

Clozapine and Obsessions in Patients With Recent-Onset Schizophrenia and Other Psychotic Disorders

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Background: The increase or emergence of obsessions was compared in young patients with recent-onset schizophrenia or other psychotic disorders taking clozapine and other antipsychotic drugs.

Method: We conducted a retrospective cohort study. Subjects were 121 consecutively admitted patients diagnosed with DSM-III-R schizophrenia, schizoaffective disorder, schizophreniform disorder, or psychotic disorder not otherwise specified. Obsessions were diagnosed according to DSM-IV criteria.

Results: More clozapine-treated subjects (20.6%) than subjects treated with other antipsychotic drugs (1.3%) experienced an emergence or increase of obsessions ($p < .01$).

Conclusion: Use of clozapine is associated with the emergence or increase of obsessions in early-phase schizophrenia.

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Clozapine is an effective drug for treating patients with psychotic symptoms who are refractory to other neuroleptics^{1,2} or have severe extrapyramidal adverse effects while taking selective dopamine-2 (D_2) antagonists.^{1,3} A risk of agranulocytosis is the most important side effect of clozapine. A less well-known, but possible, side effect we frequently encounter is emergence or increase of obsessions in the treatment with clozapine of young patients with recent-onset schizophrenia or other psychotic disorders. The decrease of psychotic symptoms and the increase of obsessive symptoms during clozapine treatment suggest that these 2 types of symptoms are discrete phenomena.

A review of the literature concerning the association between obsessive-compulsive symptoms and clozapine treatment showed contradictory results. The coincidence

of worsening obsessive symptoms when clozapine is taken has been reported in 13 case reports.^{4–10} All report an improvement of psychotic symptoms and an increase in obsessions during clozapine treatment. A dose-response relationship between clozapine and obsessive symptoms has been reported¹⁰; a decrease in obsessions has been found after initiating comedication with a selective serotonin reuptake inhibitor (SSRI)^{6,7} and after stopping clozapine therapy.⁸ However, in a chart review of 142 patients taking clozapine, Ghaemi et al.¹¹ could not find a definitive relationship between obsessive-compulsive disorder and clozapine treatment. However, only 41 subjects in their sample had a diagnosis of schizophrenia, and most obsessions and compulsions occurred during clozapine treatment in patients with schizophrenia.

Baker et al.¹² conducted a prospective study concerning the relationship of olanzapine and obsessive-compulsive symptoms. Olanzapine is comparable to clozapine in its structure and its relatively strong serotonin-2A ($5-HT_{2A}$) receptor antagonism. In a 6-week double-blind design, 7 patients received placebo, 11 received olanzapine, 1 mg daily, and 7 received olanzapine, 10 mg daily. There were no significant differences in obsessive-compulsive symptoms found between these groups. Baseline evaluations revealed that 8 of the 25 subjects had mild obsessions, and 6 of the 25 subjects had mild compulsions. The small sample size, short duration of treatment, and very low dose of olanzapine limit the conclusions of this study.

The purpose of the present study is to examine whether the increase or emergence of obsessive symptoms is more frequent during clozapine treatment than treatment with other antipsychotic drugs in a large group of young patients with recent-onset schizophrenia and related disorders, and whether comedication with SSRIs diminishes obsessions.

METHOD

Subjects

Initial diagnosis was made in a clinical consensus meeting (3 psychiatrists and 2 psychiatrists-in-training) with the use of all available information (medical reports, interviews with patients and parents) according to DSM-III-R

criteria. We studied 91 patients with schizophrenia, 17 patients with schizoaffective disorder, 9 patients with schizophreniform disorder, and 4 patients with a psychotic disorder not otherwise specified. The mean \pm SD age at admission was 20.9 ± 2.2 years; 25 subjects were women, and 96 were men.

Assessment

In this retrospective cohort study of 121 patients consecutively admitted to the Adolescent Clinic at the Academic Medical Center of the University of Amsterdam (the Netherlands), 2 investigators (R.G. and L.H.) used chart review to identify patients who experienced emergence or increase of obsessions while taking antipsychotic medication. These investigators worked independently and were blind to the medications taken by the subjects ($\kappa = 0.94$). Obsessions were diagnosed according to DSM-IV criteria. We also estimated global improvement of obsessions during comedication with SSRIs. Clozapine treatment was studied over a mean \pm SD period of 7.3 ± 1.9 months. The mean \pm SD period of observation of patients taking other antipsychotic drugs was 10.1 ± 3.1 months. Thirty-two patients (26%) were taking clozapine at the time of the study, and 2 patients had taken clozapine before but were not taking it at the time of the chart review. Fifty-seven patients took typical antipsychotics, and 19 patients took risperidone. Eleven patients refused to take medication. There were no differences concerning sex, age at admission, or diagnosis between the clozapine receivers and the nonclozapine receivers. Clozapine receivers more often had extrapyramidal adverse effects of greater severity and more often were nonresponders to typical antipsychotics.

RESULTS

Seven patients (20.6%) reported an increase in obsessions after the start of clozapine, in contrast with 1 patient (1.3%) treated with another antipsychotic drug (Fisher exact test, 1-tailed, $p < .01$). Five patients had no obsessions before the start of clozapine treatment. One patient stopped taking clozapine after 3 months, which was followed by disappearance of obsessions. Seven patients were cotreated with SSRIs (6 with paroxetine, 1 with fluoxetine). Lowering the dose of clozapine and comedication with SSRIs was associated with improvement in 3 patients. In 4 patients, comedication with an SSRI did not diminish the obsessions.

DISCUSSION

In this study, one fifth of the patients treated with clozapine experienced an emergence or increase of obsessive

symptoms. There was a significant difference compared with other antipsychotic drugs. It is possible that obsessive symptoms are a remainder when psychotic symptoms disappear. Furthermore, differences in biological side effect liabilities between the 2 populations examined (clozapine receivers and nonclozapine receivers) could account for the difference found. However, the results suggest that clozapine induced or worsened obsessions in a subgroup. Obsessions are associated with a hyposerotonergic neurotransmission, and SSRIs can have a therapeutic effect on obsessive-compulsive disorder. In this study, comedication with an SSRI diminished obsessions in less than half of the patients. Obsessions might be a transient adverse effect,⁴ which is one of the reasons we are not able to attribute the improvement to the SSRIs. When SSRIs and clozapine are administered together, attention should be paid to the possibility that an SSRI can induce a greatly elevated plasma clozapine level.^{13,14}

In this retrospective study, obsessions were frequently encountered during treatment with clozapine. Prospective and controlled studies of emergence or increase of obsessive symptoms during clozapine (and olanzapine) treatment are necessary.

Drug names: clozapine (Clozaril), fluoxetine (Prozac), olanzapine (Zyprexa), paroxetine (Paxil), risperidone (Risperdal).

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