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Suicidality in clozapine-treated patients with schizophrenia: Role of obsessive-compulsive symptoms

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ABSTRACT

Patients with schizophrenia have an increased lifetime risk of comorbid obsessive-compulsive symptoms. Up to 30% of these patients experience such symptoms and 12% may be diagnosed with obsessive-compulsive disorder. The presence of these symptoms in schizophrenia seems to be associated with poor outcomes including a greater suicidal risk. A subgroup of patients develops this symptomatology after the initiation with Second Generation Antipsychotics (SGA). Also, there is evidence of a causal relationship for this association, particularly for clozapine. The primary aim of this study was to investigate the association of this comorbidity with suicidality in a population of clozapine-medicated schizophrenic and schizoaffective patients ($N=65$). The prevalence of obsessive-compulsive symptoms in our sample was 29.2% ($N=19$) and the prevalence of obsessive-compulsive disorder was 13.8% ($N=9$). Significant positive correlations between suicidality and total Y-BOCS score and between Y- BOCS score and depressive symptoms were found. Further analysis indicated that a Y-BOCS score greater or equal than 8 was an independent predictor of suicide attempt during clozapine treatment. Routine screening for this adverse event should be warranted for this population.

1. Introduction

Patients with schizophrenia have an increased lifetime risk of comorbid obsessive-compulsive symptoms (OCS). These are characterized by obsessive, distressing, intrusive thoughts and related compulsions (Poyurovsky et al., 2004). Up to 30% of these patients experience OCS and up to 12% may be diagnosed with obsessive-compulsive disorder (OCD) (Swets et al., 2014). Since the prevalence of OCD in the general population has been reported to be 1.6% (Kessler et al., 2005) obsessive-compulsive symptomatology appears more often in schizophrenia than expected. Furthermore, recent large cohort studies reported that OCD patients carry an increased risk for schizophrenia spectrum disorders (Cederlöf et al., 2014; Meier et al., 2014).

Whereas some patients experience OCS onset simultaneously with psychosis onset, others experience OCS onset after the initiation of Second Generation Antipsychotics (SGA) being prevalence rates in later disease stages significantly higher than in the early course of psychotic illness (De Haan, 2015). A recent study found that 13% of at-risk mental state patients reported OCS, while 5.4% fulfilled the criteria for OCD. Slightly higher averaged rates for OCS (17.1%) and OCD (7%) were found in first-episode patients (Zink et al., 2014). These rates are significantly lower than that descripted in cross sectional studies of chronic or late stage, as described above. Additionally, there has been an increase in the prevalence and in the study of this subject over the last 20 years that overlaps with the appearance of SGA in the market (Bleakley et al., 2011).

A review of case reports (Lykouras et al., 2003) describes over 55 cases of de novo development or exacerbation of OCS during treatment with clozapine (30 cases), olanzapine (8 cases), risperidone (16 cases) and quetiapine (1 case). A comparison of schizophrenia patients under antipsychotic monotherapy with either mainly antiserotonergic SGAs (CLZ or OLZ; group I) or mainly dopaminergic SGAs (AMS or APZ; group II) revealed that more than 70% of group-I-patients suffered from OCS while less than 10% of patients in group-II reported OCS (Schirmbeck et al., 2011). Another study reported a prevalence of 28.4% of clozapine-induced OCS in a sample of one hundred and two patients with schizophrenia (Lin et al., 2006). Additionally, there is evidence of a causal relationship between OC symptomatology and treatment with SGA, particularly clozapine. This comes from retrospective cohort studies (Mahendran et al., 2007) and prospective ones (Schirmbeck et al., 2013a). Furthermore, a dose-response pattern (Lin et al., 2006; Schirmbeck et al., 2011) and an association between duration of clozapine treatment and OCS severity (Schirmbeck et al., 2011) have been described. This pharmacological argument based on correlations between OCS severity and

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dosage as well as duration of clozapine application indicate a causal interaction and suggest OCS induction as a side effect of clozapine treatment (Scheltema Beduin et al., 2012). Atypical antipsychotics achieve their effects through preferential occupancy of 5HT2 receptors over D2 (Kapur et al., 1998;1999; 2006). This profile of antiserotoninergic properties is thought to be the cause of the OC symptomatology. Three lines of evidence supports this: first, SSRI drugs alleviate SGA induced OCS (Dodt et al., 1997; Rahman et al., 1998), second, first generation antipsychotics do not cause and even improve OCS (Keuneman et al., 2005) and finally, the disinhibition of the dopaminergic neurotransmission caused by the blockade of 5HT2a receptors is thought to activate the circuits involved in the OC symptomatology as explained by the antiobsessive effects of others SGA characterized by a more antidopaminergic effect (Schirmbeck et al., 2011; 2013a; Schirmbeck and Zink, 2012, 2013).

The presence of OCS in schizophrenia seems to be associated with poor outcomes such as earlier age of onset (Faragian et al., 2012), poorer treatment response (Zink et al., 2014), more depressive (de Haan et al., 2013) and negative symptoms (Owashi et al., 2010) and greater cognitive deficits (Patel et al., 2010; Schirmbeck et al., 2013b). It remains unknown whether treatment for the OCS reverts these outcomes.

Recent studies suggest that OCD and OCS are associated with a greater suicidal risk in patients with schizophrenia. OCD-schizophrenia comorbid patients are more likely to have a previous history of suicidal ideation and attempts. Also, OCS severity is associated with suicidality in adolescents at ultra-high risk for psychosis (Niendam et al., 2009; Sevincok et al., 2007).

There are some controversies regarding the prevalence of this outcome in schizophrenia. While some authors estimated that 10% of persons with schizophrenia will die from suicide (Miles, 1977) other longer-term follow up studies found lower figures. For instance, Inskip et al. (1998) estimated lifetime risk to be 4% for schizophrenia and Palmer et al. (2005) 5.6%. Either way, deliberate self-harm or previous suicidal attempts increase the risk approximately two fold (Nordentoft et al., 2011). Therefore, suicide attempt should be considered a very important risk factor among patients with schizophrenia and other mental disorders, as underlined by the recent findings in a large Swedish cohort study (Runeson et al., 2010). Suicidality is a continuum phenomenon and the probability of making an attempt in a patient with suicidal plans is around 50% (Scocco et al., 2008) and with suicidal ideation 32.3% (Lee et al., 2012). This underlines the importance of the study of non-fatal aspects of suicidality in order to prevent death by suicide.

There is some evidence suggesting that clozapine may have a beneficial effect on suicidality (Meltzer et al., 2003; Thomas et al., 2015; Ringbäck et al., 2014) and even treatment algorithms suggest its use in patients with schizophrenia with associated suicidality (Moore et al., 2007). In addition, this antipsychotic embarks important protective effects against suicidal behavior resulting in lower overall mortality of schizophrenics as documented in the large, naturalistic FIN11-study (Tiihonen et al., 2009).

In general, OCS are neglected by clinicians when comorbid with an acute or chronic psychotic illness. The primary aim of this study was to investigate the association of this comorbidity with suicidality in a population of clozapine-medicated schizophrenic and schizoaffective patients.

2. Methods

2.1. Subjects

The study sample was recruited from the totality of clozapine-medicated patients in the Hospital de Emergencias Psiquiátricas Torcuato de Alvear by September 2014 ($N=98$). Data was obtained from pharmacy and pharmacovigilance program databases. Patients were screened for participation in the present study from September 2014 to January 2015.

Inclusion criteria were: age 18 years or older; DSM-IV diagnosis of schizophrenia or schizoaffective disorder based on the Mini International Neuropsychiatric Interview (MINI); being on treatment with clozapine for 18 weeks or longer. The exclusion criteria were: OCS or OCD previous to clozapine treatment, history of mental retardation, neurological diseases and inability to participate due to severe psychotic symptoms or deafness.

Of the initial 98 subjects, 65 were recruited for the study. The 33-nonincluded subjects either did not met inclusion criteria or met exclusion criteria or refused to participate. 8 patients refuse to provide written consent, 5 patients were under 18 years old, 8 patients presented previous history of OCS/OCD and 5 patients did not meet DSM-IV criteria for a diagnosis of schizophrenia or schizoaffective disorder, 2 patients were mentally retarded, 3 patients were unable to participate due to acute psychotic symptoms, 1 patient was excluded due to neurologic disease and 1 patient was deaf.

The Ethics Committee of the Hospital de Emergencias Psiquiátricas Torcuato de Alvear approved recruitment and assessment procedures. All included subjects provided written informed consent after receiving a complete description of the study.

2.2. Assessment

Interviews were conducted by physicians in a quiet testing room according to a standardized order. The total procedure was done in an interview of 1–2 h with one or two breaks to avoid fatigue. Interviewers were trained and unaware of patient's previous history.

2.2.1. Diagnosis

Diagnoses were confirmed using the MINI-International Neuropsychiatric Interview (Sheehan et al., 1998).

2.2.2. Obsessive-compulsive symptomatology

Subjects were evaluated with the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) in order to measure the severity of OCS. This scale is considered suitable for assessing OCS in schizophrenia (de Haan et al., 2006; Boyette et al., 2011). A cut-off score of 8 was established to determine the presence of OCS as previously used by Schirmbeck et al. (2011; 2013a). In addition, the corresponding section of the MINI was used to assess the presence of OCD. Subjects were asked to respond for symptoms that appeared after the initiation of clozapine treatment. Patients who reported symptoms onset prior to clozapine initiation were excluded from the analysis.

2.2.3. Depressive symptoms

Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1994) was used to identify the presence of depressive symptoms.

2.2.4. Suicidality assessment

Suicidality during clozapine treatment was assessed using the items 102–107 of the Mood Spectrum Self-Report (MOODS-SR) Spanish Version. This scale evaluates whether the subject has ever experienced a period of 3–5 days or more when he or she: (1) felt like life was not worth living; (2) hoped to die; (3) wanted to die; (4) made suicide plans, and two questions asking; (5) whether he/she actually made a suicide attempt and (6) whether medical attention was required following the attempt.

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