

Utjecaj dugodjelujućih antipsihotika na hospitalizaciju oboljelih od shizofrenije u Republici Hrvatskoj

/ The Impact of Long-Acting Antipsychotics on the Hospitalization of Patients with Schizophrenia in the Republic of Croatia

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Shizofrenija je bolest s velikim rizikom od relapsa, koji je još veći ako oboljela osoba ne uzima terapiju antipsihoticima. Mala adherentnost na terapiju je veliki problem u liječenju shizofrenije, ali uporaba dugodjelujućih antipsihotika dokazano povećava adherentnost. Cilj ovog rada bio je utvrditi postoji li veza između uporabe dugodjelujućih antipsihotika i hospitalizacija osoba koje boluju od shizofrenije u Republici Hrvatskoj. Prikupljeni su podatci o potrošnji dugodjelujućih antipsihotika i o hospitalizaciji oboljelih od shizofrenije u četverogodišnjem razdoblju od 2018. do 2021. godine. Statistička analiza učinjena je Pearsonovim testom korelacije. Iz rezultata je vidljivo da se broj hospitalizacija zbog shizofrenije smanjuje iz godine u godinu, a potrošnja svih atipičnih antipsihotika u dugodjelujućoj formulaciji povećava. Rezultati upućuju na snažnu negativnu korelaciju među varijablama: broj hospitaliziranih pacijenata, broj hospitalizacija, duljina bolničkog liječenja i potrošnja dugodjelujućih antipsihotika, ali korelacija ni za jednu varijablu nije statistički značajna. Zaključujemo da povećanje primjene dugodjelujućih antipsihotika kod oboljelih od shizofrenije u Republici Hrvatskoj može utjecati na smanjenje broja hospitaliziranih bolesnika, broja hospitalizacija i trajanja hospitalizacije. Stoga je preporuka da se dugodjelujući atipični antipsihotici kod oboljelih od shizofrenije počnu primjenjivati u što ranijoj fazi bolesti i/ili već u prvoj epizodi.

/ Schizophrenia is an illness with a high risk of relapse, which is even higher if the affected person does not take antipsychotic therapy. Low adherence to therapy represents a major problem in the treatment of schizophrenia, however the use of long-acting antipsychotics has been shown to increase adherence. The aim of this paper was to determine whether there is a connection between the use of long-acting antipsychotics and hospitalizations of individuals suffering from schizophrenia in the Republic of Croatia. Data on the use of long-acting antipsychotics and the hospitalization of patients with schizophrenia were collected over the four-year period from 2018 to 2021. Statistical analysis was performed using the Pearson correlation test. It is evident from the results that the number of hospitalizations due to schizophrenia decreased year after year, while the use of all atypical antipsychotics with long-acting formulation increased. The results indicate a strong negative correlation between the variables: the number of hospitalized patients, the number of hospitalizations, the duration of hospital care and the use of long-acting antipsychotics, but the correlation is not statistically relevant for any variable. We can conclude that an increase in the administration of long-acting antipsychotics in patients with schizophrenia in the Republic of Croatia could result in a decrease in the number of patients hospitalized, the number of hospitalizations and their duration. The recommendation is, therefore, to start administering the long-acting atypical antipsychotics in patients with schizophrenia at the earliest possible stage of the illness and/or as early as the first episode.

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UVOD

Shizofrenija je kronična psihička bolest koja pripada u skupinu psihotičnih poremećaja. Simptomi koji ju karakteriziraju svrstavaju se u 5 skupina: pozitivni, negativni, depresivni/anksiozni, kognitivni i agresivno-hostilni simptomi (1). Većina bolesnika suočava se s učestalim relapsima i posljedičnim hospitalizacijama (2). Teret koji nosi shizofrenija očituje se u onesposobljenosti ljudi koji od te bolesti boluju, a 2016. godine shizofrenija je rangirana kao 12. najčešća onesposobljujuća bolest. Fakorede (3) navodi da 7 od 10 osoba oboljelih od shizofrenije pokazuje neki oblik onesposobljenosti u smislu brige o sebi, socijalnog funkcioniranja, radne sposobnosti i mobilnosti. Onesposobljenost se primarno očituje zbog negativnih simptoma bolesti (4). Srisudha i sur. (4) povezuju negativne simptome sa smanjenom kognitivnom funkcijom koja se očituje smanjenom pažnjom, koncentracijom i pamćenjem. Oboljeli imaju veću stopu pretilosti, kardiovaskularnih i metaboličkih bolesti u odnosu na mentalno zdravu populaciju, što doprinosi smanjenoj fizičkoj funkciji i skraćenom životnom vijeku (5).

Incidencija shizofrenije iznosi oko 1 % te se nije značajno mijenjala tijekom posljednjih 200 godina, koliko su podatci dostupni. Također, incidencija je slična u različitim populacijama (6). Prevalencija iznosi od 4 do 7 na 1000 ljudi (7). Može se zaključiti da je shizofrenija bolest sa stalnom incidencijom i prevalencijom u prostoru i vremenu. Početak bolesti u ranoj

INTRODUCTION

Schizophrenia is a chronic mental illness that belongs to the group of psychotic disorders. Its characteristic symptoms are classified into five groups: positive, negative, depression/anxiety, cognitive and aggressive-hostile symptoms (1). Most patients experience frequent relapses and consequent hospitalizations (2). The burden of schizophrenia is reflected in the disability of people suffering from this illness, and in 2016 schizophrenia was ranked as the 12th most common disabling condition. Fakorede (3) states that seven out of ten individuals suffering from schizophrenia display some form of disability in terms of self-care, social functioning, working ability and mobility. Disability is primarily manifested due to the negative symptoms of the illness (4). Srisudha et al. (4) associate the negative symptoms with reduced cognitive function which is reflected in reduced attention, concentration and memory. There is a higher rate of obesity, cardiovascular and metabolic diseases among these patients when compared to the mentally healthy population, which contributes to the reduced physical function and a shorter life expectancy (5).

The incidence of schizophrenia is about 1% and has not significantly changed over the last 200 years, as far as data are available. Furthermore, its incidence is similar in different populations (6). Prevalence amounts to between four and seven per 1000 people (7). It can be concluded that schizophrenia is an illness with constant incidence and prevalence in space and time. The onset of the illness in early adulthood with peak

odrasloj dobi s vrhuncem prevalencije oko 40. godine života (kada bi osoba trebala biti radno aktivna) te niska stopa remisije doprinose težini bolesti (6).

Za liječenje akutne epizode shizofrenije te kao kronična terapija koriste se antipsihotici. Dokazano je da njihova kontinuirana primjena smanjuje rizik od relapsa (8), broj hospitalizacija (8,9), kognitivni i funkcionalni deficit (10), a poboljšava funkcioniranje i kvalitetu života oboljelih (8). Atipični antipsihotici preporučeni su kao terapija prve epizode shizofrenije te kao terapija održavanja (11), koja bi nakon prve psihotične epizode trebala trajati od jedne do tri godine (12), a nakon ponovljenih epizoda doživotno (11). Problem u liječenju je velika neadherentnost pacijenata na terapiju. Posljedice su povećan broj relapsa i hospitalizacija te negativan učinak na tijek bolesti i funkcioniranje osobe. Prema Velliganu i sur. (13) najvažniji uzroci loše adherentnosti su nedostatak uvida u bolest i potrebu za liječenjem, nuspojave, perzistencija simptoma unatoč terapiji, kognitivni deficit, narušen odnos između liječnika i pacijenta, manjak podrške, financijski problemi i nedostatak rutine. Do hospitalizacije oboljelih dolazi zbog pojave akutne psihotične epizode ili agresivnog ponašanja, a najčešće su kratkog trajanja (10). Hospitalizacija u većini zemalja najviše doprinosi trošku koji nosi shizofrenija kao bolest (8). Rizik za relaps nakon prve psihotične epizode i nakon prestanka uzimanja terapije je 80 % u prvih 12 mjeseci i 95 % u 24 mjeseca, a većina relapsa dogodi se u prvih nekoliko tjedana i mjeseci od prestanka uzimanja terapije (2).

Prevenција relapsa i hospitalizacija danas je veliki javnozdravstveni izazov. Antipsihotici u usporedbi s placebom smanjuju rizik od relapsa. Dugodjelujuće formulacije antipsihotika pokazuju se boljima od oralnih formulacija (14–17). Istraživanje iz 2017. godine (18), u koje je bilo uključeno gotovo 30.000 pacijenata, pokazalo je da je uporaba dugodjelujućih antipsihotika i

prevalence around the age of 40 (when an individual should be working), as well as a low rate of remission, contribute to the severity of the illness (6).

Antipsychotics are used to treat acute episodes of schizophrenia, and they are also used as chronic therapy. It has been proved that their continued use decreases the risk of relapse (8), the number of hospitalizations (8, 9), cognitive and functional deficit (10), and also improves the functioning and quality of life of the patients (8). It is recommended to use atypical antipsychotics as therapy in the first episode of schizophrenia, as well as maintenance therapy (11) which, after the first psychotic episode should last for one to three years (12), and after repeated episodes it should be lifelong (11). High non-adherence of patients to therapy represents a problem during treatment. This results in a higher number of relapses and hospitalizations, as well as in a negative effect on the course of the illness and the individual's functioning. According to Velligan et al. (13), the most important causes of poor adherence lie in the lack of insight into the illness and the need for treatment, its side effects, persistence of symptoms despite therapy, cognitive deficit, disrupted doctor-patient relationship, lack of support, financial issues and a lack of routine. Patients are hospitalized due to the onset of acute psychotic episodes or aggressive behavior, which are usually of short duration (10). In most countries, hospitalization accounts for the largest expense that results from schizophrenia as an illness (8). The risk of relapses after the first psychotic episode and after discontinuation of therapy is 80% in the first 12 months, and 95% in the period of 24 months, while most relapses occur in the first several weeks and months after discontinuation of therapy (2).

Nowadays, the prevention of relapses and hospitalizations represents a major public health challenge. When compared to placebo, antipsychotics indeed decrease the risk of relapse. Long-acting formulations of antipsychotics have proved to be a better choice than oral formulations (14–17). The results of a study conducted in 2017 (18), which included almost 30,000 patients

klozapina najbolji izbor za prevenciju relapsa. Drugo istraživanje iz 2017. (19) potvrdilo je da je za povećanje adhezije na terapiju bolja uporaba dugodjelujućih od oralnih antipsihotika.

Učestalost uporabe dugodjelujućih antipsihotika varira od 6,3 % (Kanada) do 80 % (Ujedinjeno Kraljevstvo). Mali broj psihijatara (4 %) odlučuje se za njih kao prvi izbor terapije održavanja (20). S obzirom na svoju sigurnost i efikasnost dugodjelujući antipsihotici se premalo propisuju (21). Neki od mogućih razloga rjeđeg propisivanja su percepcija psihijatara o mogućim ozbiljnim nuspojavama s posljedičnim narušavanjem odnosa s pacijentom, teškoće u predstavljanju dugodjelujućeg oblika kao najpovoljnije terapije održavanja te slaba dostupnost (21).

Istraživanja potrošnje lijekova, pa tako i psihofarmaka, zahtijevaju znanstvenu aktivnost čiji je cilj poboljšanje uporabe lijekova i racionalizacija farmakoterapije (22, 23). Razlikuju se prema obuhvatu, postoje nacionalne i regionalne studije te međunarodni programi kao što je npr. Regionalni ured za Europu Svjetske zdravstvene organizacije (SZO). U svrhu istraživanja rade se i analize potrošnje lijekova pojedinih terapijskih skupina. Model istraživanja odabire se prema istraživačkom pitanju (24–26). Potrošnja lijekova na nekom području (država, regija) prikazuje se brojem definiranih dnevnih doza (DDD, engl. *Defined Daily Dose*) na 1000 stanovnika na dan. Na taj način dobivamo udio stanovništva koji svaki dan koristi pojedini lijek. DDD lijeka je prosječna dnevna doza terapije održavanja za odraslu osobu u najčešćoj indikaciji, prema anatomsko-terapijsko-kemijskoj klasifikaciji (ATK). Važno je napomenuti da DDD nije preporučena terapijska doza ili točna slika terapije, nego je dogovorno utvrđena statistička jedinica mjerenja potrošnje lijekova (27–32). Ako se želi promijeniti i racionalnije propisivati psihofarmake, konkretno dugodjelujuće

have shown that long-acting antipsychotics and clozapine are the best choice for the prevention of relapses. Another study conducted in 2017 (19) confirmed that the use of long-acting antipsychotics is a better choice than oral antipsychotics when it comes to increasing adherence to therapy.

The frequency of long-acting antipsychotics consumption varies between 6.3% (Canada) and 80% (United Kingdom). Few psychiatrists (4%) opt for this medication as the first choice for maintenance therapy (20). Considering the safety and efficiency of their use, long-acting antipsychotics are not prescribed enough (21). Some of the possible reasons for their less frequent prescription lie in the perception of psychiatrists when it comes to their possible side effects and, consequently, a disrupted relationship with their patient, difficulty in presenting the long-acting type of the medication as the most favorable form of maintenance therapy, as well as their low availability (21).

Studies addressing the use of medications, including psychopharmaceuticals, require scientific activities the aim of which is to improve the use of medications and rationalize pharmacotherapy (22, 23). They vary in scope, and national and regional studies exist, as well as international programs such as the World Health Organization (WHO) Regional Office for Europe. Analyses of the medication use of individual therapy groups are also conducted for research purposes. The research model is selected in accordance with the research question (24–26). Medication use in a certain area (country, region) is presented as the number of defined daily doses (DDD) per 1000 inhabitants per day. In this way we can calculate the proportion of the population that uses a particular medication every day. According to the Anatomical Therapeutic Chemical (ATC) classification system, the DDD of a medication is an average daily maintenance dose for a medication used for its main indication in adults. It should be noted that DDD is not a recommended therapeutic dose or an accurate representation of therapy, but is an agreed statistical unit of measurement of medication use (27–32). If we want to change

antipsihotike, neophodne su informacije o njihovoj uporabi (33).

Glavna hipoteza je da povećanje uporabe dugodjelujućih antipsihotika dovodi do smanjenja broja hospitalizacija, kao i dana bolničkog liječenja oboljelih od shizofrenije u Republici Hrvatskoj. Cilj ovog rada bio je utvrditi postoji li veza između navedenih varijabli.

MATERIJALI I METODE

Retrospektivna analiza napravljena je na temelju podataka koji se odnose na Republiku Hrvatsku i obuhvaćaju razdoblje od 2018. do 2021. godine. Prikupljeni su podatci o potrošnji dugodjelujućih antipsihotika i podatci o hospitalizaciji oboljelih od shizofrenije. U navedenom četverogodišnjem razdoblju svi današnji dugodjelujući antipsihotici bili su u upotrebi u Republici Hrvatskoj.

Kao izvor podataka o pokazateljima bolničkog liječenja osoba s dijagnozom shizofrenije korištena je web stranica Hrvatskog zavoda za javno zdravstvo, Registar za psihoze (34). Prezeti su ovi podatci: broj bolnički liječenih bolesnika, broj hospitalizacija i broj dana bolničkog liječenja osoba oboljelih od shizofrenije. Broj dana bolničkog liječenja izražen je u tisućama ('000) (tablica 1).

Izvor podataka o dostupnim dugodjelujućim antipsihoticima u Republici Hrvatskoj je internetska stranica Hrvatskog zavoda za zdravstveno osiguranje (HZZO), arhiva liste lijekova (35). Lijekovi u tablicama su raspoređeni po sustavu ATK prema kojem su lijekovi za psihoze

and rationally prescribe psychopharmaceuticals, specifically long-acting antipsychotics, information on their use is essential (33).

The main hypothesis is that an increase in the use of long-acting antipsychotics leads to a lower number of hospitalizations and hospital care days of patients suffering from schizophrenia in the Republic of Croatia. The aim of this paper was to determine whether there was a connection between the aforementioned variables.

MATERIALS AND METHODS

A retrospective analysis was conducted based on the data relating to the Republic of Croatia, which encompass the period between 2018 and 2021. The collected data referred to the use of long-acting antipsychotics and the hospitalization of patients suffering from schizophrenia. In the four-year period stated above, all of the long-acting antipsychotics prescribed nowadays were in use in the Republic of Croatia.

The website of the Croatian Institute of Public Health, Croatian Psychoses Registry (34), was used as the source of information on the hospital treatment indicators of patients with schizophrenia. The following data were obtained: number of hospital-treated patients, number of hospitalizations and number of hospital care days of patients suffering from schizophrenia. The number of hospital care days was expressed in thousands ('000) (table 1).

The website of the Croatian Health Insurance Fund (CHIF), the list of medications archive (35), was used as the source of information on the available long-acting antipsychotics in the Repub-

TABLICA 1. Bolnički liječeni pacijenti oboljeli od shizofrenije u razdoblju od 2018. do 2021. godine
TABLE 1. Hospital-treated patients suffering from schizophrenia in the period from 2018 to 2021

Bolnički liječeni pacijenti oboljeli od shizofrenije / Hospital-treated patients suffering from schizophrenia				
Godina / Year	2018.	2019.	2020.	2021.
Broj bolesnika / Number of patients	6352	5945	5208	4923
Broj hospitalizacija / Number of hospitalizations	10040	9228	8345	7943
Broj dana bolničkog liječenja u '000 / Number of hospital care days in '000	441	424	377	375

navedeni pod šifrom N05A (36), a s obzirom da dugodjelujući antipsihotici dolaze u obliku injekcija (37), uzeti su podatci o antipsihoticima dostupnim u tom obliku. To su: haloperidol, flufenazin, risperidon, olanzapin, paliperidon, aripiprazol.

Podatci o potrošnji dugodjelujućih antipsihotika prikupljeni su s internetske stranice Hrvatske agencije za lijekove i medicinske proizvode (38–42). Potrošnja je izražena kao DDD na 1000 stanovnika na dan (DDD/1000/dan). Za svaki zaštićeni oblik lijeka izražena je DDD/1000/dan u pojedinoj godini, a potom su te vrijednosti zbrojene kako bi se dobila DDD/1000/dan za pojedini generički oblik lijeka u pojedinoj godini (29) (tablica 2).

Podatci su uneseni u program *Microsoft Office Excel* te su organizirani za statističku obradu.

Statistička analiza učinjena je Pearsonovim testom korelacije.

REZULTATI

Tablica 1. prikazuje podatke vezane uz bolničko liječenje pacijenata oboljelih od shizofrenije. Iz prikupljenih podataka vidljivo je da se u Republici Hrvatskoj broj bolesnika hospitaliziranih zbog shizofrenije sukcesivno smanjuje iz godine u godinu tijekom promatranog četverogodišnjeg razdoblja (od 2018. do 2021. godine). Broj hospitaliziranih bolesnika 2018. godine iznosio je 6352, a 2021. godine 4923, što je smanjenje od 22,5 %. Broj hospitalizacija se

lic of Croatia. The medications referred to in the tables were arranged according to the ATC system, which lists medications for psychoses under the code N05A (36), and since long-acting antipsychotics are administered in the form of injections (37), data on the antipsychotics available in such form were obtained. These medications include the following: haloperidol, fluphenazine, risperidone, olanzapine, paliperidone, aripiprazole.

Data on the use of long-acting antipsychotics were obtained from the website of the Croatian Agency for Medicinal Products and Medical Devices (38–42). Their use was presented as DDD per 1000 inhabitants per day (DDD/1000/day). For each protected form of a medication, DDD/1000/day for a particular year was presented, and the values were then added together in order to obtain DDD/1000/day for an individual generic form of a medication in a certain year (29) (Table 2).

The data were entered into the Microsoft Office Excel program and organized for statistical analysis purposes. Statistical analysis was performed using the Pearson Correlation Test.

RESULTS

Data relating to the hospital treatment of patients suffering from schizophrenia are presented in Table 1. It is evident from the collected data that the number of patients in the Republic of Croatia hospitalized due to schizophrenia successively decreased from year to year in the four-year period observed (from 2018 to 2021). The number of hospitalized patients amounted to 6352 in

TABLICA 2. Potrošnja dugodjelujućih antipsihotika u DDD/1000/dan u razdoblju od 2018. do 2021. godine.

TABLE 2. The use of long-acting antipsychotics in DDD/1000/day in the period from 2018 to 2021

DDD/1000/dan dugodjelujućih antipsihotika / DDD/1000/day for long-acting antipsychotics							
Godina / Year	Haloperidol	Flufenazin / Fluphenazine	Risperidon / Risperidone	Olanzapin / Olanzapine	Paliperidon / Paliperidone	Aripiprazol / Aripiprazole	Ukupno / Total
2018.	0,104	0,229	0,153	0,213	0,860	0,107	1,665
2019.	0,223	0,375	0,132	0,223	1,030	0,115	2,135
2020.	0,172	0,296	0,117	0,209	1,170	0,191	2,155
2021.	0,119	0,251	0,106	0,217	1,360	0,232	2,286

također sukcesivno smanjuje iz godine u godinu: 2018. godine broj hospitalizacija iznosio je 10.040, a 2021. godine 7943, što je smanjenje od 20,9 %. Broj dana bolničkog liječenja, odnosno duljina hospitalizacije, također se sukcesivno smanjuje tijekom četiri godine: 2018. godine iznosila je 441 dan, a 2021. godine 375 dana na 1000 hospitaliziranih, što je smanjenje od 15 %.

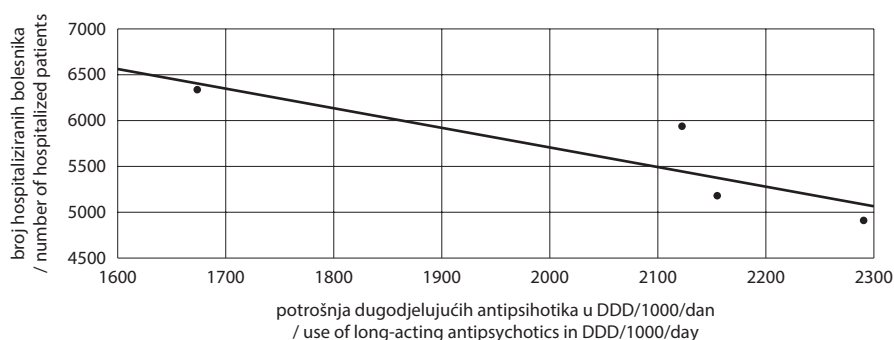
Tablica 2. prikazuje podatke vezane uz potrošnju dugodjelujućih antipsihotika. Potrošnja dugodjelujućih antipsihotika tijekom promatranog četverogodišnjeg razdoblja se sukcesivno povećava: u 2018. godini iznosila je 1,665 DDD/1000/dan, a 2021. godine 2,286 DDD/1000/dan, što je povećanje od 37,3 %. Uočavaju se razlike u potrošnji pojedinih antipsihotika i skupina antipsihotika. Potrošnja klasičnih dugodjelujućih antipsihotika haloperidola i flufenazina te atipičnog antipsihotika olanzapina nije se značajno mijenjala u promatranom razdoblju. Potrošnja dugodjelujućeg atipičnog antipsihotika risperidona sukcesivno se smanjuje, a potrošnja novijih atipičnih dugodjelujućih antipsihotika paliperidona i aripiprazola iz godine u godinu se povećava.

Grafikoni 1., 2. i 3. prikazuju rezultate Pearsonovog testa korelacije. Rezultati Pearsonovog testa korelacije indiciraju da postoji snažna negativna korelacija među varijablama broj hospi-

2018, while in 2021 it was 4923, which is 22.5% less. The number of hospitalizations successively decreased from year to year as well: the number of hospitalizations amounted to 10,040 in 2018, while in 2021 it was 7943, which is 20.9% less. The number of hospital care days, i.e. the duration of hospitalization, successively decreased in the four-year period as well: it amounted to 441 days in 2018, while in 2021 it was 375 days per 1000 hospitalized patients, which is 15% less.

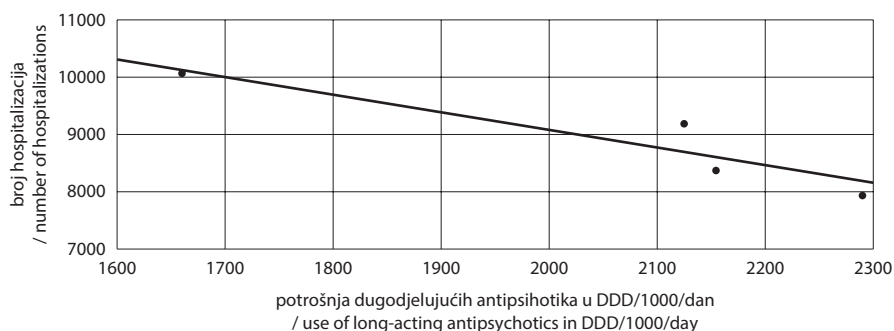
Data relating to the use of long-acting antipsychotics are presented in Table 2. The use of long-acting antipsychotics during the observed four-year period successively increased: it amounted to 1.665 DDD/1000/day in 2018, while in 2021 it was 2.286 DDD/1000/day, which is an increase of 37.3%. Differences in the use of individual antipsychotics and groups of antipsychotics were observed. The use of classic long-acting antipsychotics haloperidol and fluphenazine, and the atypical antipsychotic olanzapine did not significantly change in the observed period. The use of long-acting atypical antipsychotic risperidone successively decreased, while the use of newer atypical long-acting antipsychotics paliperidone and aripiprazole increased from year to year.

The results of the Pearson correlation test are presented in Diagrams 1, 2 and 3. The results of the Pearson correlation test indicate a strong negative correlation between the variables of the number of hospitalized patients and the use of long-acting



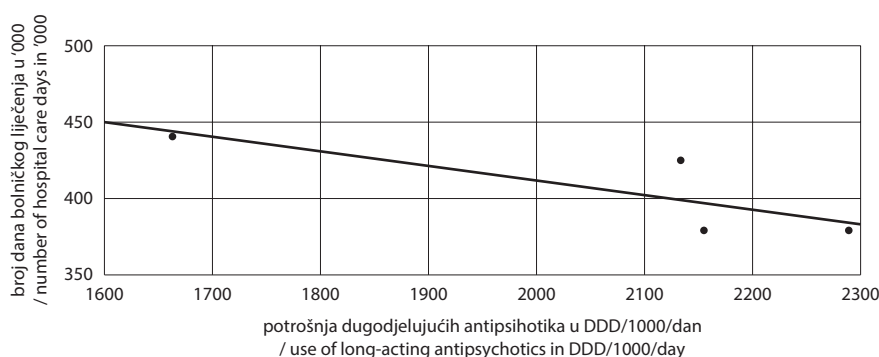
GRAFIKON 1. Korelacija između varijabli broj hospitaliziranih bolesnika i potrošnja dugodjelujućih antipsihotika u DDD/1000/dan u razdoblju od 2018. do 2021. godine.

DIAGRAM 1. Correlation between the number of hospitalized patients and the use of long-acting antipsychotics variables in DDD/1000/day in the period from 2018 to 2021.



GRAFIKON 2. Korelacija među varijablama broj hospitalizacija i potrošnja dugodjelujućih antipsihotika u DDD/1000/dan u razdoblju od 2018. do 2021. godine.

DIAGRAM 2. Correlation between the number of hospitalizations and the use of long-acting antipsychotics variables in DDD/1000/day in the period from 2018 to 2021.



GRAFIKON 3. Korelacija među varijablama broj dana bolničkog liječenja u '000 i potrošnja dugodjelujućih antipsihotika u DDD/1000/dan u razdoblju od 2018. do 2021. godine.

DIAGRAM 3. Correlation between the number of hospital care days in '000 and the use of long-acting antipsychotics variables in DDD/1000/day in the period from 2018 to 2021.

taliziranih pacijenata i potrošnja dugodjelujućih antipsihotika. Pearsonov koeficijent korelacije iznosi -0.8606 , ali korelacija nije statistički značajna (p-vrijednost je $0,1394$).

Utvrđena je i snažna negativna korelacija između varijabli broj hospitalizacija i potrošnja dugodjelujućih antipsihotika. Pearsonov koeficijent korelacije iznosi -0.9096 , ali korelacija nije statistički značajna (p-vrijednost je 0.090).

Snažna negativna korelacija postoji i između varijabli duljina bolničkog liječenja i potrošnja dugodjelujućih antipsihotika. Pearsonov koeficijent korelacije iznosi -0.8171 , ali korelacija nije statistički značajna (p-vrijednost je $0,1829$).

antipsychotics. The Pearson correlation coefficient amounts to -0.8606 , however the correlation has no statistical significance (p-value is 0.1394).

A strong negative correlation between the number of hospitalized patients and the use of long-acting antipsychotics variables was observed. The Pearson correlation coefficient amounts to -0.9096 , however the correlation has no statistical significance (p-value is 0.090).

There is a strong negative correlation between the duration of hospitalization and the use of long-acting antipsychotics variables. The Pearson correlation coefficient amounts to -0.8171 , however the correlation has no statistical significance (p-value is 0.1829).

RASPRAVA

Prevenција relapsa, a time i (re)hospitalizacija je velik terapijski izazov u liječenju osoba oboljelih od shizofrenije (2,9,13,15,16). Ponavljajući relapsi i hospitalizacije negativno utječu na klinički tijek i prognozu bolesti, zdravlje i kvalitetu života oboljelih te na ukupne troškove liječenja. Smanjenje broja hospitalizacija, produljenje vremena bez hospitalizacije i smanjenje trajanja hospitalizacije čimbenici su koji snažno utječu na učinkovitost i ekonomičnost liječenja.

Bolesnici oboljeli od shizofrenije skloni su učestaloj, dugotrajnoj ili stalnoj hospitalizaciji jer ih njihove obitelji najčešće ne mogu kontrolirati zbog težine kliničke slike (praćene razdražljivošću, sumanutim idejama, halucinacijama, autoagresivnim i heteroagresivnim ponašanjima), što je veliko financijsko opterećenje ne samo za njih nego i za sustav zdravstvene i socijalne skrbi. Prema našim saznanjima, duljina bolničkog liječenja i broj hospitalizacija oboljelih od shizofrenije u Republici Hrvatskoj do sada nisu bili u fokusu istraživanja.

Od pokreta „deinstitutionalizacije” za psihijatrijske bolesnike tijekom 1970-ih i pozitivnih učinaka novih atipičnih antipsihotika 1990-ih broj, učestalost i duljina hospitalizacije oboljelih od shizofrenije postupno se smanjuje (43). To je smanjenje, osobito u zemljama s financijskim poteškoćama i neadekvatnim zdravstvenim sustavima, više bilo potaknuto ograničavanjem troškova psihijatrijske skrbi zbog učestale i duge psihijatrijske hospitalizacije oboljelih od shizofrenije, nego otvaranjem programa izvanbolničkog liječenja i funkcionalnog oporavka u zajednicama (44,45). Istraživanja duljine bolničkog liječenja pokazuju kraće trajanje liječenja u zemljama u razvoju nego u razvijenim zemljama: prosječna duljina boravka na bolničkom liječenju pacijenata oboljelih od shizofrenije u Kini je iznosila 73,3 dana (46), 78 dana u Južnoj Koreji (47), 111,79 dana u

DISCUSSION

The prevention of relapses, and consequently (re) hospitalizations, represents a major therapeutic challenge in the treatment of patients suffering from schizophrenia (2, 9, 13, 15, 16). Recurrent relapses and hospitalizations have a negative impact on the clinical course and prognosis of the illness, the health and quality of life of the patients, and the overall costs of treatment. Decreased number of hospitalizations, longer periods without hospitalization and decreased duration of hospitalization are factors that have a strong impact on the efficiency and cost-effectiveness of the treatment.

Patients suffering from schizophrenia are more likely to undergo frequent, long-lasting or permanent hospitalization since their families generally cannot control them due to the severity of their clinical picture (which includes irritability, delusional ideas, hallucinations, auto-aggressive and hetero-aggressive behaviors), which represents a major financial burden not only for them, but also for the healthcare and welfare systems. According to our findings, there have been no studies focusing on the duration of hospital treatment and the number of hospitalizations of patients suffering from schizophrenia in the Republic of Croatia so far.

Since the movement of “deinstitutionalization” of psychiatric patients during the 1970s and the positive effects of new atypical antipsychotics in the 1990s, the number, frequency and duration of hospitalization for patients with schizophrenia have been gradually decreasing (43). This decrease, particularly in countries with financial difficulties and inadequate health facilities, was prompted more by the limitation of psychiatric care expenses due to frequent and long-term psychiatric hospitalizations of schizophrenic patients, than by the establishment of programs of outpatient treatment and functional recovery in communities (44, 45). Studies addressing the duration of hospital treatment indicate shorter treatments in developing countries as opposed to developed countries: the average duration of

Izraelu (44), 96,6 dana u Kanadi (48) i 290,6 dana u Japanu (49, 50).

Iz naših rezultata vidljivo je da se i u Republici Hrvatskoj broj hospitalizacija zbog shizofrenije, broj bolesnika i broj dana bolničkog liječenja sukcesivno smanjuju iz godine u godinu. U promatranom razdoblju od 2018. do 2021. godine nije došlo do bitnih smanjenja bolničkih kapaciteta za tu kategoriju bolesnika niti je osiguravatelj (HZZO) uveo financijska ograničenja koja bi se mogla povezati sa smanjenjem hospitalizacija. Došlo je do određenog povećanja kapaciteta u izvanbolničkom zbrinjavanju pacijenata, ali uglavnom u dnevnim bolnicama, što se smatra hospitalizacijskim tretmanom, a ne izvanbolničkim liječenjem. Nisu oformljeni centri za zbrinjavanje u zajednici niti mobilni timovi koji bi utjecali na smanjenje hospitalizacija. Promatrano razdoblje uključuje i pandemiju COVID-19, no oboljelima od shizofrenije hospitalizacija je bila stalno dostupna i tijekom pandemije, nitko nije bio zakinut za bolničko liječenje, za razliku od oboljelih od drugih psihičkih poremećaja, koji su preusmjeravani na online liječenje i u bolnicu su zaprimani samo u izričito akutnim stanjima. Naše rezultate stoga ne možemo povezati ni s izolacijom ni s drugim mjerama vezanim uz pandemiju COVID-19. S obzirom da je shizofrenija bolest sa stalnom incidencijom i prevalencijom u prostoru i vremenu, razloge smanjenja broja hospitaliziranih bolesnika, ukupnog broja hospitalizacija i duljine bolničkog liječenja morali smo potražiti u drugim mogućim čimbenicima, konkretno u većoj potrošnji dugodjelujućih antipsihotika.

Istraživači su dosad na različitim uzorcima proveli brojne studije (51–54) koje su pokazale niz potencijalno utjecajnih čimbenika na smanjenje broja i duljine hospitalizacije pacijenata oboljelih od shizofrenije. Većina su bili demografske i kliničke varijable, a među kliničkima bila je i antipsihotička terapija. Mi smo izabrali antipsihotičku terapiju kao varijablu za istraži-

hospital treatment of patients suffering from schizophrenia was 73.3 days in China (46), while in South Korea it was 78 days (47), in Israel it was 111.79 days (44), in Canada it was 96.6 days (48), and in Japan it was 290.6 days (49, 50).

It is evident from our results that the number of hospitalizations due to schizophrenia, the number of patients and the number of hospital care days in the Republic of Croatia successively decreased each year. No significant decrease of hospital capacities for this patient category was recorded in the observed period from 2018 to 2021, and the insurance provider (CHIF) also did not introduce any financial limitations which might be associated with the decreased number of hospitalizations. There was some increase in capacity in terms of outpatient care, but it was mainly in day hospitals, which is considered as hospitalization treatment, and not outpatient treatment. No community care centers or mobile units were formed which would affect the decrease in hospitalizations. The observed period also included the COVID-19 pandemic, however hospitalization was available to schizophrenic patients at all times even during the pandemic and no one was deprived of hospital treatment, as opposed to those suffering from other mental disorders who were redirected to treatment online and were only admitted to hospitals in case of extremely acute conditions. Our results, therefore, cannot be associated neither with isolation nor with other measures relating to the COVID-19 pandemic. Considering that schizophrenia is an illness with constant incidence and prevalence in space and time, we had to search for the reasons for the decrease in the number of hospitalized patients, the total number of hospitalizations and the duration of hospital treatment in other possible factors, more specifically in the higher use of long-acting antipsychotics.

Researchers have so far conducted numerous studies on different samples (51–54), which have resulted in a series of factors that could potentially influence the reducing number and duration of hospitalizations of patients suffering from schizophrenia. Most were demographic or clinical variables, and antipsychotic therapy was among

vanje, i to konkretno potrošnju dugodjelujućih antipsihotika.

Kod psihijatrijskih bolesnika oboljelih od shizofrenije često izostaje uvid u bolest: bolesnik negira probleme, simptome i samu bolest, nema realan uvid u svoje stanje i ponašanje, pa ni uzimanje lijekova ne smatra potrebnim. Gotovo sve smjernice i algoritmi za liječenje shizofrenije slažu se u činjenici da ne treba podržavati tzv. povremenu ili intermitentnu terapiju antipsihoticima te preporučuju kontinuiranu antipsihotičku terapiju tijekom jedne do tri godine nakon prve psihotične epizode (12).

Liječenje oboljelih od shizofrenije zahtijeva kontinuirano, dugotrajno, a često i doživotno uzimanje antipsihotika zbog čega je suradljivost pacijenta u procesu liječenja jedan od najvažnijih čimbenika oporavka. Najčešći uzrok relapsa i rehospitalizacija je prestanak uzimanja propisane terapije antipsihoticima. Tiuhonen i sur. (18) pokazali su da 35,7 % bolesnika koji su prvi put zaprimljeni na liječenje lijekove prestane uzimati 30 dana nakon otpusta iz bolnice, a 54,3 % 60 dana nakon otpusta.

Dugodjelujući antipsihotici su posebna formulacija lijeka koja omogućuje održavanje stalne razine lijeka u krvi tijekom duljeg vremena. Dugodjelujući antipsihotici unijeli su veliku novost u psihijatriju jer su uvelike smanjili problem suradljivosti. U usporedbi sa standardnom peroralnom antipsihotičkom terapijom dokazano je da primjena dugodjelujućih formulacija antipsihotika smanjuje rizik od hospitalizacija i bolesnicima u ranim fazama shizofrenije (do pet godina trajanja bolesti) produljuje vrijeme bez hospitalizacije. To se u prvom redu postiže povećanjem adhezije bolesnika na terapiju (55).

Iz naših rezultata vidljivo je da se potrošnja svih atipičnih antipsihotika u dugodjelujućoj formulaciji u Republici Hrvatskoj u promatranom četverogodišnjem razdoblju suk-

the clinical ones. We chose antipsychotic therapy as our research variable – more specifically, the use of long-acting antipsychotics.

In psychiatric patients suffering from schizophrenia, there is often a lack of insight into the illness: the patient ignores the problems, the symptoms and the illness itself, has no real insight into their own condition and behavior, and therefore does not consider it necessary to take medications. Almost all guidelines and algorithms for schizophrenia treatment agree on the fact that the so-called occasional or intermittent antipsychotic therapy should not be supported, and they recommend continuous antipsychotic therapy over a period of one to three years following the first psychotic episode (12).

Treatment of patients suffering from schizophrenia requires continuous, long-term, often lifelong use of antipsychotics, thus making patient cooperation in the treatment process one of the most important factors in their recovery. The most common cause of relapses and rehospitalizations is the discontinuation of the prescribed antipsychotic therapy. Tiuhonen et al. (18) observed that 35.7% of patients who were admitted for treatment for the first time stop taking their medications 30 days after being discharged from the hospital, and 54.3% do the same 60 days after their discharge.

Long-acting antipsychotics are a special formulation of the medication that allows a constant level of the medication to be maintained in the blood over a longer period of time. Long-acting antipsychotics were a major breakthrough in psychiatry because they greatly reduced the problem of patient cooperation. Compared to the standard oral antipsychotic therapy, it has been proved that the administration of long-acting formulations of antipsychotics reduces the risk of hospitalization and extends the time without hospitalization for patients in the early stages of schizophrenia (up to five years of illness duration). This is primarily achieved by increasing the adherence of patients to therapy (55).

It is evident from our results that the use of all atypical long-acting antipsychotics in the Republic of Croatia successively increased during the observed four-year period: it amounted to

cesivno povećava: u 2018. godini iznosila je 1,665 DDD/1000/dan, a u 2021. godini 2,286 DDD/1000/dan, što je povećanje od 37,3 %. Postoje razlike u potrošnji između pojedinih antipsihotika i skupina antipsihotika. Potrošnja klasičnih dugodjelujućih antipsihotika haloperidola i flufenazina te atipičnog antipsihotika olanzapina ujednačena je u promatranom četverogodišnjem razdoblju. Potrošnja dugodjelujućeg atipičnog antipsihotika risperidona sukcesivno se smanjuje, a potrošnja novijih atipičnih dugodjelujućih antipsihotika paliperidona i aripiprazola povećava se iz godine u godinu. Ovakav rezultat u skladu je sa svjetskim trendovima: potrošnja novijih atipičnih antipsihotika se povećava, a klasičnih smanjuje ili stagnira (56). Stagnacija potrošnje atipičnih antipsihotika risperidona i olanzapina u Republici Hrvatskoj može se objasniti pojavom paliperidona, poboljšane inačice risperidona te ograničenjem u primjeni olanzapina, posljedično potrebnoj opservaciji nakon aplikacije injekcije u trajanju od najmanje tri sata te aplikaciji u bolničkim uvjetima umjesto u ambulanti obiteljske medicine.

Rezultati našeg istraživanja upućuju na snažnu negativnu korelaciju među varijablama: broj hospitaliziranih pacijenata (Pearsonov koeficijent korelacije iznosi -0.8606), broj hospitalizacija (Pearsonov koeficijent korelacije iznosi -0.9096), duljina bolničkog liječenja (Pearsonov koeficijent korelacije iznosi -0.8171) i potrošnja dugodjelujućih antipsihotika. Korelacija je jaka za sve tri varijable (najjača za varijablu broj hospitalizacija), ali ni za jednu varijablu nije statistički značajna. Naši rezultati upućuju na povezanost između smanjenja broja hospitaliziranih bolesnika, broja hospitalizacija i duljine hospitalizacija s povećanom potrošnjom dugodjelujućih antipsihotika, napose novih atipičnih formulacija dugodjelujućih antipsihotika. Najjača korelacija uočena je između broja hospitalizacija i potrošnje dugodjelujućih antipsihotika, što potvrđuje pretpostavku da du-

1.665 DDD/1000/day in 2018, while in 2021 it was 2.286 DDD/1000/day, which is an increase of 37.3%. There are differences in the use of individual antipsychotics and groups of antipsychotics. The use of classic long-acting antipsychotics haloperidol and fluphenazine, and the atypical antipsychotic olanzapine, was roughly equal in the observed four-year period. The use of long-acting atypical antipsychotic risperidone successively decreased, while the use of newer atypical long-acting antipsychotics paliperidone and aripiprazole increased from year to year. These results are in line with the global trends: the use of newer atypical antipsychotics is increasing, while the use of classic antipsychotics is decreasing or stagnating (56). The stagnation in the use of atypical antipsychotics risperidone and olanzapine in the Republic of Croatia could be explained by the appearance of paliperidone, an improved version of risperidone, as well as the limitations in olanzapine use, due to the necessary observation after the administration of the injection lasting at least three hours and its administration in hospital settings instead of in a family medicine practice.

The results of our study indicate a strong negative correlation between the following variables: the number of hospitalized patients (Pearson correlation coefficient amounts to -0.8606), the number of hospitalizations (Pearson correlation coefficient amounts to -0.9096), the duration of hospital treatment (Pearson correlation coefficient amounts to -0.8171) and the use of long-acting antipsychotics. The correlation of all three variables is strong (it is the strongest for the number of hospitalizations variable), but represents no statistical significance for any of the variables. Our results indicate that the decrease in the number of hospitalized patients, the number of hospitalizations and the duration of hospitalizations is associated with the increased use of long-acting antipsychotics, particularly the new atypical formulations of long-acting antipsychotics. The strongest correlation was observed between the number of hospitalizations and the use of long-acting antipsychotics, which confirms the hypothesis that long-acting antipsychotics contribute to the treat-

godjelujući antipsihotici svoj doprinos u liječenju oboljelih od shizofrenije daju poboljšanjem adherentnosti, a time i smanjenjem rehospitalizacija, odnosno prevencijom rehospitalizacija. Propisuju se kao lijekovi izbora obično kod ponovljenih epizoda, a rijetko u prvoj epizodi, pa je korelacija jače izražena prema varijabli broj hospitalizacija nego prema broju hospitaliziranih bolesnika.

Rezultati našeg istraživanja u skladu su s dosadašnjim istraživanjima u svijetu koja pokazuju da dugodjelujući antipsihotici potencijalno mogu smanjiti rizik hospitalizacije uz snažnije pridržavanje režima uzimanja lijekova, ali se rijetko uzimaju u obzir za liječenje rane faze shizofrenije ili prve epizode shizofrenije (14). Korištenje dugodjelujućih antipsihotika kod osoba s ranom fazom shizofrenije pokazalo je značajno i klinički značajno smanjenje od 44 % u stopi incidencije prve hospitalizacije i broj bolesnika koje treba liječiti (NNT, eng. *Number needed to treat*) od 7 za prevenciju hospitalizacije (14, 55). NNT je mjera koja se koristi za usporedbu učinkovitosti standardne i nove terapije te označava koliki broj ljudi treba liječiti da bi 1 dodatna osoba imala koristi (57).

Preskripcija dugodjelujućih antipsihotika 2. i 3. generacije donosi značajno povećanje troškova liječenja. Svakako bi bilo bolje kada bismo noviji dugodjelujući antipsihotici bili i cijenom pristupačniji, no već postoje studije koje pokazuju njihovu dugoročnu financijsku korist u zdravstvenom sustavu radi smanjenja broja hospitalizacija, bolje kontrole somatskih bolesti i manjeg broja nuspojava. Važno je da su dostupni putem osnovnog zdravstvenog osiguranja (58).

Ograničenja ovog istraživanja su retrospektivni dizajn, činjenica da nisu promatrane druge kliničke i demografske varijable, nije napravljena analiza jesu li oboljeli od shizofrenije uzimali dugodjelujući antipsihotik kao monoterapiju te nije poznat udio oboljelih od terapijski rezistentne shizofrenije za koju ne postoji dugodjelujuća formulacija antipsihotika.

ment of schizophrenic patients by improving adherence, thereby reducing the number of rehospitalizations, i.e. preventing rehospitalizations. They are usually prescribed as medications of choice for recurrent episodes, but rarely for the first episode, therefore the correlation is more expressed for the number of hospitalizations variable than for the number of hospitalized patients.

The results of our study are consistent with the studies conducted globally so far, which have shown that long-acting antipsychotics can potentially decrease the risk of hospitalization with stronger adherence to medication regimens, but are rarely considered for the treatment of the early phase of schizophrenia or during the first episode of schizophrenia (14). The use of long-acting antipsychotics in individuals in the early stage of schizophrenia has resulted in a significant and clinically significant decrease of 44% in the incidence rate of first hospitalization, and the number of patients needed to treat (NNT) amounts to 7 in terms of hospitalization prevention (14, 55). NNT is a measure used to compare the efficiency of standard and new therapies, and identifies the number of people that need to be treated in order for one additional person to experience benefits (57).

The prescription of long-acting antipsychotics of the second and third generation brings about a significant increase in the costs of treatment. It would surely be better if the new long-acting antipsychotics were also more affordable, however there are already studies that have proved their long-term financial benefit to the health system due to a decreased number of hospitalizations, better control of somatic diseases and a reduced number of side effects. What is important is that they are available through the basic health insurance (58).

The limitations of this study lie in its retrospective design, the fact that other clinical and demographic variables were not observed, no analysis was performed as to whether schizophrenic patients were taking long-acting antipsychotics as monotherapy, and there is no data with regard to the share of patients suffering from treatment-resistant schizophrenia for which no long-acting formulation of antipsychotics exists.

Jedan od glavnih izazova u liječenju shizofrenije je prevencija relapsa koji rezultira rehospitalizacijom. Najčešći uzrok relapsa je slaba adherencija. Adherenciju poboljšava primjena dugodjelujućih antipsihotika, a naročito novih atipičnih antipsihotika. Povećanje primjene dugodjelujućih antipsihotika kod bolesnika oboljelih od shizofrenije u Hrvatskoj može utjecati na smanjenje broja hospitaliziranih bolesnika, smanjenje broja hospitalizacija i kraće trajanje hospitalizacije. Preporuka je da se dugodjelujućim antipsihotici kod oboljelih od shizofrenije počnu primjenjivati u što ranijoj fazi bolesti i/ili već u prvoj epizodi.

One of the main challenges in the treatment of schizophrenia is the prevention of relapses resulting in rehospitalization. The most common cause of relapses is low adherence. Adherence is improved by the use of long-acting antipsychotics, particularly the new atypical antipsychotics. An increase in the administration of long-acting antipsychotics in patients suffering from schizophrenia in the Republic of Croatia could result in a decrease in the number of patients hospitalized, the number of hospitalizations and their shorter duration. Our recommendation is to start applying the long-acting antipsychotics in patients with schizophrenia at the earliest possible stage of the illness and/or as early as the first episode.

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