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ANXIETY DISORDERS (A PELISSOLO, SECTION EDITOR)

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 (OCSs) 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 have 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.

Keywords 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 3978 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

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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 physiopathological 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 [23]. 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 introductive remarks, in the latest meta-analysis of 3978 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, 24, 25]. 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 [26]. 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 [27]. 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 [27–30]. 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 [31].

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) [32].

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]) [33•]. 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 [34•]. 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 [35].

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 ($r = 0.433$, $p = 0.01$) [36]. 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, $p = 0.002$) [25]. 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) [24]. 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 [37]. 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 [38]. Indeed, OCS in SZ is significantly associated with lower global functioning and quality of life [39]. In a 5-year 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) ($p = 0.033$) [24]. 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 [40–42]. 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) [43••]. 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 [44]. 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) [45••]. 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 [46]. 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 [47]. 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 [48].

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 [49, 50]. 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, 51]. 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% [52].

Concerning clozapine, a recent comprehensive review reported that, after several months of clozapine treatment, OCS incidence reaches 76% in some studies [51]. 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%) [49]. 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 [53, 54], 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 [55–57, 58••, 59–61]. 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 [55]. 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 [61].

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 [59].

The role of the serotoninergic pathways in this specific association has been incriminated, considering that a corticostriatal serotoninergic deficiency has been highlighted as a major physiopathological pathway underlying OCD, and that high dose of SSRI represents the current first line of pharmacological options for treatment of OCD [32, 56]. 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, $p = 0.03$) [62]. 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 [53], and another suggested that this association might be deleterious during psychotic exacerbation [63].

However, OCD patients display high resistance rates of 40–60% to SSRIs, suggesting implication of various neurotransmission channels [64]. The role of dopamine in the pathophysiology of OCD has been hypothesised [65] and confirmed by growing evidence supporting the anti-obsessive effect of various SGAP, with a specific efficacy of aripiprazole on OCS [66–70]. Although first-generation AP (FGAP) finds 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) [49, 71, 72]. Consistently, amisulpride and aripiprazole have a low $5HT_{2A}$/D2 receptor occupancy and are found to provide less-induced OCS symptoms [73]. Considering the current evidence on SGAP as add-on in the treatment of OCD, and more specifically of aripiprazole [66], numerous studies highlighted a positive impact of aripiprazole adjunction on clozapine-induced OCS [58•, 74, 75]. 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 [57]. 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) [72, 76]. 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 [77]. However, the effect of ECT could be related to either decrease clozapine or psychotic symptom improvement. Lastly, a recent review argued for the efficacy of cognitive behavioural therapy (CBT) on OCS symptoms among patients with SZ [77].

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.

Compliance with Ethical Standards

Conflict of Interest Chloé Tezenas du Montcel, Franck Schürhoff, and Baptiste Pignon each declare no potential conflicts 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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