Serotonin Reuptake Inhibitor Treatment of Obsessive-Compulsive Symptoms in Clozapine-Medicated Schizophrenia

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- Serotonin reuptake inhibitors such as fluvoxamine, fluoxetine, or clomipramine may be prescribed as add-on treatments for obsessive-compulsive symptoms in schizophrenia patients.
- Fluvoxamine (and to a lesser extent, fluoxetine) will inhibit clozapine metabolism, raise clozapine levels, and increase the risk of seizures and other dose-dependent adverse effects of clozapine. Obtaining blood levels of clozapine can guide the adjustment of clozapine dosing to contain the risk.
- Clomipramine may lower the seizure threshold and increase anticholinergic and sedative adverse effects of clozapine.
- SRIs such as paroxetine, sertraline, citalopram, and escitalopram can probably be combined with clozapine with low risk of adverse interactions.

Each month in his online column, Dr Andrade offers practical knowledge, ideas, and tips in psychopharmacology to *JCP* readers in psychiatric and general medical settings.

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Mr L, a 25-year-old man, was diagnosed with schizophrenia 4 years ago. After failing trials with different antipsychotic drugs, prescribed in adequate doses for adequate durations, he was started on clozapine treatment.

Mr L has now crossed a year of treatment with clozapine (400 mg/d), and the response to the drug has been good. However, there is a fresh clinical problem: he has repeated thoughts about making mistakes in his everyday routine, with resultant repetitive counting and checking behaviors. Mr L realizes that these thoughts and behaviors are not justifiable but does not make much effort to resist them. The symptoms are present for over an hour a day, on average, and they interfere with his activities of daily living. He cannot say for certain when the symptoms began, but it is clear that they attained their present degree of severity only during the past few months.

His psychiatrist is aware of the literature that associates obsessive-compulsive symptoms (OCS) in schizophrenia with atypical antipsychotic use. However, his psychiatrist is hesitant to switch him from clozapine to a typical antipsychotic, or even to reduce the dose of clozapine, because of the risk of loss of treatment efficacy. Rather, in consultation with Mr L, he prefers to continue clozapine treatment without change, along with a therapeutic trial of fluoxetine, fluvoxamine, or clomipramine, the efficacy of which is well established in obsessive-compulsive disorder (OCD). What might be the risks associated with the addition of any of these drugs to a prescription of clozapine?

Clinical Notes on the Comorbidity of Obsessive-Compulsive Disorder and Schizophrenia

Although psychosis and OCS were first described to coexist in the same patient as early as in the 19th century,[1] OCS were considered rare and protective in schizophrenia.[2] *DSM-III* did not allow the diagnosis of OCD if schizophrenia was present because schizophrenia was higher in the hierarchy of psychiatric illness.[3] However, after Fenton and McGlashan[4] showed a 13% prevalence of OCS in schizophrenia, with poorer outcome in schizo-obsessive patients, there was an explosion of research on the subject.

A recent meta-analysis of the prevalence of anxiety disorders in schizophrenia found that 12.1% of patients with schizophrenia also had OCD.[5] OCD has been described in both adolescent[6] and elderly[7] patients with schizophrenia. Comparably high prevalences of OCS in schizophrenia have been described in ultra-high-risk patients; during the schizophrenia prodrome; in first-episode, drug-naive, or minimally drug-exposed patients; and in adults with schizophrenia, including those whose psychosis has responded to treatment.[3,8,9]

According to *DSM-IV*,[10] patients must meet diagnostic thresholds for both disorders for Axis I comorbidity to be recorded. More specific criteria have, however, been proposed: obsessions/compulsions must be present for at least an hour a day, the symptoms should not be due to the content of current delusions or hallucinations, the symptoms should cause distress or interference independent of psychosis, the symptoms should

not be due to drugs or organic factors, and the symptoms should have been present for a substantial period during the course of the illness.[3]

Evidence suggests that in most schizo-obsessive patients OCS precede psychotic symptoms or are coincidental in onset[11,12]; they are associated with fair to good insight, they exhibit symptom dimensions similar to those in pure OCD, and they are commonly moderate to severe.[3,13] A meta-analysis found greater positive, negative, and global symptom burden in schizophrenia patients with OCS.[14] Psychosocial impairment is greater in affected patients.[15]

Notes on the Management of Obsessive-Compulsive Symptoms in Schizophrenia

In general, atypical antipsychotic drugs alone do not suffice to contain OCS in schizophrenia.[3] In fact, the inhibitory effect of these drugs on serotonin receptors has been suggested to be responsible for OCS in those patients whose OCS symptoms develop after the onset of psychosis.[16,17] Favoring a causal effect with the atypicals is the observation that OCS have not been reported to arise after the initiation of neuroleptic drugs[17] (but this may have been due to a lack of awareness or lack of reporting). Kwon et al[18] even reported a possible linking of atypical antipsychotic–associated OCD to the glutamate transporter gene *SKC1A1*.

Against an etiologic role for the atypicals, however, is the consideration that, in about half of schizo-obsessive patients, OCS precede the onset of psychotic symptoms.[12] The implication is that if there is a biological overlap between OCS and schizophrenia, OCS may well occur after the onset of psychosis in some patients. Therefore, in these patients, the introduction of atypical antipsychotic therapy may be coincidental rather than causal.

Given the seriousness of schizophrenia, it is unlikely that discontinuation of atypical antipsychotic medication or reduction in antipsychotic dose would be clinically feasible in most schizo-obsessive patients whose psychotic symptoms have responded to medication. Given the absence of evidence in support, there does not appear to be a case for the substitution of atypical antipsychotic drugs with neuroleptic agents. Although aripiprazole monotherapy or augmentation therapy has been suggested for OCS in schizophrenia,[19,20] the data are presently too weak to support recommendations. Adherence to cognitive-behavior therapy for OCS could prove challenging to most schizophrenia patients. Treatment therefore falls back on augmentation of antipsychotic medication with established anti-OCD agents, that is, the serotonin reuptake inhibitors (SRIs).[3]

Interactions Between Clozapine and Fluvoxamine or Fluoxetine

Mr L (whose case was described at the start of this article) is receiving clozapine, and add-on therapy with fluvoxamine, fluoxetine, or clomipramine is being considered. Is there a risk of drug interactions between clozapine and these SRIs?

Clozapine is mainly metabolized by the cytochrome P450 (CYP) enzyme CYP1A2[21–23]; however, CYP2C19 and CYP3A4 also contribute to its metabolism, though to a smaller extent.[21] Fluvoxamine is a potent inhibitor of CYP1A2 and CYP2C19[24-26] and a weaker inhibitor of CYP3A4.[27] Fluvoxamine could therefore increase the blood levels of clozapine several-fold,[24,28] resulting in an increase in the adverse effects of clozapine. The most serious consequence would be an increased risk of seizures, a dose-dependent adverse effect of clozapine.[29]

Fluoxetine inhibits both CYP2C19[30] and CYP3A4.[27] Thus, fluoxetine is also likely to increase clozapine levels and hence the risk of dose-dependent adverse effects with clozapine, including the risk of seizures.[31] However, the risk with fluoxetine will not be as high as that with fluvoxamine because fluoxetine does not inhibit CYP1A2 as does fluvoxamine.

The best way of anticipating the pharmacokinetic drug interaction between fluvoxamine or fluoxetine and clozapine would be to obtain blood levels of clozapine and its active metabolite, norclozapine, before and periodically after initiating add-on therapy with fluvoxamine or fluoxetine. The dose of clozapine can be adjusted on the basis of the blood level estimations.

CYP enzyme inhibition with a drug is immediate, and so blood levels of the substrate should immediately rise after the start of treatment with the enzyme inhibitor. It could be wise, therefore, to obtain blood levels and adjust clozapine doses every 2–3 days until the clozapine level stabilizes close to its initial value. If the enzyme inhibitor is discontinued, it would take about 5 half-lives for the inhibitor to be washed out of the body and up to a further week or two for sufficient quantities of new CYP enzyme to be synthesized, which is around when the dose of clozapine would need to be up-titrated back to its baseline value. Again, blood level estimations could guide the process.

Interactions Between Clozapine and Clomipramine

There is no evidence that clomipramine affects any of the CYP enzymes that metabolize clozapine; therefore, clomipramine probably has no effect on the pharmacokinetics of clozapine. However, clomipramine is associated with a dose-dependent increase in the risk of seizures,[32] and it is therefore likely that the combination of clomipramine with clozapine would be pharmacodynamically additive or synergistic in increasing the seizure risk. Additionally, clomipramine is strongly anticholinergic and sedating[32] and could increase the anticholinergic and sedating adverse effects of clozapine. Although clomipramine is associated with better anti-OCD outcomes than other selective serotonin reuptake inhibitor drugs,[33–36] there is no simple solution to contain the adverse pharmacodynamic interactions between clomipramine and clozapine; the addition of an anticonvulsant such as valproate could reduce the risk of seizures but could introduce the risk of new adverse effects or new drug interactions.

Interactions Between Clozapine and Other Serotonin Reuptake Inhibitors

Although there is at least 1 report of paroxetine-related increase in blood clozapine levels,[37] neither paroxetine nor sertraline affect the CYP enzymes that metabolize clozapine[26]; therefore, neither drug would be expected to pharmacokinetically interact with clozapine. Citalopram and escitalopram do not inhibit CYP enzymes to any appreciable extent.[26] These drugs could therefore be safely administered along with clozapine. However, the evidence base for the use of these drugs in OCD is less strong than that for fluoxetine, fluvoxamine, and clomipramine.

Closing Questions

Does schizo-obsessive disorder merit independent nosologic status? How effective is SRI augmentation of antipsychotic medication in patients with comorbid schizophrenia and OCD? What are other possible interventions for such patients? The answers to these important questions should emerge in future research.

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