- Metformin is the treatment of choice for type 2 diabetes, followed by a sulfonyurea.
- **Ketoacidosis: Hyperglycemia and Ketoacidosis**
  - Serum glucose often 350-500mg/dL with metabolic acidosis and symptoms of nausea, vomiting, abdominal pain usually evolving rapidly over a 24 hour period.
  - Can occur in those with no history of diabetes and does not appear to be related to dose or duration of treatment.
  - Suspected cases should be referred to emergent medical care as it can be quickly fatal.

**Nocturnal Enuresis**
- **Timeline**: within the first 3 months
- **Mechanism**: Unclear. May be multifactorial and influenced by sedation, adrenergic and anticholinergic mechanisms.
- **Incidence**: The reported incidence of clozapine-induced nocturnal enuresis (CINE) ranges from <1% to over 40%. Low estimates may simply reflect the embarrassing nature of reporting this relatively common adverse effect.
- **Non-pharmacological management**:  
  - Limit fluid intake during the evening  
  - Void at night  
  - Schedule middle of the night awakening to void  
  - Reassurance, most cases resolve spontaneously and effective treatments are available.
- **Pharmacological management**: literature limited to case reports and a small cohort study  
  - Desmopressin  
  - TCAs  
  - Oxybutynin (anticholinergic)  
  - Ephedrine (alpha adrenergic agonist)- use caution as can worsen anxiety and psychosis

**Hepatic Impairment**
- Clozapine has been associated with transaminitis, toxic hepatitis, and fulminant liver failure.
- **Timeline**: Clozapine-induced transaminitis usually occurs within the first 6 weeks of treatment, is transient and often asymptomatic. Spontaneous resolution is common and usually occurs within 13 weeks of initiating treatment.
- **Incidence**: The incidence of clozapine-induced transaminitis is around 30%.
- **Prognosis**: Clozapine-induced transaminitis spontaneously resolves in 60% of cases without altering the dose or discontinuing treatment. Although usually benign, there are case reports of 14 people who developed jaundice, hepatic encephalopathy, toxic hepatitis, liver toxicity, or fatal acute fulminant liver failure.
- **Mechanism**: Unclear, but the latency period is consistent with a hypersensitivity reaction. Some adverse effects of clozapine, including obesity and diabetes, can complicate acute and chronic liver impairment as they are associated with fatty liver and further increase the risk of hepatotoxicity.
- **Types of liver impairment**
- Clozapine use is contraindicated in progressive liver disease, hepatic failure, and active liver disease associated with nausea, anorexia, or jaundice.
- Cirrhosis: at risk as the number of functioning hepatocytes and thus metabolizing enzymes are reduced
- Chronic hepatitis: less likely to impair metabolism or drug kinetics
- Liver cancer: less likely to impair metabolism or drug kinetics
- Hepatosplenic schistosomiasis: less likely to impair metabolism or drug kinetics

**Mechanism of clozapine accumulation in severe liver impairment:**
- From reduction in first pass metabolism to the inactive metabolite clozapine-N-oxide, as clozapine undergoes moderate first pass metabolism (bioavailability 50-60%).
- From an increase in unbound clozapine as it is extensively protein bound (clozapine 95%, norclozapine 90%, clozapine-N-oxide 75%).

**Enzymes effected by liver impairment**
- Early hepatic dysfunction: 2C19
- Later more severe liver impairment: CYP1A2, CYP 2D6, CYP3A4

- Current classification systems which rate the severity of liver disease aren’t sensitive enough to be used to guide dose adjustment, but may help identify those requiring closer monitoring and more cautious prescribing.

The Child-Pugh classification

<table>
<thead>
<tr>
<th>Points</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Encephalopathy</strong></td>
<td>None</td>
<td>Minimal</td>
<td>Advanced (coma)</td>
</tr>
<tr>
<td><strong>Ascites</strong></td>
<td>Absent</td>
<td>Controlled</td>
<td>Refractory</td>
</tr>
<tr>
<td>Serum bilirubin (umol/L)</td>
<td>&lt;34</td>
<td>34-51</td>
<td>&gt;51</td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
<td>&gt;35</td>
<td>28-35</td>
<td>&lt;28</td>
</tr>
<tr>
<td>Prothrombin (s)</td>
<td>&lt;4</td>
<td>4-6</td>
<td>&gt;6</td>
</tr>
</tbody>
</table>

Mild 5-6 points, Moderate 7-9 points, Severe 10-15 points

**Monitoring:**
- Liver function tests should be monitored at baseline and then repeated at least annually or earlier if clinically indicated.
Any signs or symptoms of liver impairment should prompt additional monitoring to prevent development of transaminitis and/or acute liver disorders, or to prevent worsening of chronic liver impairment.

For use in those with liver impairment, current classification systems which rate the severity of liver disease aren’t sensitive enough to be used to guide dose adjustment, but may help identify those requiring closer monitoring and more cautious prescribing.

When initiating clozapine to those with liver disease start at a low dose (12.5mg daily) and titrate slowly, using plasma levels to guide dosing.

- Management:
  - If asymptomatic, dose adjustment may not be necessary as most cases of clozapine-induced transaminitis are benign and spontaneously resolve within 13 weeks of starting clozapine.
  - Transaminitis of three times the normal level, reduce the dose, or discontinue especially if clinical signs or symptoms of liver damage are evident.
  - Rechallenging with clozapine after liver toxicity, with increased monitoring, has been successful in some cases, but should be guided by clinical judgment and severity of the liver impairment.

The following side effects rarely warrant discontinuation
- Thrombocytosis
- Thrombocytopenia
- Eosinophilia
- Leukocytosis
- Drug-Induced Fever
- Sinus Tachycardia

**Thrombocytosis**
- While extremely rare, elevated thrombocyte counts have been reported during clozapine treatment.
- Although thrombocytosis predisposes to thrombosis, mild, transient thrombocytosis should not lead to discontinuation.
- Thrombocyte levels >750,000/μL – 1,000,000/μL warrant the discontinuation of clozapine.

**Thrombocytopenia**
- Low thrombocyte counts may occur in isolation or accompanied by other cell line changes.
- Clozapine-induced thrombocytopenia is usually transient and rarely merits a discontinuation.
- Persistent thrombocytopenia is rare.
- The problem may be resolved by pausing until values return to normal.
- The sequelae of thrombocytopenia are petechiae and increased risk of bleeding.
- Thrombocyte counts below 50,000/μL should lead to discontinuation.

**Eosinophilia**


Prognosis: Majority of cases are benign, but occasionally is associated with eosinophilic cardiomyopathy or other organ involvement (pancreatitis, hepatitis, colitis, nephritis).

Management:
- Discontinue clozapine is eosinophil count rises above 3.0x10⁹/L
- In case of eosinophilia, assess for organ involvement (myocarditis, cardiomyopathy, pancreatitis, hepatitis, colitis, nephritis) and discontinue if these occur.

Rechallenge: Only after count is below 1x10⁹/L.

Leukocytosis
- Paradoxically, clozapine may cause not only leukopenia, but also leukocytosis.
- The mechanism is unknown.
- Clinicians should rule out non-clozapine related reason for leukocytosis.
- It occurs often transiently in the first weeks of treatment.
- It is viewed as benign and should not lead to discontinuation.
- An exception is leukocytosis due to Neuroleptic Malignant Syndrome, in which clozapine should be discontinued.

Fever
- Timeline: onset between weeks 2 and 4, resolves in 1 to 5 days
- Dose dependent: no
- Non-pharmacological management
  - Rule out infection, NMS, agranulocytosis, and myocarditis.
  - Consider physical exam, CBC with diff, EKG, cardiac enzymes, chest X-ray, and urine culture.
  - Note the timeline of benign fever occurs earlier than the usual timeline for agranulocytosis and myocarditis.
  - Treatment may be cautiously continued if indications to stop are ruled out (NMS, agranulocytosis, myocarditis).
  - Reassurance. In the vast majority of cases, the fever spontaneously resolves.
- Pharmacological management
  - Stop clozapine and refer for medical assessment of myocarditis for concurrent cardiac symptoms (dyspnea, chest pain).
  - Acetaminophen to reduce temperature and ease symptoms.
  - For high grade fever (>39°C) temporarily suspend clozapine until resolution.
  - Re-challenging with clozapine is usually appropriate and fever usually does not recur.

Tachycardia
- Timeline: within the first 2 weeks, tolerance over 4-6 weeks
• Dose dependent: yes
• Incidence: Occurs in about 25% of patients.
• Non-pharmacological management:
  For asymptomatic patients:
  o As tolerance usually occurs over 4-6 weeks and the expected increase of 10-25
    beats per minute is thought to be rarely clinically significant, tachycardia should
    not be treated in asymptomatic patients.
  For persistent or symptomatic/distressing tachycardia:
  o Consider myocarditis: persistent tachycardia at rest, fever, hypotension, sedation,
    chest pain, in first 8 weeks of treatment.
  o Slow titration or lower dose to diminish adverse effects which may be benign
    (tachycardia, fever, hypotension, sedation) while evaluating for myocarditis.
  o EKG, serum troponin, WBC with differential
  o Do not stop clozapine unless there is strong evidence for myocarditis
• Pharmacological management:
  o Slower titration or dose reduction
  o Atenolol
    ▪ preferred as it is not metabolized by the liver limited effect on clozapine
      metabolism
    ▪ Cardio-selective properties make it more suitable for patients with asthma
      or diabetes.
  o Propranolol- if atenolol is not effective

**Warrant discontinuation with the potential to restart later**
*(with appropriate surveillance and management or prophylactic therapy)*
• Ileus or subileus
• Neuroleptic Malignant Syndrome
• Venous Thromboembolism
• Diabetic Ketoacidosis
• Hyperosmolar Coma
• Anticholinergic Toxicity

**Ileus**
• Constipation can lead to pseudo-obstruction, obstruction, ileus, acute colitis, and/or
  perforation. Clozapine should be discontinued in these cases.
• Mortality risk associated with clozapine-induced hypomotility and constipation may be
  greater than risk associated with agranulocytosis without appropriate monitoring.
• This is why monitoring and prevention of constipation is important.
• Mechanism: muscarinic blockade
• Dose dependent: yes
• Management consists of prevention of ileus by monitoring and treating constipation. For
  cases of pseudo-obstruction, obstruction, ileus, acute colitis, and/or perforation, clozapine
  should be discontinued. See constipation management and monitoring strategies below:
• Non-pharmacological management
  o Monitoring weekly when starting clozapine.
  o Encourage adequate hydration, physical activity, and diet rich in plant fiber
• Psychoeducation to seek medical care immediately if they experience constipation with abdominal pain or vomiting.

• Pharmacological management
  - Stool softeners: docusate sodium and docusate calcium.
  - Osmotic laxatives: 70% Sorbitol or Lactulose or Polyethylene glycol (Miralax).
  - Stimulant laxatives: Senna (Sennakot) or Bisacodyl (Dulcolax).
  - Avoid bulking agents such as psyllium.
  - For 3 days without a bowel movement, add as needed milk of magnesia, magnesium citrate, or phosphor-soda and/or Fleet or soapsuds.

<table>
<thead>
<tr>
<th>Constipation Assessment Scale</th>
<th>No Problem</th>
<th>Some Problem</th>
<th>Severe Problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal distention or bloating</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in amount of gas passed rectally</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less frequent bowel movements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oozing liquid stool</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectal fullness or pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectal pain with bowel movement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small volume of stool</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unable to pass stool</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Straining</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sense of difficulty in passing stools</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete evacuation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hard lumpy stools</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged time to stools</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Need for manual maneuvers to pass stool</td>
<td></td>
<td></td>
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</tbody>
</table>

If “Some problem”, monitor bowel function, stat treatment, consider medical consultation.
If “Severe Problem” and/or if patient has nausea/vomiting, refer for urgent medical assessment.

Neuroleptic Malignant Syndrome
• NMS is a life threatening neurologic emergency associated with the use of neuroleptic agents.
• It is characterized by a distinctive clinical syndrome of mental status change, rigidity, fever, and dysautonomia.
• Bipolar disorder, extreme agitation, and acute catatonia are overrepresented in those who develop NMS.
• It is considered a type of malignant catatonia and is treated by ICU supportive care, high dose benzodiazepines, and ECT.
• It is not dose-dependent, but higher doses are a risk factor.
• There is no evidence that use of long acting antipsychotic formulations increases risk.
• Mortality is between 10-20% and mortality and disability increases past 4 days.
• Elevated creatine kinase of 1,000 IU/L – 100,000 IU/L can be seen, with more severe rigidity leading to more profound CK elevation
• Leukocytosis typically 10,000 – 40,000/mm³
• Management includes
  • stopping clozapine and other potentially causative agents
• supportive ICU care to maintain cardiorespiratory stability, lower fever, maintain euvoletic state, lower blood pressure, and treat complications
• The use of dantrolene, bromocriptine, and amantadine
• Controversial and largely unsupported but frequently used.
• Use of high dose benzodiazepines and ECT are used based on the conceptualization of NMS as a form of malignant catatonia.
• Rechallenging: Slower titration should be used in case of rechallenge.

Venous Thromboembolism
• Timeline: Highest risk within first 3 months of treatment.
• Mechanism: Unknown.
• Dose dependent: unclear.
• Incidence: Rare but potentially fatal adverse effect of antipsychotics. Second generation and low potency first generation antipsychotics carry greater risks than others. Among antipsychotics, clozapine has the most reports with incidence of 1 per 2000-6000 exposures.
• Risk factors:
  o Reduced mobility for at least 3 days
    ▪ increases DVT risk tenfold
    ▪ In psychiatric inpatients, reduced mobility is inability to walk 10 meters for 1-2 weeks.
    ▪ Cataract
    ▪ Prolonged physical restraint
      o Medical hospitalization
      o Anesthesia
      o Surgical procedure
      o Central venous catheter
      o Age > 60 years
      o Dehydration
      o Known thrombophilia
      o Obesity
      o Medical comorbidities
      o Personal or first degree relative history of VTE
      o Use of hormone replacement therapy or oral contraceptive
      o Varicose veins with phlebitis
      o Pregnant or puerperal
• Clinical features
  o DVT: fever, pitting edema, prominent superficial veins, swelling, tenderness, unilateral leg pain.
  o PE: breathlessness, chest pain, collapse, hemoptysis, hypotension, tachycardia, cyanotic hypoxia, elevated jugular venous pressure, tachypnea.
• Diagnosis: Bilateral lower extremity Doppler ultrasound or chest CT as appropriate.
• Non-pharmacological management:
  o Prevention through early identification of those at risk
  o Regular physical exercise
  o Adequate fluid intake
• With ≥ 1 risk factor, consider anti-embolism stockings, or intermittent pneumatic compression devices.
• For suspected DVT or PE, emergent medical referral

Pharmacological management
• For significant risk, consider prevention with heparin until risk subsides
• For confirmed DVT or PE, treatment with heparin usually followed by at least 3 months of warfarin
• Diagnostic and treatment algorithms for venous thromboembolism have been produced by the American Institute for Clinical Systems Improvement.

Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State
• Diabetic ketoacidosis and diabetic hyperosmolar coma are very rare adverse effects of antipsychotics, but clozapine has been the agent most likely to be associated with this potentially life-threatening effect.
• These side effects can either occur suddenly early in treatment or be a late sign of longer-standing diabetes that was unrecognized and untreated.
• Patients can present with dehydration, fruity-smelling breath, shortness of breath, lethargy, and confusion.
• In more severe cases, patients can develop seizures, coma, and death.
• DKA and HHS are distinguished by the absence of ketoadcidosis and usually greater degree of hyperglycemia in HHS.
• DKA can occur in those with no history of diabetes and does not appear to be related to dose or duration of treatment.
• Suspected cases should be referred to emergent medical care as it can be quickly fatal.
• Clozapine may need to be held or discontinued (until adequate glucose control has been achieved)
  • If fasting glucose levels are too high (>350 mg/dL)
  • If significant clinical symptoms develop (dizziness, syncope, lethargy, confusion) that cannot be managed acutely with rehydration and lowering of blood sugar
  • Clozapine should generally be reintroduced with appropriate antidiabetic management and close glucose monitoring

Diabetic Ketoacidosis (DKA)
• Characterized by ketoacidosis and hyperglycemia
• Usually precipitated (infection, inadequate insulin therapy, dehydration, medical illness, etc.)
• Usually develops rapidly, over 24 hour period
• Hyperventilation and abdominal pain are usually limited to DKA (compared to HSS).
• Patients may have a fruity odor due to exhaled acetone (the scent of nail polish remover) and deep Kussmaul respirations reflecting the compensatory hyperventilation.
• DKA is characterized by the triad of hyperglycemia, anion gap metabolic acidosis, and ketonemia.
• Metabolic acidosis is often the major finding.
• Serum glucose concentration:
• usually less than 800 mg/dL
• often 350 – 500 mg/dL
• may exceed 900 mg/dL in patients who are comatose.
• In certain settings (starvation, pregnancy, treatment with insulin prior to ED arrival, or use of SGLT2 inhibitors), the glucose level may be only mildly elevated.

Hyperosmolar Hyperglycemic State (HHS)
• Severe hyperglycemia but no ketoacidosis.
• Usually precipitated (infection, inadequate insulin therapy, dehydration, etc.)
• Usually develops insidiously, often persisting for several days
• Early symptoms: polyuria, polydipsia, and weight loss
• Later symptoms: Neurological symptoms such as lethargy, focal signs, and obtundation. Can progress to coma in later stages.
• Mental obtundation and coma are more frequent in HHS than DKA because of the greater degree of plasma osmolality.
• In HHS:
  • there is little or no ketoacid accumulation
  • the serum glucose concentration frequently exceeds 1000mg/dL
  • the plasma osmolality may reach 380 mosmol/kg
  • neurologic abnormalities are frequently present (including coma in 25-50% of cases).
• Most patients with HHS have:
  • pH >7.30
  • serum bicarbonate >20 mEq/L
  • serum glucose >600mg/dL
  • test negative for ketones in serum and urine, although mild ketonemia may be present

Anticholinergic Toxicity
• Clinical features:
  o Tachycardia
  o Anhidrosis, as sweat glands are innervated by muscarinic receptors. “Dry as a bone”
  o Anhydrotic hyperthermia, due to interference with sweating “Hot as a hare”
  o Cutaneous vasodilation to compensate for loss of sweat production. “Red as a beet”
  o Blurry vision from nonreactive mydriasis related to muscarinic control over pupillary constriction and accommodation. “Blind as a bat”
  o Reduced desire to void due to muscarinic control of the detrusor muscle and muscarinic control over the urethral sphincter prevents normal opening. “Full as a flask”
  o Gastric hypomotility and constipation due to muscarinic blockade.
  o Psychiatric symptoms due to blockade of muscarinic receptors in the central nervous system. Symptoms include anxiety, agitation, dysarthria, confusion, disorientation, visual hallucinations, bizarre behavior, delirium, paranoia, coma, and seizures. Hallucinations are often change in scale in which people appear
larger or smaller (Alice in Wonderland-like or Lilliputian type). Central effects may persist after resolution of peripheral effects. “Mad as a Hatter”

- **Management:**
  - Prevention by limiting anticholinergic polypharmacy and caution with co-administration of other anticholinergic agents.
  - Referral to emergent medical services for evaluation and treatment.
    - Emergency medical services diagnostic investigations
      - Finger stick glucose to rule out hypoglycemia
      - Acetaminophen and salicylate levels to rule out common co-ingestions
      - EKG to rule out conduction system poisoning by co-ingestants affecting QRS or QTc intervals
      - Creatine Kinase levels to rule out rhabdomyolysis for those with severe psychomotor agitation or seizures
  - Treatment
    - Prolonged QRS intervals or arrhythmias: Sodium bicarbonate
    - Agitation: benzodiazepines, avoid phenothiazines and butyrophenones as they have anticholinergic properties
    - Seizures: benzodiazepines
    - Decontamination for ingestions with activated charcoal (1g/kg, max 50g) for those with intact mental status who are able to protect their airway.
    - Antidotal therapy with physostigmine (for pure anticholinergic toxicity only) is controversial.
      - It is relatively contraindicated for those with reactive airway disease, intestinal obstruction, epilepsy, and cardiac conduction abnormalities.
      - It requires cardiac monitor and atropine and resuscitative equipment at bedside.
      - Adult doses physostigmine 0.5-2mg (0.02 mg/kg IV).
      - Pediatric doses max 0.5mg.
      - Dose should be administered by slow IV push over five minutes as rapid administration may result in cholinergic symptoms or seizures.

*Warrant discontinuation and restarting later is not recommended*
- Agranulocytosis
- QTc > 500ms or Torsades de Pointes
- Myocarditis
- Cardiomyopathy
- Liver toxicity
- Acute Interstitial Nephritis

**Agranulocytosis *Black Box Warning***