Clozapine-associated Development of Second-onset Obsessive Compulsive Symptoms in Schizophrenia: Impact of Clozapine Serum Levels and Fluvoxamine Add-on

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Abstract
Among antiserotonergic second generation antipsychotics (SGA), particularly treatment with clozapine (CLZ) is associated with the development of second-onset obsessive compulsive symptoms (OCS) in schizophrenia. However, less is known regarding the factors that increase the individual susceptibility for the development of SGA-associated second-onset OCS in schizophrenia. Here we present the case of a 29-year-old female patient with disorganized schizophrenia who exhibited OCS due to fluvoxamine-induced elevation of CLZ serum levels via inhibition of CYP 1A2 and 2C19. The severity of the observed OCS featured an association with CLZ serum levels. The case illustrates the interaction between fluvoxamine add-on and CLZ serum levels on the development of OCS in schizophrenia and emphasizes the need of regular therapeutic drug monitoring.

Key words
adverse drug reactions · antipsychotic treatment · second generation antipsychotics · side effects · therapeutic drug monitoring

Introduction
Epidemiological studies indicate that patients diagnosed with schizophrenia feature a considerable lifetime risk for obsessive compulsive (OC) symptoms with prevalence rates ranging from 10–25% [1–4]; occasionally estimates even vary between 0.5 and 55% [5]. The neurobiological processes underlying this comorbidity have not yet been fully elucidated. Besides several heterogeneous pathogenic concepts regarding OC symptoms in schizophrenia (e.g., independent disorders that coincide accidentally [6] or “schizo-obssive subtype of schizophrenia” [7,8]), especially treatment with second-generation antipsychotics (SGA) is associated with a significant risk for the development of OC symptoms [9]. This particular adverse drug reaction (ADR) was first reported for treatment with clozapine (CLZ) [10,11]. In accordance with this observation, it was hypothesized that antiserotonergic SGA (such as CLZ or olanzapine [OLZ]) might be responsible for SGA-induced second-onset OC symptoms in schizophrenia [12–14]. Indeed, although there is evidence that OLZ may also facilitate therapeutic effects on second-onset OC symptoms in patients with schizophrenia [15,16], clinical studies showed that OC symptoms were significantly more prevalent and severe in patients treated with CLZ or OLZ vs. amisulpride or aripiprazole [12,14]. Among the group of antiserotonergic SGA, CLZ was assessed to be particularly capable of inducing OC symptoms in patients with schizophrenia [6,9,14,17,18]. Here, selective serotonin reuptake inhibitors (such as fluvoxamine [FLV] as an add-on) were reported to be successful not only in the treatment of OC symptoms in schizophrenia [19], but also in CLZ-induced second-onset OC symptoms in schizophrenia [20]. In order to contribute to the available experience regarding the pharmacological conditions that may trigger the development of OC symptoms in patients with schizophrenia we report the following case of a patient who developed second-onset OC symptoms under a therapeutic regimen consisting of CLZ, OLZ, and add-on of FLV.

Case Report
A 29-year-old female patient was admitted to our psychiatric ward due to OC symptoms which had been increasing for 6 weeks and which induced significant psychological impairment in daily life. She was diagnosed with schizophrenia (originally classified as disorganized subtype according to DSM-TV-TR 295.10 criteria) 6 years ago (cranial MRI and cerebrospinal fluid without pathological findings); the family anamnesis was positive only for major depressive disorder (patient’s brother); she did not use any psychotropic substances (alcohol, nicotine or any illicit drugs). Leading psychopathological findings on admission were reduced attention, slowed thinking and psychomotor function, blunted affect and OC symptoms (distressing intrusive thoughts and obsessive counting/aritmethomania; the Yule-Brown obsessive compulsive scale (Y-BOCS) [21] was not performed) without unambiguous positive symptoms of schizophrenia. Notably, OC symptoms occurred for the first time in the patient’s course of disease. Current medication was CLZ (250 mg per day; 50 mg–0–200 mg-0), FLV (50 mg O.D.), and OLZ (20 mg O.D.). During the last psychiatric in-patient treatment (2 years prior to the current hospital admission), a regimen of CLZ (250 mg per day) and FLV add-on (25 mg per day) was established. FLV was additionally given as an inhibitor of the cytochrome P450 monooxidase ([CYP] 1A2 and 2C19 [22]) in order to increase CLZ serum levels and to reduce side effects as well as negative symptoms [23,24]. At this time the patient already exhibited CLZ serum levels in the upper therapeutic range. Approximately 2 months prior to the current readmission, FLV was increased (from 25 to 50 mg per day) for unknown reasons and OLZ had been established as a new pharmacological strategy in the context of the ambulant treatment. After consultation of the psychiatrist, who was responsible for the ambulant treatment, it turned out that OLZ had been administered due to problems with sleep. Apart from overweight (body mass index 31.9 kg/m²) and several anticholinergic side effects such as obstipation (defecation 2–3 times per week), dryness of the mouth and occasionally blurred vision, physical examination was without any pathology. The medication was taken in correspondence to the medicinally administered dose and regimen; CLZ serum levels on admission time were 834 ng/mL (reference range 350–600 ng/mL) and N-desmethyl-CLZ 288 ng/mL, respectively [CLZ serum levels were measured by high-performance liquid chromatogra-

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Due to significant anticholinergic side effects, we tapered OLZ (the serum levels of which presumably have also been gradually increased by FLV-induced inhibition of CYP1A2 [25]; OLZ serum levels on day of admission 60 ng/mL) during the first week after admission; subsequently anticholinergic ADR subsided completely. As OC symptoms persisted thereafter and, based on corresponding evidence [5, 17, 26], the elevated CLZ serum level was suggested to be a possible trigger of the second-onset OC symptoms, the daily doses of FLV (25 mg per day) and CLZ (200 mg per day) were reduced 10 days after admission. Accompanied by a slight clinical improvement of OC symptoms, CLZ serum levels measured after one week under the above described regimen were still increased (CLZ 778 ng/mL; N-desmethyl-CLZ 435 ng/mL). Thus, CLZ was reduced to a daily dose of 150 mg and FLV was kept at 25 mg per day. After further 2 weeks, OC symptoms subsided completely and CLZ serum levels where within the reference range, albeit still comparatively high (CLZ 528 ng/mL; N-desmethyl-CLZ 304 ng/mL).

Conflict of Interest

The authors declare no conflicts of interest.

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