Side-effects associated with clozapine therapy

The table below outlines the more common side effects related to clozapine and signs and symptoms should be carefully monitored (outlined in the *Guidelines for the safe and quality use of clozapine therapy in the WA health system*). For a list of pharmacological options and actions, the treating team should contact the clinical pharmacist.

Side-effect / Signs and symptoms	Rate	Recommended Action
Haematological effects		
Neutropenia WBC <3.0 x 109/L or Neutrophils < 1.5 x 109/L. Flu-like symptoms such as sore throat & fever. (This is common within the first 18 weeks – but may uncommonly occur after this maximal risk period)	3.2%	Contact Doctor. Stop clozapine. Contact haematologist at ClopineCentral™ or clozapine patient monitoring centre if further advice required. Re-introduction of clozapine should only occur with haematologist support
Agranulocytosis WBC <3.0 x 109/L or Neutrophils < 1.5 x 109/L. Flu-like symptoms such as sore throat & fever. (First 18 weeks – but may occur at any time)	0.8%	Contact Doctor. Stop clozapine. Contact haematologist at ClopineCentral™ or clozapine patient monitoring centre if further advice required. Re-introduction of clozapine should only occur with haematologist support.
Benign ethnic neutropenia	Rare	The presence of benign ethnic neutropenia should not prevent treatment with clozapine however a haematologist review prior to commencing clozapine is of benefit which may lead to an adjustment of the white blood cell count green, yellow and red ranges.
Cardiac effects		
Myocarditis Tachycardia at rest with rapid breathing, dyspnoea, hypotension, raised jugular venous pressure, fatigue, flu-like symptoms, chest pain or fever. Myocarditis usually occurs within 1 - 4 to 6 weeks of starting)	0.7-1.2%	Contact Doctor and team. Refer to cardiologist. Check Troponin and C-reactive protein (CRP) levels. Withhold clozapine. Repeat ECG and Echocardiogram. If confirmed contact cardiologist at clozapine monitoring centre. Submit the 'Therapy Event' form and 'TGA Adverse Event' form. Re-introduction of clozapine should only occur with cardiologist support.
Cardiomyopathy Cardiomyopathy may occur at any time. The possibility of cardiomyopathy must always be considered there is clinical evidence of heart failure including resting tachycardia, tachypnea, shortness of breath or hypotension.	0.1 %	Contact Doctor and team. Refer to cardiologist. Check Troponin and C-reactive protein (CRP) levels. Withhold clozapine. Repeat ECG and Echocardiogram. If confirmed contact cardiologist at clozapine monitoring centre. Submit the 'Therapy Event' form and 'TGA Adverse Event' form. Re-introduction of clozapine should only occur with cardiologist support.
Tachycardia	25%	Contact Doctor. Check FBC, WBC, ECG, ECHO. Note that a benign tachycardia can occur in up to 25% of patients which is often self-limiting.
Orthostatic hypotension May be problematic for patients on clozapine therapy; it often improves as tolerance develops.	9%	Best managed with slow and gradual titration of clozapine. Patients must be provided with advice on managing postural dizziness (take time standing up) and the modification of dietary salt and fluid intake. Specialist support may be needed if the symptom persists. Treatments to address the hypotension are available (including anti-hypotensives) but must only be used under specialist support. Note that some patients may develop hypertension on clozapine.
Venous thromboembolism	Rare 0.02%	Avoid Immobilization; early detection important as potentially life threatening event.
Central nervous system effects		
Sedation First 4 weeks. This may persist but generally improves. This is the most common side effect of clozapine.	50%	Give smaller dose in the mornings. Some patients can only tolerate single night-time dosing. Reduce dose if necessary. Consider plasma level monitoring. Avoid other sedating agents.
Seizures This dose dependent risk increases with higher plasma levels (especially dosages greater than 600 mg/day), rapid dose titration, concurrent use of drugs that lower seizure threshold and pre-existing seizure disorders	up to 5%	Contact Doctor. Consider reduction in dose. Clozapine need not be discontinued. Check with Clinical Pharmacist for pharmacological anticonvulsant options. Valproic Acid is commonly used due to lack of interactions with clozapine and rapid titration schedule.

and illness. (Seizures may occur at any time).		Monitor serum clozapine levels regularly.
Myoclonus	2%	Uncommon side effect. May be a precursor to seizures and may require an anticonvulsant.
Gastrointestinal effects		
Hypersalivation Excessive drooling – very troublesome at night. (First few months especially but can be ongoing). This is the second most common side effect.	50% (up to 85%)	Give hyoscine hydrobromide 300 micrograms sucked and swallowed at night. Hyoscine patches may be considered as an alternative. Atropine-related oral anticholinergics or sublingual ipratropium may also be considered. Wrapping a towel around a pillow at night and frequent swallowing during the day can assist.
Constipation Less frequent bowel motions, hard stools, abdominal bloating, cramping or pain, decrease appetite or fatigue. (Usually persists).	14 – 25%	Recommend high-fibre diet and increased fluid intake; stimulant laxatives if required. Review other medications that may cause constipation ***Constipation should be considered a serious adverse effect, as it can have potentially fatal complications.***
Nausea Can develop early or later in the course of treatment.	11%	May give antiemetic. Avoid prochlorperazine and metoclopramide if previously experienced Extra Pyramidal Side Effects (EPSE).
Parotid swelling Painful swelling of the parotid glands associated with hypersalivation. In some instances this spontaneously resolves but may persist.	Rare	Cessation of clozapine; or use of minimal effective dose. A combination of benztropine and terazosin may be considered.
Weight gain and metabolic effects		
Weight gain This may occur early in treatment and be can be significant.	50%	Dietary and lifestyle counselling before weight gain occurs. Ongoing monitoring and support.
Hyperglycaemia This may occur at any time in treatment and may progress to diabetes type II.	10%	Regularly screen for evidence of diabetes. Use oral hypoglycaemics or insulin as per guidelines for managing diabetes. Consider specialist referral
Hyperlipidaemia	Up to 50%	Regularly screen for evidence of elevated triglycerides and lipids. Use lipid lowering agents (as per guidelines for managing hyperlipidaemia) especially the addition of a statin.
Other		
Benign Fever (Temperature $\geq 38^0$ C within first 3 weeks * Note: a benign fever can occur in up to 20% of patients initiated on clozapine which is generally self-limiting within 3 days of onset.	Up to 20%	Contact Doctor. Reduce rate of dose titration of clozapine. Check FBC, WBC, troponin and CRP. Physical examination for signs of infection. Consider ECG, Echo. Do not give paracetamol until doctor notified and agranulocytosis / myocarditis excluded.
Nocturnal enuresis Loss of bladder control, especially at night (bed wetting). (May occur at any time).	23-30%	Avoid high intake of fluids in the evening and ensure adequate voiding at bedtime; plan middle-of-the-night awakenings to empty bladder Consider the careful addition of an α adrenergic agonist / anticholinergic medication such as a tricyclic antidepressant. Desmopressin may be an effective symptomatic treatment (in nasal or oral form). Consider a continence referral.
Obsessive Compulsive Behaviour Symptoms may be transient but can follow a more persistent and chronic course and can be disabling	10-40%	Dose reduction may lead to symptom improvement. Cognitive behavioural therapy or pharmacological agents such as serotonin-specific reuptake inhibitors (antidepressants). Caution must be applied as many antidepressants can have an effect on clozapine serum levels.
This is not an exhaustive list of side-effects. Please see Clozapine Product Information for further advice.		

Reference: Taylor, D., Paton, C. and Kapur, S. 2015. The Maudsley Prescribing Guidelines in Psychiatry. 12th Revised edition. New York: John Wiley & Sons Inc. https://archive.org/details/TheMaudsleyPrescribingGuidelinesInPsychiatry12thEdition