



Clozapine: safe prescribing

KEY MESSAGES:

- A co-ordinated approach is required between the mental health and primary care teams so that patients treated with clozapine do not experience gaps in care; monitoring may be delegated to primary care on a case-by-case basis following discussion and documentation
- All health professionals caring for patients taking clozapine should be aware that clozapine-induced constipation is highly prevalent, often difficult to detect and potentially fatal. Prophylactic laxatives are recommended when clozapine is initiated and constipation should be considered at every consultation.
- Patients taking clozapine should be monitored for symptoms and signs of cardiac toxicity and neutropenia. Regular blood tests are mandatory to detect blood dyscrasias and for continued supply of the medicine.
- Patients with schizophrenia often need support to maintain their cardiovascular health due to the adverse metabolic effects of antipsychotic medicines and the additional challenges typical of the illness
- When prescribing other medicines, consider whether they may interact with or exacerbate the adverse effects of clozapine
- Substantial changes in cigarette or caffeine consumption may necessitate a dose adjustment of clozapine

In 2014, bpac^{NZ} published an article on the safer prescribing of clozapine. Since this time, a number of fatalities, along with new research, has reiterated the need for close monitoring of patients treated with this high-risk medicine. Clozapine is often effective for patients with treatment-resistant schizophrenia, however, proactive and co-ordinated management is required, which is the primary responsibility of the initiating prescriber. In particular, patients should not necessarily be relied on to report symptoms of adverse effects. The primary care team can improve safety through monitoring and management of constipation, neutropenia, metabolic effects and cardiac toxicity, and being aware of medicines which may interact with clozapine or exacerbate its adverse effects.

Initiating clozapine for treatment-resistant schizophrenia

Clozapine is an atypical (second generation) antipsychotic, first used in the 1960s and subsequently withdrawn after it was linked to a number of deaths.¹ The medicine was reintroduced following a landmark study in 1988 demonstrating that patients with schizophrenia who were unresponsive to other medicines often found clozapine beneficial.² Since then, clozapine has been shown to be the only medicine to reduce suicidal behaviour in patients with schizophrenia and it is now the medicine of choice for treatment-resistant schizophrenia.³ However, due to the risk of serious adverse effects, e.g. significant constipation, blood dyscrasias, metabolic and cardiac toxicity, clozapine is limited to treatment-resistant patients and the initiating prescriber needs to ensure that careful monitoring occurs. In 2016, approximately 4,300 patients in New Zealand were prescribed clozapine.⁴

Prescribing of clozapine is restricted

Clozapine treatment is initiated by a psychiatrist, ideally as soon as treatment-resistant schizophrenia is identified.³ Early treatment with clozapine is beneficial, i.e. six to 12 months after diagnosis, as disability typically develops in patients with unresolved symptoms.³ There are no subsidy restrictions on clozapine treatment, however, under the Medicines Act (1981) clozapine can only be prescribed by:⁵

- Vocationally registered psychiatrists
- Medical practitioners or nurse practitioners who are prescribing under the supervision of a psychiatrist
- Vocational registered general practitioners who are prescribing in collaboration, or following consultation, with a Community Mental Health Team for a patient whose illness is well controlled with clozapine treatment (see: "Prescribing of clozapine in primary care").

Clozapine is relatively contraindicated in patients with severe cardiac or renal disorders, or a history of neutropenia, bone-marrow disorders, paralytic ileus, acute substance-induced psychosis or intoxication, circulatory collapse or epilepsy.⁶

Patients may take months to respond

Clozapine dosing ideally starts low and is slowly titrated upwards over three weeks to minimise adverse effects, usually to a daily maintenance dose of 300–450 mg.⁷ Some patients may require higher doses, with a maximum daily dose of 900 mg.⁷ A therapeutic response may take some time to develop, therefore 12 months of continuous treatment is recommended before deciding on the efficacy of clozapine.³

Co-ordination of care is essential

Co-ordination between the mental health team and primary care teams is vital to prevent gaps in care from emerging. Local protocols may vary, a typical arrangement, however, would be for prescriptions for clozapine to be provided by the mental health team every 12 weeks with dispensing determined by the frequency of mandatory blood tests, e.g. every seven days for the first 18 weeks of treatment or every four weeks thereafter. Pharmacists are required to confirm that prescriptions for clozapine have been issued by an appropriate prescriber and that a satisfactory blood test has been performed in the previous three days.⁸

The mental health team will oversee treatment

The mental health team will register the patient with the manufacturer to allow them to monitor the patient's blood results and to ensure that patients who have previously developed agranulocytosis are not prescribed clozapine a second time. It is recommended that pharmacists confirm that registration has occurred. If the patient develops abnormal test results the mental health team will liaise with a haematologist and request additional testing from the primary care team, as required. The mental health team will provide a clear written plan for primary care outlining shared care arrangements or transition of responsibility to the primary care team, according to the individual needs of the patient. The mental health team may also provide the primary care team with templates to monitor the patient's metabolic parameters.

The primary care team takes responsibility for the patient's overall health

The role of the primary care team, i.e. general practitioners, practice nurses and pharmacists, is to take responsibility for the patient's overall health, including:

- Preventing and managing adverse effects, e.g. prescribing prophylactic laxatives and assessing the patient for constipation
- Monitoring the patient for cardiac toxicity and managing cardiovascular health
- Encouraging adherence to clozapine treatment and mandatory testing to detect blood dyscrasias
- Avoiding or managing the use of other medicines that may interact with or exacerbate the adverse effects of clozapine

Every interaction, whether or not related to the dispensing of clozapine, is an opportunity for the primary care team to build rapport with the patient, assess for adverse effects and optimise care. These patient contacts are also an opportunity to emphasise the importance of continuing treatment and the need for regular monitoring.

Monitoring and managing the adverse effects of clozapine

Clozapine use is frequently associated with:^{3,10}

- Constipation and other anticholinergic adverse effects, including sinus tachycardia and cognitive dysfunction
- Hypersalivation
- Urinary incontinence
- Dyslipidaemia
- Hyperglycaemia
- Orthostatic hypotension
- Sedation
- Weight gain

Clozapine has also been associated less frequently with QT prolongation, neutropenia/agranulocytosis and cardiac toxicity, particularly myocarditis in the first weeks of treatment.⁸ In addition, patients taking higher doses are at an increased risk of seizures.³ ¹¹ Testing of plasma clozapine levels is not routinely required, but may be requested if there are concerns with toxicity or to confirm adherence with treatment if there is a lack of response.¹²

If patients find the adverse effects of clozapine intolerable, a dose reduction may be appropriate, following a discussion with the psychiatrist overseeing the patient's care. More serious adverse effects, e.g. agranulocytosis or myocarditis, require clozapine to be withdrawn permanently.

Clozapine-related constipation is under-recognised and potentially fatal

Constipation is an under-recognised and under-reported consequence of clozapine treatment.¹³ The need for increased awareness of clozapine-related constipation has been highlighted recently with reports of several avoidable fatalities. Clozapine-related constipation has been linked to the deaths of at least 13 people in New Zealand since 1992.¹³

Clozapine-related constipation results from gastrointestinal hypomotility (paralytic ileus) thought to be caused by the medicine's combined anticholinergic and antiserotonergic properties.¹³ If untreated, the lack of peristalsis causes stasis and the retention of intestinal contents, which can reduce mucosal perfusion and lead to toxic megacolon, bowel perforation, peritonitis, sepsis and death.^{8, 14} The risk of constipation is increased in patients who are prescribed higher doses of clozapine and in patients who develop fever, as this may slow the metabolism of clozapine.¹⁵

Constipation may be difficult to detect

Clozapine-induced constipation can be difficult to detect as patients with schizophrenia often have a high tolerance to pain, may under-report symptoms or not know that they are constipated or that symptoms should be reported.^{8, 13} At every consultation, clinicians should ask patients taking clozapine about the consistency of their stools, their ease of passage, and how often they go two days or more without a bowel movement. Where appropriate, patients should also be assessed for signs of constipation.

The most frequent symptoms of clozapine-induced constipation include an absence of bowel movements for two days or more, abdominal pain, abdominal distension, overflow diarrhoea, reduced appetite, nausea and vomiting.⁸ A meta-analysis of survey results suggests that one-third of patients taking clozapine will be constipated at any point in time.¹⁶

 Information on clozapine for patients is available from: www.healthnavigator.org.nz/medicines/c/clozapine

Preventing clozapine induced constipation

Patients with schizophrenia may struggle with lifestyle measures to prevent constipation, e.g. a high fibre diet with plenty of fluids and regular exercise, therefore additional measures are required, including:^{3, 17}

- Prophylactic laxatives for all patients when clozapine is initiated, with treatment continued as necessary (see: "The Porirua protocol")
- Avoiding the concurrent use of medicines that can exacerbate constipation, e.g. opioids, calcium channel blockers, tricyclic antidepressants and other medicines with anticholinergic properties

Prescribe laxatives to all patients taking clozapine

The Porirua protocol is a regimen of laxatives for the prevention and treatment of clozapine-related constipation that was first published in 2014 by researchers at the University of Otago, Wellington. The protocol primarily uses docusate sodium with sennoside B, with an additional laxative for patients with resistant constipation. A small study of 14 patients taking clozapine found that the Porirua protocol reduced the average time for material to pass along the colon by two days.¹⁸

Monitoring patients for cardiac toxicity

Clozapine treatment frequently causes orthostatic hypotension and sinus tachycardia, and less often QT prolongation, myocarditis and cardiomyopathy.^{3, 10} Patients taking clozapine must be assessed for cardiac abnormalities before treatment is initiated (Table 2).

Prescribing of clozapine in primary care

Some DHBs, e.g. Capital and Coast and Wairarapa, have protocols in place for prescribing of clozapine in primary care to stable patients, as identified by the mental health team. Before this occurs, the mental health team will liaise with the general practitioner to confirm that the transfer of the patient to primary care is appropriate.⁹ Patients must meet certain criteria to be considered for clozapine prescribing by their general practitioner, e.g.:

- No admissions for mental health-related issues in the previous 12 months
- Two years continuous treatment with clozapine
- No medicines concurrently prescribed that require monitoring by a psychiatrist
- A history of adherence to treatment and scheduled appointments

When the patient is transferred, the responsibility for monitoring their blood tests will be passed to the primary care team and the dispensing pharmacist and manufacturer will be contacted by the mental health team.⁹ A period of shared-care, e.g. for three months, may be arranged to ensure a smooth transition for the patient.⁹

Clozapine prescribing in primary care would typically begin with the patient scheduled to meet with the general practitioner every four weeks for the first three months of treatment.⁹ Ideally, the patient will have blood tests on a Tuesday or Wednesday before the consultation (to avoid public holidays). Requests for blood tests should indicate on the form that the patient is taking clozapine to ensure the results are sent to the manufacturer. The general practitioner checks the results and records them on the patient's prescription.⁹ If there are concerns about the patient's white blood cell count a haematologist should be contacted and daily blood counts requested.⁹ Treatment with granulocyte colony stimulating factor can be beneficial to patients with reduced white blood cell counts.⁹ Prior discussion with the community pharmacist may be helpful to ensure prompt access to this product. If clozapine treatment is withdrawn the mental health team should be contacted to allow the patient's treatment to be stabilised.

If the pharmacist reports that a blood test has not been performed within the last three days, it is appropriate to authorise sufficient clozapine to be dispensed until the patient is able to undergo another blood test.⁹

Once treatment is initiated, reduced fitness, e.g. breathlessness when walking, difficulty breathing at night or oedema may suggest cardiac complications. There is no evidence that regular ECGs or echocardiograms will detect cardiac complications in asymptomatic patients, however, these investigations are useful in confirming a diagnosis.⁸ Clozapine should be permanently withdrawn if a patient develops myocarditis, cardiomyopathy or QT prolongation greater than 500 milliseconds.⁸

Orthostatic hypotension may be prevented by the slow initial titration of clozapine dosing. Patients can manage orthostatic hypotension by drinking more fluids (e.g. 1.25 - 2.5 litres of water per day) and modestly increasing their salt intake if appropriate (e.g. 10 - 20 g of salt per day*) until their blood pressure stabilises.¹⁰ ²⁰ If this is insufficient, compression garments, e.g. abdominal binders and socks may be trialled.²⁰ Pharmacological treatment options include pyridostigmine (unapproved use) for moderate orthostatic hypotension and fludrocortisone (unapproved use) for more severe cases.²⁰

* A high salt diet may not be appropriate for some patients, e.g. if they also have hypertension, and should not be maintained over a long period of time. Increasing dietary salt intake can be achieved by adding table salt to meals or increasing consumption of salty foods such as soy sauce, vegemite, prepared soups, cured meats or pretzels.

Sinus tachycardia occurs most frequently at the start of treatment when clozapine is being titrated upwards.¹⁰ This is often harmless, but new-onset tachycardia in a previously stable patient, with no changes to clozapine treatment for at least one month, suggests cardiomyopathy (see below).¹⁰ Treatment options for sinus tachycardia include a reduction in the dose of clozapine or initiation of a once-daily cardioselective beta-blocker, e.g.

bisoprolol or metoprolol succinate.¹⁰ Beta-blockers should not be initiated in the first six weeks of clozapine treatment as this may obscure a diagnosis of myocarditis.¹⁰

Myocarditis is most likely to occur in the first weeks after clozapine is initiated; the risk is low, but it is associated with a high mortality rate.⁸ For monitoring, the patient's serum troponin and CRP are taken at baseline and weekly for the first four weeks of treatment.⁸

The symptoms and signs of myocarditis are fever, tachycardia, chest pain, dry cough, diarrhoea, vomiting, dysuria, rash and investigations may show an elevated white blood count and peripheral eosinophilia.⁸ If myocarditis is suspected, an ECG should be performed immediately. Ventricular arrhythmias, heart block or findings similar to myocardial infarction or pericarditis on ECG are consistent with myocarditis.²¹ If myocarditis is suspected the patient should be referred to the Emergency Department. CRP, creatine kinase, full blood count and serum troponin testing can help to clarify the clinical picture.¹⁷

Cardiomyopathy may occur at any stage of clozapine treatment and is typically of the dilated type.¹⁰ Patients taking clozapine should be assessed for symptoms of heart failure at least four times a year, which may be secondary to cardiomyopathy.⁸

The most frequent symptoms and signs of clozapine-induced cardiomyopathy are fatigue, dyspnoea and tachypnoea.¹⁰ On ECG the patient will often display T-wave and P-wave abnormalities and signs of left ventricular hypertrophy.¹⁰ If cardiomyopathy is suspected refer the patient to the Emergency Department. CRP, creatinine kinase, full blood count, serum troponin and B-type natriuretic peptide (BNP) can help to clarify the clinical picture.⁸

The Porirua protocol

When clozapine is initiated, all patients should be concurrently prescribed two tablets of docusate sodium with sennoside B each night to prevent the onset of constipation.¹⁸ *

- If the patient has not had a bowel movement for two days, increase the dose of docusate sodium with sennoside B by one tablet in the morning and review the patient within 48 hours
- If still constipated, increase the dose again by one tablet in the morning and review the patient within 48 hours
- If the patient remains constipated, a rectal examination should be performed to exclude impaction:
 - If impacted, docusate sodium with sennoside B should be stopped and the patient discussed with a member of the mental health team or a gastroenterologist; manual dis-impaction and enemas may be required
 - If not impacted, continue with two tablets of docusate sodium with sennoside B, twice daily, and review after 48 hours
- If constipation persists, add one macrogol sachet,[†] twice daily, and review the patient after 48 hours.

If constipation is ongoing the patient should be discussed with a gastroenterologist.

- * If the patient develops diarrhoea it may be appropriate to reduce the dose or withdraw treatment; close monitoring is essential to detect constipation
- † Special Authority approval is now no longer required for subsidy for macrogol sachets (macrogol 3350 + sodium chloride + potassium chloride + sodium bicarbonate – Molaxole)

Red flags for constipation in patients taking clozapine that require urgent medical review:¹⁸

- Moderate to severe abdominal pain which lasts for more than one hour
- Any abdominal pain or discomfort which lasts for more than one hour and one or more of:
 - Abdominal distension
 - Diarrhoea, especially if bloody
 - Vomiting
 - Absent or high-pitched bowel sounds
 - Haemodynamic instability
 - An elevated white blood cell count
 - Metabolic acidosis
 - Additional signs of sepsis

Managing other adverse effects

Hypersalivation is reported to affect approximately 30% of patients treated with clozapine.²² Excessive saliva production is often more prominent at night and generally occurs shortly after clozapine is initiated.²² The exact mechanism of clozapine-induced hypersalivation is not known.²² Chewing sugarless gum is often recommended, but may not be effective.²² If a reduction in clozapine dose is not appropriate, there are a number of pharmacological options that can be trialled (Table 1).²² Pharmacists and community mental health teams may be able to provide waterproof pillowcases from the supplier of clozapine for nocturnal symptoms.

Urinary incontinence associated with clozapine use can have a complex pathophysiology. Following discussion with the mental health team, it may be appropriate to reduce the patient's dose of clozapine.³ Nocturnal symptoms may be alleviated by limiting fluid intake during the evening and voiding before bedtime. If incontinence persists, desmopressin nasal spray may be an effective treatment option.¹⁷ Oxybutynin or solifenacin may be helpful for urinary incontinence in patients without an anticholinergic cause, however, caution is required as these medicines may exacerbate other adverse effects such as constipation. Ephedrine can be effective in the treatment of clozapine-related urinary incontinence but is unavailable in primary care.¹⁷ Urinary incontinence can also be associated with constipation due to the proximity of the related anatomical structures. Urodynamic testing may be required to determine the most appropriate treatment for the patient.

 Further information is available from: "Urinary incontinence in adults" www.bpac.org.nz/BPJ/2013/October/urinary-incontinence.aspx

Maintaining the cardiovascular health of patients taking clozapine

Cigarette smoking and excessive use of alcohol are common in patients with schizophrenia.³ When these behaviours are combined with a disrupted lifestyle, generally impaired insight and motivation, and the sedating effects of antipsychotic medicines it can be very difficult for patients to achieve a healthy lifestyle.

Metabolic adverse effects are a feature of most antipsychotic medicines, however, clozapine is particularly noteworthy for its tendency to cause dyslipidaemia, hyperglycaemia and weight gain; frequent monitoring is required (Table 2).³ It may be appropriate to prescribe metformin, statins or antihypertensives depending on the age and cardiovascular risk of the patient. Clozapine should not be withheld from patients with diabetes, but close monitoring and management of HbA_{1c} levels is recommended.

Establishing routines may help patients with schizophrenia improve their health, e.g. planning meals, making a shopping list, and going to the supermarket at the same time each week. The assistance of family or carers may encourage patients to adhere to a routine involving regular physical activity with increased consumption of fresh fruit and vegetables.

Testing for abnormal white blood cell counts is required throughout treatment

Patients taking clozapine require a weekly white blood cell count for the first 18 weeks of treatment and every four weeks thereafter (Table 2).^{3,8} Clozapine can only be dispensed from pharmacies that are contracted to do so and dispensing is prohibited if a blood test with a satisfactory result has not been performed in the previous three days.⁸ Pharmacists are required to contact the patient's prescriber or general practitioner if there are abnormalities in the patient's white blood cell counts. It may be appropriate for general practitioners to discuss with the dispensing pharmacy how abnormal test results will be managed.

Table 1: Examples of subsidised medicines* for the treatment of clozapine-induced hypersalivation.²²

Medicine	Class	Dose	Comments
Benzatropine	Antimuscarinic	2 mg, daily	May exacerbate anticholinergic adverse effects.
Hyoscine hydrobromide	Antimuscarinic	1.5 mg patch every 72 hours	Special Approval Authority criteria required where at least two other treatments have been ineffective. May exacerbate anticholinergic adverse effects. Improvement in symptoms is likely to be long-lasting.
Metoclopramide	Antidopaminergic and antiserotonergic	10 mg per day, increased by 10 mg over a week, to 30 mg per day, if required,	Due to the risk of extrapyramidal effects and tardive dyskinesia caution is advised. See www.nzf.org.nz No adverse effects were reported in a small group of patients treated for this indication.
Terazosin	Alpha-adrenoceptor antagonist	2 mg at night	Reduces hypersalivation more than benztropine, may be combined with antimuscarinics

* All unapproved indications

Always assess patients for symptoms and signs of systemic infection

Patients with symptoms consistent with a systemic infection, e.g. a fever or sore throat, require a full blood count to exclude neutropenia. When the blood test is requested, note that the patient is taking clozapine, so that the results will be sent to the manufacturer, and that the result is required the same day and request a copy be sent to the dispensing pharmacy.

If neutropenia occurs, i.e. a neutrophil count of $0.5\text{--}1.5 \times 10^9/\text{L}$,⁸ clozapine should be stopped and management urgently discussed with a member of the mental health team. Treatment may be continued when the patient's blood count normalises.⁸ Neutropenia may occur at any stage of treatment, even in patients who have been taking clozapine for 20 years.⁸ Clozapine should be withdrawn permanently if the patient's neutrophil count falls below $0.5 \times 10^9/\text{L}$, i.e. agranulocytosis occurs.⁸

Avoiding clinically significant interactions with clozapine

Clinically significant pharmacological interactions with clozapine should be minimised. Clozapine is metabolised in the liver, predominantly by CYP1A2, and induction or inhibition of this enzyme may influence the patient's plasma clozapine levels. Check for interactions when new medicines are prescribed and ask the patient to report changes in their caffeine and tobacco intake.

Medicines that interact with clozapine

There are four broad mechanisms by which substances may produce clinically significant interactions with clozapine, i.e. induction or inhibition of the CYP1A2 enzyme, additive adverse effects and increased sensitivity to centrally acting depressants (Table 3).

Table 2: Recommended schedule for managing patients treated with clozapine.^{3,8}

Cardiac toxicity						
	Baseline	First four weeks			Every three months	
Serum troponin and CRP	✓ ECG	✓			Assess for symptoms of heart failure	
Immune suppression						
	Weekly for the first 18 weeks	Every four weeks			At every consultation	
White blood cell count	✓	✓			Assess for symptoms and signs of systemic infection	
Constipation						
	At initiation			At every consultation		
	Ensure laxatives have been prescribed or discussed			Ask about frequency and ease of bowel movements and assess for symptoms and signs of constipation		
Metabolic monitoring						
Measurement	Baseline	Four weeks after initiation	Eight weeks after initiation	12 weeks after initiation	24 weeks after initiation	Annually
BMI	✓	✓	✓	✓	✓	✓
Waist circumference	✓			✓	✓	✓
HbA _{1c}	✓			✓	✓	✓
Blood lipids	✓			✓	✓	✓
Lifestyle						
	Baseline			At every consultation		
	Record smoking status and frequency and level of caffeine and alcohol consumption			Ask about substantial changes in tobacco, caffeine or alcohol intake		

N.B. The prescriber who initiates clozapine is responsible for ensuring that appropriate monitoring is occurring

Key: Secondary care/mental health team responsibility Can be managed in primary care on request from secondary care/mental health team

 The NZF interactions checker provides details on medicines that interact with clozapine and their clinical significance, available from: www.nzf.org.nz

Smoking cessation may require dose reductions of clozapine

Smoking tobacco causes induction of CYP1A2 and abrupt cessation of cigarettes can cause a rapid and significant increase in plasma clozapine levels.³ This effect is caused by the aromatic hydrocarbons in tobacco smoke and is not affected by nicotine replacement therapy.³

Encourage smoking cessation in all patients taking clozapine, but those taking high doses, i.e. greater than 450 mg per day, will usually require a reduced dose of clozapine.³ Varenicline is reported to be a safe and effective smoking cessation medicine in patients with schizophrenia and is not known to interact with

clozapine.²³ Bupropion is not recommended in patients taking clozapine due to an increased risk of seizure.²³

Caffeine intake can affect clozapine levels

Caffeine is an inhibitor of CYP1A2 and patients taking clozapine should be encouraged to keep their caffeine intake stable and to report substantial changes to their prescriber.^{7,24} High levels of caffeine consumption can increase plasma clozapine levels, e.g. greater than 400 mg/day;¹¹ equivalent to approximately six cups of instant coffee or 1–1.5 L of an energy drink. If a patient with a high caffeine intake goes caffeine-free their levels of plasma clozapine can decrease by almost 50% after five days.⁶

Clozapine can potentiate the effects of alcohol

Alcohol's depressant effect can be increased by the concurrent use of clozapine. Advise patients taking clozapine to ideally avoid alcohol or to drink cautiously if they do consume alcohol.

Table 3: Mechanisms and examples of interactions with clozapine.

Induction of CYP1A2 may decrease clozapine plasma levels	Inhibition of CYP1A2 may increase clozapine plasma levels	Additive adverse effects	Increased sensitivity to centrally acting depressants
Examples include: <ul style="list-style-type: none"> ■ Carbamazepine ■ Omeprazole ■ Phenytoin ■ Rifampicin ■ Tobacco smoke 	Examples include: <ul style="list-style-type: none"> ■ Cimetidine ■ Ciprofloxacin ■ Caffeine 	Additive bone marrow suppression, e.g. <ul style="list-style-type: none"> ■ Co-trimoxazole ■ Chemotherapy medicines ■ Nitrofurantoin QT prolongation, e.g. <ul style="list-style-type: none"> ■ Amiodarone ■ Domperidone Constipation, e.g. <ul style="list-style-type: none"> ■ Anticholinergics ■ Opioids 	Examples include: <ul style="list-style-type: none"> ■ Benzodiazepines ■ Zopiclone ■ Sedating antihistamines ■ Alcohol

Table 4: A recommended checklist for members of the primary care team caring for patients treated with clozapine.

For general practitioners and practice nurses		For pharmacists	
When treatment is initiated	At every consultation	When treatment is initiated	At every consultation
<ul style="list-style-type: none"> ■ Confirm laxatives have been prescribed ■ Confirm patient understands the need for regular testing and monitoring ■ Record smoking status and caffeine intake ■ Place an alert on the patient's record indicating that they require ongoing monitoring 	<ul style="list-style-type: none"> ■ Confirm adherence to treatment and report any signs of a relapse to the mental health team ■ Assess the patient for constipation ■ Confirm adherence to blood monitoring ■ Perform metabolic monitoring as required and ensure appropriate recalls are in place ■ Assess for cardiac symptoms ■ Query any changes in cigarette or caffeine intake, where appropriate 	<ul style="list-style-type: none"> ■ Ensure patient is registered on the manufacturer's database ■ Patients should not be supplied with more than seven days of clozapine in the first 18 weeks of treatment ■ If a general practitioner is prescribing for the first time, confirm the patient has been transferred from the mental health team 	<ul style="list-style-type: none"> ■ Confirm a satisfactory recent blood test; contact the patient's prescriber if the test has not been performed in the last three days or the results are abnormal ■ If the patient is changing pharmacies inform the manufacturer ■ Inform the patient's prescriber if they miss a dispensing

A summary checklist for the primary care team

A systematic approach is recommended when caring for patients treated with clozapine to ensure continuity and to inform other team members of the patient's needs (Table 4).

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