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Comorbidity between obsessive-compulsive disorder and schizophrenia: Prevalence, explanatory theories, and nosological status

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ABSTRACT. This theoretical study reviews the main findings and research on comorbidity between obsessive-compulsive disorder (OCD) and schizophrenia. On the one hand, it is argued that high prevalence of comorbidity implies common risk factors (neuroanatomical and neuropsychological correlates) and a causal relationship between these mental illnesses, OCD usually preceding schizophrenia. On the other hand, independent nosological status of this "comorbidity" is supported on the basis of several external criteria (negative symptomatology, depressed mood, psychosocial impairment, neurobiological and neuropsychological correlates), which distinguish this mixed clinical entity from OCD and schizophrenia separately. These conclusions are discussed, considering the lack of recognition of "schizo-obsessive disorder" within the current diagnosis reference manuals.

Key words: Schizo-obsessive disorder, Schizophrenia, Obsessive-compulsive disorder, Comorbidity, Theoretical study

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Comorbilidad entre trastorno obsesivo-compulsivo y esquizofrenia: prevalencia, teorías explicativas y estatus nosológico

RESUMEN. En el presente estudio teórico se revisan los principales hallazgos e investigaciones sobre la comorbilidad entre trastorno obsesivo-compulsivo (TOC) y esquizofrenia. Por una parte, se señala que la alta prevalencia de esta comorbilidad obedece tanto a factores de riesgo comunes (correlatos neuroanatómicos y neuropsicológicos) como a una relación causal entre ambas patologías mentales, precediendo generalmente el TOC a la psicosis. Por otro lado, se sostiene el estatus nosológico independiente de esta comorbilidad sobre la base de diversos criterios externos (síntomatología negativa, humor depresivo, disfuncionalidad psicosocial, correlatos neurobiológicos y neuropsicológicos), los cuales diferencian esta entidad clínica mixta de la esquizofrenia y el TOC por separado. Dichas conclusiones son discutidas considerando la falta de reconocimiento nosológico del denominado "trastorno esquizo-obsesivo".

Palabras clave: Trastorno esquizo-obsesivo, Esquizofrenia, Trastorno obsesivo-compulsivo, Comorbilidad, Estudio teórico

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INTRODUCTION

The association between obsessive-compulsive disorder (OCD) and schizophrenia are far from being a recently observed phenomenon. Even though the first references go back to the end of the XIX century,¹ it was not until the first third of the XX century that the idea of this link was consolidated. In said context, it was postulated that the obsessive-compulsive symptoms are part of the prodromic phase of psychoses,^{2,3} acting as "neurotic defense" in line with its incipient irruption.⁴ During the 1960's and 1970's, interest decreased in this area of study, mainly when considering a hardly prevalent psychopathological phenomenon in the registry of cases implemented.⁵ With the coming of the DSM-III (1980), empirical investigations were begun. These questioned the low prevalence of this comorbidity and the idea that the obsessive condition "protected" against psychosis.⁶ Equally, the previous psychopathological models became flexible, accepting the thesis that some cognitions could fluctuate longitudinally between intrusive and delusional.⁷ Beginning in the 1990's, sensitivity towards this subject increased, partially after observing that atypical neuroleptics induced obsessive-compulsive symptoms in schizophrenic subjects.⁸ During this same period, similar terms were coined, such as "delusional OCD,"⁹ "obsessive delusions"¹⁰ or "schizo-obsessive."¹¹ Since the beginning of the XXI century and up to the present time, scientific literature has been oriented towards the validation of a new clinical condition called "Schizo-obsessive disorder,"¹² promoting its inclusion in a nosological continuum whose extremes are represented by schizophrenia and OCD.¹³

METHODOLOGY

In this general historical context, the main objective of this present review has been to offer an updated descriptive framework of the most important empirical evidence in relation to the association between OCD and schizophrenia. To do so, a bibliographic search was made within PubMed including the period between 1980 and March of 2012. The following keywords were used: *schizophrenia AND obsessive-compulsive disorder; schizo-obsessive; psychotic AND obsessive-compulsive disorder*. The investigations collected were re-grouped on the basis of three fundamental areas of study, that is: 1) prevalence of comorbidity, 2) explanatory theories of the OCD-schizophrenia association and 3) nosological status of said comorbidity.

PREVALENCE OF THE COMORBIDITY BETWEEN OCD AND SCHIZOPHRENIA

The first cardinal issue in the study of comorbidity between OCD and schizophrenia speaks about the prevalence

of this association. Specifically, an important part of these investigations seeks 1) to determine the magnitude of said comorbidity and 2) to know if its ratio is greater than that expected by pure chance (general population). To this end, empirical studies were performed in *community and clinical samples*, there being methodological differences that condition the generalization of the findings obtained. Among these procedural limitations are the conceptualization per se of the obsessive symptom, since one part of the studies analyzed used the DSM-IV diagnostic criteria to define it (OCD), while other investigations have considered the presence of prominent obsessive-compulsive symptoms (OCS) on the basis of the scores reached on scales, regardless of whether the symptom was independent or not of the psychotic pathology.

In regards to the research in *community samples*, it is argued that the prevalence of this comorbidity in subjects with a primary diagnosis of schizophrenia is 12%.¹⁴ This is important because the prevalence of OCD in the general population is 0.8-2.5%.¹⁵ On the other hand, when the presence of prominent obsessive-compulsive symptoms (OCS) is considered in this population, the "comorbidity" found increases up to 25%.¹⁶ This proportion of psychotic subjects with OCS is similar to that found in the entire population (21-24%).¹⁷ Thus, the findings in community samples indicate that the having schizophrenia increases the risk of suffering OCD (versus OCS) with a likelihood ratio equal to 5.0-6.0.

In regards to the prevalence studies in *clinical samples*, those performed in subjects with a primary diagnosis of schizophrenia should be distinguished from those that have been implemented in OCD samples, the former being much more frequent. Regarding the studies in *psychotic samples*, the prevalence of this "comorbidity" ranges from 25-40% when OCS is evaluated,¹⁸⁻²⁰ but it is reduced to 14-26% if OCD is diagnosed.^{10,21-24} As a whole, no significant differences have been observed in the prevalence of this comorbidity when comparing psychotic patients 1) from community samples versus hospital ones, 2) evaluated in different periods of evolution of the disease ("primary episodes" versus "chronic" patients) or 3) with diagnostic criteria of disparate laxity ("schizophrenia" versus "psychotic spectrum").²⁵⁻²⁷ However, different prospective studies in schizophrenic patients indicate that the comorbid obsessive condition is reduced or fluctuates during the longitudinal course of the psychosis,²⁸⁻³⁰ this being seen in only half the patients (7-11%) after five years of follow-up.³¹ The latter findings do not exclude the therapeutic effect derived from the psychotropic treatments administered. In regards to the studies in *OCD samples*, the prevalence of schizophrenia is in the interval between 1-5%.³²⁻³⁴ It should be stated that most of the investigations in this clinical population have been aimed at determining the presence of schizotypal traits of the personality, this comorbidity being found in 15-35% of this population.³⁵

In conclusion, the comorbidity between OCD and schizophrenia is, on the average, 12-15% of the patients with a primary diagnosis of psychotic spectrum, this prevalence being six times greater than that expected in the general population.

EXPLANATORY THEORIES OF THE ASSOCIATION BETWEEN OCD AND SCHIZOPHRENIA

Over the last century, different etiopathogenic mechanisms have been proposed to explain the association between OCD and schizophrenia. In relation to the concept of comorbidity, mainly two explanatory models have been postulated: 1) the possibility that *one disorder is a risk factor for another one* and 2) the assumption of some *common risk factors* for both mental disorders. In addition, from an evolutionary perspective, the hypothesis has been formulated that 3) the OCD may constitute an integral part of the *psychotic prodrome*, this remitting once it reaches a peak. Finally, different empirical investigations have been carried out with schizophrenic subjects in order to determine if 4) the obsessive pathology could appear *or become exacerbated* by the *administration of neuroleptics*.

OCD as psychotic prodrome

The traditional theoretical approach in relation with the association between OCD and schizophrenia is represented by the hypothesis of OCD as a *psychotic prodrome*. Even though this hypothesis has been extended up to date uncritically, some empirical investigators have recently been performed in order to elucidate the role of the OCD as a psychotic prodrome. To corroborate this theory, two conditions must be met: 1) the subjects with psychotic vulnerability must have a high prevalence of OCD and 2) this obsessive symptomatology should remit (versus persist) more among those subjects in whom the psychotic process finally becomes established. In relation to the first premise, it has been possible to determine cross-sectionally that 20% of the subjects with ultra-high risk for psychosis (UHRP) have OCD.^{36,37} However, in the single long term prospective study (seven years), a greater likelihood of suffering psychosis between those patients with UHRP and those in whom the OCD subsequently remitted was not observed.³⁸

In conclusion, there is preliminary empirical evidence to justify that the obsessive-compulsive symptom is found in one fifth of the subjects with psychotic vulnerability, but that it does not act as a prodrome of a later schizophrenic process.

A disorder as a risk factor of another one

Within the area of research on comorbidity between OCD and schizophrenia, one of the main lines of study is

about the possibility that *one of the disorders could become a risk factor for another one*.

Regarding this hypothesis, most of the investigations have been aimed at determining the role of OCD as a potential risk factor for schizophrenia. To corroborate this condition, two premises must be met: 1) the OCD usually must precede the psychosis and 2) it must persist (versus remit) more among those subjects who finally develop a psychotic process. For this purpose, two types of samples have been considered. First, patients with UHRP evaluated prospectively. Second, subjects with both conditions already established, which are analyzed retrospectively. Regarding the studies in persons with psychotic vulnerability (UHRP), the results indicate a biphasic effect, that is less risk of suffering psychosis in the mid term (one year) if in the initial evaluation the subject is diagnosed of OCD,³⁶ but a greater likelihood of developing a psychotic process in the long term (seven years) if the obsessive condition persists or has an impact.³⁸ Regarding the studies with samples of "mixed" patients (comorbidity OCD-schizophrenia), the retrospective analyses are relatively conclusive, it having been observed that the obsessive-compulsive pathology generally precedes psychosis.^{24,39-43}

In conclusion, there is empirical evidence to propose that the persistent obsessive-compulsive symptoms constitute a risk factor for schizophrenia, exercising its influence in an unclear way or delayed after an apparent protector effect during the initial course.

Factors of common risk

Notwithstanding if one disorder can become a risk factor of another, another thesis hypothesizes about whether the comorbidity between schizophrenia and OCD is related with the presence of *common risk factors*, that is, third variables similar to both conditions. To this end, many empirical investigations have been undertaken which, as a whole, can be included in three basic areas: *neuroendocrinology*, *neuroanatomy* and, finally, *neurocognition*. Methodologically, two types of sampling procedures have been considered to corroborate if there are similarities between OCD and schizophrenia. On the one part, investigations in which control subjects versus schizophrenics versus persons with OCD are directly compared. On the other part, "independent" studies that compare a control group either with OCD patients or with schizophrenic subjects.

Neuroendocrinology

In the field of *neuroendocrinology*, most of the studies implemented are "independent" and have used serotonin, dopamine and glutamate as the main neurotransmitters

involved. The etiopathogenic approaches postulated have largely come from the response seen to the psychopharmaceuticals administered.

Regarding serotonin, the findings in OCD samples suggest a deficit,^{44,45} while in schizophrenia, it is suggested that there is an increase of its production in the prefrontal cortex.⁴⁶ Regarding dopamine, it is suggested that there is a dopamine excess in the basal ganglia of subjects with OCD.⁴⁷ In contrast, in patients with schizophrenia, bimodal distribution is observed, that is, an increase in the mesolimbic pathway and a deficit in the prefrontal cortex.^{48,49} Finally, in regards to glutamate, an excess of it is supported in the caudate and prefrontal cortex in subjects with OCD,^{50,51} while a deficit in the prefrontal deficit is postulated in psychotic patients.⁵²

As a whole, all the findings presented refute the idea that OCD and schizophrenia share a similar neuroendocrine dysfunction. In fact, they manifest some neuroendocrine correlates or functioning that are relatively incompatible, considering the serotonin/dopamine ratio, above all on the level of the post-synaptic receptors (5-HT)₂/D₂.⁵³

Neuroanatomy

In regards to the *neuroanatomy*, there are "independent" and "comparative" studies whose main areas of interest are the prefrontal cortex and different subcortical nuclei (caudate nucleus, thalamus, hippocampus and cerebellum).

Regarding the prefrontal cortex, hyperactivation of the orbitofrontal cortex in the OCD⁵⁴ and hypoactivation of the dorsolateral cortex in patients with schizophrenia⁵⁵ are postulated. Regarding the caudate nucleus, hyperactivation has been found in OCD subjects,⁵⁶ while involvement of the dorsolateral area has been suggested in patients with schizophrenia.⁵³ In relation with the thalamus, evidence indicates that there is hypoactivation in both conditions,^{57,58} and less asymmetry of the pulvinar area.⁵⁹ Greater deformity of the anterolateral area has also been found in OCD subjects and of the posteromedial area in persons with schizophrenia.⁵⁹ Regarding the hippocampus, both disorders show bilateral reduction.⁶⁰ In addition, patients with OCD have an enlargement of the left amygdala.⁶⁰ Finally, another structure evaluated is the cerebellum and there are preliminary findings to support the existence of a cerebellar dysfunction in both conditions.^{56,61}

In conclusion, both conditions show abnormalities in the fronto-striatal structures and circuits, with noticeable convergence regarding the thalamic alterations. On the other hand, similar structural dysfunctions have been found in the hippocampus and cerebellum. These findings suggest a cerebral aberration common to OCD and schizophrenia.

Neurocognition

In regards to the *neurocognitive* functioning of patients with OCD and schizophrenia, given the enormous literature on the subject, only "comparative" studies on OCD versus schizophrenia (versus controls) were selected. The main functions evaluated were: visual/auditory memory, visuospatial skills, processing speed and different executive competencies (verbal fluency, working memory and inhibition of response).

Regarding visual/auditory memory capacity, both conditions show a deficit, although its intensity is greater in schizophrenic patients.^{44,62} Regarding visuospatial skills, there were hardly any differences between both disorders, although one study found that patients with OCD had better performance than control and schizophrenic patients in tasks that implied said skill.⁶² Regarding processing speed, both conditions entail a deficit, this deviation being greater in schizophrenic patients.^{44,62} In relation to working memory, the results indicate that this function is damaged in subjects with schizophrenia, but not in patients with OCD.^{44,63} Finally, regarding response inhibition, both patients with OCD and with schizophrenia manifest less performance in the tests implemented.^{63,64}

In conclusion, both conditions have deficits in memory capacities and in various frontal functions (processing speed, verbal fluency and inhibition of response). As a whole, the neurocognitive differences between OCD and schizophrenia are quantitative, there being greater intensity of these limitations in schizophrenic subjects. On the contrary to the traditional approach,⁶⁵ the comparative studies rule out that the executive deficits are specific for each disorder, except for working memory.

In summary, regarding the hypothesis of the common risk factors, there are neuroanatomic correlates (frontostriatal, hippocampus and cerebral) and neuropsychological ones (memory and frontal functions) that are similar for both conditions, suggesting the possibility that there is a similar neurobiological dysfunction.

Neuroleptic induced OCD

A more recently developed line of research is related with the possible *inducement or exacerbation of the obsessive symptoms with the administration of antipsychotics*. Up to now, different investigations have been carried out with typical neuroleptics, observing the anti-obsessive properties of haloperidol as coadjuvant in the treatment of refractory OCD patients.^{66,67} However, the atypical neuroleptics have caused greater controversy given their particular pharmacodynamics in comparison with their traditional homologues. For this reason, several cross-sectional and prospective studies with psychotic subjects

have been implemented, evaluating the risk of presenting obsessive symptoms with the prescription of an atypical neuroleptic versus another antipsychotic (or placebo). It should be mentioned that there are methodological differences that condition the generalization of these results, above all because the patients of prospective trials (versus cross-sectional-retrospective) are monitored with lower doses of antipsychotics during shorter evaluation periods (duration of treatment).

Regarding amisulpiride, there is a single prospective study that states its anti-obsessive capacity.⁶⁸ In regards to risperidone, there is one prospective trial that indicates an anti-obsessive tendency,⁶⁹ and two other comparative investigations that corroborate a greater anti-obsessive effective in comparison to olanzapine.^{29,70} The findings for olanzapine are divergent. On the one hand, there is an important pro-obsessive capacity in the cross-sectional studies in which it is compared to clozapine.⁷¹⁻⁷³ On another hand, there is an absence of clinical significance in the only prospective study implemented.⁷⁴ Finally, in regards to clozapine, there is a frank pro-obsessive tendency, that is observed more in the cross-sectional studies^{75,76} than in the prospective ones.⁷⁷

In conclusion, both clozapine and olanzapine are two atypical neuroleptics with special pro-obsessive potential. In comparison with other antipsychotics, their greater inductor capacity has been related with a more notorious antagonistic affinity on the serotonergic receptors (5-HT)_{2A}.⁷⁸⁻⁸⁰ On the other hand, the differences found between prospective studies versus cross-sectional-retrospective ones suggest that the pro-obsessive potential of both psychopharmaceuticals is modulated by the treatment dose and duration. In this way, higher doses increase the antagonistic affinity on the receptors (5-HT)_{2A},⁸¹⁻⁸³ while longer treatments cause increasing regulation in the expression of these receptors.^{29,73,77}

NOSOLOGICAL STATUS OF THE COMORBIDITY BETWEEN OCD AND SCHIZOPHRENIA

The findings presented on prevalence and etiopathogeny have been giving rise to an incipient controversy in relation with the *nosological status* of these patients with comorbidity. Different empirical investigations, mostly cross-sectional, have been carried out within this context. These have aimed to determine if there are differences between schizophrenic and "schizo-obsessive" subjects, including on rare occasions a third comparative group of patients with OCD. Parallel to this question, two lines of additional debate have been developed. The first, in regards to the possibility that this "mixed" psychopathology constitutes a clinical entity having a *good or bad prognostic/adjustment* compared to "pure" psychosis. The second, on

the likelihood of suggesting several "*schizo-obsessive*" subtypes of subjects based on the criteria adopted to evaluate the obsessive symptoms (OCD versus OCS).

In said context, the general objective of this section is to offer a descriptive framework of the main findings. To do so, the results have been divided on the basis of three external criteria: *psychopathological characteristics* (psychotic symptoms, obsessive-compulsive symptoms and depressive mood); *course and functionality* (age at onset, psychosocial dysfunctionality and re-hospitalizations); *neuropsychological and neuroanatomical correlates*.

Psychopathological characteristics

In regards to the *psychotic symptoms*, no consistent significant differences were found between productive symptoms and *insight* of subjects with schizophrenia versus "schizo-obsessive" ones.^{20,21,27,31,40,84,85} Regarding negative symptoms, differences have been found between schizophrenic and "schizo-obsessive" subjects, although these findings are modulated by the characteristics of the "mixed" group. In this way, when the "schizo-obsessive" subjects have comorbidity with OCS, it has been seen that these patients generally have more negative symptoms.^{26,86-89} On the contrary, when "mixed" patients with OCD are considered, no significant inter-group differences have been observed.^{22,25,27,31,41,42,84} In order to elucidate this question, more ambitious studies have directly compared "mixed" patients with OCS versus OCD, adding more confusion on finding that patients with OCD comorbidity generally have more negative symptoms than those with OCS.^{23,30,76} Independently of this, these discrepancies indicate that the characteristics per se of the obsessive condition modulate the impact this has on the negative symptoms.

Regarding the *obsessive symptoms*, no significant differences have been observed between "mixed" patients versus "pure" OCD, both in severity/content of the obsessions-compulsions,^{34,35,90,91} as in *insight* of said symptoms.^{91,92} However, a study found greater *insight* on the intrusive ideas in "schizo-obsessive" subjects.⁹⁰

Finally, in regards to *depressive symptoms*, there is consensus on stating that "mixed" patients have more depressed mood^{19,30,31,40,42} and parasuicidal behaviors^{31,71} than psychotics without comorbidity. This tendency is replicable even when a third comparative group with "pure" OCD is added.⁹¹ The consistency of these results pose the role of the neuroendocrine correlates similar to OCD and depression (low levels of serotonin and high levels of glutamate), which could provide an explanation for this overlapping.⁹³

In conclusion, from a psychopathological point of view, there are significant differences between "schizo-obsessive" and "pure" schizophrenic patients, the former showing

greater depressive and negative symptoms, the latter finding being more associated to "mixed" patients with OCD (versus OCS).

Psychosocial course and functionality

Regarding *age of onset of the psychosis*, no conclusive data are found when comparing "mixed" patients and schizophrenics without comorbidity. On the one hand, some investigations indicate an early debut of the psychotic process in "schizo-obsessive" subjects.^{6,23,24,43,41,94} On another hand, different studies have not found inter-group differences.^{26,39,91} As a counterpoint, in regards to *age of onset of the obsessive-compulsive symptoms*, an earlier onset has also been shown in "mixed" patients compared to persons with "pure" OCD.^{32,90}

In regards to the *grade of psychosocial dysfunctionality*, wide consensus exists when stating that "schizo-obsessive" subjects have worse psychosocial functioning than "pure" psychotics.^{20,23,25,64,87,91,95} above all if they have comorbidity with OCD (versus OCS).³¹

Regarding *number and duration of the re-hospitalization*, the results are not totally consistent. Different investigations indicate that the psychiatric admissions are longer in "mixed" patients than in subjects with "pure" psychosis,^{87,94} above all if there is comorbidity with OCD (versus OCS).²⁴ However, other recent studies indicate that there are no inter-group differences in the number and duration of the re-hospitalizations.^{31,40,91}

In conclusion, there are significant inter-group differences in the psychosocial course and functioning, the "schizo-obsessive" patients manifesting an earlier onset of the psychopathology and greater psychosocial interference. In general, the impact of the obsessive symptoms on the daily functioning of the "mixed" subjects is more negative in presence of OCD (versus OCS).

Neuropsychological and neuroanatomic correlates

Regarding the *neuropsychological correlates*, there are many comparative studies regarding different neurocognitive capacities, that is, selective and sustained attention, visual/auditory memory, visuospatial skills and different executive functions (verbal fluency, working memory and inhibition of response). Regarding selective attention, no differences have been found between "pure" and "mixed" psychotic patients.^{20,96} Regarding sustained attention, "schizo-obsessive" patients have worse functioning than their counterparts without comorbidity.^{64,88} In the visual/auditory memory setting, no conclusive results have been found in relation with possible inter-group differences.^{64,88,96,97} Regarding visuospatial skills, "mixed" subjects have greater

capacity than "pure" schizophrenics, at least during the initial stage of the psychosis.^{96,97} In relation with verbal fluency, there are no consistent results in one direction or another.^{20,97} Regarding working memory, there is a biphasic response in "mixed" patients: better performance than the "pure" schizophrenics during the first years of evolution of the psychosis, but a decreased improvement of said capacities when they become chronic.^{64,87,88,96-98} Finally, in relation with inhibition of response, the studies tend to indicate worse functioning in "mixed" subjects.^{64,99-101} It can be stated that when a third "pure" OCD group is included in these comparative studies, the "pure" group has always manifested greater performance than both samples of psychotics in all the functions evaluated.^{64,96,98}

In the setting of *neuroanatomy*, there are investigations which, mainly using functional and structural neuroimaging techniques, have compared "pure" and "mixed" psychotic patients in different cortico-subcortical structures. Regarding the frontal lobe, it has been found that the size of this area in "schizo-obsessive" subjects, on the contrary to the "pure" schizophrenics, is inversely proportion to the duration of the psychosis.⁸⁶ Likewise, activation of the left dorsolateral cortex shows a negative relation with intensity of the obsessive-compulsive symptoms.¹⁰² Regarding the hippocampus, a smaller size has been observed in "mixed" patients during the initial stage of the psychoses.⁸⁶ Regarding the ventricles, enlargement has been observed in "schizo-obsessive" patients with few years of evolution of the disease, both in comparison with psychotics^{103,104} as in "pure" OCD subjects.¹⁰⁵ In regards to the striate, there is indirect evidence that suggests greater dysfunctionality of the basal ganglia in "schizo-obsessive" patients, mainly due to the presence of more induced abnormal movements^{16,83,106} and non-induced movements^{22,39,83} due to neuroleptics in said subgroup. Finally, no conclusive inter-group differences have been obtained with the neuropsychological batteries evaluating capacity of motor sequencing in relation to the cerebellum.^{47,107,108}

In conclusion, "mixed" patients generally show worse neurocognitive functioning than the "pure" psychosis, mainly in sustained attention, inhibition of response and working memory. However, the impact of the obsessive symptoms are conditioned by the years of evolution of the psychosis and it is possible that this has a neuroprotective effect during its initial stages. Regarding the neuroanatomical correlates, the "schizo-obsessive" patients show distinctive functional and structural alterations that affect the frontal cortex, striate, hippocampus and ventricles in a greater degree.

CONCLUSIONS

The present theoretical study has aimed to review the main empirical findings and relationship to the comorbidity between OCD and schizophrenia. Many investigations in

samples of psychotic patients indicate that there is an estimated co-occurrence between both disorders of 12-15%,^{14,23,24} this being reduced to half in the long-term follow-up.³¹ In relative terms, this prevalence is much greater than is expected by pure chance. The likelihood of having OCD in the general population is observed to be six times greater if the subject has been previously diagnosed of schizophrenia or another condition within the psychotic spectrum (e.g., disorder or schizoaffective disorder).

Faced with this elevated prevalence, different hypotheses have been proposed as explanatory mechanisms, mainly that 1) one disorder is predisposing to another one and that 2) there are third variables common to both conditions. Regarding the first question, it has been found that persistent obsessive symptoms act as a risk factor for psychosis in subjects with UHRP, having an unclear or "delayed" effect after an apparent short term protective effect.^{36,38} These results would suggest the adequacy of implementing prophylactic treatments with this type of "poor prognostic" patients. In regards to the second question, there are different neuroanatomical and neuropsychological correlates that are common to both conditions,^{44,59,60,62} this suggesting a similar cerebral aberration. In spite of these findings, the neuroendocrine mechanisms from which two such different disorders interact on that level must be clarified.¹⁰⁹

In regards to the differential diagnosis, a source of spurious comorbidity is related with the potential iatrogenic action of clozapine and olanzapine,^{76,77} especially at elevated doses and/or prolonged prescription.^{80,83} This possibility should be studied in those subjects in whom the obsessive symptom begins after the psychosis. In this frame, a promising line of research would be regarding the treatment of the neuroleptic induced obsessive condition,¹¹⁰ a subject of great importance considering the cost-benefit ratio of maintaining clozapine in a refractory psychotic patient. Up to now, there is only one control-placebo prospective study indicating that incorporation of aripiprazole is effective in the treatment of iatrogenic obsessive symptoms.¹¹¹ On the other hand, trials with electroconvulsive therapy should be promoted in order to determine its therapeutic efficacy.¹¹²

On the basis of the epidemiological and etiopathogenic advances, many studies have been designed to evaluate the nosological status of this comorbidity. For this end, "mixed" patients have been compared with schizophrenia and/or "pure" OCD patients.^{20,23,64,91,95} In the former, it was found that they had 1) more negative symptoms, 2) greater depressive mood, 3) higher level of psychosocial dysfunctionality, 4) early onset of the psychopathology, 5) more neuroanatomical dysfunctions from the onset of the disease and 6) some neurocognitive capacities that deteriorated more when the psychosis becomes chronic. As a whole, all the empirical evidence supports a newly created

diagnostic entity called "schizo-obsessive disorder,"¹¹³ constituting a nosological construct of worse adjustment and prognosis than the "pure" OCD and psychoses. In spite of these findings, there are still some questions to be clarified in relation to the distinctive characteristics of the "schizo-obsessive" patients. The most important one lies in the *differential response* to the psychopharmacological interventions, a variable that has not been considered in any prospective comparative trial. Up to now, the therapeutic research in "schizo-obsessive" patients has been oriented towards treatment of the comorbid obsessive symptoms, for which a significant decrease has been obtained through the use of antidepressants,^{94,114} antipsychotics,¹¹⁵ mood stabilizers^{93,116} and, exceptionally, by the use of electroconvulsive therapy^{117,118} and deep brain stimulation.¹¹⁹ In this decision tree, the use of antidepressants as drugs of first choice should be reconsidered when evaluating if the psychotic symptoms could be exacerbated by their administration.¹²⁰

Finally, there is an emerging debate on the possible existence of several subtypes of "schizo-obsessive" subjects. To this end, "mixed" patients OCD versus OCS have been compared, finding differences both from a functional point of view as well as on the clinical severity/prognostic one. In relation to the first variable, the cross-sectional evidence (correlations) in OCS samples suggest that the obsessive symptoms tend to be associated to the psychotic symptom so that a functional relation is established between both types of psychopathology (e.g. more compulsive washing in the face of a more intense delusion of infestation).^{20,71,121} On the contrary, the "mixed" subjects with OCD manifest obsessive symptoms independent of the psychotic one.^{31,41,122} In regards to the second criterion, there are different findings that confirm that the comorbidity of OCD (versus OCS) is an indicator of greater psychopathological and psychosocial severity.^{23,24,30,76} As a whole, these differences between subtypes open the question on whether the OCS (versus OCD) symptoms could be a sort of coping or adaptation mechanism to cope with the psychotic symptoms.

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