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Long-Term Benzodiazepine Prescription During Maintenance Therapy of Individuals With Psychosis Spectrum Disorders—Associations With Cognition and Global Functioning

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Background: Cognitive difficulties have a significant impact on life functioning and overall well-being in patients with psychosis spectrum disorders (PSDs). There are indications that continuous use of benzodiazepines (BZDs) in various patient groups has a detrimental effect on cognition. Our aim was to explore the association between long-term BZD prescription, global functioning, and cognitive functioning in persons with PSD.

Methods: This exploratory study included 55 PSD patients, recruited from 2 outpatient services in Serbia. Patients were grouped into BZD long-term prescription group and BZD-other group. Brief Psychiatric Rating Scale was used for symptom assessment, functioning was measured by Global Assessment and Functioning Scale, and cognition was assessed by the Global Assessment of Functioning–Cognition in Schizophrenia Scale.

Results: The sample comprised 52.7% patients who were prescribed with BZD for 6 months or more continually (29/55), with a mean daily dose of 3.16 ± 0.66 mg lorazepam equivalents. There were no differences between study groups in any of the sociodemographic characteristics, duration of illness, or antipsychotic daily dosages. The BZD long-term prescription group had lower global ($P < 0.01$) and cognitive functioning ($P < 0.01$), higher Brief Psychiatric Rating Scale scores (1.86 vs 1.58, respectively, $P < 0.01$), and more psychotropic drugs prescribed on a daily basis than the other group (median: 4 vs 2, respectively, $P < 0.01$).

Conclusions: The study explored a topic that continues to be underresearched, especially in the Balkans. Prospective studies and comprehensive cognitive batteries are needed to further elucidate the associations between polypharmacy, long-term BZD use, cognitive functioning, and global functioning during maintenance therapy of individuals with PSD.

Key Words: psychosis, functioning, cognition, BPRS, GAF, benzodiazepine therapy

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For many decades, the primary goal of treating patients with psychosis spectrum disorders (PSDs) has focused on reducing/controlling psychotic symptoms (hallucinations, delusions, and disorganization in particular). In the meantime, it became evident that improvement is not sufficient if cognitive deficits are neglected. Cognitive deficits in persons with PSD are highly contributing to poor functioning as they hinder adequate recovery after the acute phase of the illness.[1] Thus, cognitive functioning is established as one of the most significant functional markers of schizophrenia and PSD. Patients with pronounced cognitive deficits are having difficulties with functioning in various aspects of life, such as social functioning, work performance, etc.[2] The importance of cognitive deficits is further substantiated by recent investigations, which have confirmed that cognitive symptoms had an indisputable impact on all aspects of life functioning, and should be considered a key target for novel therapeutic approaches.[3,4]

Benzodiazepines have, for many years broadly, been used in treatment of schizophrenia as anxiolytics, in attempt to alleviate agitation, extrapyramidal adverse effects, aggressiveness, and psychotic symptoms.[5] Recent large-scale study of hospital discharge benzodiazepine (BZD) prescription in Croatia, North Macedonia, and Serbia showed that patients with PSD had approximately 2 times higher odds of receiving BZDs in comparison with patients with all other major psychiatric categories of *International Classification of Diseases*, *10th Revision*.[6] However, recent international guidelines do not recommend long-term BZD (BZD-LT) prescription in persons with schizophrenia,[7] in particular because of the evidence showing association between BZD use and increased mortality risk in patients with schizophrenia.[8]

Long-term benzodiazepine (BZD) use has been associated with changes in cognitive performance (memory, attention, concentration, visuospatial abilities[9]). The meta-analysis results of Barker et al[9] involving studies of patients who had used BZD to treat anxiety, depression, or insomnia support extreme caution related to the BZD-LT use. Although these findings suggest that BZD-LT use may lead to impairments in cognition, some degree of improvement in cognitive function after withdrawal could be expected, suggesting that previous BZD users are likely to experience the benefit of improved cognitive functioning after the withdrawal.[9]

Throughout the maintenance phase of therapy in persons with PSD, the treatment goals are to avoid relapses and to promote recovery toward integration into society. The rate of BZD prescription and use in this population is varying widely, from 16% to 79.2%, depending on definition of long-term drug use, the treatment setting, prescribing habits across countries,[6] and so on.

To the best of our knowledge, the association between BZD-LT prescription (continual prescription of at least 6 months) with global functioning and cognitive functioning in PSD outpatients from a real-world setting has not been sufficiently evaluated. The goal of the present study was to overcome this gap by

exploring the levels of global and cognitive functioning among patients exposed to BZD-LT and other PSD patients (prescribed either with BZD for some periods continuously, but not for the whole index period, or not prescribed with BZD) during the maintenance therapy in the outpatient setting.

METHOD

The present exploratory research was conducted as a part of the larger study "IMPULSE" exploring the implementation of the psychosocial intervention DIALOG+ for patients with psychotic disorders in low- and middle-income countries in Southeastern Europe (Grant Agreement No. 779334).[10] Study participants were recruited from 2 outpatient clinics—university psychiatric hospital and special psychiatric hospital, thus covering both urban and rural part of the country (for more details, see the study by Marić et al[11]). Patient eligibility criteria included the following: primary diagnosis of psychosis or related disorder (*International Classification of Diseases*, *10th Revision,* diagnoses: F20–29, ie, PSD), older than 18 years, history of at least 1 lifetime psychiatric hospital admission, capacity and will to provide informed consent, and a history of attending the outpatient clinic for at least 6 months with available medication data before the inclusion. Age at first diagnosis was provided from the medical documentation, whereas the duration of illness was calculated on the basis of first reported psychotic symptoms, as per medical documentation.

In addition to patient involvement, for the purposes of present research, we contacted informants (parents, partners, or others who live with a patient and who are willing to participate) who were interviewed to provide their rating of patient's cognition (for more information, see the assessment section). Patients were excluded if the informant was unavailable and if having a diagnosis of an organic brain disorder or severe cognitive deficits (thus being unable to provide informed consent and reliable information to study instruments).

Every patient underwent a structured sociodemographic interview that included the following: age, sex, marital status, employment status, and the highest level of educational achievement. All participants provided written informed consent before the study onset. The study was conducted in accordance with the Declaration of Helsinki, and its design was approved by the medical ethics committee of the Faculty of Medicine University of Belgrade (Number 2650/VI-3) and by the professional boards of both study sites.

The Assessment

The 24-item Brief Psychiatric Rating Scale (BPRS)[12] was used to assess patients' symptom status, whereas each symptom was rated on a 7-point Likert scale (1, not present; 7, extremely severe). Total average scores vary from 1.00 to 7.00 with lower scores indicating less severe psychopathology. We also calculated 4 BPRS subdimensions: disorganization, reality distortion, depression, and negative symptoms.[12]

Global Assessment of Functioning (GAF) is a widely used generic instrument of the *Diagnostic and Statistical Manual of Mental Disorders*, *Fourth Edition Text Revision* (APA, 2000). Global Assessment of Functioning is intended to be a generic rather than a diagnosis-specific scoring system covering the range from mental health to severe psychopathology.[13] It measures the degree of mental illness by rating psychological, social, and occupational functioning.[14] Global Assessment of Functioning recorded values can be used as separate scores for symptoms (GAF-S) and functioning (GAF-F). Both the GAF-S and GAF-F Scales are rated on a 100-point scale with lower scores indicating more severe symptoms/impairment.[15]

The clinical global impression of cognition was scored with GAF–Cognition in Schizophrenia (GAF-CogS) Scale upon conducting Cognitive Assessment Interview (CAI)[16]—an interview-based assessment of cognition that involves interviews with patients and informants. As CAI highly correlates with cognitive scales such as the GAF-CogS, detailed interviewing on subjective cognitive difficulties during CAI was used to facilitate the scoring of GAF-CogS.[17] The GAF-CogS Scale is intended to supplement the CGI-CogS global severity ratings and parallels the *Diagnostic and Statistical Manual of Mental Disorders*, *Fourth Edition*, GAF scale. The anchors for the GAF-CogS instruct the rater to evaluate the extent of functional impairment associated with cognitive impairment rather than more traditionally rated psychiatric symptoms. A high level of functioning with no cognitive impairment is rated "100" as compared with a rating of "1" on GAF-CogS, which indicates the lowest level of functioning that is associated with severe levels of cognitive impairment.[18] Clinical assessment has been conducted by authors of this study (B.S., I.R., S.J., M.Z.) who were all trained for BPRS and CAI.

Medication

Patients in this study were treated by medication according to clinician preference (treatment as usual). Medical chart review was used to list all psychotropic medications prescribed over the 6-month period preceding the assessment, either on a regular basis (continually) or as needed (discontinually). The data about prescribed psychotropic drugs included the generic and trade names of each drug and daily dose. The use of the following psychotropic drugs was recorded in the study: antipsychotics (APs), antidepressants, mood stabilizers, BZDs, drugs used to treat addictive disorders, and nonpsychotropic concomitant medication.

Antipsychotic drugs were classified as either first-generation agent (FGA; chlorpromazine or promazine, fluphenazine, haloperidol, levomepromazine, sulpiride), second-generation agent (SGA; clozapine, risperidone, olanzapine, quetiapine, ziprasidone, paliperidone), or third-generation agent (TGA, aripiprazole). The mean AP dose during the last month was calculated and transformed into olanzapine equivalents.[19,20] In cases where more than 1 AP was used, olanzapine equivalent dosages were summed to obtain a total daily AP dose (AP DD).

Benzodiazepine medication included all available BZDs and presented as lorazepam equivalent doses.[21] Lorazepam 1-mg equivalent doses were calculated as follows: diazepam 5 mg; bromazepam 3 mg; clonazepam 0.5 mg; alprazolam 0.25 mg; midazolam 7.5 mg; and zolpidem 5 mg (midazolam and zolpidem were considered as hypnotics, whereas all other were grouped into anxiolytics). The equivalent doses given previously are representative of information from 2 resources, as per previous articles.[6,22,23] In cases when more than 1 BZD was used, lorazepam equivalent doses were summed to obtain a total daily dose of BZD (BZD DD). According to the Anatomical Therapeutic Chemical/Defined Daily Dose system, the mean daily dose of greater than 2.5 mg of lorazepam equivalents (DDD) was considered high.[24]

Long-term BZD prescription was defined if any of the drugs from this class was prescribed for 6 months or more, on a continual basis. All patients who had this prescription pattern were classified into the category BZD-LT. For all other patients (with "as needed" BZD prescription during the index period, with those who had some periods of continual BZD use but not during the whole index period and for patients with no prescribed BZD during the observational period), we used the category BZD-other.

Statistical Analysis

All statistical analyses were performed by the SPSS Version 20.0 statistical software. Descriptive statistics (sociodemographic and clinical measures) were presented using absolute and relative

numbers, means, standard deviations, medians, and ranges. After initial testing for data normality (Kolmogorov-Smirnov test), the between-group analyses (BZD-LT/other) were accordingly assessed using appropriate parametric or nonparametric tests (χ^2 test, Mann-Whitney *U* test, Student *t* test for independent samples). Person correlation coefficient was used to assess for associations between continuous variables. Effect sizes (Cohen *d*) were provided as appropriate and interpreted as follows: 0.2, small; 0.5, medium; and 0.8, large.

RESULTS

The sample consisted of 52.7% BZD-LT patients (29/55). There were no significant differences between BZD-LT and BZD-other group in either age, sex, education, marital status, or employment status (sociodemographic data are presented in Table 1). No differences were found for age at first diagnosis and duration of illness between the groups.

The means of BZD DD were 3.2 ± 0.7 mg in BZD-LT and 0.2 ± 0.6 mg in BZD-other group. In 25.4% of the sample (14/55), a BZD DD was greater than 2.5 lorazepam equivalents. Psychotropic polypharmacy was common in this sample—median number of prescribed psychotropics was 3 (ranging from 1 to 6). The BZD-LT and BZD-other groups were significantly different in terms of psychotropic polypharmacy: BZD-LT group was prescribed with more psychotropic drugs in comparison with the BZD-other group (3.7 ± 0.9 vs 2.4 ± 1.0, $P \leq 0.00$). The number of prescribed psychotropic medication positively correlated with mean BZD dose ($r = 0.50$, $P < 0.01$). However, no differences were observed in the AP daily dose (olanzapine equivalents: Mann-Whitney $U = 300.00$, $Z = -1.299$, $P = 0.194$) between the groups. Sociodemographic and clinical characteristics of the sample are presented in Table 1.

In comparison with BZD-other group, the BZD-LT group had higher scores on BPRS scale (average BPRS score = 1.6 ± 0.4 vs 1.9 ± 0.1, $P = 0.03$), lower GAF-S (GAF-S = 53.4 ± 10.7 vs 62.4 ± 10.2, $P = 0.00$), lower global functioning (GAF-F: 53.4 ± 10.2 vs 62.3 ± 11.4, $P = 0.00$), and lower scores on clinical global impression of cognition (GAF-CogS: 55.0 ± 10.6 vs 64.8 ± 12.4, respectively, $P = 0.00$). The BZD-LT group had more pronounced symptoms of reality distortion in comparison with the BZD-other group, measured by the BPRS (1.4 ± 0.7 vs 1.0 ± 0.3, respectively, $P = 0.00$), whereas no significant differences were observed in the subdomains: negative symptoms, depression, or disorganization. A moderate positive correlation was found between mean BZD DDs (lorazepam equivalents) and intensity of the reality distortion symptoms ($r = 0.39$, $P = 0.03$).

DISCUSSION

This study included a group of "moderately ill" persons with PSD during the maintenance therapy, and it indicated that more than half of them were prescribed with BZD continuously for more than 6 months. The BZD-LT users reported more severe clinical symptoms, lower global functioning, and poorer cognition than patients with short-term or no BZD prescription. An important finding of the present study is that the mean BZD dose was relatively high in long-term users, with levels of above DDD lorazepam equivalents.[24]

In line with previous literature,[25] our finding suggest that cognitive functioning can be negatively affected by long-term BZD prescription, as shown by the large effect size (Cohen $d = 0.86$). However, as in the present study, the evaluation of cognition was not performance based but a subjective report of patients and their carers, definitive conclusions cannot be made.

TABLE 1. Sociodemographic and Clinical Characteristics of the Sample

	BZD-LT (n = 29)	BZD-Other (n = 26)	*P*	Cohen *d*
Sociodemographic characteristics				
Age, mean ± SD, y	46.0 ± 10.1	41.4 ± 10.2	0.10	—
Sex, n (%)	15 (51.7%)	19 (73.1%)	0.16	—
Education, high school or more, n (%)	26 (89.6%)	23 (88.5%)	0.17	—
Marital status, n (%)	9 (31.0%)	7 (26.9%)	0.77	—
Employment status, n (%)	3 (10.3%)	4 (15.4%)	0.14	—
Clinical characteristics				
Diagnosis (ICD-10)				
F20	13 (41.0%)	8 (31.0%)	0.47	—
F25	6 (25.0%)	5 (19.0%)		
F29	10 (34.0%)	13 (50.0%)		
Age at first diagnosis, mean ± SD, y	32.1 ± 9.7	27.8 ± 7.5	0.07	—
Duration of illness, mean ± SD, y	13.5 ± 9.1	14.0 ± 10.1	0.86	—
Medication				
Total no. prescribed psychotropic drugs, mean ± SD / median	3.7 ± 0.9 / 4	2.4 ± 1.0 / 2	**0.00***	1.41
AP daily dose olanzapine equivalents, mean ± SD, mg	17.4 ± 9.0	14.3 ± 8.6	0.19	—
Benzodiazepine daily dose, lorazepam equivalents, mean ± SD, mg	3.2 ± 0.7	0.2 ± 0.6	**0.00***	4.60
Symptoms and functioning				
BPRS average score, mean ± SD	1.9 ± 0.1	1.6 ± 0.4	**0.03**†	0.59
GAF-CogS, mean ± SD	55.0 ± 10.6	64.8 ± 12.4	**0.00***	0.86
GAF-F, mean ± SD	53.4 ± 10.2	62.3 ± 11.4	**0.00***	0.82
GAF-S, mean ± SD	53.4 ± 10.7	62.4 ± 10.2	**0.00***	0.86

†$P < 0.05$.

*$P < 0.01$.

Indeed, it could be possible that because the BZD long-term group presents with more severe psychiatric symptoms, their general level of cognitive abilities (memory, attention, executive functions) is somewhat lower than that in the other group regardless of medication use.

Interestingly, when Baandrup et al[26] examined whether objective cognitive performance would improve after BZD discontinuation by studying 80 patients with PSD, they demonstrated improvement across all cognitive domains after BZD withdrawal in chronic users. Further support for cognitive improvement after BZD discontinuation in patients with schizophrenia in Japan comes from the study of Kitajima et al.[27] Tapering and discontinuation of BZD-LT use in 30 patients with schizophrenia led to improvements in both cognitive performance and subjective quality of life.

On the basis of findings from 2 large-scale Asian and European studies, the suggestion was that ideal rates of various maintenance treatments of schizophrenia could be as follows: AP polypharmacy, 30%; combined mood stabilizer, 15%; combined antidepressant, 10%; combined anxiolytics, 30%; and combined hypnotic, 10%.[28] Our finding, in line with previous research conducted in Greece and Taiwan showing between 39.0% and 62.9% of BZD-LT users, is confirming that in the real-world setting, the rates of BZD-LT prescription are far from ideal (as suggested by Lin[28]).

Although there is evidence of higher prevalence of BZD prescription in women (2-folder higher risk) compared with men,[29] our results did not indicate this trend. This could be possibly due to limited sample size or cultural factors. Nevertheless, in a study of a large sample of patients at discharge from several psychiatric hospitals in the Balkans region, sex differences related to BZD prescription were not observed.[6] Similarly, sex difference in BZD long-term use was not found in Greek outpatients with psychosis.[30] Thus, it might be that cultural factors could play an important role in relation to sex differences in the use of BZD in the literature.

The present study provides important insight regarding the prescription patterns of BZD in outpatients with PSD amplified with clinically relevant information. Long-term BZD prescription could be considered as a therapeutic strategy targeted toward patients with more severe forms of PSD in outpatient practice; however, that is not supported by guidelines. Our results could also suggest a link between BZD-LT prescription and disabling adverse effects, particularly related to cognitive functioning. Because we noticed that patients who are BZD-LT users have higher levels of reality distortion symptoms, it could be that instead of increasing daily dose of APs, clinicians were more prone to add and continue with BZD to prevent complications and achieve control of the agitation. It should be taken into consideration that in our sample, age at first diagnosis was borderline higher in the BZD-LT group (approximately 4 years higher in comparison with BZD-other group). It could be that the duration of untreated psychosis (before receiving first diagnosis) was higher in these patients, which indicates worse course of the disorder, and could be related to greater BPRS scores.[31] However, with the current study design, it was not possible to address this implication further.

A potential implication of this study is a call for action to reduce BZD prescription to nonacute moderately ill outpatients with PSD (who also exhibit lower cognitive functioning) and to reconsider a daily dose of AP, which, at present, do not differ between the groups. Benzodiazepine reduction is not always an easy task as the patients may resist to dose reduction or discontinuation, but the question arises if patients have ever been educated or advised about the optimal BZD use and adverse effects. The other question that follows from this line of reasoning is do the clinicians generally follow recommendations on informed decision making? Reasons for long-term BZD prescription could be multifactorial —one of them is lack of appropriate information and effective education at multiple levels and lack of relevant national guidelines for rational prescription of BZDs. In Serbia, national guidelines for BZD prescriptions have not been published yet. However, in the countries where such guidelines based on the best available evidence at the time of its development exist, for example in Singapore,[32] use of BZD in persons with psychotic disorders will be recommended only as a short-term trial. Psychotic patients who will be candidates for short addition of BZD are persons with persistent and clinically significant symptoms of anxiety, dangerous or assaultive behavior (evidence grade/level A/1[32(p18)]).

Besides the guidelines, another important aspect to be considered is the duration of routine psychiatric appointments for patients—approximately 20 minutes in PSD,[33] which is possibly an obstacle for implementation of an intervention that does require additional time in the outpatient settings. In addition, it is possible that clinicians are reluctant to change the treatment regimen in nonacute patients with psychotic disorders to avoid the risk of relapse, without sufficient recognition of all aspects related to the patient satisfaction and well-being.[34] There is no evidence that reduction/discontinuation of BZD in maintenance therapy may lead to relapse; however, clinicians may nevertheless be reluctant to reduce the medication and contribute to eventual relapse.

The present study has both strengths and limitations. The study explored a topic that continues to be underresearched, especially in the Balkans. Furthermore, studies on medication use of individuals with PSD are largely focused on acute/inpatient treatment. This study included well-defined sample of outpatients with psychotic disorders living in the community. Patients were recruited from 2 centers, thus increasing the chance that observed BZD prescription patterns will not be influence by the culture of prescribing present in a single center. We used a medical chart review to collect data on prescribed medications, which is well-established methodology in large-scale studies. The main limitation of the study is relatively small sample size; however, it could be considered as adequate for exploratory studies. In the present study, we did not gather data on the mean years of BZD use in BZD-LT users. Thus, we were not able to observe any potential associations between cumulative lifetime exposure to BZDs and levels of psychopathology/functional status, an issue that should be addressed in future studies. Finally, using of GAF-CogS for scoring the cognitive functioning may not provide comprehensive assessment of cognitive functioning; however, it could be used successfully in everyday clinical practice. If clinicians are familiar with instruments such as CAI,[16] they could try to use GAF-CogS routinely, as they have been using the GAF scale.

Although BZDs have been used extensively as an adjunct therapy in PSD, effects on cognition and overall functioning are not sufficiently explored in this patient population. Future prospective studies and comprehensive performance- and interview-based cognitive assessments are needed to further elucidate the associations between polypharmacy, BZD-LT use, cognitive functioning, and global functioning during maintenance therapy of PSDs and to explore the role of psychotropic polypharmacy in the context of recovery.

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