

# Case Report: Augmentation with Blonanserin for a Schizophrenia Patient with Insufficient Response to Clozapine

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## Abstract

**Background:** Clozapine is the most efficacious among antipsychotics for patients with schizophrenia. Nevertheless, clozapine is not effective in more than about 50% of treatment refractory schizophrenia patients, and several pharmacological strategies are used to augment it. Several reviews including meta-analyses have been published, but the efficacy of augmentation therapy for clozapine-resistant patients is not adequately supported. Though there is a weak connection between the oral dose and plasma concentration of clozapine, there is no report of augmentation therapy considering the plasma concentration of clozapine. Blonanserin is reported to be effective in treatment of both positive and negative symptoms of schizophrenia and well tolerated. **Methods:** We obtained consent to evaluate clinical presentations and clozapine plasma concentrations at the Okayama Psychiatric Medical Center and had not identified the individual for ethical reasons. This is a case report. **Results:** This case fulfilled the diagnostic criteria of neuroleptic-induced dopamine supersensitivity psychosis. Monotherapy with blonanserin was not effective, but augmentation of blonanserin with clozapine was effective and well tolerated by a clozapine-resistant schizophrenia patient. **Conclusion:** Because clozapine may ameliorate dopamine supersensitivity psychosis, the addition of blonanserin to clozapine may be effective even if monotherapy with blonanserin was not.

## Keywords

Treatment Refractory Schizophrenia, Clozapine, Blonanserin, Clozapine

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## 1. Introduction

Clozapine (CZP), one of the second-generation antipsychotics, is the most efficacious among the antipsychotics for treatment of patients with schizophrenia [1]. Nevertheless, 40% to 70% of patients defined as treatment refractory according to Kane's criteria [2] do not respond to CLZ [3] [4] [5], and several pharmacological strategies are employed to treat them [6] [7] [8]. Several reviews including meta-analyses have been published, but the efficacy of augmentation therapy for CZP-resistant patients is not well supported [6] [7] [8]. Though there is a weak relationship between the oral dose and the plasma concentration of CZP [9], there is no report of augmentation therapy based on the plasma concentration of CZP. Blonanserin (BNS) is reported to be effective in treatment of both positive and negative symptoms of schizophrenia in Japan, Korea, and China [10] [11] [12] and is well tolerated [13] [14]. Here we present a case in which supplemental BNS was effective and tolerated by a CZP-resistant schizophrenia patient and discuss it considering the pharmacological profiles of BNS, CZP concentration, and neuroleptic-induced dopamine supersensitivity psychosis (DSP).

## 2. Method

We obtained consent to evaluate clinical presentation and CZP plasma concentrations at the Okayama Psychiatric Medical Center and have not identified the individual for ethical reasons. This is a case report.

## 3. Case Presentation

A 44-year-old man started to fear he had an unpleasant body odor at 10 years old. At 14 years old, he started to experience auditory hallucinations, thought insertion, thought broadcasting, delusions of being observed, and persecution. He started high school but quit. He started several jobs, but he was able to continue only a short time because of psychiatric symptoms. At 20 years old, he consulted a hospital for the first time and was diagnosed with schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV). He was administered a low dose of haloperidol. However, because he believed haloperidol was poison and not effective for his psychiatric symptoms, he refused it many times. We administered fluphenazine decanoate at 50 mg per 4 weeks for 6 months, but it did not ameliorate his symptoms. We administered 20 to 40 mg/day of olanzapine from the ages of 31 to 36 years, 24 mg/day of BNS from 36 to 39 years, and 8 mg/day of risperidone from 39 to 40 years. He was able to continue a job only a short time, even at a community workshop, because of psychiatric symptoms. His psychiatric symptoms worsened, and he hit the walls and floor during hallucinations, and he continued

walking on the road aimlessly. At 40 years old, he was hospitalized for the first time. We administered 50 mg of risperidone long-acting injectable depot (Risperdal Consta) every two weeks with 750 mg/day of quetiapine, and he was discharged after four months. His abnormal behavior and agitation stopped, but he was afraid of having hallucinations and hospitalized again after one month. Thus, he fulfilled the criteria for treatment refractory schizophrenia [2], and CZP was tried. His Positive and Negative Syndrome Scale (PANSS) scores were: positive 30, negative 26, total 120; Clinical Global Impressions-severity (CGI-S): 6, and Global Assessment of Functioning (GAF): 25. We increased CZP to 275 mg/day at one month after initiation. Because he had general myoclonus and his electroencephalogram showed general slow waves from 4 to 6 Hz, we decreased CZP to 200 mg/day and added 300 mg/day of valproic acid and 50mg/day of lamotrigine. His myoclonus stopped, and he was discharged. Because he had started to smoke again, we supposed that the CZP concentration had decreased due to the CYP1A2 induction and increased CZP to 400 mg/day. He started to work as a newspaper deliverer, but he felt stress. His PANSS scores were: positive 17, negative 15, total 62; CGI-S: 3, and GAF: 60. At 43 years old, his psychotic syndrome worsened; he drank agricultural chemicals to kill himself following hallucinations and was hospitalized. We increased CZP to 600mg/day, and his hallucinations were reduced slightly, but he became anorexic. His PANSS scores were: positive 23, negative 20, total 100; CGI-S: 5, and GAF: 30. We reduced CZP to 500 mg/day and added 4 mg/day of BNS. His mood improved following a reduction of hallucinations, and he was discharged. After discharge, we increased BNS to 12 mg/day and he started working at a community workshop. His PANSS scores were: positive 16, negative 15, total 62; CGI-S: 3, and GAF: 58. His CZP concentration was 237.6 ng/ml (Okayama Psychiatric Medical Center), and his prolactin concentration was 15.90 ng/ml (normal range 4.29 - 13.69).

#### 4. Discussion

Though augmenting CZP with a second antipsychotic is one of the treatments for treatment refractory schizophrenia, the efficacy of augmentation therapy for CZP-resistant patients is not well supported [6] [7] [8]. In this case, a high dose of antipsychotics was administered for a long time, and a high dose of BNS was also not effective. CZP at 200 mg/day was effective, but he relapsed because of stress. Though CZP was increased to the maximum dose, it was not very effective and not well tolerated. Thus, this case filled the diagnostic criteria of DSP [15]. CZP may ameliorate the DSP induced by previous antipsychotic treatment because it may decrease the number of dopamine receptors [16], and augmentation with a low dose of BNS was partly effective. We may consider exclusively augmenting CZP with a second antipsychotic in the case of DSP.

In the cases of augmenting CZP with a second antipsychotic, uses of dopamine antagonists, *i.e.*, risperidone, amisulpiride, and sulpiride are well reported but car-

ry a risk of hyperprolactinemia, and risperidone has the risk of QTc prolongation [6] [7] [8]. BNS strongly blocks dopamine 2 (D2) receptors, 5-hydroxytryptamine (5-HT) 2 receptors, D3 receptors, and weakly blocks 5HT-2C, dopamine1 (D1), and  $\alpha_1$  receptor activities while being almost devoid of histamine H1 and muscarinic M1 blocking activity [17]. The pharmacological binding profile is similar to that of sulpiride and amisulpiride except for 5-HT 2 receptor binding affinity [14]. BNS may be comparatively safer than alternative agents for sedation [13], hyperprolactinemia [14], and QTc prolongation [18]. Polypharmacy with antipsychotics is reported to increase the risk of side effects [19], and we should consider the safety profile of agents in the setting of co-administration with CZP. In this case, there was mild hyperprolactinemia but no clinical symptoms. The BNS profile may be related to its safety.

The effective concentration of CZP is reported to differ substantially between individuals [9]. Because CZP and BNS are both metabolized by CYP3A4 [17], BNS administration may increase the blood CZP concentration. However, in our case, the CZP concentration might decrease because of increasing cigarette consumption after discharge. The AGNP Consensus Guidelines for Therapeutic Drug Monitoring in Psychiatry (2011) recommend a therapeutically effective blood concentration of CZP between 350 and 600 ng/ml. In our case, the blood concentration of CZP was under 350 ng/ml. Because the maximum dose of CZP was not tolerable due to side effects, the CZP concentration may not have been adequate to improve his symptoms.

## 5. Conclusion

Though it is needed more cases for a clear and strong conclusion, the addition of BNS to CZP may be effective in cases of DSP, even if monotherapy with BNS is not.

## Conflicts of Interest

N.Y. has received unrestricted research funding from Daiichi Sankyo, Eisai, Pfizer, Otsuka, Astellas, and Merck Sharp & Dohme, which was deposited into research accounts at Okayama University. N.Y. has received honoraria for his participation as a speaker at educational events from UCB Japan, Tsumura, Pfizer, Dainippon-Sumitomo, Daiichi-Sankyo, Merck Sharp & Dohme, Pfizer, Eisai, Meiji-Seika, and Mochida. M.T. has received honoraria for his participation as a speaker at educational events sponsored by Otsuka. S.K., Y.Y., K.K. and Y.K. report no additional financial or other relationship relevant to this article.

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