

# Supersensitivity psychosis in a case with clozapine tolerance

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**Abstract.** – Despite its serious side effects, clozapine is still the golden standard in treatment of schizophrenia due to its effectiveness and lack of extrapyramidal side effects. Some studies have mentioned withdrawal symptoms, including withdrawal psychosis after stopping clozapine, and have tried to explain this severe symptom through dopamine receptor supersensitivity. This phenomenon, called supersensitivity psychosis, can be explained by the development of tolerance towards the effect of the medication. In literature, there are several cases of supersensitivity psychosis while using other neuroleptics. However, to our knowledge, there are no published cases reporting an association between clozapine and supersensitivity psychosis. The current patient, who has been diagnosed as resistant schizophrenia, responded well to the clozapine in the beginning of treatment. Due to an effective dose of clozapine, he had psychotic exacerbation with significant positive symptoms. We discuss the probable reasons causing this situation and the relationship between tolerance to the treatment effect and the dopamine supersensitivity.

*Key Words:*

Clozapine, Drug tolerance, Psychosis, Schizophrenia.

the need of doing many blood examinations<sup>3</sup>. A rapidly developing psychotic exacerbation has been reported in these cases, possibly as a result of the reorganization of dopaminergic receptors or cholinergic rebound effects<sup>4,6</sup>.

Occurrence of a psychotic exacerbation is generally considered as treatment resistance. Fallon<sup>7</sup> reported the occurrence of minor life events before the exacerbation of psychosis in treatment compliant cases. Chouinard<sup>8</sup> has suggested that the loss of effectiveness during a regular treatment is related to dopamine supersensitivity and added that the dopamine supersensitivity develops due to neural adaptation after a long duration of treatment with neuroleptics. Dopamine supersensitivity may also result in a susceptibility to mild life events for schizophrenia patients<sup>3,8</sup>.

In this report we presented a patient with treatment-resistant schizophrenia who responded well to clozapine in the beginning. However, later in the clozapine treatment, the patient developed positive psychotic symptoms. We hypothesized that this psychotic exacerbation might be due to the patient's tolerance to clozapine, and attempted to discuss the probable underlying causes and their relationship with dopamine supersensitivity.

## Introduction

Clozapine is the prototype for novel antipsychotic drugs. Fatal side effects such as agranulocytosis limit its usage as a first line treatment<sup>1</sup>. Despite its serious side effects, it continues to be the golden standard treatment for schizophrenia due to its effectiveness and lack of extrapyramidal side effects, and it has been the drug of choice for resistant schizophrenia patients who do not respond to other antipsychotics<sup>2</sup>. Several follow-up studies have shown that 50% of patients who were under clozapine treatment discontinued them, mainly due to its side effects and

## Case Report

Mr. C, a 31-year-old unemployed patient with a history of paranoid schizophrenia for the last 12 years, was brought to the attention of Emergency Services after stabbing and injuring his two brothers while experiencing delusions. He had been hospitalized as an inpatient several times and had been treated previously with several antipsychotics like risperidone, olanzapine and pimozide. At the time of admission to the hospital, Mr. C. has been taking haloperidol 10 mg/day and chlorpromazine 100 mg/day; however, he experienced compliance problems. Despite improvement in several symptom domains, as

confirmed by his family and care givers, he never had complete remission. In his psychiatric examination, he was disheveled and had incongruent affect and psychomotor restlessness. He also had persecutory and reference delusions and no insight into his delusions and disease. Although he had previously experienced perceptual disturbances (i.e., voices arguing and discussing), he had experienced no auditory hallucinations in the previous year [Positive and Negative Syndrome Scale (PANSS) = 123]. After his admission to the hospital, he was prescribed haloperidol 20 mg/day, biperiden 4 mg/day and chlorpromazine 100 mg/day. As he showed no clinical improvement at day 22 of his hospitalization, electroconvulsive therapy (ECT) was started and all other drugs have been dropped. Paliperidone 6 mg/day was introduced. Four days later paliperidone dosage was increased to 9 mg/day. Despite the application of 7 sessions of ECT (2-3 times a week) and concomitant assumption of paliperidone 9 mg/day, no response to the treatment was observed. He was diagnosed as having treatment-resistant schizophrenia on day 50 of his hospitalization. Clozapine was initiated (PANSS 117) (Table I), and the dosage was incrementally increased after starting with a daily dose of 25 mg/day. On a 100 mg/day clozapine dosage, his complaints began to decrease, and his PANSS score was 50 (Table I). Clozapine dosage was then increased until it reached 400 mg/day. Because his admission was legally required, he has been followed for a period of two years to gauge his treatment progress.

After the first 4 months of clozapine, the patient's complaints decreased, and he got insight for his symptoms. However, after the first 4 months, he abruptly began having auditory and persecutory delusions. Thus, his clozapine dosage was increased to 500 mg/day. His auditory hallucinations then significantly decreased, but they did not disappear. As clozapine dosage could not be increased due to side effects, 200 mg/day amisulpride was added. The patient was

followed for two months with this protocol. His PANSS score stabilized (PANSS 54), and no additional psychotic symptoms have been observed since then (Table I).

## Discussion

When the effectiveness of a medication in treatment compliant cases decreases, this has generally been accepted as tolerance to the medication. In the current case, the patient was hospitalized as an inpatient, and because of the routine close follow-up in inpatient unit, we were quite sure that he was treatment compliant. During this period, there were no life events or triggers that could have affected his physical or mental state. Thus, we considered his situation to have been the result of the loss of treatment efficacy rather than a stress-induced exacerbation due to life events. The best explanation for this loss of drug efficacy may be the development of tolerance to treatment. Both pharmacodynamic and pharmacokinetic mechanisms are examined to understand why tolerance to medication developed. As there is no evidence that clozapine induces its own metabolism and as the patient was not using any other medication that could induce the increase of liver enzymes, the mechanism in this situation seems more likely to be pharmacodynamic (i.e., physiological in nature). Physiological tolerance is a kind of homeostasis in which the body compensates for the pharmacological impact of a substance that has been taken constantly<sup>9</sup>.

Quetiapine is an atypical antipsychotic drug. Reports have shown that patients taking quetiapine develop tolerance to its antipsychotic effects and that patients have psychotic exacerbation during the maintenance treatment<sup>10</sup>. To date, no publications other than experimental studies have shown tolerance toward clozapine. Goudie et al<sup>11</sup> showed that clozapine induces dose-dependent

**Table I.** The change in PANSS scores of patient during clozapine treatment

	Clozapine initiation	1 <sup>st</sup> month (400 mg/day)	4 <sup>th</sup> month (500 mg/day)	6 <sup>th</sup> month (500 mg/day)
PANSS Total	117/210	50/210	62/210	54/210
PANSS Positive Syndrome	34/49	12/49	26/49	14/49

PANSS: Positive and Negative Syndrome Scale.

hypothermia. However, tolerance develops against this effect, and deprivation of clozapine subsequently leads to hyperthermia in animal studies. After acute clozapine utilization, dopamine turnover increases in nucleus accumbens and c-fos mRNA increases in the prefrontal cortex of rats. It has been hypothesized that these findings may suggest the development of tolerance<sup>12,13</sup>. In our case, response to clozapine decreased, resulting in the patient taking higher doses to maintain the same efficacy. The pattern we saw appeared to be similar to the development of tolerance to antipsychotics and can be related to the development of adaptation in the central nervous system.

Tolerance to antipsychotics has been considered to be a part of supersensitivity. If the effect of a substance increases with the repetitious usage of that substance, it is called sensitization (i.e., inverse tolerance). Our knowledge about its mechanism is limited, notwithstanding with our understanding that this phenomenon seems to be related to limbic system, especially the mesolimbic dopaminergic system. Psychosis development with the continual usage of psychostimulants such as cocaine and amphetamines is thought to be related to psychomotor sensitization toward these substances<sup>9</sup>.

Chouinard and Jones<sup>14</sup> declare that the response to chronic dopamine blockage induced by neuroleptics causes a relative gain in dopamine functions in the mesolimbic pathway and that the psychotic symptoms following the reduction or cessation of neuroleptics may be the clinical result of mesolimbic postsynaptic receptor supersensitivity. This phenomenon is called "supersensitivity psychosis" or "supersensitivity syndrome." This syndrome is caused by long-term usage of neuroleptics, and it includes positive symptoms such as hallucinations and delusions. It is related to CNS tolerance, which requires a gradual increase in the dosage of neuroleptic medications to maintain the treatment effect. Chouinard's case series<sup>8</sup> which defined this phenomenon, only studied patients who were using typical antipsychotics. Additionally, there were no data related to clozapine or other typical antipsychotics in that case series.

Previous studies mention about psychotic exacerbation, withdrawal psychosis, and supersensitivity psychosis following clozapine withdrawal. For example, Baldessarini et al<sup>15</sup> described early clinical disruption following clozapine withdrawal by dopaminergic mechanisms. Previ-

ous reports have also shown that repetitious clozapine practice selectively increases the consistency of D4 receptors in the mammalian limbic forebrain. After long-term usage of clozapine, faster elimination of clozapine from the brain causes increased dopamine release, and it is suggested that this stimulates the supersensitive or up-regulated D4 receptors<sup>16</sup>.

Clozapine has the weakest D2 receptor binding among antipsychotic agents. For this reason, clozapine can easily clear off D2 receptors, leaving them free for endogenous dopamine, which may be the cause of rapid relapse.

After the patient stops taking clozapine, residual clozapine, which occupies D2 receptors, leaves the receptors rapidly. This causes an impulse trigger that suddenly elevates dopamine levels, which may raise the psychosis<sup>17</sup>. Taking this into consideration, the efficacy of adding amisulpride augmentation to clozapine for resistant schizophrenia may be due to efficacy of amisulpride acting on D2 and D3 receptors and increasing dopamine transmission in mesolimbic areas<sup>18</sup>.

In the current case, the patient only experienced exacerbation of positive symptoms, as in supersensitivity psychosis. The patient experienced no auditory hallucinations during psychotic exacerbation before hospitalization. Instead, they appeared as new symptoms, which is consistent with supersensitivity psychosis.

Finally, because our patient has been on a stable regular treatment with an effective dose of clozapine, we thought that his lack of response to the late phases of treatment and his psychotic exacerbation could be a manifestation of supersensitivity psychosis. However, it is not uncommon to see effective doses of antipsychotic drugs display reduced effectiveness after a period of time. This is generally thought to be related to irregular usage of the medicine. Nonetheless, these cases could also be considered cases of supersensitivity psychosis, and the consideration of a new treatment plan may be reasonable.

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