

CLOZAPINE 101: Side Effects At-A-Glance

COMMON

RARE

Side Effect	Treatment	Comment
Sedation / Sleepiness	•When psychosis is well controlled: Modafinil, bupropion, high-dose famotidine	Sleep heals; up to 12 hours per day can be healthy on clozapine.
Constipation	•Stool softeners & laxatives (Miralax®) •Linzess® (linaclotide) or Trulance® (plecanatide)	Treat proactively to prevent bowel obstruction; do not use fiber supplements.
Hypersalivation (drooling, especially at night)	•Atropine drops or ipratropium spray (sublingual) •Glycopyrrolate, consider salivary gland Botox®	Treat proactively to prevent aspiration pneumonia. No bedtime food or drinks, and elevate the head of the bed.
Weight gain / excessive hunger / diabetes risk	•Metformin (consider adding SGLT2 inhibitor, GLP-1 agonist)	Treat proactively within first weeks of starting clozapine.
Elevated heart rate (high pulse)	•Beta blocker (i.e. propranolol / metoprolol / atenolol)	Treat proactively to prevent cardiomyopathy.
Nausea / vomiting	•Zofran® (ondansetron) •Reglan® (metoclopramide) secondary	Also shown to improve mood symptoms.
Heartburn / acid reflux / nighttime "cough"	•Famotidine, proton pump inhibitor secondary	Do not use Tums® (calcium carbonate) which blocks clozapine absorption.
Bedwetting / urinary urgency or frequency	•Desmopressin •Myrbetriq® (mirabegron) secondary	Often resolves over time, minimize bedtime liquids.
Mild fever, sweating, increased white blood cells	•Wait and watch (treatment usually unnecessary)	Mild symptoms common during clozapine initiation, resolve over time.
Body pain or numbness	•Advocate for slower dose escalation •Acetaminophen or ibuprofen	Occurs with large dose increases over 25mg. Hospitals and inexperienced providers often increase daily dose by 50mg at a time or more.
Orthostasis (drop in blood pressure, dizziness, fainting, blurry vision)	•Advocate for slower dose escalation •Increase salt & water intake •Fludrocortisone if persists, midodrine secondary	Improves over time as the body adjusts; slowing clozapine introduction is helpful.
Atonic seizure activity (muscles becoming limp, dropping objects, falls, poor balance) Or any type of seizure	•Lamotrigine •Vimpat® (lacosamide), Keppra® (levetiracetam), gabapentin or topiramate. Valproate only as a last resort due to clozapine interaction.	Risk increases at higher clozapine serum levels. Prevent occurrence with adjunctive anticonvulsant medications. Avoid spikes in serum levels (i.e. careless use of fluvoxamine, inflammatory illnesses, abruptly quitting smoking, large dose fluctuations)
Retrograde ejaculation (reduced sperm production)	No available treatment	Does not affect erectile function, orgasm or fertility.
Movement disorder (dystonia, tardive dyskinesia, oculogyric crisis)	•Split clozapine dosing throughout the day •VMAT2 inhibitors, Benadryl® or benztropine	Can occur at high clozapine serum levels in patients with history of non-clozapine antipsychotic use.
Myocarditis, pericarditis, cardiac arrhythmias	•Advocate for slow titration The Meaningful Recovery protocol increases daily clozapine dose by 25mg each week to prevent severe side effects.	Hospitals and inexperienced providers may increase daily clozapine doses by 100mg (or more) each week which can be dangerous for many patients. Interrupting clozapine also carries risks (i.e. due to REMS or bloodwork).
Neutropenia (ANC below 1500/mL) Agranulocytosis (ANC below 500/mL)	•Retest ANC in afternoon after exercising •Adjunctive lithium, GCSF secondary	Most cases of low ANC are benign, transient and unrelated to clozapine. Historically, most interruptions in treatment have been unwarranted.
Other rare / serious complications	Most are treatable, many patients can continue clozapine.	Examples: embolism, thrombosis, liver toxicity, NMS, pancreatitis.