

The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided. The patient described in this column is a composite with characteristics of several real patients.

Clozapine-induced obsessive-compulsive symptoms: mechanisms and treatment

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A 35-year-old man with treatment-resistant schizophrenia was prescribed clozapine. Three weeks later, at a dose of 400 mg/d, his psychosis improved substantially, but contamination obsessions and cleaning compulsions developed, occupying a lot of his time. His family history was positive for obsessive-compulsive disorder (OCD); he had an aunt with OCD. Clozapine was thought to be the cause of his obsessive-compulsive symptoms (OCS), so the dose was reduced to 300 mg/d over a period of 1 week. Although the OCS abated, his psychosis worsened. Clozapine was reincreased to 400 mg/d and the OCS returned. Aripiprazole (15 mg/d) was added, and the OCS gradually diminished, with complete resolution after 5 weeks.

Determining the origin of OCS in individuals with schizophrenia is a clinical challenge, because OCS can be an idiopathic component of positive symptoms or an adverse effect of antipsychotic medications.¹ Clozapine is the antipsychotic most well known to induce OCS.^{2,3} Although the prevalence of OCS among patients treated with clozapine tends to vary widely owing to methodological heterogeneity among studies, a recent study reported a mid-point prevalence of 47%.⁴

Mechanisms underlying clozapine-induced OCS have not been fully delineated. However, theories implicating various neurotransmitter systems, in particular serotonin and dopamine, have been put forward.

As selective serotonin reuptake inhibitors (SSRIs) are known to treat OCD and OCS,⁵ clozapine's antiserotonergic effects (e.g., antagonism of

5-HT_{2A} and 5-HT_{2C} receptors) are potential causal factors.^{6,7} However, the mechanism may be more complex, given the evidence that 5-HT_{2C} receptor antagonists have beneficial effects in animal models of OCD.^{8,9} Such an effect may be region-specific (e.g., orbitofrontal cortex).^{9,10} It has been hypothesized that hypersensitivity of 5-HT_{2C} receptors, as a result of chronic antagonism, may play a role in clozapine-induced OCS.^{11–13} This is in line with evidence that SSRIs act not only by enhancing 5-HT neurotransmission, but also by normalizing 5-HT_{2C} receptor function via its desensitization.¹⁴

In patients with SSRI-resistant OCD, antipsychotic augmentation has been particularly effective, implying dopaminergic involvement in OCD.¹⁵ Neuroimaging studies implicate hyperdopaminergic activity in the pathophysiology of OCD, where dopaminergic and serotonergic pathways have reciprocal relationships.¹⁶ In this regard, clozapine's strong antagonism of 5-HT_{2A} receptors is posited to disinhibit nigrostriatal dopaminergic neurons. Another hypothesis implicates dopamine supersensitivity secondary to treatment with antipsychotics with high affinities for D2 receptors.^{17,18} Thus, when switching patients to clozapine, increased dopaminergic activity resulting from reduced striatal dopaminergic inhibition may unmask OCS.¹⁸

Other causal factors need to be considered. For instance, genetics may play a role, according to a finding that individuals with polymorphisms in the genes that regulate glutamate transmission, such as *SLC1A1* and *GRIN2B*, were more susceptible to clozapine-induced OCS.¹⁹ Findings of abnormal brain activation patterns and neurocognitive deficits associated with treatment with antiserotonergic antipsychotics (e.g., clozapine and olanzapine) also need to be considered in relation to clozapine-induced OCS.^{7,10}

Clozapine-induced OCS may improve if the dose is reduced or discontinued.^{2,3} However, some case reports found OCS to improve when the dose of clozapine was increased.² The conflicting results may be explained by the heterogeneous etiology of OCS.^{1,3} As clozapine dose reduction or discontinuation carries the risk of exacerbation of target symptoms (e.g., psychosis), other treatment options may be preferred.

Add-on SSRIs can be effective in treating clozapine-induced OCS.² Mechanisms may involve enhancement of 5-HT neurotransmission and normalization of 5-HT_{2C} receptor function.¹⁴ Of note, SSRIs, in particular fluvoxamine, can increase clozapine blood levels, and given that higher plasma clozapine and norclozapine concentrations may be associated with the development of clozapine-induced OCS,²⁰ careful drug monitoring should be considered when using add-on SSRIs.

Add-on antipsychotics can also be considered. Studies have found add-on aripiprazole to be effective in treating clozapine-induced OCS.^{21,22} The antiobsessive effect of aripiprazole may come from its 5-HT_{1A} partial agonism.²³ Another candidate is amisulpride, a selective D2/D3 antagonist without an affinity for 5-HT₂ receptors.⁶ However, evidence for amisulpride, as an add-on or a switch, to treat clozapine-induced OCS is lacking, although a switch to amisulpride was shown to improve OCS induced by other atypical antipsychotics.²⁴

Other pharmacological considerations include adjunct clomipramine and mood stabilizers (e.g., lamotrigine and valproic acid).³ Evidence for the effectiveness of nonpharmacological treatment, such as cognitive behavioural therapy, on clozapine-induced OCS is not clear.

Current evidence suggests that clozapine may induce OCS via complex

serotonin–dopamine mechanisms and could be treated with adjunct agents (e.g., SSRIs and aripiprazole) that alter these neurotransmitter systems. Clinicians need to be vigilant for clozapine-induced OCS and consider appropriate treatment strategies for these symptoms when they become a clinical concern.

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