



Depressive symptoms among patients with schizophrenia in acute and remission phases

Simptomi depresivnosti kod bolesnika obolelih od shizofrenije u akutnoj fazi i u remisiji

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Abstract

Background/Aim. Researchers suggest that among people with schizophrenia, the prevalence of depressive symptoms ranges from 7% to 80%. The rate of depressive symptoms among people with schizophrenia varies widely because of the phase of the disease, type of study applied, rating scale for depressive symptoms and diagnostic criteria. The aim of this research was to determine the prevalence of depressive symptoms and the clinical correlation of depressive symptoms with other clinical parameters (type and severity of psychotic symptoms, severity of illness, insight and global functioning) among patients with schizophrenia in acute and remission phases. **Methods.** This prospective clinical study enrolled 100 consecutive patients with schizophrenia both in acute and remission phases. Psychometric assessments were made using the Positive and Negative Syndrome Scale (PANSS) for rating the symptoms of schizophrenia, Scale to Assess the Unawareness of Mental Disorder (SUMD), Calgary Depression Scale for Schizophrenia (CDSS), and Global Assessment of Functioning Scale. **Re-**

sults. The prevalence of depressive symptoms among patients with schizophrenia in the acute phase was 23% at the study group, while in the remission phase it was 13%. In the acute phase, the CDSS scale correlated with a depressive and positive subscale of the PANSS scale as well as SUMD scale. In the remission phase, the CDSS scale correlated only with a depressive subscale of the PANSS scale. The CDSS scale did not correlate with the negative subscale of the PANSS scale. The subjective nature of depressive symptoms is more pronounced in the remission phase. **Conclusion.** Our findings showed that depressive symptoms were more pronounced in the acute psychotic phase than in the remission phase of schizophrenia. Targeted, patient oriented, and algorithm-based approach for treatment management, with taking into account different phenotypic expressions of the disorder (patients with and without affective symptoms) is warranted in patients with schizophrenia.

Key words: depression; schizophrenia; prevalence; acute disease; remission induction.

Apstrakt

Uvod/Cilj. Istraživanja pokazuju da se kod bolesnika koji boluju od shizofrenije, prevalenca depresivne simptomatologije kreće od 7% do 80%. Varijabilnost u studijama potiče od faze bolesti u kojoj su se bolesnici nalazili u trenutku opservacije, metoda procene, vrste mernih instrumenata kao i različitih dijagnostičkih kriterijuma za shizofreniju i depresiju. Cilj rada bio je da se ispita prevalenca depresivnih simptoma i korelacije depresivnih simptoma sa drugim kliničkim parametrima (vrsta i težina psihotičnih simptoma, težina bolesti, uvid, opšta funkcionalnost) kod

bolesnika obolelih od shizofrenije u akutnoj fazi bolesti i u remisiji. **Metode.** Istraživanje predstavlja kliničku prospektivnu studiju kod 100 konsektivnih bolesnika obolelih od shizofrenije u odnosu na fazu bolesti (faza akutnog pogoršanja i faza remisije). Psihometrijske procene težine bolesti i prisutne psihopatologije vršile su se korišćenjem Skale za procenu pozitivnog i negativnog sindroma shizofrenije (PANSS), Skale za procenu nedostatka uvida u mentalni poremećaj (SUMD), Kalgari skale za procenu depresije u shizofreniji (CDSS) i Skale za opštu procenu funcionisanja (GAF). **Rezultati.** Prevalenca depresivne simptomatologije kod bolesnika obolelih od shizofrenije u akutnoj fazi bolesti

u studijskoj grupi iznosila je 23%, a u fazi remisije 13%. U akutnoj fazi, Kalgari skala za procenu depresije u shizofreniji korelirala je sa depresivnom i pozitivnom podskalom PANSS kao i sa skalom uvida, dok u remisiji samo sa depresivnom podskalom PANSS. Kalgari skala nije korelirala sa negativnom podskalom PANSS. Subjektivni korelati depresije bili su izraženiji u remisiji u odnosu na akutnu fazu. **Zaključak.** Depresivni simptomi u shizofreniji izraženiji su

tokom akutne psihotične faze u odnosu na fazu remisije. Prepoznavanje depresivne simptomatologije otvara mogućnosti ciljane farmakoterapije, psihoterapije i socioterapijskih intervencija, što može voditi ka boljem terapijskom ishodu.

Ključne reči:
depresija; shizofrenija; prevalenca; akutna bolest; remisija, indukcija.

Introduction

Depressive symptoms are frequently observed in people with schizophrenia. Although they can be observed during the course of schizophrenia¹, depressive symptoms are frequently not considered during diagnostics of schizophrenia, except as post-psychotic depression.

During the eighties and nineties of the XX century, scientists were intensively engaged in studying depressive symptoms in schizophrenia to construct a unique nosological entity. Despite several studies, the unified nosological entity remains undefined. Recent attempts have been made for conducting cross-sectional and longitudinal assessments using new research tools for better understanding of this syndrome. Concerning the nosological debate on depression in schizophrenia, recent work of Gaebel and Wolwer² concluded that depressive symptoms among patients with schizophrenia seem to reflect a subjective impression of affective flattening combined with unspecific depressive symptoms. This is in contrast to the more specific depressive symptoms, such as depressive mood or inhibition, in major depression^{3,4}. From a phenomenological point of view, there are three different meanings of depression in schizophrenia: depression as a reaction to schizophrenia, depression as an integral part of it, and depression as an independent disorder⁵. Moreover, the differential diagnosis of depressive symptoms is often difficult among patients with schizophrenia. There were several reasons reported and they included organic factors, negative symptoms of schizophrenia, consequence or adverse effects of treatment with neuroleptics (neuroleptic-induced dysphoria, akinesia, or akathisia)⁶, reaction to disappointment, or stress resulting from the disease⁷.

The emergence of depressive symptoms among patients with schizophrenia was associated with an increased rate of relapse⁸, longer hospitalization⁹, weak response to pharmacotherapy¹⁰, disturbed social activities, and feeling of hopelessness, which is an important risk factor for suicide^{11,12}.

The aim of this study was to determine the prevalence of depressive symptoms among the patients with schizophrenia in the acute and remission phases. We also sought to determine the clinical correlation of depressive symptoms with other clinical parameters (type and severity of psychotic symptoms, severity of illness, insight and global functioning) in the acute and remission phases.

Methods

Patients

Patients who were admitted to the Institute of Mental Health were recruited consecutively. Study inclusion criteria were as follows: diagnosis of acute phase of schizophrenia based on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV)¹³; age 18–65 years. The follow-up was done in the remission phase. Patients were excluded if they had any other DSM-IV axis I or axis II disorder, or any comorbid medical disease. They were also excluded if they had been treated with antidepressants at the time of the first assessment. Sociodemographic and clinical data were collected by trained psychiatrists.

Design and assessments

This was a prospective clinical study which was carried out at the Institute for Mental Health, Belgrade between 2011 and 2013. The study was approved by the Ethics Committee and written informed consent was obtained from all participants prior to participation in the study. The study was a part of a study that examines, using the same model, patients from the Psychiatric Hospital of Attica (Athens, Greece) as well as patients from psychiatric hospitals at St. Pancras Hospital, Highgate Mental Health Hospital and St Luke's Hospital (London, United Kingdom).

The patients were observed in two different phases of the disease: 1) the acute phase during hospitalization and 2) the stage of initial remission (approximately after six weeks of treatment as outpatients after they had been discharged). A cut-off score of $\leq 50\%$ for the Positive and Negative Syndrome Scale (PANSS) for rating the symptoms of schizophrenia was considered to indicate that remission was achieved¹⁴.

Psychometric assessments of the severity of the disease and existing psychopathological symptoms were made both at the admission and end of the inpatient treatment using the Structured Clinical Interview for Mental Disorders (SCID-I)¹³, PANSS scale¹⁵, Scale to Assess the Unawareness of Mental Disorder (SUMD)¹⁶, Calgary Depression Scale for Schizophrenia (CDSS)¹⁷, and Global Assessment of Functioning Scale (GAF)¹⁸.

The PANSS scale is used for assessing positive, negative and depressive symptoms as well as general psychopathology. It comprises 30 items, each item rated 0–7. We used four subscales to assess positive symptoms (the

PANSS-P total score, 49), negative symptoms (the PANSS-N total score, 49), depressive symptoms (the PANSS-D total score, 28), and general psychopathology (the PANSS-G total score, 112). A cut-off score of ≥ 16 was used to define depression as measured by the PANSS-D subscale. Based on other studies, remission was defined by reducing the scale value by ≤ 3 on each item¹⁴.

The SUMD scale (abbreviated version) is in the form of semi-structured interview developed to assess insights into mental illness¹⁶. The scale ranges from 0 to 15. A score of ≤ 9 represents the existence of insight into the mental illness.

The CDSS scale is used to assess depression among patients with schizophrenia, avoiding significant overlap between extrapyramidal, negative and depressive symptoms¹⁷. The scale includes nine items and each item is scored from 0 to 3. In accordance with previous studies, a value higher than six was the cut-off score for depression diagnosis. Similar to previous studies, we used a score higher than six on the CDSS scale to indicate the presence of depression symptoms. The CDSS scale was shown as a more specific instrument than the HAMD-D and Beck Depression Inventory in the evaluation of depression in schizophrenia¹⁷.

The GAF Scale assigns a clinical judgment in a numerical fashion to an individual's overall functioning level¹⁹. It considers psychological, social and occupational functioning on a hypothetical continuum of mental health illness. It is divided into 10 intervals of 10 points and a count from 1 to 100, where 100 indicate superior performance.

Statistical analysis included parametric and non-parametric descriptive statistics, depending on the nature of data. Further analysis included inferential statistical methods (unifactorial analysis of variants, Students' *t*-test, Mann-Whitney's U-test, Pearson's χ^2 -test of independence, and Spearman's rank correlation). The Statistical Package for Social Sciences –SPSS for Windows, Version 19.0 (SPSS Inc. Chicago, IL) was used for this analysis.

Results

The original sample comprised 109 consecutive patients who were admitted to the Institute of Mental Health. Nine patients were excluded because of failure of remission or noncompliance; therefore, the final sample comprised 100 patients with schizophrenia. The age range of patients was between 19 and 63 years, with male comprising 55% of the sample. The majority of patients (86%) were unemployed and 90.7% were single. All patients received antipsychotic treatment (71.7% were atypical antipsychotics).

Our findings showed that the prevalence of depressive symptoms among patients with schizophrenia was 23% in the acute phase. After hospital treatment, in the remission phase, the prevalence of depressive symptoms was 13%. From a total of 23% patients with depressive symptoms in the acute phase, 12% achieved complete remission, whereas 11% remained with depressive symptoms. Two (2%) patients from the group without depressive symptoms in the acute phase developed depressive symptoms at the end of the treatment.

We have identified a significant difference between the patients with and without depressive symptoms relative to the time of admission, regarding clinical correlates and psychopathology [Wilks' $\Lambda = 0.74$, $F(8.91) = 4.07$, $p < 0.01$]. An additional univariate analysis revealed the differences in the PANSS-P and PANSS-D subscales and SUMD scale (Table 1).

The data analysis indicated one significant discriminant function [Wilks' $\Lambda = .75$, $\chi^2(3, N = 100) = 27.48$, $p < 0.001$]. The canonical correlation analysis was 0.49. Correlations between the discriminant function and variables showed the highest projection for insight ($r = 0.80$) and less for the PANSS-D1 subscale ($r = -0.49$) and PANSS-P1 subscale ($r = 0.44$). The significant discriminant function indicated that the patients without depression (0.31) were at the positive extreme and the patients with depression (-1.04) were at the negative extreme.

Table 1
Depressive symptoms in the acute stage among patients with schizophrenia compared to clinical parameters at the admission

| Questionnaires | Non-depressive | | Depressive | | df _b | df _w | F | p |
|---------------------------|----------------|-------|------------|-------|-----------------|-----------------|-------|------|
| | M | SD | M | SD | | | | |
| PANSS-P1 ^a | 21.57 | 5.41 | 18.57 | 3.89 | 1 | 98 | 6.13 | .015 |
| PANSS-N1 ^b | 23.13 | 8.40 | 24.74 | 7.32 | 1 | 98 | 0.69 | .409 |
| PANSS-G1 ^c | 58.34 | 8.78 | 58.13 | 7.80 | 1 | 98 | 0.01 | .919 |
| PANSS-Total1 ^d | 102.64 | 16.70 | 101.43 | 13.56 | 1 | 98 | 0.10 | .753 |
| SUMD1 ^e | 10.90 | 3.11 | 7.43 | 3.53 | 1 | 98 | 20.65 | .000 |
| PANSS-D1 ^f | 15.90 | 3.47 | 18.13 | 3.00 | 1 | 98 | 7.77 | .006 |
| GAF1 ^g | 30.70 | 9.29 | 32.13 | 11.91 | 1 | 98 | 0.37 | .546 |

^aSubscale for positive symptoms from The Positive and Negative Syndrome Scale for Rating the Symptoms of Schizophrenia (PANSS) in acute phase; ^bSubscale for negative symptoms from the PANSS in acute phase; ^cSubscale for general psychopathology from the PANSS in acute phase; ^dTotal score of the PANSS in acute phase; ^eScale to Assess the Unawareness of Mental Disorder (SUMD) in acute phase; ^fSubscale for depressive symptoms from the PANSS in acute phase; ^gGlobal Assessment of Functioning Scale (GAF1) in acute phase; M – mean score; SD – standard deviation.

Table 2

Depressive symptoms in remission among patients with schizophrenia compared to clinical parameters at the remission

| Questionnaires | Non-depressive | | Depressive | | df _b | df _w | F | p |
|---------------------------|----------------|-------|------------|------|-----------------|-----------------|------|-------|
| | M | SD | M | SD | | | | |
| PANSS-P2 ^a | 11.29 | 2.66 | 10.08 | 2.36 | 1 | 98 | 2.40 | 0.125 |
| PANSS-N2 ^b | 14.22 | 5.73 | 14.62 | 5.72 | 1 | 98 | 0.05 | 0.816 |
| PANSS-G2 ^c | 31.13 | 5.26 | 31.00 | 3.83 | 1 | 98 | 0.01 | 0.934 |
| PANSS-Total2 ^d | 57.11 | 10.53 | 55.69 | 7.20 | 1 | 98 | 0.22 | 0.640 |
| SUMD2 ^e | 6.29 | 2.28 | 5.69 | 2.05 | 1 | 98 | 0.78 | 0.378 |
| PANSS-D2 ^f | 8.06 | 1.78 | 9.46 | 1.85 | 1 | 98 | 6.96 | 0.010 |
| GAF2 ^g | 56.28 | 9.01 | 58.23 | 7.87 | 1 | 98 | 0.55 | 0.461 |

^aSubscale for positive symptoms from The Positive and Negative Syndrome Scale for Rating the Symptoms of Schizophrenia (PANSS) in remission; ^bSubscale for negative symptoms from the PANSS in remission; ^cSubscale for general psychopathology from the PANSS in remission; ^dTotal score of the PANSS in remission; ^eScale to Assess the Unawareness of Mental Disorder (SUMDR) in remission; ^fSubscale for depressive symptoms from the PANSS in remission; ^gGlobal Assessment of Functioning Scale (GAF2) in remission; M – mean score; SD – standard deviation.

Table 3

Mean scores and the proportion on items on the Calgary Depression Scale for Schizophrenia (CDSS)

| CDSS Items | Acute phase | | Remission | |
|---------------------------|-------------|------|-------------|------|
| | M ± SD | % | M ± SD | % |
| Depression | 0.67 ± 0.54 | 29.8 | 1.01 ± 0.71 | 14.6 |
| Hopelessness | 0.60 ± 0.42 | 18.1 | 0.91 ± 0.86 | 13.2 |
| Self depreciation | 1.02 ± 0.72 | 17.6 | 0.84 ± 0.66 | 12.4 |
| Guilty ideas of reference | 0.76 ± 0.70 | 7.8 | 0.67 ± 0.54 | 5.7 |
| Pathological guilt | 0.64 ± 0.68 | 4.9 | 0.54 ± 0.56 | 3.1 |
| Morning depression | 0.82 ± 0.76 | 10.6 | 0.71 ± 0.67 | 8.0 |
| Early wakening | 1.11 ± 0.96 | 19.3 | 0.80 ± 0.48 | 9.1 |
| Suicide | 0.61 ± 0.72 | 1.8 | 0.13 ± 0.37 | 1.2 |
| Observed depression | 0.23 ± 0.94 | 20.7 | 0.66 ± 0.72 | 11.9 |

M – mean; SD – standard deviation.

We identified a statistically significant difference between the patients with and without depressive symptoms relative to the time of remission, regarding clinical correlates and psychopathology [Wilks' $\Lambda = 0.85$, $F(8,91) = 2.00$, $p = 0.055$]. An additional univariate analysis revealed the differences in the PANSS-D subscales (Table 2).

The proportions on each item and the mean scores on the CDSS scale in the acute and remission phases are shown in Table 3.

The correlation among depressive symptoms (total score of the CDSS scale and PANSS-D subscale) and other scales in the acute and remission phases were examined. During the acute phase, the CDSS scale had a high positive correlation with the PANSS-D subscale ($r = 0.38$, $p < 0.001$) as well as high negative correlation with the PANSS-P subscale ($r = -0.37$, $p < 0.01$) and SUMD scale ($r = -0.47$, $p < 0.01$). There was no correlation with the negative factor of the PANSS-N, PANSS-G and PANSS-total subscales.

Correlation between the CDSS scale and PANSS-D subscale with other clinical parameters in the acute phase did not change during remission.

Discussion

Our findings showed that the prevalence of depressive symptoms among patients with schizophrenia was 23% patients in the acute phase of the disease. After hospital treat-

ment, the prevalence of patients with depressive symptoms decreased in remission phase. In addition, we also found that the insight was related not only to the positive psychotic symptoms but also to depressive symptoms in schizophrenia. Moreover, the results indicated the difference in the profile of depressive symptoms in the different phases of the disease.

The rate of patients with schizophrenia who exhibited depressive symptoms during their lifetime ranged from 25% to 80%²⁰. Depressive symptoms were more frequent in the acute phase with a point of prevalence ranging from 20% to 80%²¹. However, our findings are in accordance with a review of Siris and Bench⁷ who showed a modal rate of 25%.

Lower prevalence was found in the chronic phase of the disease with a point of prevalence as low as 4% and as high as 15%²². This finding led some authors to conclude that there was a specific relationship between affective symptoms and positive symptoms of schizophrenia⁷. Our rate of depressive symptoms after hospital treatment was 13% in the remission phase.

The rate of depressive symptoms among people with schizophrenia varies widely because of the phase of the disease, type of study that was applied (cross-sectional vs. longitudinal), depressive rating scale, diagnostic criteria, and whether depressive symptoms, depressive syndrome, or a depressive disorder as a whole are being considered²³. Additionally, few studies explored the prevalence of depressive

symptoms in a patient with schizophrenia using the CDSS scale. It was shown that the CDSS scale had greater validity in patients with schizophrenia than other assessment tools, such as the Hamilton Depression scale and Montgomery-Asberg scale²⁴.

Evaluation of depressive symptoms in a sample of 249 patients with schizophrenia with acute exacerbation by Schennach-Wolff using the CDSS scale registered a prevalence of depressive symptoms of 36% at admission, with 23% remaining depressed at discharge²⁴. Maggini and Raballo²⁵ in 2006 evaluated a sample of 161 outpatients with chronic schizophrenia in remission and determined a prevalence of depression of 30%. Majadas et al.²⁶ in the Spanish sample of 95 patients with stable schizophrenia found a prevalence of depression of 31%. However, Gorna et al.²⁷ used the same scale in a sample of 74 patients with remission and found a higher prevalence of depression of 45.9%. Roche et al.²⁸, in a sample of 165 patients with the acute phase of the first episode of schizophrenia, registered low prevalence of 10.4%. The differences between our findings and those previously mentioned may be related not only to cultural differences in perception of depressive symptoms but also to the differences in patient's selection, inclusion of other similar diagnostic groups (schizoaffective or schizophreniform disorder), sample size, and treatment applied.

During hospital treatment, in both groups of our patients, there was a reduction of psychotic symptoms. Our study indicated that the improvement was independent of the decrease in depressive symptoms. Moreover, we observed that depressive symptoms persisted in almost half of patients during the remission phase. However, the inclusion of more patients with schizophrenia and a longer follow-up period might be of informative additional value in determining differences among those with and without depressive symptoms in schizophrenia. Few studies tried to answer the question of "treatment-resistant" depressive symptoms within schizophrenia. Schennach-Wolff et al.²⁴ found that a greater number of patients with multiple, recurrent episodes were treatment-resistant compared to patients experiencing their first episode. This was later confirmed by Aranz et al.²⁹ in a sample of nonaffective acute remitting psychosis as well as by our study.

The rate of patients who developed depressive symptoms in the course of treatment was lower in our study than that in a study by Möller and von Zerssen³⁰ (14% in a sample of 280 hospitalized patients).

Apart from the moderate rate of depressive symptoms in schizophrenia observed in our study, our results also highlight the importance of insight and positive symptoms and depressive symptoms in schizophrenia. The subjects with depressive symptoms in the acute phase had psychometric properties related to the less severe form of schizophrenia. However, in remission, the same group of patients exhibited a similar clinical profile to those with no depressive symptoms, apart from pronounced depressive symptoms on the subscales of PANSS.

We found that the CDDSS scale scores had a negative correlation with the PANSS-P subscale which might be correlated with the intensity of positive symptoms. Some

studies showed a low but significant positive correlation between depressive symptoms and positive symptoms²⁷ while other studies did not find this association^{31, 32}. The explanation of the positive correlation can be associated with less intensity of positive symptoms in the observed sample.

There is still a debate on whether depression within schizophrenia is an autonomous domain, or is a part of the negative symptoms. Some authors found a correlation between negative symptoms and depressive symptoms³³ while other studies did not confirm this relationship^{20, 34}. As with the prevalence of depressive symptoms, the association between depressive and negative symptoms may be caused by tools of assessments as well as the phase of the disease at the time of observation. In our study, the correlation between the CDSS scale and the PANSS-N subscale was not found, which is in line with the findings of other authors who stated that depressive and negative symptoms existed as two separate syndromes within schizophrenia³⁵. Additionally, if we observe the percentage of answers on items of CDSS scale, we will see that in the acute phase, the most common were depression, morning depression, early awakening, feelings of hopelessness and self-depreciation. Moreover, the lowest rates were ideas based on guilt and suicide. The remission phase of our patients included persisting symptoms of depression, feelings of hopelessness and self-depreciation. Therefore, the nature of the symptoms in remission was more subjective in nature, whereas the acute phase included biological symptoms. This finding of the absence of a correlation with the PANSS-N subscale is in accordance with Siris's view that the major difference between depressive and negative symptoms is a "blue mood"⁷.

In the literature, there is little data on the correlation between the CDSS scale and the SUMD. Sim et al.³⁶ in a sample of 66 patients with the first psychotic episode in schizophrenia found that patients with depressive symptoms had greater insight into their mental illness. In our sample of patients with depressive symptoms, there was a negative correlation between the CDSS and the SUMD which implies better insight into mental illness.

This study has several limitations as well as strengths to be considered in the interpretation of the results. The study sample was relatively small to allow for an analysis of more complex variables, especially if there is a division of a sample according to the presence of depressive symptoms. Evaluation of interplay between pharmacotherapy and depressive symptoms is not explored in the study, but should be taken into account in interpretation of the results. In addition, the short follow-up period did not allow a complete analysis of the development of depressive symptoms from the acute phase to remission. However, we overcame the limitations of previous studies and analyzed depressive symptoms in schizophrenia both in the acute and remission phases, in representative sample of clinical patients, excluding those with poor treatment response as well as those with potential cognitive problems. Moreover, and unlike the majority of previous studies in the assessment of depressive symptoms we used CDSS, an instrument specifically developed to evaluate depressive symptoms among patients with schizophrenia.

Conclusion

By searching the literature, we noticed that this has been the first study in Serbia so far, to assess the rate of depressive symptoms among the patients with schizophrenia. Our findings clearly show that depressive symptoms are more pronounced during the acute psychotic phase than in remission in patients with schizophrenia. Although the rate of depressive symptoms in remission is low, these symptoms can persist or occur during hospital treatment in some patients.

Based on these findings, we cannot say with certainty whether each patient suffering from schizophrenia may be located on a point of the continuum of depressive symptoms during the course of schizophrenia, or, whether, on the other side, there is a clear categorical distinction between the depressive and non-depressive groups. However, it is certain that the distinction between these two groups and the recognition of depressive symptoms in patients suffering from schizophrenia have clinical and therapeutic importance. Recognizing depressive symptoms raises the possibility of targeted interventions and consequently better therapeutic outcome.

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