The emergence or exacerbation of obsessive–compulsive (OC) symptoms during treatment with atypical antipsychotics, mostly clozapine, has been documented by numerous case reports (reviewed by Lykouras et al., 2003). In six recent reports involving nine cases, (Jonkers and de Haan, 2002; Lykouras et al., 2003) olanzapine was found either to cause de novo emergence or to exacerbate OC symptoms. In six of these cases olanzapine caused exacerbation and in three cases caused de novo emergence of OC symptoms.

We report three more cases, one with schizophrenia, one with schizophrenia comorbid with major depression and one with bipolar I disorder, in which olanzapine caused de novo emergence of OC symptoms. The last case is the second report of de novo emergence of OC symptoms in a non-psychotic patient without comorbid psychotic symptoms during treatment with olanzapine.

Case reports

Case 1

Mrs G was a 38-yr-old single woman with a 6-yr history of paranoid schizophrenia, according to DSM-IV (persecutory delusion of being followed, auditory hallucinations, misinterpretations and ideas of reference). She was treated with 20 mg/d haloperidol and 4 mg/d biperiden and showed a significant clinical improvement. After 2 yr of treatment the haloperidol dosage was decreased to 10 mg/d and the biperiden dosage to 2 mg/d. To avoid emergence of extrapyramidal side-effects, haloperidol was replaced by 10 mg/d olanzapine within 2 wk during which the two agents were concurrently given in doses of 5 mg/d each. Biperiden was discontinued at the end of the 2-wk period of replacement. No other medication was taken during the entire treatment period. After 10 wk on olanzapine, Mrs G reported new-onset obsessional thoughts that she would get a knife or some other object to hit persons close to her and compulsions of checking (locks, electricity, sockets). These behaviours progressively worsened and became more distressing and time-consuming. She would become very anxious when being close to other people because of her obsessional fear that she might attack them. She also avoided contact with knives and other sharp objects and avoided being close to other people at work. She realized that these symptoms were irrational and bizarre, resisted the ideas but could not avoid them and experienced marked distress. During the following 2 months the symptoms progressively worsened and Mrs G was given fluoxetine at a starting dose of 20 mg/d, which was increased to 40 mg/day over 2 wk. This resulted in a marked improvement over the following 6 wk. Mrs G did not have a prior history of OC symptoms.

Case 2

Ms I was a 23-yr-old single woman with a 3-year history of paranoid schizophrenia comorbid with major depressive episode, according to DSM-IV criteria. Her predominant symptoms were persistent suspiciousness, paranoid delusions, auditory hallucinations as well as depressed mood, anhedonia, feelings of guilt and loss of interest. She was hospitalized and treated with 15 mg/d haloperidol, 30 mg/d paroxetine and 4 mg/d biperiden. Her psychotic condition significantly improved (suspiciousness, some ideas of reference) but she was still moderately depressed (depressed mood in the morning, reduced energy, low self-esteem). Paroxetine was replaced by 112.5 mg/d clomipramine (cross-taper: 10 mg paroxetine for 37.5 mg clomipramine every 5 d), resulting in remission of depressive symptoms over 3 wk. Haloperidol was tapered to 10 mg/d for 3 d, 5 mg/d for 5 d and then stopped, and 5 mg/d olanzapine, increased to 10 mg/d over 3 d, was instituted. After a 4-month treatment period the dose of clomipramine was reduced to 75 mg/d. After approximately 6 months on olanzapine, Ms I experienced OC behaviour, including ‘wishes’ concerning the death of her parents, repetitive thoughts to curse God and the Virgin Mary in church and compulsions to enumerate uneven numbers, to repeatedly number objects and to phone.
repetitively for confirmation of dates and telephone numbers. These symptoms reached their peak in about 4 wk. She acknowledged that these thoughts and actions were irrational, but could not avoid them and was overtaken by intense worry and anxiety. The dose of clomipramine was increased to 150 mg/d resulting in a marked improvement of the OC symptoms over the next 4 wk.

**Case 3**

Mrs H was a 43-yr-old woman with bipolar I disorder since the age of 23. Her predominant manic symptoms were elevated mood, talkativeness, irritability and quarrels with her husband and decreased need for sleep. Depressive episodes were presented with depressed mood, loss of energy, anhedonia, feelings of guilt, etc. She was given 1320 mg/d lithium sulphate and 200 mg/d lamotrigine. Because she remained hypomanic, 5 mg/d olanzapine, increased to 10 mg/d over 3 d, was added.

After 3 months of treatment with olanzapine, Mrs H experienced new-onset OC symptoms, such as opening and closing her handbag several times to make certain that all of her things were there, checking many times to be sure that she had locked the door, shutting off the heater and the electricity, checking that she had extinguished her cigarette, etc. She also opened and closed her files to make certain that all documents were there and asked repeatedly for dates or telephone numbers. These symptoms reached their peak in about 2 wk. The drug was re instituted in the same dose along with 100 mg/d sertraline, without any beneficial effect during the next 5 wk. Sertraline was replaced by 150 mg/d venlafaxine, resulting in remission of the OC symptoms within the following 4 wk.

**Discussion**

In the two cases with psychotic symptomatology (cases 1 and 2) the new symptoms were fundamentally different from the pre-existing psychotic symptoms and insight, a basic feature of OC symptoms (Eisen and Rasmussen, 1993), was present. All patients also acknowledged the content of their thoughts as meaningless and irrational. Most of the reported patients who have developed OC symptoms during treatment with atypical antipsychotics have presented these symptoms for the first time (de novo): 21 out of 30 cases with clozapine, 8 out of 16 patients with risperidone and 3 out of 9 patients with olanzapine (Jonkers and de Haan, 2002; Lykouras et al., 2003). Jonkers and de Haan (2002) described the case of a patient with bipolar II disorder as the first report of de novo emergence of OC symptoms by a non-psychotic patient without comorbid psychotic symptoms during treatment with olanzapine. However, two more such cases have been reported with other atypical antipsychotics: one of a patient with bipolar disorder with clozapine (Poyurovsky et al., 1996) and one of a patient with bipolar II disorder with risperidone (Ramasubbu et al., 2000).

To our knowledge, our case 3 is the second of a non-psychotic patient without comorbid psychotic symptoms who developed de novo OC symptoms with olanzapine.

The three cases reported here increase the total number of reported cases of olanzapine-induced OC symptoms to 12. However, apart from schizophreneia or psychotic disorders, OC symptoms with atypical antipsychotics may occur in major depression with psychotic symptoms also, as in OCD (exacerbation) (Lykouras et al., 2003). The interval between olanzapine administration and the onset of OC symptoms (10, 12 and 24 wk) in the cases we report here was longer than in previously reported cases (days to 12 wk) and also longer than with risperidone (several weeks) and shorter than with clozapine (several months).

In all three cases the dose of olanzapine was low (10 mg/d), while in previous reports doses ranged between 5 and 25 mg/d. Thus, no conclusion can be drawn regarding the role of low vs. high doses in the onset of OC symptoms.

A dose of 40 mg/d fluoxetine was effective in controlling OC symptoms in case 1, while sertraline was ineffective in case 3, which responded favourably to venlafaxine. In case 2, OC symptoms emerged in spite of taking clomipramine and subsided after the dose was increased to 150 mg/d.

Olanzapine possesses potent 5-HT_A receptor- and DA_A receptor-blocking actions (Bymaster et al., 1996). The antagonistic action of atypical antipsychotics at post-synaptic 5-HT_A receptors may underlie the production or exacerbation of OC symptoms.

It has been suggested that the emergence of OC symptoms in some patients may be related to genetic diversity (Jonkers and de Haan, 2002), since 5-HT_A promoter polymorphism has been reported to be associated with OC symptoms (Enoch et al., 1998). The precise 5-HT_A/DA_A receptor blockade ratio seems not to account for the production of OC symptoms.
symptoms since all the commonly used atypical antipsychotics have similar potential to cause such symptoms. The emergence of OC symptoms in a case with bipolar II disorder (Jonkers and de Haan, 2002) and in our case 3 (bipolar I) indicates that the psychotic symptomatology (schizophrenia or comorbid psychotic symptoms) is not a prerequisite for the emergence or worsening of OC symptoms. However, atypical antipsychotics are not homogenous but differ in the spectrum of receptors they influence and exert a differential action in selective regions (Arnt and Skarsfeldt, 1998).

The low dose of olanzapine together with its greater similarities to clozapine rather than to risperidone in 5-HT\textsubscript{2}/D\textsubscript{4} receptor blockade or an unknown time-dependent complex mechanism may account for the delayed appearance of OC symptoms in our patients.

The potential for emergence of OC symptoms during treatment with atypical antipsychotics must be borne in mind since they appear to be under-diagnosed and under-reported, especially in patients with schizophrenia. Vigilance is especially warranted due to the increasing use of these medicines and the fact that these symptoms are treatable with standard anti-OC agents.

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Statement of Interest
None.

References

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