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Obsessive-Compulsive Symptoms in Schizophrenia: an Up-To-Date Review of Literature

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Abstract

Purpose of Review

This review will aim to summarize the current body of epidemiological, clinical and therapeutic knowledge concerning specific co-occurrence of obsessive-compulsive symptoms (OCS) and schizophrenia spectrum disorder.

Recent Findings

Almost 30 % of the patients with schizophrenia display OCS, and three main contexts of emergence are identified: prodromal symptoms of schizophrenia, co-occurrence of OCS and schizophrenia, and antipsychotics-induced OCS. Recent clinical studies show that patients with SZ and OCS has more severe psychotic and depressive symptoms, higher suicidality and lower social functioning. A recent cognitive investigation found that OCS and delusions share specific metacognitive profiles, particularly through a heightened need to control thoughts. Finally, a recent cross-sectional study of clozapine-induced OCS found a dose-response relationship between clozapine and OCS.

Summary

OCS appeared reliably as linked to poorer outcomes among patients with schizophrenia. However, the specific clinical value of OCS among other prodromal symptoms of schizophrenia remains unknown.

Key-words

Schizophrenia, Obsessive-compulsive symptoms, Obsessive-compulsive disorder, Schizo-obsessive disorder, ultra-high risk (UHR) of psychosis, antipsychotics

Introduction

In the past decade, the classification of psychiatric disorders has been reorganized through the increasing importance of dimensional thinking, nurturing a large body of literature concerning co-occurring and/or comorbid disorders [1,2]. In the field of schizophrenia (SZ), the specific co-occurrence of obsessive-compulsive symptoms (OCSs) and SZ has been reported for more than a century, with the pioneer work of Westphal in 1878 who gave the first description of obsessive-compulsive disorder (OCD) among patients with SZ, followed by Janet in 1903 and Bleuler in 1911 [3–6]. In 2011, a meta-analysis of 50 studies reported that the prevalence of anxiety disorders among patients with SZ was about 38.3 % (95 % CI [26.3-50.4]) [7]. The prevalence of OCD was estimated at 12.1 % (95 % CI [7.0-17.1]), largely higher than in the general population, where the prevalence approximates 1.9 to 2.5 % [8]. These data have been confirmed in a meta-analysis in 2013 of 3,978 patients suffering from SZ, with a prevalence of OCD of 12.3 % and of OCS of 30.3 % [9]. Since, the great amount of work focusing on the presence of OCS among patients with SZ empowered the emergence of the concept of “schizo-obsessive disorder” as a specific clinical entity on various aspects [10–12]. Moreover, a large amount of epidemiological studies tried to weigh the association of baseline OCD or OCS diagnosis and risk of psychotic transition, with inconsistent results. More recently, in a large longitudinal and multi-generational study, Cederlöf et al. showed that patients diagnosed with OCD displayed a higher rate of schizophrenia than in general population (relative risk (RR) = 12.3, 95% CI [10.9-14.0]) [13]. More specifically, they had an increased risk of receiving a subsequent diagnosis of SZ (RR = 2.7, 95 % CI [2.2-3.3]) with a median time between diagnoses of 2.4 years (Interquartile Range = 3.6 years). This study also showed that first-degree relatives of patients with OCD displayed an increased risk of SZ (RR = 1.9, 95 % CI [1.6-2.1]). Similar results were provided in two nationwide studies in Denmark (SZ: Incidence Rate Ratio (IRR) = 6.9, 95% CI [6.25-7.60], SZ spectrum disorder: IRR = 5.77, 95% CI [5.33-6.22]) and in the Netherlands (Psychotic disorders: Odds-Ratio (OR) = 2.7, 95 % CI [1.2-6.0]) [14,15]. Interestingly, these studies also showed an increased risk of OCD for patients with SZ (RR = 7.0, 95 % CI [5.5-9.0], and OR = 7.7, 95% IC [3.2-18.4]). This bidirectional association raises the

question of the clinical and pathophysiological links between obsessive-compulsive and psychotic symptoms and disorders.

This review aims to summarize the recent epidemiological, clinical and therapeutic knowledge on the presence of OCS and OCD in patients with schizophrenia, according to the three types of context of emergence: (i) OCS as prodromal symptoms of psychotic disorders, (ii) co-occurring OCS and psychotic symptoms, with or without phenomenological overlap, (iii) and antipsychotics-induced OCS or OCD. We will present the different characteristics of these three situations, discussing existing arguments for the existence of distinctive clinical and cognitive characteristics. Then, we will try to give an overview of the therapeutic options for these patients, in light of pathophysiological hypotheses.

Obsessive-compulsive symptoms as prodromal of psychotic disorders

Currents criteria of individuals at ultra-high risk (UHR) of psychosis are identified when presenting one or more among attenuated psychotic symptoms, brief limited intermittent psychotic symptoms (BLIPS) (less than a week, with spontaneous resolution), or trait and state factor (e.g., presence of schizotypal personality traits) [16]. However, describing the UHR population, many clinical studies and meta-analysis showed a clinical heterogeneity, dragging scientists to focus on clinical characteristics or dimensions that could impact the risk of transition to psychotic disorder, or broad clinical outcome of UHR [17]. The presence of OCS has been one of the areas of interest. Of note, OCS is a criterion of UHR according to certain definitions, e.g., the definition based of the Comprehensive Assessment of At Risk Mental State (CAARMS) [18]. Various cohorts evaluated prevalence of OCD in UHR population with results between 8.4 and 20 % [19,20].

However, so far, studies on small samples provided insignificant results concerning specifically the risk of transition associated with co-occurrence of OCS/OCD in UHR individuals [21]. In a retrospective cohort of 64 UHR subjects, including 20 % that exhibited diagnosed OCD, the authors showed a non-significantly lower risk of psychotic transition rate among subjects with OCD (transition rate of 0 % in the OCD group vs. 22 % in the non-OCD group, $p =$

0.06) [22]. Fontenelle et al. followed-up during 7-years 37 UHR subjects, and differentiated baseline OCD, incident OCD, remitting OCD and persistent OCD [18]. They reported 8.1 % of OCD at baseline, 5.4 % of incident OCD, 8.0 % at follow-up, with 6.4 % patients exhibiting remittent OCD (N = 20) and (N = 17). Results did not show any differences in psychotic transition according to baseline characteristics. Incident OCDs were associated with greater risk of transition to delusional disorder, psychotic disorders not otherwise specified, and either depression or bipolar disorder with psychotic features ($p < 0.001$ for all), but not with SZ and schizoaffective disorder [19]. The authors suggest heterogeneity within the OCS/OCD population, and argue that incident OCS could have a specific role during transition to non-SZ psychotic and mood disorders. However, many patients were lost to follow-up, underestimating transition rate and prevalence of persistent OCD.

Overall, as OCS can be prodromal symptoms of psychotic disorders, the presence of OCS among young subjects should be discussed as such, especially considering specific early interventions [24]. However, the specific clinical value of OCS in comparison to other prodromal symptoms remained unknown, and more longitudinal studies are needed on this topic.

Co-occurring schizophrenia and obsessive-compulsive symptoms

As mentioned in introductory remarks, in the latest meta-analysis of 3,978 patients suffering from SZ, 12.3 % were suffering from OCD and 30.3 % from OCS [9]. These results are consistent with previous studies evaluating a prevalence of OCD in SZ around 12 % as well as recent studies on populations during a first episode of psychosis (FEP), where the prevalence of OCD has been evaluated between 9.1 and 10.6 %, while the prevalence of OCS 30.3 % [7,25,26]. This subsection will focus on the clinical characteristic of this subpopulation of patients with SZ.

How can we differentiate obsessive symptoms and delusional ideas?

Obsessive thoughts are considered as recurrent intrusive and unwanted thoughts causing significant distress. They are frequently described as ego-dystonic, which means that the subject is able to recognize that his obsessive ideas are in conflict with his state of mind and that he can

criticise the irrational nature of these thoughts [11]. This ego-dystonic notion is close to the insight of psychiatric disorders, and this last criterion is a core difference with delusional ideas [6]. Thus, patients exhibiting obsessions with poor insight (i.e., egosyntonic) could be mistaken for delusional. Poyurovsky et al. questioned the impact of comorbid OCS and SZ on awareness of both disorders [27]. The authors used the Brown Assessment of Beliefs Scale (BABS) and the Scale to Assess Unawareness of Mental Disorder (SUMD) to evaluate respectively awareness of OCS and of SZ, as well as global impairment. They showed that, among patients with comorbid OCS/SZ, only 15.8 % of patients had a lack of insight on their OCS, and 43.8 % were considered unaware of their SZ diagnosis, while among the non-OCS SZ group, 60 % were unaware of the SZ diagnosis. The awareness of OCS was positively correlated with awareness of SZ ($r = 0.29$, $p = 0.005$), but not with awareness of delusions ($r = -0.18$, $p = 0.26$). In the DSM-5 criteria of OCD, the awareness of disorder is not part of a criterion itself, and a specifier is defined according to the level of insight, with three categories: “*with good or fair insight*”, “*with poor insight*”, or “*with absent insight/delusional belief*”. Concerning this last category, considering for instance fire obsessions, the subject is convinced that the house will burn down if the stove is not checked. Therefore, the awareness of disease seems only partially informative for the distinction between delusional and obsessive and ideas. Poor or absent insight appears to be fairly common within OCD population, with prevalence between 13.8 and 30.7 % depending on studies [28]. Moreover, various studies characterized this subpopulation and showed that poor insight was associated with earlier age-at-onset, poorer outcome, lower global functioning, increased OCD severity and increased rate of SZ in their first-degree relative [28–31]. Oulis et al. provided a phenomenological approach beyond insight considerations, introducing the importance of mental reflexivity, through which individuals have the capacity to reflect their consciousness and ideas on their experiential content with a confrontation of their beliefs to the environment. Hence, OCD patients with “poor insight” might still experience a conflict with the unreasonable nature of imposed obsessions, and thus display mental reflexivity skill, whereas delusional ideas would not be submitted to the subject's reflexivity [32].

To help clinicians identify obsessions in the presence of psychotic symptoms, Bottas et al. suggested a 6-point toolbox: obsession and compulsion similar to those present in pure OCD as described in the DSM-IV, presence of OCS outside acute psychotic episodes or thought form disorder, compulsion in response to an obsession and not a psychotic ideation, reassessment of

obsessive ideas after acute episode in case of thought form disorder, eventuality of empiric treatment with selective serotonin reuptake inhibitors (SSRI) to differentiate both ideas [11]. Indeed, concerning this last criterion, evidence-based pharmacotherapy now provided enough to the clinicians to consider SSRI as valuable empiric treatment of OCD (see below) [33].

Patients with obsessive-compulsive symptoms have more severe psychotic symptoms

In order to characterize the clinical specificities of patients with SZ and OCS, many studies evaluated the impact of such diagnosis on psychotic symptoms. In 2009, Cunill et al. performed a meta-analysis on the matter, and showed that, among patients with SZ, the presence of OCS was associated with greater severity of global (Standardized Mean Difference (SMD) = 0.39, 95 % CI [0.14-0.64]), positive (SMD = 0.28, 95 % CI [0.00-0.56]), and negative psychotic symptoms (SMD = 0.36, 95 % CI [0.11 to 0.62]) [34]. Analysing specifically OCD, the authors did not highlight any significant differences between the groups, suggesting that the categorical definition of OCD seem irrelevant to characterize the patients with SZ. OCS symptoms in SZ have been associated with greater antipsychotic doses at first episode ($p = 0.018$) and for each episode ($p = 0.012$), independently of PANSS severity [35]. To our knowledge, only one study evaluated the content of obsessions or psychotic symptoms in comorbid OCS/SZ compared to OCD-patients. It showed that OCD-patients described more aggressive, contamination-related, sexual and somatic obsession than in the SZ/OCD group [36].

Depressive symptoms and suicidality

The impact of OCS on depressive dimension among patients suffering from SZ has been showed in several studies. In a study of 65 patients with SZ, Szmulewicz et al. showed a positive correlation between suicidality and intensity of OCS evaluated with Yale-Brown Obsessive-Compulsive Scale (YBOCS, $r = 0.513$, $p = 0.01$), and with both obsession ($r = 0.444$, $p = 0.01$) and compulsion YBOCS subscales ($r = 0.433$, $p = 0.01$) [37]. Moreover, the total YBOCS was also significantly correlated with depressive symptoms ($r = 0.389$, $p = 0.01$) and a YBOCS higher than 8 was a significant independent predictive factor of suicide attempt. The impact on suicidality has been confirmed in a study of 246 patients after a FEP, where presence of OCD (N = 26, 10.6 %) was associated with more suicidal behaviours, plans and attempts in the month

before hospitalization ($p = 0.009$) (and with depressive symptoms, $p = 0.002$) [26]. Finally, in a 5-year longitudinal follow-up study on 176 patients with a FEP, de Haan et al. have studied the course of OCS and OCD groups (respectively 39.2 and 9.1 % of the FEP patients) [25]. Patients with OCD displayed more severe depressive symptoms at admission and during the follow-up (p between 0.028 and 0.33).

Overall, OCS appeared reliably associated to depressive symptoms and suicidality among patients with SZ. Of note, none of these studies evaluated depressive symptoms with the Calgary Depression Scale for Schizophrenia, a reliable questionnaire designed to assess depressive symptoms and differentiate them from negative symptoms of SZ [38]. Therefore, further studies seem necessary to acknowledge the impact of OCS on depressive symptoms in SZ.

Global outcome

Considering previous data on clinical characteristics associated with obsessive-compulsive symptomatology, exhibiting more severe psychotic, more depressive symptoms and higher suicidality, one could easily figure the impact on global outcome, mentioned in the earliest description of SZ/OCS population [39]. Indeed, OCS in SZ are significantly associated with lower global functioning and quality of life [40]. In a 5-years longitudinal study of patients after a FEP, de Haan et al. showed that presence of comorbid OCS and OCD was associated with poorer baseline social functioning on the Premorbid Adjustment scale ($p = 0.019$), and were predictors of lower global functioning at follow-up (defined by residential living or not following studies or regular job) ($p = 0.033$) [25]. However, the authors showed no significant differences in terms of relapse rates (exacerbation of psychotic symptoms or increase of prescribed antipsychotic medication) or symptomatic recovery between groups in this sample.

Cognitive defects

In the field of SZ research, a great body of evidence suggests the impact of cognitive defects on multiple outcomes, including global functioning and quality of life [41–43]. Some studies have tried to identify evidences for specific cognitive profiles characterizing patients with SZ and OCS. In 2013, Michalopoulou et al. performed a study comparing SZ and SZ/OCS patients during a neuropsychological test evaluating the ability of inhibition interference capacities using a Stroop Word Test (the patient is asked to mention the content of a word

meaning a colour, while this word is written in another colour) [44]. They showed that SZ/OCS patients exhibited a lower processing speed, independently of OCD or SZ severity. This task could predict 75 % of patients' group memberships, sustaining evidence of a specific cognitive profile. A 12-month longitudinal study showed lasting cognitive impairment in patients suffering from SZ/OCS disorders, and more specifically deficits in shifting and impulsivity defining the hypothesis of a specific cognitive trait [45]. Pallanti et al. performed a study comparing neurofunctional patterns recording event-related potential during a discriminative response task of patients suffering from SZ, OCD and SZ/OCD (using a Go No-Go task where patients are asked to respond to a specific target, and inhibit response to another stimulus) [46]. They showed that the SZ group performed worse than SZ/OCD, who performed worse than OCD group. Moreover, the SZ/OCD group exhibited a distinct neurophysiologic pattern of activation, mixing characteristics observed in the SZ group, i.e. reduced amplitude in the No-Go condition as an expression of a response inhibition deficit, and some of the OCD group, i.e. increased activation in the Go condition compared to SZ patients as an expression of impulsivity. Taken together, it appears that SZ patients suffering from co-occurring OCS specifically exhibit inhibition deficit interfering with goal-directed behaviours, impacting their cognitive functioning.

Finally, a recent study in the general population evaluated the association between delusions, paranoid symptoms, OCS and metacognition [47]. Metacognitive processes refer to thought and beliefs that monitor and interpret thinking. Their role in the vulnerability to psychotic symptoms have been investigated in a cognitive model suggesting that paranoid ideas could be seen as a coping strategy induced by metacognitive beliefs [48]. Using hierarchical multiple linear regression models in patients with OCS, SZ and in healthy participants, they showed that OCS (evaluated with the revised Obsessive-compulsive inventory (OCI-R)) and metacognitive dysfunction (evaluated with the Metacognitive questionnaire (MCQ)) both showed a significant influence and accounted for important variance of paranoid ideation (OCI-R: $\beta = 0.339$, MCQ: $\beta = 0.455$, $p < 0.001$, $r^2 = 0.54$) and hallucinations (OCI-R: $\beta = 0.30$ and MCQ: $\beta = 0.42$, $p < 0.001$, $r^2 = 0.43$). Taken together, metacognition and OCS could explain 43.8 % of hallucinations scores and 53.8 % of paranoia scores. These data suggest that the link between OCS and SZ could be found in the shared metacognitive profiles, through a strong need to control thoughts (e.g., thinking it is bad to think certain things) and dysfunctional beliefs [49].

Antipsychotics-induced OCS

The observation of antipsychotics (AP)-induced OCS came from the work of Baker et al. and de Haan et al. who first reported cases of patients exhibiting OCS after the introduction of clozapine [50,51]. Before this identification of AP-induced OCS in SZ, they might have been considered as incident OCS, and thus now considered as a specific entity [8,52]. Since, a large body of evidence argued the implication of many second-generation AP (SGAP) in AP-induced OCS [21]. A review considering SGAP-induced OCS incriminated more specifically clozapine, with de novo OCS rates between 20 and 28 % and, considering exacerbation of pre-existing OCS, 38.2 to 76 % of overall clozapine-treated patients. Considering olanzapine, de novo rates achieved 11 %, while overall rates achieved 20 %. Finally, for risperidone, these rates were respectively 3.4 % and 23.2 % [53].

Concerning clozapine, a recent comprehensive review reported that, after several month of clozapine-treatment, OCS incidence reaches 76 % in some studies [52]. Consistently with precedent reviews, the incidence of AP-induced OCS was higher in patients undergoing clozapine compared to other SGAP (36.7 % vs. 16.7 %) [50]. Pharmacodynamic arguments specified the link between clozapine treatment and OCS, among which a strong correlation between OCS severity and duration of treatment, with a greater risk after 12 weeks of treatment [54,55], whereas most of risperidone and olanzapine-induced OCS occurred after 4 weeks. Considering the introduction of clozapine with progressively increasing dosage, it seems congruent to consider a correlation between time, dosage and side-effects. Moreover, several studies suggested a dose-response pattern with a positive correlation between OCS severity and plasma levels of clozapine, with a decrease of OCS after decrease of clozapine dosage [56–62]. In a cohort of patients with SZ treated by clozapine, patients exhibiting OCS had higher clozapine plasma concentration (595.1 ng/mL +/- 364 , vs. 433 +/- 252 ng/mL, $p = 0.001$), indicating a concentration-effect relationship [56]. Among the studies on dose-response pattern of AP, only one study addressed the effects of olanzapine serum levels on OCS, and found no significant correlation [62].

Insights on therapeutic interventions and pathophysiological issues

As mentioned earlier, clozapine-induced OCS has been associated to a dose-response pattern. Therefore, we could hypothesise that decreasing doses of clozapine could efficiently reduce OCS; but it might as well increase the risk of psychotic exacerbation, and could not be considered as a reasonable therapeutic alternative [60].

The role of the serotonergic pathways in this specific association has been incriminated, considering that a cortico-striatal serotonergic deficiency has been highlighted as a major physio-pathological pathway underlying OCD, and that high-dose of SSRI represents the current first-line of pharmacological options for treatment of OCD [33,57]. Stryjer et al. showed that the adjunction of escitalopram 20 mg in 15 patients suffering from SZ and OCD treated by SGAP (clozapine, risperidone or quetiapine) led to significant improvement of both OCS (20 % Y-BOCS decrease, $p < 0.001$) and total PANSS score (from 81.46 ± 20.94 to study completion 75.46 ± 23.36 , $p = 0.03$) [63]. However, this study focused on co-occurring SZ/OCS without specifying the AP-induced OCS. Moreover, results on the matter are contradictory with one case report showed no efficacy on AP-induced OCS [54], and another suggested that this association might be deleterious during psychotic exacerbation [64].

However, OCD patients display high resistance rates of 40-60 % to SSRIs, suggesting implication of various neurotransmission channels [65]. The role of dopamine in the pathophysiology of OCD has been hypothesized [66], and confirmed by growing evidence supporting the anti-obsessive effect of various SGAP, with a specific efficacy of aripiprazole on OCS [67–71]. Although first-generation AP (FGAP) find their efficiency through the sole dopamine D2 receptor antagonism, SGAP (as clozapine, olanzapine, risperidone and aripiprazole) are known to have a specific antagonistic action on the serotonin 5HT_{2A} receptor. The 5HT_{2A}/D2 occupancy ratio is considered as a major pharmacodynamic issue in AP-induced OCS, given the fact that the incriminated agents, i.e. clozapine, olanzapine and risperidone, are found to have the highest 5HT_{2A} binding affinity (with respective 5HT_{2A}/D2 occupancy ratio of 20:1, 12:1, 11:1) [50,72,73]. Consistently, amisulpride and aripiprazole have a low 5HT_{2A}/D2 receptor occupancy, and are found to provide less induced-OCS symptoms [74]. Considering the

current evidence on SGAP as add-on in the treatment of OCD, and more specifically of aripiprazole [67], numerous studies highlighted a positive impact of aripiprazole adjunction on clozapine-induced OCS [59,75,76]. Englisch and Zink evaluated the improvement of clozapine-induced OCS after aripiprazole add-on in a case series of seven patients suffering from clozapine-induced OCS, and showed a decrease in YBOCS scores with aripiprazole-add-on [58]. Later, in a review article combining 11 trials on a total of 94 patients undergoing combined clozapine-aripiprazole treatment for various reasons (mainly for refractory psychotic symptoms or side-effects limiting dose enhancement), the same authors showed that aripiprazole add-on permitted to lower clozapine doses and serum levels (523.3 +/- 173 ng/mL vs. 611 +/- 138 ng/mL, $p < 0.05$) (62). Finally, the case of risperidone seems of particular relevance, considering a dose-dependent occurrence of OCS. Surprisingly, two studies showed an inverse dose-severity correlation, where risperidone-induced OCD was reversed by increasing doses of risperidone that must be related to the specific occupancy of 5HT_{2A} at low dosage (1-2 mg) and of D2 receptors at higher dosage (7-10 mg) [73,77]. Therefore, aripiprazole and risperidone could be advantageous to treat patients with SZ and OCS.

Beyond pharmacological interventions, the literature only provide one case-report on electro-convulsivo-therapy (ECT) in a case of psychotic disorder with comorbid clozapine-induced OCD and showed immediate remission of OCS, correlated with possibility of clozapine decrease through ECT-efficacy on psychotic symptoms [78]. However, the effect of ECT could be related to either decrease clozapine or psychotic symptoms improvement. Lastly, a recent review argued for the efficacy of Cognitive Behavioural therapy (CBT) on OCS symptoms among patients with SZ [79].

Conclusions

This review provided evidences that clinicians should investigate OCS in patients with SZ as the existence of OCS is frequent and could represent a specific subtype of SZ with clinical specificities and targeted therapeutic options.

According to current literature, OCS could be considered as prodromal signs of SZ. Multiples studies focused on OCS in the UHR population and data did not show converging

evidence on an association between OCS and a specific risk of transition to psychosis, but evidences for global lower quality of life, professional and social functioning, and poorer course of OCD.

In the case of co-occurring disorders, patients suffering from SZ/OCS exhibit greater psychotic symptoms, with significantly higher score on the PANSS and receive higher doses of antipsychotics during their FEP and in subsequent episodes. Higher severity of psychotic and depressive symptoms is predictive of higher concurrent OCS severity. Recent studies showed that they suffer from more severe illness major complications: earlier age of onset, poorer outcome, lower functioning, greater depressive symptoms and suicidality. The importance of the level of insight, or awareness of the disorder, has been highlighted recently in a study showing that the awareness of OCS was positively correlated with awareness of SZ, but not with awareness of delusions. Moreover, a good awareness of OCS and SZ is associated with better outcome. Finally, these patients exhibit specific cognitive defects such as inhibition deficit interfering with goal-directed behaviours and enhanced impulsivity, impacting their cognitive and global functioning.

Finally, the case of AP-induced OCS in SZ has been a major concern for decades. Pharmacodynamic evidences promoted a better understanding of the arousal of AP-induced OCS and revealed a more specific association with clozapine, with a specific association with the prior duration of treatment and a dose-response pattern. Other SGAP, such as olanzapine and risperidone, have also been incriminated.

Interestingly, recent evidences suggest an efficacy of aripiprazole add-on in clozapine-induced OCS, with no need of interruption of clozapine. However, studies arouse from case series of meta-analysis of case series and need to be confirmed with longitudinal studies on wider samples of patients.

Taken together, the current literature provides various evidences for patterns of associations between OCS and SZ. The main striking information appears that OCS could be considered as a severity marker in SZ. Considering the importance of such association, the influence of OCS in SZ needs to be polished through the results of large-scale longitudinal studies of patients.

References

1. Kelly JR, Clarke G, Cryan JF, Dinan TG. Dimensional thinking in psychiatry in the era of the Research Domain Criteria (RDoC). *Ir J Psychol Med.* 2018;35:89–94.
2. Leboyer M, Schurhoff F. Searching across diagnostic boundaries. *Schizophr Bull.* 2014;40:946–8.
3. Westphal K. U"ber Zwangsvorstellungen. *Archiv fu"r Psychiatr und Nervenkr.* 1898. p. 734–750.
4. Bleuler M, Bleuler R. Dementia praecox oder die Gruppe der Schizophrenien: Eugen Bleuler. *Br J Psychiatry.* 1986;149:661–4.
5. Janet P, Raymond F. Les obsessions et la psychasténie. Felix Alcan.
6. Attademo L, Bernardini F, Paolini E, Quartesan R. History and conceptual problems of the relationship between obsessions and hallucinations. *Harv Rev Psychiatry.* 2015;23:19–27.
7. Achim AM, Maziade M, Raymond E, Olivier D, Mérette C, Roy M-A. How prevalent are anxiety disorders in schizophrenia? A meta-analysis and critical review on a significant association. *Schizophr Bull.* 2011;37:811–21.
8. Fontenelle LF, Mendlowicz MV, Versiani M. The descriptive epidemiology of obsessive-compulsive disorder. *Prog Neuropsychopharmacol Biol Psychiatry.* 2006;30:327–37.
9. Swets M, Dekker J, van Emmerik-van Oortmerssen K, Smid GE, Smit F, de Haan L, et al. The obsessive compulsive spectrum in schizophrenia, a meta-analysis and meta-regression exploring prevalence rates. *Schizophr Res.* 2014;152:458–68.
10. Attademo L, De Giorgio G, Quartesan R, Moretti P. Schizophrenia and obsessive-compulsive disorder: from comorbidity to schizo-obsessive disorder. *Riv Psichiatri.* 2012;47:106–15.
11. Bottas A, Cooke RG, Richter MA. Comorbidity and pathophysiology of obsessive-compulsive disorder in schizophrenia: is there evidence for a schizo-obsessive subtype of schizophrenia? *J Psychiatry Neurosci JPN.* 2005;30:187–93.
12. Poyurovsky M, Weizman A, Weizman R. Obsessive-Compulsive Disorder in Schizophrenia. *CNS Drugs.* 2004;18:989–1010.
13. Cederlöf M, Lichtenstein P, Larsson H, Boman M, Rück C, Landén M, et al. Obsessive-Compulsive Disorder, Psychosis, and Bipolarity: A Longitudinal Cohort and Multigenerational Family Study. *Schizophr Bull.* 2015;41:1076–83.

14. Van Dael F, van Os J, de Graaf R, ten Have M, Krabbendam L, Myin-Germeys I. Can obsessions drive you mad? Longitudinal evidence that obsessive-compulsive symptoms worsen the outcome of early psychotic experiences. *Acta Psychiatr Scand*. 2011;123:136–46.
15. Meier SM, Petersen L, Pedersen MG, Arendt MCB, Nielsen PR, Mattheisen M, et al. Obsessive-Compulsive Disorder as a Risk Factor for Schizophrenia: A Nationwide Study. *JAMA Psychiatry*. 2014;71:1215–21.
16. Nelson B, Yuen K, Yung AR. Ultra high risk (UHR) for psychosis criteria: are there different levels of risk for transition to psychosis? *Schizophr Res*. 2011;125:62–8.
17. Fusar-Poli P, Cappucciati M, Borgwardt S, Woods SW, Addington J, Nelson B, et al. Heterogeneity of Psychosis Risk Within Individuals at Clinical High Risk: A Meta-analytical Stratification. *JAMA Psychiatry*. 2016;73:113–20.
18. Yung AR, Yuen HP, McGorry PD, Phillips LJ, Kelly D, Dell’Olio M, et al. Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. *Aust N Z J Psychiatry*. 2005;39:964–71.
19. Fontenelle LF, Lin A, Pantelis C, Wood SJ, Nelson B, Yung AR. A longitudinal study of obsessive-compulsive disorder in individuals at ultra-high risk for psychosis. *J Psychiatr Res*. 2011;45:1140–5.
20. Łucka I, Fryze M, Cebella A, Staszewska E. [Prodromal symptoms of schizophrenics syndrome in children and adolescent]. *Psychiatr Pol*. 2002;36:283–6.
21. Poyurovsky M, Zohar J, Glick I, Koran LM, Weizman R, Tandon R, et al. Obsessive-compulsive symptoms in schizophrenia: implications for future psychiatric classifications. *Compr Psychiatry*. 2012;53:480–3.
22. Niendam TA, Berzak J, Cannon TD, Bearden CE. Obsessive compulsive symptoms in the psychosis prodrome: correlates of clinical and functional outcome. *Schizophr Res*. 2009;108:170–5.
23. Schmidt SJ, Schultze-Lutter F, Schimmelmann BG, Maric NP, Salokangas RKR, Riecher-Rössler A, et al. EPA guidance on the early intervention in clinical high risk states of psychoses. *Eur Psychiatry J Assoc Eur Psychiatr*. 2015;30:388–404.
24. de Haan L, Sterk B, Wouters L, Linszen DH. The 5-year course of obsessive-compulsive symptoms and obsessive-compulsive disorder in first-episode schizophrenia and related disorders. *Schizophr Bull*. 2013;39:151–60.
25. Hagen K, Hansen B, Joa I, Larsen TK. Prevalence and clinical characteristics of patients with obsessive-compulsive disorder in first-episode psychosis. *BMC Psychiatry*. 2013;13:156.

26. Poyurovsky M, Faragian S, Kleinman-Balush V, Pashinian A, Kurs R, Fuchs C. Awareness of illness and insight into obsessive-compulsive symptoms in schizophrenia patients with obsessive-compulsive disorder. *J Nerv Ment Dis.* 2007;195:765–8.
27. Jacob ML, Larson MJ, Storch EA. Insight in adults with obsessive-compulsive disorder. *Compr Psychiatry.* 2014;55:896–903.
28. Cherian AV, Narayanaswamy JC, Srinivasaraju R, Viswanath B, Math SB, Kandavel T, et al. Does insight have specific correlation with symptom dimensions in OCD? *J Affect Disord.* 2012;138:352–9.
29. Catapano F, Perris F, Fabrazzo M, Cioffi V, Giacco D, De Santis V, et al. Obsessive-compulsive disorder with poor insight: a three-year prospective study. *Prog Neuropsychopharmacol Biol Psychiatry.* 2010;34:323–30.
30. Fontenelle JM, Harrison BJ, Santana L, Conceição do Rosário M, Versiani M, Fontenelle LF. Correlates of insight into different symptom dimensions in obsessive-compulsive disorder. *Ann Clin Psychiatry Off J Am Acad Clin Psychiatr.* 2013;25:11–6.
31. Oulis P, Konstantakopoulos G, Lykouras L, Michalopoulou PG. Differential diagnosis of obsessive-compulsive symptoms from delusions in schizophrenia: A phenomenological approach. *World J Psychiatry.* 2013;3:50–6.
32. Fineberg NA, Gale TM. Evidence-based pharmacotherapy of obsessive-compulsive disorder. *Int J Neuropsychopharmacol.* 2005;8:107–29.
33. Cunill R, Castells X, Simeon D. Relationships between obsessive-compulsive symptomatology and severity of psychosis in schizophrenia: a systematic review and meta-analysis. *J Clin Psychiatry.* 2009;70:70–82.
- 34.* Baytunca B, Kalyoncu T, Ozel I, Erermiş S, Kayahan B, Öngür D. Early Onset Schizophrenia Associated With Obsessive-Compulsive Disorder: Clinical Features and Correlates. *Clin Neuropharmacol.* 2017;40:243–5.

In a retrospective chart review of 29 patients with early onset SZ (10 with OCS/SZ, 19 SZ), patients suffering from SZ/OCS received significantly higher doses of antipsychotics during the first episode and at assessment (no sociodemographic differences, similar duration of illnesses and had comparable severity scores on PANSS).

- 35.* Tonna M, Ottoni R, Paglia F, Monici A, Ossola P, DE Panfilis C, et al. Obsessive-Compulsive Symptoms in Schizophrenia and in Obsessive-Compulsive Disorder: Differences and Similarities. *J Psychiatr Pract.* 2016;22:111–6.

In this clinical study of the content of obsessions and compulsions in 66 patients suffering from SZ/OCD (n= 35) or OCD (n=31), OCD patients had a greater level of distress for obsession and compulsion, and obsessive ideas were more aggressive, contamination-related, sexual and

somatic obsession in the OCD group than in the SZ group. Patients had similar severity levels, and no association were found between OCS severity and PANSS scores, but delusional symptoms were positively associated with the presence of washing compulsion and hoarding obsession.

36. Szmulewicz AG, Smith JM, Valerio MP. Suicidality in clozapine-treated patients with schizophrenia: role of obsessive-compulsive symptoms. *Psychiatry Res.* 2015;230:50–5.
37. Addington D, Addington J, Maticka-Tyndale E, Joyce J. Reliability and validity of a depression rating scale for schizophrenics. *Schizophr Res.* 1992;6:201–8.
38. Fenton WS, McGlashan TH. The prognostic significance of obsessive-compulsive symptoms in schizophrenia. *Am J Psychiatry.* 1986;143:437–41.
39. Hur J-W, Shin NY, Jang JH, Shim G, Park HY, Hwang JY, et al. Clinical and neurocognitive profiles of subjects at high risk for psychosis with and without obsessive-compulsive symptoms. *Aust N Z J Psychiatry.* 2012;46:161–9.
40. Marder SR, Fenton W. Measurement and Treatment Research to Improve Cognition in Schizophrenia: NIMH MATRICS initiative to support the development of agents for improving cognition in schizophrenia. *Schizophr Res.* 2004;72:5–9.
41. Bulzacka E, Boyer L, Schürhoff F, Godin O, Berna F, Brunel L, et al. Chronic Peripheral Inflammation is Associated With Cognitive Impairment in Schizophrenia: Results From the Multicentric FACE-SZ Dataset. *Schizophr Bull.* 2016;42:1290–302.
42. Roux P, Urbach M, Fonteneau S, Berna F, Brunel L, Capdevielle D, et al. Psychiatric disability as mediator of the neurocognition-functioning link in schizophrenia spectrum disorders: SEM analysis using the Evaluation of Cognitive Processes involved in Disability in Schizophrenia (ECPDS) scale. *Schizophr Res.* 2018;201:196–203.
43. Michalopoulou PG, Konstantakopoulos G, Typaldou M, Papageorgiou C, Christodoulou GN, Lykouras L, et al. Can cognitive deficits differentiate between schizophrenia with and without obsessive-compulsive symptoms? *Compr Psychiatry.* 2014;55:1015–21.
- 44.** Schirmbeck F, Rausch F, Englisch S, Eifler S, Esslinger C, Meyer-Lindenberg A, et al. Stable cognitive deficits in schizophrenia patients with comorbid obsessive-compulsive symptoms: a 12-month longitudinal study. *Schizophr Bull.* 2013;39:1261–71.

In this 6-months longitudinal study of SZ patients (N = 56) and their unaffected siblings (N = 49), higher severity of positive, negative, and depressive symptoms was positively associated with higher concurrent OCS severity across subject and significantly predicted OCS severity 4 weeks later and vice-versa.

45. Pallanti S, Castellini G, Chamberlain SR, Quercioli L, Zaccara G, Fineberg NA. Cognitive event-related potentials differentiate schizophrenia with obsessive-compulsive disorder

(schizo-OCD) from OCD and schizophrenia without OC symptoms. *Psychiatry Res.* 2009;170:52–60.

- 46.** Hagen K, Solem S, Opstad HB, Hansen B, Hagen R. The role of metacognition and obsessive-compulsive symptoms in psychosis: an analogue study. *BMC Psychiatry.* 2017;17:233.

Among a non-clinical sample (N = 194), OCS were moderately-strongly correlated with psychotic symptoms (paranoia and hallucinations). OCS and metacognitive dysfunction both showed a significant influence and accounted for important variance on the levels of paranoid ideation and hallucinations.

47. Morrison AP, Haddock G, Tarrier N. Intrusive Thoughts and Auditory Hallucinations: A Cognitive Approach. *Behav Cogn Psychother.* 1995;23:265–80.
48. Moritz S, Peters MJV, Larøi F, Lincoln TM. Metacognitive beliefs in obsessive-compulsive patients: a comparison with healthy and schizophrenia participants. *Cognit Neuropsychiatry.* 2010;15:531–48.
49. de Haan L, Linszen DH, Gorsira R. Clozapine and obsessions in patients with recent-onset schizophrenia and other psychotic disorders. *J Clin Psychiatry.* 1999;60:364–5.
50. Baker RW, Chengappa KN, Baird JW, Steingard S, Christ MA, Schooler NR. Emergence of obsessive compulsive symptoms during treatment with clozapine. *J Clin Psychiatry.* 1992;53:439–42.
51. Grillault Laroche D, Gaillard A. Induced Obsessive Compulsive Symptoms (OCS) in schizophrenia patients under Atypical 2 Antipsychotics (AAPs): review and hypotheses. *Psychiatry Res.* 2016;246:119–28.
52. Fonseka TM, Richter MA, Müller DJ. Second generation antipsychotic-induced obsessive-compulsive symptoms in schizophrenia: a review of the experimental literature. *Curr Psychiatry Rep.* 2014;16:510.
53. Zink M. Comorbid Obsessive-Compulsive Symptoms in Schizophrenia: Insight into Pathomechanisms Facilitates Treatment. *Adv Med.* 2014;2014:317980.
54. Schirmbeck F, Konijn M, Hoetjes V, Zink M, de Haan L, For Genetic Risk and Outcome of Psychosis (GROUP). Obsessive-compulsive symptoms in psychotic disorders: longitudinal associations of symptom clusters on between- and within-subject levels. *Eur Arch Psychiatry Clin Neurosci.* 2018;
55. Lin S-K, Su S-F, Pan C-H. Higher plasma drug concentration in clozapine-treated schizophrenic patients with side effects of obsessive/compulsive symptoms. *Ther Drug Monit.* 2006;28:303–7.

56. Meltzer HY. Clinical studies on the mechanism of action of clozapine: the dopamine-serotonin hypothesis of schizophrenia. *Psychopharmacology (Berl)*. 1989;99 Suppl:S18-27.
57. Englisch S, Esslinger C, Inta D, Weinbrenner A, Peus V, Gutschalk A, et al. Clozapine-induced obsessive-compulsive syndromes improve in combination with aripiprazole. *Clin Neuropharmacol*. 2009;32:227–9.
58. Englisch S, Zink M. Combined antipsychotic treatment involving clozapine and aripiprazole. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008;32:1386–92.
- 59.** Fernandez-Egea E, Worbe Y, Bernardo M, Robbins TW. Distinct risk factors for obsessive and compulsive symptoms in chronic schizophrenia. *Psychol Med*. 2018;48:2668–75.

In this study of risk factor of clozapine-induced OCS in a sample of clozapine-treated SZ patients (N = 118), 47 % of the sample reached threshold criteria for OCD and were on anti-OCD medication. Length of clozapine treatment was correlated with checking severity and authors showed a direct correlation between OCS and clozapine plasma levels. Patients on polypharmacy had higher OCS scores and higher OCD prevalence.

60. Schirmbeck F, Zink M. Comorbid obsessive-compulsive symptoms in schizophrenia: contributions of pharmacological and genetic factors. *Front Pharmacol*. 2013;4:99.
61. Schirmbeck F, Esslinger C, Rausch F, Englisch S, Meyer-Lindenberg A, Zink M. Antiserotonergic antipsychotics are associated with obsessive-compulsive symptoms in schizophrenia. *Psychol Med*. 2011;41:2361–73.
62. Stryjer R, Dambinsky Y, Timinsky I, Green T, Kotler M, Weizman A, et al. Escitalopram in the treatment of patients with schizophrenia and obsessive-compulsive disorder: an open-label, prospective study. *Int Clin Psychopharmacol*. 2013;28:96–8.
63. Poyurovsky M, Faragian S, Shabeta A, Kosov A. Comparison of clinical characteristics, comorbidity and pharmacotherapy in adolescent schizophrenia patients with and without obsessive-compulsive disorder. *Psychiatry Res*. 2008;159:133–9.
64. Sugarman MA, Kirsch I, Huppert JD. Obsessive-compulsive disorder has a reduced placebo (and antidepressant) response compared to other anxiety disorders: A meta-analysis. *J Affect Disord*. 2017;218:217–26.
65. Denys D, Zohar J, Westenberg HG. The role of dopamine in obsessive-compulsive disorder: preclinical and clinical evidence. *J Clin Psychiatry*. 2004;65 Suppl 14:11–7.
66. Pignon B, Tezenas du Montcel C, Carton L, Pelissolo A. The Place of Antipsychotics in the Therapy of Anxiety Disorders and Obsessive-Compulsive Disorders. *Curr Psychiatry Rep*. 2017;19:103.

67. van Nimwegen L, de Haan L, van Beveren N, Laan W, van den Brink W, Linszen D. Obsessive-compulsive symptoms in a randomized, double-blind study with olanzapine or risperidone in young patients with early psychosis. *J Clin Psychopharmacol*. 2008;28:214–8.
68. Temmingh H, Stein DJ. Anxiety in Patients with Schizophrenia: Epidemiology and Management. *CNS Drugs*. 2015;29:819–32.
69. McDougle CJ, Goodman WK, Price LH. Dopamine antagonists in tic-related and psychotic spectrum obsessive compulsive disorder. *J Clin Psychiatry*. 1994;55 Suppl:24–31.
70. Matsunaga H, Nagata T, Hayashida K, Ohya K, Kiriike N, Stein DJ. A long-term trial of the effectiveness and safety of atypical antipsychotic agents in augmenting SSRI-refractory obsessive-compulsive disorder. *J Clin Psychiatry*. 2009;70:863–8.
71. Kapur S, Zipursky RB, Remington G. Clinical and theoretical implications of 5-HT₂ and D₂ receptor occupancy of clozapine, risperidone, and olanzapine in schizophrenia. *Am J Psychiatry*. 1999;156:286–93.
72. Ramasubbu R, Ravindran A, Lapiere Y. Serotonin and Dopamine Antagonism in Obsessive-Compulsive Disorder: Effect of Atypical Antipsychotic Drugs. *Pharmacopsychiatry*. 2000;33:236–8.
73. Schirmbeck F, Zink M. Comorbid obsessive-compulsive symptoms in schizophrenia: contributions of pharmacological and genetic factors. *Front Pharmacol* [Internet]. 2013 [cited 2018 Dec 9];4. Available from: <https://www.frontiersin.org/articles/10.3389/fphar.2013.00099/full>
74. Villari V, Frieri T, Fagiolini A. Aripiprazole augmentation in clozapine-associated obsessive-compulsive symptoms. *J Clin Psychopharmacol*. 2011;31:375–6.
75. Eryılmaz G, Hızlı Sayar G, Ozten E, Gögcegöz Gül I, Karamustafalıoğlu O. Aripiprazole augmentation in clozapine-associated obsessive-compulsive symptoms in schizophrenia. *Ann Gen Psychiatry*. 2013;12:40.
76. Jacobsen FM. Risperidone in the treatment of affective illness and obsessive-compulsive disorder. *J Clin Psychiatry*. 1995;56:423–9.
77. Hanisch F, Friedemann J, Piro J, Gutmann P. Maintenance electroconvulsive therapy for comorbid pharmacotherapy-refractory obsessive-compulsive and schizoaffective disorder. *Eur J Med Res*. 2009;14:367–8.
78. Tundo A, Necci R. Cognitive-behavioural therapy for obsessive-compulsive disorder co-occurring with psychosis: Systematic review of evidence. *World J Psychiatry*. 2016;6:449–55.