduced speech (**19)**.

Additional advantages include reducing suicidal tendencies, improving cognitive and social functions, enhancing the quality of life, minimizing hospitalization needs, improving treatment adherence, and lowering aggressive behavior (**20)**.

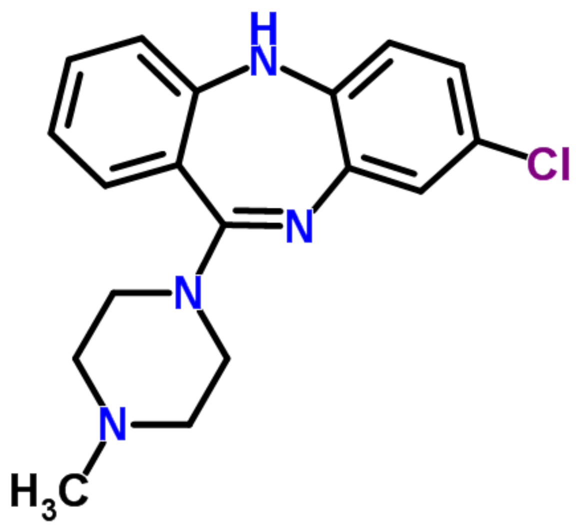
Unlike first-generation antipsychotics, which may exacerbate substance abuse, studies suggest that clozapine may help reduce the use of substances like nicotine, alcohol, and other drugs among patients with schizophrenia (**21)**.

Clozapine was introduced in the 1970s to address the limited efficacy and severe side effects, such as extrapyramidal symptoms, associated with first-generation antipsychotics, which often rendered them ineffective. As a result, clozapine became the prototype for second-generation or atypical antipsychotics, offering comparable therapeutic efficacy with fewer adverse effects **(9)**.

However, its use has been associated with agranulocytosis, a potentially fatal condition characterized by critically low white blood cell levels, impairing immune function. This led to its withdrawal in many countries. It was later reintroduced in the 1990s following evidence of its superiority in refractory schizophrenia, with mandatory blood monitoring protocols to ensure patient safety (**22)**.

Chemistry

The chemical name of clozapine is 8-Chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzodiazepine (**23)**. The molecular structure of clozapine is shown in (Figure 1).



(Figure 1): The molecular structure of clozapine (**23)**.

Physical Properties

Clozapine is a yellow crystalline powder that is either odorless or has a mild characteristic odor. Its melting range is between 182.0°C and 186.0°C. It is slightly soluble in water, freely soluble in methylene chloride, soluble in ethanol and acetone, and highly soluble in chloroform (**24)**.

Drug Preparations

There are three different forms of Clozapine: oral tablets, oral disintegrating tablets, and oral solution.

Suspension, oral:50mg/ml (100ml)

Tablet, oral: 25mg ,50mg ,100mg ,200mg

Tablet, oral disintegrating: 12.5mg ,25mg,100mg ,150mg ,200mg **(17)**

Tablets are each round, pale yellow, uncoated, easily breakable, scored tablets can be split in half. **(25).**

Trade Names

Clozapine is marketed under various trade names, including Clozapex, Leponex, Clozaril, Versacloz, Fazaclo, Clopine, and Denzapine **(26).**

Pharmacokinetics

Absorption

Clozapine is absorbed rapidly from the gastrointestinal tract, with an absorption rate of 90–95%. Due to moderate first-pass metabolism, its oral bioavailability is 50–60%. Peak plasma concentrations are achieved approximately 2.5 hours after oral administration, and food does not affect its absorption **(27**).

Distribution

Depending on the daily dosage, the normal plasma half-life of clozapine in steady state circumstances is 14–16 hours. **(27, 28).**

Clozapine is widely distributed throughout the body and can easily cross the blood-brain barrier. Its volume of distribution is approximately 6 L/kg, and it binds to plasma proteins at a high rate of around 95% (**22**).

Metabolism and Elimination

Clozapine undergoes extensive metabolism in the liver, primarily through the cytochrome P450 enzyme system. It is converted into polar metabolites, such as N-desmethylclozapine and clozapine-N-oxide, which are eliminated through the urine and feces (**29**).

Clozapine metabolism is mostly carried out by the isoenzyme CYP1A2, however CYP2D6, CYP3A4, and CYP2C19 also seem to be involved. Clozapine metabolism may be increased or decreased by substances that stimulate or inhibit CYP enzymes. **(30).**

Pharmacodynamics:

Mechanism of Action

Clozapine exerts its effects by interacting with a variety of receptors in the central nervous system. It has a strong affinity of blocking dopaminergic D4 receptors and demonstrates potent blocking activity at serotonergic, noradrenergic, histaminergic, and cholinergic M2 receptors (**31**).

Unlike traditional antipsychotics, clozapine has a relatively weak effect on D2 receptors, which significantly reduces the risk of extrapyramidal side effects. Additionally, some of its metabolites have receptor-binding profiles similar to the parent drug (**32**).

Drug Interactions

Pharmacokinetic Interactions

- Clozapine is metabolized by CYP450 enzymes; inducers (e.g., carbamazepine, phenytoin) can lower its plasma levels, while inhibitors (e.g., erythromycin, fluvoxamine) increase levels (**33)**.

- Smoking cessation can elevate clozapine levels due to reduced CYP1A2 activity. Regular monitoring is recommended (**34)**.

Pharmacodynamic Interactions

- Bone marrow suppressants (e.g., captopril, carbamazepine) may increase the risk of hematological toxicity of acute clozapine toxicity (**35)**.

- Clozapine enhances CNS depressant effects of alcohol, MAO inhibitors, and benzodiazepines (**17)**.

Dosing regimen

Due to the potential for serious side effects, clozapine treatment starts at a low dose of 12.5 mg once or twice on the first day, gradually increasing until a therapeutic dose is achieved. Most patients benefit from doses ranging between 200–450 mg/day, while treatment-refractory cases may require doses exceeding 400 mg/day (**36)**.

The maximum recommended dose is 900 mg/day. Plasma levels are monitored to guide treatment, with effective levels generally ranging between 350–420 ng/mL, although lower levels may also be effective when doses are divided (**17)**.

Side Effects

Sedation, postural hypotension, tachycardia, nausea, vomiting, constipation, elevated liver enzymes, sialorrhea, disorientation or confusion, incontinence or urinary retention, and benign hyperthermia are all common side effects of clozapine. **(36).**

However, agranulocytosis, a potentially fatal illness marked by abnormally low white blood cell counts, has been linked to the usage of clozapine. In the majority of countries, this resulted in its withdrawal. Evidence of its clinical superiority in refractory schizophrenia led to its reintroduction in the early 1990s **(37).**

Regulations were put into place mandating that patients' blood profiles should be checked on a regular basis. **(38)**

Therapeutic Uses

As Clozapine treat both positive and negative symptoms in Schizophrenia, It has been ideal for patient resistant to or intolerant of traditional drugs **(19)**

It also successfully lowers the risk of recurrent suicidal ideations, or inducing remission of substance use disorder in schizophrenic patients (**39).**

Moreover, it can be used in drug-induced psychosis in Parkinson without making it worse. Additionally, used to treat developmental abnormalities like autism Patients (**40**)

TOXICITY

Acute Clozapine Toxicity

Acute toxicity has become increasingly common, particularly in young females and young males with a history of substance abuse , as it is used to prevent relapse. Clozapine is highly toxic in naïve individuals due to it is narrow therapeutic index **(41)**

Even small exposures can be fatal in children, and single doses of 300–400 mg can result in coma in adults who are not accustomed to the drug. Ingesting more than 2 g has been reported to cause fatalities in adults (**42**).

Signs and Symptoms of Toxicity

Toxic effects primarily involve the central nervous system, including lethargy, confusion, slurred speech, sedation, and seizures. Cardiovascular effects include sinus tachycardia, mild hypotension, QT prolongation, and in rare cases, arrhythmias. It also may lead to sudden death, especially in individuals naïve to the drug . (**43**).

Clozapine also cause respiratory depression, aspiration, and anti-muscarinic effects such as agitation, delirium, and urinary retention. Hypersalivation is a characteristic symptom of toxicity, contributing to delayed gastric emptying and prolonged drug effects (**44**).

While neuroleptic malignant syndrome is rare with clozapine due to its minimal extrapyramidal effects, it can occur in severe cases and is characterized by hyperthermia, muscle rigidity, autonomic instability and altered mental status. Laboratory findings include elevated creatine kinase and white blood cell counts (**45**).

Causes of death related to Clozapine

Clozapine has been associated with fatalities including: Agranulocytosis ,neutropenia ,arrhythmias, myocarditis/cardiomyopathy ,seizures ,diabetic ketoacidosis ,fulminant hepatic failure ,circulatory collapse ,thromboembolism and bowel obstruction (**46**).

Management of Acute Clozapine Toxicity

Effective management of acute clozapine toxicity involves detailed diagnostic measures:

Diagnosis:

A through history, physical examination and continuous cardiac monitoring, measurement of cardiac enzymes. In addition to Monitoring of CBC, Liver Function, Kidney Function **(17).**

Screening for co-ingestion is advisable as acetaminophen, salicylate, ethanol, and lithium based on clinical history and examination (**31**).

Plasma concentrations of most antipsychotics are not routinely measured in acute overdose, clozapine levels may need monitoring (**47**).

Treatment of acute clozapine toxicity

Management of acute clozapine toxicity is primarily supportive, as no antidote exists (**17**).

- Stabilization:

Air way should be secured and provide Supportive care .all patients should receive continuous cardiac and respiratory monitoring with 12-lead ECG(**47**).

patients with altered mental status or seizures should receive dextrose, naloxone, oxygen, and thiamine (**31**).

GIT decontamination: activated charcoal should be administrated within six hours of ingestion, provided there are no contraindications such as sedation or vomiting .Gastric lavage is not routinely recommended due to its limited benefit and low associated mortality (**17**).

- Symptomatic and Supportive TTT:

Hypotension should be treated with intravenous fluids or plasma expanders, progressing to vasopressors (e.g., dopamine, noradrenaline) if needed. Adrenaline is contraindicated. Refractory cases may benefit from vasopressin (**48**).

There is no special treatment needed for sinus tachycardia **(49)**. **Rostagno et al. (50)** recommended the use of ACE inhibitors and β-blockers if the condition persisted in order to reduce the danger of tachyarrhythmias, cardiomyopathies, and sudden death caused by clozapine. Other than treating possible contributory factors like hypokalemia and hypomagnesemia. There is no special therapy needed for QTc prolongation **(51).**

Seizures can be Managed with benzodiazepines. Avoid carbamazepine due to its hematological toxicity (**52**).

Physostigmine may effectively reverse clozapine-induced delirium (**17**).

Neuroleptic Malignant Syndrome (NMS) can be managed by discontinue clozapine immediately, provide supportive care (e.g., fluid and electrolyte balance), and consider pharmacological interventions like benzodiazepines,dopamine agonists (bromocriptine or amantadine), and dantrolene (**53**).

- Elimination:

Techniques like hemodialysis, urinary alkalinization, or multiple-dose charcoal are ineffective due to clozapine's high protein binding and large volume of distribution .Also ,close supervision should be maintained for at least five days to manage potential delayed reactions (**17**).

Chronic Clozapine Toxicity

Hematotoxicity

Agranulocytosis and neutropenia are the most severe hematological toxicities. Risk peaks at three months of therapy and decreases after six months but remains present **(54).** .

Agranulocytosis occurs more frequently in individuals younger than 21 years, elderly patients, and women, with a mortality rate of 3–4% **(55).**

Baseline WBC and differential counts must be established. Clozapine should not be started if WBC is < 3500/mm³. Weekly monitoring is required for the first six months, biweekly for the next six months, and monthly thereafter .Treatment must be discontinued if WBC falls below 2000/mm³ or an absolute neutrophil count is < 500/mm³ (**56**).

Immediate cessation of clozapine and initiation of hematological consultation are required (**47**).

Supportive measures include isolation, prophylactic antibiotics, and agents like granulocyte colony-stimulating factor (G-CSF) (**17**).

Cardiotoxicity

Clozapine may cause myocarditis, cardiomyopathy, heart failure, or pericarditis. Symptoms are often non-specific (e.g., fever, chest pain, palpitations) Risk increases with rapid dose titration, older age, and concomitant ingestion of sodium valproate (**57**).

Early discontinuation of clozapine improves outcomes. Supportive care includes ACE inhibitors, β-blockers, and corticosteroids in cases of eosinophilic myocarditis (**58**).

Contraindications of Clozapine

Clozapine is contraindicated in patients with serious hypersensitivity to the drug or its components. The FDA has issued the following boxed warnings :neutropenia (risk of agranulocytosis) , Orthostatic hypotension, bradycardia, and syncope ,Seizures, Myocarditis and mitral valve incompetence ,increased mortality in elderly patients with dementia-related psychosis (risk of cardiovascular events) (**36**).

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