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Anxiety, Obsessive Compulsive, and Related Disorders (B Brennan and D Dougherty, Section Editors)

Schizo-Obsessive Disorder: the Epidemiology, Diagnosis, and Treatment of Comorbid Schizophrenia and OCD

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Opinion statement

Schizophrenia and obsessive–compulsive disorder (OCD) appear to share clinical features and tend to co-occur more commonly than would be expected by chance. Obsessive–compulsive symptoms (OCS) are commonly observed in schizophrenia. Large-scale follow-up studies are needed to probe this intriguing relationship and to examine the diagnostic stability of the subgroup of patients, who present with features of both. In addition, there is a need for valid and reliable diagnostic instruments in this population. Treatment of schizo-obsessive patients is a challenging endeavor. Though the evidence base is small, patients with schizophrenia and co-occuring OCS are clinically challenging, as their response to traditional treatments can be unusual. Typical antipsychotics are seldom used to treat schizo-obsessive patients owing to their limited serotonergic properties and heightened sensitivity to motor side effects. Evidence points toward a potential bidirectional effect of atypical antipsychotics (improvement and worsening) on OCS in schizophrenia patients. Compared with risperidone and clozapine, olanzapine may show more ameliorating effects on both OCS and schizophrenic symptoms, while aripiprazole has shown a meaningful clinical improvement of OCS in schizophrenia patients. Second-generation antipsychotics may be effective as monotherapy, but a combination with antiobsessional agents is usually required. Cognitive–behavioral therapy,

electroconvulsive therapy, and other nonpharmacological interventions may be useful options in select patients with this comorbidity. Most importantly, clinician awareness of the co-occurrence of obsessive–compulsive and psychotic symptoms is important for early identification and treatment of both.

Introduction

Schizophrenia and obsessive–compulsive disorder (OCD) are distinct nosological entities in contemporary psychiatric nomenclature. Despite different clinical presentations and prognoses, schizophrenia and OCD share some demographic and clinical characteristics, certain aspects of pathophysiology, and treatment strategies [1••]. The remarkably high co-occurrence of OCD and obsessive–compulsive symptoms (OCS) in schizophrenia has resulted in a growing interest in the topic, sometimes called "schizo-obsessive disorder (SOD)" during the last 15 years [2–4].

A prior OCD diagnosis is a risk factor, which increases the risk of developing schizophrenia approximately sixfold; even an OCD diagnosis in a parent is reported to raise the likelihood of schizophrenia in the offspring. Of note, controlling for psychiatric history of parents did not reduce the association of OCD and schizophrenia, and the association was specific, as there was no increased risk for other childhood-onset disorders, such as ADHD, autism, and bulimia nervosa in people with a prior OCD diagnosis [5].

The comorbidity of schizophrenia and OCD may have clinical implications. Previous studies have found that this comorbidity is associated with greater dysfunction, poorer quality of life, more depressive symptoms, and suicide attempts, as well as more severe cognitive deficits, more social isolation, and more resistance to treatment [6–11]. However, there are other reports that failed to show refractory treatment response in SOD patients in comparison to "pure" schizophrenia patients [12]. The discrepancies in this literature and other aspects of the SOD literature are likely to be secondary to heterogeneity in patient samples. To improve the identification and treatment of this subtype, there is a need for a more consistent and widely accepted diagnostic approach. This need is compounded by the fact that adequate management of OCS/OCD in schizophrenia is of great clinical importance, since serotonergic antidepressants (a successful treatment for OCD) may have additional positive effects in schizophrenia [13].

This review summarizes the literature on the co-occurrence of OCS/OCD with schizophrenia, the clinical presentation, some practical diagnostic considerations, and possible treatment strategies.

Epidemiology

Prevalence studies are essential to estimate the clinical significance of the phenomenon. Several studies have examined the prevalence of OCD/OCS in schizophrenia. The reported prevalence rates show a striking variation. A wide range of 10–64 % for OCS and 0–31 % for OCD have been reported in schizophrenia [3, 4, 14–17]. Even with this wide range, these rates are much higher than reported prevalence rates of OCD and OCS in the general population, which are 1 ~ 3 % [18, 19].

A systematic review and meta-analysis of the rates of OCD and other anxiety disorders in patients with schizophrenia-spectrum psychotic disorder based on 34 studies with more than 3000 participants estimated the prevalence of OCD in schizophrenia at 12.1 % [16]. The prevalence of OCD in schizophrenia patients was much more common than other anxiety disorders. The reason for this high comorbidity of OCD and schizophrenia is still not fully understood.

A number of factors including diagnostic instruments and thresholds, sampling methods, patient characteristics, cultural background, severity, and chronicity of psychotic disorder and treatment setting have been reported to be associated with the prevalence estimate of OCD/OCS in schizophrenia [15, 16]. Aiming to provide a best estimate of the OCS/OCD prevalence in schizophrenia patients controlling for these factors, Swets and colleagues conducted a meta-analysis and meta-regression, which included 43 studies (3978 subjects) after addressing different thresholds used on the Yale–Brown Obsessive–Compulsive Scale (Y-BOCS) [3]. The mean OCD prevalence was 12.3 %, slightly increasing to 13.6 % after adjustment in meta-regression. The prevalence rate of OCS was 30.7 % (30.3 % adjusted).

Though atypical antipsychotics are known to induce de novo OCS/OCD [20•, 21], evidence suggests that this OCS/OCD phenomenon in schizophrenia is not accounted for by medication effects and is a true comorbidity. The most recent prevalence study published in 2015 was conducted by Devi and colleagues [4]. They evaluated 200 consecutive patients with a Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) diagnosis of schizophrenia using the Structured Clinical Interview for DSM-IV Axis I disorders (SCID), Positive and Negative Syndrome Scale (PANSS), and Y-BOCS. The prevalence of OCS and OCD was 24 and 18.5 %, respectively. Notably, about two thirds of all patients developed OCD before treatment with any antipsychotics in this study. The reported prevalence of OCS/OCD in first episode patients (with fewer than 12 weeks of exposure to atypical antipsychotics) was 12–15 %, also higher than that of other anxiety disorders [7, 8].

Clinical features and diagnosis

Both schizophrenia and OCD are characterized by equal distribution between men and women, early age of onset, and earlier onset age in men [22]. Indeed, OCS can associate with psychotic symptoms. Although large-scale studies that evaluate the course of OCS in schizophrenia are still lacking, some of the potential OCS trajectories in schizophrenia have been described based on clinical experience. OCS may occur during the prodromal phase, co-occur with, or follow the emergence of schizophrenia symptoms [23–27].

On the other hand, advanced technology in the field of neuropsychiatry is beginning to allow researchers to differentiate the similarities and differences in the neurobiological underpinnings of OCD, of schizophrenia, and of SOD. For example, Aoyoma found that pediatric cases with schizophrenia plus OCS possess brain differences in comparison to cases with pure schizophrenia. They demonstrated that the left hippocampus was significantly smaller in children suffering from SOD in comparison to pure schizophrenia children [28]. However, there is still an enormous gap regarding neuroimaging studies focusing on SOD in the field.

The diagnostic framework of schizo-obsessive disorder presents a major difficulty. In particular, the distinction between obsessions and delusions is critical to ensure the validity and reliability of the diagnosis, but this is often very difficult. The canonical definition provided in the DSM-IV suggests that delusions are beliefs, which patients give their full assent as being true [29],

while obsessions are thoughts, images or impulses interrupting the patients' consciousness without being believed as true. In other words, patients' insight into the unreasonableness of their obsessions is typically preserved [30].

Insight has consistently been considered as one of the key distinguishing features between obsessions and delusions. However, contemporary studies indicate that patients with OCD may exhibit varying degrees of insight into their obsessions, ranging from total lack of insight to full insight [31–34]. For example, Poyurovsky and colleagues find that a substantial proportion of SOD patients possessed poor insight into their OCS [35]. As a result, DSM-V has revised the criteria for OCD to permit a range of insight in this condition [36]. Thus, insight is not sufficient as a distinguishing parameter for use in this condition.

Although many patients have presentations that are more clearly delusional or obsessive, some patients present with what appear to be genuinely mixed features, with intense obsessive symptoms into which the patient has lost all insight or with more traditional delusional themes, which feed into obsessive thinking and compulsive behaviors. This suggests that there may indeed be a continuum between the two symptom domains and that a satisfying distinction between them may not be possible in some patients. Many review articles have summarized clinical features of obsessions versus delusions or compulsions versus delusional repetitive behaviors based largely on clinical experience and limited research. In general, there are no widely accepted practical methods to distinguish these symptom domains [1••, 22, 30]. An equally valuable practical contribution would be to consistently recognize OCS in the presence of major psychotic illness. Poyurosky and Bottas recently provided guidelines, which may assist in this goal [22, 37]. We list here their proposed provisional diagnostic criteria for schizo-obsessive disorder in Table 1 [22].

Treatment

Although well-designed controlled studies are still lacking, there is general consensus that SOD patients are difficult to treat and require a special therapeutic approach.

Table 1. Proposed diagnostic criteria for schizo-obsessive disorder

A. Symptoms are present that meets criterion A for obsessive–compulsive disorder at some time point during the course of the schizophrenia.

B. If the content of the obsessions and/or compulsions is interrelated with the content of delusions and/or hallucinations (e.g., compulsive hand washing due to command auditory hallucinations), additional typical OCD obsessions and compulsions recognized by the person as unreasonable and excessive are required.

C. Symptoms of obsessive–compulsive disorder are present for a substantial portion of the total duration of the prodromal, active, and/or the residual period of schizophrenia.

D. The obsessions and compulsions are time consuming (more than 1 h a day), cause distress, or significantly interfere with the person's normal routine, in addition to the functional impairment associated with schizophrenia.

E. The obsessions and compulsions in the patient with schizophrenia are not due to the direct effect of antipsychotic agents, a substance of abuse (e.g., cocaine), or an organic factor (e.g., head trauma).

Pharmacotherapy

Typical antipsychotics are seldom used to treat for SOD patients owing to their limited serotonergic properties and significant side effects [38–40]. A large number of studies to date indicate that second-generation antipsychotics (SGAs) might induce de novo OCS or aggravate pre-existing OCS in schizophrenia patients due to their enhanced antiserotonergic binding profile [20•, 41–45]. However, there is preliminary evidence pointing toward a potential bidirectional effect of SGAs on OCS in schizophrenia.

The effect of olanzapine on OCS in schizophrenia patients has long been investigated [44, 46–50]. Compared with other SGAs (e.g., risperidone and clozapine), olanzapine has shown ameliorating effects on both schizophrenia and OCS in some SOD patients reported in clinical trials [21, 51]. However, its tendency to induce or aggravate OCS in some patients and its other potential side effects should also be taken into account in the selection of this medication.

Administration of clozapine, currently the only SGA effective against treatment resistant schizophrenia, requires particular caution and monitoring due to a heavy side effect burden [52]. Most studies have shown that clozapine can induce de novo OCS in schizophrenia patients [20•, 53, 54]. However, there are also preliminary data indicating that clozapine in a low dose range may exert a beneficial effect in some SOD patients [55]. Notwithstanding this one study, clinicians should be mindful that the majority of published studies suggest a possible increased risk of OCS when starting clozapine.

One report suggests that ziprasidone within a dose range of 80 to 200 mg/day may have bimodal effects on SOD patients. This medicine had an ameliorating effect on both OCS and schizophrenia symptoms in roughly half of the SOD patients, but the remainder were not responsive in terms of OCS or ziprasidone in fact triggered OCS in these patients [56].

Acting as a D_2/5-HT_{1A} partial agonist and an antagonist at the 5-HT_{2A} receptor, aripiprazole is distinguished from other SGAs associated with a potential inherent antiobsessive activity [57–59]. Aripiprazole has shown meaningful clinical improvement of OCS in schizophrenia patients, who were partially responsive to other antipsychotic agents [60–62]. Several studies reported the remission of schizophrenia symptoms and reduction of OCS after adding aripiprazole to clozapine or olanzapine [61, 63–65]. The combination of clozapine and aripiprazole may have several other benefits. However, even aripiprazole may have the potential to aggravate OCS [66, 67].

Given the mixed profile of all SGAs in relation to OCS, the main generalization that can be made is that SGAs are of limited efficacy as monotherapy in SOD patients, and the addition of an antiobsessive agent is usually required[22, 27]. Serotonin reuptake inhibitors (SRIs) and tricyclic antidepressants have shown favorable effects on OCS in schizophrenia patients [13, 27, 68, 69], although there are also negative reports [70, 71]. Treaters should be aware of one clinically significant pharmacokinetic drug interaction: adjunctive fluvoxamine treatment can elevate plasma concentrations of clozapine significantly [72]. Although it is best avoided, the best way of monitoring this pharmacokinetic drug interaction in cases where it is the best option is to follow clozapine blood levels before and after initiating add-on fluvoxamine therapy.

In addition, preliminary findings suggest promising results when augmenting SGAs with mood stabilizers for some SOD patients. To date,

only three case reports have mentioned the efficacy of combining valproic acid or lamotrigine with SGAs in the treatment of OCD induced by SGAs [73–75].

Nonpharmacological interventions

Cognitive–behavioral therapy (CBT) is first-line therapy for OCD along with pharmacotherapy [76, 77]. Exposure and response prevention, a typical CBT approach, is an effective treatment for OCD, and its efficacy has been confirmed in some open label and controlled studies [78]. By contrast, the role of CBT in treating OCS in schizophrenia patients remains unclear for several reasons. First, strong treatment adherence to CBT may be a challenge for some schizophrenia patients. Second, as an exposure-based intervention, CBT may increase the vulnerability to relapse in schizophrenia [79]. The only study to address this issue indicated that some SOD patients do adhere to CBT [80] and that adjunctive CBT may be a promising choice for this subtype.

Although electroconvulsive therapy (ECT) is not an approved therapy for OCD [36], some promising results have indeed been reported [81, 82]. Case reports indicate that ECT is effective for SOD patients who were refractory to pharmacotherapy or could not tolerate psychotropic agents [83–86]. Side effects and patients' preferences often determine whether a given patient will be appropriate for an ECT referral.

Deep brain stimulation (DBS) has received FDA approval for OCD in 2009. Multiple studies have shown its efficacy for refractory OCD [87, 88]. Repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are gaining popularity as noninvasive therapeutic tools, with the former already having FDA approval for treatment of depression [89]. Saba and colleagues have reviewed clinical trials using rTMS and tDCS in the treatment of OCD patients [90] and suggested that rTMS and tDCS were promising options. Larger scale and adequately powered RCTs are needed to better understand the therapeutic role of these approaches, both for the OCD patients and for the comorbidity of OCD and schizophrenia.

The treatment of SOD patients is challenging, since their clinical presentations and treatment responses vary widely and are difficult to predict. Several well-designed review articles have summarized most relevant studies up until recent years [1••, 6, 22, 91, 92]. Here, we add to this literature by presenting in summary format the relevant studies published since 2012 (Table 2).

Summary

The summarized data support the observation that OCS are frequent in schizophrenia. In order to obtain a clearer picture of the subgroup of schizophrenia patients experiencing OCS, more studies using standardized criteria and methodologies are required. Progress has been made in the search for effective therapy options during the last 15 years, but large-scale randomized controlled trials are still needed to substantiate most current recommendations, particularly when it comes to the role of SGAs. Ultimately, additional research is

Table 2. Case reports of treatment options for schizo-obsessive disorder after 2012

Study	Age/sex	Clinical presentations	Medication	Psychotic outcomes	OCS outcomes
Negueruela [93]	19/M	Obsessions and compulsions in the prodromal schizophrenia	Fluvoxamine (200 mg/day) + aripiprazole (10 mg/day)	Mild social withdrawal	Disappearance of the OCS after treatment
Eryilmaz [62]	51/M	Delusions, clozapine associated contamination obsessions and cleaning compulsions	Aripiprazole (30 mg/day) + clozapine	PANSS from 151 to 50 (4 weeks)	Y-BOCS from 40 to 20 (4 weeks)
	28/M	Clozapine associated control and symmetry obsessions and compulsions	Aripiprazole (30 mg/day) + clozapine	PANSS from 78 to 49 (4 weeks)	Y-BOCS from 40 to 15 (4 weeks)
	34/M	Delusions and hallucinations, clozapine associated repeating and cleaning compulsions	Aripiprazole (15 mg/day) + clozapine	PANSS from 141 to 50 (4 weeks)	Y-BOCS from 40 to 20 (4 weeks)
	27/M	Delusions and hallucinations, clozapine associated contamination obsessions and frequent hand washing	Aripiprazole (15 mg/day) + clozapine	PANSS from 159 to 46 (4 weeks)	Y-BOCS from 30 to 10 (4 weeks)
Krause [94]	44/F 27 ~ 33/M	Initially contamination obsessions and cleaning compulsions	Ziprasidone(240 mg/day) + quetiapine/clozapine/flupenthixol	No relapse during 12 months	A significant decrease in Y-BOCS
Hung [95]	23/M	Initially obsessions and compulsions	Milnacipran (100 mg/day) + aripiprazole	Improvement in daily functioning	Y-BOCS from 24 to 13 (1 week)
Rosli [96]	17/F	Initially obsessions and compulsions, resistant psychotic symptoms	Risperidone (2 mg/day)	Improvement	Improvement
Sachdeva [97]	24/M	Schizo-obsessive disorder, borderline intelligence, seizure disorder who was tube-fed by family members for more than 3 years because he refused to eat	Trifluoperazine (20 mg/day) + fluoxetine (60 mg/day) + trihexyphenidyl (4 mg/day) + phenytoin (300 mg/day)	BPRS from 42 to 24 (6 weeks)	Y-BOCS from 24 to 18 (6 weeks)
Makhinson [98]	27/F	OCD with severe catatonic symptoms	12 ECT + fluoxetine (80 mg/day) + lorazepam	Moving fluidly, happy, groomed and dressed well	No OCS observed
Johnson [99]	25/M	Self injurious behavior, suicidal gestures and delusions, ego-dystonic fixation on intrusive graphic sexual images and circumstantial thought processes	Eight ECT + diazepam + fluoxetine + quetiapine	An increased ability to maintain orientation and memory	Significant reduction of OCS, still anxiety
Haack [84]	18/M	compulsions and catatonia	ECT for 18 months + clozapine + clomipramine	Catatonic symptoms disappeared	Psychomotor slowing

OCS obsessive–compulsive symptoms, *PANSS* positive and negative syndrome scale, *Y-BOCS* Yale–Brown Obsessive–Compulsive Scale, *BPRS* brief psychiatric rating scale, *ECT* electroconvulsive therapy

needed to delineate the neurobiology and psychopathology of this distinct subgroup and to point the way to novel interventions.

Compliance with ethical standards

Conflict of interest

TianHang Zhou declares that she has no conflict of interest. Burak Baytunca declares that he has no conflict of interest. Xin Yu declares that he has no conflict of interest.

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Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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