Obsessive-compulsive symptoms in schizophrenia during treatment with clozapine an conventional antipsychotic drugs

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Síntomas obsesivo-compulsivos en esquizofrenia durante el tratamiento con clozapina y antipsicóticos clásicos

Summary

Introduction. *We compare the prevalence of obsessive-compulsive symptoms in schizophrenic patients in treatment with clozapine and those who receive classic antipsychotic drugs.*

Method. *Outpatients with schizophrenia treated with clozapine (n = 56) or classic antipsychotic drugs (n = 54) at the Honorio Delgado-Hideyo Noguchi Specialized Institute in Mental Health (Lima-Peru), were evaluated for the presence of obsessive-compulsive symptoms by means of the Obsessive-Compulsive Disorder Module of Structured Clinical Interview for DSM-IV and Yale-Brown Obsessive-Compulsive Symptoms Checklist.*

Results. *46.4 % of patients treated with clozapine presented obsessive-compulsive symptoms while this occurred in 20.4 % of those with classic antipsychotic drugs (*p = *0.005). In addition, 21.4 % of patients with clozapine and 13 % of those treated with classic antipsychotics presented obsessive-compulsive disorder according to DSM-IV criteria (*p = *0.31).*

Conclusion. *In schizophrenic patients, treatment with clozapine is associated with a higher rate of obsessive-compulsive symptoms than treatment with classic antipsychotic drugs.*

Key words: *Obsessive-compulsive symptoms. Obsessive-compulsive disorder. Schizophrenia. Clozapine. Classic antipsychotic drugs*

Resumen

Introducción. *Se trata de comparar la prevalencia de síntomas obsesivo-compulsivos en pacientes con esquizofrenia que reciben tratamiento con clozapina con la de los que reciben antipsicóticos clásicos.*

Métodos. *Se evaluaron pacientes ambulatorios con esquizofrenia en tratamiento con clozapina (n = 56) o con antipsicóticos clásicos (n = 54) en el Instituto Especializado en Salud Mental Honorio Delgado-Hideyo Noguchi (Perú) para determinar la presencia de síntomas obsesivo-compulsivos a través del Módulo de Trastorno Obsesivo-Compulsivo de la Entrevista Clínica Estructurada para el DSM-IV y la Lista de Chequeo de Síntomas Obsesivo-Compulsivos de Yale-Brown.*

Resultados. *El 46,4 % de los pacientes en tratamiento con clozapina presentaron síntomas obsesivo-compulsivos, mientras que esto ocurrió en el 20,4 % de los pacientes en tratamiento con antipsicóticos clásicos (*p = *0,005). Además, 21,4 % de los pacientes que recibían clozapina y 13 % de los tratados con antipsicóticos clásicos presentaron trastorno obsesivo-compulsivo según los criterios del DSM-IV (*p = *0,31).*

Conclusión. *En pacientes esquizofrénicos el tratamiento con clozapina está asociado con una mayor prevalencia de síntomas obsesivo-compulsivos que la terapia con antipsicóticos clásicos.*

Palabras clave: *Síntomas obsesivo-compulsivos. Trastorno obsesivo-compulsivo. Esquizofrenia. Clozapina. Antipsicóticos clásicos.*

INTRODUCTION

The association between obsessive-compulsive symptoms and psychotic symptoms has been recognized for some time. Before the introduction of the Diagnostic and Statistical Manual for Mental Disorders (DSM), several studies had tried to quantify the presence of obsessive-compulsive symptoms in schizophrenia with very different results. However, it must be considered that these studies had a deficiency in regards to psychometric instruments and criteria to define the symptoms clearly[1]. There are few studies available and their methodology varies greatly in relationship with obtaining data, variable control (including medication) and number of subjects. Thus, the very diverse prevalences of obsessive-compulsive symptoms that go from 3.5 to 46 % are not surprising[2,3].

Clozapine is an effective drug in the treatment of patients with psychotic symptoms that are refractory to other antipsychotic drugs or who have severe extrapyramidal symptoms while they are taking neuroleptics. How-

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ever, the emergence or increase of obsessions has been described in patients with schizophrenia or other psychotic disorders during treatment with this atypical antipsychotic drug. A review of the literature has shown contradictory results regarding the association between clozapine and obsessive-compulsive symptoms[3]. Levkovitch et al.[4] described 13 cases of increase in obsessive-compulsive symptoms with the use of clozapine with concomitant improvement of the psychotic symptoms. This suggests a dose-response relationship between clozapine and obsessive-compulsive symptoms as well as a decrease of the latter after the onset of a selective serotonin reuptake inhibitor or after withdrawal of clozapine. Equally, Linszen et al.[5] performed a study in order to examine if the increase in obsessive symptoms was more frequent when clozapine was used than during treatment with other antipsychotic drugs (classic and atypical), finding that 20.6 % of the patients presented an increase or appearance of obsessive symptoms with the onset of clozapine while the value was 1.3 % in those treated with other antipsychotic drugs.

Increase of obsessive-compulsive symptoms with clozapine has been described by other authors, but continues to be controversial. Checking rituals and contamination and sexual content obsessions during treatment with clozapine were observed by Patil[6] and Baker et al.[7] Cassady and Thaker[8] added religious type obsessions to the list. None of these patients had previous backgrounds of obsessive-compulsive symptoms. The drug dose at which the first symptoms appeared varied, ranging from 125 to 800 mg/day; the latency time was also variable (varying from two months to one year of treatment). Some cases presented a correlation between clinical improvement and appearance of obsessive-compulsive symptoms, these disappearing when clozapine was withdrawn and reappearing when it was reintroduced[9].

Evidence suggests that the serotoninergic system is involved in the physiopathological mechanisms of obsessive-compulsive disorder (OCD), given the improvement observed with the use of serotonin reuptake inhibitors and with clomipramine. Furthermore, the efficacy of the dopamine antagonists to potentiate OCD treatment refractory to serotonin reuptake inhibitors and associated to the Tourette syndrome supports the theory of the close relationship between the dopaminergic and serotoninergic system. Serotonergic and dopaminergic blockage converts atypical antipsychotic drugs, especially clozapine, into drugs with a unique profile. It is speculated that an imbalance in serotonin and dopamine transmission would be the cause of the appearance of obsessive-compulsive symptoms, taking into account that these obsessive-compulsive symptoms appeared during drug titration in some of the cases recorded[10]. However, contrary to that mentioned previously, some patients, in whom obsessive-compulsive symptoms and symptoms similar to those of the Tourette syndrome appeared after clozapine use was discontinued and disappeared it was reintroduced, have also been described[10].

Finally, there are no studies that compare the prevalence of obsessive-compulsive symptoms in patients under treatment with clozapine and classic antipsychotic drugs so that it is not clear if the obsessive-compulsive symptoms are related with the clozapine action on the receptors in the central nervous system, are undulations of the natural history of OCD[11] or represent a tendency after the decrease or disappearance of the psychotic symptoms[12]. In addition, the importance that the identification of a schizo-obsessive subtype of schizophrenia would have for the application of effective therapeutic measures (pharmacological, cognitive-behavioral, rehabilitation, etc, is clear)[2].

METHODS

A cross-sectional study was performed in schizophrenic patients who were receiving treatment with clozapine or with some classic antipsychotic drug in the Outpatient clinics of the Adult and Geriatrics Department (AGD) of the Institute Specialized in Mental Health Honorio Delgado-Hideyo Noguchi (ISMH HD-HN) during the months of December 2002 to January 2003.

The subjects included should be diagnosed of schizophrenia based on a clinical history of the ISMH HD-HN, should have given their consent to participate in the study, should not have presented obsessive-compulsive symptoms before the onset of treatment according to the clinical record, should have received antipsychotic treatment regularly when evaluated, should have an attitude of collaboration in regards to the interview and should not have simultaneously taken the combination of clozapine and a classic antipsychotic drug.

The information was obtained by an instrument made up of a demographic sheet, Yale-Brown Checklist of Obsessive-Compulsive Symptoms and Structured Clinical Interview for DSM-IV (SCID) for OCD.

Using the DSM-IV definitions, it was considered that:

- The patient had obsessive symptoms if he/she presented recurrent and persistent ideas, thoughts, images or impulses that the subject considered intrusive or inappropriate and whose content was bothersome and sometimes even shameful for oneself.
- The patient had compulsive symptoms if he/she had repeated behaviors performed according to certain rules or stereotypal forms in order to decrease anxiety, that could be behavior compulsions (observable rituals) or cognitive compulsions (non-observable rituals that occur in the mind of the subject).
- The patient had obsessive-compulsive symptoms (OCS) if he/she had at least one of the two previously mentioned symptom types.

RESULTS

Tables 1 and 2 compare the clozapine treatment group with those patients who received classic antipsy-

TABLE 1. Characteristics of the group with clozapine versus the classic antipsychotic group (numeric variables)

Mean ± SD	*Clozapine (n = 56)*	*Classic antipsychotics (n = 54)*	*p**
Age (years)	30.04 ± 6.69	33.63 ± 10.87	0.04
Onset age (years)	18.54 ± 3.85	25.28 ± 11.78	0.001
Disease time (years)	11.25 ± 7.45	8.46 ± 7.96	0.061
Treatment time (months)	34.66 ± 23.92	32.93 ± 43.17	0.798
Dose (mg)	196.01 ± 96.43		

* Student's *t* test. SD: standard deviation.

chotics. It was found that the subjects with clozapine had significantly lower age, lower age at onset of disease, greater percentage of males, less proportion of mestizo race, more OCS as a whole (OR = 3.48, CI: 1.43-8.50), more obsessive symptoms (OR = 3.48, CI: 1.43-8.50) and more aggressive type obsessions. In addition, a tendency towards a greater percentage of OCD according to the DSM-IV criteria, compulsive symptoms and several types of obsessions and compulsions, among the patients with clozapine, is observed.

TABLE 2. Characteristics of the clozapine group versus the classic antipsychotic group (categorical variables)

	Clozapine (%) (n = 56)	*Classic antipsychotics (%) (n = 54)*	*p**
Men	83.9	66.7	0.046
Mixed race	76.8	94.4	0.013
Obsessive symptoms	41.1	16.7	0.006
Compulsive symptoms	35.7	20.4	0.091
Obsessive-compulsive symptoms	46.4	20.4	0.005
Obsessive-compulsive disorder	21.4	13	0.31
Obsessions			
Aggressive	21.4	3.7	0.008
Miscellaneous	17.9	7.4	0.15
Contamination	16.1	7.4	0.23
Sexual	14.3	5.6	0.20
Symmetry	5.4	5.6	1.0
Somatic	3.6	7.4	0.43
Religious	5.4	0	0.24
Compulsions			
Miscellaneous	17.9	13	0.6
Washing/cleaning	17.9	9.3	0.26
Checking	12.5	1.9	0.06
Repeating rituals	5.4	5.6	1.0
Ordering/arranging	2.4	3.8	1.0
Counting	0	3.8	0.23
Hoarding/saving	2.4	0	0.49

* Chi^2 test.

Table 2 shows the OCS by types, using the Yale-Brown Checklist. In the group with clozapine, the most frequent obsessions were the aggressive, miscellaneous and contamination ones; and the most frequent ones in the classic antipsychotic drugs were contamination, somatic and miscellaneous obsessions. In relationship with compulsions in both the clozapine as well as classic antipsychotic group, the most frequent were washing/cleaning and miscellaneous. The only type of obsessive or compulsive symptoms that showed statistically significant differences between the two groups were the aggressive obsessions (table 2).

Finally, the characteristics of the patients are compared according to whether they have an OCS or not within the clozapine group (table 3) and with classic antipsychotic drugs (table 4). A statistically significant difference was only found in the group with clozapine for the case of treatment time that was longer in the OCS patients than in the individuals without these symptoms. No statistical difference was found in regards to the clozapine dose. Although no statistically significant differences were found in the classic antipsychotic group in any of the variables (table 4), it is important to observe that the OCS patients had younger disease onset age and greater treatment time.

CONCLUSIONS

The present study finds a significantly greater prevalence of OCS and a tendency towards greater prevalence of OCD in schizophrenic patients under treatment with clozapine in regards to those receiving treatment with classic antipsychotic drugs.

It can be stressed that few studies have compared the prevalence of OCS between individuals with clozapine and with other antipsychotics. Linszen et al.[5] found a

TABLE 3. Comparison between patients with obsessive-compulsive symptoms (OCS) and without OCS within the clozapine group

	OCS (n = 26)	*Without OCS (n = 30)*	*p**
Percentage (%)			
Men	92.3	76.6	0.15
Mixed race	76.9	76.6	0.98
Mean ± SD			
Age (years)	30.12 ± 6	29.97 ± 4.34	0.93
Onset age of schizophrenia (years)	18.15 ± 3.82	18.87 ± 3.9	0.494
Disease time (years)	11.57 ± 6.55	10.96 ± 8.26	0.763
Treatment time (meses)	43.46 ± 20.15	27.03 ± 24.61	0.009
Dose (milligrams)	199.03 ± 105.77	193.4 ± 89.6	0.83

* Student's *t* test. SD: standard deviation.

TABLE 4. Comparison between patients with obsessive-compulsive symptoms (OCS) and without OCS within the classic antipsychotic group

	OCS (n = 11)	*Without OCS (n = 43)*	*p**
Percentage (%)			
Men	90.9	60.4	0.055
Mixed race	90.9	95.3	0.5
Mean ± SD			
Age (years)	29.45 ± 6.31	34.7 ± 11.57	0.155
Onset age of schizophrenia (years)	20.64 ± 4.61	26.47 ± 12.77	0.145
Disease time (years)	9.24 ± 6.57	8.26 ± 8.34	0.720
Treatment time (months)	50 ± 55.18	28.46 ± 39.02	0.142

* Student's *t* test. SD: standard deviation.

prevalence of 20.6% obsessive symptoms defined according to the DSM-IV criteria, with the use of clozapine in schizophrenic patients in the first episode. The differences between our results and those of Linszen et al.[5] could be explained by the fact that the disease time and treatment are different. In our study, most of the patients had a prolonged treatment time, which could condition adaptive changes in the receptor profile. In addition, it can be stressed that the patients with clozapine who presented OCS had a greater treatment time with this drug. If a greater treatment time with clozapine favors the appearance of OCS, this would explain the greater prevalence of these symptoms found in our study. Finally, the fact that the diagnoses were performed retrospectively in the Linszen et al[5]. study based on the revision of clinical histories and that the sample had been obtained from hospitalized patients are very important factors to take into account when explaining the differences between the studies.

Another study of Linszen et al.[13] in hospitalized patients with recent onset of schizophrenia and other psychotic disorders finds a prevalence of 30 of OCS and 15% of OCD in patients treated with olanzapine or risperidone, values inferior to those found in individuals with clozapine (46.4 and 21%, respectively). The mentioned study found greater intensity of OCS in those who received olanzapine than in those treated with risperidone. It may be mentioned that the difference in regards to intensity was related with the treatment period, however, the short exposure time to the drugs does not make it possible to generalize these findings.

Increase or appearance of OCS in patients with schizophrenia who receive clozapine could be related with the interactions between serotonin and dopamine, especially the proportion in the 5-HT2/D2 antagonism. The relationship in the 5-HT2/D2 blockade of clozapine is two times greater than that of risperidone, which could explain the greater rate of OCS observed in the patients who take clozapine, in relationship with that found in patients with olanzapine and risperidone[1].

However, the proportion of 5-HT2/D2 antagonism alone cannot completely explain the phenomenon. It is interesting to mention that long term treatment with clozapine may result in supersensitivity due to denervation of the 5-HT2c receptors. These receptors are found in high concentrations in the basal ganglia and, considering the importance of these structures in the OCD, it would be possible to try to explain the presence of the OCS also in relationship with this subtype of receptors[1,14].

On the other hand, in our study, no relationship is established with the clozapine dose. Some case registers report a tendency to the decrease of OCS with a decrease in the clozapine dose, without clearly establishing the validity of this statement; however, other proposals would indicate that the antagonist activity on the serotoninergic receptors at low doses of clozapine may induce OCS and that the antidopaminergic activity would be more prominent than high doses and may counteract the antiserotoninergic activity[14].

The study carried out by Baker et al.[7] in 25 schizophrenic patients did not find any differences between the olanzapine and placebo group in regards to the presence of OCS in spite of the potent 5HT-2 antagonism that this drug also has. The absence of this association would be due to the fact that the 5HT-2 antagonism would not be sufficient or be the only reason for the appearance of OCS, given the probable high coexistence between these symptoms and schizophrenia[2,3,14,16]. On the other hand, the physiopathology of the obsessive-compulsive symptoms has not been completely defined and the 5HT-1c and 5HT-2 antagonism presented by the different atypical antipsychotic drugs differs considerably in regards to their strength and sites of impact in the central nervous system. In addition, the action could be due to a dose-dependent effect and, in the case of the Baker et al. study, sufficient dose or time may not have been reached for the OCS to occur[7]. Furthermore, these symptoms seem to have continuity with the psychotic symptoms and thus are difficult to distinguish. The scales to measure OCS were not designed for or extensively used for schizophrenic patients, so that they may not be optimum, it not being ruled out that there is an association between the use of olanzapine and the appearance of OCS[7].

It is important to take into account that the prevalence of OCD in our study in the clozapine group (21%) was greater than in the classic antipsychotic group (13%), although without a statistically significant difference. On the other hand, these values are found in the range of the OCD rate in schizophrenia of other studies that use the same diagnostic criteria but that do not take the treatment into account. For example, the studies performed by Poyurovsky[3], Poyurovsky et al.[2], Tibbo et al.[14] and Porto et al.[16] find, respectively, that 14%, 23.5%, 25% and 26% of patients with schizophrenia fulfill the criteria for OCD. As we can see, the findings observed using the same diagnostic criteria present similarities, and the type of patient interviewed (mainly out-patient vs. hospitalized), disease time and type of antipsychotic drug received

(classic vs. atypical) may be able to explain the differences.

In relationship to the type of OCS found, these seem to have a similar pattern to those of persons with OCD wi-thout schizophrenia in the Kozak study[17], as well as to those of the schizophrenic patients in the Porto et al.[16] and Poyurovsky et al.[2] studies, the latter studies using the Yale-Brown Obsessive-Compulsive Symptoms Checklist. The three studies mentioned found aggressive, contamination and sexual obsessions together with checking, washing/cleaning and rituals in the first place, findings more or less similar to those of our study. In the group with clozapine, the aggressive obsessions were the most frequent and had a significantly greater proportion than in the classic antipsychotic group, which could reflect a relationship between this type of obsessions and delusions of the patients treated with clozapine[16].

The OCD study in schizophrenia represents a field having great interest from the clinical, pharmacological and biological point of view. Construction of a clear theoretical framework continues to search for the best diagnostic methods and treatment strategies. This would help to answer the questions on whether the obsessive-compulsive symptoms in schizophrenia may be considered a subclass of schizophrenia, the effect of the antipsychotic treatment or only a reflection of two comorbid psychiatric diseases. Future research in these areas should include search for more appropriate scales, use of different tools such as neuroimaging studies, familial studies and pharmacological research, in order to verify and explain the findings of this and other studies.

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