Obsessive-compulsive Symptoms Associated with Clozapine and Risperidone Treatment: Three Case Reports and Review of the Literature

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Treatment-emergent obsessive-compulsive symptoms (OCSs) have raised concern since the widespread introduction of serotonin-dopamine antagonists (SDAs) for the treatment of schizophrenia. Further investigations of SDA-emergent OCSs and their response to anti-obsessional agents will be beneficial for clinicians in helping patients who suffer from this problem. We present three cases of schizophrenia in which distressing OCSs occurred during clozapine or risperidone treatment. OCSs were assessed consecutively using the Yale-Brown Obsessive-Compulsive Scale. The OCSs of these three patients were responsive to anti-obsessional agents, including fluvoxamine, clomipramine, and paroxetine. We also review the current literature and discuss the possible pathophysiology and psychopathology of SDA-emergent OCSs.

Key Words: obsessive-compulsive symptoms, clozapine, risperidone, schizophrenia, serotonin-dopamine antagonists
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Clozapine and risperidone bind strongly to serotonin (5-HT_2) and dopamine (D_2) receptors, improving both the positive and negative symptoms of schizophrenia [1]. Serotonin-dopamine antagonists (SDAs) carry a smaller risk of extrapyramidal symptoms than dopamine receptor antagonists, and eliminate the need for concurrent anticholinergic drugs with adverse effects [2]. SDAs have been recommended for patients with schizophrenia in various clinical stages [3].

However, the adverse effects of SDAs reported in the literature are numerous [1]. One of the side effects is treatment-emergent obsessive-compulsive symptoms (OCSs) in patients with a favorable antipsychotic response to clozapine [4,5], risperidone [6,7], and olanzapine [8]. Although the imbalance in serotonin-dopamine neurotransmission with a preponderance of serotonin antagonism was proposed as a possible explanation of this side effect [5,9], the causal relationship between OCSs and SDA treatment has not been established. Few of the case reports discuss the effects of anti-obsessional agents, including fluvoxamine [9], sertraline [10,11], and clomipramine [12], in the treatment of SDA-emergent OCSs. Further investigation of the pathophysiology and psychopathology of treatment-emergent obsessive-compulsive features is needed, as well as research into the pathology of OCSs and the pharmacologic mechanisms of SDAs and anti-obsessional agents.

We report three cases with a diagnosis of schizophrenia according to DSM-IV [13], in which OCSs emerged during the course of clozapine or risperidone treatment. The response of OCSs to anti-obsessional agents, including fluvoxamine, clomipramine, and paroxetine, is also reported. OCSs were assessed consecutively using the Yale-Brown Obsessive-Compulsive Scale (YBOCS) [14] during a trial of anti-obsessional agents with ongoing clozapine or ris-

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peridone treatment with at least a 7-month follow-up. In current reviews, only a few case reports of OCSs have been assessed using rating scales [8,9,12,15]. To the best of our knowledge, this is the first report demonstrating the efficacy of paroxetine treatment of SDA-related OCSs in schizophrenic patients. We also review the current literature and discuss the possible pathology of SDA-emergent OCSs.

Case Presentations

Case 1

A 24-year-old man met the DSM-IV criteria for schizophrenia at the age of 19, with initial manifestations of severe auditory and visual hallucination, disorganized speech and behaviors, and delusions of reference and persecution. He had been hospitalized four times in our hospital's acute ward, and received multiple trials of conventional antipsychotics, SDAs, and electroconvulsive therapy. He had no history of obsessive-compulsive disorder (OCD) or personality disorder (OCPD). However, during a trial of risperidone 6 mg/day, he obsessively worried that his father would die, and complained that he felt disgusted while intrusive sexual images were overplayed in his mind. Clozapine treatment was started and titrated up to 400 mg/day, with significant improvement of auditory hallucination and delusion.

Due to a seizure attack after 17 weeks of clozapine treatment, medication dosage was reduced to 300 mg/day. Eight months after administration of clozapine 300 mg/day, the patient became anxious and restless, compulsively asked the same questions, and repeatedly asked for confirmation from the staff in our day hospital. He was obsessed with minutiae and was often preoccupied with thoughts of breakage of the wash basin and viral infection of his liver. He persistently requested laboratory examinations to evaluate his liver function even after reassurance had been given. In addition, he worried irrationally that the traffic signals might not work, and he therefore rode a motorcycle about, checking repeatedly to make sure that the traffic lights worked. His obsessive and compulsive behavior caused significant distress and impairment of his daily activities and function. For these OCSs, clozapine was increased to 325 mg/day with the consideration of super-sensitivity of 5-HT receptors with long-term clozapine treatment. However, his OCSs were not responsive to this treatment and persisted. Clozapine was decreased back to 300 mg/day and fluvoxamine treatment was added, beginning with 50 mg/day and progressively increased to 200 mg/day in increments of 50 mg. The severity of OCSs decreased after the initiation of fluvoxamine treatment. Fourteen weeks later, the total YBOCS score had decreased from 32 to 1 (Figure 1). Interestingly, his obsession with viral infection of his liver recurred when fluvoxamine was tapered to 100 mg/day. This obsessive symptom subsided again after the dosage of fluvoxamine was increased back to 150 mg/day. Improvement of OCSs remained after 10 months' follow-up with fluvoxamine at 150–200 mg/day.

Case 2

A 20-year-old man had a 3-year history of schizophrenia,

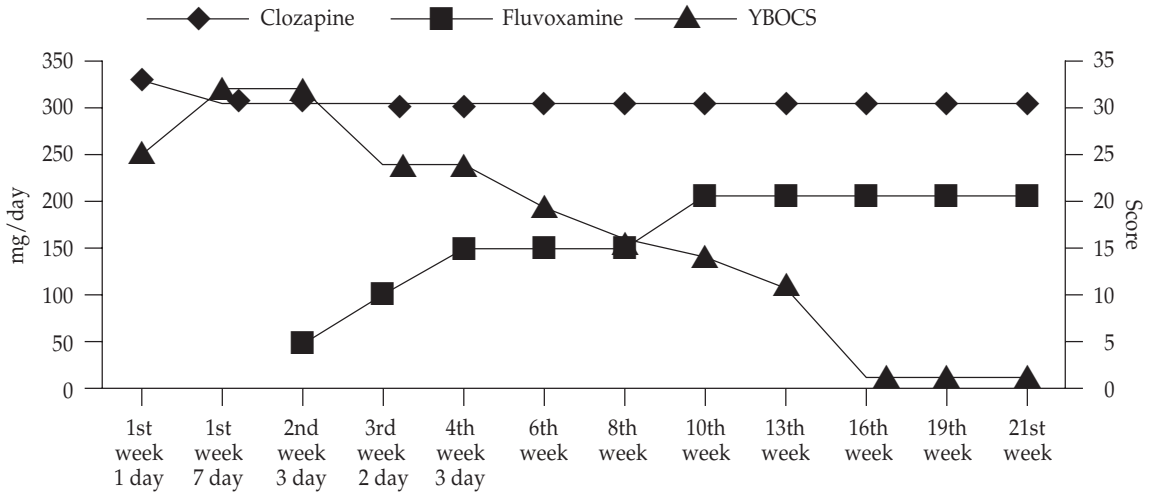

Figure 1. *Medication dosages and Yale-Brown Obsessive-Compulsive Scale (YBOCS) scores in Case 1.*

paranoid type, episodic with inter-episode residual symptoms. He presented with progressive social withdrawal, apathy, affective flattening, poor personal care, auditory hallucination, and delusion of persecution in the initial episode, and he was treated using electroconvulsive therapy. Risperidone 3 mg/day was prescribed in the following 2 years. With this treatment, he was able to join a rehabilitation program and even obtain sheltered work. There was no history of OCSs.

Risperidone was increased to 4 mg/day for persistent voice commenting and delusion of reference. However, 2 weeks later, he suffered from severe egodystonic obsession symptoms and was preoccupied with ruminations about past unpleasant events. Recurrent sexual images were experienced as intrusive. The severity of obsessive thinking led to a trial of clomipramine 25 mg/day. Three weeks after clomipramine was introduced, the obsessive symptoms attenuated, with the YBOCS score decreasing from 14 to 1. Simultaneously, risperidone was adjusted again due to apparent positive symptoms. Unfortunately, obsessive thinking about mistakes, with obsessive anxiety and compulsive behaviors, developed again 2 weeks later when the dosage of risperidone reached 6 mg/day. Paroxetine 20 mg/day was added to replace clomipramine, with ongoing risperidone regimen. A marked reduction in his obsession was found 2 weeks later (Figure 2). The substantial improvement was observed at 10 months' follow-up with paroxetine at doses of 20–30 mg/day. However, these obsession symptoms worsened when paroxetine was decreased, and even relapsed transiently over a 2-month period of treatment with paroxetine 20 mg/day.

Case 3

A 31-year-old man had been diagnosed with schizophrenia, paranoid type, 4 years previously, with presentations of severe auditory and visual hallucination and delusions of persecution, reference, and grandeur for several years. He was troubled by psychotic symptoms and reacted irritably and violently, abusing alcohol to overcome fear and perceptual disturbance. Neither a history of OCD nor OCPD had been reported.

Risperidone was administered at 4–6 mg/day during hospitalization 1 year ago. His condition was responsive to the treatment but, unfortunately, he suffered from post-psychotic depression after nearly full remission of delusion and hallucination, under treatment with risperidone 4 mg/day. The depressive episode, which was carefully differentiated from negative symptoms and extrapyramidal symptoms, resolved 1 month later without any antidepressant medication. However, he suddenly became obsessive 3 months after risperidone was introduced. He was totally preoccupied by the thought of his drunken state and a past contractual obligation. He repetitively talked about the same thing all day long, even after his family confirmed to him that he was not responsible for this contract. He was extremely worried that he would be arrested and jailed because he had not fulfilled it, and he attempted suicide by drug overdose. The obses-

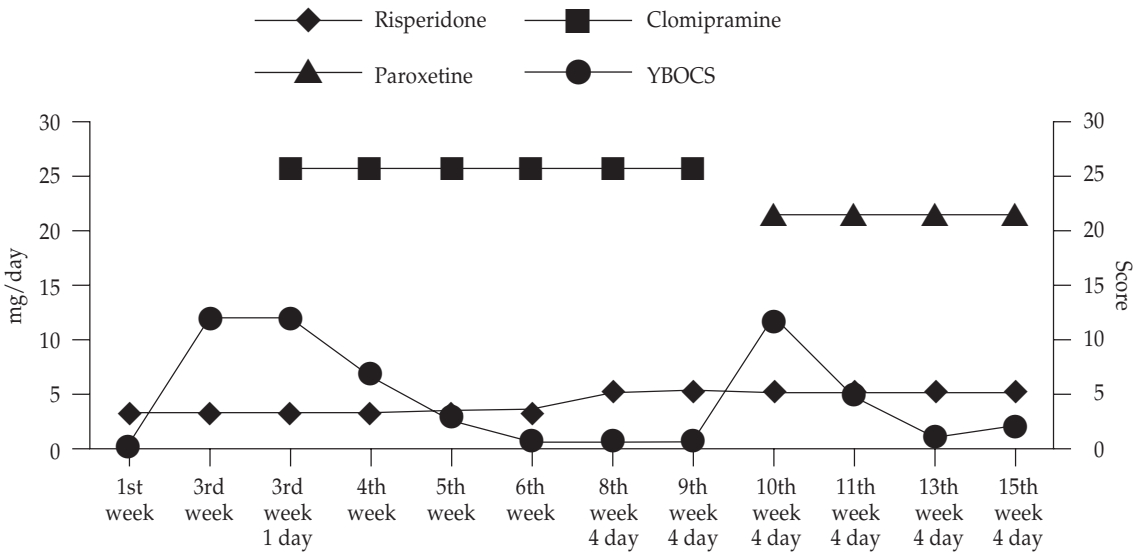

Figure 2. *Medication dosages and Yale-Brown Obsessive-Compulsive Scale (YBOCS) scores in Case 2.*

sive thinking persisted and was not responsive to benzodiazepine and paroxetine 20 mg/day over a 1-month period. Clomipramine was started. Risperidone was withdrawn later and olanzapine was administered. The OCSs improved with a 3-week regimen of olanzapine 10 mg/day and clomipramine 75 mg/day, and YBOCS score decreased from 39 to 5 (Figure 3). The improvement persisted in the following 7 months' follow-up. Clomipramine was decreased gradually without recurrence of OCSs.

Discussion

Reports of atypical antipsychotic drug-related OCSs are mostly linked to clozapine and risperidone, and are found in up to 10% of clozapine-treated patients [16]. A few cases with olanzapine [8] and quetiapine [17] have also been reported. All these SDAs have potent 5-HT_2 and D_2 antagonism at therapeutic doses. The hypothesis of the role that serotonin plays in OCD was based on the observation that treatment involves manipulating serotonin activities [18]. It has been suggested that the anti-serotonergic effects of SDAs are responsible for the emergence of OCSs [10]. The favorable responses of the treatment-emergent OCSs to selective serotonin reuptake inhibitors (SSRI), clomipramine, and potent serotonin reuptake inhibitors further support this viewpoint.

In addition, several lines of evidence show that dopamine is implicated in the mediation of some obsessive-compulsive behaviors [19,20]. The importance of anatomic and functional interactions between serotonergic and dopaminergic neurons must be considered. The decreases in 5-HT tonic inhibitory influences on dopamine neurons could lead to increased dopaminergic function due to the functional connections between dopamine and 5-HT neurons in the basal ganglion [19,20]. As a result, it has been postulated that the hyperactivity of the dopaminergic system in the striatum contributes to the rise in OCSs [12].

Norepinephrine is another member of the monoamine system involved in the pathophysiology of OCSs [21]. Both Cases 2 and 3 experienced a clinical improvement in OCSs with clomipramine and paroxetine treatment. Both drugs inhibit serotonin reuptake and display potent norepinephrine reuptake antagonism [19]. This indirectly suggests that abnormalities in norepinephrine may play a role in SDA-related OCSs.

All three cases had no history of OCD or OCPD. In previous studies, some cases had a history of OCD [5–7,9,22], but most had no history of OCD or OCPD [6,9,10,12,16,18,23,24]. Remington and Adams reported that a subgroup of schizophrenic patients who already manifest obsessive-compulsive features as a part of their illness may be at particular risk for treatment-emergent OCSs [22].

There may be a subset of patients vulnerable to the development of obsessive phenomena associated with atypical antipsychotics [6]. At high doses, SDAs block the postsynaptic receptors in the nigrostriatal dopamine pathway rather than mesolimbic pathway, and are, therefore, responsible for extrapyramidal side effects and more commonly associated with the emergence of OCSs [19,20]. This differential dose effect on dopamine and 5-HT systems, along with the beneficial effect of low doses of SDAs on refractory OCD, may indicate that the primary abnormality is in the serotonin-dopamine balance.

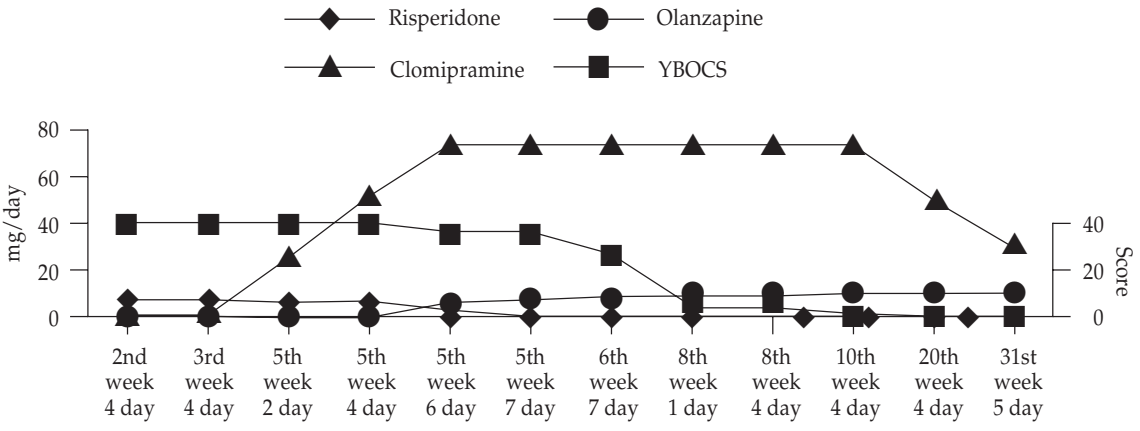

Figure 3. *Medication dosages and Yale-Brown Obsessive-Compulsive Scale (YBOCS) scores in Case 3.*

Greater sensitivity for the development of extrapyramidal side effects in patients may be consistent with this abnormality [6]. However, the underlying mechanisms and risk factors are far from clear.

There is no gender prevalence in OCD [2], but SDA-induced OCSs are more common in men according to previous reported cases. We have reviewed 28 cases of clozapine- or risperidone-induced OCSs [5–7,9,10,12,16, 18,22–26] reported between 1990 and 2003. There were 24 male patients and only four females [5,6,18]. Their ages ranged from 19 to 56 years, with most patients in their twenties or thirties. Our three cases were young male patients, which is consistent with previous studies. The effect of gender and age factors should be further investigated.

SDA-induced OCSs seem to be dose-related. Several case reports suggest that clozapine-induced OCSs emerge only at doses above a certain threshold; the mean dose of the cases in the literature is moderate to high at 454.2 ± 187.9 mg [8]. In all reported cases, the risperidone dose exceeded 3 mg/day [6]. However, the onset of OCSs does not seem to be predictable. Treatment-induced OCSs emerged within weeks to months of SDA therapy or dose increase [5–7,9,10,12,16,18,22–26]. Biondi et al reviewed cases and reported that the latency of appearance of OCSs related to the beginning of clozapine treatment ranged from 2 months to 1 year [12]. In risperidone-treated patients, the OCSs, which emerged within days to weeks, appeared earlier than in clozapine-treated patients [6,7,18,22,26].

Poyurovsky et al reported that OCSs appeared during the period of clozapine dose titration in reviewed cases [16]. In certain vulnerable individuals treated chronically with clozapine, "withdrawal" or "tardive" OCSs may develop, possibly because of the pathophysiologic development of a super-sensitivity in 5-HT receptors as a result of the potent 5-HT antagonistic activity of clozapine [27].

In contrast, Poyurovsky et al also reported the disappearance of OCSs in two cases during a subsequent titration of clozapine [9]. Two other patients in their report [9] and our first case showed improvement with the addition of fluvoxamine, which had a similar effect to the addition of fluoxetine [9] or clomipramine [12] to clozapine pharmacotherapy. However, it is likely that patients had their clozapine "dose" effectively increased by the addition of fluvoxamine [28] due to significant drug interaction between clozapine (metabolized through liver P450 2D6 and IA2 isoenzymes) and fluvoxamine (inhibition of P450 IA2) [19]. On the other hand, it may be postulated that increasing 5-HT_2/D_2 antagonism and simultaneously increasing serotonin activity improves SDA-induced OCSs. Rahman et al reported that the addition of fluvoxamine interfered with the efficacy of clozapine, even though the plasma level was higher [25]. Fluvoxamine is effective in risperidone-induced OCSs [7].

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Clozapine 和 Risperidone 治療期間出現之強迫症狀－三例病歷報告和文獻回顧

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從新一代抗精神病藥物 serotonin-dopamine antagonists (SDAs) 被廣泛使用於治療精神分裂症患者以來，治療中出現的強迫症狀已引起臨床治療者的注意。進一步探討強迫症狀生成與使用 SDAs 之間的關聯性，以及它對治療強迫症狀藥物的反應，將有助於增加臨床醫師對此議題的認識，協助受此症狀困擾的患者。我們報告三位精神分裂症患者，他們在接受 clozapine 和 risperidone 治療中出現強迫症狀，在分別接受 fluvoxamine ， clomipramine 和 paroxetine 後其強迫症狀嚴重程度逐漸減緩。我們並回顧相關文獻，對於使用 SDAs 所產生的強迫症狀可能的病理學原因做進一步的討論。

關鍵詞：強迫症狀， clozapine ， risperidone ，精神分裂症，serotonin-dopamine antagonists

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