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Obsessive-compulsive symptoms in patients with schizophrenia: Relationships with olanzapine pharmacological parameters, psychopathology, and quality of life

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ABSTRACT

Obsessive-compulsive symptoms (OCS) occur in a substantial portion of schizophrenia patients and have significant impacts on clinical course. This study was intended to investigate the relationships of OCS with pharmacological parameters of olanzapine, psychopathology, and quality of life. Totally 151 schizophrenia patients were recruited, and rated using Yale-Brown Obsessive-Compulsive scale (YBOCS), Positive and Negative Syndrome Scale (PANSS), Montgomery-Åsberg Depression Rating Scale (MADRS), and World Health Organization Questionnaire on Quality of Life: Short Form (WHOQOL-BREF). The concentrations of olanzapine and *N*-desmethylolanzapine were determined by HPLC. Twenty-five patients (16.6%) revealed the presence of OCS. OCS group had significantly higher olanzapine dose, more numbers of past hospitalizations, higher PANSS total, positive, negative, and general psychopathology scores, and higher MADRS score than those in non-OCS group. The WHOQOL-BREF physical subscale score in schizophrenia patients with OCS was significantly lower. Olanzapine dose, PANSS score, and MADRS score were significantly correlated with YBOCS score. Our findings highlight that OCS is highly prevalent in schizophrenia patients under olanzapine treatment, especially those at high doses. Schizophrenia patients with OCS had higher severity of psychotic and depressive symptoms and poorer quality of life. Clinicians should monitor OCS in patients with schizophrenia receiving olanzapine treatment.

1. Introduction

Schizophrenia and obsessive-compulsive disorder (OCD) are two chronic and debilitating mental disorders. The lifetime prevalence for schizophrenia is about 0.55% (McGrath et al., 2008), and that for OCD it is 2–3% (Ruscio et al., 2010). The studies of meta-analyses reported that the prevalences of cormorbid OCD and obsessive-compulsive symptoms (OCS) in patients with schizophrenia are about 12–23% and 25–30%, respectively (Achim et al., 2011; Schirmbeck and Zink, 2013; Swets et al., 2014). Comorbidity rates for OCD/OCS among patients with schizophrenia are significantly higher than those expected to occur independently. The reason for the high comorbidity of OCD/OCS in schizophrenia is still not fully understood.

Early studies suggested that the appearance of OCS among patients with schizophrenia could prevent the progression of psychosis and possibly have a less degree in severity of psychopathology (Zink, 2014). But later studies generally have not supported this finding. Clinically, the presence of OCD/OCS in schizophrenia is associated with earlier onset of psychosis, higher prevalence of comorbid depression, more severe psychopathology and cognitive impairment, poorer social function, as well as higher rates of hospitalization (Cunill et al., 2013; Faragian et al., 2012; Owashi et al., 2010).

The onset of OCD/OCS could start throughout the entire course of schizophrenia (Schirmbeck and Zink, 2013; Zink, 2014). The prevalence of OCS/OCD would vary according to the types of antipsychotic medications. Second generation antipsychotics (SGAs) have been associated with the emergence and worsening of OCS among schizophrenia patients (Grillault Laroche and Gaillard, 2016). Compared to

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other antipsychotics, clozapine and olanzapine have greater potential to induce OCS, probably due to their having more potent serotoninergic antagonistic effects (Grillault Laroche and Gaillard, 2016; Kim et al., 2009). But some studies have also reported therapeutic advantages of adjunctive olanzapine therapy in the reduction of OCS among patients with treatment-resistant OCD (Bogetto et al., 2000), and even in schizophrenia patients with comorbid OCD (Poyurovsky et al., 2000).

The levels of olanzapine and its metabolite (N-desmethylolanzapine) have been reported to be related to some side effects (Lu et al., 2018; Skogh et al., 2002), but other studies had contradictory result (Zabala et al., 2017). Furthermore, Schirmbeck et al. (2011) reported olanzapine dose or olanzapine serum level is not associated with OCS severity among patients with schizophrenia. However, clozapine dose (Schirmbeck et al., 2011) and clozapine concentration (Lin et al., 2006) have been reported to be associated with OCS severity. The relationship between pharmacological parameters of olanzapine and OCS remains unclear.

This study was intended to investigate the prevalence of OCS in olanzapine-treated patients with schizophrenia as well as the relationships of OCS with olanzapine pharmacological parameters, psychopathology, and quality of life.

2. Methods

2.1. Patients

The study protocol was approved by the Joint Institutional Review Board of Taipei Medical University (approval number: F950206). All aspects of this study were conducted according to the principles expressed in the Declaration of Helsinki. The patients were inpatients or outpatients at Taipei Medical University-Wan Fang Hospital. We recruited patients who were aged 20–65 years, met the *DSM-IV* diagnostic criteria of schizophrenia, and received olanzapine monotherapy with a stable dose for more than three months. Included were those who had full capacity and were willing to provide written informed consent. Excluded were those who had substance use disorder, pregnancy, being in lactation periods, other disease status which may interfere the study assessment. We also excluded patients with concurrent antidepressant treatment.

2.2. Measures

Patients were assesses by a trained and certificated psychiatric nurse using a comprehensive set of clinical rating scales. The primary outcome measure was the Yale-Brown Obsessive-Compulsive scale (YBOCS) total score. The YBOCS consists of 10 items (5 items for obsessions and 5 items for compulsions) and each item is rated from 0 (no symptom) to 4 (extreme symptom) (Goodman et al., 1989). YBOCS has been reported to be suitable for the assessment of comorbid OCS in schizophrenia (Boyette et al., 2011; de Haan et al., 2006). A cut-off score of 8 has been proposed to verify the presence of OCS (Schirmbeck et al., 2011, 2013).

The severity of schizophrenic psychopathology was assessed using Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Comorbid depressive symptoms were assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). Quality of life (QOL) was assessed with The World Health Organization Questionnaire on Quality of Life: Short Form (WHOQOL-BREF) – Taiwanese version (Yao et al., 2002). The WHOQOL-BREF-Taiwan version contains 28 five-point items assessing general domain (2 items) and 4 specific domains of QOL, including physical health (7 items), psychological domain (6 items), social relationships domain (4 items), and environmental domains (9 items) (The WHOQOL Group, 1998; Yao et al., 2002). The scores of four QOL specific domains are transformed in the range of 0–100. Higher WHOQOL-BREF-Taiwan version scores reveal a better perceived QOL.

Blood sample was drawn in the morning after overnight fasting, about 12 hours after receiving the last olanzapine dose. The quantification of olanzapine and *N*-desmethylolanzapine levels applied a modified high-performance liquid chromatography with electrochemical detection in our previous study (Lu et al., 2013, 2016).

2.3. Statistical analyses

Descriptive statistics were presented as the mean ± standard deviation (SD) for continuous variables and rate for categorical variables. The differences between groups were compared using the Student's *t*-test for continuous variables, and Fisher's exact test for categorical variables. The Spearman's rank order correlation method was applied analyzing the correlations between YBOCS score and clinical parameters. To correct possible errors during multiple comparisons, the modified Bonferroni's method was used (Benjamini et al., 2001). All statistical tests were two-tailed, with a significant level of $p < 0.05$.

3. Results

3.1. Clinical and demographic characteristics

In this study, we recruited 151 patients with schizophrenia. The mean scores of PANSS, MADRS, and YBOCS were 57.2 ± 16.4, 2.0 ± 3.6, and 3.2 ± 6.3, respectively. The mean olanzapine dose and concentration were 14.2 ± 5.4 mg/day and 37.0 ± 25.6 ng/mL, respectively. Twenty-five patients (16.6%) revealed the presence of OCS (defined as YBOCS score ≥ 8). Table 1 shows the demographic and clinical characteristics of study subjects. There were no differences in gender distribution, age, age of onset, and duration of illness between two groups, except OCS group had more numbers of past hospitalizations than non-OCS group.

Compared with the non-OCS group, the OCS group had significantly higher YBOCS scores (including total, obsession, and compulsion scores) (all $p < 0.001$). There were significantly higher MADRS score

Table 1
Clinical and demographic characteristics of study subjects.

	OCS (+) (n = 25)	OCS (-) (n = 126)	p value
Age (years)	40.1 ± 11.6	41.1 ± 12.7	0.71
Female/male	15/10	65/61	0.514
Age of onset (years)	23.2 ± 9.6	25.3 ± 8.7	0.283
Duration of illness (years)	17.0 ± 9.1	15.8 ± 10.4	0.614
Number of past hospitalization	7.9 ± 6.2	4.9 ± 5.0	0.011
PANSS-Total	82.8 ± 14.9	52.1 ± 11.1	<0.001
PANSS-Positive	20.6 ± 5.8	14.1 ± 4.5	<0.001
PANSS-Negative	22.0 ± 5.6	13.6 ± 4.7	<0.001
PANSS-General	40.2 ± 7.9	24.4 ± 5.2	<0.001
MADRS	8.0 ± 3.2	0.9 ± 2.3	<0.001
YBOCS	15.4 ± 6.5	0.8 ± 1.8	<0.001
YBOCS-Obsession	7.8 ± 3.7	0.5 ± 1.1	<0.001
YBOCS-Compulsion	7.6 ± 3.6	0.4 ± 0.8	<0.001
WHOQOL-BREF-Physical	59.2 ± 11.3	63.6 ± 9.9	0.048
WHOQOL-BREF-Psychological	56.9 ± 15.2	58.9 ± 12.4	0.49
WHOQOL-BREF-Social	56.6 ± 15.9	58.7 ± 12.9	0.471
WHOQOL-BREF-Environmental	60.4 ± 12.9	61.7 ± 11.7	0.638
olanzapine level (ng/mL)	37.8 ± 27.4	36.8 ± 25.3	0.330
N-desmethylolanzapine level (ng/mL)	7.7 ± 3.9	6.7 ± 4.9	0.854
olanzapine dose (mg/day)	16.8 ± 4.3	13.7 ± 5.5	0.008

Values are presented as mean ± standard deviation.
Using the Student's *t* test for continuous variables and Fisher's exact test for categorical variables.
MADRS, Montgomery-Åsberg Depression Rating Scale; OCS, obsessive-compulsive symptoms; PANSS, Positive and Negative Syndrome Scale; WHOQOL-BREF, World Health Organization Questionnaire on Quality of Life: Short Form; YBOCS, Yale-Brown Obsessive-Compulsive scale.

Table 2
Correlation tests for obsessive-compulsive measures and clinical parameters.

	YBOCS	Obsession	Compulsion
Olanzapine dose			
r_s	0.192	0.200	0.175
p	0.018	0.014	0.032
Olanzapine level			
r_s	−0.074	−0.075	−0.067
p	0.370	0.359	0.416
N-desmethylolanzapine level			
r_s	0.073	0.067	0.085
p	0.373	0.411	0.299
Duration of illness			
r_s =	−0.021	−0.026	−0.009
p =	0.800	0.756	0.910
Number of past hospitalization			
r_s	0.147	0.151	0.146
p	0.072	0.065	0.074
PANSS-Total			
r_s	0.597*	0.616*	0.606*
p	<0.001	<0.001	<0.001
PANSS-Positive			
r_s	0.495*	0.520*	0.505*
p	<0.001	<0.001	<0.001
PANSS-Negative			
r_s	0.469*	0.494*	0.464*
p	<0.001	<0.001	<0.001
PANSS-General			
r_s	0.608*	0.610*	0.622*
p	<0.001	<0.001	<0.001
MADRS			
r_s	0.757*	0.719*	0.750*
p	<0.001	<0.001	<0.001
WHOQOL-BREF - Physical			
r_s	−0.096	−0.087	−0.114
p	0.241	0.288	0.164
WHOQOL-BREF - Psychological			
r_s	0.010	0.003	0.009
p	0.905	0.973	0.909
WHOQOL-BREF - Social			
r_s	−0.048	−0.066	−0.045
p	0.557	0.420	0.586
WHOQOL-BREF - Environmental			
r_s	−0.061	−0.082	−0.048
p	0.456	0.314	0.560

Using Spearman's rank order correlation method.
MADRS, Montgomery-Åsberg Depression Rating Scale; OCS, obsessive-compulsive symptoms; PANSS, Positive and Negative Syndrome Scale; WHOQOL-BREF, World Health Organization Questionnaire on Quality of Life: Short Form; YBOCS, Yale-Brown Obsessive-Compulsive scale.
* Remained significant ($p < 0.05$) after the modified Bonferroni's correction.

and PANSS scores (including total, positive, negative, and general psychopathology scores) in OCS group (all $p < 0.001$) than those in non-OCS group. After correction for MADRS score, the between-group differences measured with PANSS total and subscale scores remained significant (all $p < 0.001$). Among the assessment of quality of life, only QOL-physical subscale score differed significantly between groups ($p = 0.048$) and this difference became non-significant after using MADRS score as a covariate.

OCS group had significantly higher olanzapine dose than non-OCS group ($p = 0.008$). However, there were no differences in plasma levels of olanzapine and *N*-desmethylolanzapine between two groups.

3.2. Correlation analysis

Table 2 shows the correlations between three YBOCS scores (total, obsession, and compulsion scores) and parameters of interest. Olanzapine dose, PANSS scores (total, positive, negative, and general psychopathology scores), and MADRS score were significantly correlated with all three YBOCS scores (total, obsession, and compulsion scores). After the modified Bonferroni's correction, positive correlations of YBOCS scores with PANSS scores and MADRS score remained statistically significant.

4. Discussion

Among the patients with schizophrenia under olanzapine treatment in our study, the prevalence of OCS was 16.6%. Previous studies revealed that the prevalence of cormorbid OCS in olanzapine-treated patients with schizophrenia is about 5–20% (Lim et al., 2007; Scheltema Beduin et al., 2012). The wide differences may result from discrepancies in the OCS assessment and subject characteristics among different studies. The strength of our study is the homogeneity of antipsychotic medication, which can control confounding effects of treatment on the clinical manifestations.

The finding of a significant relationship between olanzapine treatment and OCS is of particular interest. The correlation of YBOCS score with olanzapine dose suggests dose-dependent effect. The obsessive-compulsive potential of olanzapine might be related with serotoninergic antagonistic effect (Grillault Laroche and Gaillard, 2016; Lim et al., 2007). Higher doses of olanzapine increase the antagonistic effect on the serotoninergic receptors. But the plasma levels of olanzapine and *N*-desmethylolanzapine were not correlated with YBOCS scores in our study. One possibility for our findings of dose-dependent effect is that olanzapine dose is related to the severity of psychosis rather than that of OCS (Fernandez-Egea et al., 2018). Previous study explored the effects of olanzapine dose and serum concentration on OCS having also shown no correlation (Schirmbeck et al., 2011). It has been hypothesized that pharmacological, neurobiological and genetic risk factors dispose patients with schizophrenia to develop OCS (Lykouras et al., 2003; Zink 2014). Further studies are warranted to clarify the effects of pharmacological and other potential parameters on OCS in patients with schizophrenia.

Our results revealed that schizophrenia patients with OCS had significantly higher PANSS scores (total, positive, negative, and general psychopathology scores). In addition, OCS severity was positively correlated with PANSS total and all subscales scores. This finding is in keeping with that in previous studies (Cunill et al., 2009; Kim et al., 2015). One possibility for the association between OCS and schizophrenic psychopathology is that schizophrenia patients with comorbid OCS are more resistant to antipsychotic medication (Opakunle et al., 2017). Another possible explanation is that a phenomenological overlap exists between schizophrenia and OCS (Insel and Akiskal, 1986).

Whether OCS in schizophrenia is associated with the deleterious impact on psychosis remains contestable. In particular, a longitudinal five-year follow-up study with first-episode schizophrenia reported that OCS/OCD comorbidity is not associated with a higher severity of psychopathology (de Haan et al., 2013). These incongruous results may be due to different study designs, such as sample size, subject characteristics, definition of OCS/OCD, antipsychotic medication, and stage of illness (Kim et al., 2015).

In this study, olanzapine-treated schizophrenia patients with OCS had significantly more previous hospitalizations than those without OCS. Previous studies also reported that schizophrenia patients with OCS differ from those without OCS in the number of previous hospitalization (Opakunle et al., 2017; Szmulewicz et al., 2015). In addition to higher severity of psychopathology, schizophrenia patients with OCS may also have impaired drug compliance (Figueiredo et al., 2016), consequently lead to relapse and hospitalization.

In our study, higher YBOCS scores were significantly correlated with higher degrees of depression. This finding of our study is concordant with the results of previous studies (Ongur and Goff, 2005; Szmulewicz et al., 2015). The comorbidity of major depressive disorder among patients with OCD is prevalent and is proposed to deliberate similar underlying pathophysiology (Blier and Abbott, 2001). Serotonin dysfunction is a common biological characteristic of OCS and depression in

schizophrenia patients (Ma et al., 2007).

Our results showed that patients with OCS had lower scores on WHOQOL-BREF physical health domain. This result supports findings of previous studies, reporting a relationship between comorbid OCS and poor QOL in patients with schizophrenia (Kim et al., 2015; Ucok et al., 2014). But other studies have revealed contradictory results (de Haan et al., 2013; Devi et al., 2015). The reason for these inconsistent findings remains unclear. One possible explanation is that the relationship between global function and OCS in schizophrenia may be presented by a reverse U-shaped curve, with change from a positive association (for mild OCS) to a negative association (for moderate to severe OCS) (Tonna et al., 2016). In addition, the impact of OCS on schizophrenia may be related to the disease stage, and it may have protecting effect in the early stage of schizophrenia and detrimental effect in chronic schizophrenia (Cunill et al., 2009). In this study, the majority of our patients was having chronic schizophrenia and hence explained the presence of negative impact.

Several limitations should be considered in interpreting our study results. The study was cross-sectional in study design. Therefore, the direction of causality between OCS and other variables cannot be ascertained. Since the measures of OCS were based on YBOCS, subjects in this study might have recall and reporting bias. Our samples were relatively long in duration of illness, and mild to moderate in severity of psychopathology. We lack the information about temporal relationship between the onset of OCS and the introduction of olanzapine, which could have given us arguments favoring or opposing the hypothesis that olanzapine induce OCS. In addition, the same rater administered YBOCS, PANSS, and MADRS, therefore, ratings of psychopathology were potentially subject to bias. Further study is warranted in random, longitudinal and representative sample of patients with different stages (first episode versus multiple episodes) and phases (acute versus stable status) of schizophrenia.

In conclusion, our findings highlighted that OCS was highly prevalent in patients with schizophrenia under olanzapine treatment, especially at high doses. Schizophrenia patients with OCS had higher severity of psychotic and depressive symptoms and poorer QOL. We suggest that clinicians should monitor OCS in patients with schizophrenia when prescribing olanzapine. The early detection and subsequent treatment of OCS may prevent negative outcomes and improve quality of life.

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Supplementary materials

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References

Achim, A.M., Maziade, M., Raymond, E., Olivier, D., Merette, C., Roy, M.A., 2011. How prevalent are anxiety disorders in schizophrenia? A meta-analysis and critical review on a significant association. Schizophr. Bull. 37 (4), 811–821.

Benjamini, Y., Drai, D., Elmer, G., Kafkafi, N., Golani, I., 2001. Controlling the false discovery rate in behavior genetics research. Behav. Brain Res. 125 (1-2), 279–284.

Blier, P., Abbott, F.V., 2001. Putative mechanisms of action of antidepressant drugs in affective and anxiety disorders and pain. J. Psychiatry Neurosci. 26 (1), 37–43.

Bogetto, F., Bellino, S., Vaschetto, P., Ziero, S., 2000. Olanzapine augmentation of fluvoxamine-refractory obsessive-compulsive disorder (OCD): a 12-week open trial. Psychiatry Res. 96 (2), 91–98.

Boyette, L., Swets, M., Meijer, C., Wouters, L., 2011. Factor structure of the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) in a large sample of patients with schizophrenia or related disorders and comorbid obsessive-compulsive symptoms. Psychiatry Res. 186 (2-3), 409–413.

Cunill, R., Castells, X., Simeon, D., 2009. Relationships between obsessive-compulsive symptomatology and severity of psychosis in schizophrenia: a systematic review and meta-analysis. J. Clin. Psychiatry 70 (1), 70–82.

Cunill, R., Huerta-Ramos, E., Castells, X., 2013. The effect of obsessive-compulsive symptomatology on executive functions in schizophrenia: a systematic review and meta-analysis. Psychiatry Res. 210 (1), 21–28.

de Haan, L., Hoogeboom, B., Beuk, N., Wouters, L., Dingemans, P.M., Linszen, D.H., 2006. Reliability and validity of the Yale-Brown Obsessive-Compulsive Scale in schizophrenia patients. Psychopharmacol. Bull. 39 (1), 25–30.

de Haan, L., Sterk, B., Wouters, L., Linszen, D.H., 2013. The 5-year course of obsessive-compulsive symptoms and obsessive-compulsive disorder in first-episode schizophrenia and related disorders. Schizophr. Bull. 39 (1), 151–160.

Devi, S., Rao, N.P., Badamath, S., Chandrashekhar, C.R., Janardhan Reddy, Y.C., 2015. Prevalence and clinical correlates of obsessive-compulsive disorder in schizophrenia. Compr. Psychiatry 56, 141–148.

Faragian, S., Fuchs, C., Pashinian, A., Weizman, R., Weizman, A., Poyurovsky, M., 2012. Age-of-onset of schizophrenic and obsessive-compulsive symptoms in patients with schizo-obsessive disorder. Psychiatry Res. 197 (1-2), 19–22.

Fernandez-Egea, E., Worbe, Y., Bernardo, M., Robbins, T.W., 2018. Distinct risk factors for obsessive and compulsive symptoms in chronic schizophrenia. Psychol. Med. 1–8.

Figueiredo, T., Segenreich, D., Mattos, P., 2016. Fluoxetine adjunctive yherapy for obsessive-compulsive symptoms associated with olanzapine in schizophrenic patients. J. Clin. Psychopharmacol. 36 (4), 389–391.

Goodman, W.K., Price, L.H., Rasmussen, S.A., Mazure, C., Fleischmann, R.L., Hill, C.L., et al., 1989. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. Arch. Gen. Psychiatry 46 (11), 1006–1011.

Grillault Laroche, D., Gaillard, A., 2016. Induced obsessive compulsive symptoms (OCS) in schizophrenia patients under atypical 2 antipsychotics (AAPs): review and hypotheses. Psychiatry Res. 246, 119–128.

Insel, T.R., Akiskal, H.S., 1986. Obsessive-compulsive disorder with psychotic features: a phenomenologic analysis. Am. J. Psychiatry 143 (12), 1527–1533.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13 (2), 261–276.

Kim, S.W., Jeong, B.O., Kim, J.M., Shin, I.S., Hwang, M.Y., Paul Amminger, G., et al., 2015. Associations of obsessive-compulsive symptoms with clinical and neurocognitive features in schizophrenia according to stage of illness. Psychiatry Res. 226 (1), 368–375.

Kim, S.W., Shin, I.S., Kim, J.M., Youn, T., Yang, S.J., Hwang, M.Y., et al., 2009. The 5-HT2 receptor profiles of antipsychotics in the pathogenesis of obsessive-compulsive symptoms in schizophrenia. Clin. Neuropharmacol. 32 (4), 224–226.

Lim, M., Park, D.Y., Kwon, J.S., Joo, Y.H., Hong, K.S., 2007. Prevalence and clinical characteristics of obsessive-compulsive symptoms associated with atypical antipsychotics. J. Clin. Psychopharmacol. 27 (6), 712–713.

Lin, S.K., Su, S.F., Pan, C.H., 2006. Higher plasma drug concentration in clozapine-treated schizophrenic patients with side effects of obsessive/compulsive symptoms. Ther. Drug Monit. 28 (3), 303–307.

Lu, M.L., Chen, C.H., Kuo, P.T., Lin, C.H., Wu, T.H., 2018. Application of plasma levels of olanzapine and N-desmethyl-olanzapine to monitor metabolic parameters in patients with schizophrenia. Schizophr. Res. 193, 139–145.

Lu, M.L., Lin, C.H., Chen, Y.C., Yang, H.C., Wu, T.H., 2013. Determination of olanzapine and N-desmethyl-olanzapine in plasma using a reversed-phase HPLC coupled with coulochemical detection: correlation of olanzapine or N-desmethyl-olanzapine concentration with metabolic parameters. PLoS One 8 (5), e65719.

Lu, M.L., Wu, Y.X., Chen, C.H., Kuo, P.T., Chen, Y.H., Lin, C.H., et al., 2016. Application of plasma levels of olanzapine and N-desmethyl-olanzapine to monitor clinical efficacy in patients with schizophrenia. PLoS One 11 (2), e0148539.

Lykouras, L., Alevizos, B., Michalopoulou, P., Rabavilas, A., 2003. Obsessive-compulsive symptoms induced by atypical antipsychotics. A review of the reported cases. Prog. Neuropsychopharmacol. Biol. Psychiatry 27 (3), 333–346.

Ma, N., Tan, L.W., Wang, Q., Li, Z.X., Li, L.J., 2007. Lower levels of whole blood serotonin in obsessive-compulsive disorder and in schizophrenia with obsessive-compulsive symptoms. Psychiatry Res. 150 (1), 61–69.

McGrath, J., Saha, S., Chant, D., Welham, J., 2008. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol. Rev. 30, 67–76.

Montgomery, S.A., Asberg, M., 1979. A new depression scale designed to be sensitive to change. Br. J. Psychiatry 134, 382–389.

Ongur, D., Goff, D.C., 2005. Obsessive-compulsive symptoms in schizophrenia: associated clinical features, cognitive function and medication status. Schizophr. Res. 75 (2-3), 349–362.

Opakunle, T., Akinsulore, A., Aloba, O.O., Fatoye, F.O., 2017. Obsessive-compulsive symptoms in schizophrenia: prevalence and associated factors in a Nigerian population. Int. J. Psychiatry Clin. Pract. 21 (3), 195–200.

Owashi, T., Ota, A., Otsubo, T., Susa, Y., Kamijima, K., 2010. Obsessive-compulsive disorder and obsessive-compulsive symptoms in Japanese inpatients with chronic schizophrenia – a possible schizophrenic subtype. Psychiatry Res. 179 (3), 241–246.

Poyurovsky, M., Dorfman-Etrog, P., Hermesh, H., Munitz, H., Tollefson, G.D., Weizman, A., 2000. Beneficial effect of olanzapine in schizophrenic patients with obsessive-compulsive symptoms. Int. Clin. Psychopharmacol. 15 (3), 169–173.

Ruscio, A.M., Stein, D.J., Chiu, W.T., Kessler, R.C., 2010. The epidemiology of obsessive-

compulsive disorder in the National Comorbidity Survey Replication. Mol. Psychiatry 15 (1), 53–63.
Scheltema Beduin, A.A., Swets, M., Machielsen, M., Korver, N., 2012. Obsessive-compulsive symptoms in patients with schizophrenia: a naturalistic cross-sectional study comparing treatment with clozapine, olanzapine, risperidone, and no antipsychotics in 543 patients. J. Clin. Psychiatry 73 (11), 1395–1402.
Schirmbeck, F., Esslinger, C., Rausch, F., Englisch, S., Meyer-Lindenberg, A., Zink, M., 2011. Antiserotonergic antipsychotics are associated with obsessive-compulsive symptoms in schizophrenia. Psychol. Med. 41 (11), 2361–2373.
Schirmbeck, F., Rausch, F., Englisch, S., Eifler, S., Esslinger, C., Meyer-Lindenberg, A., et al., 2013. Differential effects of antipsychotic agents on obsessive-compulsive symptoms in schizophrenia: a longitudinal study. J. Psychopharmacol. 27 (4), 349–357.
Schirmbeck, F., Zink, M., 2013. Comorbid obsessive-compulsive symptoms in schizophrenia: contributions of pharmacological and genetic factors. Front. Pharmacol. 4, 99.
Skogh, E., Reis, M., Dahl, M.L., Lundmark, J., Bengtsson, F., 2002. Therapeutic drug monitoring data on olanzapine and its N-demethyl metabolite in the naturalistic clinical setting. Ther. Drug Monit. 24 (4), 518–526.
Swets, M., Dekker, J., van Emmerik-van Oortmerssen, K., Smid, G.E., Smit, F., de Haan, L., et al., 2014. The obsessive compulsive spectrum in schizophrenia, a meta-analysis and meta-regression exploring prevalence rates. Schizophr. Res. 152 (2-3), 458–468.
Szmulewicz, A.G., Smith, J.M., Valerio, M.P., 2015. Suicidality in clozapine-treated patients with schizophrenia: role of obsessive-compulsive symptoms. Psychiatry Res. 230 (1), 50–55.
The WHOQOL Group, 1998. Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group. Psychol. Med. 28 (3), 551–558.
Tonna, M., Ottoni, R., Paglia, F., Ossola, P., De Panfilis, C., Marchesi, C., 2016. Obsessive-compulsive symptom severity in schizophrenia: a Janus Bifrons effect on functioning. Eur. Arch. Psychiatry Clin. Neurosci. 266 (1), 63–69.
Ucok, A., Kivrak Tihan, A., Karadayi, G., Tukel, R., 2014. Obsessive compulsive symptoms are related to lower quality of life in patients with Schizophrenia. Int. J. Psychiatry Clin. Pract. 18 (4), 243–247.
Yao, G., Chung, C.W., Yu, C.F., Wang, J.D., 2002. Development and verification of validity and reliability of the WHOQOL-BREF Taiwan version. J. Formos. Med. Assoc. 101 (5), 342–351.
Zabala, A., Bustillo, M., Querejeta, I., Alonso, M., Mentxaka, O., Gonzalez-Pinto, A., et al., 2017. A pilot study of the usefulness of a single olanzapine plasma concentration as an indicator of early drug effect in a small sample of first-episode psychosis patients. J. Clin. Psychopharmacol. 37 (5), 569–577.
Zink, M., 2014. Comorbid obsessive-compulsive symptoms in schizophrenia: insight into pathomechanisms facilitates treatment. Adv. Med. 2014, 317980.