Clozapine Side effects V002

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Side Effects

The most commonly discussed side effect of clozapine is severe neutropenia (defined as <500 cells per cubic mm). However, clozapine is associated with a variety of side effects, some of which may be intuitive, while others are less so. Other side effects include constipation (and potential bowel obstruction), sialorrhea, seizures, sedation, myocarditis, tachycardia, orthostatic hypotension, benign fever, and cardio-metabolic effects.

Constipation

Constipation occurs in up to 60% of patients taking clozapine, likely due to the drug's anticholinergic effects. It should be considered even more dangerous than possible agranulocytosis in terms of its long-term consequences. In fact, **there have been more deaths from constipation and subsequent bowel obstruction than there have been from neutropenia**. To treat clozapine-related constipation, healthcare providers should initially minimize or discontinue other unnecessary **anticholinergic medications**. Patients should also be drinking plenty of water to prevent constipation. Providers can also begin a bowel regimen for patients on clozapine. All patients should start **docusate** 250 mg PO BID. Normally, an osmotic laxative, such as **polyethylene glycol 17g q am**, is also added and is superior to lactulose 30 ml BID (which can also be tried). If the combination of docusate and polyethylene glycol fails, a stimulating laxative such as **bisacodyl 5 mg PO qhs (max 30mg per day)** is added. If all three agents fail to treat the constipation, the stimulating agent is replaced with a secretive agent, such as **lubiprostone 8mcg bid (max dose 24 mcg bid)**, a PGE analog that binds to chloride channels in the small intestine to promote motility. Lubiprostone may control the constipation well enough to the point where other agents can slowly be removed from the regimen. Physicians should also begin lubiprostone prophylactically in patients who have developed ileus as a result of clozapine. Additionally, newer agents that act on guanylate cyclase C, such as linaclotide or plecanatide, can also be tried.

In treating constipation, one should never give a bulk-forming laxative. This only worsens the constipation and slows motility. For example, the average stool transit time is approximately 24 hours. When a bulk-forming laxative is added, the transit time increases to 110 hours.

Sialorrhea

Sialorrhea or drooling is another common side effect and may in fact contribute to the increased incidence of aspiration pneumonia in individuals taking clozapine. Sialorrhea seems like a counterintuitive problem as clozapine is known for its anticholinergic side effects. However, it is not

clozapine itself that induces sialorrhea but its metabolite, norclozapine (N-desmethylclozapine), that acts as a muscarinic agonist. It is for this reason that patients taking clozapine can exhibit both anticholinergic and cholinergic side effects, as illustrated by constipation and sialorrhea, respectively.

To treat sialorrhea, providers should **avoid systemic anticholinergics**, which can potentially worsen constipation. Firstly, clozapine should be given at night. Then, medications of choice should be local anticholinergic agents. First line treatments include **three sprays of ipratropium nasal spray** (0.3% or 0.6%) in the mouth two or three times per day. Another first line treatment is **1% atropine eye drops**. One to two drops should be given at bedtime then gradually titrated up to two or three drops three times per day. Both ipratropium and atropine work to decrease salivary production by the parotid glands.

If local treatments fail, there are some systemic options, although they are second line. One can consider glycopyrrolate 2-4 mg at night as it does not cross the blood brain barrier and cause confusion. An interesting alternative is terazosin. The salivary nucleus has downstream actions on the parotid and salivary glands, which are centrally mediated by alpha-2 receptors. Terazosin can block those receptors, decreasing salivation but potentially causing orthostatic hypotension. Terazosin 1 mg should be given at night and if blood pressure is stable, then 2 mg at night can be given. Interestingly, **botulinum A** has been used for the treatment of primary neurologic sialorrhea. A 32 gauge needle is inserted into each gland with effects lasting three to four months. Botulinum A has also been shown to be effective for clozapine-induced sialorrhea.

Seizures

Although a less common side effect, clozapine does lower the seizure threshold more than other antipsychotic medications. Seizures are typically tonic-clonic or myoclonic. In regard to myoclonic seizures, it may be wise for the provider to first rule out orthostasis. Seizures most normally occur after the clozapine dose has been increased, particularly if it has been titrated too quickly at a concentration greater than 700 ng/mL. Titration must be done slowly. Clozapine can be started at 12.5 mg, then increased to 12.5 mg twice a day, and by the end of the first week titrated to a total of 100 mg. Another 100 mg should be added by the end of the second week, with the total clozapine dosage 200 mg by the end that week. No single dose should be greater than 50 mg until the target dose has been reached. It is also helpful to divide the doses as sometimes it is just that single large clozapine dose that can cause the high peak plasma level that lowers the seizure threshold enough to induce a seizure.

If a patient does suffer a seizure, then providers can return to the prior tolerated dose. Additionally, an antiepileptic medication should be given. **Depakote** is the treatment of choice because it is both effective and broad-spectrum. Additionally, it will not lower the plasma levels of clozapine like Dilantin or Tegretol. Second line agents include **Keppra**. Moreover, even if a patient does experience a seizure, it is not an indication to stop clozapine.

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Sedation

Up to 40% of patients may experience sedation as a side effect, and it may be a reason why patients decide to stop taking clozapine. Clozapine should be titrated slowly so that acetylcholine, histamine, and alpha receptors have time to accommodate to clozapine. Once titration is complete the drug can be given at bedtime up until single doses of 500 mg. Giving clozapine at bedtime decreases its plasma level while the patient is awake while simultaneously maintaining its efficacy. Additionally, the patient should discontinue unneeded anticholinergic medications to decrease the likelihood of sedation. If sedation persists, however, several medication options are available. **Methylphenidate** and its immediate release form can be considered as there have been anecdotal reports of its effectiveness, but providers must prescribe this cautiously due to the drug's addictive potential. There have also been clinical trials of **modafinil** as a potential treatment. However, it has not been shown to be better than placebo in controlled trials, but modafinil may still be considered as there are some who have responded. Modafinil should be started at 100 mg and can be titrated up to 300 mg.

Myocarditis

Myocarditis is a relatively rare side effect; it is estimated that 2-3% of patients taking clozapine experience this complication. All reported cases of clozapine-induced myocarditis occurred within the **first six weeks of treatment** with 90% of cases occurring within the first four weeks. Although rare, if not promptly recognized and treated, myocarditis may lead to serious complications such as dilated cardiomyopathy and even death.

If a patient on clozapine begins developing evolving signs of **congestive heart failure, fever, chest pain, and shortness of breath**, clinical suspicion for myocarditis should be high. Providers should immediately obtain troponin and CRP levels. Troponin levels twice the upper limit of normal indicate myocardial injury. In rare cases, CRP alone may be elevated. If troponin and CRP levels are positive, clozapine should be stopped and an echocardiogram should be done. Additionally, it is not useful to measure eosinophils alone, as only half of clozapine-induced myocarditis cases show eosinophilia. Additionally, most eosinophilia in these cases are benign or not active. Discontinuing clozapine normally resolves the myocarditis. One can also consider giving IV steroids to reduce the inflammation, but research is still unsure if this changes the overall course of the acute myocarditis.

If clozapine is stopped abruptly there is a potential for **cholinergic rebound and subsequent delirium**. To prevent this an equivalent amount of benztropine should be given. For a non-smoker, benztropine 1 mg is equivalent to clozapine 50 mg. For a patient who smokes, benztropine 1 mg is equivalent to clozapine 100 mg. Sufficient amounts of benztropine should be given so that central nervous system effects, such as vivid dreams, delirium, and nightmares, are avoided.

After a patient has been treated for myocarditis clozapine can be restarted as exhibited by seven out of twelve studies in which the drug was safely re-administered. Discussion about restarting the medication

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should be done with patients and their caregivers to see if they can receive intense medical monitoring, such as weekly labs.

Tachycardia

Tachycardia or a heart rate greater than 100 beats per minute may be secondary to orthostasis, therefore orthostasis should be managed first. Additionally, clozapine should be titrated slowly and the lowest effective dose used. Providers should decrease simultaneous use of agents such as alpha-1 antagonists and M1 antagonists, as these may exacerbate the problem. If tachycardia continues to be an issue, providers can prescribe atenolol 12.5 mg in the morning and titrate as needed to reach a goal heart rate of less than 100 beats per minute or even ideally less than 90 beats per minute. **Atenolol** is the ideal beta-blocker because it does not cross the blood brain barrier to cause unnecessary central nervous system effects, is relatively inexpensive, and can be given as once per day dosing. Twenty percent of patients on clozapine will experience persistent tachycardia, and providers should treat these patients as tachycardia is a long-term risk factor for **dilated cardiomyopathy**.

Orthostatic Hypotension

Clozapine is a potent **blocker of the alpha-1 receptor**. The slowest dose titration should be used, and the use of other alpha-1 antagonists and benzodiazepines should be minimized as both can exacerbation orthostasis. Additionally, patients should always be encouraged to drink enough fluids. If the patient is still symptomatic despite conservative management, providers can consider modifying any anti-hypertensive medications the patient may be taking. In addition, **salt** can be added to encourage volume expansion. **Fludrocortisone**, a mineralocorticoid, can be given to help absorb water and electrolytes. However, fludrocortisone should not be given to patients with congestive heart failure.

Benign Fever

Benign fever is relatively common especially in the first month of treatment. It may affect up to **55% of patients taking clozapine**. However, if a patient on clozapine develops a fever, providers should rule out infection, myocarditis, eosinophilia, acute interstitial nephritis, and inflammatory conditions.

Cardio-Metabolic Effects

Like other second generation antipsychotic medications, clozapine has metabolic side effects. Although the mechanism of clozapine-induced dyslipidemia is unknown, the weight gain is likely due to the blockade of the H1 and 5-HT2c receptors, which results in sedation and impaired satiety. To treat clozapine-induced obesity, healthy lifestyle changes should be implemented. Prescribing metformin is another option as an increasing number of providers are considering it as prophylactic treatment. **Metformin** should be started at 500 mg per day for the first week then gradually titrated to an effective dose. Research has shown that metformin is safe and is most efficacious when concurrently started with clozapine.

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Severe Neutropenia (<500 cells/mm^3)

Although relatively uncommon, severe neutropenia may be clozapine's most well-known side effect. With careful monitoring mortality from severe neutropenia is 1/10,000. Unlike neutropenia caused by chemotherapy drugs, severe neutropenia caused by clozapine is an autoimmune mediated process. The highest risk for clozapine-induced severe neutropenia is within the first month of treatment when the risk is approximately 1%. After the first month, the risk steadily declines and after one year, the risk becomes approximately 0.38%. After two years, the risk decreases to 6/10,000.

If an ANC level meets the FDA's definition of neutropenia of less than 500 cells/mm^3, clozapine should be halted and a tapering dose of benztropine should be given beginning at 2 mg twice a day and gradually decreasing it by 0.5 mg of the daily dose per week. If benztropine is not used, another anticholinergic agent would be sufficient. The main goal is to prevent cholinergic rebound after abruptly stopping clozapine or else patients could experience delirium, nausea, vomiting, and diarrhea. To treat the agranulocytosis, 480 µg of filgrastim, a colony-stimulating factor, should be given subcutaneously as soon as the drug is available. This is an imperative life-saving intervention. Initially, daily filgrastim is needed, and the average response time is approximately 12 days. During this period, the patient should be in reverse isolation and carefully monitored. If the patient develops a fever greater than 104°F mortality increases from 1/10,000 to 5-10%.

Previously, restarting clozapine after agranulocytosis was not recommended as it was believed that exposing the body to clozapine again would only stimulate the antibodies against the neutrophil progenitor cells. However, now the FDA states that you can in fact restart clozapine after treating the agranulocytosis if clozapine is the only viable option for the patient. Providers should wait until the ANC is greater than 1500 cells/mm^3, which takes approximately four to six weeks. After clozapine is restarted, the patient should be carefully monitored and ongoing filgrastim 300 µg once to twice per week should be given. With this method, 70% of cases can restart clozapine.