# Olanzapine Treatment After Clozapine-Induced Granulocytopenia in 3 Patients

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***Background:*** How to best treat psychotic patients who have had past clozapine-induced agranulocytosis or granulocytopenia remains a problem.

***Case reports:*** We report 3 patients with chronic schizophrenia who had previously stopped clozapine due to hematologic side effects. The patients evidenced improvement with olanzapine that equated to 16- to 31-point decreases in rating scale scores during 1-year follow-up without any hematologic abnormalities.

***Conclusion:*** The results suggest that olanzapine may be useful in treating patients with clozapine-induced granulocytopenia without the risk of recurrence of hematologic side effects.

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Clozapine is an effective antipsychotic medication,[1] but its use is restricted by the risk of agranulocytosis that it presents.[2–6] Medication-induced granulocytopenia can persist for several months after cessation of the drug treatment and can lead to long-term consequences, including infection and sepsis. Therefore, strict guidelines with close monitoring are followed when administering clozapine.

Rechallenge with clozapine in patients with a history of clozapine-induced agranulocytosis is contraindicated.[7] Thus, alternative antipsychotic medication therapy is necessary. Treatment of these patients poses a difficult clinical situation both in efficacy and in safety, because alternative antipsychotic medications should be both clinically effective and hematologically safe.

Olanzapine is a thienobenzodiazepine, which is a structural analogue to clozapine (a dibenzodiazepine) with novel antipsychotic properties similar to those of clozapine.[8] Olanzapine is reported to be clinically effective in treating both positive and negative symptoms of schizophrenia without significant extrapyramidal symptoms or hematologic toxicity.[9]

In a double-blind clinical drug trial, we noted that 3 patients who were randomly assigned to receive olanzapine for 12 months had been previously removed from clozapine treatment as a result of hematologic side effects. Patients between 18 and 65 years old were entered into the study based on diagnosis of schizophrenia per DSM-IV criteria and normal physical health and laboratory values. This series of case reports addresses the question of whether clozapine-induced granulocytopenia or leukopenia predisposes a patient to hematologic side effects during treatment with olanzapine. The hematologic safety of olanzapine in these 3 patients is reported in this article. All 3 patients gave written consent to participate in the clinical drug trial after procedures and possible side effects were explained to them.

## CASE REPORTS

### Case 1

A 28-year-old unmarried Japanese American man with a 10-year history of paranoid schizophrenia could not tolerate even small doses of neuroleptics because of severe extrapyramidal side effects not responsive to a variety of antiparkinsonism interventions. As a result of inadequate neuroleptic treatment, he had repeated psychiatric emergency room visits and hospitalizations marked by auditory hallucinations, paranoid delusions, inappropriate affect, and intermittent psychotic agitation. He decided to start clozapine; his baseline complete blood count when treatment was initiated showed a total white blood cell (WBC) count of 6300/mm$^3$ and an absolute neutrophil count (ANC) of 3465/mm$^3$.

Eight months later, his clozapine dose had been titrated up to 500 mg daily. At this time, he developed a fever (temperature, 102°F) with a WBC count of 3000/mm$^3$ and an ANC of 1350/mm$^3$. Because of the low ANC and the fever with no evidence of infection, clozapine had to be discontinued. Over the next few weeks, his temperature decreased, his total WBC count increased to 6300/mm$^3$,

  

Table 1. White Blood Cell (WBC) Measurements During 1 Year of Olanzapine Treatment[a]

| | Case Number | | |
|---|---|---|---|
| WBC Count | 1 | 2 | 3 |
| Baseline | 5.83 | 5.47 | 4.12 |
| 1 Year | 6.21 | 4.12 | 5.12 |
| Highest | 6.72 | 5.47 | 5.12 |
| Lowest | 4.90 | 4.12 | 3.64 |
| Mean ± SD | 5.89 ± 0.18 | 4.8 ± 0.17 | 4.30 ± 0.12 |

[a]All measurements are × $10^3$/$mm^3$.

and his ANC increased to 3843/$mm^3$. One month later, the patient began olanzapine treatment. After receiving olanzapine 20 mg daily for 1 year, his Positive and Negative Syndrome Scale (PANSS)[10] score had improved from 88 to 57 and his Brief Psychiatric Rating Scale (BPRS)[11] score had dropped from 28 to 11 without any hematologic side effects (Table 1).

### Case 2

A 38-year-old unmarried white man with a 20-year history of undifferentiated schizophrenia marked by multiple persecutory delusions, auditory hallucinations, formal thought disorder, disorganized behavior, and noncompliance with treatment had been nonresponsive to various neuroleptics over several years and had been hospitalized multiple times. Subsequently, he was placed on a regimen of clozapine. About a year later, he developed a skin infection that did not heal properly. The wound opened and his infection worsened, resulting in a high temperature of 102°F. As a result, the patient was hospitalized for 7 days on a medical ward. At admission, his total WBC count was 2800/$mm^3$, and clozapine was discontinued. The patient received intravenous antibiotics and recovered from this illness, and then started olanzapine treatment. After receiving olanzapine 20 mg daily for 1 year, his PANSS score had decreased from 96 to 65, and his BPRS score had decreased from 31 to 11 without any hematologic side effects (see Table 1).

### Case 3

A 26-year-old African American man with a 13-year history of paranoid schizophrenia marked by hallucinations, persecutory delusions, and prominent social withdrawal had been nonresponsive to high doses of several neuroleptics. He decided to try clozapine, titrating up to 150 mg daily in 1 week. At baseline, his WBC count was 6700/$mm^3$ with an ANC of 1742/$mm^3$. After only 1 week, his WBC dropped to 4600/$mm^3$ with an ANC of 1242/$mm^3$. Because of this drop in total WBC count with an ANC under 1500/$mm^3$, clozapine was discontinued. Six weeks later, his ANC remained low at 1210/$mm^3$. He began haloperidol decanoate, and continued on this therapy for 2 years until starting olanzapine. After a year on olanzapine therapy, his PANSS score dropped from 87 to 69, and his BPRS score dropped from 35 to 19. He suffered no hematologic side effects (see Table 1).

## CONCLUSION

Olanzapine was effective and safe in these 3 cases of schizophrenia in which previous clozapine treatment had been terminated owing to hematologic side effects. While receiving olanzapine treatment, all 3 patients showed improvement in both PANSS and BPRS scores compared with their baseline scores. With regard to safety, none of these patients developed any hematologic abnormalities during olanzapine treatment. In addition, none of the 61 patients treated with olanzapine in our center for 1 year developed any hematologic side effects.[12] Minn noted that a male patient with clozapine-induced agranulocytosis recovered after colony-stimulating factor administration and did not develop any hematologic complications after 1 year of olanzapine treatment (K. Minn, M.D., oral communication, 1997). Although it is difficult to draw definite conclusions from only 3 cases, these results suggest that olanzapine treatment is a safe alternative to clozapine treatment and is free of hematologic side effects among patients who have had to discontinue clozapine because of WBC count or ANC declines. These findings are consistent with the non–cross-reactivity of clozapine-induced agranulocytosis[13] and support the hypothesis of a highly specific mechanism. This underlying mechanism is not triggered by rechallenge with olanzapine, which is a structural analogue of clozapine.

The other question that arises from our case reports is that of the comparative efficacy of olanzapine and clozapine. The first 2 of our patients had received clozapine for a sufficient duration and responded positively, but switched to olanzapine because of hematologic toxicity. The third patient did not receive clozapine for a sufficient duration of time to be effective. Therefore, this question of comparative efficacy cannot be answered from our report and needs to be established in future trials.

*Drug names*: clozapine (Clozaril), haloperidol (Haldol and others), olanzapine (Zyprexa).

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