OVERVIEW

This document contains the best practice guidelines for the prescribing and monitoring of clozapine within Bay of Plenty District Health Board's (BOPDHB) Mental Health & Addiction Services (MH&AS). The clozapine best practice guidelines were developed by Auckland and Waitemata District Health Boards and are being used as the National Standard.

OBJECTIVE

This document is to ensure people receiving clozapine are treated appropriately and safely.

The advice provided here is not intended to replace clinical judgment in uncommon clinical scenarios. Where the needs of an individual taking clozapine fall outside of the advice given within these guidelines, it is the responsibility of the health care practitioners involved to recognise the need for specialist advice and seek it without delay.

STANDARDS TO BE MET

1. Indications For Service User Selection

1.1. Clozapine is indicated for treatment-resistant schizophrenia in patients who are non-responsive or intolerant to other antipsychotic drugs.

a) Treatment resistance is defined as a lack of satisfactory clinical improvement despite adequate trials of at least two different antipsychotics at optimal doses and duration (minimum 6 weeks each) (1) **OR**

b) Treatment intolerance is defined as the impossibility to achieve an adequate clinical benefit despite trials of least two different antipsychotic drugs due to severe adverse reactions

c) NB: **Off label use (2)**

i. The decision to use clozapine outside the licensed indication is the responsibility of the prescriber and would usually require second opinion and / or peer review. There is increasing evidence supporting the use of clozapine outside the licensed indication, for example:

- In psychotic symptoms associated with Lewy body dementia or Parkinson disease;
- Treatment-resistant bipolar disorder;
- Psychosis associated with significant suicide risk.

ii. Re-challenge following a previous confirmed "red" blood result is also off-label. There is evidence that re-challenge can be successful, but there are risks of prolonged agranulocytosis (3). Prescribers considering re-challenging with clozapine should first discuss the individual with a BOPDHB or CareLink Plus Haematologist.

1.2. Contraindications

a) Previous hypersensitivity to clozapine.
b) Service user unable or unwilling to undergo regular blood tests
c) History of neutropenia or agranulocytosis (except for neutropenia or agranulocytosis induced by chemotherapy)
d) Impaired bone marrow function
e) Uncontrolled epilepsy.
f) Alcoholic and other toxic psychoses, drug intoxication or comatose conditions.

g) Circulatory collapse and/or central nervous system depression of any cause.
h) Severe renal or cardiac disease (e.g. myocarditis).
i) Active liver disease associated with nausea, anorexia or jaundice; progressive liver disease or liver failure.
j) Paralytic ileus

Clozapine should not be prescribed concurrently with drugs known to have substantial potential for causing agranulocytosis (see relevant Clozaril® or Clopine® Product Information Sheets see MedSafe Data Sheets)

Carbamazepine should not be prescribed concurrently with clozapine. Concomitant long acting or depot antipsychotics should be avoided because of the inability of these medications to be rapidly removed from the body in situations of granulocytopenia.

2. Consent

2.1. The following **must** be discussed before treatment commences:
a) Indications, possible adverse effects, monitoring requirements, and other treatment options.
b) Supplement with written information.

2.2. Consent should be obtained from the service user and documented in the clinical notes.

2.3. Where the service user is unable to give informed consent, refer to the Health Information Privacy and Information Sharing protocol for guidance on information sharing and involvement of family / whānau.

Document the consent process and the discussion clearly in the patient's health record clinical notes.

3. Who Can Prescribe Clozapine - *Note: amendments to these specifications could be gazetted at any time.*

3.1. Clozapine may only be prescribed by:
a) A medical practitioner who is vocationally registered by the Medical Council of New Zealand in the scope of practice of psychiatry (hereinafter referred to as a Psychiatrist)
b) A medical practitioner or nurse practitioner who is prescribing under the supervision of a Psychiatrist
c) A medical practitioner who is registered by the Medical Council of New Zealand in a general scope of practice provided the medical practitioner is prescribing clozapine for a patient whose illness is being well controlled by clozapine and the prescribing decision is taken in collaboration with, or following consultation with, a Community Mental Health Team.

BOPDHB requires that transfer of consumers once they are stable to primary care for prescribing will only occur when the GP has completed a recognised clozapine training programme.

4. Pre-Treatment Physical Review - (See FM.C35.2 Clozapine Initiation Checklist)

4.1. The following list outlines recommended baseline monitoring to be performed prior to clozapine initiation. Document in the clinical notes.

a) Baseline observations (record on EWS chart)
   i. Respiratory rate
   ii. Heart rate
   iii. Lying and standing blood pressure
   iv. Temperature
b) Baseline bowel habit (frequency and Bristol stool chart)
c) Baseline blood tests
   i. Electrolytes and renal function
   ii. C reactive protein
   iii. Full blood count (must be within 10 days prior to commencing clozapine)
   iv. Fasting lipid profile
   v. Fasting plasma glucose and HbA1c
   vi. Liver function tests
d) Weight (BMI and waist circumference)
e) Chest x-ray (referral made for baseline chest x-ray if none available within the past 5 years)
f) Echocardiogram referral
g) ECG (within four weeks prior to commencing clozapine)
h) Document smoking status, caffeine intake, lifestyle and diet
i) Investigate and document potential problems with prescribed, OTC or herbal medicines, illicit drugs or alcohol
j) Investigate and document past medical and mental health history. This includes blood disorders, seizures, thromboembolism, cardiac, bowel or bladder dysfunction, glaucoma, obsessive compulsive disorder and liver or renal impairment

⚠ Potentially fatal adverse effects of clozapine include faecal impaction, cardiac conditions and blood dyscrasias. See appendix 1, appendix 2 and section 6 respectively.

Parameter / test	During 1st month of initiation / dose titration	At 3 months	At 6 months	Annual	Management strategy if result outside reference range
Lying and Standing Blood Pressure	Frequently	✓	✓	✓	If hypotensive: consider slower titration or dose reduction If hypertensive: offer lifestyle advice and consult with GP and/or specialist for consideration of treatment.
Pulse	Frequently	✓ Documented formal review for signs of heart failure recommended at least four times a year (ongoing)	✓	✓	If tachycardia is persistent at rest or an increase by >30 bpm above recent results, observe for other indicators of myocarditis or cardiomyopathy and refer to a cardiologist if symptoms present. Stop clozapine if tachycardia occurs in context of chest pain or heart failure.

Parameter / test	During 1st month of initiation / dose titration	At 3 months	At 6 months	Annual	Management strategy if result outside reference range
Temperature	Frequently	✓	✓	✓	Give clozapine but repeat FBC immediately. Consider reducing the rate of dose titration. Spiking temperatures may be indicative of myocarditis.
Respiratory Rate	Frequently	Repeat if clinically indicated			Investigate as clinically appropriate
Electrolytes and eGFR	-	-	-	✓	Investigate as clinically appropriate
Full blood count	Refer to section X of guidelines				
Echocardiogram	At baseline, then repeat if clinically indicated				
ECG	Baseline and repeat if clinically indicated Repeat if signs of cardiac effects (See Appendix 2), high risk of cardiac disease or taking interacting medication. Risk of QTc prolongation may be increased by cardiac disease, electrolyte disturbance, female gender, older age, stress, polypharmacy and high doses of medication (6).				If in doubt, consult a cardiologist
Lipids – fasting	-	✓	✓	✓	Offer lifestyle advice and consult with GP and/or specialist for consideration of treatment
Weight (BMI and waist circumference)	weekly	✓	✓	✓	Offer lifestyle advice. Consider if additional medication is appropriate.
Fasting plasma glucose	Monthly for the first three months				Offer lifestyle advice. Consult with GP and/or specialist as appropriate.
HbA1c		✓	✓	✓	Offer lifestyle advice. Consult with GP and/or specialist as appropriate
Liver function tests	-	✓	-	✓	Investigate as clinically appropriate
Troponin I or T	Weekly for 8 weeks		Repeat if clinically indicated		Investigate as clinically appropriate
C-reactive protein	Weekly for 8 weeks		Repeat if clinically indicated		Investigate as clinically appropriate
Hypersalivation	✓	✓	✓	✓	May persist and often worse at night See Appendix 3
Constipation	✓	✓ Documented formal review of bowel function recommended at least four times a year (ongoing)	✓	✓	Use laxative from the outset. Treat worsening constipation assertively. Recommend high fibre diet. See Appendix 1 for notes on prevention, screening and management.
Sedation	✓	✓	✓	✓	Give smaller dose in the morning. Reduce dose if necessary. Consider a plasma clozapine level.

Parameter / test	During 1st month of initiation / dose titration	At 3 months	At 6 months	Annual	Management strategy if result outside reference range
Sexual dysfunction	✓	✓	✓	✓	Likely fewer problems than first generation antipsychotics. Consider dose reduction. If intolerable consider switching treatment.
EEG	Repeat if clinically indicated				EEG abnormalities are common in those on clozapine. Seizures are related to clozapine serum concentration and rate of dose increase. Consider prophylactic sodium valproate for service users with clozapine serum concentration > 1800 nmol/L (refer to appendix 4). After a seizure, withhold clozapine for one day, restart at a reduced dose, start sodium valproate.
Clozapine plasma level	Measure once maintenance dose is achieved, repeat if clinically indicated. See Appendix 4 for further guidance.				Consider clinical presentation and history of service user when reviewing dose.

5. Starting clozapine

5.1. Switching from another antipsychotic

a) All antipsychotics carry a risk of agranulocytosis. Any cross-titration period should be as short as possible.
b) Some antipsychotics share a similar adverse effect profile to clozapine, for example sedation and postural hypotension, therefore cautious dose titration may be required (2)
c) No further depot antipsychotics should be given after commencement of clozapine

5.2. Target Dose

a) A maintenance dose of 300 - 600 mg / day is usually required for efficacy. Doses higher than 900 mg / day are not usually recommended (off-label use) and the risk of seizure becomes more apparent at doses higher than 600 mg / day.
b) In the elderly and medically ill population the titration may need to be slower, and maintenance doses are typically much lower, e.g. 100 to 150 mg/day range.
c) There is significant inter-individual variability in clozapine metabolism: some patients can reach toxic levels at low doses of 100 mg/day, some patients fail to achieve therapeutic levels with 900 mg / day. See Appendix 4 for interpretation of serum levels.


Risk of seizures is dose-dependent and rises substantially with doses over 600 mg/day, serum clozapine levels >1800 nmol/L, or with rapid serum level increases.

5.3. Starting clozapine in an inpatient facility


Clozapine causes marked gastrointestinal hypomotility in at least 80% of service users (see section 7). Pre-existing constipation must be treated before starting clozapine. Start laxatives pre-emptively (See Appendix 2)

a) Chart clozapine titration

i. Using the Clozapine Titration Chart (see FM.C35.1)
OR
ii. Clinicians may wish to individualize the titration depending on the clinical circumstance. Individualised titrations are prescribed on the National Medication chart.

b) Refer to section 6 for patients restarting clozapine.
c) Physical observations such as temperature, HR, lying and standing BP and bowel function, as well as any adverse effects should be documented at least once a day during titration.
d) Indications for medical review:
   i. Temperature rises above 38°C (this is very common and is not a good reason, on its own, for stopping clozapine)
   ii. Pulse > 120 bpm or increases by >30 bpm (also common but may rarely be linked to myocarditis)
   iii. Postural drop of > 30 mmHg
   iv. Patient is clearly over-sedated
   v. Any other intolerable adverse effect.

Signs of life-threatening bowel conditions (e.g. abdominal pain, abdominal distension, vomiting) require urgent medical review (see appendix 1).
If at any stage during the dose titration the service user experiences significant adverse effects, the speed of dose escalation should be reviewed.

5.4. Starting Clozapine in the Community

While community initiation of clozapine may allow service users to remain in a familiar environment it is a labour-intensive process and requires significant staffing resource to ensure success. The following may indicate community initiation is appropriate:

a) No significant medical problems
b) Few concurrent medications
c) Supportive family or caregivers or access to appropriate respite accommodation
d) Ability of community team to supervise and monitor treatment
e) Good compliance and insight
f) Acceptance of, and consent for, treatment with clozapine
g) *Required Resources*
   i. Community Mental Health (CMH) team support, including weekend and out of hours contact numbers for the service user and caregiver (which may include respite facility staff).
   ii. First dose should be at a DHB facility or at the patient's residence if a caregiver or community mental health nurse can be present/easily accessible for at least 3 hours. If the first dose is to be given at a DHB facility, a caregiver must be available to accompany the patient back to their place of residence. The patient's blood pressure and pulse should be checked at baseline and then 3 - 6 hours after the first dose.
   iii. Ideally a caregiver will be available to stay with the service user for at least six hours following the first dose of clozapine, preferably overnight. Consider respite care for service users who have limited support.
   iv. Daily assessment from a community mental health nurse on weekdays during the first two weeks and then three times a week for the remainder of the titration period.

v. The service user or care giver is able to monitor and report on bowel movements, pulse, temperature and degree of sedation.
vi. Psychiatrist / MOSS / Psychiatric Registrar should review the service user at least weekly to assess mental and physical state during titration.

Table 1. Dosing and monitoring recommendations for outpatient initiation (2,6)
Note: a slower titration is suggested than with inpatient titration. Dose increases are not recommended at the weekend when staff are not available to continue physical observations.

Day	Total daily dose (mg) Doses may be split	Monitoring
1: Monday	12.5	Consider the timing of dose for staff availability CMH nurse to monitor the following before giving the first clozapine dose and 3-6 hours after: blood pressure, pulse, level of sedation and temperature.
2: Tuesday	25	CMH nurse to monitor the following: blood pressure, pulse, level of sedation and temperature. Record daily bowel habit and manage to maintain regularity.
3: Wednesday	37.5	As for day 2
4: Thursday	50	As for day 2
5: Friday	62.5	As for day 2
6: Saturday	62.5	Dose increases not recommended on weekends. Observations by staff not required if no concerns noted days 1-5.
7: Sunday	62.5	Dose increases not recommended on weekends. Observations by staff not required if no concerns noted days 1-5.
8: Monday	75	Psychiatrist or psychiatric registrar to review mental and physical state. CMH nurse/psychiatrist/registrar to monitor for hypersalivation and other parameters as for day 2 Ensure patient has blood form for FBC and troponin I
9: Tuesday	87.5	FBC and troponin I due CMH nurse/psychiatrist/registrar to monitor for hypersalivation and other parameters as for day 2
10: Wednesday	100	As for day 2
11: Thursday	112.5	As for day 2
12: Friday	125	As for day 2
13: Saturday	125	Dose increases not recommended on weekends. Observations by staff not required if no concerns noted days 8 -12.
14: Sunday	125	Dose increases not recommended on weekends. Observations by staff not required if no concerns noted days 8 -12.
15: Monday	137.5	Psychiatrist or psychiatric registrar to review mental and physical state. CMH nurse/psychiatrist/registrar to monitor for hypersalivation and other parameters as for day 2 Ensure patient has blood form for FBC and troponin I
16: Tuesday	150	FBC and troponin I due No monitoring required
17: Wednesday	175	CMH nurse/psychiatrist/registrar to monitor for hypersalivation and other parameters as for day 2
18: Thursday	200	No monitoring required
19: Friday	225	CMH nurse/psychiatrist/registrar to monitor for hypersalivation and other parameters as for day 2
20: Saturday	225	No monitoring required
21: Sunday	225	No monitoring required

Day	Total daily dose (mg) Doses may be split	Monitoring
22: Monday	250	Psychiatrist or psychiatric registrar to review mental and physical state. CMH nurse/psychiatrist/registrar to monitor for hypersalivation and other parameters as for day 2 Ensure patient has blood form for FBC and troponin I
23: Tuesday	275	FBC and troponin I due No monitoring required
24: Wednesday	300	CMH nurse/psychiatrist/registrar to monitor for hypersalivation and other parameters as for day 2
25: Thursday	Maintain dose at 300mg or continue titration by 25mg per weekday if appropriate until 350mg	No monitoring required
26: Friday		CMH nurse/psychiatrist/registrar to monitor for hypersalivation and other parameters as for day 2
27: Saturday		No monitoring required
28: Sunday		No monitoring required
⚠	If a more rapid titration is appropriate – increase dose by 25-50mg daily from day 3 onwards until a good clinical response is seen or a dose of 300 mg is reached. The dose should not be increased over the weekend unless adequate clinical follow up is available (i.e. easy access to medical staff and Community Mental Health Nurse available for recommended monitoring). Monitoring parameters should be observed as above.	

⚠ If at any stage during the titration period, the person experiences significant dose related adverse effects the rapidity of titration should be reviewed and documented

Physical observations and any adverse effects should be documented as part of the management plan.

h) *Community mental health nurses should alert a doctor if the service user experiences:*
   i. Temperature > 38°C (this is very common and is not a good reason, on its own, for stopping clozapine)
   ii. Pulse > 120 bpm or increases by >30 bpm (also common but may rarely be linked to myocarditis)
   iii. Postural drop of > 30 mmHg
   iv. Patient is clearly over-sedated
   v. Any other intolerable adverse effect
   vi. Signs of life-threatening bowel conditions (e.g. abdominal pain, abdominal distension, vomiting) require urgent medical review (see appendix 1).
   vii. If at any stage during the dose titration the service user experiences significant adverse effects, the speed of dose escalation should be reviewed.

6. Monitoring - Full Blood Counts

6.1. Mandatory FBC monitoring

a) Full blood count monitoring is performed weekly for the first 18 weeks following clozapine initiation then four weekly thereafter.

⚠ Please endorse all clozapine FBC blood test forms with "**CC: CareLink Plus**"

Range	Blood cell count (x10^9/L)		Course of action
	WBC	Neutrophil	
Green	≥ 3.5	≥ 2	Continue clozapine
Amber	≥ 3 – < 3.5	≥ 1.5 – < 2	Continue clozapine but with an increased frequency of FBCs. Usually twice a week, unless otherwise directed by a Haematologist.
Red	< 3	< 1.5	Discontinue clozapine immediately. Arrange for an urgent repeat FBC to confirm the red result. Consult with a Haematologist to discuss next course of action (details for Haematologist contracted to CareLink Plus can be obtained from CareLinkPlus staff ph 0800 535 020). *Note: continued use of clozapine or reinstatement of clozapine once FBC has normalised – is unlicensed use.*

Drop of 3 or "Rule of 3":
FBC result where there has been:

- A fall in total white cell count OR neutrophil count of > 3 x10^9/L
- A drop of > 3 x10^9/L from the baseline FBC

These are treated as amber until neutrophils and WBC count increases.

6.2. Sign and Symptoms of Infection

a) An immediate FBC must be performed when any signs or symptoms of infection occur. Early signs of infection may be subtle, for example fatigue/malaise, sore throat, mouth ulcers

Particular attention should be paid to "flu-like" complaints such as fever or sore throat, or any other signs which may be indicative of infection.

6.3. Deranged FBC parameters requiring clozapine discontinuation

a) White cell or neutrophil count falling in the red range according to the monitoring parameters listed above.
b) Eosinophil count above 3 x10^9/L. Clozapine should only be restarted once the eosinophil count has fallen below 1 x10^9/L.
c) Platelet count below 50 x10^9/L. Clozapine should not normally be restarted. If consideration is being given to restart clozapine, the service user's platelet count should be greater than 100x10^9/L, and a Haematologist must be consulted.

6.4. Missed Doses (14)

Duration of missed doses	Required changes to dose and/or FBC monitoring frequency
<48 hours	No change needed – continue with current clozapine dose and FBC monitoring frequency.
48-72 hours	Re-titration of clozapine dose required. Re-titration can be carried out at a faster rate. No change to FBC monitoring.
72 hours – 4 weeks	If **weekly** FBC monitoring: Re-titration of clozapine dose required. Can be carried out at a faster rate. Weekly FBC monitoring is required for an additional 6 weeks if the service user has been on weekly FBC monitoring for >12 weeks. For example: • If dose interruption occurs after 13 weeks of completed weekly FBCs, weekly monitoring would be extended to 19 weeks before switching to 4 weekly FBC monitoring. • If dose interruption occurs after 16 weeks of completed weekly FBCs, weekly monitoring would be extended to 22 weeks before switching to 4 weekly FBC monitoring, and so on. Ensure online monitoring service is updated with therapy event and appropriate FBC frequency is adjusted.
	If **FOUR weekly** FBC monitoring: Re-titrate of clozapine dose required. Can be carried out at a faster rate. Weekly monitoring for 6 weeks before resuming 4 weekly monitoring.
>4 weeks	Clozapine is officially stopped – the service user must be re-registered with the relevant online portal if clozapine is to be trialed again. Clozapine titration and FBC monitoring is as per the regular initiation protocol. Ensure online monitoring service is updated with appropriate FBC frequency.

6.5. Service user refusal of FBC monitoring

a) If the service user refuses FBC monitoring at any stage of treatment, and cannot be persuaded to reconsider, then clozapine must be discontinued.

⚠ Community pharmacies are prohibited from dispensing clozapine without a current FBC result.

6.6. FBC monitoring after clozapine stops

a) The service user's physical condition must be monitored for 28 days following discontinuation to allow for a complete washout of clozapine. An FBC should ideally be taken one month following discontinuation (if on monthly FBC monitoring prior to discontinuation) or weekly for 4 weeks (if on weekly FBC monitoring). Neutropenia may still occur in the weeks following discontinuation.

6.7. Restarting therapy after a blood dyscrasia

a) Clozapine re-initiation is contraindicated in those who have previously experienced agranulocytosis secondary to clozapine.

b) For service users in whom clozapine has previously been discontinued because of FBC results in the red range as per section 7.1, clozapine must only be reinitiated following discussion with a haematologist. This is off license use.

7. Monitoring – Constipation and Serious Bowel Dysfunction

⚠ Pre-existing constipation must be treated before starting clozapine. Start laxatives pre-emptively (see Appendix 1).

7.1. Aetiology and Prevalence (2,15)

a) Clozapine-induced constipation is a leading cause of clozapine related deaths.
b) Marked gastrointestinal hypomotility has been demonstrated in at least 80% of those taking clozapine.
c) Clozapine can cause gastrointestinal hypomotility throughout the entire gut, from oesophagus to rectum resulting in dysphagia, delayed gastric emptying, bowel obstruction, ischemia, perforation and aspiration.

7.2. Risk Factors (2,6)

a) Concurrent administration with other constipating medications such as anticholinergics (e.g. benztropine or tricyclic antidepressants), opiates and oral iron.
b) High doses/plasma concentrations of clozapine.
c) Concurrent administration with CYP1A2 enzyme inhibiting medication
d) Co-morbid medical illness/fever (can inhibit or reduce clozapine metabolism and increase serum concentrations).

7.3. Signs and Symptoms (2,6)

a) The majority of those with marked clozapine-induced gastrointestinal hypomotility do not report constipation. Serious complications often present late and can rapidly deteriorate to life-threatening within hours of the first presentation. A high suspicion for complications is warranted.
b) Red flags include:
   i. Reduced frequency of bowel motions
   ii. Abdominal pain, cramp and/or distension
   iii. Watery diarrhoea (overflow diarrhoea)
   iv. Feculent smelling breath
   v. Non bowel-specific symptoms such as fever, nausea and drowsiness.

⚠ Moderate/severe abdominal pain, abdominal distension, and vomiting are the most commonly reported signs of life-threatening bowel conditions.
If these symptoms are present urgent surgical (or medical) referral and treatment is required. Clozapine treatment should be withheld

c) For screening and management of constipation, refer to Appendix 1.

8. Dispensing and Transfer of Care

8.1. Dispensing

a) For BOPDHB, clozapine is only available from pharmacies contracted by BOPDHB for dispensing clozapine.
b) Community pharmacies may only dispense clozapine for service users who are registered with CareLink Plus – the clozapine FBC monitoring system used by BOPDHB. To dispense a full supply of clozapine (either 7 or 28 days, consistent with the monitoring frequency), the FBC must be 'current' defined as:
   i. Weekly FBC monitoring – a FBC has been taken within the 24 hours prior to dispensing.
   ii. Four-weekly monitoring – a FBC result has been taken within the 72 hours prior to dispensing.

iii. If the FBC is outside these limits, a reduced supply will be dispensed equal to the quantity needed until the next due FBC date.

c) For BOPDHB inpatients: individual patient supply of clozapine is dispensed from the inpatient dispensary. Service users must be registered with Carelink Plus and up to date with FBC as per the monitoring protocol.

8.2. Transfer of Care

a) Registration to either of the two available monitoring systems (ClopineConnect or Clozaril CareLink Plus) is brand specific. When transferring care between DHBs, the service user will need to be registered with the FBC monitoring system used by the DHB receiving them.

i. *Service user is transferring from a Clozaril DHB to another Clozaril DHB:*
- The relevant actions on the online portal system should be completed to confirm the transfer to another clinician and pharmacy.

ii. *Service user is transferring from a Clopine DHB to a Clozaril DHB:*
- The receiving service must be advised that the service user has been prescribed Clopine.
- The ClopineConnect Co-ordinator for the discharging service must also be informed of the transfer.
- The ClopineConnect registration details will need to be passed on to the receiving service:
  - Date that Clozapine was initiated
  - The pre-treatment FBC
  - The date the baseline FBC was taken
  - The current frequency of monitoring
  - The FBC history (or at least the last 3 results).
  - The receiving service then uses this information to register the service user onto CareLink Plus.
  - Once registered with CareLink Plus the ClopineConnect coordinator arranges to inactivate the service user on ClopineConnect.

iii. *Service user is transferring from Clozaril DHB to a Clopine DHB:*
- The relevant ClopineConnect coordinator must be informed of the transfer.
- The relevant registration details are to be sent (as per above).
- The details are used to register the patient into the ClopineConnect system.
- The patient file in CareLink Plus is inactivated once they are registered in ClopineConnect.

9. Withdrawal of Treatment

9.1. Discontinuing treatment

a) Where possible, clozapine should be gradually tapered over at least 1-2 weeks (2) before discontinuation. Clinical experience has indicated that longer periods of dose reduction (six weeks or longer) may be required in many cases.

b) Abrupt cessation of clozapine, necessary in potentially life-threatening medical situations, is associated with severe rebound psychosis (about 20% of cases) and cholinergic rebound symptoms. Rebound psychosis may occur within 1-2 days of abrupt discontinuation and be more severe than preceding psychotic episodes (2).

c) Should treatment be withdrawn for any reason, CareLink Plus should be notified with the date of discontinuation and the reason for discontinuation. Post-discontinuation FBCs may be required, as per section 7.6.

9.2. Indications for stopping clozapine

a) Adverse events that may be life-threatening or result in significant morbidity. (note: abrupt discontinuation would be justified). For example:
   i. Aspiration pneumonia secondary to hypersalivation
   ii. Suspicion of (or confirmed) cardiotoxicity
   iii. Bowel obstruction
   iv. Haematological adverse effects
   v. Uncontrolled seizures
   vi. Neuroleptic malignant syndrome.

b) Severe and unremitting adverse effects that significantly impair the service user's quality of life. For example, severe sedation.

c) Lack of clinically significant change in mental state with a clozapine serum level above 1000 nmol/L over a period of at least 6 months.

d) Gastrointestinal hypomotility and severe constipation, where there is a poor response to active management measures.

e) Service user withdrawal of consent to treatment if not under the Mental Health Act.

f) On-going non-adherence to treatment or mandatory FBC monitoring despite supportive interventions and psychoeducation for the service user and their family / whānau / carer(s).

9.3. Re-challenge

Re-challenge may be considered in some service users who have previously experienced severe adverse effects, where alternatives to clozapine have failed to adequately manage symptoms. In general, re-challenge should involve:

a) A full documented discussion of the risks and benefits of clozapine re-challenge with the service user and the service user's family/whanau/carer(s). Once consent is gained it should be documented in the clinical record.

b) A documented second opinion from another psychiatrist, particularly where re-challenge may constitute unlicensed use of clozapine. For example, where clozapine was previously discontinued secondary to neutropenia.

c) Liaison with a relevant medical specialist (e.g. consultant haematologist or cardiologist) to formulate an individualised monitoring plan.

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ASSOCIATED DOCUMENTS

- Bay of Plenty District Health Board policy 2.5.1 protocol 2 Health Information Privacy & Information Sharing - Mental Health & Addiction Services
- Bay of Plenty District Health Board Form FM.C35.1 Clozapine Titration Chart
- Bay of Plenty District Health Board Form FM.C35.2 Clozapine Initiation Checklist
- Bay of Plenty District Health Board Form FM.C35.1 Clozapine Transfer to GP Checklist
- Bay of Plenty District Health Board. Clozapine: Consumer Information Sheet

Appendix 1: Prevention, Screening and Management of Constipation

1. General Principles

1.1. Significant gastrointestinal hypomotility is an expected side effect of clozapine (15).

1.2. Many people experiencing clozapine-induced constipation may be unaware of it (15).

1.3. Stimulant laxatives should be started pre-emptively when initiating clozapine (16).

1.4. Service users taking clozapine should be warned about constipation risks before starting clozapine and given information on diet, fluid intake and exercise.

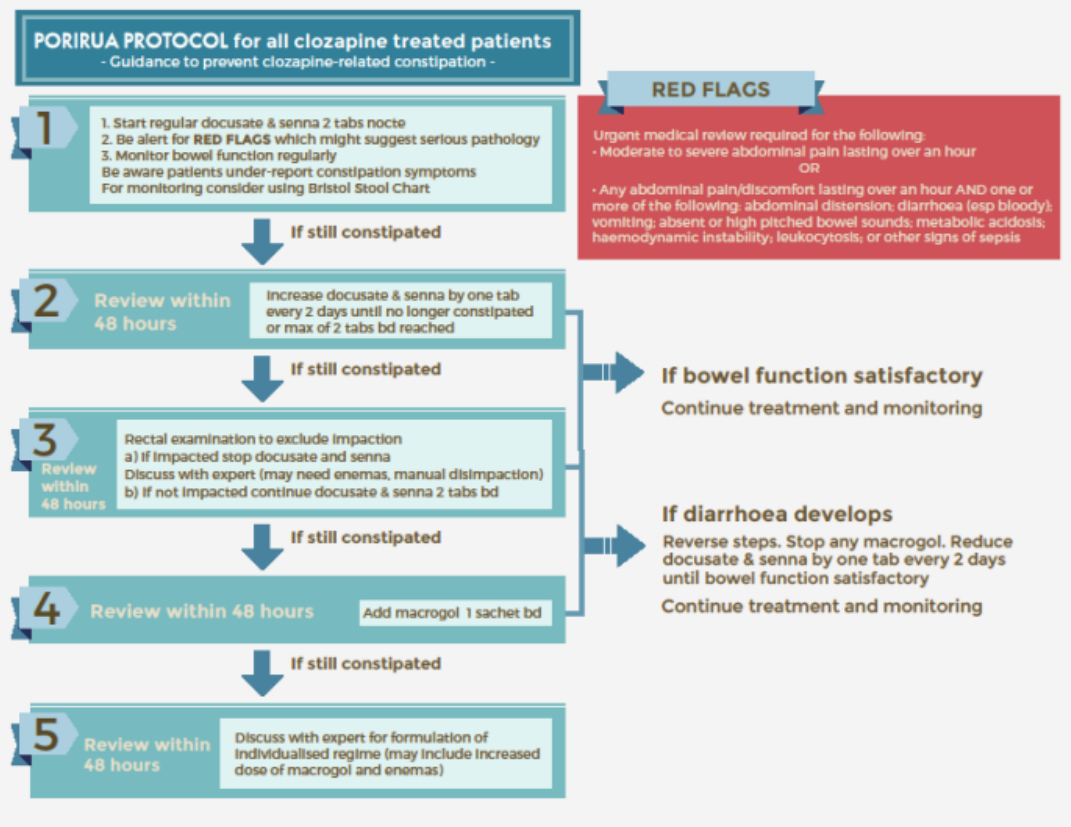
1.5. Service users at risk of constipation are advised to stay upright as much as possible, engage in light exercise that moves the abdomen, drink adequate amounts of water, and eat fresh fruit, vegetables and other high fibre foods such as prunes or kiwifruit. Input from a dietician may be useful.

1.6. If dietary fibre intake is increased, fluid intake also needs to be increased to avoid intestinal obstruction – at least two litres/day.

1.7. Avoid co-prescription of constipating medications wherever possible e.g. opiates, benztropine, tricyclic antidepressants, antihistamines, antispasmodics and oral iron.

1.8. Service users are often reluctant to discuss bowel function due to shyness or embarrassment. Those prescribed clozapine may require on-going education and encouragement to ensure open discussion.

2. Pre-Emptive Treatment (The Porirua Protocol) (16)



3. Screening

3.1 Regular assessment of bowel habit is recommended. Medsafe advises that a formal review of bowel function should be performed at least 4 times a year (9). Constipation is difficult to accurately assess and requires a level of motivation and openness from the service user that is sometimes not possible to achieve.

3.2 Assessing constipation involves 3 components:

a) Subjective difference between bowel motions pre- and post-clozapine start
b) Assessment of the form and frequency of bowel motions

i A bowel frequency diary could be used (especially in those with a history of constipation or if you suspect constipation may be an issue) in conjunction with the Bristol Stool Chart [17] – see below.

⚠ Bowel motion frequency of less than one stool every three days may be indicative of constipation, as is a Bristol Stool Scale score 1 or 2.

c) Assessment of other symptoms that may indicate constipation.
   i Diarrhoea (overflow)
   ii Tenesmus (feeling that bowel is not completely emptied after defecation)
   iii Abdominal discomfort and/or pain
   iv Urinary frequency
   v Anal burning
   vi If a person taking clozapine acknowledges constipation, then abdominal and rectal examination and timely treatment is needed. A plain abdominal x-ray may be helpful.
d) Red flags requiring urgent review:
   i Reduced frequency of bowel motion
   ii Abdominal pain, cramp and/or distension
   iii Watery diarrhoea (over-flow diarrhoea)
   iv Feculent smelling breath
   v Non-bowel specific symptoms such as fever, nausea and drowsiness

⚠ Moderate/severe abdominal pain, abdominal distension, and vomiting are the most commonly reported signs of life-threatening bowel conditions.
If these symptoms are present urgent surgical (or medical) referral and treatment is required. Clozapine treatment should be withheld.

3.3 Management

The general principle is to use medications with different mechanisms of action, along with the preventative interventions. An example would be the use of stimulant laxatives, stool softeners increased fluids and keeping the person mobile. Osmotic laxatives can also be added and continued if working for a particular individual.

a) *Stimulant laxatives*
   i **Senna (usually combined with docusate [a softener] as "Laxsol")**
   - Acts by inducing gastrointestinal contractions.
   - May cause abdominal cramping and diarrhoea.
   - Contraindicated in acute abdominal conditions e.g. suspected faecal impaction or intestinal obstruction due to risk of rupture.
   - Previous concerns about myenteric nerve damage and "lazy bowel" have been disproven. Stimulant laxatives can be used on an ongoing basis.
   - Recommended dose:

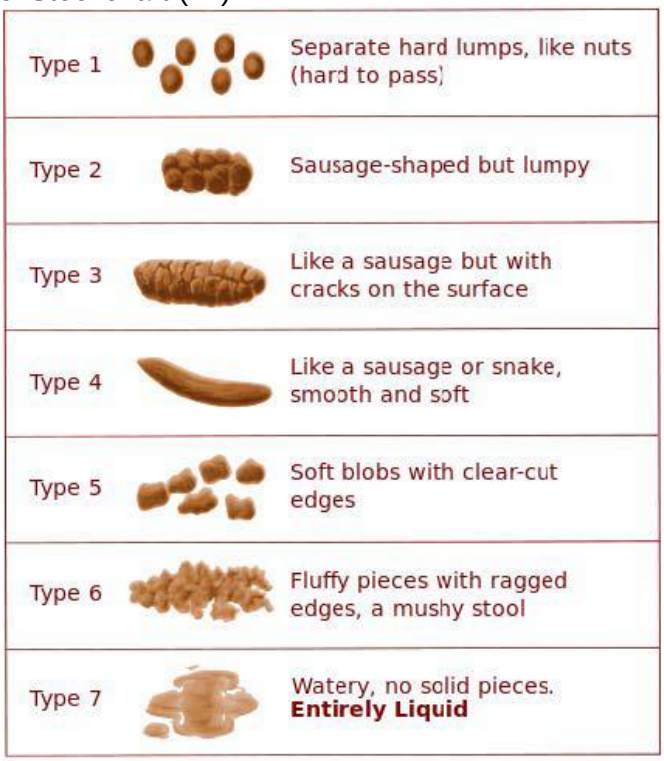
- 2 tablets at night
- increasing to 2 tablets BD as needed

b) *Osmotic laxatives – e.g. Macrogols* (Lax-Sachets®, Movicol®, Molaxole®)
   i Evidence supports the benefit of macrogols in improving the symptoms of constipation without any serious adverse effects (18)
   ii Can be used where faecal loading is diagnosed / suspected
   iii Recommended dose:
   - Prevention: 1-2 sachets/day initially
   - Treatment of faecal impaction up to 8 sachets/day

c) *Enemas – e.g. Phosphate* (Fleet®) or sodium citrate (Microlax®/Micolette®)
   i May be used to help clear the lower colon and remove impaction
   ii Sodium citrate is a faecal softener that liberates water present in faeces causing a softening of the stools and defaecation
   iii Sodium citrate is preferred in the community setting because repeated use of phosphate may cause electrolyte imbalances
   iv Contraindicated in gastrointestinal obstruction
   v Recommended treatment dose: 1 enema up to twice daily

d) *Bulk Forming Agents – e.g. Psyllium Powder* (Metamucil®, Konsyl-D®, Bonvit®), Kiwicrush
   i Contraindicated in obstruction and faecal impaction
   ii Not recommended for most service users taking clozapine as can worsen existing constipation
   iii If prescribed, ensure adequate fluid intake and discuss potential risks with service user

e) *Bristol Stool chart* (17)



Appendix 2 – Cardiac Adverse Effects

1. Myocarditis

1.1 Inflammation of the heart muscle (myocarditis) is a rare complication of clozapine. Myocarditis can be fatal. It is most likely to occur in the first 8 weeks of clozapine treatment but may happen later.

1.2 Symptoms can include (19, 20):

a) New onset or marked worsening of tachycardia
b) Flu-like symptoms, which may include GI upset
c) Fevers/chills
d) Chest pain/pressure/tightness
e) Severe/new shortness of breath
f) ECG changes consistent with heart damage
g) Elevations in inflammatory markers (CRP/ESR). Myocarditis may be accompanied by eosinophilia.
h) Troponin will increase, but this may be delayed. Beware of false negative results

1.3 Admit to hospital

a) There should be a low threshold for admission to the general medicine service (ideally cardiology) if these symptoms occur, especially during the first 12 weeks or during any dose titration. Consult with liaison psychiatry and cardiology.

1.4 Investigations

a) FBC, troponin, CRP, clozapine level, Chest X-ray (PA and Lateral) and ECG in addition to routine investigations. Secondary sources of symptoms should also be considered such as viral infection, but myocarditis must be thoroughly investigated. Consider nasal swabs for a respiratory virus panel (11).

⚠ A transient, high (38°C) fever may occur during the first 3-4 weeks of treatment with clozapine. Although most likely benign, these patients should be evaluated for neutropenia, myocarditis and monitored for neuroleptic malignant syndrome (NMS).
Tachycardia is common in the early stages of treatment. More caution is needed for a pulse > 120 bpm, or for those with rises ≥ 30 bpm above recent results, especially in the first four weeks of treatment.

Diagram 1 – Typical evolution of clozapine-induced myocarditis (19):

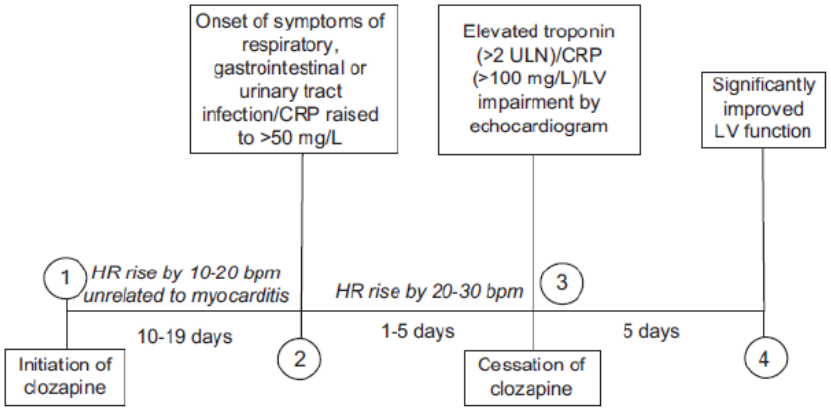
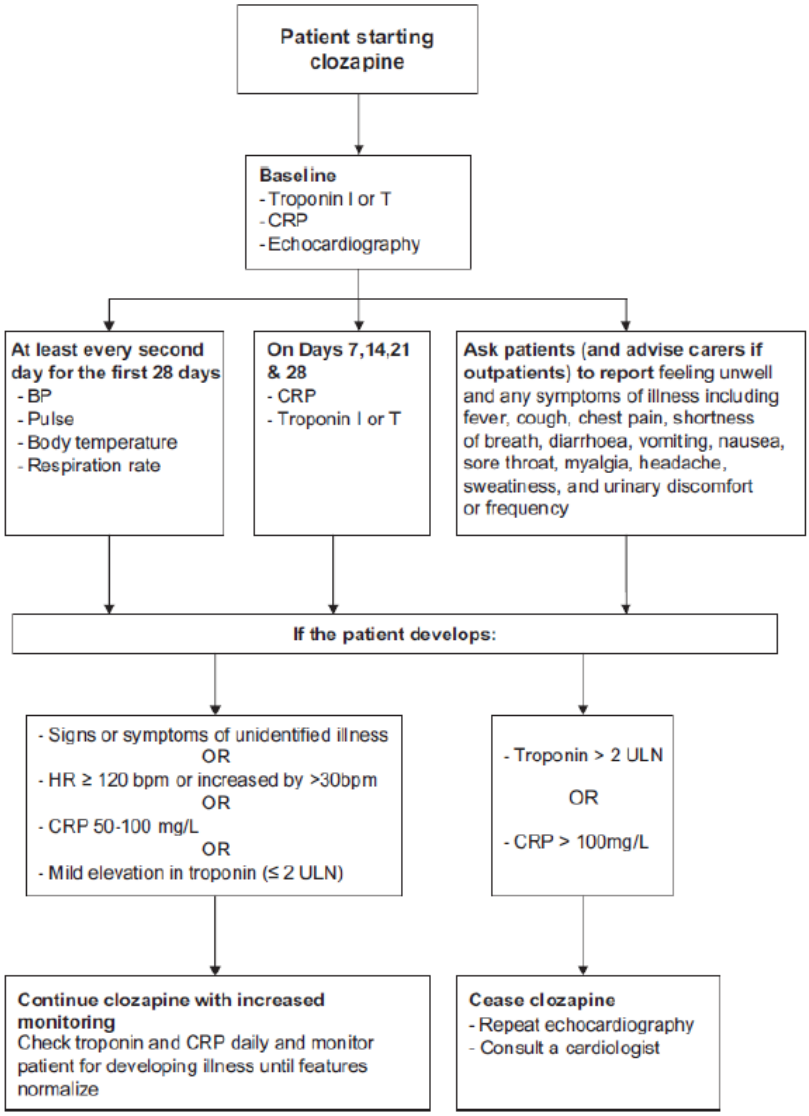


Diagram 2 – monitoring for clozapine-induced myocarditis (19)



2. Cardiomyopathy

2.1 This is a weakening of the heart muscle that can lead to heart failure. The risk is about 1:2000 person years (21). Cardiomyopathy normally develops several months after starting clozapine. Symptoms are similar to heart failure (22-28).

2.2 Symptoms can include:

a) Flu-like symptoms (e.g. cough, fever)
b) Fatigue – new or worsening, pervasive (differs from clozapine sedation)
c) Palpitations
d) Chest discomfort
e) Dyspnoea (shortness of breath) and reduced exercise capacity – new onset
f) Waking in the night unable to breathe (N.B. check for choking due to hypersalivation). Needing to sleep with head elevated (e.g. recliner or 3+pillows)
g) Ankle oedema

2.3 Signs on investigation:
a) Sinus tachycardia
b) Hypotension
c) Physical signs of cardiac failure (pulmonary oedema, elevated JVP)
d) Abnormal or new heart sounds (S3 gallop or S4)
e) ECG changes consistent with an enlarged heart
f) Enlarged heart on CXR
g) Abnormal echocardiogram – cardiomegaly and reduced ventricular fraction

2.4 Admit to hospital
a) Patients with severe / significant symptoms should be admitted to general medical services for evaluation. Consult with liaison psychiatry and cardiology. An urgent echocardiogram should be requested.

2.5 Monitor in the community
a) Patients with mild symptoms should be followed closely (every 1 – 2 months), discussed with specialists (through Liaison Psychiatry and/or Cardiology) and there should be a low threshold for requesting an echocardiogram (specifying that the patient is on clozapine).
b) All patients with symptoms of cardiomyopathy should receive these investigations:
c) FBC, troponin, BNP, CRP, clozapine level, CXR (PA and lateral), ECG, TFTs, HIV screen if not performed within 3 years in addition to routine investigations (11).

Appendix 3 – Treatment Recommendations for Clozapine-Induced Hypersalivation (Sialorrhoea) (29-34)

1. Background (2)

1.1 Hypersalivation usually develops during the initial titration phase or during later dose increases.

1.2 It is usually most problematic at night during sleep. Nocturnal coughing or choking may lead to disrupted sleep.

1.3 Available treatments for hypersalivation are usually only partially effective and may have significant adverse effects (particularly when combined with clozapine).

1.4 The underlying mechanism is poorly understood and most likely multifactorial. alpha-adrenergic and muscarinic mechanisms may increase salivary flow, whereas reduced laryngeal peristalsis and an impaired swallowing reflex may reduce saliva clearance.

2. General Practice Points

2.1 The evidence base for treatment options is poor.

2.2 Hypersalivation often improves gradually with time (weeks to months) independent of any pharmacological intervention. Review periodically (at least once every 3 months) to determine if treatment for hypersalivation is still indicated.

2.3 Hypersalivation may be a cause of chronic sleep disturbance (coughing and choking, waking to clear accumulated saliva) and should be considered as a contributor to daytime sedation.

2.4 Severe and untreated hypersalivation may progress to aspiration pneumonia. There are also several case reports of clozapine-induced parotitis.

2.5 Worsening salivation long after the initiation of clozapine treatment may be due to fluctuating clozapine serum levels. Consider increases in caffeine intake, cessation or reduction in smoking, medicine interactions, and intermittent adherence as possible causes.

3. Non-pharmacological management

3.1 Non-pharmacological approaches should be trialled prior to, or alongside, the pharmacological strategies detailed below.

3.2 Propping up pillows at night may help to minimise nocturnal coughing and choking. Be aware that sleeping in an upright position to minimise night-time breathlessness may also indicate heart-failure (clozapine-induced cardiomyopathy – see Section 13.2) (29)

3.3 Interventions that help to stimulate the swallowing of saliva e.g. sucking on sugar-free lozenges or mints should be offered.

3.4 Consider discussing with a speech language therapist. Exercises that target the swallowing reflex may be of benefit in some cases.

4. Stepwise Pharmacological intervention

4.1 Response should be assessed over one month, or sooner in more severe cases.

4.2 All pharmacological treatment is off-license. It is important to clearly document and communicate the indication for treatment.

5. First line: oral medication that does not block acetylcholine

5.1 Doxazosin 1-2 mg PO nocte (α1 adrenoceptor antagonist)

- Note: terazosin is no longer available – doxazosin suggested in place of – however there is low quality and low-level evidence for use
- Potential for additive postural hypotension with clozapine, particularly during titration phase.
- Can consider higher doses (3-4 mg PO nocte) where salivation is severe and doxazosin is well tolerated (nil postural drop), although the evidence base for higher doses is minimal

OR:

5.2 Metoclopramide 10 mg PO nocte (D2 antagonist antiemetic) (33)

- If no improvement observed after 1 week the dose can be increased in weekly steps to 10 mg TDS.
- Improvements accumulate over at least 3 weeks.
- Avoid in those with a history of EPSEs (including tardive dyskinesia) or neuroleptic malignant syndrome (NMS).
- Additive risk of EPSEs with other potent D2 antagonists (e.g. haloperidol, risperidone).
- Unlikely to be effective in those also taking aripiprazole.

6. Second line: locally acting anticholinergics (+/- first line options)

6.1 Ipratropium Nasal Spray 0.03% (21 microgram/dose): two doses to sublingual/parotid areas of mouth to maximum of three times per day

- Avoid eating, drinking or brushing teeth after use as this may reduce efficacy

OR:

6.2 Atropine 1% 0.25-0.5 mL (3 to 6 drops) mixed with 10-15 mL water and used as an oral rinse (focusing on sublingual and parotid application) to maximum of three times per day

- Spitting out will minimise potential for systemic adverse effects (see third line agents below).
- Note: atropine drops are only funded for ocular use in the community.
- Can use to augment doxazosin (if only partially effective) or as replacement.
- Locally acting anticholinergics (particularly atropine) have a short receptor-binding half-life. Overuse may result in rebound salivation.

7. Third line: systemically acting anticholinergics

Third line agents must only be prescribed following a documented discussion of risks and benefits with a consultant psychiatrist.
If the risks of using systemically acting anticholinergic medications are likely to exceed the benefits, and treated of hypersalivation is still indicated, proceed directly to fourth line treatment.

7.1 The use of systemically acting (particularly oral) anticholinergic medication in service users receiving clozapine significantly increases the risk of bowel complications arising from clozapine-induced gastric hypomotility.

7.2 Use is therefore only recommended where:

a) Salivation is severe, has not responded to steps 1 and 2, and threatens continued adherence to clozapine or the service user's health (aspiration risk, perioral maceration/super-infection).
b) Use of a daily bowel chart for inpatients is essential. Also ensure that suitable laxatives have been pre-emptively prescribed and that there is a regular on-going review of bowel function.
c) If outpatient use is being considered, then a comprehensive bowel monitoring plan MUST be put in place.
d) Also note other potential anticholinergic effects:
    - Cognitive impairment (may also exacerbate psychosis)
    - Tachycardia and QTc prolongation
    - Urinary retention
    - Visual disturbance
    - Anticholinergic medication is frequently abused. Be alert for possible attempts at drug-seeking.

7.3 Step 3a: transdermal anticholinergic (+/- doxazosin)

a) Hyoscine (1 mg/72 hours) patch applied every 72 hours behind the ear
    - Special authority is available for funding use in the community.
    - Criteria are "control of clozapine-induced hypersalivation where trials of at least two other alternative treatments have proven ineffective."

Or:

7.4 Step 3b: oral anticholinergic (+/- doxazosin)

a) Benztropine 1-2 mg PO to a maximum of twice daily
    - Evidence for efficacy appears to be greatest for a combination of alpha-blocker plus benztropine (31). This must be weighed against the risks of constipation and other anticholinergic effects.
    - Procyclidine, amitriptyline, oxybutynin and doxepin have also been used. Note that many of the anticholinergics indicated in international guidelines (e.g. hyoscine lozenges, pirenzepine) are not available for use in New Zealand.

8. Fourth line:

8.1 In extreme cases, clonidine and botulinum toxin have been used. Please discuss with Mental Health Pharmacist before prescribing. Some funding restrictions may apply.

Appendix 4 – Serum Levels – Use, Timing, Rationale and Interpretation

Routine testing of clozapine level is not recommended.
The service user's clinical presentation should be at least as important a consideration as the serum level in deciding to change a dose, especially in the context of seemingly high serum levels.
Clozapine serum levels should not be viewed in isolation. Consider trends over time.

1. Indications for monitoring of clozapine serum concentration (35-40)

Indication	Timing and frequency of serum level
Poor clinical response	When dose target reached and clinical response inadequate. Aim to increase the level to >1000 nmol/L.
To establish correct dose or level following dose change	One week after dose change.
Patient showing signs of toxicity, e.g. increasing sedation, increasing hypersalivation or myoclonus/seizures.	When symptoms occur, ensure a trough level is taken. Aim to reduce dose to bring clozapine serum concentration to <1800 nmol/L
Prevention of toxicity – especially where serum concentration >1800 nmol/L or dose >600 mg/day	Individually assessed as per MDT decision – documented in clinical notes.
Monitoring clinically relevant interaction	One week after interacting medication started.
Smoking cessation	Prior to smoking cessation to establish baseline. One week after smoking cessation if no dose reduction Two weeks after stopping if dose is reduced. *Note: Service users may report hypersalivation and sedation (starting 2-3 days after stopping smoking) which are indications of a rising serum level*.
Suspected non-adherence / monitoring adherence / relapse prevention	Every 3 months. More frequent monitoring for a limited period may be appropriate in some cases.
Liver disease	Every 3 months.
Clozapine induced constipation	Ensure constipation resolves before altering dose of clozapine

Processing clozapine serum concentrations by the laboratory can take several days as this is performed off-site. If toxicity is suspected assess on the service user's clinical presentation

1.1 <u>Therapeutic range</u>

a) Evidence suggests that in those people who have shown an insufficient response, a therapeutic response may be more likely with serum levels above 1000 nmol/L (41-43).
b) An agreed upper limit to the clozapine target range has not been established. However, the risk of seizures increases with increasing dose (12-13). Therefore, a prophylactic anticonvulsant (lamotrigine or sodium valproate) should be considered in those whose serum levels are >1800 nmol/L) (2).
c) Levels above 3000 nmol/L should be avoided where possible as seizure risk increases substantially above this level (2,43).

2. Factors which can influence clozapine serum levels (2)

Factors of likely clinical significance	Factors of potential clinical significance
Adherence	Constipation: • May result in lower serum levels than normal • Care must be exercised when increasing Clozapine dose during acute constipation episode.
Timing of sample	Respiratory infections: severe infection may increase clozapine levels by 50%.
Dose	Age - clozapine levels increase with age.
Pharmacokinetic interactions e.g. fluvoxamine, cimetidine, ciprofloxacin, omeprazole, citalopram, sodium valproate, caffeine.	
Smoking status: Smoking cessation can increase clozapine levels by 50%, restarting smoking after a period of abstinence can halve levels.	

2.1 Assessment of adherence

a) There are many factors that can influence clozapine levels. Changes in serum levels are not necessarily due to adherence. For help with interpreting Clozapine levels, please contact a Mental Health Pharmacist. Nor-clozapine levels can give a better indication of the patient's true clozapine level.

2.2 Timing of sampling and collection method

a) Clozapine serum levels should be taken as a trough level, i.e. in the morning and 10-14 hours after the last dose (34). Morning doses should be withheld until after the blood sample has been taken. Results from samples drawn at significantly different times to one another will not be comparable.

b) Only collect blood using plain RED top non-gel containing tubes for clozapine levels (11).
   i. Serum or Plasma Separator tubes (SST or PST) with Gel are **NOT** acceptable as there is significant adsorption of clozapine and its metabolite to the collection tube causing falsely low results.

c) Steady state serum levels are reached approximately five days after a dose change (range between 2-10 days) (14,35); this should be considered when planning serum level monitoring.

d) Clozapine serum levels should be ordered on the standard laboratory test request form and should include a statement as to the indication (see above) for the test and the time of last dose.

3. Smoking cessation (2,6)

3.1 On stopping smoking, clozapine levels increase rapidly over the first 4 days and can continue to rise for the next 2 weeks.

3.2 It is recommended that clozapine levels should be taken before stopping smoking and that the dose be reduced gradually by 25-50% over the first week post-smoking cessation.

3.3 Further dose adjustments should be made based on emerging side effects or toxicity.

3.4 This is particularly relevant when someone who smokes moves to smoke free environment (e.g. admission to an inpatient unit) or restarts smoking after they are discharged.

The effects on clozapine serum levels from tobacco smoking are a direct effect of cigarette smoke NOT the nicotine. Use of NRT does not affect clozapine serum levels. Therefore, checking serum levels is indicated when service users cease smoking and start NRT.

4. Guidelines to interpreting clozapine serum concentrations

Trough clozapine conc (nmol/L)	Clinical Response	Comment
<1000	Good	Consider repeating assay at 6 months, then annually unless response deteriorates, or side-effects become troublesome.
	Poor/incomplete	If poor adherence is suspected, consider supervised administration. **N.B. If a suspension of clozapine is used, ensure accurate dose is administered by shaking the bottle to re-suspend the solution and measure a dose free of air bubbles. Refer to your hospital pharmacy for advice.** Consider psychoeducation. Review patient and repeat assay after adherence intervention. Consider cautious dose increase (especial caution if dose already ≥ 450 mg/day due to increased risk of adverse-effects, particularly seizures). Monitor mental state and adverse effects. Review patient and repeat assay after at least 1 week on new dose.
1000-1800	Good	Consider repeating assay at 6 months, then annually unless response deteriorates, or adverse effects are troublesome. If adverse effects are persistent/serious consider cautious dose reduction (e.g. by 25 mg increments every 7 days) but bear in mind possible loss of response.
	Poor/incomplete	If clozapine treatment has continued at least 3-6 months at current dose, consider psychosocial interventions. Some have found augmentation with other psychoactive drugs to be of benefit. It is important any such attempts should be carefully considered with respect to adverse-effects (including risk of neutropenia) and possible interactions. Clozapine should not be used with drugs known to have a substantial potential for causing agranulocytosis.
1800-3000	Good – no clinical features of toxicity	Review. Consider cautious dose reduction (e.g. by 25 mg increments every 7 days) but balance against risk of diminishing the response to clozapine. Consider anticonvulsant (not carbamazepine) as seizure prophylaxis if dose reduction thought inadvisable. Monitor mental state. Repeat assay after at least 1 week on the new dose, otherwise 3-monthly.
	Poor/incomplete/ reduced and/or clinical features of toxicity	Cautious dose reduction (see above) to bring plasma clozapine concentration <1800 nmol/L. Monitor mental state. Repeat assay after at least 1 week on the new dose.

Trough clozapine conc (nmol/L)	Clinical Response	Comment
3000-5000	Good – no clinical features of toxicity	Review. Consider cautious dose reduction (e.g. by 25 mg increments every 7 days) to bring plasma clozapine concentration <3000 nmol/L and possibly <1800 nmol/L, but balance against risk of diminishing the response to clozapine. Consider anticonvulsant prophylaxis (not carbamazepine). Monitor mental state. Repeat assay at least 1 week after dose reduction. Plasma clozapine concentration may continue to rise in the short term even after the dose has been reduced
	Poor/ incomplete /reduced and/or clinical features of toxicity	Cautious dose reduction (see above) to bring plasma clozapine concentration <3000nmol/L and possibly <1800nmol/L. Monitor mental state. Repeat assay after at least 1 week on a new dose. Plasma clozapine concentration may continue to rise in the short term even after the dose has been reduced
5000 and above	Good – no clinical features of toxicity	Urgent review. Consider cautious dose reduction (by e.g. 25 mg increment every 7 days) to bring plasma Clozapine <3000nmol/L, and possibly <1800nmol/L. Consider anticonvulsant prophylaxis (not carbamazepine). Monitor mental state. Repeat assay at least 1 week after dose reduction. Plasma clozapine may continue to rise in the short term even after the dose has been reduced
	Poor/ incomplete /reduced and/or clinical features of toxicity	Urgent review. If patient is in the community, consider admitting for observation. Withhold clozapine for 24 h and re-start at 75 % of last dose, thereafter, reduce dose slowly (e.g. by 25 mg increments every 7 days) to bring plasma clozapine <3000nmol/L, and possibly <1800nmol/L. Consider anticonvulsant prophylaxis (not carbamazepine). Monitor mental state. Repeat assay after at least 1 week on new dose. Plasma Clozapine concentration may continue to rise in the short term even after the dose has been reduced

4.1 Post-mortem clozapine levels (2)

Interpretation of post-mortem clozapine levels is complex and requires specialist advice to avoid falsely implicating clozapine toxicity as the cause of death.