Obsessive compulsive symptoms in patients with Schizophrenia on Clozapine and with Obsessive Compulsive disorder: A comparison study

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1. Introduction:

A growing literature suggests obsessive compulsive symptomatology (OCS) may be present in many of those with schizophrenia, and that this is associated with higher rates of both positive and negative psychotic symptoms [1, 2].

The relationship between OCS and schizophrenia is not clear. Studies have distinguished between OCS and co-morbid Obsessive-compulsive Disorder with the latter being less prevalent, though much higher than the general population. Clinical and epidemiological studies suggest that more than one-third of individuals with schizophrenia display OCS, and prevalence rates for OCD have ranged between 7.8% and 40.5%.[3-5].

Some have argued that the s OCS is medication related, with atypical antipsychotics including clozapine [6-9]. However the literature regarding the relationship between OC symptoms and clozapine therapy is contradictory. One study [10] suggested that dosage of Clozapine is an important factor in the presence of OC symptoms in psychosis, while another claims no such dose effect exists [11]. A recent review article suggested that atypical anti-psychotics may 'unmask' OCS in those that might be genetically predisposed [12]. Growing evidence suggests

the existence of a 'schizo-obsessive' subtype within schizophrenia [12, 13]. However little is known about the symptom profile of this group of patients compared to non-schizophrenia OCS patients. Some research [14, 15] has suggested that certain types of obsessions and underlying meta-cognitions, specifically cognitive obsessions, may be more linked to schizophrenia than OCS in non-psychotic patients. This is some limited evidence to suggest that that OCS may be more covert or cognitive than overt or behavioural in nature in a psychotic population [16, 17]. We hypothesised that the prevalence, nature and severity of the obsessive-compulsive symptom complex in a group of patients with a diagnosis of schizophrenia on clozapine treatment would differ qualitatively from those with OCD in particular those with schizophrenia would have more cognitive than behavioural obsessive compulsive symptoms.

2. Methods:

2.1 Subjects

This is a cross sectional observational study and was carried out in a suburban community based mental health service in a geographically defined catchment area of 175,000. A list of patients registered with the clozapine monitoring service was compiled by cross checking registered patients with the pharmacy service, a nurse led monitoring clinic and consultant lists of patients. A total of one hundred and twenty three patients were registered with the clozapine monitoring service at the time of the study in 2007. On the advice of the Ethics Committee who approved the study, patients who were participating in another study were excluded. There were no other exclusion criteria. This reduced the sample size to one hundred and one potential candidates.

Patients with schizophrenia treated with clozapine were recruited at a clozapine clinic situated on two clinical sites.

The comparison group was recruited from patients referred to a cognitive behaviour therapy group for obsessive compulsive disorder. Inclusion criterion was a DSM-IV diagnosis of OCD based on clinical assessment.

All participants gave written informed consent to participate in the study. Exclusion criteria were a diagnosis of Dementia, pervasive developmental delay or participation in a concurrent study. Demographic data relating to age, gender, marital status (dichotomized to single or other), employment status (dichotomized to those receiving a state benefit for a disability or other), housing status (dichotomized to independent living or not) was compiled. Information regarding hospitalizations, diagnosis and pre-existing obsessive compulsive symptoms, was obtained from patient electronic and paper records. Information was also gathered on current medication use from the electronic patient record. Patients' records were reviewed to determine whether obsessive compulsive symptoms were recorded before the introduction of clozapine. Accurate dates were available recording the initiation date of clozapine treatment.

2.2. Instruments

All participants also completed the Obsessive Compulsive Inventory: a self-report measure of obsessive compulsive symptoms [18]. This was developed from the Maudsley Obsessive Compulsive Inventory and includes 7 subscales: Washing, Checking, Ordering, and Hoarding (which are more overt behavioural symptoms) and Obsessing Doubting and Mental Neutralizing (which are more covert cognitive symptoms). The full scale and most subscales have satisfactory internal consistency. The alpha coefficients of the full scale for the clozapine

and OCD groups were both high (range .86 to .95), indicating that the distress and frequency items within each subscale converge on a common construct. Total scores were used in the analysis as the cut-off has not been determined for a population with schizophrenia.

The Hospital Anxiety and Depression Scale was completed by participants [18]. This is a fourteen item questionnaire, seven for anxiety and seven for depression. It has been found to have good reliability and showed high internal consistency in this study ($\alpha=0.89$ for both subscales).

The Brief Psychiatric Rating Scale (BPRS) is a clinician rated questionnaire [19]. The version used in the present study comprised of 24 items rated from 1-7 from 'Not Present' to 'Extremely Severe'. Previous research has found high inter-rater reliability ($\alpha = 0.83.$) and this study found good internal consistency ($\alpha=0.767$).

Data were analyzed using SPSS version 12 and STATA Version 10. Power calculations were performed using GPower [20]. Means and standard deviations were calculated for continuous data. Numbers and percentages were obtained for categorical variables. Data were normally distributed, as assessed by p-p plots. Uni-variate analyses were performed using t tests and χ^2 as appropriate. Bonferroni corrections were used and set the statistical significance at $p < .002$.

3. Results:

3.1 Demographics:

The sample size of eligible candidates for the clozapine study was 101 representing 82% of patients prescribed clozapine at the time of the study. 62 patients with schizophrenia treated with clozapine agreed to participate; this represented a response rate for the Clozapine group was 62% and a sample rate of 50% of clozapine population in the service. The 22 (17% of Clozapine

registered patients) who were not eligible to be included on ethical grounds were participating in a first episode study. A total of 35 patients with OCD who had been participated in a study on CBT and OCD agreed to consent for data to be used in this study which represented a 95% response rate. The demographic characteristics of the sample are reported in Table 1. Age profile was similar in both groups. There were significant gender differences with more men in the Clozapine group and more women in the OCD group. Overall the OCD group appeared to be higher functioning as indicated by higher rates of employment, greater homeownership and fewer hospitalisations.

Table 1: Demographics of Clozapine(CLZ) and OCD group participants

Variables			CLZ n=62	OCD n=35	t or χ^2	Power
Age		M	38.32	38.94	-.256	ES=.051 (1- β prob =0.95)
		SD	9.6	14.1		
Gender	Male	N	42	16	4.51	P<.05
		%	68	46		
	Female	N	20	46		
		%	32	54		
Married		N	4	8	7.605 27.43	P<.000
		%	6.5	22.9		
Employment Status	Employed	N	10	18	13.24	P<.00
		%	17	51		
	Disability	N	26	0		
		%	45	0		
Housing Status	Homeowner	N	7	13	4.87	P<.000
		%	12	37		
	Transitional	N	12	1		
		%	20.3	2.9		
Hospitalisations		M	7.03	1.06		
		SD	6.6	2.9		
Clozapine Dose		M	385.6			ES=1.17 (1- β prob =0.95)
		SD	140.2			

3.2 Clozapine sample: Within group Analysis

The mean clozapine dose was 385 (SD=140). Nine (11%) had documented OC symptoms pre-clozapine. Overall 14 (23%) of the clozapine group had clinically significant total OCI scores, of those 2 (3%) had documented OCS pre clozapine and 12 (19%) were new cases documented. Seven (11%) appeared to have resolved symptoms, 12 (19%) developed new symptoms and 2 (3%) remain unchanged. Neither demographics, medication (neither including clozapine dose or use of SSRI, symptom severity (as measured by BPRS) nor pre-existing OCS was predictive of OCS in Clozapine group. Clozapine group had low psychiatric symptom severity on the BPRS, suggesting psychotic symptoms are well controlled on clozapine.

3.3 Differences between Clozapine and OCD group.

Fifty eight out of 61 patients (94%) with schizophrenia treated with clozapine reported at least one OC symptom on the OCI. Thirty four out of 35 patients (97%) in the OCD group reported at least one OC symptom. Twenty three per cent of the Clozapine group had clinically significant total scores on the OCI significantly lower than the rate of 60% in the OCD group ($\chi^2=13.58$, $df=1$, $p=.000$). The mean scores of the Clozapine and OCD groups on the subscale items are shown in Table 2. The OCD group had significantly higher anxiety scores ($t=-3.4$, $df=90$, $p=0.001$). There was no significant difference in antidepressant use between the Clozapine group and the OCD group.

Table 2: Symptom Profile of Clozapine and OCD group

			CLZ	OCD	t-test	Power
HADS	Anxiety*	X	8.75 <	12.18 >	df=90	ES=.74 (1- β
		SD	4.62	4.55	t=-3.435 p=0.001	prob=0.95)
	Depression	X	5.34<	7.61 <	df=90	ES=.53 (1- β
		SD	4.55	3.91	t=-2.403 p=0.018	prob=0.95)
OCI	OCI Wash F*	X	0.74 <	1.97 >	df=95	ES=.92 (1- β
		SD	0.89	1.67	t= -4.724 p=0.000	prob=0.95)
	OCI Wash D*	X	0.54<	1.65>	df=95	ES=1.04 (1- β
		SD	0.77	1.30	t=-5.314 p=0.000	prob=0.95)
	OCI Check F	X	1.12<	1.75>	df=61.723#,	ES=.66 (1- β
		SD	0.87	1.02	t=-3.078 p=0.003	prob=0.95)
	OCI Check D*	X	0.80<	1.64>	df=95	ES=.92 (1- β
		SD	0.79	1.03	t=-3.822 p=0.000	prob=0.95)
	OCI Doubt F	X	1.30<	1.92>	df=95,	ES=.48 (1- β
		SD	1.14	1.42	t= -2.362, p=0.02	prob=0.95)
	OCI Doubt D*	X	1.01<	1.91<	df=95,	ES=.73(1- β
		SD	1.02	1.42	t=-3.628, p=0.000	prob=0.95)
	OCI Order F*	X	0.86<	1.66<	df=57.040#,	ES=.80 (1- β
		SD	0.86	1.12	t=-3.651, p=0.001	prob=0.95)
	OCI Order D*	X	0.59<	1.44<	df=95,	ES=.91 (1- β
		SD	0.71	1.11	t=-4.603, p=0.000	prob=0.95)
	OCI Obsess F*	X	1.17<	1.92>	df=64.396#,	ES=.77 (1- β
		SD	0.92	1.03	t=-3.582, p=0.001	prob=0.95)
	OCI Obsess D*	X	1.11<	1.92>	df=67.049,	ES=.84 (1- β
		SD	0.93	0.99	t=-3.957, p=0.000	prob=0.95)
	OCI Hoard F	X	0.93<	1.63>	df=95,	ES=.61 (1- β
		SD	0.92	1.35	t=-3.031, p=0.003	prob=0.95)
	OCI Hoard D	X	0.56<	1.25>	df=95,	ES=.62 (1- β
		SD	0.87	1.30	t=-3.098, p=0.003	prob=0.95)
	OCI Neut F	X	0.95<	1.32<	df=-1.903#,	ES=.40 (1- β
		SD	0.89	0.94	t=-1.903, p=.061	prob=0.95)
	OCI Neut D*	X	0.64<	1.20<	df=95,	ES=.66 (1- β
		SD	0.72	0.95	t= -3.204, p=0.002	prob=0.95)
	OCI Total F*	X	41.04<	71.77>	df=64.012#,	ES=1.02 (1- β
		SD	30.59	29.56	t=-5.540, p=0.000	prob=0.95)
	OCI Total D*	X	31.94<	67.28>	df=64,	ES=1.19 (1- β
		SD	27.90	31.38	t=-5.383, p=0.000	prob=0.95)

< below clinical cut off, > above clinical cut off. * Bonferroni correction sets alpha at .002.

#Note these subtests had unequal variance based on Levine test for equality of variance

3.4 OC Symptom Profile:

The OCD group reported significantly more OC symptoms than the Clozapine group ($t=-5.540$, $df=64$ $p=0.000$). Mean scores on OCI on Washing, Ordering, Obsessing and Hoarding were significantly higher in the OCD group compared to the Clozapine group based on bonferroni correction. Mean scores in the OCD group were above the threshold for clinical significance on all subscales bar Ordering and Neutralising. None of the mean scores in the Clozapine group reached the clinically significant range. The highest mean score for OC symptoms in the OCD group was on the Washing subscale. The highest mean score in the Clozapine group was on the Doubting symptom scale. The distress associated with OC symptoms was greater in the OCD group compared with the Clozapine group ($t=-5.38$, $df=64$, $p=.000$). Both groups were more distressed by cognitive than behavioural symptoms

Figure1: Differences in Behavioural OCS

Overall, the OCD group reported higher rates of behavioural OCS. Differences in rates of Checking and Hoarding were not significantly different, based on Bonferonni correction. However, there were significant differences in rates of Ordering and Washing symptoms, with the OCD group reported much greater frequency of these symptoms. With regard to cognitive symptoms, there were fewer between group differences with similar mean scores for Doubting and Neutralising subscales. There was a significant difference between groups in rates of Obsessing. The OCD reported significantly higher level compared to the Clozapine group.

Figure 2: Differences in Cognitive OCS

**p=.001

3.5 Relationship between OC symptoms and other psychiatric symptoms

In the OCD group, anxiety did not correlate significantly with any OCI subscales whereas in the Clozapine group, anxiety correlated with Obsessing ($r=.640$, $p=.000$) and Total Frequency ($r=.500$, $p=.000$). This suggests that anxiety has a possible impact on the presence of OC symptoms, specifically Obsessing in the Clozapine group. There was no significant relationship between OCI total frequency and BPRS total score ($r=.356$, $p=.005$). None of the individual BPRS items correlated significantly with Total OCI score. The OCI Obsessing subscale was the only subscale that correlated strongly with the BPRS total score ($r=.535$, $p=.000$). When the individual BPRS items and the Obsessing subscale were assessed for correlations only one item, Unusual Thought Content was significant ($r=.553$, $p=.000$). This suggests that the association is specific; there is a high correlation between different subscales Unusual Thought Content and Obsessing. When the effect of anxiety was controlled for using a partial correlation, the following items correlated significantly with Obsessing subscale: Unusual thoughts remains highly correlated ($r=.595$, $p=.000$) and two new items: Grandiosity ($r=.571$, $p=.000$) and Hallucinations ($r=.595$, $p=.000$) emerged as correlating strongly. When the potential effect of Clozapine was controlled for using a partial correlation, Unusual Thought Content was the only variable to correlate significantly with the Obsessing subscale ($r=.635$, $p=.000$).

4. Discussion:

Overall, the Clozapine group reported significantly lower mean scores on all OC symptoms compared to the OCD group and none of the OC symptoms in the Clozapine reached clinical significance. There was a greater difference between the OCD and Clozapine groups in terms of behavioural OCS than cognitive OCS. Compared to the OCD group, the Clozapine group scored significantly lower on Ordering and Washing but not Checking or Hoarding. With regard to cognitive symptoms, there were fewer between group differences with similar mean scores for Doubting and Neutralising subscales. The Clozapine group scored significantly lower on the Obsessing subscale compared to the OCD group.

This suggests some differences in the symptom profile, with the schizophrenia patient treated with Clozapine more likely to report cognitive rather than behavioural symptoms. Furthermore, people with OCD reported more distress associated with OC symptoms than reported by those with schizophrenia treated with Clozapine. Among those on clozapine, there was no dose-OC symptoms relationship irrespective of whether the person was prescribed an SSRI or other anti-depressant. Anxiety correlated highly with OC symptoms in the clozapine but not the OCD group. There was also a correlation between psychiatric severity and OC symptoms, specifically Unusual Thought Content and Obsessing (a cognitive OC symptom). This suggests that those OC symptoms in clozapine patients may be related to other psychiatric symptoms whereas in the OCD group, OC symptoms appear to be independent of other symptoms.

The present study found no relationship between Clozapine dose and OC symptoms as measured by the OCI. This appears to contradict recent findings by Sa et al (2009) who found that compared to patients on Haloperidol, those on Clozapine had significantly more severe OC symptoms [23]. When found a relationship between Obsessing symptoms and Unusual Thought

Content as measured by the BPRS, which was independent of Clozapine dose. Our research suggests a more subtle relationship between OC and psychiatric symptom severity that does not appear to be mediated by Clozapine.

There have been a number of suggestions put forward for the presence of OC symptoms in those with schizophrenia and for those on Clozapine. Cunill et al [1] suggested that this is an artefact of the overlap between psychosis and obsessive-compulsive disorder. Twenty per cent had clinically significant OCS symptoms, the majority of whom reported emergence of symptoms after commencing Clozapine. However, a significant minority who had documented pre-clozapine symptoms reported improvement in symptoms. Previous studies have highlighted differential impact of clozapine on OCS in schizophrenia [10, 11]. The reported rate of 11% pre-clozapine OCS was relatively low when compared to other studies. Studies have found 15-20% (even up to 50% with moderate OCS) under antipsychotic medication except Clozapine, which suggests rates of OCS symptoms pre-Clozapine may have been under reported in this cohort [22]. Nevertheless, it does point to the possibility that Clozapine may have unmasked OCS in some patients. What is not clear from this study is what differentiates these patients from those whose OCS improves with Clozapine and those who do not develop clinically significant OCS. Several researchers have suggested a subgroup of Schizophrenia “Schizoid-obsessive” that may have implications for diagnosis and management [12, 13].

Previous research would suggest that the severity of schizophrenia relates to the degree to which OCD symptoms are present. Indeed Kayahan et al. [24] conceded that the severity of schizophrenia symptoms in their study population may have led to an overestimation of OC symptoms and reported that severity of psychosis was related to OC symptoms. This present

study found OCI scores correlated with BPRS scores, specifically in terms of Obsessing symptoms and Unusual Thought symptoms, which suggests that OCS may be related to severity of schizophrenia. It is possible that this correlation is an indication that the BPRS may detect some elements of OC symptoms as it gives an overall score of psychiatric severity. Our findings suggest a possible link between OC and psychosis but that this may be confounded by assessment issues.

Our findings raise some questions about differences between OC symptoms and OCD. Stein [25] highlights the difficulty at a psychological level differentiating between symptoms in OCD patients and individuals who have OC symptoms without OCD in terms of process and mechanisms that maintain symptoms. Moritz et al [14] suggest that schizophrenic patients may experience stronger alienation from their thoughts when intrusions occur compared to non-psychotic patients with intrusive thoughts. Others suggest that the experience of affect is not related to the expression of affect in schizophrenia [15]. Obsessing appears to be highly correlated with Unusual thought Content and this does not appear to be mediated by either anxiety or treatment with Clozapine. Previous research has indicated that the relationship between self-reported OC symptoms and positive symptoms appears complex [2, 15, 23]. Patients may experience delusions as intrusive thoughts, which may differ from a clinician rated perspective. It is possible that measures of OC symptoms do not discriminate accurately between Thought Disorder and OCD. We agree with Poyurovsky et al in calling for the development of reliable and valid diagnostic instruments for assessing psychotic related obsessive compulsive symptoms [12].

A significant shortcoming of this study in terms of elucidating the relative impact of Clozapine medication is the absence of a comparison group of psychotic patients not on Clozapine. Although the sample size is relatively small, it is similar to previous studies. It is a cross-sectional study and our conclusions are limited by this. The “pre clozapine” data available for the clozapine group was collected from case records and as such may be subject to information bias, although other studies have used this methodology to retrospectively record pre-clozapine OCS [26]. Exclusion of a first episode cohort from the study may have reduced the representativeness of our sample. However there were no other exclusion criteria so this is unlikely to have skewed data. We used the clinician rated Brief Psychiatric Rating Scale, which provided a detailed assessment of psychotic symptoms among the clozapine group. We also assessed subjective wellbeing. We report on a community clinical sample rather than an inpatient sample, thus improving the generalisability of the results. BPRS scores suggested that this group were stable and not experiencing a lot psychiatric symptomatology, which allowed for subtle symptom profiles to emerge. The use of a robust self-report measure, which assesses a range of obsessive-compulsive symptoms, is strength as it offers a detailed analysis of different OC symptom types. Previous research has tended to use the YBOC but the OCI offers more detailed information on symptomatology [17, 18].

5. Conclusions:

This study suggests a relatively high proportion of people on clozapine may develop new OC symptoms. However, these symptoms seem to differ from the symptoms experienced by the non-psychotic OCD group. The symptoms are more likely to be cognitive and less distressing. In the Clozapine group, there was a significant correlation between anxiety and OC symptoms, whereas

in the OCD group OC symptoms were independent of anxiety. Our findings suggest a specific relationship between psychiatric severity and OC symptoms, namely Unusual Thought Content correlated highly with Obsessing. This does not appear to be mediated by either anxiety or Clozapine dose. This suggests that there may be a Schizo-obsessive subtype of Schizophrenia, the symptoms of which are detected by both OC and psychiatric symptom severity measures.

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