

Clozapine Dosing and Side Effects Management Part 1

The Care Transitions Network

National Council for Behavioral Health
Montefiore Medical Center
Northwell Health
New York State Office of Mental Health
Netsmart Technologies



Objectives

At the completion of this webinar, listeners will be able to:

1. Understand how to start clozapine
2. Understand the timeline of clozapine side effects
3. Manage side effects not generally warranting discontinuation

Outline

- Starting Clozapine
- Factors Effecting Clozapine Level
- Troubleshooting Clozapine
- Conceptualizing Side Effects of Clozapine
- Side effects not Generally Warranting Discontinuation

Starting Clozapine

Initial Titration Schedule

- In general, initial target dose is 300mg to 400mg per day by 2 weeks.
- That being said, initial dosing schedule should be individually tailored.
- Consider clinical status, severity of adverse reactions, level of agitation, and treatment setting.

Initial Titration Schedule

- Titration is started with 12.5mg once or twice daily on day 1.
- (Half of a 25 mg tablet broken along the score line, or orally disintegrating formulation available in 12.5mg tablet).
- If well tolerated, daily dose can be increased in increments of 25mg to 50mg daily.

Initial Titration Schedule

- Just as titration schedule should be customized, dosing schedule can be customized.
- Twice daily dosing is standard.
- Agitated inpatients may do better with thrice daily dosing.
- Sedated patients may do better with once daily evening dosing.

What is the target dose?

- **300mg to 400mg per day by 2 weeks is a general starting goal, however...**
- Side effects from clozapine are often dose/concentration dependent.
- Clozapine is metabolized by the liver and therefore is exposed to drug interactions.

How do dose and serum level correlate?

- Serum concentrations at a given dose are age and gender dependent.
- Serum concentrations at a given dose can vary widely between individuals (8-20 fold variation)
- Serum concentrations for an individual at a constant dose are more stable (<20% variation).

How do dose, serum level, and clinical response correlate?

- Serum concentrations associated with clinically meaningful response range from 200 ng/mL to 450 ng/mL (from 350 ng/mL to 450 ng/mL in some studies).
- Plasma levels associated with clinical response in reported studies corresponded to oral doses between 250mg and 650mg.
- For the vast majority of patients, this range may represent an estimated **optimal mean dose of 400-500mg by 6 weeks.**
- **PORT guidelines recommend a trial of 300 – 800mg/day for at least 8 weeks.**

What is the target serum level?

- **The target plasma level for the vast majority of patients may be approximately 350 ng/mL.**
- **Patients who have not responded after 6 weeks with plasma levels of 350 ng/mL should have doses increased to new goal of plasma level about 450 ng/mL.**

It has been 6 weeks with no response... Now what?

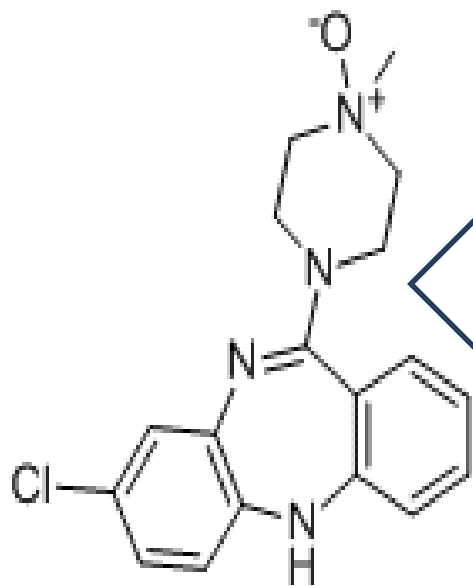
- 30% of patients will respond by 6 weeks
- 20% of patients will respond by 3 months
- 10-20% of patients will respond by 6 months
- Some patients will take more than 6 months to respond
- A trial of clozapine monotherapy of 6-12 months is reasonable
- Consider augmentation strategies including lamotrigine or ECT after suboptimal response at adequate plasma level (450ng/mL) for adequate duration.

Factors Effecting Clozapine Level

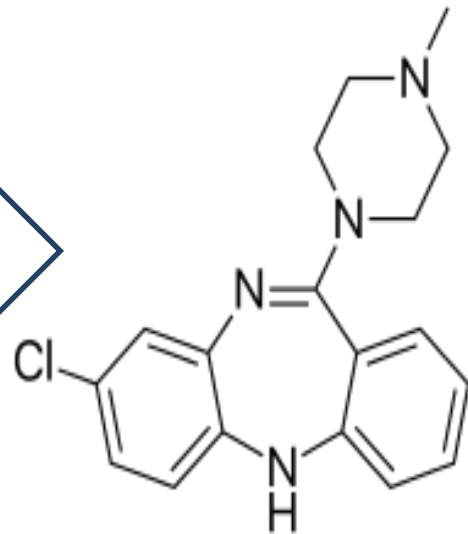
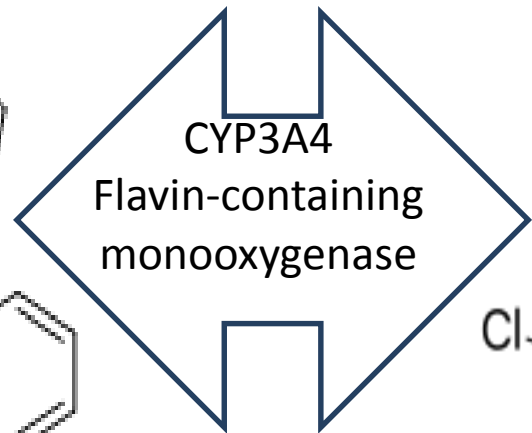
Which factors influence clozapine plasma levels?

Most important factors

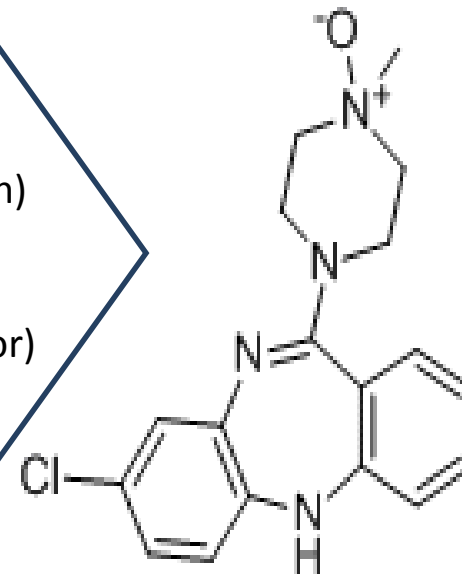
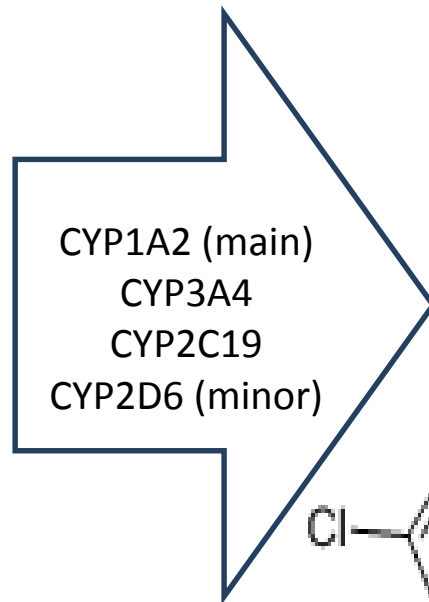
- Clozapine is metabolized in the liver by CYP1A2, CYP2D6, and CYP3A4.
 - Medications that inhibit these enzymes increase clozapine plasma levels.
 - Concomitant use of strong CYP1A2 inhibitors (fluvoxamine, ciprofloxacin, enoxacin) reduce clozapine dose to one-third.
 - Medications that induce these enzymes decrease clozapine plasma levels.
 - Concomitant use of strong CYP3A4 inducers is not recommended.
 - Consider reducing clozapine dose when CYP1A2 inducers (tobacco smoking) or CYP3A4 inducers (carbamazepine) are discontinued.
- Please see companion materials for a list of medications affecting clozapine levels.



Clozapine-N-oxide
(inactive)



Clozapine
(active)



Norclozapine
(active)

Clozapine is Protein-bound

- Clozapine is extensively protein-bound in circulation and may increase the free concentrations of other protein-bound drugs by displacement.
- Communication with the patients primary care physician is important when starting, stopping, or changing clozapine dosage.
- This is especially regarding protein bound medications which are dangerous in overdose such as warfarin and digoxin.

Which factors influence clozapine plasma levels?

May be clinically significant

- Sex: Females metabolize clozapine more slowly than males.
- Age: Younger patients metabolize clozapine faster.
- Ethnicity: Asian patients may show higher levels than other groups
- Body weight: Slightly higher doses are needed in heavier people.
- GI hypomotility: can result in delayed absorption
- Caffeine intake: may increase clozapine levels via competitive inhibition of CYP 1A2
- Tobacco: decreased clozapine levels via inhibiting CYP1A2
- Grapefruit juice: increased clozapine levels
- St. John's Wort: decreases clozapine levels

Renal Impairment

- Clozapine is almost completely metabolized before excretion.
- 50% of the metabolized drug clozapine-N-oxide is excreted in urine, but this metabolite's activity is not known.
- Clozapine would not be expected to accumulate extensively in those with renal impairment, but there is no supporting literature and the manufacturer contraindicates use in severe renal impairment.

Troubleshooting Clozapine

When should I check a Clozapine level?

- To examine response at a given dose and plasma level.
- To monitor and minimize dose related side effects.
- For any patient receiving more than 600mg/day given the increased risk of seizure above that dose.
- To inform decision about dose adjustment based on drug-drug interactions that alter clozapine metabolism.
- To check compliance.

What if my patient misses 1 dose of clozapine?

- If a dose of clozapine is missed, give the regular amount at the next scheduled intake
- Do not make up missing doses by given more that scheduled.

What if my patient misses more than 1 dose of clozapine?

- If 2 or more days of clozapine doses are missed, restarted with one half of a 25mg tablet (12.5 mg) once or twice daily.
- If that dose is well tolerated, titration can occur more quickly than recommended for initial treatment.
- This is also the case for patients already taking an adequate dose of an anticonvulsant such as divalproex sodium.

The clozapine level came back labeled “toxic”... Now what?

- Do not reflexively stop clozapine.
- Abrupt discontinuation can often lead to rapid relapse that is worse than the initial episode.
- There is no clear definition of what constitutes a toxic level nor is there any reference to toxic levels in the FDA monogram.
- For clozapine, a rapid change in blood level is more important than the absolute level itself.

The clozapine level came back labeled “toxic”... Now what?

- Toxicity is a clinical diagnosis based on the new appearance of excessive adverse effects rather than an absolute number.
- Verify the time of the blood level and if not a trough level, repeat in AM at appropriate time.
- Check the clinical status of the patient for distress, excessive or new onset drooling, sedation, hypotension, myoclonus, and tachycardia.
- If concerned about possible significant adverse effects, consider lowering the dose.

Conceptualizing Side Effects of Clozapine

Clozapine Side Effects Can be Conceptualized in Many Ways

- Most Common
- Timeline of Symptom Onset
- Dose Dependence and Rate of Increase
- Discontinuation and Rechallenge

Most Common Adverse Reactions (>5%)

- CNS reactions
 - Sedation
 - Dizziness/vertigo
 - Headache
 - Tremor
- Cardiovascular reactions
 - Tachycardia
 - Hypotension
 - Syncope
- Autonomic nervous system reactions
 - Hypersalivation
 - Sweating
 - Visual disturbances
- Gastrointestinal reactions
 - Constipation
 - Nausea
- Fever

Discontinuing and Rechallenging

1. Discontinuation of clozapine treatment can increase the risk of relapse, aggression, and suicidal behavior.
2. Some side effects don't warrant discontinuation.
3. Some side effects rarely lead to discontinuation.
4. Discontinuation with potential rechallenge is indicated.
5. Discontinuation is indicated and rechallenge is contraindicated.

Side effects not generally
warranting discontinuation

Think before you Stop

- Discontinuation of clozapine treatment can increase the risk of relapse, aggression, and suicidal behavior.
- Clozapine is prescribed because of treatment refractory psychosis and can make a DRAMATIC difference for many patients.
- It can be helpful to conceptualizing side effects in terms of:
 - Which warrant discontinuation
 - Which can be managed while continuing clozapine, and
 - Under which circumstances rechallenging is contraindicated

Cheat Sheet #1

Side effects not generally warranting discontinuation

- Neutropenia
- Sialorrhea
- Orthostatic Hypotension
- Sedation
- Constipation
- Myoclonus
- Seizures
- Metabolic Abnormalities
- Nocturnal Enuresis
- Clozapine-induced Transaminitis

Neutropenia

- Clozapine should be continued with increased ANC monitoring for mild neutropenia.
- It should only be discontinued for moderate neutropenia or severe neutropenia (agranulocytosis).
- The threshold for neutropenia is lower for those with Benign Ethnic Neutropenia.

ANC Level (General Population)	Treatment Recommendations	Frequency of ANC Monitoring
Normal range: ANC \geq 1500/mm ³	Initiate Rx If Rx interrupted < 30 days, continue monitoring \geq 30 days, monitor as if new pt	Weekly in first 6 months Every 2 weeks from 6-12 months Monthly after 12 months
Mild neutropenia: ANC: 1000-1499/mm ³	Continue Rx	Thrice weekly until ANC \geq 1500/mm ³ Then return to pt's last "normal range" schedule
Moderate neutropenia: ANC : 500-999/mm ³	Hematology consultation Stop treatment Resume once ANC \geq 1000/mm ³	Daily until ANC \geq 1000/mm ³ Thrice weekly until ANC \geq 1500/mm ³ Weekly for 4 weeks Then return to pt's last "normal range" schedule
Agranulocytosis: <500/mm ³	Hematology consultation Stop treatment *Only rechallenge if benefits > risks	Daily until ANC \geq 1000/mm ³ Thrice weekly until ANC \geq 1500/mm ³ *If rechallenged, resume monitoring as if new patient

*Contrary to REMs recommendations, we do not advice rechallenging for ANC <500/mm³.

Benign Ethnic Neutropenia (BEN)

- Occurs in 25-50% of people of African descent and has been reported in Jewish, Middle Eastern, and Afro-Caribbean groups.
- It is thought to occur because mature granulocytes are retained in the marrow storage pool rather than being released to peripheral circulation.
- It is the most common cause of neutropenia but is not associated with agranulocytosis or impaired immune system.

ANC Level (BEN Population)	Treatment Recommendations	Frequency of ANC Monitoring
Mild neutropenia: ANC : 1000-1499/mm ³	Mild Neutropenia is normal range Obtain at least 2 baseline ANC levels before initiating Rx If Rx interrupted < 30 days, continue monitoring ≥ 30 days, monitor as if new pt	Weekly in first 6 months Every 2 weeks from 6-12 months Monthly after 12 months
Moderate neutropenia: ANC: 500-999/mm ³	Hematology consultation Continue Rx	Thrice weekly until ANC ≥ 1000/mm ³ or ≥ pt's baseline Weekly for 4 weeks Then return to pt's last "normal BEN range" schedule
Agranulocytosis: <500/mm ³	Hematology consultation Stop treatment *Only rechallenge if benefits > risks	Daily until ANC ≥ 500/mm ³ Thrice weekly until ANC ≥ 1000/mm ³ or ≥ pt's baseline *If rechallenged, resume monitoring as if new patient

*Contrary to REMs recommendations, we do not advice rechallenging for ANC <500/mm³.

Sialorrhea

- Timeline: within the first 2 weeks
- Mechanism: muscarinic stimulation
- Dose dependent: generally dose independent but lowering dose may decrease severity in some cases.
- Incidence: occurs for 30-80% of patients, the second most common side effect (following sedation)

Sialorrhea: Non-pharmacological Management

- Psychoeducation to expect sialorrhea:
 - To inform you immediately if awakening due to choking on saliva occurs,
 - And about nonpharmacologic management strategies prior to starting trial
- Place a towel over the pillow at night.
- Use sugar-free chewing gum during the day

Sialorrhea: Pharmacological Management

- Reduce dose, especially if the patient awakens due to choking.
 - There are case reports of respiratory arrest due to clozapine induced sialorrhea.
- Caution with anticholinergic agents as treatment.
 - They can worsen clozapine's anticholinergic side effects and impair gag reflex increasing risk of aspiration.
- Psychoeducation about monitoring for worsening of anticholinergic signs (blurry vision, confusion, nausea, and constipation) prior to anticholinergic trial.

Sialorrhea: Pharmacological Management

Muscarinic Medications

- Atropine 1% ophthalmic solution, 1 drop sublingually at bedtime offers relatively low systemic absorption which may limit adverse effects (Bird et al. 2011).
- Glycopyrrolate demonstrated significant reduction of hypersalivation in a randomized controlled trial.
- Other agents investigated in case reports and small trials include benztropine, trihexyphenidyl, amitriptyline, ipratropium bromide, and scopolamine.

Sialorrhea: Pharmacological Management

Adrenergic Medications

- Clonidine- does not contribute to development of constipation and may have some benefit on focus and concentration problems
- Guanfacine
- Terazosin- showed promise in a retrospective study, but can exacerbate clozapine-induced orthostasis

Hypotension, Bradycardia, and Syncope *Black Box Warning*

- Timeline: onset within the first 2 weeks, usually temporary, tolerance over 4-6 weeks
- Mechanism: adrenergic blockade
- Dose dependent: yes

Hypotension, Bradycardia, and Syncope: Non-pharmacological Management

- Psychoeducation warning patients about hypotension and reassurance it will improve with time.
- Counseling to move slowly when rising from lying or seated position.
- Warning about the seriousness of falls risk.
- Encourage adequate fluid intake to prevent dehydration which may worsen orthostasis.

Hypotension, Bradycardia, and Syncope: Pharmacological Management

- For severe orthostasis or high falls risk, consider slowing titration or maintaining dose for a few days to allow time to adjust.
- Examine medication list for other agents causing orthostasis and consider switching or holding those meds until clozapine-induced orthostasis has resolved.

Sedation

- Timeline: Onset within the first 2 weeks, tolerance develops over 2-3 months for most or remain persistent and severe for a minority.
- Mechanism: histaminergic blockade
- Incidence: Occurs in 45% of people. The most common side effect of clozapine.
- Dose dependent: yes

Sedation

- Non-pharmacological management
 - Counseling to expect sedation and reassurance that effect is often transient.
- Pharmacological management
 - Reducing or eliminating other sedating medications
 - Consider reducing dose, guided by plasma levels, efficacy, and risk-benefit.
 - Give higher dose in evening, or once daily evening dosing.
 - Avoid use of stimulants, as there is not much data supporting their use and they include the risk of worsening psychosis, agitation, and tachycardia.

Constipation

- Timeline: onset between weeks 2 and 4
- Mechanism: muscarinic blockade
- Dose dependent: yes
- Incidence: 33.3% in acute treatment phase. 22.8% in maintenance phase.
- 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.

Constipation: Non-pharmacological Management

- Monitoring weekly when starting clozapine.
- (Please see companion materials for Constipation Assessment Scale)
- 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.

Constipation: 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.

Myoclonus

- Timeline: onset between weeks 2 and 4
- Mechanism: Not fully understood. Can be cortical or subcortical in origin.
- Dose dependent: yes but can occur at low doses

Myoclonus: Clinical features

- Psychoeducation so patient is aware of symptoms of myoclonus to be able to alert you.
- Myoclonus can herald the onset of a tonic-clonic seizure.
- Orofacial myoclonus can present as speech disturbances, and dysarthria.

Myoclonus: Clinical features

- Positive myoclonus: the sudden involuntary jerking of a muscle group or group of muscles.
- Twitching and electric shock-like sensations are also symptoms.

Myoclonus: Clinical features

- Negative myoclonus may present as sudden unexpected falls or buckling at the knee or folding of the leg and may be misidentified as due to hypotension.
- Clozapine has a low risk of inducing EPS, so dyskinetic appearing movements should raise suspicion for myoclonus.
- Negative myoclonus can also present as dropping objects.

Myoclonus: Pharmacological management

- Do not discontinue clozapine.
- Dose reduction
- Addition of antiepileptic drug such as valproate.
 - ❖ Lamotrigine has been shown to occasionally worsen some types of myoclonic epilepsy, so it is relatively contraindicated for the treatment of myoclonus.

Seizures *Black Box Warning*

- Timeline: onset usually between weeks 2 and 4, but may occur at all stages of treatment
- Mechanism: The mechanism by which clozapine lowers the seizure threshold is not fully understood. Its higher pro-convulsant tendency than other antipsychotics is probably reflects its broad and unique receptor profile.
- Dose dependent: yes, risk is higher with rapid titration and with higher doses
- Incidence: Occurs in 1 to 5% of clozapine treated patients and in 4-5% of patients receiving greater than 600mg/day.
- Tonic-clonic seizures are the most common. Myoclonic, atonic, and partial seizures are in the minority.

Seizures: Non-pharmacological Management

- Careful history about prior head trauma, seizures, and review of current medication list for those that lower seizure threshold.
- If patient is a smoker counsel patient to inform you of efforts to cut down or quit as clozapine levels will increase and dose may need to be lowered.
- Note, Clozapine-induced EEG changes are strongly related to both the dose and plasma concentration of clozapine, but a clear relationship to these changes with actual epileptiform activity has not been found.

Seizures: Pharmacological Management

- Consider other medications which lower seizure threshold with lower risk alternatives.
- Titrate clozapine dose slowly.
- Use minimum effective dose.
- Consider using prophylactic sodium valproate (1-2g/day) if
 - Prior history of seizures or head trauma
 - Using > 600mg clozapine/day
 - Clozapine plasma level >500ng/mL
- Sodium valproate
 - 1-2 g/day
 - target valproate blood level is 50-100 mcg/mL

In Case of Seizure...

- Hold dose for 24 hours then reintroduce at 50% lower dose
- Consider referral to a neurologist and EEG, especially if this is the patient's first seizure.
- For those who need to be re-titrated to a higher dose after the reduction, or those who have recurrent seizures, an anticonvulsant should be used.

Valproate

- Drug of first choice due to broad spectrum, mood stabilization and anti-manic properties.
- It remains underutilized for those at risk.
- Contraindicated for women of childbearing age due to teratogenic properties.

Lamotrigine

- Although benign rash is common, requires gradual titration to avoid Steven Johnson Syndrome.
- Is a useful augmentation strategy to those refractory to monotherapy clozapine.
- Has mood stabilizing and antidepressant properties.

Topiramate

- Requires gradual dose titration to test for tolerability.
- Common adverse reactions include cognitive dysfunction, mood changes, and visual disturbances.
- Can induce weight gain.

Gabapentin

- An option if other anticonvulsants are poorly tolerated.
- Dose adjustment recommended in renal impairment.
- Has anxiolytic properties.

Phenytoin, Phenobarbital, Carbamazepine

- All induce CYP450 1A2 and 3A4 which would reduce clozapine plasma levels and require dose increase to maintain efficacy.
- All 3 are associated with bone marrow suppression including agranulocytosis
 - (Carbamazepine > Phenytoin & Phenobarbital).

If pt receiving ECT...

- Check blood level post ECT as it may cause an increase in blood levels
- While ECT increases seizure threshold, by 47% in 56% of patients in one study (Coffey 1995), there are case reports of prolonged or tardive seizures with co-administered ECT.
- This is not a contraindication to use of ECT with clozapine. ECT is an effective augmentation strategy for clozapine refractory schizophrenia.

Hyperglycemia and Diabetes Mellitus

- Timeline: Any time but >50% of cases occur in the first 3 months
- Mechanism: Unclear and probably multifactorial. Clozapine-induced diabetes can occur independently of weight gain.
- Dose dependent: No
- Incidence: 37% at 5 years, 43% at 10 years.
- Definitions:
 - Prediabetes: Fasting plasma 110-125mg/dL
 - Diabetes: Fasting plasma glucose \geq 126 mg/dL

Hyperglycemia and Diabetes Mellitus: Monitoring

- Early recognition: ADA/APA Protocol for monitoring antipsychotic use suggest fasting glucose monitoring at baseline, at week 12, and then annually.
- As 50% of cases occur within the first 3 months, our recommendations include monitoring at 3 months after initiation of treatment as well.
- Hemoglobin A1C levels are also useful at these timepoints.

Hyperglycemia and Diabetes Mellitus: Management

- At least annually counseling about healthy diet and active lifestyle should be encouraged and patients and family should be counseled about signs and symptoms of diabetes.
- Coordination of care with pt's primary physician is recommended.
- Metformin is the treatment of choice for type 2 diabetes, followed by a sulfonurea.

Obesity and Metabolic Syndrome

- Timeline: begins early, manifests late. Weight gain and increases in triglycerides are relatively early markers occurring in the first 3 months compared to disturbances in glucose metabolism.
- Mechanism: Those with schizophrenia are at increased risk for metabolic syndrome. Its prevalence is more than double that found in the general population. This is related to sedentary lifestyle, poor diet, stress, smoking, and second generation antipsychotic use. Precise mechanisms of SGA associated weight gain are not well understood.

Obesity and Metabolic Syndrome

- Metabolic syndrome is a collection of risk factors that arises from insulin resistance accompanying abnormal adipose deposition and function.
- Diagnosis: 3 of 5 of the following
 - Fasting glucose ≥ 100 mg/dL (or receiving drug therapy for hyperglycemia)
 - Blood pressure $\geq 130/85$ mmHg (or receiving drug therapy for hypertension)
 - Triglycerides ≥ 150 mg/dL (or receiving drug therapy for hypertriglyceridemia)
 - HDL-C < 40 mg/dL in men or < 50 mg/dL in women (or receiving drug therapy for reduced HDL-C)
 - Waist circumference ≥ 102 cm (40 in) in men or ≥ 88 cm (32 in) in women

Management

- Weight Gain
 - Closer monitoring of weight
 - Weight management program
 - Adjunctive treatment to reduce weight such as Metformin or Topomax
 - Prevention of weight gain and obesity is the goal given the difficulty to lose weight once gained.

Management

- Fasting Glucose
 - Refer to PCP for fasting glucose consistent with prediabetes (100-125 mg/dL) or new onset diabetes (>125 mg/dL) or hemoglobin A1c in range 5.7-6.4%.
 - If less than 60 years old, consider Metformin trial for those in above categories with one other risk factor such as first degree relative with diabetes, obesity, hypertriglyceridemia, low HDL-C, or hypertension.

Management

- Fasting Lipids
 - Altering diet (lean meat, fish, and reducing saturated fat intake) and improving physical activity.
 - Omega-3 supplementation (triglycerides reduce but LDL-C may increase).
 - Statin therapy to reduce atherosclerotic cardiovascular disease is recommended based on subgroupings:
 - Clinical atherosclerotic cardiovascular disease (ASCVD)
 - LDL \geq 190 mg/dL without clinical ASCVD
 - Diabetes, without clinical ASCVD, ages 40-75 years, with LDL 70-189 mg/dL
 - Without diabetes, without clinical ASCVD, ages 40-75 years, with LDL 70 – 189mg/dL

Nocturnal Enuresis

- Timeline: within the first 3 months
- Mechanism: Unclear. May be multifactorial and influenced by sedation, adrenergic and anticholinergic mechanisms.
- Dose dependent:
- 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.

Nocturnal Enuresis: 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.

Nocturnal Enuresis: Pharmacological Management

- Literature is 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

Clozapine-induced Transaminitis

- Clozapine has been associated with transaminitis, toxic hepatitis, and fulminant liver failure.
- Clozapine use is contraindicated in progressive liver disease, hepatic failure, and active liver disease associated with nausea, anorexia, or jaundice.
- Timeline: Clozapine-induced transaminitis usually occurs within the first 6 weeks of treatment.
 - It 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%.

Clozapine-induced Transaminitis

- Prognosis: Clozapine-induced transaminitis spontaneously resolves in 60% of cases without altering the dose or discontinuing treatment.
 - 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.

Summary

- We have reviewed a large number of clozapine side effects (and will present more in the next webinar)
- It is important to consider these in the context that clozapine has unique positive benefits for patients
- For the vast majority of patients clozapine side effects are manageable and the benefits outweigh the side effect burden

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Thank you!

www.CareTransitionsNetwork.org

CareTransitions@TheNationalCouncil.org

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for People with Serious Mental Illness