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Obsessive-compulsive disorder in UK clozapine-treated schizophrenia and schizoaffective disorder: a cause for clinical concern

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Abstract

The association between schizophrenia and obsessive-compulsive disorder (OCD) is complex. This study systematically examined a UK cohort of clozapine-treated individuals with schizophrenia/schizoaffective disorder. Fourteen of 59 cases (24%) scored positively on item H of the Mini-International Neuropsychiatric Interview (MINI) for OCD. The mean Yale–Brown Obsessive-Compulsive Scale (Y-BOCS) score in MINI-positive cases was 17.6 (SD ± 6.3). Sixty-four percent scored 16 or more on the Y-BOCS, representing clinically meaningful illness severity. Seven (50%) patients with OCD had previously received the diagnosis by their treating clinicians and were already receiving with selective serotonin re-uptake inhibitors (SSRIs) treatment. OCD cases scored significantly worse than their non-OCD counterparts on the Abnormal Involuntary Movement Scale ($P = 0.01$) and the Simpson Angus Scale (SAS; $P = 0.01$). There was also a non-significant trend toward higher ratings for OCD cases on the Clinical Global Impression-Schizophrenia scale ($P = 0.06$). Comparing the OCD cases taking SSRI ($n = 7$) with those not on SSRI ($n = 7$), significant differences emerged on the SAS ($P = 0.03$). Our results suggest that OCD is common among patients receiving clozapine for schizophrenic disorders and that the comorbidity is associated with greater motoric impairment. The role of medication in this condition remains unclear.

Key words

clozapine; OCD; schizophrenia

Introduction

Interest in the complex relationship between obsessive-compulsive disorder (OCD) and schizophrenia dates back at least to Bleuler (1911). Studies have generally found a greater level of co-occurrence of the two disorders than would be expected by chance (Pallanti, *et al*., 2006). Possible explanations have included (a) OCD naturally occurring as a subsyndrome within the schizophrenia spectrum (Poyurovsky, *et al*., 2003), or (b) treatment for schizophrenia unmasking OCD previously hidden by schizophrenic symptoms (Ertugrul, *et al*., 2005), or (c) treatment for schizophrenia causing OCD de novo, or (d) a factor, as yet unidentified, predisposing individuals to both OCD and schizophrenia. It has been proposed, for example, that the neurobiology underpinning some forms

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of OCD may overlap with that of schizophrenia and involve monoaminergic dysfunction (Tibbo and Warneke, 1999), thus, leading to increased rates of co-occurrence of the two illnesses. In line with this hypothesis, OCD has been found to be associated with a higher than expected frequency of neurological soft signs and motor abnormalities such as tics (Hollander, *et al*., 2005; McDougle, *et al*., 2000) reflecting basal-ganglia involvement. Studies investigating neurocognitive function have also reported overlapping domains of impairment involving frontal or fronto-striatal mechanisms, across the two disorders (Berman, *et al*., 1998; Lysaker, *et al*., 2000; Hwang, *et al*., 2000; Lysaker, *et al*., 2002; Whitney, *et al*., 2004). In a recent study, Ma, *et al.* (2007) found low blood serotonin levels in OCD and in schizophrenia with co-morbid OCD, suggesting alterations in serotonin metabolism as a common biological characteristic in both these groups.

The exact prevalence of OCD occurring with schizophrenia remains uncertain. Estimates have ranged from as low as 0.5% to as high as 55% (Table 1). The considerable variability between studies has been attributed to methodological and sampling differences. Studies mainly included multiple different treatments, and the intensity of the OCD was rarely reported.

Other evidence suggests that OCD is commoner in schizophrenia treated with antipsychotics. However, in the absence of prospective controlled studies evaluating the effect of treatment over time on obsessive-compulsive symptomatology, it is not possible to infer a causal relationship. Second-generation antipsychotics have been associated with OCD symptoms in reports of cases of schizophrenia. Clozapine, arguably, has been implicated in most reports (De Haan, *et al*., 1999; Lykouras, *et al*., 2003; Ongur and Goff, 2005). Several studies have identified emergence of obsessive-compulsive symptoms during treatment with clozapine (Baker, *et al*., 1992; Biondi, *et al*., 1999; Reznik, *et al*., 2004; Galvez-Buccollini, *et al*., 2004). Reznik, *et al*. (2004) reported a dose-related pro-obsessive influence of high-dose clozapine and found a poor response to clozapine monotherapy when obsessive-compulsive symptomatology preceded the development of schizophrenia. In the chart review by De Haan, *et al.* (2004), 4 of 41 (9.8%) schizophrenic inpatients receiving clozapine were diagnosed with comorbid OCD before treatment and another four patients (9.8%) developed OCD during treatment. In the group treated with other antipsychotics, 10 of 154 (6.5%) showed OCD before treatment and none developed OCD during treatment. Clozapine was associated with statistically more OCD cases at discharge than other antipsychotics. In a survey of outpatients with schizophrenia, Galvez-Buccollini, *et al.* (2004) reported significantly higher rate of obsessive-compulsive symptoms (46.4%, $P = 0.005$) in 56 clozapine-treated schizophrenic patients compared with 54 who received other antipsychotic drugs (20.4%). The association between clozapine and OCD may be related to its particular profile of pharmacodynamic actions at dopaminergic and/or serotonergic receptors. However, clozapine is also the recognised treatment for severe, multiple antipsychotic-resistant schizophrenia, and in the UK, its use is largely reserved for this patient group. Thus, greater levels of illness comorbidity might be expected in these patients anyway.

The effect of the co-occurrence of OCD and schizophrenia on levels of clinical impairment also remains unclear. Few

Table 1 Prevalence of OCD in schizophrenia: published studies

Authors	OCD (%)	Cohort size (*n*)	Type of study
Fenton, McGlashan, 1986	12.9	163	Chart review, inpatients
Bland, *et al*., 1987	55	20	Cross sectional survey, community sample
Berman, *et al*., 1995a,b	25	108	Chart review, outpatients
Eisen, *et al*., 1997	7.8	77	Cross sectional survey, outpatients
Porto, *et al*., 1997	26	50	Cross sectional survey, day-treatment patients
Berman, *et al*., 1998	47	30	Cross sectional survey, inpatients
De Haan, *et al*., 1999[a]	21.9	121	Retrospective cohort study, inpatients
Poyurovsky, *et al*., 1999a,b[b]	14	50	Cross sectional survey, inpatients
Kruger, *et al*., 2000	15.8	76	Cross sectional survey, inpatients
Lysaker, *et al*., 2000	45	46	Cross sectional survey, outpatients
Tibbo, *et al*., 2000	25	52	Cross sectional survey, community sample
Poyurovsky, *et al*., 2001	23.5	68	Cross sectional survey, inpatients
Lysaker, *et al*., 2002	17	63	Cross sectional survey, outpatient
Nechmad, *et al*., 2003[a]	26	50	Cross sectional survey, inpatients
Ohta, *et al*., 2003	18.3	71	Cross sectional survey, inpatients/outpatients
De Haan, *et al*., 2004	7	200	Chart review
Byerly, *et al*., 2005	23	100	Cross sectional survey, outpatients
Niehaus, *et al*., 2005	0.5	509	Cross sectional survey, inpatients, outpatients
Ongur, Goff, 2005	8.8	118	Cross sectional survey, outpatients

[a]In adolescents.

[b]Consecutively admitted first episode cases.

studies have examined this area; some suggested a poorer prognosis (Fenton and McGlashan, 1986; Berman, *et al*., 1995a, b; Poyurovsky, *et al*., 1999a, b), whereas others reported that the presence of obsessive-compulsive symptoms was associated with a more favourable outcome of schizophrenia (Poyurovsky, *et al*., 2000; Hwang and Hollander, 1993). Ohta, *et al*. (2003) investigated 71 schizophrenic patients taking a range of treatments who could manage to complete the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS; Goodman, *et al*., 1989). Thirteen (18.3%) were diagnosed with OCD, and these cases reported significantly higher levels of extra-pyramidal motor symptoms on the Abnormal Involuntary Movement Scale (AIMS; Guy, 1976) and the Simpson Angus Scale (SAS; Simpson and Angus, 1970), but not on the Barnes Akathisia Scale (Barnes, 1989), than those without OCD. In a systematic survey of 76 schizophrenic subjects, Kruger, *et al*. (2000) reported significantly greater impairment on the AIMS, but not on the SAS, in those cases with OCD ($n = 12$) compared with non-OCD cases although another study by Poyurovsky, *et al*. (2001) did not discriminate between those with ($n = 16$) and without OCD ($n = 52$) using the AIMS and the Barnes Akathisia Scale. It instead identified greater impairment in the schizo-obsessive group on the Social Behaviour Scale (Wykes and Sturt, 1986). Clarification of the rates and clinical implications of OCD–schizophrenia comorbidity, using systematic techniques within defined groups of patients, will contribute toward better understanding of the aetiologies of these major neuropsychiatric disorders and may point toward new treatment strategies for those enduring the two disorders together.

Aims

We report the first study to examine OCD in a UK cohort of clozapine-treated cases. Our aims were to identify the point prevalence and clinical impact of OCD on schizophrenic patients treated with a specific antipsychotic (clozapine) previously considered to be associated with increased rates of OCD, using direct and detailed enquiry with validated diagnostic and severity-rating instruments, including measures of social disability. We hypothesised (1) that there would be a substantial prevalence of clinically relevant OCD in this cohort, (2) that many of these cases would have been undiagnosed under normal clinical treatment up until the point of investigation and (3) that the comorbid cases would be more severely impaired in measures of global schizophrenia symptomatology, psychosocial adjustment and motor function.

Methods

A systematic, cross-sectional survey of all clozapine-treated individuals with schizophrenia/schizo-affective disorder attending the Queen Elizabeth II Hospital (QEII), Welwyn Garden City, United Kingdom, was performed. East and North Hertfordshire Hospitals Local Research Ethics Committee granted ethical approval for the project on 15 July, 2004. Recruitment took place from 08 September, 2004 to 11 November, 2006. All patients attending the Clozapine Clinic were invited to take part. To receive clozapine in this locality, patients needed to be registered in the Clozapine Clinic under the care of a consultant psychiatrist. Their well-being was monitored regularly by designated nursing and ancillary staff during each clinic visit. Thus, we were able to access all patients receiving clozapine in the locality. A patient information pack was distributed at least 24 h before patients were recruited and valid written consent was obtained from each patient who took part. Patients were interviewed in a quiet room and were allowed comfort breaks as required.

Inclusion criterion

All patients fulfilling DSM-IV (American Psychiatric Association, 2000) criteria for schizophrenia and/or schizoaffective disorder, defined from clinical case notes attending the Clozapine Clinic, were included.

Exclusion criterion

Clozapine-treated patients with psychotic illness that was not associated with schizophrenia/schizoaffective disorder, defined from case notes, were excluded.

Psychometric instruments

All patients were evaluated on the following scales:

- Clinical Global Impression Scale for Schizophrenia (CGI-SCH; Haro, *et al*., 2003) – a brief clinician rated scale that evaluates the severity of negative and positive symptoms.
- Abnormal Involuntary Movement Scale (AIMS; Guy, 1976) – an observer rated scale that measures the severity of involuntary motoric activity.
- Simpson Angus Scale (SAS; Simpson and Angus, 1970) – a clinician rated measure for extra-pyramidal symptoms.
- Sheehan Disability Scale (SDS; Leon, *et al*., 1992) – a self-rated scale measuring three key aspects of social impairment.
- Item H of the Mini – International Neuropsychiatric Interview (MINI; Sheehan, *et al*., 1998). Item H screens for DSM-IV OCD and takes about 5 min to administer.

All those scoring positive for OCD on the MINI were evaluated using the observer-rated Yale–Brown Obsessive Compulsive Scale (Y-BOCS; Goodman, *et al*., 1989) for severity of obsessive-compulsive symptomatology.

Statistical analysis

Differences between comorbid and non-comorbid cases were tested using the non-parametric Mann–Whitney test. Further exploratory analyses were carried out on the data from comorbid cases to examine differences between those medicated with

a selective serotonin reuptake inhibitor (SSRI) and those not taking an SSRI.

Results

Sixty-eight patients were registered with the Clozapine Clinic. Sixty patients consented to participate in the study. Five refused to consent and three patients moved out of the area before they were approached and hence could not be recruited. One patient stopped taking clozapine before he could be recruited. Altogether, 59 patients were recruited, of whom 22 were women and 37 were men. Fifty-six patients had schizophrenia and 3 had schizoaffective disorder. The mean age was 41.9 years (SD = 13.3), and the mean length of illness was 10.4 years (SD = 5.0). Of the 59 clozapine-treated cases, four were taking an additional antipsychotic (amisulpride, $n = 3$; trifluoperazine, $n = 1$), sixteen were taking an antimuscarinic (procyclidine, $n = 6$; pirenzepine, $n = 6$; hyoscine, $n = 3$; benzhexol, $n = 1$), sixteen were taking an antidepressant (SSRI, $n = 12$; moclobemide, $n = 1$; venlafaxine, $n = 1$; tricyclic, $n = 2$), four were taking a mood stabiliser (lithium, $n = 2$; valproate, $n = 2$) and 5 were taking a hypnotic (temazepam, $n = 2$, diazepam, $n = 2$; zopiclone, $n = 1$).

Fourteen out of 59 cases (24%) scored positively on the MINI for OCD. MINI-positive and MINI-negative cases were similar on demographic parameters such as age, gender and length of illness. MINI-positive cases were significantly more likely to be receiving SSRI (Chi squared, $P < 0.05$). There were no other significant between-group differences relating to prescribed medication. The mean dose of clozapine was 432 mg in MINI-positive cases and 351 mg in MINI-negative cases (NS). The mean Y-BOCS score in MINI-positive cases was 17.6 (range 9–29; SD = 6.3). Figure 1 shows the distribution of Y-BOCS scores in the MINI-positive cases. Sixty-four percent scored 16 or more on Y-BOCS, representing clinically meaningful illness severity.

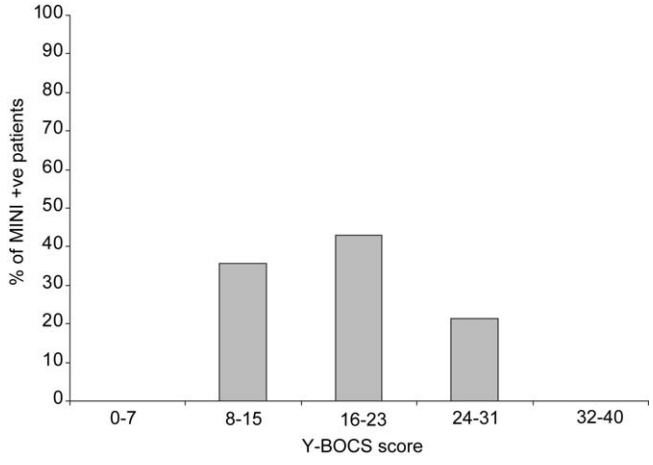

Figure 1 Distribution of Y-BOCS scores in MINI-positive group ($n = 14$).

Table 2 Mean clinical ratings in MINI-positive and MINI-negative groups

	Mean (SD)			
	CGI-SCH	AIMS	SAS	SDS
MINI positive	2.9 (0.9)	4.4 (4.4)*	5.1 (3.3)*	13.6 (6.5)
MINI negative	2.4 (0.8)	1.3 (2.9)	2.6 (2.6)	10.5 (6.8)

*$P < 0.05$.

Mean clinical ratings in MINI-positive and MINI-negative groups are presented in Table 2. OCD cases were distinguishable from non-OCD cases by significantly higher scores on the AIMS ($U = 172$; $P = 0.01$) and the SAS ($U = 175$; $P = 0.01$). On the CGI-SCH, OCD cases also scored higher compared with non-OCD cases although this difference did not quite reach statistical significance ($U = 209.5$; $P = 0.06$). In addition, OCD cases reported a numerically higher mean composite score on the SDS compared with non-OCD cases, but this difference also failed to reach statistical significance ($U = 213$; $P = 0.08$).

Of the MINI-positive cases, seven (50%) had previously received a diagnosis of OCD by their treating clinicians and were already receiving SSRI treatment (two on citalopram 30 mg and 40 mg, respectively, two on paroxetine 40 mg, two on fluoxetine 60 mg, one on sertraline 150 mg – all receiving SSRI for more than 3 years). Seven cases (50%) had neither been diagnosed nor been treated for OCD before the study. The mean Y-BOCS score in the SSRI-treated group was 19.7 (SD = 4.8) compared with 15.4 (SD = 7.2) in the non SSRI–treated group (NS). No association was found between Y-BOCS scores and severity of schizophrenic symptoms as measured by each of the five CGI-SCH items.

Table 3 presents the mean clinical ratings in OCD cases on SSRI ($n = 7$) and cases not on SSRI ($n = 7$). A significant difference emerged on SAS score, with the group on SSRI scoring higher ($U = 7.5$; $P = 0.03$).

Discussion

Study limitations

This was a cross-sectional survey of clozapine-treated schizophrenic/schizoaffective patients conducted within a naturalistic

Table 3 Mean clinical ratings in MINI-positive cases taking SSRIs and MINI-positive cases not taking SSRIs

	Mean (SD)			
	CGI-SCH	AIMS	SAS	Sheehan
MINI positive on SSRI	3.0 (1.0)	5.7 (4.9)	6.9 (3.1)*	13.9 (7.6)
MINI positive not on SSRI	2.9 (0.9)	3.1 (3.7)	3.3 (2.5)	13.4 (5.7)

*$P < 0.05$.

setting and without a control group for comparison. Patients were taking various medications although clozapine was a constant factor, and most patients (55/59) were receiving a single antipsychotic. On the basis of our design, neither could we establish the temporal relationship between the onset of obsessional and schizophrenic symptoms and treatment nor could we compare the findings for this group could be compared with those for other patient groups and other forms of treatment. In the UK, the use of clozapine is restricted to otherwise antipsychotic-resistant individuals. Thus, recruitment of suitable cases at a single site is limited. Nonetheless, this is, as far as we are aware, the largest cohort of clozapine-treated cases examined for OCD. To maximise patient participation, we chose rating scales that were quick and easy to apply. We specifically chose the 5-item CGI-SCH for this reason. We managed to recruit all but nine registered clozapine cases in the area. Nonetheless, our sample size was not large ($n = 59$), which to some extent compromised our study's statistical power.

General discussion

In line with our first two a priori hypotheses, we reported OCD occurring in a substantial proportion (point prevalence = 24%) of an almost complete cohort (59 of 68 cases) of clozapine-treated schizophrenia/schizoaffective cases in the UK. Our results do not suggest that clozapine necessarily increases the frequency of OCD in schizophrenia. Indeed, the frequency of OCD was roughly similar to that previously reported in several recent studies, which included cases of schizophrenia receiving treatments other than clozapine (Berman, *et al*., 1995a, b; Byerly, *et al*., 2005; Nechmad, *et al*., 2003; Poyurovsky, *et al*., 2001; Tibbo, *et al*., 2000) (Table 1). Around two-thirds of the MINI-positive cases scored above 16 points on the Y-BOCS, representing at least moderate levels of symptomatology. This is a clinically relevant score that merits treatment. For half of these patients, the OCD had been previously unrecognised despite similar illness severity compared with the patients whose OCD had been diagnosed by their treating teams and who were receiving SSRI treatment. Mean total Y-BOCS scores in the SSRI-treated group were slightly higher than the untreated cases on the day of testing (19.7 vs 15.4; NS). In most cases, those on treatment had been receiving therapeutic doses of SSRI for at least 12 weeks, which is usually a sufficient time for the anti-OCD effect to develop in non-comorbid OCD (Fineberg and Gale, 2005). Interpretations of this finding include either greater baseline morbid load of OCD within the SSRI-treated group or relative lack of anti-OCD efficacy of SSRI in highly resistant cases of schizophrenia receiving clozapine.

We only partially substantiated our third hypothesis. The mean values for CGI-SCH were rather low overall, representing, on average, mild to moderate illness. However, there was a numerically (but not statistically) higher mean score in the OCD group than the in the non-OCD group, hinting that either they had a more severe form of schizophrenia or clozapine is less successful in treating schizophrenia with co-morbid OCD. Similarly, there was a non-significantly worse score for OCD cases on the self-report Sheehan Disability Scale. Larger subject numbers are needed to address this issue adequately.

In contrast, the results for motor dysfunction were clear-cut. In our study, patients with OCD scored significantly worse than their non-OCD counterparts on both the AIMS and the SAS. Thus, our findings were in line with those of Ohta, *et al*. (2003) and Kruger, *et al*. (2000). Higher scores on the AIMS represent greater severity of involuntary movements associated with antipsychotic drugs such as tardive dyskinesia, dystonia and chronic akathasia, as well as spontaneous motor disturbances related to the illness itself. On the SAS, higher scores represent greater severity of parkinsonian symptomatology. Abnormalities on these scales could reflect basal-ganglia disturbance. The abnormally high-mean SAS and AIMS scores in our OCD group were at a level considered clinically relevant. Thus, in terms of abnormal extraneous movements and parkinsonian dysfunction, the OCD cases were more severely impaired, suggesting greater neural involvement in cortico-striato-thalamic circuitry. Given that clozapine is usually associated with a low level of extra-pyramidal side effects (Conley and Kelly, 2005; Strejilevich, *et al*., 2005; Iqbal, *et al*., 2003), observed motor dysfunction in these cases is likely to reflect, at least to some degree, underlying neural pathology. However, the higher doses of clozapine in the OCD group, although not statistically significant, may also have contributed to the greater severity of observed extra-pyramidal side effects in these patients. Interestingly, OCD cases who were receiving SSRI treatment showed greatest dysfunction on the SAS (but not on the AIMS) and were significantly more parkinsonian than untreated OCD cases. SSRIs are reported to occasionally cause extrapyramidal effects, particularly at higher daily dosages, thought to be mediated by antagonist effects upon activity in ascending dopamine pathways, inter alia. Our findings suggest a particular vulnerability to this effect in the OCD group, implicating abnormal dopaminergic sensitivity in individuals with schizophrenia and OCD. This result should, however, be interpreted with particular caution because of the small sample size.

Although these were well worked-up cases who underwent at least four-weekly clinical review, a significant number of OCD cases were missed/undiagnosed (50% of MINI positive) and were detected for the first time in the course of this study. The degree and severity of OCD and motor dysfunction that was identified was nevertheless clinically meaningful. Pallanti, *et al*. (2006) emphasised the difficulty in distinguishing obsessions and compulsions against a background of schizophrenia in the naturalistic setting and the importance of detailed clinical assessment. There is, thus, an argument for routine screening of individuals for OCD and motor signs in clozapine clinics (Ohta, *et al*., 2003). However, those receiving pharmacological treatment for OCD in our study were not apparently symptomatically improved – indeed from a motor point of view they were more impaired. A number of controlled and uncontrolled

Table 4 Summary of studies showing effect of SRI on OCD

Author, year	Size (*n*)	Type of study	SRI	Outcome on OCD
Allen and Tejera, 1994	1	Case study	Sertraline	Improved
Berman, *et al.*, 1995a,b	6	Cross-over study[a]	Clomipramine vs placebo	Improved on clomipramine > placebo
Poyurovsky, *et al.*, 1996	4	Case series	Fluvoxamine	Improved
Poyurovsky and Weizman, 1998	1	Case report	IV clomipramine	Improved
Poyurovsky, *et al.*, 1999a,b	10	Open-label study	Fluvoxamine	Improved
Rahman, *et al.*, 1998	1	Case study	Sertraline	Improved
Strous, *et al.*, 1999	1	Case study	Paroxetine	Improved
Reznik and Sirota, 2000	14 vs 16	RCT[b]	Fluvoxamine	Improved on fluvoxamine
Dwivedi, *et al.*, 2002	1	Case study	Fluvoxamine	Improved
Sievers, *et al.*, 2005	1	Case study	Citalopram	Improved
Ozer, *et al.*, 2006	1	Case study	Fluoxetine	Improved
Zohar, *et al.*, 1993	5	Open-label study	Clomipramine	Improved

[a]Placebo-controlled double-blind crossover trial.

[b]Randomised trial under open-label conditions, 14 received fluvoxamine + neuroleptic, 16 received neuroleptic only.

treatment trials have showed that combining clomipramine or an SSRI with an atypical antipsychotic might improve OCD symptoms in cases of schizophrenia with co-morbid OCD (Table 4). Careful monitoring is recommended, as there is potential for adverse effects and drug interactions with this treatment combination (Pallanti, *et al.*, 2006).

Conclusions

Roughly one quarter of a cohort of clozapine-treated schizophrenic/schizoaffective patients were found to suffer with OCD. Of these, 50% were previously undiagnosed. OCD cases were more motorically impaired suggesting a separate neurobiology for the comorbid group and a possible effect of combined SSRI – antipsychotic treatment on motor functioning.

Clinical action points

- Clinicians should exercise a low threshold for suspecting OCD in individuals with schizophrenia – especially those receiving clozapine.
- Patients due to start clozapine should be screened for OCD and motor dysfunction before treatment commences and reviewed for these problems during treatment.
- The implications of co-morbid OCD, including its impact on clinical function, treatment options and potential adverse effects, should be discussed with affected patients.

Future research directions

- Randomised treatment trials comparing the clinical effectiveness of specific antipsychotics and SSRIs, individually and combined, in patients with schizophrenia and OCD.
- Exploration of the neurobiological basis of observed motor abnormalities in patients with schizophrenia and OCD, using neurocognitive and brain imaging techniques.
- Investigation of families of co-morbid patients, including unaffected first degree relatives, for evidence of specific neurobiological endophenotypes.

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