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# Thrombocytopenia associated with clonidine in a case of clozapine-induced sialorrhea

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## Abstract

Clozapine is approved by the US Food and Drug Administration for treatment-resistant schizophrenia and mitigation of suicidality in patients with schizophrenia or schizoaffective disorder. Clozapine requires monitoring of adverse events, such as hypotension, myocarditis, cardiomyopathy, seizures, severe neutropenia, and gastrointestinal hypomotility. Sialorrhea is another adverse event that can be bothersome for patients and result in nonadherence or the development of aspiration pneumonia. Clonidine, an $\alpha_{2A}$ adrenergic receptor agonist, is one medication option that can reduce or eliminate sialorrhea. Clonidine is generally well tolerated but can contribute to hypotension and sedation. One adverse event associated with clonidine not described in the literature is thrombocytopenia. Reported is a case of clonidine-associated thrombocytopenia when used for the treatment of clozapine-induced sialorrhea.

**Keywords:** clozapine, sialorrhea, thrombocytopenia, drug safety, clonidine

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## Background

Clozapine is a second-generation antipsychotic that is approved by the US Food and Drug Administration for treatment-resistant schizophrenia and mitigation of suicidality in patients with schizophrenia or schizoaffective disorder.[1] Clozapine requires intensive clinician monitoring to detect and prevent adverse events including, but not limited to, severe hypotension, myocarditis/cardiomyopathy, seizures, severe neutropenia, gastrointestinal hypomotility, metabolic abnormalities, and sialorrhea.[1] The side effect of sialorrhea can be bothersome for patients and may contribute to nonadherence.[2] Clozapine-induced sialorrhea may be transient during an initial titration or persistent, with severity ranging from mild to copious. Clozapine-associated sialorrhea may contribute to the development of aspiration pneumonia and secondary infection–associated clozapine toxicity.[3-7] These medical complications reinforce the need for vigilant monitoring and appropriate treatment of clozapine-induced sialorrhea.

Clozapine influences the increase of salivation through muscarinic $M_4$ receptor agonism, as well as $\alpha_{2A}$ adrenergic receptor antagonism. These mechanisms provide a rationale for the treatment approach of sialorrhea.[2] Anticholinergic ophthalmic drops (ie, atropine, tropicamide) administered sublingually have minimal systemic absorption, but there is a lack of robust literature supporting their use.[2,8,9] If these agents fail or are not suitable, systemically absorbed anticholinergic agents, such as benztropine or glycopyrrolate, can be considered. Botulinum toxin, metoclopramide, and tricyclic antidepressants are additional agents that have varying degrees of evidence for the management of clozapine-induced

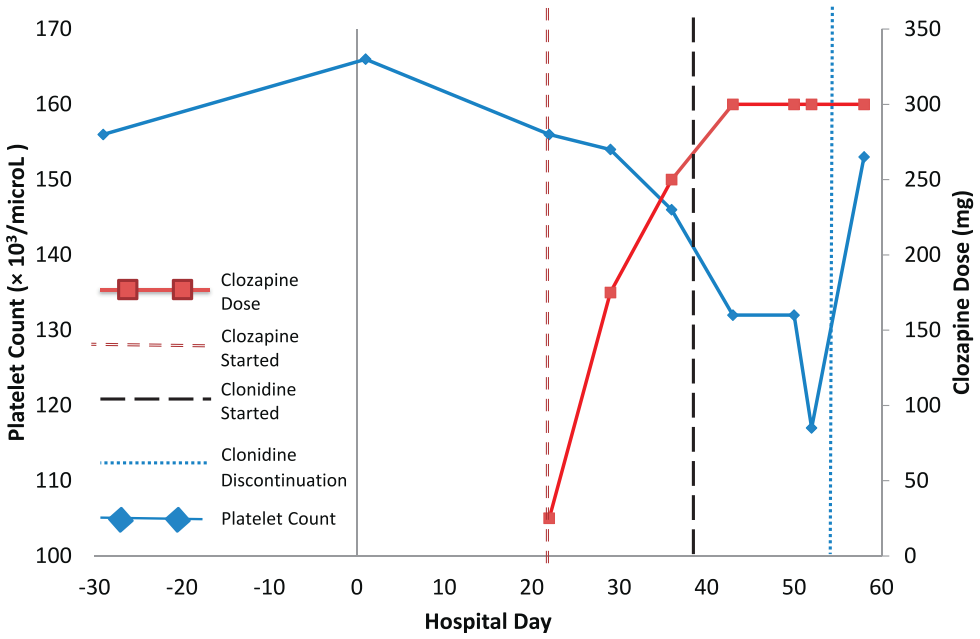


**FIGURE: The timeline of the case report events**

sialorrhea.[10-12] $\alpha_{2A}$ Adrenergic receptor agonists, such as clonidine, have also been reported in case reports[2,13,14] to be effective at managing clozapine-induced sialorrhea. Clonidine is generally well tolerated, but it is imperative that clinicians monitor a patient's blood pressure if clonidine is used concomitantly with clozapine.[15] One side effect of clonidine listed in the prescribing information is thrombocytopenia, but the incidence is not reported.[16] There are also no prior case reports of clonidine-associated thrombocytopenia in the medical literature. We report a case of thrombocytopenia arising during treatment of clozapine-induced sialorrhea with clonidine, followed by complete resolution of thrombocytopenia upon clonidine discontinuation.

## Case Report

A 30-year-old male with no past medical history, except a diagnosis of schizophrenia, had a second psychiatric hospitalization for the treatment of worsening delusions and hallucinations. His first hospitalization occurred approximately 1 month prior, and discharge medication was olanzapine 20 mg at bedtime. Also, at that time his platelet count was $156 \times 10^3/\mu L$; reference range is $135 \times 10^3/\mu L$ to $317 \times 10^3/\mu L$ (Figure). Three days prior to the current admission, the patient had self-discontinued olanzapine because of blurry vision. During the hospitalization the patient was trialed on multiple antipsychotics without benefit. Because of persistent psychotic symptoms, clozapine 25 mg at bedtime was initiated on hospital day (HD) 24. A complete blood count (CBC) with differential at that time revealed no derangements, including a platelet count of $156 \times 10^3/\mu L$.

By HD 29, clozapine was titrated to 175 mg at bedtime, at which time the patient started to complain of sialorrhea with nighttime predominance. One drop of ophthalmic atropine 1% sublingually administered at bedtime was initiated but was ineffective after 5 days of use, and the patient was not agreeable to an increase of the drops. The patient reported awakening at least 5 times throughout the night to "spit into a water bottle" and complained of having a wet pillow every morning. Both the bottle of saliva and wet pillow were observed by staff. Clinically, clozapine was increased to target psychotic symptoms, but it was divided as 50 mg in the morning and 150 mg at bedtime in an attempt to minimize sialorrhea. This was not successful to reduce the excessive salivation. Clozapine was further increased to a total daily dose of 250 mg by HD 36 with improvement in psychotic symptoms, although sialorrhea persisted. Clonidine 0.05 mg by mouth twice daily was added on HD 37 to target sialorrhea. On HD 39, the patient reported improvement of sialorrhea, and objectively his pillowcase was found to be dry during morning rounds.

During the first week of clonidine treatment (HD 37-43), the patient's platelet count decreased from $146 \times 10^3/\mu L$ to $132 \times 10^3/\mu L$. Clozapine had reached a total daily dose of 300 mg by HD 43. On HD 50 the platelet count remained the same, but on HD 52 the platelet count was found to be $117 \times 10^3/\mu L$. All other cell line values were within normal limits. There were no concerns for bleeding, evidence of bruising, or petechiae, but the decision was made to discontinue clonidine given the new thrombocytopenia. Sialorrhea was treated with continued sublingual ophthalmic atropine 1%, 1 drop at night, with the patient

accepting additional as needed doses, using on average an extra 2 to 3 drops per day. Five days later, on HD 58, a CBC with differential revealed that the platelet count was within normal limits at $153 \times 10^3/\mu L$. At this time the patient was also noted to be psychiatrically ready for discharge. Delays related to placement issues resulted in the patient leaving the acute care psychiatric hospital on HD 84. Discharge medications included clozapine 150 mg in the morning and 150 mg at bedtime; atropine 1% drops, 1 drop sublingually at nighttime and as needed; melatonin 3 mg at bedtime; and senna/docusate 8.6/50 mg twice daily as needed for constipation.

## Discussion

Thrombocytopenia is defined as a platelet count less than $150 \times 10^3/\mu L$.[17] A platelet count of less than $50 \times 10^3/\mu L$ is associated with spontaneous bruising/purpura and prolonged bleeding from wounds. Clinically significant spontaneous bleeds, such as gastrointestinal bleeding or intracranial hemorrhage, typically do not occur until platelets fall below $20 \times 10^3/\mu L$.[18] There are many causes of thrombocytopenia, including medications. Drug-induced thrombocytopenia can be stratified into non–immune-mediated and immune-mediated categories. Non–immune drug-induced thrombocytopenia is associated with agents that induce bone marrow suppression, such as myeloablative chemotherapy agents, which typically affect all hematopoietic stem cell lines. Time to platelet nadir and time from platelet nadir to recovery are dependent on the specific agent.[19] A search of the literature did not find information suggesting clonidine induces bone marrow suppression. Immune-mediated thrombocytopenia is associated with platelet destruction due to the development of platelet-specific antibodies. This category typically occurs 1 to 2 weeks after drug initiation or following a single administration if the patient has previously been exposed to the drug and has preexisting antibodies. Platelets typically start to recover 1 to 2 days after discontinuation of the offending drug, with full recovery within 1 week.[20]

The diagnosis of drug-induced thrombocytopenia is challenging and largely made by excluding other causes and based on the timing of thrombocytopenia with the administration of a suspected medication. A possible limitation in this case when considering the association between clonidine and thrombocytopenia was that the empiric discontinuation of clonidine was the sole intervention in this case. No medical consultation or confirmatory testing was sought, namely because of the lack of clinical signs and symptoms from the thrombocytopenia and the temporal relationship between clonidine, thrombocytopenia, and platelet recovery. Testing for drug-dependent platelet antibodies is becoming more widely available to confirm whether a medication is the culprit.[19] This was not pursued in the present case, again, given the resolution of the thrombocytopenia and lack of negative outcomes associated with the reduction in platelet count. Another consideration is the possibility of pseudothrombocytopenia. This is an in vitro phenomenon that occurs from a number of reasons, such as platelet clumping induced by ethylenediaminetetraacetic acid in the collection tubes or improper collection technique.[21,22] The CBC analyzer machines at our institution flag samples with the potential presence of platelet clumps, and in this case there was no such flag. The identification of potential platelet clumps would have prompted the need for manual assessment via a stained peripheral blood smear.

There were no published reports identified in a literature search associating thrombocytopenia with clonidine, and this adverse effect is only documented in the prescribing information with unknown incidence. Drug manufacturers of clonidine were contacted to gather additional information, but they could not provide any additional details related to thrombocytopenia (Boehringer-ingelheim, Teva, Mylan, Mayne; oral communication, February 2019). Many medications, such as carbamazepine, valproic acid and derivatives, and antipsychotics, have been documented[18,19,23,24] as inducing thrombocytopenia in patients without other risk factors for low platelet count. Clozapine is also associated with isolated thrombocytopenia in postmarketing reports and case reports.[25,26] In these case reports, platelet counts only recovered upon clozapine discontinuation, making clozapine an unlikely culprit in the case presented above. The only other medications the patient was administered during the time the platelet count declined were melatonin and atropine drops, neither of which has a known association with thrombocytopenia, and they were still continued at the time of discharge. There were no other medications administered during the hospitalization that could explain thrombocytopenia (eg, heparin for venous thromboembolism prophylaxis, histamine H2-receptor antagonists). Delayed thrombocytopenia as a result of risperidone, haloperidol, or olanzapine also is unlikely given the temporal relationship between platelet count decline following clonidine initiation and platelet recovery following clonidine discontinuation. Assessment of the case using the Naranjo probability scale[27] indicates objective evidence of thrombocytopenia, confirmed by CBC testing (+1). Although there have not been previous conclusive reports of this event (+0), the thrombocytopenia did appear after clonidine administration (+2), and platelet count improved upon clonidine dose lowering and discontinuation (+1, +1). A lack of formal testing made it unknown if there were other causes of thrombocytopenia (+0), and serum clonidine levels were not warranted (+0). There was no rechallenge (+0), placebo given (+0), or history of thrombocytopenia occurring prior to this event (+0). In

summary, there was a probable relationship between the initiation of clonidine and the decline in the patient's platelet count.

## Conclusion

Clozapine is associated with a significant number of adverse events, including sialorrhea. Sialorrhea is bothersome to patients and can be treated pharmacologically, but monitoring for adverse events from added medications is crucial. In this case clonidine was used to mitigate sialorrhea but was associated with thrombocytopenia that resolved upon discontinuation. Although this is the first known case report of this adverse event published in the medical literature, clinicians should be aware of the potential for thrombocytopenia in patients treated with clonidine.

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