De Novo Emergence of Obsessive-Compulsive Symptoms With Atypical Antipsychotics in Asian Patients With Schizophrenia or Schizoaffective Disorder: A Retrospective, Cross-Sectional Study

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Objective: The objective of our study was to establish the incidence of de novo emergence of obsessive-compulsive symptoms (OCS) in patients taking atypical antipsychotics in an Asian population.

Method: Outpatients with schizophrenia or schizoaffective disorder (DSM-IV criteria) who were prescribed any of the 4 atypical antipsychotics approved by the U.S. Food and Drug Administration at the time of the study (clozapine, olanzapine, risperidone, and quetiapine) during a 2-month period (April through May) in 2003 at a tertiary psychiatric hospital were identified. Demographic information was gathered, and the Yale-Brown Obsessive Compulsive Symptom Checklist and the Yale-Brown Obsessive Compulsive Scale (YBOCS) were used for assessment by an independent rater who was blinded to the patients' treatment.

Results: Three hundred three patients met the entry criteria and consented to participate in the study. These subjects included 180 women and 123 men. The mean age was 41 years (range, 21–76 years), and the outpatients were predominantly of Chinese ethnicity (86%). Obsessive-compulsive symptoms emerged de novo in 9 of the 303 patients (3.0%); 2 of the 9 patients were taking clozapine, 4 were taking olanzapine, and 3 were taking risperidone.

Conclusions: This study highlights the need for clinical awareness of the possible occurrence or exacerbation of OCS with atypical antipsychotics. It also highlights the need for careful assessment and mental state examination of these patients and the need to educate the patient on the possibility of these side effects.

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Obsessive-compulsive disorder (OCD) is one of the most disabling disorders, with a lifetime prevalence between 1% and 3%.[1,2] Obsessive-compulsive disorder follows a chronic, fluctuating course, and only rarely does the disorder resolve spontaneously.[3] Case reports and retrospective studies have indicated that atypical antipsychotics may induce or exacerbate obsessive-compulsive symptoms (OCS). Most of the cases of atypical antipsychotic–induced OCS have been associated with patients with schizophrenia,[4] delusional disorders,[5] major depressive disorder with psychotic features,[6] and OCD.[7] Adjunctive use of atypical antipsychotics, in particular risperidone, has also been shown to ameliorate treatment-refractory OCD.[8] A MEDLINE search from 1990 to 2005 revealed 35 reports involving 63 cases of de novo emergence or exacerbation of OCS during treatment with atypical antipsychotics. These include 31 cases with clozapine, 21 cases with risperidone, 8 cases with olanzapine, and 3 cases with quetiapine.

It is estimated that OCD is prevalent in 14% of first-episode schizophrenia patients,[9] and the comorbidity of OCD and bipolar disorder is reported to range from 8% to 35%.[10] The estimates for the rate of occurrence of obsessive-compulsive phenomena in schizophrenia range widely, from 3.8% to 59.2%,[11] all of which indicates that the rate of occurrence of OCS or OCD as a comorbidity is considerably higher than the prevalence of OCD in the general population (1%–3%).[1,2]

A few cases of de novo emergence or exacerbation of OCS during treatment with atypical antipsychotics have been reported previously in our local practice.[12,13] To determine the extent of the problem in our Asian population, we conducted a retrospective study to establish the incidence of de novo OCS emergence in patients taking atypical antipsychotics.

METHOD

The cross-sectional study was conducted at the Institute of Mental Health in Singapore, which is a tertiary psychiatric hospital with a large outpatient clinic. The

study protocol was approved by the hospital's Clinical Research Committee. Outpatients with schizophrenia or schizoaffective disorder (DSM-IV criteria) who were prescribed any of the 4 atypical antipsychotics approved by the U.S. Food and Drug Administration at the time of the study (clozapine, olanzapine, risperidone, and quetiapine) during a 2-month period (April through May) in 2003 were identified from the hospital's electronic prescribing system. The attending psychiatrists of the cases were approached for permission to recruit their patients to the study, and informed patient consent was taken for an interview and for their medical records to be reviewed.

Only patients aged 21 years and older, taking atypical antipsychotics, who had no past history of OCD or OCS, were included in the study. Patients with comorbid OCD or other anxiety disorders, as well as those with obsessive-compulsive personality disorder or traits, were excluded. The investigator (R.M.) interviewed patients who consented to participate in the study. Demographic information was gathered, and the Yale-Brown Obsessive Compulsive Symptom Checklist[14] and the Yale-Brown Obsessive Compulsive Scale (YBOCS)[14] were used for assessment by an independent rater who was blinded to the patients' treatment.

The Yale-Brown Obsessive Compulsive Symptom Checklist was used as an aid for identifying current obsessive-compulsive symptoms. The YBOCS itself is a rating scale designed to rate the severity and type of symptoms in patients with OCD. Both are intended for use as a semistructured interview. The characteristics of each symptom are rated for the prior week up until and including the time of the interview. Scores reflect the average (mean) occurrence of each item for the entire week.

If the patient was unable to provide information about onset of symptoms or details of treatment with atypical antipsychotics, the individual medical records were looked up to verify the information. Psychiatrists in charge of patients who were diagnosed with OCS were informed of the diagnosis, and the investigator (R.M.) followed up these patients for 1 year to determine the outcome.

RESULTS

Demographics

During the study period, 958 outpatients received atypical antipsychotics: 138 patients (14.4%) received clozapine, 99 patients (10.3%) received olanzapine, 99 patients (10.3%) received quetiapine, and 622 patients (65.0%) received risperidone. Three hundred three patients met the entry criteria and consented to participate in the study. These included 180 women and 123 men (female to male ratio 1.46:1). The majority of the patients were single (199 [66%]), 92 (30%) were married, and 12 (4%) were divorced or separated. The mean ± SD age was 41 ± 11 years (range, 21–76 years). The subjects were predominantly of Chinese ethnicity (86%); 5% were Malay, 7% were Indian, and 2% belonged to other ethnicities. Of the 303 patients, 57 (18.8%) received clozapine, 48 (15.8%) olanzapine, 30 (9.9%) quetiapine, and 168 (55.4%) risperidone.

Cases With De Novo Obsessive-Compulsive Symptoms

Obsessive-compulsive symptoms emerged de novo in 9 of the 303 patients (3.0%); 2 patients were taking clozapine, 3 were taking olanzapine, and 4 were taking risperidone (Table 1). The cases involved 5 females and 4 males (female to male ratio, 1.25:1). Four were married and 5 single. The mean age of this group was 38.8 years (range, 23–64 years), which is quite similar to that of the study group. They were also predominantly Chinese (88.9%), with only 1 Indian (11.1%).

Dosage of Atypical Antipsychotics in the Obsessive-Compulsive Symptoms–Emergent Group

The mean doses of atypical antipsychotics patients in this group received were as follows: clozapine 325 mg/day (2 patients receiving 400 mg and 250 mg/day, respectively), olanzapine 16.6 mg/day (range, 10 to 20 mg/day), and risperidone 3.25 mg/day (range, 2 to 4 mg/day).

Some of the patients were receiving concomitant medications such as hypnotics (benzodiazepines) and anticholinergic agents (benzhexol) for extrapyramidal effects, and 2 patients were receiving valproate sodium for mood stabilization.

Nature of Obsessive-Compulsive Symptoms

Three of the 9 patients who developed OCS had only compulsions, which were in the form of checking, counting, and washing behavior. Two patients had only obsessions, which were in the form of ruminations and recurrent visual imagery. Four patients had both obsessions and compulsions. Care was taken during the assessments to distinguish obsessive and compulsive symptoms from schizophrenic symptoms of hallucinations and delusions. Obsessions were distinguished from schizophrenic symptoms by the recognition of features of a feeling of subjective compulsion, a resistance to it, and the preservation of insight. The patients who experienced the ruminations and recurrent visual imagery recognized these events as arising within their minds and as senseless and persisting without cause.

Onset of Obsessive-Compulsive Symptoms

Patients had received treatment with atypical antipsychotics for periods that ranged from less than 1 year to 6 years, and OCS emerged at varying intervals after starting atypical antipsychotics. The earliest appearance was at 16 days and the latest at 18 months after initiation of atypical antipsychotic treatment, with a mean onset of 5.78 months.

Table 1. Characteristics and Treatment Outcomes of Patients Who Developed Obsessive-Compulsive Symptoms With Atypical Antipsychotics

Characteristic	Patient No.								
	1	2	3	4	5	6	7	8	9
Sex	Male	Female	Male	Male	Female	Male	Female	Female	Female
Age, y	44	31	38	64	26	53	37	33	23
Race/Ethnicity	Indian	Chinese	Chinese	Chinese	Chinese	Chinese	Chinese	Chinese	Chinese
Diagnosis	Schizoaffective disorder	Schizoaffective disorder	Schizophrenia	Schizophrenia	Schizophrenia	Schizophrenia	Schizophrenia	Schizophrenia	Schizophrenia
Atypical antipsychotic	Clozapine	Clozapine	Risperidone	Risperidone	Risperidone	Olanzapine	Olanzapine	Olanzapine	Risperidone
Daily dose, mg	400	250	4	3	2	20	20	10	4
Obsessions	None	Ruminations	Recurrent visual images	None	Ruminations	None	Ruminations	Ruminations	Ruminations
Compulsions	Checking, counting	Checking	None	Checking, washing	None	Checking, counting	Checking	Checking	Checking
Onset of OCS	16 mo	6 mo	18 mo	1.5 mo	16 d (0.53 mo)	1 mo	1 mo after dose increased	3 mo	5 mo
YBOCS score	20	15	20	21	11	27	21	20	34
Treatment of OCS	None	Fluoxetine added	Dose reduced and drug switched	Clomipramine added and drug switched	Clomipramine added and drug stopped	Clomipramine added, dose reduced, and drug switched	Drug stopped	Fluoxetine added	None
OCS outcome (1-year follow-up)	Still present	Still present	Not present	Not present	Not present	Not present	Not present	Still present	Still present

Abbreviations: OCS = obsessive-compulsive symptoms, YBOCS = Yale-Brown Obsessive Compulsive Scale.

Treatment of Obsessive-Compulsive Symptoms

Five of the patients required pharmacologic treatment for the de novo–emergent OCS: Clomipramine was used for 3 patients and fluoxetine for 2 patients. One patient had his dose of atypical antipsychotic reduced, and 3 patients had a switch of atypical antipsychotic with good effect. One patient was switched from olanzapine to quetiapine, and 2 patients were switched from risperidone to quetiapine.

Outcome

Obsessive-compulsive symptoms were still present in 4 patients at the time of our study. Of these, 2 patients received treatment with fluoxetine, while the remaining patients were not treated pharmacologically, as their OCS was mild.

DISCUSSION

This is one of the largest studies in patients prescribed atypical antipsychotics to determine the de novo emergence of OCS. The study of OCS in schizophrenia is confounded by similarities in psychopathology. In addition, schizophrenic patients often have obsessive-compulsive features, and OCD patients may have psychotic features. The emergence or exacerbation of OCS with atypical antipsychotic use further compounds the problem.

The incidence of de novo OCS with atypical antipsychotic use in our schizophrenic patients was 3% (8.3% for patients taking olanzapine, 3.5% for patients taking clozapine, and 1.8% for patients taking risperidone). In a study of clozapine and obsessions in patients with recent-onset schizophrenia and other psychotic disorders, a fifth of the patients treated with clozapine experienced an emergence or increase of obsessive symptoms.[15] In a prospective study, de Haan et al.[16] found no difference between olanzapine and risperidone in inducing or exacerbating OCS, but patients treated with olanzapine had significantly more severe OCS than those treated with risperidone after 6 weeks. In another series of 6 cases treated with risperidone, de novo OCS appeared in 4 patients.[17]

A recent study conducted by Ongur and Goff[18] in stable schizophrenia outpatients found that 8.8% of study patients met the criteria for clinically significant OCD (YBOCS score greater than 16). Depressive symptoms were strongly associated with YBOCS scores, but cognitive functioning and quality of life were not adversely affected by OCS. The researchers concluded that patients with OCS had more severe positive symptoms and were more likely to be taking clozapine or olanzapine than patients without OCS. Our sample was similar to their study sample in being stable outpatients diagnosed with schizophrenia or schizoaffective disorder. Seven patients (2.3%) in our study had YBOCS scores greater than 16, and they were taking clozapine, olanzapine. or risperidone.

However, we did not assess our sample for depression or cognitive functioning.

Alevizos et al.[17] reported an earlier onset of OC symptoms, i.e., within 1 to 4 weeks of treatment, as compared with our population. Poyurovsky et al.[19] suggested that, in the majority of the patients with olanzapine- or risperidone-induced OCS, symptoms appeared early, within a mean ± SD time of 2.1 ± 1.3 weeks. By contrast, the clozapine-treated patients had both an early (4–12 weeks) and a delayed (15–96 weeks) onset of OCS, which is comparable with that seen in our patients with clozapine.

The main limitation of this study is that we did not establish the incidence of de novo OCS emergence in patients prescribed typical antipsychotics in the same time period. In the absence of this comparator group, we are limited in concluding that atypical antipsychotics caused OCS in these patients. Thus, this study does not address questions about the association between atypical antipsychotics and OCS but highlights the need for clinical awareness of the possible occurrence or exacerbation of OCS with atypical antipsychotics. It also highlights the need for careful assessment and mental state examination of these patients and the need to educate the patient on the possibility of these side effects. Patients with schizophrenia or schizoaffective disorder treated with atypical antipsychotics should be assessed for OCS at the start of treatment and at regular intervals thereafter.

Drug names: clomipramine (Anafranil and others), clozapine (FazaClo, Clozaril, and others), fluoxetine (Prozac and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), valproate sodium (Depacon and others).

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