

## CLOZAPINE

### Introduction

**Clozapine**, (trade name “**Clopine**” and “**Clozaril**” in Australia) is a second generation “atypical” antipsychotic agent.

Due to its potential for significant toxicity, it is reserved for patients who are **unresponsive** to, or **intolerant** of, other antipsychotics.

It is more effective in reducing symptoms of schizophrenia than the first generation “typical” antipsychotics, and has more pronounced effects in those who have responded poorly to other medication

Clozapine is a **restricted drug** that has specific prescribing indications including:

1. Acute and chronic psychoses (e.g. schizophrenia):
  - Schizophrenia in people **unresponsive** to, or **intolerant** of, other antipsychotics (i.e. lack of satisfactory clinical response, despite the use of adequate doses of drugs from at least 2 groups of antipsychotics for a reasonable duration; or the development of serious extrapyramidal side effects, such as tardive dyskinesia).
2. Bipolar disorder.

**Clozapine has 4 important idiosyncratic potentially life-threatening reactions that can occur with normal therapeutic dosing.**

**These include:**

1. **Neutropenia**
2. **Myocarditis/ cardiomyopathy**
3. **Neuroleptic malignant syndrome**
4. **Lowering of seizure threshold.**

**Clozapine prescribing requires specific registration of medical practitioners, pharmacists and patients**

**All patients taking clozapine are registered at an approved clozapine monitoring service where ongoing monitoring is required for the detection of neutropenia and agranulocytosis.**

See also separate documents on:

- **Clozapine Toxicity (in Toxicology folder)**
- **Febrile Neutropenia (in Infectious Diseases folder)**
- **Myocarditis (in CVS folder)**

### History

Although often conceived of as a new drug clozapine was first synthesized in 1958 by Wander AG, a Swiss pharmaceutical company.

It was based on the chemical structure of the tricyclic antidepressant **imipramine**.

Clozapine was introduced into clinical practice in 1972, in Switzerland and Austria as “Leponex”.

In 1975, after reports of fatal agranulocytosis leading to death in some clozapine-treated patients, clozapine was voluntarily withdrawn by the manufacturer. It then fell out of favor for more than a decade.

When further studies demonstrated that clozapine was more effective against **treatment-resistant** schizophrenia than other antipsychotics, the FDA and health authorities in other countries approved its use only for **treatment-resistant schizophrenia**. Prescribing was strictly controlled including a Patient Registry and regular hematological monitoring to screen for granulocytopenia.

In December 2002, clozapine was approved in the US for reducing the risk of suicide in schizophrenic or schizoaffective patients judged to be at chronic risk for suicidal behavior.

### Chemistry

Clozapine is a tricyclic di-benzo-diazepine derivative.

### Classification

There is no formal classification of the antipsychotic agents, however by tradition they are loosely divided into two principal groups.

1. The older “**first generation**” or “**typical**” group.
2. The newer “**second generation**” or “**atypical**” group.

**In general the second generation agents have significantly less adverse effects profiles such as sedation, extrapyramidal side effects, anticholinergic effects or the development of neuroleptic malignant syndrome. The risk of these particular adverse effects although small is not completely eliminated with the second generation agents.**

It has also been claimed that the second generation agents are more effective against the “negative” symptoms of schizophrenia, but this has *not* been convincingly proven as a *class* effect.

It should be noted that designating antipsychotics as first generation and second generation may be of limited value as it probably exaggerates the differences between groups and overstates similarities between members within each group. On this basis some prefer not to use this classification; nonetheless the terminology remains widely used.

### **First Generation Antipsychotic Agents :**

These fall into two major groups:

#### **1. Phenothiazines:**

- *Lower potency:*
  - Chlorpromazine.
  - Pericyazine.
  - Thioridazine.
- *Higher potency:*
  - Fluphenazine.
  - Flupenthixol
  - Prochlorperazine
  - Trifluoperazine.
  - Zuclopenthixol

#### **2. Butyrophenones:**

- Droperidol.
- Haloperidol.

## Second Generation Antipsychotic Agents :

These include:

1. Amisulpride
2. Aripiprazole
3. Asenapine
4. **Clozapine**
5. Olanzapine
6. Paliperidone
7. Quetiapine
8. Risperidone
9. Ziprasidone

### Preparations

Clozapine as:

#### Tablets:

- 25 mg
- 50 mg
- 100 mg
- 200 mg

#### Oral liquid:

- 50 mg/mL, 100 mL

### Mechanism of Action

In general terms, antipsychotic actions are thought to be mediated (at least in part) by blockade of dopaminergic transmission in various parts of the brain (in particular the limbic system).

Evidence suggests:

1. All effective antipsychotics block D2 receptors
2. Differential blockade of other dopamine receptors (e.g. D1) may influence therapeutic and adverse effects
3. Antagonism of other receptors may influence antipsychotic activity, e.g. 5HT2 antagonism with some agents.

Clozapine has relatively weak D2 and D1-receptor blocking activity.

It has potent:

- Noradrenolytic activity.
- Anticholinergic activity.
- Antihistaminic activity.
- Arousal reaction inhibiting effects.
- It has also been shown to possess **anti**-serotonergic properties, (and so would not be expected to cause/ aggravate serotonin toxicity).

### Pharmacodynamics

Clozapine produces rapid and marked **sedation**, and **exerts antipsychotic** effects.

In particular, the latter have been shown in people with schizophrenia that are resistant to other drug treatment.

In such cases, clozapine has proven effective in relieving both positive and negative symptoms of schizophrenia, with about one-third of patients showing clinically relevant improvement.

### Pharmacokinetics

#### Absorption:

- Clozapine is well absorbed orally, however is subject to a moderate first pass metabolism, resulting in an absolute bioavailability of around 50 - 60%.

#### Distribution

- It has a moderate Vd, at 0.5 - 3 liters /Kg.
- Clozapine is around 95% bound to plasma proteins.
- Clozapine can cross the human placenta.

- Clozapine is excreted in human breast milk.

#### Metabolism and excretion:

- Clozapine is almost completely metabolized by the cytochrome P450 system (1A2 & 2D6) prior to excretion.

Of the main metabolites, only one, the des-methyl metabolite, was found to be active. Its pharmacological actions resemble those of clozapine, but are considerably weaker and of shorter duration.

- Half-life is around 12 hours.

#### Indications

Clozapine is a **restricted drug** that has specific prescribing indications including:

1. Acute and chronic psychoses (e.g. schizophrenia):
  - Schizophrenia in people **unresponsive** to, or **intolerant** of, other antipsychotics (i.e. lack of satisfactory clinical response, despite the use of adequate doses of drugs from at least 2 groups of antipsychotics for a reasonable duration; or the development of serious extrapyramidal side effects, such as tardive dyskinesia).
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#### Contra-indications/precautions

These include:

1. Known hypersensitivity to clozapine.
2. Patients with a history of drug induced granulocytopenia/ agranulocytosis.
3. Bone marrow disorders (relative contraindication) :
  - Patients with a history of bone marrow disorders may be treated only if the benefit outweighs the risk.

They should be carefully reviewed by a **haematologist** prior to starting treatment with clozapine.

**Drugs** known to have a substantial potential to depress bone marrow function should not be used concurrently with clozapine.

In addition, the concomitant use of long acting depot antipsychotics should be avoided because of the inability of these medications, which may have the potential to be myelosuppressive, to be rapidly removed from the body in situations where this may be required, e.g. granulocytopenia.

4. Circulatory collapse and/or CNS depression due to any cause.
5. Alcoholic and other toxic psychoses; drug intoxication; comatose conditions.
6. Severe renal disease
7. Cardiac disease (in particular **myocarditis**).
8. Severe hepatic disease including active hepatic disease associated with nausea, anorexia or jaundice; progressive hepatic disease; hepatic failure.
9. Poorly controlled epilepsy:
  - Clozapine can cause EEG changes, including the occurrence of spike and wave complexes.

Clozapine lowers the seizure threshold in a dose dependent manner and may induce myoclonic jerks or generalized seizures.

Caution should be used in administering clozapine to patients having a history of seizures or other predisposing factors.

These symptoms are more likely to occur with **rapid dose increase** and in patients with **pre-existing epilepsy**. In this case the dose should be reduced and, if necessary, anticonvulsant treatment initiated.

10. Paralytic ileus.
11. Pregnancy/ lactation (see below)

### Pregnancy

Clozapine is a category C drug with respect to pregnancy.

Category C drug drugs are those drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or

neonate without causing malformations. These effects may be reversible. Specialised texts should be consulted for further details.

From the limited information available, clozapine has not been associated with an increased risk of congenital malformations.

However, the accumulation of clozapine in the fetus may increase the risk of gestational metabolic complications diabetes, floppy infant syndrome and neonatal seizures. Consultation with a perinatal psychiatrist is recommended if the initiation, continuation or discontinuation of clozapine therapy is required during pregnancy.

If clozapine is used during pregnancy, consider tapering the medicine to the lowest effective dose prior to the onset of labour, as this will lower the drug load in the newborn and may reduce the risk of infant exposure.

However, this decision should be individualised, as dose reduction is associated with a risk of relapse in the mother.

In addition to the routine monitoring of clozapine blood levels, close monitoring of maternal blood glucose levels is required throughout the pregnancy.

Inform neonatal care providers about the maternal use of clozapine as potential adverse effects or withdrawal symptoms may present in the newborn.

There is still a lack of information regarding the long term behavioural and cognitive outcomes of infants exposed to clozapine in utero.

### Breast feeding

There is limited safety information available following the use of clozapine during breastfeeding.

High concentrations of clozapine have been found in breast milk, and the breastfed infant may develop serious adverse events such as seizures and cardiovascular instability.

To date, the theoretical risk of leukopenia or agranulocytosis has not been demonstrated in breastfed infants.

When considering clozapine for breastfeeding women, each case needs to be considered individually.

However, due to potential serious adverse effects in the breastfed infant, it is recommended that women avoid breastfeeding while on clozapine.

Consultation with a perinatal psychiatrist for further advice is recommended.



## Adverse Effects

Clozapine has 4 important idiosyncratic potentially life-threatening reactions that can occur with normal therapeutic dosing.

These include:

### 1. Neutropenia

- **Patients who present with a fever, should be considered as potential “febrile neutropenic patient”.**

Development of granulocytopenia and agranulocytosis is a risk inherent to clozapine treatment.

Although generally reversible on withdrawal of the drug, agranulocytosis can prove fatal. The majority of cases occur within the first 18 weeks of treatment.

Because immediate withdrawal of the drug is required to prevent the development of life threatening agranulocytosis, monitoring of the white blood cell (WBC) count is mandatory.

**See also separate document Febrile Neutropenia (in Infectious Disease folder)**

### 2. Myocarditis/ cardiomyopathy

- In patients who develop persistent tachycardia at rest accompanied by other signs and symptoms of heart failure (e.g. tachypnoea, shortness of breath, hypotension, raised jugular venous pressure) or arrhythmias, the possibility of myocarditis or cardiomyopathy must be considered.

**See also separate document Clozapine Toxicity (in Toxicology folder)**

### 3. Neuroleptic malignant syndrome

- The risk appears to be much less than that of the first generation antipsychotic agents.

**See also separate document Neuroleptic malignant syndrome (in Toxicology folder)**

### 4. Lowering of seizure threshold

*Other adverse effects can include:*

### 5. Other hematological reactions:

### Eosinophilia:

- Unexplained leucocytosis and/or eosinophilia may occur especially in the initial weeks of treatment. In the event of eosinophilia).

It is recommended to discontinue clozapine if the eosinophil count rises above 3,000/mm<sup>3</sup> and to restart therapy only after the eosinophil count has fallen below 1,000/mm<sup>3</sup>.

### Thrombocytopenia:

- In the event of thrombocytopenia it is recommended to discontinue clozapine if the platelet count falls below 50,000/mm<sup>3</sup>.

#### 6. Sedation:

- Owing to the ability of clozapine to cause sedation (and lower the seizure threshold), activities such as driving or operating machinery and other activities where sudden loss of consciousness could cause serious risk to the patient or others should be avoided, especially during the initial weeks of treatment.

#### 7. Orthostatic hypotension:

- Tachycardia and postural hypotension with or without syncope may occur especially in the initial weeks of treatment and may represent a continuing risk in some patients.

#### 8. Extrapyrarnidal effects:

- Clozapine is relatively **free** from extrapyramidal side effects, such as acute dystonias, parkinsonian type syndromes, akathisia or tardive dyskinesia when compared with “typical” (i.e first generation) antipsychotic agents.

There have been **no** reports of tardive dyskinesia directly attributable to clozapine alone.

In contrast to typical antipsychotic drugs, clozapine therapy produces little or no prolactin elevation, sparing adverse effects such as gynaecomastia, amenorrhoea, galactorrhoea or impotence.

#### 9. Anticholinergic effects:

- Clozapine has anticholinergic activity and so may produce undesirable anticholinergic effects such urinary retention, dry mouth, blurring vision, constipation and precipitation of narrow angle glaucoma.

It is contraindicated in paralytic ileus.

10. Maculopathy:

- An underappreciated, but fortunately rare, significant ocular adverse effect is clozapine induce maculopathy.<sup>5</sup>

### Dosing

Usual adult dosing is as follows:

- Oral **12.5 mg** on the first day.

Increased to **25 - 50 mg** on second day.

If well tolerated, increase in 25 - 50 mg increments to 300 mg daily within 2 - 3 weeks.

Then increase in 50 - 100 mg increments at 4 - 7-day intervals if required.

Usual dosage range is 200 - 600 mg daily (to a maximum of **900 mg** daily).

Doses up to **300 mg** are usually given as a **single dose** in the **evening**. Larger doses may need to be divided to minimise adverse effects.

In the event of **planned** termination of clozapine therapy, a gradual reduction in dose is recommended over a 1 -2 week period.

### Monitoring:

Before starting clozapine treatment, a white blood cell (WBC) count and a differential count must be performed within ten days prior to starting clozapine treatment to ensure normal leucocyte count (WBC count > 3500/mm<sup>3</sup>, normal differential blood count, and normal absolute neutrophil counts.

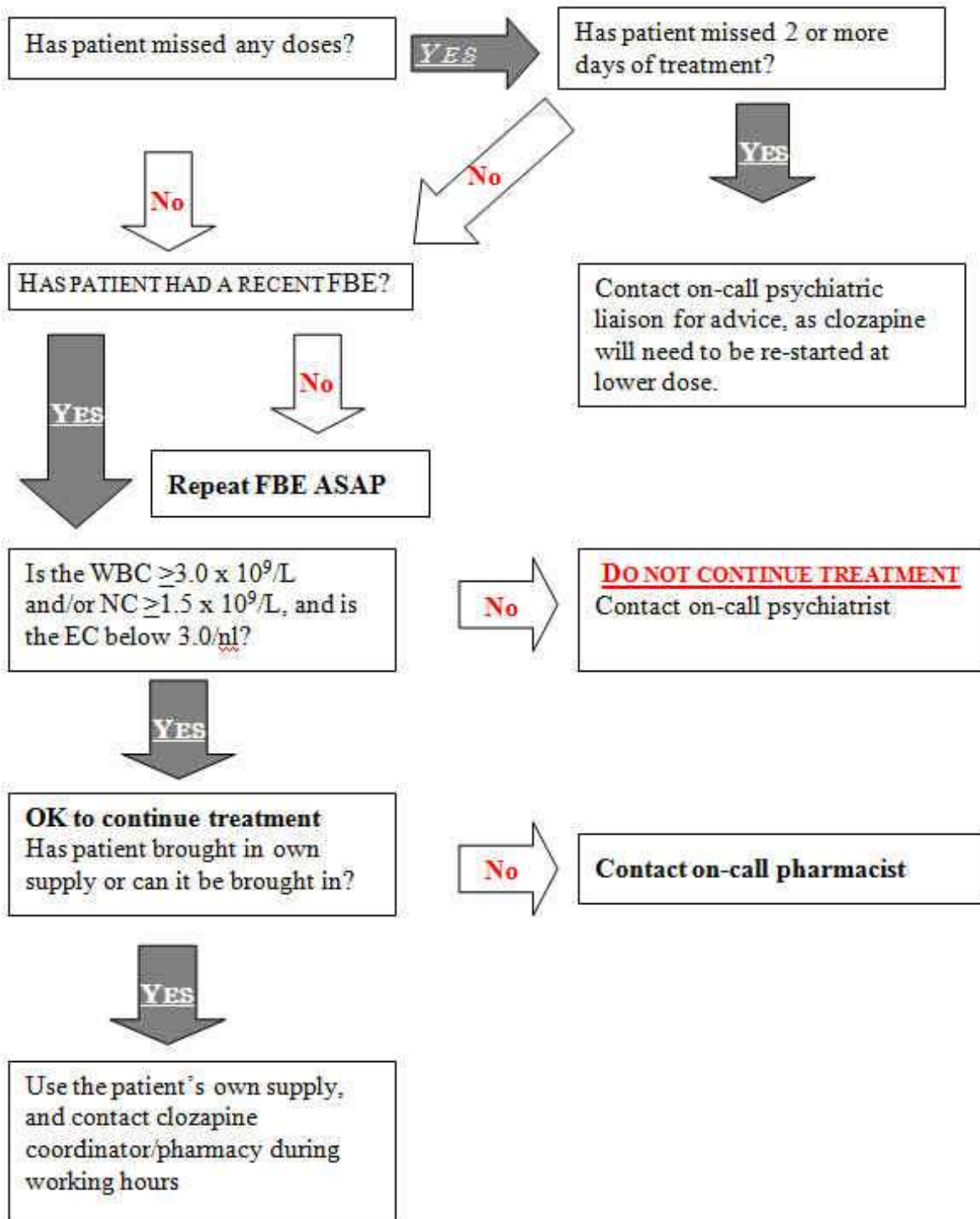
After the start of clozapine treatment the WBC and neutrophil count must be monitored weekly for **18 weeks**.

Thereafter the WBC and neutrophil must be performed at least monthly throughout treatment and for one month after complete discontinuation of clozapine.

At each consultation the patient should be reminded to contact the treating doctor immediately if any kind of infection begins to develop.

## Appendix 1

Monitoring of FBE in patients on clozapine who present to the ED:



## Appendix 2

### Monitoring and Advice Concerning Clozapine

The reason for the limited use of clozapine is because of rare but serious adverse effects e.g. agranulocytosis, seizures, myocarditis and cardiomyopathy.

It is available in Australia as Clozaril (Novartis) and Clopine (Pfizer), and both these pharmaceutical companies have Patient Monitoring Systems that have centralised databases, protocols and track relevant investigations to prevent the serious adverse effects.

For any further advice the following should be contacted:

#### **Treating Psychiatrist**

#### **Local hospital Clozapine coordinator**

#### **CLOZARIL- (Novartis)**

CPMS Office (Clozaril Patient Monitoring System): 1800 501 768 (Free Call)

Novartis Medical Information: 1800 810 644

Adverse Reaction Reporting: 1800 814 667

For 24 hours advice from Novartis: 1800 501 677

#### **CLOPINE – (Pfizer)**

Clopine Central Phone 1800 656 403

Medical information Phone 1800 675 229

## References

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4. Clozapine in RWH Pregnancy & Breastfeeding Guidelines; 18 August 2017.
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