

## ARTICLE

# Clozapine: the past, present, and future

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## Abstract

Today, even after fifty years of its manufacture, the decision to use clozapine still represents a challenge to the clinician because of the complexities involved in accurately assessing its risks and benefits. Debate and uncertainty as to what represents an adequate trial, indications, and the mechanism of action of clozapine is continuing. The authors conducted a review of studies that highlighted its historical aspect, the mechanism of action, efficacy, tolerability, and indications of clozapine in current perspective.

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Clozapine was discovered in 1958 in Bern, Switzerland. It was first studied in animal experiments in May 1960. Soon after, clinical trials with clozapine began. The drug appeared to be an effective antipsychotic agent with no extra pyramidal side effects. However, early studies with clozapine in Europe were met with skepticism because this agent was inconsistent with the dogma that effective antipsychotic agents were associated with extra pyramidal effects. This dogma was challenged by a number of European authorities, including Hans Hippus, and, as a result, clozapine was eventually approved in several countries in Europe in 1972.

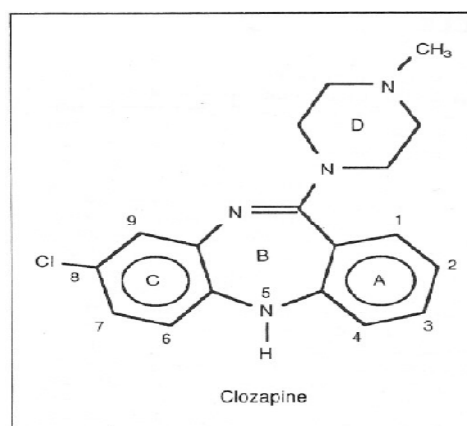
The enthusiasm about clozapine was dampened when it was discovered that the drug was associated with significant haematological toxicity. In 1975, clozapine was introduced in Finland, where 16 of 1,600 treated patients developed granulocytopenia. Eight patients in whom granulocytopenia progressed to agranulocytosis died of infections. After 50 patients around the world had died, clozapine was withdrawn from most European markets, and research with this drug came to a virtual halt. But, controlled trials in Europe showed that clozapine was more effective than conventional agents for treating schizophrenia patients who were either severely ill or resistant to other antipsychotic agents.

Discussions with the United States (US) Food and Drug Administration (FDA) led to a US multicentre trial to determine whether clozapine was effective for treatment-refractory patients. The studies, reported in

1988 by John Kane *et al.*, [1] Herbert Meltzer in 1993, [2] and others led to the approval of clozapine in US in 1990 for schizophrenia patients who are resistant to treatment with other antipsychotic drugs or who are unable to tolerate conventional drugs because of extra pyramidal side effects or severe tardive dyskinesia (TD).

## Structure/chemistry

Clozapine is a five-membered heterocyclic compound, 8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo-[b, e] [1, 4-] diazepine. Its chemical formula is  $C_{18}H_{19}N_4Cl$  with a molecular weight of 326.8.



## Absorption, distribution, metabolism, and excretion

The average minimum concentration at steady state is 168 ng/mL (range: 45-574 ng/mL), after 100 mg b.i.d. dosing. Food does not appear to affect the systemic bioavailability of clozapine. Clozapine is approximately

97% bound to serum proteins. Clozapine is almost completely metabolised prior to excretion, and only trace amounts of unchanged drug are detected in the urine and faeces. Among the major metabolites, the desmethyl metabolite (norclozapine) has only limited activity, while the hydroxylated and N-oxide derivatives are inactive. The mean elimination half-life of clozapine, after achieving steady state with 100 mg b.i.d. dosing, is 12 hours (range: four to 66 hours).

### **Mechanism of action**

**Multireceptor hypothesis:** Clozapine acts at many receptors--it binds loosely and transiently to D<sub>2</sub> receptors and interacts at dopamine (D<sub>1</sub>, D<sub>3</sub>, and D<sub>4</sub>), histamine (H<sub>1</sub>), acetylcholine muscarinic (M<sub>1</sub>), serotonin (5-HT<sub>2A</sub>, 5-HT<sub>2C</sub>, 5-HT<sub>6</sub>, and 5-HT<sub>7</sub>) receptors, and  $\alpha$ 1 adrenoceptors.[3] Postural dizziness, sedation, and increased appetite may reflect actions of clozapine at  $\alpha$ 1, H<sub>1</sub>, and 5-HT<sub>2C</sub> receptors, respectively.

It has also been proposed that the differential antipsychotic effect of clozapine is related to its low D<sub>2</sub> to 5-HT<sub>2</sub> ratio. An alternative hypothesis proposes that clozapine is effective because it has a selective preference for the mesolimbic dopamine system. In addition, the roles of N-methyl-D-aspartate (NMDA) receptors have been proposed. Clozapine blocked the expression of behavioural stereotypy induced by the NMDA antagonist MK801 in rodents.

**Loose-binding hypothesis:** Perhaps clozapine's atypical features are better explained by subtracting from, rather than adding to D<sub>2</sub> blockade. According to loose-binding hypothesis, clozapine works by blocking D<sub>2</sub> intermittently in a "hit and run" manner.[4]

**Single spike suppression hypothesis:** Dopaminergic neurons produce single spikes and bursts of spikes. According to the single spike suppression (SSS) hypothesis, single spikes, in addition to any normal functions, mediate the hallucinations and delusions of schizophrenia, and other psychoses. Clozapine mainly blocks single spikes, sparing the motor and other functions mediated by bursts.

**Blocks conditioned avoidance behaviours:** In preclinical studies, it was found that clozapine, like other antipsychotic drugs, blocks conditioned avoidance behaviours, a measure that is considered predictive of antipsychotic activity. However, unlike other antipsychotics, it does not cause catalepsy, block apomorphine- or amphetamine-induced stereotyped behaviours, elevate serum prolactin, or cause dopamine receptor hypersensitivity.[5]

**Altered expression of mRNAs encoding lipid metabolism-related proteins:** Dysfunction of retinoid-mediated transcription has been suggested to be an

important factor in the aetiology of schizophrenia. NGFI-B, Nor1, and c-fos mRNAs are increased in both motor and limbic regions of the basal ganglia acutely after the typical antipsychotic drug haloperidol, whereas the atypical antipsychotic drug clozapine only increases NGFI-B, Nor1, and c-fos in limbic parts of the basal ganglia.[6]

**Possible antiviral activity:** Clozapine and its metabolites were studied in vitro for possible antiviral activity against a model of a human neurotropic virus, human immunodeficiency virus type 1 (HIV-1). They demonstrated antiviral activity, while other atypical as well as typical antipsychotics had no effect.[7]

### **Evidences of efficacy**

#### ***Evidence for better symptom management in schizophrenia***

**CATIE findings:** Phase two of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) showed clozapine to be more effective than other atypical antipsychotics, as measured by time to all-cause discontinuation.[8] The CATIE results show that for patients whose symptoms are not wholly responsive to other antipsychotic medications, clozapine is an effective choice for the next step.

**Meta-analyses support CATIE results:** Clozapine's greater efficacy (and effectiveness) compared with other antipsychotics as demonstrated in CATIE is supported by two meta-analyses:

- A systematic review of clinical trials between January 1953 and May 2002 found clozapine effect size in reducing symptoms for patients with schizophrenia was greater than that of any other antipsychotic.[9]
- In a recent meta-analysis by Leucht *et al.*, [10] including 150 double-blind, mostly short term studies totaling 21,533 participants, clozapine showed the largest effect size when atypical antipsychotics were compared with first-generation antipsychotics.

**Evidence for antiaggressive properties:** Other than case series and retrospective studies, the evidence for clozapine's antiaggressive properties has been provided by a 12-week, double-blind, randomised trial that specifically enrolled patients with violent behaviour.[11] Clozapine was shown to be more effective than olanzapine, and olanzapine was more effective than haloperidol in reducing the number and severity of physical assaults, and in reducing overall aggression. Clozapine's antiaggressive property appears to be specific and not related to the Positive and Negative Syndrome Scale (PANSS) outcomes or sedation.

**Evidence for antisuicide properties:** The International Suicide Prevention Trial (InterSePT) was a multicentre,

randomised, two-year clinical study that compared the risk for suicidal behaviour in patients treated with clozapine vs. olanzapine with 980 patients of schizophrenia or schizoaffective disorder with high risk for suicide (past attempts or current suicidal ideation). Patients receiving clozapine showed significantly less suicidal behaviour than those treated with olanzapine.[12]

A recent study from Finland found that clozapine seems to be associated with a substantially lower mortality than any other antipsychotic.[13]

**Efficacy in negative symptoms:** An increasing body of evidence also supports efficacy of clozapine against negative symptoms. Study reported that the changes in negative symptoms occurred concurrently with significant reductions in positive, depressive, and extra pyramidal symptoms.[1,14]

However, taken together, the double-blind studies, in combination with open-label studies suggest that the effect of clozapine on negative symptoms occurs largely in the context of other clusters of psychopathology. Therefore, we cannot simply conclude whether clozapine truly treats primary negative symptoms or whether its effect is associated with secondary benefits on depressive, extra pyramidal, or positive symptoms.[15-17]

**Efficacy in neurocognitive function:** A study by McGurk *et al.*, [18] found that compared with baseline performance while receiving conventional antipsychotic medication, risperidone improved and clozapine worsened spatial working memory performance. The differential effects of these medications on spatial working memory may be due to the anticholinergic effects of clozapine and prefrontal dopamine-enhancing effects of risperidone.

Bilder *et al.* [19] examined the effects of clozapine, olanzapine, risperidone, and haloperidol on 16 measures of neurocognitive functioning in a double-blind, 14-week trial involving 101 patients. They found that clozapine yielded improvement in motor function, but not more than in other groups.

Purdon *et al.* [20] examined neuropsychological change after six weeks of clozapine treatment in 18 treatment-refractory patients. They found domain-specific gains on tests of motor and mental speed, visual spatial manipulation, and new verbal learning with clozapine.

**Clozapine in first episode schizophrenia:** Whether clozapine is more effective in acutely psychotic patients who are likely to respond to conventional antipsychotics is unclear, although few studies suggest that clozapine also has advantages in these patients.[21,22] A Cochrane review of first-episode studies reported that, "Whether the use of new generation antipsychotics really makes the treatment less off putting and enhances long-term compliance is unclear." [23]

**Long-term effectiveness:** Follow-up studies involving clozapine are very important in answering questions about whether therapeutic gains are maintained over long periods of time, and whether clozapine is safe and well-tolerated when taken over extended periods of time. The overall therapeutic efficacy across all groups ranged between 30 and 50%. [24,25]

**Schizophrenia with substance abuse:** In studies comparing different atypical and typical antipsychotics, clozapine showed better results than other treatments. Given the limited number of randomised controlled trials and the lack of placebo arms, further studies are needed to better address these findings.

### ***Mood disorder***

The available data support clozapine's effectiveness in acutely manic patient's treatment, resistant mania, schizoaffective disorder, bipolar disorder, and major depression with psychotic features.

### ***Neurological illnesses***

Clozapine has been evaluated for its effects in treating tremor or L-dopamine induced psychosis. Pakkenberg and Pakkenberg [26] evaluated the efficacy of low-dose clozapine in the treatment of benign essential tremor, tremor of idiopathic Parkinson's disease (IPD), alcohol tremor, and "tremor" of multiple sclerosis. They concluded that clozapine in doses of 75 mg or less was effective in reducing tremor in all of these disorders.

The effectiveness of clozapine in patients with IPD is supported by at least two double-blind studies. A report from the American Academy of Neurology recommends clozapine as a preferred agent for psychosis in Parkinson's disease. Patients with benign essential tremor or with Huntington's disease have also responded positively to clozapine.

**In TD:** Clozapine is frequently chosen because it has the least number of credible reports of inducing tardive symptoms. Several investigators have studied clozapine's effects on preexisting TD. Although the studies were small, uncontrolled, or just case reports, some found a therapeutic effect in reducing TD when at least moderate doses of clozapine were given. [1,27,28]

### ***Clozapine in special populations***

**Clozapine use in child and adolescent:** Despite the broad range of benefits associated with clozapine use in adults who have treatment-refractory schizophrenia, it remains underused in children and adolescents. This underuse may reflect the limited database in children to guide clinicians. [29,30]

Studies involving clozapine in treatment-refractory, early-onset schizophrenia-spectrum disorders have demonstrated the superiority of clozapine to haloperidol

and olanzapine with regard to reduction in negative symptoms and, to a certain degree, overall response.[31] Its efficacy has also been demonstrated in severe and treatment-resistant mania, and mixed episodes in adolescence.[32]

Side effects are found higher than that typically found in the adult population. It did not appear to be related to clozapine dose, clozapine or N-desmethyl clozapine plasma concentrations, or N-desmethyl clozapine/clozapine ratio.[30,33] In another study, Kumra *et al.*[34] in 1996 found that incidence of adverse events seems to be the same as reported in adults.

**Clozapine use in geriatric populations:** Controlled clinical trials with the clozapine in elderly patients with late-onset schizophrenia are lacking. Most of the studies are in the form of case series, small uncontrolled trials, or retrospective reviews.[35] Clozapine, because of its marked sedative and anticholinergic effects, has limited use in the treatment of late-onset schizophrenia. So, its use is common in the elderly with treatment resistant severely ill schizophrenia and whose psychosis is a feature of neurological morbidity (Parkinson's disease, dementia, etc.). Clozapine at a relatively low mean dose (134 mg daily) seems to be safe, tolerated, and effective in elderly psychiatric patients.[36]

There is also some suggestion that older patients are more susceptible to clozapine-induced agranulocytosis than younger patients.[37]

**Clozapine use in pregnancy and lactation:** Clozapine is rated as pregnancy category B. Studies have not revealed evidence that clozapine causes harm to the foetus. However, there are no adequate and well-controlled studies in pregnant women. Studies in animals suggest that clozapine is excreted in breast milk. As a result, women taking clozapine should not breastfeed.

## **Adverse reactions**

### ***Cardiovascular effects***

**Myocarditis:** Although the incidence of myocarditis is very low (approximately 2.8/100,000 patient-years), clinicians should consider the possibility of myocarditis when patients receiving clozapine present with unexplained fatigue, dyspnoea, tachypnoea, fever, chest pain, palpitations, and other evidence of cardiac failure. Mortality from myocarditis approaches 40%; early detection and treatment is important.

**Tachycardia:** Tachycardia from clozapine occurs in approximately 25% of patients, with a mean increase of ten to 15 beats per minute.[38] Tolerance generally develops within four to six weeks, but may limit the rate at which the dose can be raised.[39]

If sustained or symptomatic tachycardia occurs, an

electrocardiogram (ECG) can be obtained. Sinus tachycardia is the most common ECG abnormality caused by clozapine. Nonspecific ST-T segment changes, T-wave flattening, and inversions are sometimes seen, but are usually not clinically significant.

**Orthostatic hypotension:** Approximately nine per cent of patients receiving clozapine experience orthostatic hypotension.[38] It can be minimised if patients are advised to rise slowly from a sitting or lying position, especially in the morning and after meals. Increased fluid and salt intake may help by increasing blood volume. If these steps are ineffective, support stockings can be tried. Fludrocortisone, a potent mineralocorticoid, has been used to treat clozapine-related hypotension.[40]

### ***CNS adverse effect***

**Seizures:** A review of all patients exposed to clozapine during the first six months found the incidence of tonic-clonic seizures during that time to be 1.3%.[41] Seizures tend to occur during the upward titration phase of treatment or at doses greater than 600 mg per day. The incidence of abnormal electroencephalograms (EEGs) rises sharply for doses above 600 mg/day.

**Sedation:** Sedation is the most frequently reported adverse effect of clozapine, occurring in approximately 39% of patients. It appears early in treatment and patients gradually develop tolerance, usually within four to six weeks of treatment.[39]

**Delirium:** Susceptible patients, such as the elderly or those with organic cognitive deficits, may become delirious or confused when treated with clozapine. This condition has been temporarily reversed by the use of intravenous physostigmine, suggesting that the delirium is caused by the anticholinergic properties of clozapine.

**Peripheral anticholinergic effects:** Dry mouth, blurred vision, constipation, and urinary retention are commonly observed with clozapine. Constipation can be severe, particularly when patients fail to exercise or drink sufficient fluids. Other side effects of the autonomic nervous system, such as increased sweating, have also been reported.

### ***Adverse gastrointestinal effects***

Sialorrhoea occurs to some degree in most patients treated with clozapine, and tolerance does not usually develop.[42] Although hypersalivation is generally a benign side effect, patients sometimes describe a choking sensation at night and may even aspirate excess saliva.

Constipation occurs in 14% of patients treated with clozapine and can be severe. Clozapine use has been associated with impairment of intestinal peristalsis, ranging from constipation to intestinal obstruction, faecal impaction, and paralytic ileus. On rare occasions, these

can be been fatal.

Nausea tends to develop later in the course of treatment and affects 11% of patients.[39] Elevations in liver enzymes are usually mild and transient.

### ***Metabolic side effect***

**Weight gain:** Clozapine can be associated with a substantial amount of weight gain; a meta-analysis of short-term trials with clozapine found an average weight gain of 4.45 kg over ten weeks. Younger patients, including adolescents, may be more vulnerable to gaining weight on clozapine.

**Diabetes mellitus:** A growing body of evidence indicates that clozapine, along with some other second generation antipsychotics (SGAs), can increase the risk of type 2 diabetes mellitus. In a naturalistic study by David Henderson that monitored 82 patients over a five-year period, 36.6% developed diabetes.[43] It may also be helpful to inquire if patients are experiencing clinical signs of diabetes, such as polydipsia, polyuria, or weight loss.

### ***Adverse neuromuscular effects***

**Akathisia:** Akathisia has been reported in six per cent[39] to 39%[44] of patients treated with clozapine.

**Myoclonus:** Myoclonus occurs in approximately two per cent of patients treated with clozapine.[42]

**Neuroleptic malignant syndrome:** Consistent with clozapine's low affinity for D<sub>2</sub> receptors, there have been few reports of typical neuroleptic malignant syndrome developing in patients who were treated solely with clozapine; although, case reports of this syndrome developing in patients when concomitantly treated with lithium exist.

### ***Other important side effects***

**Haematopoietic system:** As per Cochrane review, blood problem occurred in participants receiving clozapine (3.2%) compared with those given typical antipsychotics (zero per cent) (n=1031, 13 RCTs, RR 7.09, CI 2.0 to 25.6).

The risk of agranulocytosis is highest in the first three months of clozapine treatment, and 95 per cent of the cases occur within the first six months.[42] Agranulocytosis occurs slightly more often in women, the elderly.[45] The pathophysiological mechanism is uncertain, but there is evidence of an immunological basis,[46] direct cytotoxicity of clozapine metabolites, and genetic risk factors. The risk can be well-managed by approved clozapine monitoring systems. If agranulocytosis is confirmed, it should be considered medical emergency; clozapine should be stopped. Further management includes haematological consultation, reverse isolation, and prophylactic antibiotics. Other drugs

that are known to suppress the bone marrow should be discontinued, if possible.[47] Recent advances in the use of granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor have decreased the morbidity of this disorder and can shorten its course.[47,48] Lithium has also been reported to speed the recovery of white cell counts when prescribed after the development of clozapine-induced agranulocytosis.[49]

Other less common haematological effects associated with clozapine include benign neutropenia, and a mild asymptomatic eosinophilia occurring in five to ten per cent of patients.

**Obsessive-compulsive symptoms:** It has been estimated that up to ten per cent of patients treated with clozapine develop obsessive-compulsive symptoms.[50]

**Enuresis:** Estimates of the incidence of urinary incontinence have ranged from 0.23 to 30%.

**Adverse thermoregulatory effects:** A benign fever occurs in about five per cent of patients during the initial phase of clozapine treatment. It usually lasts only a few days and rarely goes above 100°F. A determination of serum creatinine phosphokinase level should be considered. Mild hypothermia is seen in approximately 87% of clozapine-treated patients.[38]

### ***Overdose***

Fatal overdoses have been reported with clozapine, generally at doses above 2500 mg. There have also been reports of patients recovering from overdoses well in excess of 4 g. The commonly associated signs and symptoms with clozapine overdose reported are hypersalivation, altered states of consciousness, including drowsiness, delirium, and coma, tachycardia, hypotension, and respiratory depression or failure. Aspiration pneumonia and cardiac arrhythmias have also been reported. Seizures have occurred in a minority of reported cases. There are no specific antidotes for clozapine.

### ***Contraindications***

(1) An abnormally low white blood cell (WBC) count, i.e. less than  $3.5 \times 10^9/L$ , (2) A history of drug-induced agranulocytosis, i.e. absolute neutrophil count (ANC) of less than  $0.5 \times 10^9/L$ , (3) Bone marrow disorders, (4) Alcoholic and other toxic psychoses, (5) Drug intoxication, (6) Comatose condition, (7) Severe hepatic, renal, or cardiac diseases, (8) Previous hypersensitivity to clozapine or any other component of this drug, (9) Uncontrolled epilepsy, paralytic ileus.

### ***Dosages and administration***

**Initiating treatment:** Clozapine treatment should begin with 12.5 to 25 mg per day on the second day. The daily dose which should be administered is at least twice daily, can usually be increased by 25 mg every one or two days

until a target dose of 300 to 450 mg is reached. Subsequent dosage increases should be made no more than once or twice weekly in increments of no more than 100 mg. Patients who failed to respond in the 300 to 450 mg per day range and who do not have serious side effects can be increased gradually to doses as high as 900 mg per day.

**Duration of the treatment:** Once the appropriate dosage has been reached and the patients improve, the medication should be continued. There is evidence that patients who receive clozapine will continue to improve over a three to six months period. If there are concerns that patients are experiencing excessive side effects or an inadequate response, measurement of plasma concentration may be helpful. Levels above 350 ng/ml are an indication that patients are receiving adequate dosages of clozapine.

**Adequate trial:** In most studies, clinical response has been defined as a reduction in the Brief Psychiatric Rating Scale (BPRS) or PANSS score of at least 20%. However, the time and dose parameters for an adequate clozapine trial remain controversial. Reports suggest that response rate to clozapine and other atypical increases substantially between six weeks and six months, and more gradually between six months and a year.

**Discontinuing clozapine:** Clozapine should not be stopped abruptly (unless patients have developed agranulocytosis). In some individuals, the sudden discontinuation of clozapine has led to a severe exacerbation of their underlying illness. In addition, withdrawal of a potent antimuscarinic agent such as clozapine can lead to cholinergic rebound, with symptoms such as nausea and vomiting. For these reasons, it should be gradually cross-tapered from clozapine to another antipsychotic over two to four weeks.

### **Predictors of clozapine response**

Attempts at identifying such predictors have not been very rewarding to date and further research is necessary. According to various studies, following are the good predictors: male gender,[16] later age at onset,[16] shorter duration of illness,[16] higher levels of positive symptoms and lower levels of negative symptoms,[51] weight gain,[12] paranoid subtype of schizophrenia.[16,51]

Studies have reported conflicting results regarding an association with gender, duration of illness, and paranoid features.[16,51] Although there is considerable, if controversial, evidence that weight gain is related to the improvement in psychopathology.[12] Progression and successive psychotic exacerbations may result in diminished therapeutic responsiveness to clozapine.

Chung and Remington[52] suggested that as yet there are no predictors of response to clozapine; rather, there are markers. Higher baseline clinical symptoms and

functioning in the previous years and low cerebrospinal homovanillic acid/5-hydroxyindoleacetic acid levels were identified as reliable markers. Other potential measures reported are reduction of frontal cortex metabolic activity, reduction of caudate volume, and improvement in P50 sensory gating.

### **Pharmacogenetic prediction of clozapine response:**

Association studies of multiple candidate genes found a combination of six polymorphisms showing the strongest association with response (HTR2A 102T/C and His452Tyr; HTR2C-330GT/-244CT and Cys23Ser; 5-HTTLPR; H<sub>2</sub>-1018G/A). The results suggested that CYP1A2 polymorphisms might be associated with clozapine response, but so far attempts to replicate this finding have been inconsistent.[53]

### **Clozapine resistance**

The prevalence of treatment resistance in schizophrenia is around 18-60%. Approximately 40-70% of treatment resistant schizophrenia patients are also clozapine resistant having deficits in all domains. Despite clozapine monotherapy, such patients are called "partial responders to clozapine", "clozapine resistant", or even "super refractory".

**Clozapine augmentation strategies:** The number of controlled studies evaluating augmentation of clozapine in schizophrenia patients is highest for risperidone and lamotrigine. However, the results of recent meta-analyses studies do not support any benefit of either agent. Some evidence regarding the success of clozapine augmentation with amisulpride, aripiprazole, mirtazapine, omega 3 fatty acids and electroconvulsive therapy (ECT) have been obtained. Considering the limitations of these studies that includes small sample size, variable definitions of clozapine resistance, heterogeneity of outcome measures, and methodological designs, more research is needed to establish true efficacy and safety of clozapine augmentation strategies.[54]

Expert consensus guidelines (1999) for choice of clozapine augmentation: add anticonvulsant to clozapine, combine typical antipsychotic, combine another atypical antipsychotic, add lithium, add ECT, add benzodiazepines.

### **Clozapine related molecules**

Substitutions for the A-ring have led to other clinically effective clozapine-like agents. Clozapine-derivative antipsychotic agents are loxapine, olanzapine, and quetiapine. But, being a derivative does not translate to similar efficacy. This led to a search for novel antipsychotics with excellent efficacy and better tolerability. Because, though less in comparison to other antipsychotics, still there are reports like prolactin elevation with olanzapine,[55] and acute dystonia and tardive oculogyric crisis with quetiapine.[56,57]

**Norclozapine (N-desmethyl clozapine):** It is a major metabolite of clozapine formed by its demethylation and shares many functional properties with clozapine. At the mechanistic level, N-desmethyl clozapine has a high ratio of 5-HT<sub>1c</sub> to D<sub>2</sub> affinities, comparable to clozapine. In addition, N-desmethyl clozapine is also a potent M<sub>1</sub> muscarinic receptor agonist, considering the reported cognitive enhancing properties of muscarinic potentiators. N-desmethyl clozapine has shown potential as a procognitive compound in clinical trials. It seems that N-desmethyl clozapine may be associated with more metabolic side effects than the parent compound clozapine, which may therefore reduce its overall tolerability profile. However, there are little data on N-desmethyl clozapine alone as having specific potential antipsychotic effects. Clinical data on its antipsychotic efficacy are scant at this point.[58]

**Jl13, a pyridobenzoxazepine compound:** It is a potential new atypical antipsychotic, structurally modified from clozapine, to resist oxidation, so as to reduce haematological and cardiological side effects. Stimulation of 5-HT<sub>1A</sub> and blockade of 5-HT<sub>2A</sub> receptors may contribute to the effects.

**Clozaprexin (DHA-clozapine):** It uses the fatty acid docosahexaenoic acid (DHA) as its lipid vector. And hypothesised that by linking the known atypical antipsychotic clozapine to DHA, they could increase the effectiveness of the clozapine by targeting its effects to the brain “targaceuticals” and at the same time, reduces the peripheral activity of the drug.

**LY404039:** Is a selective agonist for metabotropic glutamate 2/3 (mGlu2/3) receptors evaluated in schizophrenia patients with olanzapine as an active control in a randomised, three-armed, double-blind, placebo-controlled study, found safe and well-tolerated; with statistically significant improvements in both positive and negative symptoms of schizophrenia compared to placebo. It is not found to be associated with prolactin elevation, extra pyramidal symptoms, and weight gain.[59]

## Conclusion

Published clinical evidence has supported clozapine as the gold standard in the treatment of refractory schizophrenia, suicidal patients of schizophrenia and schizoaffective disorder. On the other hand, the molecule is having some serious side-effects like agranulocytosis, myocarditis, and seizures. Efforts are needed to optimise clozapine's utilisation as it is a double edged sword. Since clozapine is the prototype “atypical” drug, defining the role of the individual complex actions of this drug that are responsible for its unique therapeutic profile is needed. Clearly this drug continues to present both opportunity and challenge to the field of psychiatry.

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