Factors associated with adherence to guidelines of good clinical practice during hospital treatment of patients with the first episode of schizophrenia spectrum disorders

Faktori povezani sa poštovanjem preporuka dobre kliničke prakse tokom bolničkog lečenja bolesnika sa prvom epizodom oboljenja iz shizofrenog spektra

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Abstract

Background/Aim. Adherence to the guidelines of Good Clinical Practice (GCP) during the treatment of specific disorders is considered a guarantee of the implementation of a uniform, evidence-based clinical practice in psychiatry. The aim of this study was to analyze the concordance of prescribing patterns of antipsychotic drugs with the recommendations of good clinical practice in Serbia and an insight into the effects that introduction of the National Guideline for the Diagnosis and Treatment of Schizophrenia had on the prescribing practice in this area. **Methods.** Non-interventional, observational study was conducted at the Clinic for Mental Disorders "Dr Laza Lazarević" in Belgrade. It included a consecutive sample of 675 previously untreated patients, hospitalized from January 1st, 2012 to December 31st, 2015, dismissed with a discharge diagnosis of any of schizophrenia spectrum disorders. The data about demographic and clinical characteristics of patients, characteristics of prescribers and prescribed antipsychotics were obtained retrospectively, from the patients' medical records. For the analysis of primary data, the descriptive statistical methods and methods for testing statistical hypotheses were used. A method of logistic regression was used to identify the factors associated with adherence to the GCP recommendations. **Results.** Totaly, 446 (66.1%) of subjects were treated with antipsychotic monotherapy. After the introduction of National Guideline for the Diagnosis and Treatment of Schizophrenia prescribing of second generation antipsychotic monotherapy (78.41% vs. 63.5%, respectively; $p < 0.001$) increased significantly compared to the previous period. The factors independently associated with adherence to the recommendations of the GCP were the year of hospitalization, the age of the prescriber, and the age and education of the patient. **Conclusion.** After the introduction of the National Guide to Good Clinical Practice for the Diagnosis and Treatment of Schizophrenia there have been significant, but insufficient changes in the prescribing patterns of antipsychotics during the treatment of the first psychotic episode in Serbia.

Key words:
practice guidelines as topic; guideline; serbia; schizophrenia; drug therapy; antipsychotic agents.

Apstrakt

Uvod/Cilj. Poštovanje smernica datih u vodičima dobre kliničke prakse tokom lečenja specifičnih poremećaja smatra se garancijom sprovođenja uniformne, na dokazima zasnovane kliničke prakse u psihijatriji. Cilj ovog rada bio je da se analizira usklađenost obrazaca propisivanja antipsihotičkih lekova sa preporukama dobre kliničke prakse u Srbiji i da se ostvari uvid u efekte koje je na propisivačku praksu u ovoj oblasti imalo donošenje Nacionalnog vodiča dobre kliničke prakse za dijagnostikovanje i lečenje shizofrenije. **Metode.** Neinterventna, opservaciona studija sprovedena je na Klinici za psihijatrijske bolesti "Dr Laza Lazarević" u Beogradu. Istraživanje je obuhvatilo uzastopni uzorak od 675 prethodno netretiranih bolesnika, lečenih hospitalno u periodu od 1. januara 2012. godine do 31. decembra 2015. godine, otpuštenih sa dijagnozom nekog od poremećaja iz shizofrenog spektra. Demografski podaci i podaci o kliničkim karakteri-

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stikama bolesnika, karakteristikama propisivača i propisanim antipsihoticima sakupljeni su retrospektivno, uvidom u medicinsku dokumentaciju bolesnika. Za analizu primarnih podataka korišćene su deskriptivne statističke metode i metode za testiranje statističkih hipoteza. Metoda logističke regresije korišćena je za identifikaciju faktora povezanih sa poštovanjem preporuka dobre kliničke prakse. **Rezultati.** Antipsihotičnom monoterapijom tretirano je 446 (66,1%) ispitanika. Nakon donošenja Nacionalnog vodiča dobre kliničke prakse za dijagnostikovanje i lečenje shizofrenije, propisivanje antipsihotične monoterapije antipsihoticima druge generacije bilo je značajno češće u odnosu na prethodni period (78,41% prema 63,5%; *p* < 0.001). Faktori nezavisno povezani sa poštovanjem preporuka dobre kliničke prakse su bili: starost ordinirajućeg lekara, starost i obrazovanje bolesnika i godina hospitalizacije. **Zaključak.** Nakon donošenja Nacionalnog vodiča dobre kliničke prakse za dijagnostikovanje i lečenje shizofrenije došlo je do značajnih, ali nedovoljnih promena u obrascima propisivanja antipsihotičke terapije tokom tretmana prve psihotične epizode u Srbiji.

Ključne reči:
lekarska praksa, oblici; vodiči; srbija; shizofrenija; lečenje lekovima; antipsihotici.

Introduction

Schizophrenia is a severe, chronic mental disorder that is among the twenty leading global causes of disability in the world [1]. The course and outcome of the earliest stages of schizophrenia have a pathoplastic effects on its further course [2]. It has been proven that the time period between the onset of the first psychotic symptoms and the initiation of treatment (the duration of untreated psychosis – DUP) correlates with the prolongation of the time needed to achieve remission and is associated with a poor response to treatment [3–5]. The first psychotic episode (FEP) is a critical developmental transition that may affect a further course of schizophrenia, possibly by induction of neurotoxic changes in neural networks, thus leading to disease chronicity [6].

With each subsequent relapse, further deterioration occurs in the psychopathological, neurocognitive and functional domain and the time required for achieving remission is prolonged, and the possibility for good treatment response decreases [7–9]. It is considered that a critical period of 2 to 5 years after the onset of psychosis determines the functional outcome of the disease and during this period therapeutic interventions have a maximum effect [10]. Therefore, early detection, adequate treatment and the achievement of a full symptomatic and functional recovery from FEP, maintenance of adherence to the treatment and prevention of relapse in early stages of the disease are the main goals of the treatment of schizophrenia [11–14].

Over the past two decades, the adherence to the guidelines of Good Clinical Practice (GCP) during the treatment of specific disorders, is considered a guarantee of the implementation of a uniform, evidence-based clinical practice in psychiatry [15]. For more than 15 years, GCP guidelines have been applied worldwide for the diagnosis and treatment of schizophrenia [16–18]. In Serbia, at the end of 2013, the Republic Commission for the Development and Implementation of Guidelines in Clinical Practice developed the National Guidelines of GCP for the Diagnosis and Treatment of Schizophrenia [19]. As with most other guidelines, the choice of antipsychotics (AP) is primarily based on the adverse reaction profile, since their efficacy, with the exception of clozapine, is considered practically equal. An assessment of the previous response to therapy, the presence of comorbid psychiatric and somatic diseases, the use of concomitant medication, safety in overdose and, of course, drug availability is recommended when choosing antipsychotic for the initial treatment of acute episode. The recommendation is to use one of the second generation antipsychotics (SGAs), except for clozapine, as the first-line therapy, whereas the first generation antipsychotics (FGAs) may be used as the first-line therapy only in the patients who had multiple episodes with previously favorable response and lack of significant side effects.

In the case of the first episode, the use of SGAs as the first treatment line is mandatory and it is necessary to follow the recommendation on the use of lower doses (dose from the lower part of the therapeutic range), since previously untreated patients are more sensitive to the development of adverse reaction and show a good response to lower doses of antipsychotics. Unlike most international guidelines, the Serbian treatment guideline for completely, or partially nonadherent patients recommends the use of long-acting APs in the case of FPE as well.

It is reasonable to assume that in recent years, following the introduction of the National Guideline for the Diagnosis and Treatment of Schizophrenia and the inclusion of a significant number of SGA into the List of Medicines covered by a mandatory health insurance, there has been a significant change in the prescribing patterns in everyday clinical practice in Serbia.

The aim of this study was to analyze the concordance of prescribing patterns of antipsychotic drugs with the recommendations of good clinical practice in Serbia. This analysis covered the period from 2012 to 2015 which enables a comparison of drug prescribing patterns before and after the introduction of the National Guideline for the Diagnosis and Treatment of Schizophrenia, and an insight into the effects that its introduction had on the prescribing practice in this area.

Methods

This observational cross-sectional study was conducted at the Clinic for Psychiatric Disorders "Dr Laza Lazarević" in Belgrade and it included 675 subjects. A consecutive sample included all previously untreated patients, hospitalized in the period from January 1st, 2012 to December 31st, 2015 that had been dismissed according to the International Statistical Classification of Diseases and Related Health Problems (ICD 10) discharge diagnosis with: Schizophrenia (F20.0-

F20.9), Acute polymorphic psychotic disorder with symptoms of schizophrenia (F23.1), Acute psychotic disorder similar to schizophrenia (F23.2), Schizoaffective disorder (F23.2) and Unspecified nonorganic psychosis (F29) [20].

The subjects were divided into two groups: a group discharged during 2012 and 2013 and a group discharged in 2014 and 2015. The timeline was selected because at the end of 2013, the National Guideline for the Diagnosis and Treatment of Schizophrenia was published in Serbia.

Beside above mentioned diagnostic categories, the inclusion criteria were: over 18 years of age and the first psychotic episode, defined as the first contact with antipsychotic treatment [21]. The exclusion criteria were: any previous antipsychotic treatment; diagnosis of bipolar disorder, psychotic depression, psychotic disorder caused by the use of psychoactive substances (PAS), psychotic disorder due to the general medical condition; the presence of primary and secondary cognitive deficit.

The research was approved by the Ethics Committee of the Clinic for Psychiatric Disorders "Dr Laza Lazarević". The data were obtained from the patients' medical records, including the following: demographic data, type and duration of hospitalization in days, duration of untreated psychosis in months, somatic comorbidity, suicidality, use of PAS, antipsychotics prescribed at discharge, and characteristics of prescribers (age and years of experience as a specialist). DUP is defined as the time interval between the onset of the first clear psychotic symptoms and the first prescription of antipsychotics and estimated based on the data from the history of the disease, obtained from the patients and their relatives [4,5,22]. Suicidality is defined as presence of suicidal ideas, intentions or attempts, noted during the psychiatric assessment at addmision. The presence of PAS was assessed on the basis of data obtained from the patients, their relatives and the qualitative urine tests conducted immediately after admission to hospital and it was related to the actual exposure. The analysis of antipsychotic therapy, prescribed to the discharged patients, included the class and type of prescribed antipsychotics. Antipsychotic polypharmacy is defined as the simultaneous prescription of at least two different antipsychotics. The adherence to the recommendations of GCP was assessed for each patient individually, following an analysis of the prescribed regimen of antipsychotic therapy and its compliance with the recommendations of GCP for the treatment of the first psychotic episode. For the analysis of primary data, the descriptive statistical methods and methods for testing statistical hypotheses were used. Of the descriptive statistical methods, the measures of central tendency (arithmetic mean, median), measurements of variability (standard deviation) and relative numbers were used. For testing the relationship between the categorical variables, the χ^2 test was used. The Fisher's test was used instead of the χ^2 test when any expected frequency was less than 1, or 20% of expected frequencies were less than, or equal to 5. For the comparison of continuous variables, the Student's t-test and Mann-Whitney test were used. The statistical hypotheses on differences were tested at a statistical significance level of 0.05. The method of logistic regression was used to identify the factors associated with the adherence to the GCP recommendations. We analysed the association of the sociodemographic and clinical variables related to the patients and prescribers with the outcome variable (GCP recommendation) Initially, the variables potentially associated with the outcome were analyzed by the univariate logistic regression model. The variables significant at $p < 0.05$ in the univariate logistic regression were included in the multiple logistic regression model in order to identify the factors independently associated with the adherence to GCP recommendations. We used the multicollinearity analysis to check collinearity among the explanatory variables. Multicollinearity was assessed using a variance inflation factor (VIF). The VIF higher than 5 indicated the highly correlated variables and presence of multicollinearity. All statistical analyses were carried out using the statistical program SPSS 24.0 (SPSS, Inc., Chicago, IL, USA).

Results

This study included a consecutive sample of 675 patients treated for the first time in the period from 2012 to 2015 with the diagnosis of schizophrenia and other schizophrenia–spectrum disorders. In the period 2012–2013, 330 patients (48.9% of the total sample) were discharged from hospital, whereas in 2014 and 2015 a total of 345 patients (51.1%) were discharged after treatment of the first episode of schizophrenia spectrum disorders.

The sociodemographic characteristics of patients are shown in Table 1. A majority of subjects (60.7%) were males. The average age was 28.5 ± 8.7 years. The youngest subject was 18, and the oldest one 57. Most of them had secondary education, were unemployed and single. More than two-thirds of them lived with their parents. There were no statistically significant differences between the groups, except that those who were discharged during 2014 and 2015 were more often unemployed and lived with their parents than those who were discharged during 2012 and 2013.

Of all patients who had been discharged from psychiatric hospital care 34.7% were diagnosed with schizophrenia and 34.1% with unspecified psychoses, while the schizoaffective disorder was diagnosed in only 3.6% of patients. A statistically significant difference was found between the groups. The patients dismissed from hospital in the period 2014–2015 were more often discharged with the diagnosis of acute psychotic disorder, while the frequency of diagnosis of schizophrenia declined ($\chi^2 = 37.013$; $p < 0.001$).

Other clinical characteristics of patients are shown in Table 2. No statistically significant differences were found between the groups in any clinical feature.

FGA was prescribed to a total of 410 (60.7%) subjects, while SGA was prescribed to 504 (74.7%). A statistically significant difference was found between the groups. During 2014 and 2015, the prescription of FGAs decreased significantly, while the frequency of prescribing SGA increased significantly (Table 3).

Table 1

The sociodemographic characteristics of patients

Parametres	Patients (n = 675)	2012/2013 (n = 330)	2014/2015 (n = 345)	$\chi^2/t/Z$	p
Gender, n (%)					
male	410 (60.7)	202 (61.2)	208 (60.3)	0.806	0.814
female	265 (39.3)	128 (38.8)	137 (39.7)		
Age (years), mean ± SD	28.5 ± 8.7 (18–57)	28.6 ± 8.5 (18–54)	28.5 ± 8.8 (18–57)		
Education, n (%)					
primary	135 (20.0)	68 (20.6)	67 (19.4)		
secondary	430 (63.7)	207 (62.7)	223 (64.6)	0.270	0.874
university	110 (16.3)	55 (16.7)	55 (15.9)		
Employment, n (%)					
employed	80 (11.9)	34 (10.3)	46 (13.3)		
unemployed	491 (72.7)	256 (77.6)	235 (68.1)		
retired	1 (0.1)	0 (0.0)	1 (0.3)	8.505	0.037
students	103 (15.3)	40 (12.1)	63 (18.3)		
Marital status, n (%)					
single	557 (82.5)	276 (83.6)	281 (81.4)		
married	86 (12.7)	42 (12.7)	44 (12.8)		
divorced	27 (4.0)	10 (3.0)	17 (4.9)	1.774	0.621
widowed	5 (0.7)	2 (0.6)	3 (0.9)		
Household, n (%)					
alone	70 (10.4)	43 (13.0)	27 (7.8)		
with parents	495 (73.3)	225 (68.2)	270 (78.3)		
with partner	83 (12.3)	47 (14.2)	36 (10.4)	9.210	0.027
other	27 (4.0)	15 (4.5)	12 (3.5)		

χ^2 – chi-square test; t – *t*-test; Z – Mann-Whitney test; SD – standard deviation.

Table 2

Clinical characteristics of patients

Parameters	Total number of patients (n = 675)	2012/2013 addmission (n = 330)	2014/2015 addmission (n = 345)	$\chi^2/t/Z$	p
Type of hospital admmision, n (%)					
involuntary	160 (23.7)	76 (23.0)	84 (24.3)	0.162	0.718
voluntary	515 (73.6)	254 (77.0)	261 (75.7)		
Police assistance, n (%)					
yes	362 (53.6)	165 (50.0)	197 (57.1)	0.064	0.076
no	313 (46.4)	165 (50.0)	148 (42.9)		
Duration of hospitalization (days)					
mean ± SD	36.5 ± 18.6	37.4 ± 19.8	35.7 ± 17.5	-1.348	0.178
range	(1–116)	(1–109)	(1–116)		
Duration of untreated psychosis (DUP), months					
mean ± SD	31.4 ± 49.8	27.7 ± 42.0	34.8 ± 56.1	-0.569	0.569
range	(1–348)	(1–348)	(1–333)		
Suicidality, n (%)					
no	539 (79.7)	266 (80.6)	273 (79.1)		
ideas and intentions	79 (11.7)	33 (10.0)	46 (13.3)	2.337	0.311
suicide attempt	57 (8.4)	31 (9.4)	26 (7.5)		
Substance use, n (%)					
yes	192 (28.4)	86 (26,1)	106 (30.7)	1.803	0.201
no	483 (71.6)	244 (73.9)	239 (69.3)		

χ^2 – chi-square test; *t* – Student *t*-test; Z – Mann-Whitney test; SD – standard deviation.

Table 3

Frequency of prescribing FGAs and SGAs

Antipsychotics	Total number of patients (n = 675)	2012/2013 admissions (n = 330)	2014/2015 admissions (n = 345)	$\chi^2/t/Z$	p
FGAs, n (%)	410 (60.7)	229 (69.3)	181 (52.5)	20.274	< 0.001
SGAs, n (%)	504 (74.6)	218 (66.1)	286 (82.9)	25.281	< 0.001

FGA – first generation antipsychotics; SGA – second generation antipsycotichs.

Out of a total of 675 subjects, 446 (66.1%) of them were treated with antipsychotic monotherapy (AMT). Out of 229 (33.9%) of subjects treated with antipsychotic polypharmacy, 218 (32.3% of the total sample) were discharged with two antipsychotics in regular therapy, while 11 of them (1.6% of the total sample) were discharged with more than two antipsychotics prescribed. There were no statistically significant differences in the frequency of prescribing antipsychotic monotherapy and antipsychotic polypharmacy among the patient groups treated in 2012/2013 and 2014/2015. Out of total of 446 subjects treated with monotherapy, FGA was prescribed to 129 (28.9%), and SGA to 317 (71.1%). A statistically significant difference was found between the groups in the frequency of prescribing different classes of antipsychotic as a monotherapy. During 2014 and 2015, the prescription of SGA as antipsychotic monotherapy increased significantly, while the frequency of prescribing FGA decreased significantly (Table 4).

There was the adherence to good clinical practice recommendations for the treatment of schizophrenia in a total of 227 (33.6%) of patients, with 94 (28.5%) patients discharged during 2012 and 2013, and 133 (38.6%) discharged during 2014 and 2015. The difference in the frequency of compliance with the recommendation of good clinical practice between the groups was statistically significant ($\chi^2 = 7.657$; $p = 0.007$).

The variables statistically significant associated with the adherence to the recommendations of good clinical practice in the univariate logistic regression analysis were included in the multivariate model (Table 5). The variable "Experience as a specialist" was highly correlated with the variable "Age of doctors" (VIF = 5.112), and was removed from the multivariate model.

The factors independently associated with the adherence to the good clinical practice recommendations were the age of the psychiatrist, age and education of patient, and year of hospitalization (Table 5). With every year more of patients' age, the adherence to the good clinical practice recommendations decreased by 4%. The psychiatrists younger than 46 years of age more often complied with the recommendations of good clinical practice than those over 46 years of age. When treating the patients with secondary education and university degree, the psychiatrist adhered to the recommendations of the GCP 1.9 times more often than when treating those with the primary school. Also, the adherence to the recommendations of good clinical practice was 1.5 times more often in the patients treated in 2014 and 2015 than in those treated in 2012 and 2013.

Table 4

Frequency of prescribing the antipsychotic monotherapy (FGA and SGA) and antipsychotic polypharmacy

Parametres	Total number of patients (n = 675)	2012/2013 admissions (n = 330)	2014/2015 admissions (n = 345)	χ^2	p
AMT, n (%)	446 (66.1)	219 (66.4)	227 (65.8)	0.195	0.907
FGAs, n (%)	129 (28.9)	80 (36.53)	49 (21.59)	12.108	
SGAs, n (%)	317 (71.1)	139 (63.47)	178 (78.41)		
APP, n (%)	229 (33.9)	111 (33.6)	118 (34.2)		
2AP, n (%)	218 (32.3)	105 (31.8)	113 (32.8)		
> 2AP, n (%)	11 (1.6)	6 (1.8)	5 (1.4)		

AMT – antipsychotic monotherapy; APP – antipsychotic polypharmacy; AP – antipsychotic; FGAs – first generation antipsychotics; SGAs – second generation antipsychotics.

Table 5

Factors associated with adherence to the recommendations of Good Clinical Practice according to the univariate and multiple logistic regression analysis

Variables	Univariate logistic regression		Multiple logistic regression	
	OR (95% CI)	p	OR (95% CI)	p
Years of hospitalization (2014/15 vs. 2012/13)	1.58 (1.14–2.18)	0.006	1.53 (1.09–2.15)	0.015
Age of patients	0.97 (0.95–0.99)	0.001	0.96 (0.94–0.99)	0.005
Education of patients university and secondary vs. primarly	1.82 (1.18–2.81)	0.007	1.92 (1.23–3.02)	0.004
Duration of untreated psychosis up to 12 vs. over 12 mths	1.58 (1.14–2.19)	< 0.001		
Age of doctors up to 46 vs. older than 46 years	2.06 (1.48–2.88)	< 0.001	2.06 (1.45–2.93)	< 0.001
Experience as a specialist* up to 13 vs. more than 13 years	1.94 (1.40–2.69)	< 0.001		
Diagnosis	1.19 (1.04–1.36)	0.011		

*This variable highly correlated with the variable Age of doctors and was not included in the multivariate model;
OR – odds ratio; CI – confidence interval.

Discussion

In the last twenty years, the FPE treatment is in the focus in psychiatry research because of its influence on the course and outcomes of the disorder. The average age of the patients in this study was 28.5, most of them were males, with secondary education, unemployed, not married, and more than two-thirds lived with parents. Apart from the age, employment and living within the primary family, other findings were consistent with other studies [7, 14, 23]. A somewhat higher average age when diagnosing the first episode of schizophrenic disorder than most other studies, where patients were diagnosed for the first time in the mid 20s, can be explained by longer duration of DUP in the patients in this study [24, 25]. Also, this can be partly attributed to the fact that in the mentioned studies, the upper age limit of 30–40 years was set as the inclusion criterion. In other studies, with no upper age limit, and in the large national cohort studies with a similar operational definition of FPE, the average age is similar, or even significantly higher [5, 7, 23]. It is known that in the patients with schizophrenic disorders, the neurodevelopmental and neurocognitive changes are registered at the beginning of the disease and that a clear psychotic symptomatology usually preceded by a prolonged period with reduced functionality, which has a negative impact on the educational, social and professional achievements of the afflicted [26]. The educational structure and the great number of the unemployed and unmarried subjects are also a reflection of the situation in the society: according to the latest data from the Republic Institute for Statistics from 2016, less than one third of young people under 29 are employed, about 15% had elementary education, 60% secondary and about 25% (with a significant predominance of women) had a university degree, while only about 10% of them were married [27]. The great number of subjects living within the primary family can be partly explained by the socioeconomic factors, low employment rate and specific cultural patterns that significantly delay the separation of young people from parents in Serbia. More than one half of the subjects were taken to the psychiatric examination involuntarily by the police, while almost one quarter (23.7%) were hospitalized against their will. These findings can be explained by the specificity of the population of patients who were hospitalized at the institution in which the survey was conducted. Namely, the Clinic for Psychiatric Disorders „Dr Laza Lazarević" is the only psychiatric institution in Belgrade (a city with more than 1.6 million inhabitants) where psychiatric emergencies are treated 24 hours a day, and the place where the involuntary examination and hospitalization are carried out. Therefore, it can be assumed that the proportion of agitated, auto and heteroaggressive, suicidal, partially and/or completed non-adherent patients and the patients with severe forms of illness in our sample was high. The frequency of involuntary hospitalization in the FPE varies widely from country to country, depending on the local specificities and legislative. Thus, the frequency of involuntary hospitalization in our sample was significantly higher than the average in Denmark and the United States, but significantly lower than in Canada [28–30]. The comparison data from Serbia were not available. The average duration of untreated psychosis of subjects in this study is 36.5 months and it was far above the average of about two years [31]. This finding is concerning, although it cannot be generalized due to the mentioned specificity of the sample. In the study that involved 263 patients hospitalized at the University Psychiatric Clinic in Belgrade for the first and second time, where the patients were treated exclusively voluntarily, the average duration of the disease was estimated at two years, regardless of the point at which the treatment started, which confirms our thesis [32].

Long duration of untreated psychosis has a negative impact on the treatment response, the course and outcomes of the disease, which is attributed to the maintenance of excitotoxicity in the untreated [33]. Poor outcomes include social consequences such as unemployment, homelessness, social isolation; also, the patients with a long DUP are at the increased risk of serious self-injury, suicide and heteroagression [34, 35]. The average of DUP varies across different countries, depending on the degree of development. In the developed countries, it is significantly lower in comparison to the underdeveloped and developing countries. That can be explained by a greater awareness of the disease, a more developed and accessible health service and the existence of intensive prevention and intervention programs in early psychosis [24, 36–39]. In the acute phase of the disease, the aims of the treatment are to establish control over disorganized or socially harmful behavior that endangers the safety of the patient and the environment, the mitigation of non-specific symptomatology (anxiety, agitation, insomnia), and the alleviation of positive psychotic symptoms. Ideally, all are achieved by the use of antipsychotic monotherapy which is a golden standard for the treatment of schizophrenia. The combination of antipsychotics is considered rational only in the absence of treatment response to monotherapy with FGAs, SGAs and clozapine. Since all antipsychotics (with the exception of clozapine) are considered to be practically equally effective, the choice of AP for initial treatment is primarily dependent on safety, i.e., profile of undesirable effects of the drug [16–19]. In spite of some dissonant tones, a consensus that there is no apparent difference between FGAs and SGAs in terms of efficacy, or in reducing the severity of positive psychotic symptoms is generally accepted. However, the patients treated with SGAs have lower rates of treatment discontinuation compared to FGAs, which is associated with a more frequent occurrence of extrapyramidal symptomatology and aggravation, or the induction of secondary negative and cognitive symptoms by FGAs [40]. The patients with the FPE also show certain specificities compared to those with chronic illness. Previously untreated patients often have a good response to therapy, the dose needed to achieve symptomatic remission is lower and the sensitivity to neurological and metabolic side effects of AP is greater [40, 41]. Therefore, most guidelines, including Serbian, for the people with the FPE recommend the mandatory administration of SGAs in lower and moderate doses in order to ensure the best adherence and prevention of relapses after stabilization of symptoms in the acute phase of treatment [16, 18, 19]. Four re-

cent cohort studies from the United States, Finland, Spain and the United Kingdom examined the patterns of prescribing AP in the FPE, so that they can serve for international comparisons [25, 42–44]. In our study, a total of 66.1% of subjects were treated with antipsychotic monotherapy with a total of ten antipsychotics (five from the class FGAs and SGAs). In 71.1% of patients treated with AMT, SGA is prescribed. Although there was no difference in the frequency of prescribing AMT before and after the introduction of a national guideline, a positive trend in the choice of AMT medication was observed. After 2013, the frequency of prescribing SGA as the AMT increased significantly compared to the previous period (78.41% vs. 63.5%). In the US and Finnish studies, the frequency of AMT and FGAs in the AMT was similar, about 90%, or about 9%, respectively [25, 42]. In the Spanish study in 2016, the frequency of prescribing AMT was slightly higher than our finding (69.2%), but the frequency of prescribing FGA as a monotherapy was only 3.7% [43]. In the British study from 2017, the frequency of prescribing AMT was 77.3%, with FGA accounting for 3.9% of prescriptions [44]. These differences in the findings could mean a better adherence to the recommendations of GCP in developed countries, which can be explained by the non-binding nature of our guide and the lack of regulatory bodies that would monitor the prescribing practice, which is mandatory in the Western countries [45].

On the other hand, the difference in the frequency of prescribing AMT could also be explained by the fact that the subjects in these studies (with the exception of Finland) were recruited from the community sample and they all signed an informed consent to the treatment and participation in the research. We are very likely to argue that they were more cooperative and in the longer remission that preceded the study period compared to our patients. Physicians have a professional obligation to regularly monitor new findings and treat the patients in accordance with the current professional rules and good clinical practice. Systematization of the latest scientific knowledge and gradations of their relevance to everyday medical practice through the development and implementation of official guidelines, GCP makes it easier for them to complete this task. In this study, it was estimated that in the prescribing of antipsychotics, there was an adherence to the recommendations of the GCP in 33.6% of subjects, with a significant increase in adherence to recommendations of GCP after 2013 (28.5% vs. 38.6%).

The factors independently associated with a compliance with the recommendations of GCP in this study were the year of hospitalization, the age of the prescriber as well as the age and education of the patient. In patients hospitalized after 2013, the GCP recommendations were adhered to 1.5 times more often than in patients treated in 2012 and 2013. This finding can be explained by the positive impact of the implementation of the National Guideline in the routine clinical practice of psychiatrists. With every year more of patient's age, the adherence to good clinical practice recommendations decreased by 4%. This finding can be explained in two ways. It is known that young, previously untreated patients have a strong initial response to therapy, so it is easier

for doctors to comply with the basic principles of GCP for the treatment of FPE (SGAs antipsychotic monotherapy). On the other hand, it is possible that doctors are more attentive when treating young people, trying more to maintain adherence to the recommendations of GCP when choosing a medicine, to take more care of its safety and the long-term impact on physical health, cognition and overall functioning of patients who still have to accomplish themselves in their life roles. Perhaps this is also the case with the more educated patients, when the adherence to the recommendations was 1.9 higher than with those with the primary school. On the other hand, we cannot exclude possibility that the patients with the primary school education had lower premorbid achievements due to more pronounced neurocognitive impairments present before the appearance of the first clear psychotic symptoms, which would be in favor of more severe disease and a worse response to therapy. It is also possible that a better adherence of more educated patients with treatment facilitates the treatment process and allows for better adherence to the recommendations of the GCP. The factor most strongly associated with the adherence to the recommendations of the GCP was the age of a prescriber. Namely, those who were youger than 46 years of age complied with the recommendations of GCP twice more often than the ones over 46 years of age. It is possible that younger doctors were more motivated for continuous education, whereas older doctors may have ingrained habits and their favorite patterns of prescribing drugs and were not ready to try something new. On the other hand, it is possible that older, more experienced doctors treated more serious patients, when deviation from the recommendations of GCP is often inevitable.

Our study has some limitations. Firstly, due to the retrospective design of the study, we could not estimate objectively enough the differences in the severity of the disease in the patients. Also, we were not able to provide a clear insight into the reasons for prescribing certain antipsychotics, for switching antipsychotic therapy, or for prescribing antipsychotic polypharmacy. In addition, the research was conducted in only one, specific institution in Belgrade, which made it difficult to generalize the results.

Conclusion

After the introduction of the National Guideline of Good Clinical Practice for the Diagnosis and Treatment of Schizophrenia there have been significant, but insufficient changes in the prescribing patterns of antipsychotics during the treatment of the first psychotic episode in the daily clinical practice of psychiatrists in Serbia. There was an increase in prescribing of SGAs, which was used more often than FGAs, especially as the FGA. The use of FGA has decreased, but it has still been extremely common. One third of the patients with the FPE was treated with APF. Both of the individual characteristics of psychiatrists and patients have had a great influence on the prescribing patterns of antipsychotics. These data are important for the improvement of the rational use of drugs in the daily clinical practice of psychiatrists in Serbia.

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