LETTER TO THE EDITOR

Dilemma in Treating Clozapine-induced Obsessive-compulsive Symptoms in a Patient with Schizophrenia

Prevalence of obsessive-compulsive symptoms (OCSs) in patients with schizophrenia has been increasing since the introduction of second-generation antipsychotic drugs (SGAs). Many studies have reported de novo emergence of OCS in SGA-treated schizophrenic patients. This clinical finding brings about a major concern in clinical practice. We are reporting a treatment-refractory schizophrenic patient who started to develop de novo OCS after treatment with clozapine, in order to address the treatment issues of SGAs.

Our patient was an obese 43-year-old Taiwanese unmarried female with schizophrenia. She had received flupentixol, haloperidol, risperidone, and olanzapine, and was considered treatment refractory. She came to us in a distressed state due to her distressing compulsive behaviors. The patient received clozapine treatment at the age of 39 years. A year after clozapine treatment, which was administered at a dose of 400 mg/day, she started to develop checking compulsive behaviors for the first time. She compulsively spent 2–3 hours repeatedly checking the back door of the lottery shop when it was closed at night. She reasoned that the time spent and the inconvenience caused by more checking of the back door would save much trouble compared with those after being burglarized. However, after each checking, she was still unsure and thought that checking once more would be better and comforting.

The patient received sertraline (300 mg/day) at our outpatient clinic as a treatment for the distressing symptoms, but the drug efficacy was limited. Unfortunately, her psychotic symptoms worsened after the treatment with sertraline. We hesitated to increase her doses of clozapine in order to avoid further worsening of her condition. We added haloperidol (10 mg/day) to the existing clozapine treatment (400 mg/day), which improved her auditory hallucinations. She remained in a stable mental state for months, but later the clinical course became fluctuated at times. Finally, she received clozapine (400 mg/day), haloperidol (10 mg/day), and sertraline (300 mg/day). We attempted to cross-titrate sertraline with escitalopram in a 2-week period. Escitalopram was maintained at 20 mg/day for another 2 weeks but with limited improvement.

Despite the use of clozapine, the patient could not maintain her stable psychotic symptoms. When faced with the dilemma of choosing between two evils, i.e., worsened psychosis and compulsion, we chose the lesser of the two. We thus tapered off clozapine to 350 mg/day in order to reduce her compulsive behavior. We shifted escitalopram back to sertraline (300 mg/day) owing to its lack of efficacy and side effect (nausea). After this compromise of drug adjustment, her compulsive behaviors were still observed but with a remarkable degree of improvement. Emergence of OCS-induced by SGAs is thought to be related with its antiserotonergic properties. It is estimated that up to 70% of SGAs-treated schizophrenic patients develop de novo OCS, especially those SGAs with higher 5-HT2/D2 antagonism, such as clozapine, olanzapine, risperidone,quetiapine, and paliperidone. Clozapine, with its strong inherent antiserotonergic properties (antagonism at the 5-HT1C, 5-HT2A, and 5-HT2C receptors), is highly associated with the de novo emergence of OCS in schizophrenic patients, with a prevalence rate of 76% for OCS in clozapine-treated patients, especially those with longer clozapine treatment duration. Sequence variations in the polymorphisms of the SLC1A1 (encoding a specific single nucleotide) and DLGAP3 (encoding a postsynaptic scaffolding protein in glutamatergic synapses) are associated with susceptibility, suggesting that schizophrenic patients with those genetic findings tend to develop de novo OCS during treatment with SGAs.

Adding an antiobsessional agent to the SGA treatment in schizophrenic patient is a logical approach to improve the OCS significantly; however, such an approach increases the risk of worsening the psychotic symptoms, as experienced in our patient. Managing distressing OCS is promising with a selective serotonin reuptake inhibitor (SSRI), but many patients experience a partial response to an SSRI, and therefore, the antipsychotic augmentation strategy is proposed. The efficacy of antipsychotic augmentation is proven at least by a meta-analysis study, suggesting that risperidone and haloperidol have the strongest antiobsessional efficacy. Notably, clozapine has high 5-HT2 receptor occupancy, which causes more emergence of OCS and relatively low D2 receptor occupancy with a fast dissociation rate that is unable to cause a sufficient therapeutic effect in OCS. Interestingly, aripiprazole, a partial dopaminergic and serotonergic 5-HT1A receptor partial agonist, which is per se associated with an inherent antiobsessive potency, is also found to be efficacious in the augmentation therapy and a trial of monotherapy in treating schizophrenic patients with OCS. Adding antiobsessional potency agents might be the next great leap forward. Perhaps for those schizophrenic patients with susceptible OCS, SGA selection as principal medication for schizophrenia should also take the potential risk of OCS into consideration.

The interaction between clozapine and sertraline might pose a remarkable issue in this patient, which explains the worsened psychotic symptoms after sertraline discontinuation. Total clozapine concentration decreased by approximately 40% after the sertraline treatment was discontinued for 30 days, as sertraline probably can inhibit the metabolism of clozapine through CYP1A2, which accounts for approximately 70% of the variance of clozapine clearance. However, no significant changes in plasma clozapine
concentration and its major metabolites have been observed after a 3-week combined therapy with sertraline in patients with psychotic disorders.⁴ Clozapine carries the highest risk of causing weight gain and metabolic dysregulation,⁵ which is highly morbid to this obese patient. Adjunctive fluvoxamine inhibits clozapine-related weight gain and metabolic disturbance, and it can also reduce the clozapine dosage needed in refractory schizophrenic patients.⁶ This might be the next considerable strategy in treating this patient. The case report highlighted here is limited for generalizing the data to other patients. Apparently, there is a need to collect more clinical cases for describing SGA-induced OCS and finding the treatment strategies.

References


