FACTORS ASSOCIATED WITH DEPRESSION IN PATIENTS WITH SCHIZOPHRENIA

Boris Golubović^{1,2}, Zoran Gajić^{1,2}, Olga Ivetić^{1,2}, Jovan Milatović^{1,2}, Petar Vuleković^{1,3}, Dula Đilvesi^{1,3}, Sonja Golubović^{1,4}, Filip Vrban^{5,6}, Ante Subašić⁵ and Lukas Rasulić^{7,8}

¹University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia; ²Department of Psychiatry, Clinical Centre of Vojvodina, Novi Sad, Serbia; ³Department of Neurosurgery, Clinical Centre of Vojvodina, Novi Sad, Serbia; ⁴Clinical Centre of Vojvodina, Novi Sad, Serbia; ⁵Department of Neurosurgery, Sestre milosrdnice University Hospital Centre, Zagreb, Croatia; ⁶University of Health Applied Sciencies, Zagreb, Croatia; ⁷University of Belgrade, Faculty of Medicine, Belgrade, Serbia; ⁸Division of Peripheral Nerve Surgery, Functional Neurosurgery and Pain Management Surgery, Department of Neurosurgery, Clinical Center of Serbia, Belgrade, Serbia

SUMMARY – The aim of this study was to analyze risk factors present in schizophrenic patients with depressive symptomatology. The sample comprised of 76 respondents diagnosed with schizophrenia. In the study, we used the Positive and Negative Syndrome Scale (PANSS) and Calgary Depression Scale for Schizophrenia. The prevalence of depression was estimated to be 30%. The mean scores on the negative subscale of the PANSS were significantly higher in patients with schizophrenia and depression compared to control group (U=3.64, p=0.00), and so were those on the General Psychopathology Scale (U=4.91, p=0.00). Socio-demographic factors were identified as important factors (p<0.05). Personal and environmental factors such as loneliness, immediate social environment, social support and isolation were statistically significantly different between the groups (p<0.05). There was a correlation of poor compliance with psycho-pharmacotherapy, increased number of hospitalizations and shorter remission period with the severity of clinical presentation (p<0.05). Since the presence of these factors is associated with depression in schizophrenia, their early detection in clinical practice is vital to ensure timely prevention of the development of depressive symptomatology.

Key words: Schizophrenia; Depression; Sociodemographic factors

Introduction

Schizophrenia is a complex mental disorder with a variable phenotypic expression of symptoms in the form of impaired mental capacity, communication difficulties, affective response, difficulties in perceptions of reality and relationship with others, avolition and

E-mail: lukas.rasulic@gmail.com

urges. Depressive symptoms are common in people with schizophrenia, but often confusing or neglected by clinicians¹.

The prevalence of depressive disorder in schizophrenia has been reported to be around 40%², with an incidence varying from 13% to 60% depending on the stage of illness and the person's current medical condition^{3,4}. A vast majority of patients with schizophrenia experience one or more depressive episodes during the early stage of the illness, which makes it difficult to distinguish between schizophrenia and schizoaffective disorders. The presence of depression symptoms may be associated with a number of psychological factors

Correspondence to: *Prof. Lukas Rasulić, MD, PhD,* Division of Peripheral Nerve Surgery, Functional Neurosurgery and Pain Management Surgery, Department of Neurosurgery, Clinical Center of Serbia, Višegradska 26, 11000 Belgrade, Serbia

Received August 29, 2019, accepted December 5, 2019

such as stress, sense of insecurity, hopelessness, social exclusion, and therefore it can be manifested at any stage during the illness. In addition to depressive symptoms, recurrent depressive episodes adversely affect treatment outcomes in schizophrenia⁴, as well as the quality of life in these patients^{5,6}. Furthermore, the relationship has been identified between the presence of depression and subsequent poor mental functioning, abuse of psychoactive substances, increased risk of psychotic relapse, and difficulty in establishing appropriate relationships in family environment⁷⁻⁹.

There is a high prevalence of suicide in patients with schizophrenia, most often linked to the presence of depression¹⁰⁻¹². It has been estimated that in patients with schizophrenia, the number of attempted suicides ranges between two and five, whereas 10% of patients will take their own lives eventually¹³⁻¹⁵.

Diagnosing depression in schizophrenia may be difficult due to the problems of differentiating the symptoms of mood disorders from the presence of negative symptoms of schizophrenia. Factors associated with the manifestation of this mood and the appearance of depressive episodes can be the result of secondary negative symptoms such as avolition due to the insight into the illness and their own mental health condition, sense of shame, and self-distrust. Since the symptoms can manifest themselves in a similar way, in addition to commonly used assessment of cognitive functioning, hallucinations, anhedonia and affective gain, it is also of importance for appropriate diagnosis to assess the patient's subjective responses to his/her mood, affective gain, speculation about future prospects, the patient's subjective mood responses, and the like. Recent research indicates that age, duration of illness, education degree, community life, physical health and quality of life affect the possible consequences of illness and the need for treatment^{16,17}.

The Calgary Depression Scale for Schizophrenia (CDSS)¹⁸ can be used to measure the presence of clinically significant depressive symptoms; therefore, the aim of this study was to analyze the risk factors present in schizophrenic patients with depressive symptomatology.

Patients and Methods

The survey included 76 subjects, 44 (57%) male and 32 (43%) female, mean age 38.7 years (SD=9.14). All

subjects had been diagnosed with F20 according to the International Classification of Diseases and Related Health Problems (ICD-10)¹⁹. They were currently receiving risperidone (Risperdal Consta), a long-acting injectable antipsychotic, and fulfilled the remission criteria. The mean disease duration was 12 years (SD=3.48). Study subjects were divided into two groups according to the results obtained on CDSS, i.e. respondents with depressive symptomatology and control group of respondents without depressive symptomatology.

The inclusion criteria for participants in the research required that respondents were aged 18-60 and signed the informed consent to participate in the research. Exclusion criteria were patient age <18 or >60 years and diagnosis of a neurological disorder. The research was carried out within the premises of the Clinical Centre of Vojvodina Polyclinic, at the time when patients were receiving their regular therapy with the long-acting antipsychotic Risperdal Consta® (Janssen-Cilag Pharma GmbH, Vienna, Austria). This study included patients that were treated at a psychiatric ward and were receiving atypical antipsychotic therapy. One of the reasons for including only patients on this type of therapy was that patients treated with atypical antipsychotics had fewer side effects than those treated with typical antipsychotics, which have the advantage of reducing depressive symptoms^{5,20,21}. In addition, we thought that patients (owing to the fact that atypical antipsychotics cause much less cognitive impairment compared to typical antipsychotics) would be able to demonstrate more appropriate levels of understanding the requirements of the researcher and to actively participate in the research.

The present study was approved by the Ethics Committee of the Clinical Center of Vojvodina. All respondents were offered general information regarding the type and purpose of the study, and they voluntarily agreed to parcipate in it by signing an informed consent. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Instruments

Two instruments were used, i.e. the Positive and Negative Syndrome Scale (PANSS)^{22,23} and Calgary Depression Scale for Schizophrenia (CDSS)^{18,24}.

The PANSS comprises three subscales, Positive, Negative and General Psychopathology subscales. Each subscale was scored separately, based on the researcher's appraisal obtained during an interview, according to the PANSS Evaluation Manual for assessing each parameter. The Positive and Negative Subscales comprise 7 items each, rated by use of the severity levels from 1 to 7. Additionally, total score for each of these subscales can range from 7 to 49. The General Psychopathology subscale consists of 16 items, with a total score ranging from 16 to 112.

A composite score is derived by subtracting Total Negative from Total Positive score. The composite score can range from -42 to +42, and based on this predictive value, the presence of negative symptoms is estimated in relation to positive symptoms. The Composite Scale shows the predominance of positive or negative symptoms and its direct score ranges from -42 to +42 and is a difference score for Positive minus Negative direct scores. Therefore, all the scores greater than +11 indicate the predominance of positive symptoms, whereas the scores lower than -15 indicate the predominance of negative symptoms (5th and 95th percentile). The symptoms closer to zero-score indicate a combined type, i.e. means of symptoms are evenly distributed between the two types.

In particular, composite score obtained by subtracting the Total Negative score from the Total Positive score stands out, showing the presence and severity of negative in relation to positive symptoms. Comparing some subscale scores provides an insight into the basic structure of schizophrenia subtypes.

The CDSS was specifically designed for patients with schizophrenia and it is considered as one of the most reliable criteria for predicting depressive episodes in these patients. Compared to other scales, the CDSS is most effective in differentiating depressive symptoms from negative symptoms in schizophrenia; accordingly, the use of this scale decreases the risk of not being recognized as a depressive disorder or misdiagosed. The CDSS consists of a nine-item structured interview scale in which each of eight items is scored based on the patient's direct responses to structured interviewing, except for the last item which is rated by the researcher, based on observations of the entire interview. Items are based on the current, i.e. the last two-week time. Each item can be scored on a scale ranging from 0 to 3, with the total score ranging from 0 to 27.

The questionnaire was designed for the purpose of this study covering socio-demographic factors associated with an increased risk of depression among these patients. Respondents answered questions about the place of residence, educational level and occupational status, socio-economic status, marital status, parenting, hospitalization, and previous history of hetero-aggressive behavior. All respondents were asked whether they felt lonely, whether they believed the provision of support provided by their families and society was adequate, and whether they felt socially isolated. Moreover, patients were asked specific questions about therapy, such as how long they had been receiving the long-acting antipsychotic Risperdal Consta[®], what psychopharmaceuticals other than this one they had used, how regularly they followed their therapy and how long they were in remission, and questions about the presence of psychiatric heredity and family history of suicide.

Statistical analysis

Data were analyzed using SPSS 21 statistical software. The measures of descriptive statistics (frequencies, percentages, mean values, measures of variability) were applied. The Shapiro-Wilk test was used to assess normality of data distribution. The significance of differences was determined by nonparametric tests (χ^2 -test and Mann-Whitney U test), and multiple regression analysis was applied to check and analyze the possible relationship between variables. The level of statistical significance was set at p<0.05.

Results

The presence of clinical depression symptoms was examined using the CDSS. Furthermore, analysis of the instrument used to predict a depressive episode among patients in terms of sensitivity and specificity shows that the presence of a depressive episode can be assumed in all respondents with CDSS score greater than 6, with 82% specificity and 85% sensitivity. Of the 76 patients examined in this study, 22 (29%) patients had scores greater than 6, thus indicating the presence of depressive symptoms. All respondents were asked whether they had ever thought of taking their lives and whether they had really attempted it. In the group of patients who had the CDSS score above 6 and who

Factor		Respondents with depressive symptomatology n (%)	Respondents without depressive symptomatology n (%)	Statistical analysis
Mean age (yrs)		32.53 (SD=10.39)	38.03 (SD=8.66)	U=4.40 p= 0.31
Gender	Men Women	15 (75.00) 5 (25.00)	25 (48.08) 27 (51.92)	$\chi^2 = 4.24$ p=0.03
Place of residence	Urban area Rural area	17 (85.00) 3 (15.00)	47 (90.38) 5 (9.62)	χ ² =0.42 p=0.51
Educational level	Primary education Secondary education Higher education Academic education	$ \begin{array}{c} 1 (5.00) \\ 11(55.00) \\ 5 (25.00) \\ 3 (15.00) \end{array} $	6 (11.54) 34 (65.38) 3 (5.77) 19 (36.54)	U=5.34 p=0.29
Employment status	Employed Unemployed Retired	8 (40.00) 4 (20.00) 8 (40.00)	32 (61.54) 9 (17.31) 11 (21.15)	χ ² =3.20 p=0.20
Socio-economic status	Low Middle High	4 (20.00) 16 (80.00) 0	34 (65.38) 13 (25.00) 5 (9.62)	χ ² =18.40 p=0.00
Marital status	Single Married Divorced	12 (60.00) 2 (10.00) 6 (30.00)	40 (76.92) 12 (23.07) 0	χ ² =17.44 p=0.00
Parenting	Accomplished Unaccomplished	2 (10.00) 18 (90.00)	12 (23.08) 40 (76.92)	$\chi^2 = 1.57$ p=0.20

Table 1. Socio-demographic characteristics of the study sample

were defined as depressed, 30% of them said they had suicidal thoughts and plans for suicide, but then they did not implement the plan, while 20% of these patients had a previous suicide attempt. In the group of respondents without depressive symptomatology, 10% said they used to think of taking their lives, while 5% of these patients had attempted suicide.

The presence of positive and negative symptoms of schizophrenia was assessed using the PANSS. Among the 76 respondents examined in this study, four received a composite score of less than -15, i.e. dominance of negative symptoms was recorded. In the remaining 72 respondents, the composite score ranged between -15 and +10, yielding a similar prevalence of positive and negative symptoms in these patients. None of the patients examined had a composite score greater than +10.

The mean score on the general psychopathology subscale was 29.4 (SD=0.89). In the group of 72 respondents, on the basis of composite score, the pres-

ence of positive and negative symptoms was found to be approximately evenly represented, with the mean score on the general psychopathology subscale of 28.91. In the remaining four respondents, i.e. in the group of respondents with predominance of negative symptoms, the mean score was 34.

In four patients, the composite scores on the PANSS indicated predominance of negative symptoms, whereas one of these four patients was also in the group of patients with a score greater than 6 on the CDSS. The mean score on the PANSS general psychopathology subscale in patients who had CDSS scores greater than 6 was 35.23, whereas the mean score for the remaining patients was 26.63. The general psychopathology score was greater in those patients whose CDSS scores were greater than 6, and this difference was statistically significant (U=4.91; p=0.00). A statistically significant difference was also found on the PANS negative scale (U=3.64; p=0.00).

Factor		Respondents with depressive symptomatology n (%)	Respondents without depressive symptomatology n (%)	Statistical analysis	
Londinge	Yes	18 (90.00)	13 (25.00)	$\chi^2 = 24.89$	
Lonenness	No	2 (10.00)	39 (75.00)	p=0.00	
Equilibrium out	Present	14 (70.00)	46 (88.46)	$\chi^2 = 8.62$	
Family support	Absent	6 (30.00)	6 (11.54)	p=0.01	
Sector I among at	Present	5 (25.00)	34 (65.38)	$\chi^2 = 18.63$	
Social support	Absent	15 (75.00)	18 (34.62)	p=0.00	
	Present	16 (80.00)	17 (32.69)	$\chi^2 = 13.02$	
Social isolation	Absent	4 (20.00)	35 (67.31)	p=0.00	
Family history of mental	Present	9 (45.00)	17 (32.69)	$\chi^2 = 0.94$	
disorders	Absent	14 (70.00)	35 (67.31)	p=0.33	
	Present	2 (10.00)	11 (21.15)	$\chi^2 = 1.21$	
Suicide in family	Absent	18 (90.00)	41 (78.85)	p=0.57	
Previous hetero-aggressive	Present	15 (75.00)	27 (51.92)	$\chi^2 = 3.16$	
behavior	Absent	5 (25,00)	25 (48.08)	p=0.07	
Compliance with	Good	11 (55,00)	47 (90.38)	$\chi^2 = 11.54$	
psychopharmacotherapy	Poor	9 (45.00)	5 (9.62)	p=0.00	
Number of hospitalizations		5.48(SD-4.82)	3 23 (SD-3 31)	U=2.35	
i vulliber of hospitalizations		5.40 (5D-4.02)	5.25 (5D-5.51)	p=0.02	
Duration of remission	>1 year	8 (40.00)	7 (13.46)	$\chi^2 = 6.16$	
	<1 year	12 (60.00)	45 (86.54)	p=0.01	
Mean time elapsed		1.98 (SD=2.31)	5.30 (SD=5.37)	U=3.40	
from last hospitalization (yrs)				p=0.02	

Table 2. Factors that may have an effect on the manifestation of the symptoms of depression

Following further data analysis, four respondents with a predominance of negative symtomatology on the PANSS (score lower than -15 in the composite PANSS score) were excluded from the sample. This ensured the risk factors to be analyzed only in patients with depressive symptomatology while avoiding overlap with negative symtoms. The group with depressive symptomatology comprised 20 patients, while the group without depressive symptomatology comprised 52 patients. Table 1 shows distribution of the general sociodemographic data in both study groups.

There was a statistically significant difference according to gender structure between the groups. In the first group, respondents with depressive symptoms were slightly younger than those in the second group, but the difference was not significant. According to the place of residence, there was no significant difference between the two groups. In both groups, respondents came predominantly from urban areas. Since the most frequent level of education was secondary education, it is not surprising that the number of respondents who completed secondary school was highest. In both groups, most of the respondents were unemployed. A statistically significant difference was observed between the two groups with respect to socioeconomic status, which was assessed lower in the first group compared to the second group, who mostly assessed it as average. In both groups, the respondents were mostly single, yet with a significant betweengroup difference. The difference was not expressed in terms of parenting.

Analyzing other factors for the presence of depression in people with schizophrenia (Table 2), we found a statistically significant difference between the groups according to the feeling of loneliness, absence of family and social support, social isolation, as well as ac-

	Unstandardized coefficient		Standardized coefficient		C:	95.0% confidence interval for B	
	В	SE	Beta	t	51g.	Lower bound	Upper bound
Age (yrs)	-0.13	0.03	-0.25	-3.34	0.01	-0.21	-0.09
Marital status	1.67	0.56	0.22	2.98	0.04	0.99	3.00
Socioeconomic status	1.58	0.53	0.21	2.94	0.05	0.50	2.47
Loneliness	-5.78	0.89	-0.60	-6.43	0.00	-3.46	-0.99
Duration of Risperdal Consta® treatment	-0.25	0.08	-0.21	-2.97	0.04	-0.59	-0.30
Psychopharmacotherapy	3.63	0.99	0.30	3.65	0.00	1.75	5.34
Family support	1.08	0.53	0.15	2.01	0.04	0.48	2.60
Social support	2.16	0.44	0.43	4.89	0.00	1.90	3.21
Previous remisssion duration	3.60	0.99	0.31	3.60	0.01	2.35	6.04

Table 3. Contribution of independent variables

SE = standard error; Sig. = significance

cording to the duration of therapy, number of psychopharmaceuticals, compliance of psychopharmacotherapy, number of hospitalizations, time elapsed from previous hospitalization, and duration of remission.

Respondents were found to have a strong family support, but in those with depressed symptoms, social isolation was more pronounced with a higher incidence of hetero-aggressive behavior. Also, these individuals had worse psychopharmacotherapy complications, there were fewer of those with remissions for more than a year, and a shorter period of time had elapsed from the last hospitalization. In addition, they had been treated with Risperdal Consta® for a shorter time and in combination of more other psychopharmaceuticals. The mean duration of therapy with Risperdal Consta® was 3.42 years (SD=4.17) in the group of respondents with depressive symptomatology and 5.54 years (SD=3.83) in the control group (U=3.20; p=0.01). The mean number of psychopharmaceuticals was 3.45 (SD=1.27) in the group of respondents with depressive symptomatology and 2.21 (SD=1.51) in the control group (U=2.80; p=0.02). Compared to the group of antipsychotics, the group of benzodiazepines was more commonly used.

Multinominal logistic regression used depression (CDSS) as a dependent variable to estimate the contribution of each independent variable that had a statistical significance greater than 0.05. The variables that were singled out as predictors are shown in Table 3. The above results show that all the study variables associated with depressive symptomatology in the previous model had a statistically significant predictive value, with particular significance observed in compliace with psychopharmacotherapy, previous remission duration, social support, and loneliness.

Discussion

Depression in schizophrenia can be interpreted in a number of ways in relation to whether it is understood as an integral part of the schizophrenic process itself¹⁵ or as a consequence of a psychological reaction to the development of a schizophrenic disorder²⁵. Since the genesis of schizophrenia is considered to be multifactorial, the influence of various factors, whether environmental or individual, can contribute in a person who has predisposition towards depression to develop symptoms of depression^{3,7,25,26}. Depressive moods, anxiety, social withdrawal and emotional detachment often occur in schizophrenia, although they are not necessarily unique to schizophrenia²⁷. Given that negative symptoms in schizophrenia partially overlap with the symptoms of depression, it makes it difficult to distinguish between mood symptoms and negative symptoms in schizophrenia²⁸.

These symptoms can also be difficult to distinguish due to the fact that negative symptomatology can lead to the impoverished intrapsychic functioning, so these people do not only have difficulties in getting to the root cause of a problem, but also in clearly describing them. Therefore, on the one hand, symptoms have been similarly reported by patients as either one or the other, including negative symptoms the manifestation of which is often similar to the symptoms of depression.

In this study, depression in schizophrenia was clearly objectified using the Calgary scale designed for assessment of depression in schizophrenia, whereas negative symptoms were estimated using the PANSS. The mean PANSS score on the negative scale was significantly higher in patients with depression in schizophrenia compared to the control group, as confirmed by previous studies^{29,30}. Negative symptoms lead to reduction of adaptive coping skills and poor social functioning. They will determine the person's definite level of functioning, the level of autonomous functioning and social functioning, employment status and family relations.

In this research, gender, socioeconomic status and marital status were identified as important socio-demographic factors. The results obtained are consistent with previous studies, showing that gender, coexistence and social security are associated with depression^{7,31,32}. Although the reasons for expressing gender differences in schizophrenia are still insufficiently clear, suggesting that males have more severe clinical features, in addition to more frequent negative symptoms³³. In the study by Rocca *et al.*³², men predominated among those diagnosed with severe clinical depression features.

Socioeconomic status has been found to be a significant factor in the development of depression in previous studies^{7,31,34}, as also confirmed in this study. Although the highest prevalence of symptoms of depression was among respondents who had completed secondary school, they were mostly unemployed or retired with generally lower incomes, and probably meeting workrelated demands due to the nature of their disease or doing jobs to make extra money. It should be kept in mind that a complete clinical picture reflecting the illness can be mainly obtained in adolescence, that is, in the years that follow the end of secondary school and beyond. Thus, the onset of illness can affect a person's capacity to function at work, lowering the level of work and consequently causing unemployment.

Consequently, disease related unemployment and low income in turn lead to dependency on family and social support to meet basic socioeconomic needs. This can be seen in reduced quality of life, difficulties in so-

cial integration and participation, and patient marital status. Taking into account the early onset of disease³³, it is not surprising that the majority of respondents were unmarried. The number of divorces was also higher in the group of respondents with depression, and the divorce itself could be one of the factors for the emergence of depression due to the lack of support from the spouse. A disturbed partner relationship, or loneliness arising from divorce or not getting into marriage are important factors that lead to depression^{35,36}. The results in first-time hospitalized patients in our study were opposite to those reported by Bottlender et al.³⁰. Their study was conducted in elderly patients, meaning that a larger proportion were married, thus emphasizing loneliness to a lesser degree. Bearing in mind long-standing illness of our respondents and that they were not hospitalized for the first time, these types of data would point out the importance of illness duration and number of previous hospitalizations for the occurrence of depression.

In addition to poor socioeconomic conditions, other study factors related to social functioning of these individuals and the environment in which they reside (loneliness, environmental support, social support, social isolation) show that people with depressive symptoms in schizophrenia are more often lonely and socially isolated, with poor support from the environment and family. Loneliness was significantly more common in the group of patients with depression than in the control group. This result was expected and consistent with the results of previous studies suggesting that loneliness is common in these people as a result of social isolation and lack of support from the family and environment^{32,33,35,37}. Loneliness is in itself a risk factor for the development of depression and suicidal ideation and attempts^{10,14,37}, reducing self-esteem and increasing social anxiety. A possible explanation has been found in several segments that are not adequate and/or present. Namely, on the one hand, cognitive deficits that arise and possible insight into their condition reduce the ability to adapt to the newly arisen social relationships, and on the other hand, there is a strong social stigma of those affected by the disease. These all contribute to autostigmatization and consequent isolation and loneliness.

Inadequate family and social support revealed in this study also coincides with other studies on numerous challenges faced by the families, such as difficulty of accepting a situation in which a family member is providing medical and social needs of this person, care and uncertain unpredictable future, often accompanied by feelings of concern and guilt^{35,38}. In addition, the phenomena of stigmatization^{39,40} and 'burnout' of family members make these patients feel deprived of family and social support and report a number of problems in the interpersonal domain. Results of numeorus studies have shown the signifficant effect of social and family support on better social functioning in patients with schizophrenia^{41,42}.

The group of respondents with schizophrenia and depression had higher PANSS general psychopathology scores, which was confirmed by the results of the PANSS negative subscale showing the presence of negative symptoms, complications from poor psychopharmacotherapy compliance, greater number of hospitalizations, and shorter period of remission in relation to the severity of clinical manifestations. The results of this study are consistent with the results of other studies^{28,32,43-45}, confirmed by poor adherence to psychopharmacotherapy that is common and associated with negative outcomes in these patients. It is estimated that the recommended drug administration rate is about 50%^{43,44}. Poor compliance can increase the risk of relapse, worsening of symptoms and re-hospitalizations. Furthermore, frequent relapses of the disease with frequent rehospitalizations are risk factors for the incidence of suicide risk in schizophrenia, especially in later course of the disease^{10,14,37}. Risk factors that are positively correlated with social functioning of a person, such as social isolation, loneliness and environmental support are also contributing to poor psychopharmacotherapy compliance, increased number of hospitalizations and shorter remission periods.

Using the multiple logistic regression model, statistically significant predictors of depression in patients diagnosed with schizophrenia are prior length of remission, compliance with psychopharmacotherapy, social support, marital status, and socioeconomic status.

Compliance with psychopharmacotherapy ensures good treatment outcome and consequently good control of schizophrenic disorder leading to longer remission periods. More stability in the primary disease gives the patient further confidence in terms of controlling the disease. Consequently, patients grow in confidence and have greater self-confidence when functioning in general and hence in social interactions. Richer social life results in greater self-confidence, as well as better and more stable mood.

Negative warning signs indicate that our respondents are lonely, younger people with short-term treatment. If the results are viewed in a broader context, the absence of social support that affects almost all functioning domains of those affected by the illness, i.e. personal, family and professional, play a very important role in prediction of depression in schizophrenia. This points to the importance of greater community engagement in improving the living conditions, work environment, and everyday functioning of these people.

Bearing in mind that depression may be caused by the primary disease, i.e. schizophrenia, but also reactively triggered, after further insight derived from the findings of our study, the lack of patient functional self-assessment can be added as a potential limitation to findings. This study aimed to provide further insight into the self report. Furthermore, a larger number of respondents would contribute to greater accuracy of data, in addition to including respondents from various institutions. Since the study included only subjects receiving atypical antipsychotics, it would also be important to include patients receiving typical antipsychotic therapy.

Conclusion

It is estimated that depression occurs in one-third of respondents with schizophrenia. It is often accompanied by the lack of social and family support and may have an impact on all aspects of the individual's life and directly affect them. Namely, the number of social relationships is reduced, the chance of making new acquaintances, emotional bonding, and the chance of finding a job is decreased. The disease course continues to worsen with short periods of remission directly related to medication adherence, i.e. taking medications as prescribed. Since the presence of these factors is associated with depression in schizophrenia, their early detection in clinical practice is vital to ensure timely prevention of the development of depressive symptomatology.

References

 Bosanac P, Castle DJ. Schizophrenia and depression. Med J Aust. 2012;1(4):36-9. https://doi.org/10.5694/mjao12.10516

- Upthegrove R, Marwaha S, Birchwood M. Depression and schizophrenia: cause, consequence, or trans-diagnostic issue? Schizoph Bull. 2017;43(2):240-4. https://doi.org/10.1093/ schbul/sbw097
- Gozdzik-Zelazny A, Borecki L, Pokorski M. Depressive symptoms in schizophrenic patients. Eur J Med Res. 2011;16(12): 549-52.
- 4. Upthegrove R, Birchwood M, Ross K, Brunett K, McCollum R, Jones L. The evolution of depression and suicidality in first episode psychosis. Acta Psychiatr Scand. 2010;122(3):211-8. https://doi.org/10.1111/j.1600-0447.2009.01506.x
- Cardoso CS, Caiaffa WT, Bandeira M, Siqueira AL, Silva JT, Fonseca JO. [Depression in schizophrenia: prevalence and relationship to quality of life]. Cad Saude Publica. 2007;23(9) 2035-48. (in Portuguese)
- Huppert JD, Weiss KA, Lim R, Pratt S, Smith TE. Quality of life in schizophrenia: contributions of anxiety and depression. Schizophr Res. 2001;51(2-3):171-80.
- Balci G, Oter G, Akdag H, Bekki A, Kisa C, Goka E. Factors associated with depression in patients with schizophrenia. J Mood Disord. 2016;6(2):54. https://doi.org/10.5455/jmood. 20160328052653
- Conley RR. The burden of depressive symptoms in people with schizophrenia. Psychiatr Clin North Am. 2009;32(4):853-61. https://doi.org/10.1016/j.psc.2009.09.001
- Lako IM, Taxis K, Bruggeman R, Knegtering H, Burger H, Wiersma D, *et al.* The course of depressive symptoms and prescribing patterns of antidepressants in schizophrenia in a oneyear follow-up study. Eur Psychiatry. 2012;27(4):240-4. https:// doi.org/10.1016/j.eurpsy.2010.10.007
- Hor K, Taylor M. Suicide and schizophrenia: a systematic review of rates and risk factors. J Psychopharmacol. (Oxford). 2010;24(4 Suppl):81-90. https://doi.org/10.1177/135978681 0385490
- Keck PE Jr., Strakowski SM, McElroy SL. The efficacy of atypical antipsychotics in the treatment of depressive symptoms, hostility, and suicidality in patients with schizophrenia. J Clin Psychiatry. 2000;61 Suppl 3:4-9.
- Hawton K, Sutton L, Haw C, Sinclair J, Deeks JJ. Schizophrenia and suicide: systematic review of risk factors. Br J Psychiatry. 2018;187(01):9-20. https://doi.org/10.1192/bjp.187.1.9
- Miles CP. Conditions predisposing to suicide: a review. J Nerv Ment Dis. 1977;164(4):231-46.
- Siris SG. Suicide and schizophrenia. J Psychopharmacol. 2001; 15(2):127-35. https://doi.org/10.1177/026988110101500209
- Stahl SM. Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. Cambridge, UK: Cambridge University Press; 2013.
- Diwan S, Cohen CI, Bankole AO, Vahia I, Kehn M, Ramirez PM. Depression in older adults with schizophrenia spectrum disorders: prevalence and associated factors. Am J Geriatr Psychiatry. 2007;15(12):991-8. https://doi.org/10.1097/JGP.0b 013e31815ae34b

- Michel P, Baumstarck K, Auquier P, Amador X, Dumas R, Fernandez J, *et al.* Psychometric properties of the abbreviated version of the Scale to Assess Unawareness in Mental Disorder in schizophrenia. BMC Psychiatry. 2013;13:229. https://doi. org/10.1186/1471-244x-13-229
- Lako IM, Bruggeman R, Knegtering H, Wiersma D, Schoevers RA, Slooff CJ, *et al.* A systematic review of instruments to measure depressive symptoms in patients with schizophrenia. J Affect Disord. 2012;140(1):38-47. https://doi.org/10.1016/j. jad.2011.10.014
- 19. World Health Organization. The ICD-10: International statistical classification of diseases and related health problems. Geneva: World Health Organization; 2004.
- 20. Innamorati M, Baratta S, Di Vittorio C, Lester D, Girardi P, Pompili M, *et al.* Atypical antipsychotics in the treatment of depressive and psychotic symptoms in patients with chronic schizophrenia: a naturalistic study. Schizophr Res Treatment. 2013;423205. https://doi.org/10.1155/2013/423205
- 21. Quintin P, Thomas P. Efficacy of atypical antipsychotics in depressive syndromes. Encephale. 2004;30(6):583-9.
- Timotijević I, Paunović V. Instrumenti kliničke procene u psihijatriji. Beograd: Institut za mentalno zdravlje; 2003. (in Serbian)
- Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13(2):261-76.
- 24. Addington D, Addington J, Maticka-Tyndale E, Joyce J. Reliability and validity of a depression rating scale for schizophrenics. Schizophr Res. 1992;6(3):201-8.
- Avgustin B. Depression in schizophrenia literature overview. Psychiatria Danubina. 2009;21 Suppl 1:93-7.
- Subotnik KL, Nuechterlein KH, Asarnow RF, Fogelson DL, Goldstein MJ, Talovic SA. Depressive symptoms in the early course of schizophrenia: relationship to familial psychiatric illness. Am J Psychiatry. 1997;154(11):1551-6. https://doi. org/10.1176/ajp.154.11.1551
- Muñoz-Negro JE, Lozano V, Ibanez-Casas I, de la Cruz BG, Soler A, Alcalá JA, *et al.* Negative symptoms across psychotic spectrum disorders. Eur J Psychiatry. 2017;31(1):37-41. https:// doi.org/10.1016/j.ejpsy.2016.12.002
- El Yazaji M, Battas O, Agoub M, Moussaoui D, Gutknecht C, Dalery J, *et al.* Validity of the depressive dimension extracted from principal component analysis of the PANSS in drug-free patients with schizophrenia. Schizophr Res. 2002;56(1-2): 121-7.
- Rabany L, Weiser M, Werbeloff N, Levkovitz Y. Assessment of negative symptoms and depression in schizophrenia: revision of the SANS and how it relates to the PANSS and CDSS. Schizophr Res. 2011;126(1-3):226-30. https://doi.org/10.1016 /j.schres.2010.09.023
- Bottlender R, Strauss A, Moller HJ. Prevalence and background factors of depression in first admitted schizophrenic patients. Acta Psychiatr Scand. 2000;101(2):153-60.
- 31. Rocca P, Bellino S, Calvarese P, Marchiaro L, Patria L, Rasetti R, *et al.* Depressive and negative symptoms in schizophrenia:

different effects on clinical features. Compr Psychiatry. 2005; 46(4):304-10.

- Li R, Ma X, Wang G, Yang J, Wang C. Why sex differences in schizophrenia? J Transl Neurosci (Beijing). 2016;1(1):37-42.
- Link BG, Dohrenwend BP, Skodol AE. Socio-economic status and schizophrenia: noisome occupational characteristics as a risk factor. Am Sociol Rev. 1986;51(2):242-58. https://doi. org/10.2307/2095519
- Pješčić KĐ. Prediktori depresivnosti i suicidalnog rizika kod pacijenata obolelih od shizofrenije [PhD dissertation]. Kragujevac: University of Kragujevac, 2016. (in Serbian)
- Desousa A, Deshmukh V, Bhagat A, Shah N, Sonavane S. Factors affecting marriage in schizophrenia: a cross-sectional study. J Mental Health Hum Behav. 2016;21(2):122. https://doi. org/10.4103/0971-8990.193432
- Erlangsen A, Eaton WW, Mortensen PB, Conwell Y. Schizophrenia - a predictor of suicide during the second half of life? Schizophr Res. 2012;134(2-3):111-7. https://doi.org/10.1016 /j.schres.2011.09.032
- Webb C, Pfeiffer M, Mueser KT, Gladis M, Mensch E, DeGirolamo J, *et al.* Burden and well-being of caregivers for the severely mentally ill: the role of coping style and social support. Schizophr Res. 1998;34(3):169-80.
- Ivezic SS, Sesar MA, Muzinic L. Effects of a group psychoeducation program on self-stigma, empowerment and perceived

discrimination of persons with schizophrenia. Psychiatria Danubina. 2017;29(1):66-73.

- Masedo Gutierrez AI, Grandon Fernandez P, Bustos C, Moreno-Kustner B. Considerations about the assessment of stigma towards persons with schizophrenia: the question of gender. Asian J Psychiatry. 2017;28:148-9. https://doi.org/10.1016/j. ajp.2017.04.026
- Vidović D, Brecić P, Vilibić M, Jukić V. Insight and self-stigma in patients with schizophrenia. Acta Clin Croat. 2016;55(1): 23-8. https://doi.org/10.20471/acc.2016.55.01.4.
- Murray-Swank A, Dixon LB, Stewart B. Practical interview strategies for building an alliance with the families of patients who have severe mental illness. Psychiatr Clin North Am. 2007;30(2):167-80. https://doi.org/10.1016/j.psc.2007.01.004
- Dufort A, Zipursky RB. Understanding and managing treatment adherence in schizophrenia. Clin Schizophr Relat Psychoses. 2019; 10.3371/CSRP.ADRZ.121218: Epub ahead of print. https://doi.org/10.3371/CSRP.ADRZ.121218
- Kikkert MJ, Dekker J. Medication adherence decisions in patients with schizophrenia. Prim Care Companion CNS Disord. 2017;19(6). https://doi.org/10.4088/PCC.17n02182
- Phan SV. Medication adherence in patients with schizophrenia. Int J Psychiat Med. 2016;51(2):211-9. https://doi. org/10.1177/0091217416636601

Sažetak

ČIMBENICI POVEZANI S DEPRESIJOM U BOLESNIKA SA SHIZOFRENIJOM

B. Golubović, Z. Gajić, O. Ivetić, J. Milatović, P. Vuleković, D. Đilvesi, S. Golubović, F. Vrban, A. Subašić i L. Rasulić

Cilj ovoga rada bio je analizirati čimbenike rizika prisutne u shizofrenih bolesnika s depresivnom simptomatologijom. Uzorak se sastojao od 76 ispitanika s dijagnozom shizofrenije. U studiji smo koristili Ljestvicu za procjenu pozitivnog i negativnog sindroma kod shizofrenije (PANSS) i Kalgarijsku ljestvicu depresije. Procjenjuje se da je učestalost depresije 30%. Prosječni rezultati na negativnoj podljestvici PANSS-a bili su značajno veći u bolesnika sa shizofrenijom i depresijom u usporedbi s kontrolnom skupinom (U=3,64, p=0,00), kao i na općoj psihopatološkoj ljestvici (U=4,91, p=0,00). Socio-demo-grafski čimbenici identificirani su kao važni čimbenici (p<0,05). Osobni i okolišni čimbenici, kao što su usamljenost, nepo-sredna društvena okolina, socijalna potpora i izolacija statistički se značajno razlikuju među skupinama (p<0,05). Postoji korelacija između slabe usklađenosti s psihofarmakoterapijom, povećanog broja hospitalizacija, kao i kraćeg razdoblja remi-sije s težinom kliničke slike (p<0,05). Budući da je prisutnost ovih čimbenika povezana s depresijom u shizofreniji, njihovo rano otkrivanje u kliničkoj praksi je od vitalnog značenja za pravodobno sprječavanje razvoja depresivne simptomatologije.

Ključne riječi: Shizofrenija; Depresija; Sociodemografski čimbenici