Clozapine
Therapy, side effects, monitoring requirements
eLearning package

Version: August 2017
Custodian: Medication Safety, Quality Improvement and Change Management Unit
Learning Outcomes

- Indications and dosing for clozapine therapy
- Common side effects, impact and management options
- Monitoring requirements
- Important drug interactions with clozapine
- Clozapine chart and forms to document the clinical review
- Recommencement dose after interruption, or compliance uncertainty
- Discontinuation protocol
- Consumer and carer perspectives on clozapine therapy
Clozapine

- Clozapine, an atypical antipsychotic, is considered a high risk medication.
- It is indicated in the management of treatment resistant schizophrenia.
- Side effects can be life threatening (e.g. agranulocytosis, myocarditis).
- Clozapine therapy must be started at low doses and titrated slowly to minimise side effects.
- Even after a short cessation (> 48 hours) of clozapine therapy, consumers must be recommenced on a low dose and re-titrated to a therapeutic dose. Additional monitoring will be required if cessation is for ≥ 72 hours.
- Prescribers and pharmacists need to be registered with the clozapine monitoring system.
- Approximately 1350 consumers are on the clozapine register in WA. (April 2017)

Click on video interview: Nathan Gibson

Clozapine is an effective antipsychotic medication for the management of treatment resistant schizophrenia in cases where consumers are non-responsive, or suffer intolerable side effects, to at least two neuroleptic agents other than clozapine. Clozapine improves outcomes in around 50–60% of these consumers (Meltzer, 1997). However, because of the risk of neutropenia and agranulocytosis, as well as other potentially life threatening side effects, all consumers taking clozapine are enrolled in a registry and monitored regularly.
Clozapine Risk : Benefit Summary

Benefits
- Improvements in positive and negative symptoms.
- Reduction in suicidal ideation.
- Low extra pyramidal symptoms (EPS) compared with other antipsychotics.
- Improvement in cognition.
- Reduced tendency for aggression leading to an improvement in quality of life.

Risks
- Agranulocytosis.
- Myocarditis / cardiomyopathy.
- Seizures.
- Metabolic syndrome.
Prior to commencing clozapine

- **Obtain informed consent from the consumer.**
  (with the exception of consumers who do not demonstrate capacity or who are unable to give informed consent for treatment S25 (1) and S22 (1) WA Mental Health Act 2014).

- **Reach consumer agreement to initiate treatment and comply with regular blood monitoring regimen.**
  (Weekly for 18 weeks of initial treatment, then 4 weekly thereafter).

- **Obtain consent for inclusion on the clozapine database.**
  (clozapine privacy agreement form).

Refer to the [WA Health Consent to Treatment Policy 2016](#)
Clozapine Therapy Monitoring Requirements

- All consumers and health care professionals involved in the prescription and supply of clozapine must be registered with a Clozapine Patient Monitoring System before starting treatment e.g. ClopineCentral™

- Blood monitoring is mandatory for the prescription of clozapine. White blood cell (WBC) and Neutrophil count (NC) are measured weekly for 18 weeks and every 28 days thereafter, continuing for the duration of treatment with clozapine.

- Ongoing regular physical health monitoring and checking with the consumer as to any side effects that are problematic should complement blood monitoring protocols. (use local site monitoring forms)
WA Clozapine Initiation and Titration Chart

In 2015, a specialised chart was developed for WA Health to provide a standardisation of care for initiation, titration and monitoring of clozapine within mental health units.

The chart guides baseline testing and monitoring for consumers during the first 28 days of therapy.

Mental Health Charts and Clozapine Resources

Resources available include:

- WA Clozapine Initiation and Titration Chart
- WA Clozapine Initiation and Titration Chart Guidelines
- WA Clozapine Initiation and Titration Chart Education Resource
- Guidelines for the Safe and Quality Use of Clozapine in the WA Health System
- Clozapine Monitoring Form
- Guidelines for Clozapine Monitoring Form
- Side effects associated with clozapine therapy
- Clinician prompt checklist to assess clozapine side effects
Baseline measurements prior to commencing clozapine

Baseline measurements:

- Full blood count (FBC) including
  - White blood cell (WBC)
  - Neutrophils (NC)
- Blood group
- Urea / electrolytes
- Fasting glucose and lipids
- Liver function tests
- C-reactive protein (CRP)
- Troponin
- Echocardiogram (Echo)
- Electrocardiogram (ECG)
- Physical examination: including consumer weight, height, Body Mass Index (BMI), waist circumference.
- Monitoring
  - BP (lying and standing)
  - Temperature
  - Pulse
  - Level of consciousness
WBC and NC Blood tests

- Blood monitoring to initiate therapy and cease therapy remains the responsibility of the treating psychiatrist.
- White Blood Cell (WBC) count and Neutrophil Count (NC) are assessed by the psychiatrist prior to commencement of clozapine.
- Blood monitoring continues weekly for first 18 weeks and every 28 days thereafter.

Increase blood monitoring if:
- Consumer reports signs and symptoms of infection.
- Manifestations of infection – mouth ulceration, fever and/or sore throat.
- WBC or NC levels fall in the amber or red range for monitoring (see next slide)

## Clozapine Blood Results Monitoring System

<table>
<thead>
<tr>
<th>Clozapine Blood Results Monitoring System</th>
<th>Recommended Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Green Range</strong></td>
<td><strong>Prior to Initiation</strong>&lt;br&gt;Clozapine therapy may be commenced subject to assessment by the treating medical officer and successful registration with a Clozapine Patient Monitoring System (e.g. ClopineCentral™)</td>
</tr>
<tr>
<td><strong>Amber Range</strong></td>
<td><strong>Ongoing monitoring</strong>&lt;br&gt;Continue clozapine therapy</td>
</tr>
<tr>
<td><strong>Red Range</strong></td>
<td><strong>DO NOT START THERAPY.</strong>&lt;br&gt;Seek haematologist advice</td>
</tr>
</tbody>
</table>

### Green Range
- WBC > 3.5 x 10⁹/L and<br>NC > 2.0 x 10⁹/L

### Amber Range
- WBC 3.0 to 3.5 x 10⁹/L and/or<br>NC 1.5 to 2.0 x 10⁹/L
  - Repeat blood count after one week. If still within same range, clozapine therapy may commence subject to assessment by the treating medical officer and successful registration
  - Continue clozapine therapy with twice-weekly blood tests until return to green range.

### Red Range
- WBC < 3.0 x 10⁹/L and/or<br>NC < 1.5 x 10⁹/L
  - STOP CLOZAPINE THERAPY IMMEDIATELY.<br>Consult treating psychiatrist and contact haematologist and Clozapine Patient Monitoring System (e.g. ClopineCentral™)
Other blood tests

Bloods must be taken within 48 hours before clinic review appointment

<table>
<thead>
<tr>
<th>Troponin and CRP</th>
<th>Fasting BGL and Lipids</th>
<th>ECG</th>
<th>Echocardiogram</th>
<th>Clozapine level</th>
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</thead>
<tbody>
<tr>
<td>Baseline</td>
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<td>week 1-6</td>
<td>3 months</td>
<td>weeks 1-4</td>
<td>3-6 months</td>
<td>5 weeks</td>
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<td>3 months</td>
<td>6 monthly</td>
<td>3 months</td>
<td>as clinically indicated</td>
<td>3 months</td>
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<td>6 monthly</td>
<td></td>
<td>Yearly</td>
<td>as clinically indicated</td>
<td>6 monthly</td>
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</tbody>
</table>

Download *Clozapine monitoring form

Click to download

and *Guidelines for completing the clozapine monitoring form

Click to download

Important drug interactions with clozapine

<table>
<thead>
<tr>
<th>Potential to increase clozapine levels</th>
<th>Potential to depress bone marrow</th>
<th>Potential to decrease clozapine levels</th>
<th>Potential to depress respiration</th>
<th>Potential for hypotension</th>
<th>Potential for anticholinergic side effects</th>
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<tr>
<td>• Selective serotonin reuptake inhibitors (SSRI's)</td>
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<td>‧ Fluvoxamine (very large effect)</td>
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<td>‧ Fluoxetine</td>
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<td>‧ Paroxetine</td>
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<td>‧ Sertraline (large doses)</td>
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<td>• Ciprofloxacin</td>
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<td>• Cimetidine</td>
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<td>• Some macrolide antibiotics including:</td>
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<td>‧ Erythromycin</td>
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<td>‧ Clarithromycin</td>
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<td>‧ Azithromycin</td>
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<td>• Caffeine (large doses)</td>
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<td>• Carbamazepine</td>
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<td>• Trimethoprim / Sulamethoxazole</td>
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<td>• Nitrofurantoin</td>
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<td>• Cytotoxic medication</td>
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<td>• Immunosuppressant medication</td>
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<td>• Phenothiazines</td>
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<td>• Carbamazepine</td>
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<td>• Rifampicin</td>
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<td>• St Johns Wort</td>
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<td>• Omeprazole</td>
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<td>• Phenytoin</td>
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<td>• Phenobarbitone</td>
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<td>• Benzodiazepines (especially large parenteral doses or at start of therapy)</td>
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<td>• Antihypertensives</td>
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<td>• TCA's (Tricyclic antidepressants)</td>
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<td>• Some antipsychotics e.g.</td>
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<td>‧ Chlorpromazine</td>
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<td>‧ Pericyazine</td>
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<td>‧ Trifluoperazine</td>
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<td>‧ Risperidone (initially)</td>
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<td>‧ Quetiapine (initially)</td>
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<td>Anticholinergic TCA's e.g.</td>
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<td>• Amitriptyline</td>
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<td>• Dosulepin</td>
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<td>Anticolinergic antipsychotics e.g.</td>
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<td>• Chlorpromazine</td>
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<td>• Pericyazine</td>
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<td>• Quetiapine</td>
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<td>EPSE medication e.g.</td>
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<td>• Trihexyphenidyl</td>
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<td>• Benzaptropine</td>
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<td>• Biperiden</td>
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<td>Sedating antihistamines e.g.</td>
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<td>• Diphenhydramine</td>
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<td>• Cyproheptadine</td>
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<td>• Promethazhine</td>
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<td>• Trimeprazine</td>
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<td>Gastrointestinal antispasmodics e.g.</td>
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<td>• Atropine</td>
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<td>• hyoscine</td>
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Interactions between clozapine and other drugs: SA Health
Smoking and Caffeine

Document baseline smoking and caffeine intake habits and update at each clinical review
Lifestyle changes involving increasing/decreasing smoking and caffeine intake can affect clozapine metabolism and may lead to toxicity.

Smoking
- Cessation of smoking increases clozapine levels which may result in toxicity
- Cigarette smoke decreases clozapine levels
  (poly-hydrocarbons in the tar affect clozapine levels)
- Nicotine replacement therapy (NRT) does not affect clozapine levels

Caffeine
- Caffeine increases clozapine levels which may result in toxicity
- Be mindful of increased/decreased consumption of energy drinks e.g. Coke
Therapeutic dose range of clozapine

- Usual dosage range is **200 – 450 mg/day** (divided dose).
- Recommended maximum daily dose is **600mg**.
- Dosing up to but not exceeding **900mg/day** has been used for exceptional cases only.
- Doses > **450 mg** increase the possibility of side effects and adverse events, including seizures.

*Clopine® Product Information, approved by the Therapeutics Goods Administration 14 July 2004, amended 12 June 2009*

Ongoing clozapine clinical reviews

Protocol requirement:

- Aim to schedule appointments on the same day to **establish a routine**.
- The consumer must be reviewed **weekly** by a medical officer for the **first 18 weeks** to assess for signs and symptoms of infection.
- The consumer’s **weight, blood pressure, BMI, waist circumference, pulse, and temperature** should be measured at **each visit** (weekly or monthly) and recorded on the **clozapine monitoring form**. This may be done by a clozapine nurse prior to the doctor’s appointment.
- Treating doctor to **complete documentation** to confirm blood levels have been reviewed and prescription written for supply.
Common side effects

<table>
<thead>
<tr>
<th>Cardiovascular effects</th>
<th>Metabolic effects</th>
<th>Haematological effects</th>
<th>Gastrointestinal effects</th>
<th>Central Nervous System effects</th>
<th>Other effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Tachycardia (very common)</td>
<td>• Dyslipidaemia (very common)</td>
<td>• Neutropenia (rare)</td>
<td>• Hypersalivation (very common)</td>
<td>• Sedation (very common)</td>
<td>• Urinary incontinence (common)</td>
</tr>
<tr>
<td>• Hypertension (common)</td>
<td>• Weight gain (very common)</td>
<td>• Agranulocytosis (rare)</td>
<td>• Nausea (very common)</td>
<td>• Seizures (rare)</td>
<td>• Fever (very common)</td>
</tr>
<tr>
<td>• Hypotension (very common)</td>
<td>• Impaired glucose tolerance (common)</td>
<td>• Constipation (very common)</td>
<td>• Myoclonic jerks (common)</td>
<td>• Obsessive compulsive symptoms (common)</td>
<td></td>
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<tr>
<td>• Myocarditis (very rare)</td>
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<tr>
<td>• Cardiomyopathy (very rare)</td>
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</tbody>
</table>

Download sheet: *Side effects associated with clozapine therapy*

Clinician prompt checklist to assess clozapine side effects

It is important to check for side effects at EVERY clinical review.

Check **which side effects are most troublesome for the consumer**, especially those which interfere with his/her quality of life.

For example:

Some consumers find hypersalivation can impact their daily activities and cause embarrassment.

This may not be deemed ‘serious’ in terms of poor clinical outcome for the consumer, but it can affect their likelihood for adhering to ongoing therapy and can be reduced by pharmacological intervention.

Download the *clinician prompt checklist to assess clozapine side effects*
Consumer perspective

Many consumers find clozapine helps with their psychosis, but they often need to balance the positive effect on the psychosis with some of the side-effects that clozapine can cause.

Video interview: WA consumer perspective (Amy)

Click to watch video
Recommencing therapy after an interruption

<table>
<thead>
<tr>
<th>Period of interruption (time since last dose taken)</th>
<th>Dosage</th>
<th>Monitoring requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than or equal to 48 hours</td>
<td>No change to dosage</td>
<td>No change to monitoring</td>
</tr>
<tr>
<td>Greater than 48 hours and less than or equal to 72 hours</td>
<td>Start on 12.5mg once or twice a day. If this dose is tolerated, it may be feasible to titrate the dose to the therapeutic level more quickly than is recommended for initial treatment.</td>
<td>No additional monitoring requirements.</td>
</tr>
<tr>
<td>Greater than 72 hours and less than or equal to 28 days</td>
<td>Start on 12.5mg once daily and rapidly titrate up as per new consumer.</td>
<td>The six week rule applies. • <strong>Weekly</strong> monitored consumers: Weekly monitoring for six weeks or for as long as needed to ensure a total of 18 weeks; whichever is the greatest. • <strong>Four-weekly</strong> monitored consumers: Weekly monitoring for six weeks. If no abnormality, resume four-weekly monitoring.</td>
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<tr>
<td>Greater than 28 days</td>
<td>Restart consumer with a new consumer registration form. Start at 12.5mg once daily and titrate up as per new consumer.</td>
<td>Commence as a new consumer. New pre-treatment result and baseline monitoring. Weekly monitoring for 18 weeks.</td>
</tr>
</tbody>
</table>
Discontinuing clozapine therapy

Discontinuing dosage:
- If clozapine needs to be stopped and is planned, \textit{gradually reduce} the dose over 1 – 2 weeks.
- If clozapine needs to be stopped abruptly, the consumer should be observed for rebound exacerbation of their psychotic symptoms, and cholinergic rebound (headache, nausea, vomiting and diarrhoea).

Blood test monitoring following discontinuation:
- For weekly Consumers: weekly tests for 4 weeks.
- For monthly Consumers: one test one month after ceasing. Test on or near cessation and one month after.

Consumer needs to be commenced on alternative antipsychotic medication.
Careful consideration for choice of antipsychotic is required if the consumer has had neutropenia.
Some atypical antipsychotics can also cause neutropenia e.g. Quetiapine

\textit{Clopine \textregistered Product Information, approved by the Therapeutics Goods Administration 14 July 2004, amended 12 June 2009}
Clozapine and the carer perspective

- The **Carers Recognition Act 2004** outlines the need to include carers as partners in care.

- **People on clozapine often need support** to attend frequent blood tests, clinic reviews and pick up medication.

- The **views and needs of carers must be taken into account** (along with the views, needs and best interests of people receiving care) when decisions are made that impact carers and the role of carers.

**Video interview: carer perspective**
(Veronica, Amy’s mother)

[Click to watch video]
Summary

Key points:

- **Clozapine** is an effective antipsychotic for treatment-resistant schizophrenia.
- Adequately managing side effects can improve adherence and quality of life.
- ‘Start low and go slow’ is a general rule to minimise side effects and potential life threatening effects.
- Always use the minimum effective dose.
- Stringent blood monitoring requirements.
- Physical health should be monitored at each clinical review.
- Discontinuation therapy has monitoring requirements.
- Recommencement therapy, following interruption, has a protocol.

Download *Guidelines for the safe and quality use of clozapine therapy in the WA health system*
References


Nurse Led Clozapine Clinic assessment questions -Scott Clark March 2011, updated June 2013.


Clozapine
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ASSESSMENT

You are required to answer 8 out of 10 questions correctly to pass the test.
Before proceeding to the test you may review this section.
If you answer 2 questions incorrectly you will be invited to either review this section or reattempt the test.

Review this section  Attempt assessment