Original Research

Higher Depression Scores in Patients with Drug-Resistant Schizophrenia

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Abstract

Background: Schizophrenia is a mental illness with diverse clinical presentation, in which a significant proportion of patients show resistance to treatment. In patients with schizophrenia, symptoms from all psychotic and affective spectra are observed. On the one hand, affective symptoms determine the clinical course of schizophrenia and on the other hand, depressive symptoms are some of the most common ones in psychiatry in general. These data give us reason to explore the impact of depressive symptoms on the course of schizophrenia and its relationship with resistance to treatment. **Method**: A study of 105 patients with schizophrenia was performed. Of these, 39 were male and 66 were female. The evaluation of the effectiveness of the treatment carried out at 12 weeks of therapy showed that 45 were resistant to schizophrenia and the remaining 60 were in clinical remission. The clinical evaluation of the patients was performed with the PANSS (Positive and Negative Syndrome Scale) and BPRS (Brief Psychiatric Rating Scale) scales. The assessment of depressive complaints was conducted with the Hamilton Depression Scale. **Results**: Our study showed that in the analysis of depressive complaints with the Hamilton scale females got 12.55 points, and males got 11.44 points. We found a correlation of depressive complaints with the evaluation on the PANSS and BPRS scales, and in the analysis on the individual subscales we found a correlation on the subscale for positive and disorganized symptoms and no correlation on the scale for negative symptoms. We established a difference in the level of depression in patients with resistance in whom the level of depressive complaints was 13.82, while in those in clinical remission it was 10.87 points. **Conclusions**: The level of depressive symptoms in patients with resistant schizophrenia is higher than in clinical remission. Depressive symptoms correlate with positive and disorganized symptoms on the PANSS scale, but not with negative symptoms. Gender is not a determining factor in depressive complaints.

Keywords: schizophrenia; resistance; resistant schizophrenia; depression; consensus; Hamilton scale

1. Introduction

Schizophrenia is a chronic mental disorder of unknown etiologies and clinical presentation. The main clinical symptoms are derived from the disturbed connection with reality, the result of distorted perception and interpretation of sensory stimulation. This distorted perception also leads to characteristic changes in thinking, perception and emotions. The clinical symptoms of schizophrenia are divided into three main groups. There are studies showing that the disorder has numerous intertwined symptoms in the clinical expression as well as some typically psychotic ones with delusions and hallucinations being part of the overall presentation of the disease [1]. Other concomitant changes have also been reported, such as impaired connectivity between neuronal populations, changes in metabolism, the opioid system, and immunological parameters [2–5]. All these data suggest that schizophrenia is a systemic process in which mental symptoms as clinical presentation are part of the overall picture of the disorder. A significant proportion of patients with schizophrenia show resistance to treatment. Treatment-resistant schizophrenia (TRS) has been defined as the persistence of symptoms despite >2 trials of antipsychotic medications of adequate dose and duration.

TRS occurs in up to 34% of patients with schizophrenia [6].

Depressive symptoms, on the one hand, are some of the most common mental symptoms observed in various medical conditions. In some cases, the severity of the symptoms can lead to an independent mental disorder [7]. As a stand-alone disorder, it can be diagnosed in recurrent depression or in bipolar disorder. Depressive symptoms are a common clinical phenomenon in various disorders of fluctuating importance in terms of clinical judgement and development of the treatment plan. This is especially important in people with schizophrenia. The understanding of schizophrenic pathology goes beyond the understanding of negative and positive symptoms and includes a different set of cognitive, depressive and anxiety symptoms [1].

Data on the onset of schizophrenia also contribute to the understanding of this complex disorder. Depressive and anxious symptoms appear in the prodromal period and are usually the most common prodromal sign [8]. About 75% of patients with schizophrenia usually go through such a period. In them, the symptoms of the affective and anxiety spectrum are usually observed years before the onset of psychosis [9,10]. Depressive symptoms are not nosologically specific to schizophrenic pathology, but studies have

shown a prevalence of 7 to 75% in patients with schizophrenia [11]. The chronicity of the schizophrenic process, on the other hand, also contributes to the severity of depressive pathology [12]. Basically, depressive mood is associated with the onset of the first psychotic episode and experiencing acute psychotic state, but at the same time other authors find that depressive symptoms are characteristic throughout the longitudinal course of the disease. They find it to be more related to the chronicity of the disease [13–15].

Depressive episodes have been reported in approximately 1/3 of patients with post-psychotic depression [16]. It has been established that the onset of schizophrenia is accompanied by prodromal symptoms with depressive symptoms and the same symptoms are observed before the onset of relapse in patients [17].

These studies are indicative that the underestimation of depressive symptoms is in itself responsible for the frequent subsequent psychotic episodes because it is a marker of their occurrence. Worsening of the depressive symptoms materializes before the onset of the psychotic episode [17].

There is evidence that depressive symptoms in patients with schizophrenia are generally associated with a more severe and problematic course of the disease with impaired social functioning and elevated comorbidity with increased need for care and additional medications and hospitalizations [17–19]. In addition, other analyses add that the high suicide rate in patients with schizophrenia is associated with the presence of depressive symptoms [20].

According to some authors, the clinical significance of depression in schizophrenia is obscured by its association and overlapping with negative symptoms [21]. Some features such as impaired concentration, lack of interest, motivation, pleasure and energy can be part of both negative and depressive symptoms. [11]. While many authors report a link between depressive and negative symptoms of schizophrenia [22–24], others find significantly higher correlations between depressive and positive symptoms than negative ones [25,26]. They found that a lack of correlation between depressive and negative symptoms can be expected, since negative symptoms, unlike positive ones, are deficient with a significantly reduced capacity for inner experience. Conversely, depressive symptoms have an inner experience and discomfort to one extent or another, i.e. there is suffering.

Other authors have found that the addition of antidepressants (almost all of them in varying degree) to the stable antipsychotic therapy leads to a reduction of the negative symptoms [27].

A meta-analysis confirms these observations, showing that despite the mixed results obtained from various studies, the presence of negative symptoms has been associated with the absence of depressive symptoms [28]. On the contrary, there is evidence that after the use of antipsychotics there is a greater improvement in depressive symptoms compared to the negative ones [29]. In patients with schizophrenia,

other authors have also found a link between depressive symptoms and the presence of positive symptoms [30].

Depressive symptoms have long been considered a good prognostic factor for the prognosis of the schizophrenic process [31–36]. Other authors are of the opposite opinion, emphasizing the association with poor prognosis and tenser course of the schizophrenic process [37–39].

The relationship between psychosis and depression is interdependent. Depression can directly affect psychotic symptoms by negatively charging environmental stimuli [40].

Other authors have also found worsening of psychosis from depressive symptoms [41]. Depressive complaints make it possible to further distort perception and, consequently, psychotic symptoms [42,43]. Psychotic symptoms, on the other hand, can also cause feelings of fear and depression [44].

There have been reported no studies on the differences in the severity of depressive symptoms in patients with schizophrenia in clinical remission and in those with resistance to therapy. We hypothesized that there should be differences between the two groups with an increased level of depression in the group with resistant psychotic symptoms.

2. Material and Methods

2.1 Subjects

A total of 105 patients with schizophrenia with consecutive psychotic episode were observed. Of these, 45 have resistant schizophrenia and the remaining 60 are in clinical remission.

The patients were observed in a psychiatric clinic at the University Hospital in Stara Zagora.

Including criteria to all patients:

(1) diagnosis of schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [DSM-V, 2013];

(2) between 18 and 60 years of age;

(3) at least primary education.

Including criteria for patients with resistant schizophrenia are those who have met the resistance criteria of the published consensus on resistant schizophrenia [6]. These are:

(1) Assessment of symptoms with the PANSS (Positive and Negative Syndrome Scale) and BPRS (Brief Psychiatric Rating Scale) scale [45,46].

(2) Prospective monitoring for a period of at least 12 weeks.

(3) Administration of at least two antipsychotic medication trials at a dose corresponding to or greater than 600 mg chlorpromazine equivalents.

(4) Reduction of symptoms when assessed with the PANSS and BPRS scale by less than 20% for the observed period of time.

(5) The assessment of social dysfunction using the SOFAS [Social and Occupational Functioning Assessment Scale] scale is below 60.

The exclusion criteria are:

(1) Mental retardation;

(2) Psychoactive substance abuse;

(3) Presence of organic brain damage;

(4) Concomitant progressive neurological or severe somatic diseases;

(5) Expressed personality change;

(6) Score of MMSE [Mini-Mental State Exam] below 25 points;

(7) Pregnancy and breastfeeding.

2.2 Methods

Depressive complaints were assessed with the Hamilton Depression Scale [Hamilton, 1980].

We used the SPSS (version 26, IBM Corp, Chicago, IL, USA) statistical package. Correlation analysis was used to investigate the relationship between depressive symptoms and other clinical features as measured by PANSS and BPRS in patients with schizophrenia. Gender stratification was also performed. A non-parametric statistical method was also used /Mann Whithney U test [47].

Age, body mass index (BMI), level of education and gender are controlled as covariables.

All research procedures were carried out in accordance with the Declaration of Helsinki. All patients have signed an informed consent before admission to the clinical settings and performing diagnostic tests and therapy.

3. Results

3.1 Descriptive Statistics of the Sample

Out of a total of 105 patients with schizophrenia, we found that 66 were female and 39 were male. According to the effect of the treatment, we registered 45 patients with resistant schizophrenia and 60 patients in clinical remission.

The mean age of patients in the group of resistant schizophrenia was 36.98 years. The minimum age is 21 years and the maximum is 60 years.

The mean age of patients in the group of schizophrenia in clinical remission was 37.25 years. The minimum is 23 years and the maximum is 63 years.

We did not find a difference in the mean age of patients in the two groups at the time of the study.

The distribution by sex in the two groups of patients showed the following: in the group with resistant schizophrenia 25 were female and 20 were male, while in the group in clinical remission females predominated were 41 and males were 19, respectively.

In the group of patients in clinical remission predominated female with higher level of depressive symptoms measured on the Hamilton scale (Table 1).

Conducting a descriptive statistical analysis showed that the average level of depression in the group of females

Table 1. Distribution of patients by sex in the two groups.

	Resistant	Remission	Total
Female	25	41	66
Male	20	19	39
Total	45	60	105

was 12.55, the median was 12, and the standard deviation was 5.384.

In males we found that the average level of depression was 11.44, the median was the same as in females was 12, with a standard deviation of 4.179.

We found a slightly higher level of depressive symptoms in females, but without statistical dependence on the level of depressive scores between the sexes (Table 2).

Table 2. Link between registered depressive symptoms (according to HAMD scale) and gender ($p < 0.05$).

Gender	Mean	Median	St. deviation
Female	12.55	12	5.384
Male	11.44	12	4.179

HAMD, Hamilton Depression Rating Scale.

3.2 Correlations between Clinical Scales

Analysis of the relationship between depressive symptoms and scores on the PANSS and BPRS scales showed statistical dependence. It is presented in Table 3.

This table shows that there is significant correlation between the severity of symptoms on the PANSS and BPRS scales and the level of depressive symptoms established with the Hamilton Depression Rating Scale. In both scales there is high statistical dependence with the presence of depressive symptoms (*** $p < 0.001$).

Following a correlation analysis for the relationship with the individual subscales: positive, negative and disorganized, we obtained the results presented in Table 4.

The results show that there is a moderate correlation between positive and disorganized symptoms when assessed with the PANSS scale and depressive symptoms when assessed with the Hamilton scale ($p < 0.001$).

There is no statistically significant relationship between the registered negative symptoms and the presence of depressive complaints ($p > 0.01$).

3.3 Comparative Analysis between the Two Patient Groups

In the search for a relationship between resistance to therapy and the presence of depressive symptoms, the following results were found, presented in Table 5.

The mean on the Hamilton Depression Scale in the treatment resistance group was 13.82, the median was 12, and the standard deviation was 5.549.

In the clinical remission group, the mean Hamilton scale was 10.87, the median was 10, and the standard devi-

Table 3. Relationship between depressive symptoms assessed by Hamilton depressive scale and the PANSS and BPRS scales.

		PANSS	BPRS	Hamilton D
PANSS	Pearson Correlation	1	0.911	0.275
	Sig. (2-tailed)		0.000	0.005
BPRS	Pearson Correlation	0.911	1	0.383
	Sig. (2-tailed)	0.000		0.000
Hamilton D	Pearson Correlation	0.275	0.383	1
	Sig. (2-tailed)	0.005	0.000	

PANSS, Positive and Negative Syndrome Scale; BPRS, Brief Psychiatric Rating Scale.

Table 4. Relationship between depressive complaints assessed by Hamilton depressive scale and PANSS subscales.

			PANS positive	PANS negative	PANSNS disorganized	Hamilton D
Spearan's rho	PANS positive	Correlation Coefficient	1.000	0.532	0.727	0.349
		Sig. (2-tailed)		0.000	0.000	0.000
	PANS negative	Correlation Coefficient	0.532	1.000	0.686	0.186
		Sig. (2-tailed)	0.000		0.000	0.05
	PANS disorganized	Correlation Coefficient	0.727	0.686	1.000	0.430
		Sig. (2-tailed)	0.000	0.000		0.000
	Hamilton D	Correlation Coefficient	0.349	0.186	0.430	1.000
		Sig. (2-tailed)	0.000	0.057	0.000	

PANSS, Positive and Negative Syndrome Scale.

Table 5. Relationship between the values of ranks of depressive symptoms in patients with resistance to treatment and those in clinical remission.

	Effect of therapy	N	Mean rank	Sum of ranks
Hamilton D	resistant	45	61.87	2784.00
	remission	60	46.35	2781.00

Table 6. Relationship between the values of depressive symptoms in patients with resistance to treatment and those in clinical remission.

	Hamilton D
Mann-Whitney U	951.000
Wilcoxon W	2781.000
Z	−2.595
Asymp. Sig. (2-tailed)	0.009

ation was 4.115.

The results are presented on Fig. 1 and in Tables 5,6.
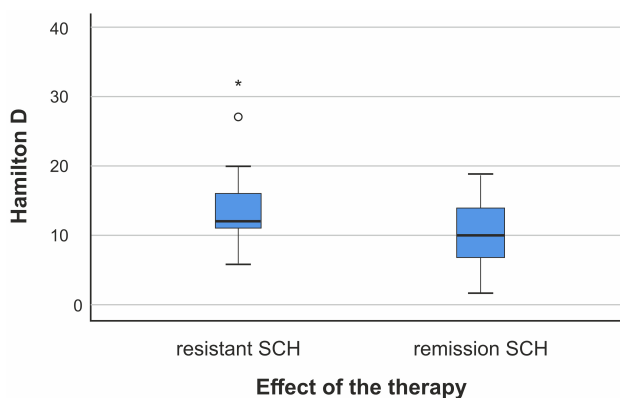
Fig. 1. Relationship between resistance to treatment and level of depressive scores.

4. Discussion

We found a difference in depressive symptoms in patients with resistance to treatment and in those in clinical remission using the Hamilton scale. These results show that depressive symptoms are part of the clinical picture of the schizophrenic process, especially in the presence of resistance to treatment. These data support the findings by other authors that depressive symptoms are observed almost all the way through the schizophrenic process and are associated with a more intense course [17–19,48]. We do not support the opinion of other authors on the association of depressive symptoms with a more favorable prognosis in patients with schizophrenia [33–36]. It is clear that negative symptoms are associated with greater resistance and there are fewer therapeutic options for it [49–51]. We did not find a correlation between the severity of depressive symptoms and the presence of negative symptoms. With this observa-

tion, we support the results of other authors that in the presence of negative symptoms, depression is usually absent [28]. If we have to analyze the relationship between these two groups of symptoms, the very presence of depressive symptoms raises the question of experiences (albeit negative) of the patient, which puts them outside the scope of negative symptoms/sadness versus apathy [52]. The presence of subclinical depressive symptoms explains why the addition of certain antidepressants is associated with an improvement in clinical signs beyond the presence of a pronounced depressive episode [27].

The assessment of the relationship between the presence of positive and disorganized symptoms showed a relationship between them and the depressive complaints of patients. These results support the data of other authors on the relationship between psychotic and depressive complaints and their interdependence [30,42,43]. Some researchers have questioned the use of the Hamilton scale in patients with schizophrenia due to overlap with negative symptoms [53]. We cannot agree with this view. On the one hand, the analysis of clinical symptoms in patients with schizophrenia is done with the PANSS and BPRS scales and the assessment is external—done by a specialist and based on the overall performance, including the patient's appearance and reactions. Hamilton's scale, on the other hand is also evaluated by a specialist, but incorporates patient's own introspective account/narrative about experiences. This is the reason why we believe that it cannot be an overlap of symptoms or if there is one, it is not precisely defined /as far as in psychiatry a precise boundary can be set between the individual symptoms. If an analysis of the patient's behaviour, outlook and appearance is made, a clear-cut distinction between negative and depressive symptoms may not be attainable.

Depressive symptoms are more pronounced in females than in males [54]. Some authors attribute this fact to the difference in attitudes towards one's own experiences and the tendency to exaggerate the significance of experiences for females [54]. Our study showed minor gender differences in the assessment of depressive complaints, a fact which can be explained by the change due to the schizophrenic process as well as the antipsychotic therapy.

Analysis of neuronal connectivity using functional magnetic resonance imaging in patients with psychosis and those with depression shows that there are differences in the relationships between different brain structures [4]. The authors find an opposite way of connection between the dorsolateral prefrontal cortex (DLPFC) and the anterior insula (AI) (in patients with depression there is reduced effective connectivity, and in those with psychosis there is an increased inhibition of DLPFC to AI) [4]. These data explain why the pronounced affective symptoms have been identified by some authors as a good prognostic sign. Pronounced depressive symptoms disarrange the relationship, i.e., the process of enhanced inhibition registered in patients

with psychosis. This is not the case with us. We found subclinical values of depressive symptoms in patients with resistance, which does not allow suppressing the process of inhibition and persistence of psychotic symptoms. These results explain the contradictory data in literature: why in some cases depressive symptoms are considered a good prognostic sign, and in others as symptoms associated with poor prognosis. Our data give us reason to assume that the factor determining the influence of affective symptoms on the course of schizophrenia is its severity.

These results give us reason to think that it is very likely that depressive complaints in the course of the schizophrenic process are part of the overall clinical presentation and demonstrate the complexity of schizophrenia as a nosological unit.

Our observation provides guidance for future research on the relationship between depressive complaints in the course of the schizophrenic process. We believe that it is necessary to conduct an analysis in a larger number of patients in order to make a more accurate assessment of the impact of depressive complaints on resistance in patients with schizophrenia.

Our observations raise another question that needs to be answered in future research. On the one hand, we find a link between depressive complaints and resistance in people with schizophrenia. On the other hand, we do not find a connection between the pronounced depressive symptoms and the severity of the negative symptoms in schizophrenia. Negative symptoms are also associated with poor prognosis found in various studies [49,51]. These differences give us reason to discuss a different course in the development of resistance, most likely associated with different subtypes of schizophrenic disorders.

On the other hand, the question arises whether in patients with resistance to treatment depressive symptoms have been more pronounced since the onset of psychosis than in patients with clinical remission. Monitoring the longitudinal aspect of the dynamics of depressive symptoms would answer the question about their place in the development of resistance.

Limitations. Our study showed an association between the presence of subclinical depressive symptoms and resistance to treatment. In order to establish the significance of this relationship, it is necessary to conduct a larger study with a larger number of patients observed over a longer period of time. These observations could provide information on the prognostic value of subclinical depressive complaints in patients with schizophrenia.

5. Conclusions

Our study found a relationship between the clinical characteristics of symptoms in patients with schizophrenia and concomitant depressive symptoms. We found a higher level of depression in patients with resistance to treatment than those who reached clinical remission. The higher level

of depression raises the question of monitoring the dynamics and the search for therapeutic strategies to influence it. The clinical observation we mentioned above led us to conclude that most of the time we underestimate these "hidden" depressive symptoms and gave us reason to think that conducting routine self-assessment tests would provide good guidelines for assessing prognosis.

Author Contributions

All work was conceived and completed by GP.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethical Committee of University Hospital "Prof. Dr. Stoyan Kirkovich" Stara Zagora, protocol code TR3-02-242/30 December 2021.

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Conflict of Interest

The author declares no conflict of interest.

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