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To cite this article: Assist. Prof. Ahmet Ozturk, Erdem Deveci, Ali Emre Dursun, Assist. Prof.  
Etem Soyucok & Prof Ismet Kirpinar (2014) Clozapine Treatment and Thrombocytopenia: a Case  
Report, Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology, 24:3, 289-291,  
DOI: [10.5455/bcp.20140220102919](https://doi.org/10.5455/bcp.20140220102919)

To link to this article: <https://doi.org/10.5455/bcp.20140220102919>



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Published online: 08 Nov 2016.



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# Clozapine Treatment and Thrombocytopenia: a Case Report



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*Bulletin of Clinical Psychopharmacology* 2014;24(3):289-91

Dear Editor,

Clozapine is an atypical antipsychotic drug, which is effective for the treatment of resistant schizophrenia<sup>1</sup>. It is suggested to use clozapine for schizophrenia cases in which no response is obtained from two different antipsychotics<sup>2</sup>. Clozapine treatment was forbidden after the death of 8 schizophrenia patients in Finland in 1974, due to agranulocytosis. However, because of its high efficacy and the lack of alternatives in treatment resistant schizophrenia, it has been approved in schizophrenia with intense hematological monitoring<sup>3</sup>.

Clozapine associated thrombocytopenia is a rare complication and there is limited number of published literature on this subject<sup>4-6</sup>. The hematologic side effects of clozapine are usually associated with leukocytes and neutrophils, therefore its effects on thrombocytes might be ignored. Thrombocytopenia, which is defined as a platelet count below  $150 \times 10^9/L$ , can cause mortality especially associated with bleeding, when platelet count is below  $10 \times 10^9/L$ . We aimed to present a clozapine related thrombocytopenia and its management in a residual schizophrenia case, which did not respond to any antipsychotics except clozapine; and to review the literature on this subject.

## CASE

We report a case of a 37 years old male patient. He has been diagnosed to have residual schizophrenia according to DSM-IV-TR. According to the patient's history obtained from himself and his family members, the symptoms started 15

years ago. No response has been observed in the patient despite the fact that he used olanzapine, amisulpride, risperidone or quetiapine in adequate dose and time on various occasions until a year ago. Since last year, he has been treated with clozapine up to 400 mg/day. With clozapine treatment, remarkable improvement has been emerged in his negative and positive symptoms. During this period, the patient had routine hematologic monitoring which showed no abnormalities. Approximately one year later, when the patient was still under 400 mg/day clozapine treatment, the platelet count was found to be  $50 \times 10^9/L$  while leukocyte or neutrophils counts were normal. After this finding, the patient consulted the internal medicine clinic. According to the hematologic examinations including INR, bleeding time, peripheral blood smear, whole blood cell count and the physical examination performed by an internist including body temperature there were no other abnormalities found that could cause thrombocytopenia, therefore thrombocytopenia had been associated with clozapine. Clozapine treatment was stopped immediately and the patient was told to come back in a week for control. The patient did not have any symptoms except mild social withdrawal and insomnia after this period of one week and the thrombocytes count was  $328 \times 10^9/L$ . We have reinitiated clozapine treatment at low doses. When it was increased to 200 mg/day, the thrombocytes count decreased to  $307 \times 10^9/L$ . After that, the clozapine dosage has been increased to 400 mg/day gradually. The thrombocyte count was above  $150 \times 10^9/L$  on weekly hemograms and the same treatment has been followed.

## DISCUSSION

One of the common reasons of hematologic abnormalities is psychotropic drugs<sup>8</sup>. Hematologic abnormalities related to clozapine, one of the most effective drugs in schizophrenia treatment, include mainly agranulocytosis, leucopenia, neutropenia, eosinophilia<sup>7</sup> and rarely low platelet count<sup>5</sup>. Thrombocytopenia is a decrease in platelet count below  $150 \times 10^9/L$ . While mild decreases in thrombocyte count cause no symptoms, platelet counts less than  $12 \times 10^9/L$  can cause spontaneous bleeding which requires medical intervention, and platelet counts less than  $6 \times 10^9/L$  can cause bleeding that may threaten life<sup>8</sup>. The marketing authorization holder of the medication suggests terminating the medication when thrombocyte count decreases below  $100 \times 10^9/L$  and continuing when it is between  $150 \times 10^9/L$  and  $450 \times 10^9/L$ . In our case, the thrombocyte count was found  $50 \times 10^9/L$  in a routine control and clozapine treatment was stopped according to this suggestion. When platelet count increased to normal range, the treatment was continued.

In a study conducted in Italy for investigating the hematologic effects of clozapine; only 2 out of 2404 patients (0.08%) had thrombocytopenia and those two cases recovered spontaneously<sup>9</sup>. Moreover, in a study conducted together in England and Ireland, 6 out of 6316 patients (0.09%) had thrombocytopenia<sup>10</sup>. While thrombocytopenia is rare and usually asymptomatic as seen in incidence studies, in one study it was manifested by bleeding from nose and the platelet counts went back to normal after stopping treatment<sup>4</sup>. In our case, absence of the clinical problems is possibly due to the identification of thrombocytopenia in a routine control.

While thrombocytopenia recovers spontaneously in most cases like ours<sup>11</sup>, it has been reported in some cases that it lasted respectively for 13 weeks and 40 months after stopping treatment<sup>6</sup>. In these cases, the long recovery periods were associated with

immunological mechanisms<sup>6</sup>.

Stopping the treatment due to hematologic abnormalities associated with clozapine, may cause difficult situations for the clinician and the patient. It can cause relapses. For the patients that do not respond to other antipsychotic drugs, reinitiating clozapine treatment is suggested despite the risks<sup>12</sup>. However, if thrombocytopenia occurs again after reinitiating clozapine treatment, the drug must be stopped permanently<sup>6</sup>. In our case, we decided to continue the clozapine treatment because there were no abnormalities found in follow up blood counts.

While leukocyte count is a main clinical procedure for the patients undergoing clozapine treatment, it is not the same for platelet count. It has been shown in a study that while clozapine has not restricted the bone marrow maturation, it impaired thrombopoiesis<sup>5</sup>. Therefore, some authors suggest routine platelet count for patients undergoing clozapine treatment in order to prevent the bone marrow suppression.

In conclusion, clozapine treatment can rarely cause thrombocytopenia. Because of this reason, when patients undergoing clozapine treatment are evaluated, the platelet count as well as leukocyte count should be monitored. If thrombocytopenia is not accompanied by other blood cell abnormalities, the patient's response to other treatments as well as the functionality and severity of psychiatric symptoms should be evaluated all together and the decision of continuing the clozapine treatment should be made separately for each patient.

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*Declaration of interest:  
A.O., E.D., A.E.D., E.S., I.K.: The authors reported  
no conflict of interest related to this article.*

*This letter was accepted for publication in  
february 20, 2014.*

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