Suicidal Obsessions as Dose Dependent Side-Effect of Clozapine

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ABSTRACT

Objective: Although numerous reports suggest that different atypical antipsychotics can exacerbate or induce (de novo) obsessive-compulsive symptoms, there is no report of the development of ego-dystonic, suicidal obsessions during treatment with these medications. Here, the authors report the first case of clozapine-induced suicidal obsessions. Method: The authors report a case of a patient diagnosed with bipolar disorder and who developed suicidal obsessions in the weeks after the dose of clozapine was increased from 150 mg/day to 300 mg/day. Results: Symptoms quickly resolved after the treatment with clozapine was changed to the treatment with quetiapine and sodium valproate. Suicidal obsessions decreased promptly, within a few days, and disappeared completely when the dose of clozapine was 100 mg/day, quetiapine 600 mg/day, and sodium valproate 900 mg/day, 16 days after the initiation of changes in the medications. Conclusion: The case report emphasizes the crucial need of differentiation between genuine suicidal desires and ego-dystonic suicidal obsessions. The authors suggest that in similar cases a change in antipsychotic medications to those with stronger antidopaminergic properties and lower 5HT2 receptor affinity should be considered, but also assume that the use of sodium valproate in treatment of obsessive-compulsive symptoms deserves further study. Psychopharmacology Bulletin. 2011;44(1):65–69.

INTRODUCTION

Numerous reports suggest that atypical antipsychotics, such as olanzapine, risperidone, quetiapine, aripiprazole, ziprasidone and in particular clozapine, can exacerbate or induce (de novo) obsessive-compulsive symptoms (OCS) in patients with different psychiatric disorders, often schizophrenia.1,2 Usually, the described symptoms are obsessions of contamination, washing, checking, counting and cleaning rituals.3 Although it has been reported that aggressive obsessions are often present in patients with obsessive-compulsive disorder,4 it seems...
that aggressive obsessions related to the use of these medications are rare. Lykouras et al.³ reviewed 30 cases reported in the period from 1990 to 2002, and found that none of the reported patients in the cases had aggressive obsessions. Subsequently to that review, Özer et al. reported the case of a patient with schizophrenia who experienced hallucinations ordering the killing of her husband and children. The hallucinations were replaced by unacceptable, ego-dystonic thoughts of harming herself or her children.⁵ Yet, there is no any report of the development of ego-dystonic, suicidal obsessions during treatment with atypical antipsychotics.

In fact, ego-alien, suicidal obsessions are considered to be an extremely rare form of adverse drug reaction. The literature survey (MEDLINE and Google Scholar search of the literature from 1990 to 2010) disclosed only three reports suggesting associations between ego-alien suicidal ideas and medications—a case of “obsessional-like” suicidal ideas after ingestion of an anti-fungal drug, ketoconazole,⁶ a case of a patient who had ego-dystonic suicidal ideas during treatment with an antibiotic, fluoroquinolone,⁷ and a case of a patient who had ego-dystonic suicidal ideas during treatment with Hypericum perforatum (St. John’s wort).⁸ In all of these cases, patients developed ego-alien suicidal ideas during a few days of treatment with the named medications, but intensities of ideation were not measured with an appropriate scale.

The authors present a patient who experienced a de novo emergence of suicidal obsessions during treatment with clozapine.

**CASE REPORT**

In April 2007, when the author (BAM) first met him, Mr. A was a 54-year-old carpenter who was retired ten years earlier because of mental disorder and who was hospitalized because of depressed mood, severe anxiety, insomnia and the “permanently” present idea of suicide by hanging. Although he lost the majority of his psychiatric documentation, it was clear that he was diagnosed with bipolar disorder (per ICD-10) and that his treatment started at least 15–20 years ago. He told of having had numerous hospitalizations, saying these were mostly related to his elevated mood, unrestrained behaviour and alcohol abuse, but that in the period of 2005–February 2007, while he was being treated only with clozapine 150 mg/day and diazepam (as needed, 5–10 mg), his condition was satisfactory and stable.

He was also diagnosed with diabetes mellitus in 2006, and was stable on an oral antidiabetic (acarbose–Glucobay 100/day).

In February 2007, because of increased anxiety he was, as an outpatient, prescribed with clozapine 300 mg/day. A month later (March 2007)
he was hospitalized because of appearance of suicidal ideation. At that time, the attending psychiatrist believed that the patient’s worsening condition was related to non-compliance, and prescribed long-acting depot risperidone (37.5 mg/2 weeks, risperidone was prescribed for the first time). As no improvement was noticed, the patient was transferred to the author’s institution, in April 2007.

It became obvious that the patient’s worsening condition was dominantly related to the development of suicidal ideas and distress related to them. However, he denied any reason to commit suicide and declared his satisfaction with life. We concluded that these ideas were not associated with a genuine suicidal desire but were ego-dystonic suicidal obsessions. According to the information obtained from the patient, he developed the symptoms in the weeks after the dose of clozapine was increased to 300 mg/day, and the subsequent adding of risperidone had no influence on his condition. Though he displayed no compulsions, his score on the Yale–Brown Obsessive–Compulsive Scale (Y-BOCS) was 18.

Long-acting risperidone was stopped, sodium valproate in a dose of 900 mg/day was prescribed, quetiapine was initiated, its dose was increased in the next three weeks to 700 mg/day, and the dose of clozapine was decreased to 75 mg/day during same period.

The intensity of suicidal obsessions decreased promptly, within a few days, and the obsessions disappeared completely when the dose of clozapine was 100 mg/day, quetiapine 600 mg/day, and sodium valproate 900 mg/day, 16 days after the initiation of changes in the medications. The patient was discharged without obsessions and in an adequate mood. Although further corrections of the medications regime were planned, they were not implemented. An attempt to further decrease the dose of clozapine was associated with the reporting of increased anxiety and problems with insomnia. Thus, the patient had insisted on taking at least 75 mg/day of clozapine, and was very reluctant to the suggested modifications of medications regime. During the last two years, the patient was treated with quetiapine 600 mg/day, clozapine 75 mg/day and sodium valproate 900 mg/day. In that period he was free of obsessions and in an adequate mood.

**DISCUSSION**

This is most probably the first report of ego-dystonic suicidal obsessions developed subsequently to an increase in clozapine dosages, which also emphasizes the crucial need of differentiation between genuine suicidal desires and ego-dystonic suicidal obsessions, and different treatment approaches accordingly. The differentiation may be difficult,
especially in patients with disorders that confer their own risks for suicide, such as bipolar disorder in this case.\textsuperscript{9}

Clozapine is not just an atypical antipsychotic usually used for managing patients with treatment-resistant psychosis; it also possesses significant protective effects for suicide.\textsuperscript{10} Thus, the idea on the development of suicidal ideation associated with the use of clozapine seems contradictory, except if the suicidal idea is not a genuine one, but rather an obsession.

Although multiple hypotheses exist, there is a lack of knowledge on the pathophysiological mechanisms underlying the induction of OCS by atypical antipsychotics. Accordingly, it is quite difficult to offer an unspeculative answer to what might have happened here. The importance of 5-HT\(_{2C}\) and particularly 5-HT\(_{2A}\) antagonisms has been emphasized in a number of articles, same as the complex interplay of dopaminergic and serotonergic systems.\textsuperscript{4,5} Though clozapine and quetiapine are considered to be drugs with similar pharmacodynamic properties, a switch from clozapine to quetiapine might be therapeutic because quetiapine possesses much lower 5-HT\(_{2A}\) and 5-HT\(_{2C}\) receptor binding affinities than clozapine.\textsuperscript{11} Whether or not this mechanism had any influence is hard to say, especially because there is a report on the spontaneous remission of OCS without a change in the clozapine dose,\textsuperscript{3} and reports on OCS emerged during treatment with conventional antipsychotics, including those with negligible 5-HT activity such is haloperidol.\textsuperscript{2}

Another possible explanation for the resolution of OCS is associated with the use of sodium valproate, though the drug was initiated dominantly as mood stabilizer. It has been reported that sodium valproate might be therapeutic for compulsive-like symptoms in patients with autism spectrum disorder,\textsuperscript{12} or in a combination with clomipramine for the treatment of compulsive sexual behaviour.\textsuperscript{13} Of note, another anticonvulsant and mood stabilizer, lamotrigine, has shown efficacy in the treatment of OCS in patients with schizophrenia or schizoaffective disorder,\textsuperscript{14} but also may induce OCS in a dose-dependent manner.\textsuperscript{15} In other words, lamotrigine shows similarity to atypical antipsychotics in a paradoxical relation to OCS. These drugs may be therapeutic, they may also induce OCS. Indeed, the possible association between OCS and anticonvulsants, and especially the possible therapeutic usage of anticonvulsants in patients with OCS, is an under-researched issue.

This case may be illustrative in a number of ways. Firstly, the association of intrusive suicidal obsessions with taking clozapine has not been previously reported. Secondly, though it has been recommended that in cases of OCS associated with atypical antipsychotics a change in antipsychotic medications to those with stronger antidopaminergic
properties and lower 5HT2 receptor affinity should be considered, there is no previous report suggesting that a switch from clozapine to quetiapine might be therapeutic. Finally, we are not able to say that the use of sodium valproate had an important or a negligible influence on the resolution of the patient’s condition, but that option deserves further study.

REFERENCES