



ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Cost/effectiveness of aripiprazole vs. olanzapine in the long-term treatment of schizophrenia

Aleksandra Dutina¹, Ivana Stašević-Karličić^{1,2}, Nikola Pandrc³, Anđelka Prokić⁴, Slobodan M. Janković⁴¹Dr. Laza Lazarević Clinic for Mental Disorders, Belgrade, Serbia;²University of Priština – Kosovska Mitrovica, Faculty of Medicine, Kosovska Mitrovica, Serbia;³Ministry of Health of the Republic of Serbia, Belgrade, Serbia;⁴University of Kragujevac, Faculty of Medical Sciences, Kragujevac, Serbia**SUMMARY**

Introduction/Objective Although effectiveness of atypical antipsychotics in patients with schizophrenia is mostly similar, there are significant differences in adverse effects rate and treatment costs, making comparison of their cost/effectiveness ratios essential for optimal drug choice. The aim of this study was to compare cost/effectiveness of aripiprazole and olanzapine in long-term treatment of schizophrenia.

Methods A four-state, three-month cycle Markov model was built to compare aripiprazole and olanzapine. The model assumed that patients who relapse on treatment with both aripiprazole and olanzapine are further treated with clozapine. The perspective of the National Health Insurance Fund was chosen, and the period covered by the model was 10 years. The model results were obtained after Monte Carlo microsimulation of a sample with 1,000 virtual patients. Both multiple one-way and probabilistic sensitivity analysis was made.

Results After base-case analysis aripiprazole was dominated by olanzapine, as net monetary benefit was negative (-390,341.96 ± 29,131.53 RSD) and incremental cost/effectiveness ratio (ICER) was above the willingness-to-pay line of one Serbian gross domestic product per capita per quality-adjusted life year (QALY) gained. Multiple one-way and probabilistic sensitivity analysis confirmed results of the base case simulation.

Conclusion Olanzapine has more beneficial cost/effectiveness ratio than aripiprazole for long-term treatment of schizophrenia in Serbian milieu.

Keywords: aripiprazole; olanzapine; cost/effectiveness; Markov model

INTRODUCTION

Schizophrenia is a hard, chronic, and debilitating disease, responsible for the health problems in about 1% of the world's adult population, i.e. 24 million people around the world suffer from it [1]. The treatment of the people suffering from schizophrenia is accompanied with high percentage of relapse and rehospitalization, since patients are largely unwilling to take the prescribed medicine. Relapse, characterized by acute psychotic deterioration, has serious consequences. Apart from the risk of the person expressing behaviour dangerous for themselves or for others, endangering their personal relationships, their education or their employment status, relapse also leads to rehospitalizations, which significantly increases treatment cost. According to various studies, from 20 to more than 90% of the patients with the first episode of schizophrenia are relapsed within two years after being released from a hospital [2, 3, 4]. The therapy using antipsychotics is an important strategy in a fight against relapse. Atypical antipsychotics, compared to the old, typical ones, represent an important step forward in the treatment of schizophrenia in terms of a better profile of undesired effects, superior tolerance, and a higher level of patient compliance [5].

Olanzapine represents an atypical antipsychotic and an antagonist of dopamine D2 and serotonin 5HT_{2A} receptors. This drug was approved for the treatment of schizophrenia, mania, depression caused by bipolar disorder, as well as for the treatment of therapy-resistant depression. Aripiprazole is an example of an atypical antipsychotic and a partial agonist of dopamine D2 receptors. FDA has approved the usage of this medicine for the treatment of schizophrenia and mania, as well as, for the treatment of some psychiatric disorders in children and adolescents. Olanzapine is an antipsychotic sedative, which often leads to increase in both body weight and cardiometabolic risk. On the other hand, aripiprazole is not a sedative, it leads to almost no increase in either body weight or cardiometabolic risk, and it does not cause the appearance of metabolic syndrome (insulin resistance, dyslipidemia, increased level of triglycerides), but in some patients it could cause a slight agitation, akathisia or problems with impulse control. As far as the efficiency of these two antipsychotics is concerned, some researches have shown that there were no differences, while others favored olanzapine [6].

If we take into consideration the limited efficiency of antipsychotics, which is often closely related to the treatment termination, relapses,

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Correspondence to:

Slobodan M. JANKOVIĆ
University of Kragujevac
Faculty of Medical Sciences
Svetozara Markovića 69
34000 Kragujevac, Serbia
slobnera@gmail.com

and rehospitalization, and thus, increased treatment costs, it is necessary to evaluate the cost/effectiveness profile of antipsychotics to make an adequate choice of antipsychotics for the treatment of schizophrenia while being aware of the health system financial reality. Moreover, pharmacoeconomic analyses represent an important parameter for the evaluating introduction of new antipsychotic on the market, with the aim of choosing a therapeutic option adapted to the needs of a patient, with superior tolerance and better compliance. So far, there have not been any cost/effectiveness or cost/utility studies that would compare olanzapine and aripiprazole (two atypical antipsychotics currently highly utilized for treatment of schizophrenia) in the health and economic milieu of the countries of South-east Europe.

The aim of our study was to compare cost/effectiveness of aripiprazole and olanzapine for long-term treatment of patients with schizophrenia.

METHODS

Our study is Markov model-based economic evaluation of aripiprazole in comparison to olanzapine for long-term treatment of patients with schizophrenia. Markov model owes its name to Andrey Andreyevich Markov (1856–1922), a Russian mathematician who first described chronic processes (like schizophrenia) through a chain of interconnected conditions. A patient transits from one state to the next according to probabilities observed from either clinical trials or observational studies. The base case population are adult patients of both sexes residing in Serbia who are in the second episode schizophrenia (of any type), and are about to receive for the second-line treatment with oral antipsychotics. Both aripiprazole and olanzapine received approved indication for the population chosen: treatment of schizophrenia in adults and in adolescents aged 15 and older. The setting for the analysis was healthcare system of the Republic of Serbia, which consists of state-owned health care facilities, and is funded by the National Health Insurance Fund (NHIF), based on the obligatory health insurance contributions from all employed adults in Serbia. Prices of drugs and health care services are controlled by NHIF and the Government of the Republic of Serbia.

The perspective for this economic analysis was that of the NHIF, and only direct medical costs were taken into account. Aripiprazole was compared with olanzapine because both drugs belong to the same pharmacotherapeutic class (atypical antipsychotics), and are alternatively prescribed for treatment of schizophrenia according to current guidelines. Aripiprazole is taken orally, 15 mg once a day, and olanzapine 5–20 mg once a day, depending on the patient's response. The period covered by the model in the study was 10 years, as it was maximal period for which earlier cohort studies reported results [7]. Costs and outcomes were discounted with annual rate of 3%, as this was the value of Referent annual interest rate of the National Bank of Serbia [8]. The main outcome of the study was the quality-

adjusted life years gained, what is common for cost/utility studies. Estimates of the effectiveness of aripiprazole and olanzapine were synthesis-based, taken from meta-analyses of systematic reviews if available, or summated from available controlled clinical trials reports, which satisfied quality standards of evidence-based medicine. Estimates of costs of health states in the model (including medication costs, health services costs and other direct medical costs) were based on published data about health care resources utilization, which were multiplied by unit costs of drugs, services and materials, set by the NHIF through its legal acts or when unavailable, taken from producers [9, 10]. The dates of estimated resource quantities depended on the published studies dates, but as a rule, the most recent studies were favored; the unit costs were taken for the year 2018. All costs were reported in Serbian dinars (RSD).

This study was done in accord with standards of the institutional Committee on Ethics.

Markov chain model was used since schizophrenia with its relapses is a chronic condition, with clearly separable health states. In total, five health states were chosen:

1. remission without adverse effects;
2. remission with adverse effects;
3. relapse;
4. second episode in spite of continuous use of the first line antipsychotics, which can be present only in the first cycle of the model, later on, only relapse is possible;
5. death, according to descriptions of the natural course of the disease, since the duration of one cycle was three months (the whole model had 40 cycles), since changes of the chosen health states fitted well in this timeframe [11].

The model is presented in the Figure 1, with health states and possible transitions. Half-cycle correction was used in the model. The model was built using Microsoft Excel 2016, and simulated by Monte Carlo microsimulation run by macros written in Visual Basic by the authors. Both one-way and probabilistic sensitivity analysis (PSA) were made, and the results presented by tornado diagram and comparative table (base case vs. PSA), respectively.

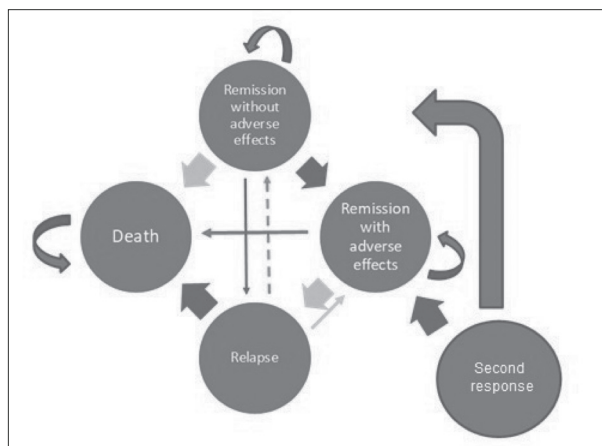


Figure 1. Graphic representation of the Markov model used in the study, with health states and possible transitions

Table 1. Values of input variables for Markov model used in the study, both for the base case and probability sensitivity analysis

Variable	Base-case value	PSA – distribution used and parameter values	Reference
Treatment response rate of second episode of schizophrenia	0.53	Beta distribution $\alpha = 53, \beta = 47$	[19]
Three-month probability of relapse in patients taking aripiprazole	0.0473	Beta distribution $\alpha = 5, \beta = 95$	[19]
Three-month probability of extrapyramidal syndrome in patients taking aripiprazole	0.0325	Beta distribution $\alpha = 3, \beta = 97$	[19]
Three-month probability of metabolic syndrome in patients taking aripiprazole	0.0025	Beta distribution $\alpha = 0.25, \beta = 99.75$	[19]
Three-month mortality rate in patients taking aripiprazole	0.0088	Beta distribution $\alpha = 0.88, \beta = 99.12$	[20]
Three-month probability of treatment response with clozapine	0.401	Beta distribution $\alpha = 40.1, \beta = 59.9$	[21]
Three-month probability of extrapyramidal syndrome in patients taking clozapine	0.0368	Beta distribution $\alpha = 3.7, \beta = 96.3$	[22]
Three-month probability of metabolic syndrome in patients taking clozapine	0.0049	Beta distribution $\alpha = 0.49, \beta = 99.51$	[23]
Three-month probability of neutropenia in patients taking clozapine	0.0021	Beta distribution $\alpha = 0.21, \beta = 99.79$	[23]
Three-month mortality rate in patients taking olanzapine or clozapine	0.004	Beta distribution $\alpha = 0.4, \beta = 99.6$	[20]
Utility of schizophrenia remission	0.919	Beta distribution $\alpha = 92, \beta = 8$	[24]
Utility of schizophrenia relapse	0.604	Beta distribution $\alpha = 60.4, \beta = 39.6$	[24]
Utility decrease due to metabolic syndrome	0.132	Beta distribution $\alpha = 13.2, \beta = 86.8$	[24]
Utility decrease due to extrapyramidal syndrome	0.256	Beta distribution $\alpha = 25.6, \beta = 74.4$	[24]
Costs of hospitalization	52,465.28 RSD	Gamma distribution $\alpha = 16, \beta = 3279.08$	[25]
Costs of daily treatment with olanzapine (5–20 mg daily)	25–122 RSD	Gamma distribution $\alpha = 16, \beta = 5.87$	[26]
Costs of three-months treatment of stable schizophrenia	5,693.14 RSD	Gamma distribution $\alpha = 16, \beta = 335.82$	[10, 25]
Costs treating relapse of schizophrenia for three months	11,142.43 RSD	Gamma distribution $\alpha = 16, \beta = 696.40$	[10, 25]
Costs of daily therapy with aripiprazole (15 mg)	54.68 RSD	Gamma distribution $\alpha = 16, \beta = 3.42$	[27]
Costs of daily therapy with clozapine (200–400 mg)	35–70 RSD	Gamma distribution $\alpha = 16, \beta = 3.25$	[28]
Costs of treating neutropenia	53,000.99 RSD	Gamma distribution $\alpha = 16, \beta = 3.312.56$	[29]
Three-month relapse rate of schizophrenia with olanzapine	2.28%	Beta distribution $\alpha = 2, \beta = 98$	[30]
Costs of one day of hospitalization at general ward	1,545.40 RSD	Administratively regulated	[10]
Costs of the first visit to a specialist	284.01 RSD	Administratively regulated	[10]
Costs of the first visit to a general practitioner	356.44 RSD	Administratively regulated	[10]
Cost of repeated visit to a specialist	186.98 RSD	Administratively regulated	[10]
Costs of repeated visit to a general practitioner	259.49 RSD	Administratively regulated	[10]
Costs of taking blood sample	105.33 RSD	Administratively regulated	[10]
Blood count – price	287.95 RSD	Administratively regulated	[10]
Creatinine level in serum – price	235.15 RSD	Administratively regulated	[10]
AST or ALT level in serum – price	229.15 RSD	Administratively regulated	[10]
ECG – price	600.00 RSD	Administratively regulated	[10]

PSA – probabilistic sensitivity analysis; ECG – electrocardiography; AST – aspartate transaminase; ALT – alanine transaminase

RESULTS

Base case

Values of input parameters for Markov model used in the study, both for the base case and probability sensitivity analysis, are shown in the Table 1. Base case Monte Carlo microsimulation for 1,000 virtual patients treated by aripiprazole gave the following results:

1. average cost per patient for 10 years was 428,082.91 ± 4,755.66 RSD (99% CI);
2. average number of quality-adjusted life years (QALYs) gained 6.82 ± 0.04.

Based on the same simulation, for patients treated by olanzapine:

1. average cost per patient for 10 years was 426,213.49 ± 4,186.63 RSD (99% CI);
2. average number of QALYs gained 7.43 ± 0.03.

When aripiprazole was compared with olanzapine, incremental cost/effectiveness ratio (ICER) per one more QALY gained was 131,417.69 ± 127,548.34 RSD (99% CI), while monetary net benefit was negative, -390,341.96 ± 29,131.53 RSD (99% CI). Figure 2 presents ICER for each virtual patient separately, and Figure 3 presents the average ICER for the whole cohort, with 99%-confidence interval. X- and y-axes of both figures measure difference in effects and difference in costs, respectively, of the two therapeutic alternatives, aripiprazole and olanzapine. In order to be cost/effective in comparison with olanzapine, virtual patients on these graphs should be in the lower-right quadrant or below the lines shown on the graphs that pass through origin of the coordinates (axes). From Figure 3, one may learn that the majority of ICER values is above the lines that reflect RFHI's willingness to pay for one more QALY gained with new drug (aripiprazole) in comparison with the old one (olanzapine). The lines presented are lambda 1 (one GDP per capita per QALY gained), lambda 2 (three GDP per capita per QALY gained) and lambda 3 (nine GDP per capita per QALY gained).

Acceptability curve

The acceptability curve shows dependence of probability that aripiprazole is cost/effective (in comparison with olanzapine) on amount that NHIF is willing to pay for one more QALY gained with aripiprazole (again in comparison with olanzapine). If willingness of NHIF to pay for one more QALY gained ranges from 200,000 RSD to 20,000,000 RSD, changes in percentage of virtual patients from Monte Carlo simulation who fall below current willingness to pay line in ICER diagram (i.e. the probability that aripiprazole is cost/effective in comparison to olanzapine) could be read from the acceptability curve. From Figure 4 one may see that the probability of aripiprazole being cost/effective is about 13% only if the NHIF is willing to pay one to nine GDPs per capita for a QALY gained (634,156 RSD).

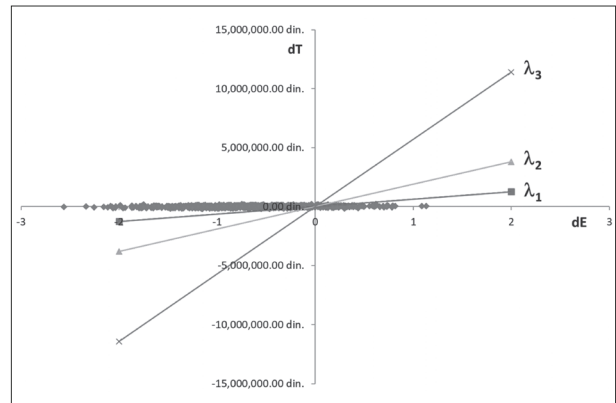


Figure 2. Base case incremental cost/effectiveness ratio for each virtual patient in the model: long-term treatment of schizophrenia with aripiprazole vs. olanzapine; the effect is on the scale marked as number of quality-adjusted life years gained

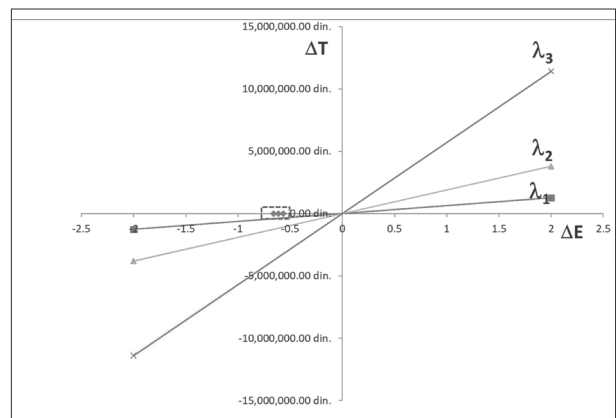


Figure 3. Base case average incremental cost/effectiveness ratio with 99% confidence intervals: long-term treatment of schizophrenia with aripiprazole vs. olanzapine; the effect is on the scale marked as number of quality-adjusted life years gained

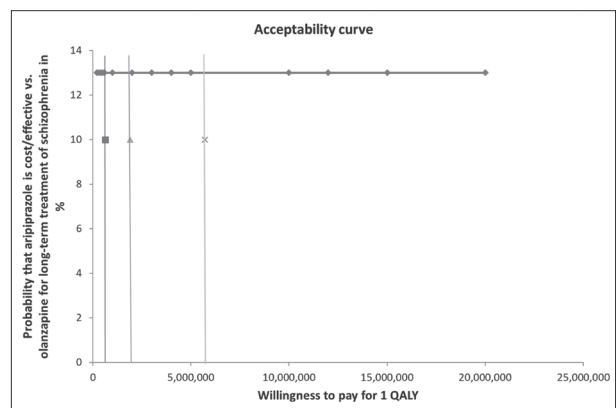


Figure 4. Acceptability curve

Red vertical line – one gross domestic product per capita for a quality-adjusted life year gained; green vertical line – three gross domestic products per capita for a quality-adjusted life year gained; yellow vertical line – nine gross domestic products per capita for a quality-adjusted life year gained
QALY – quality-adjusted life year

One-way sensitivity analysis

Within the framework of one-way sensitivity analysis values of input variables were varied $\pm 50\%$ one by one, and net monetary benefit calculated for each of the varied values. Results of the analysis are shown only for four the most influential variables (for the sake of clarity) in the tornado diagram (Figure 5). One-way sensitivity analysis showed that varying values of input variables did not change results of the cost/utility analysis, since net monetary benefit remained negative even with the extreme input values.

Probabilistic sensitivity analysis

For the PSA, values of the input variables were replaced with distributions, beta distribution being used for rate and utility variables, and gamma distribution for cost variables. After Monte Carlo microsimulation, more dispersed values of output variables were recorded, and their means with 99% confidence intervals are presented in Table 2. With supra-threshold value of ICER and negative value of net monetary benefit, the PSA confirmed that aripiprazole was not cost/effective when compared with olanzapine for long-term treatment of schizophrenia.

DISCUSSION

The efficiency of olanzapine and aripiprazole in the treatment of schizophrenia has already been tested and proved in randomized controlled clinical trials. However, although both of them belong to the group of atypical antipsychotics, they have different pharmacoeconomic profiles that need to be compared in every single socioeconomic environment individually. There have been numerous cost/effectiveness analyses done worldwide with the aim of comparing olanzapine and aripiprazole, but none of them was made in the Southeast European settings. According to our model, after base-case analysis, aripiprazole was dominated by olanzapine, as net monetary benefit was negative and incremental cost/effectiveness ratio (ICER) was above the willingness-to-pay line of one Serbian GDP per capita per QALY gained. The results of our model show that olanzapine has more beneficial cost/effectiveness ratio than aripiprazole for long-term treatment of schizophrenia in Serbian milieu. Multiple one-way and probabilistic sensitivity analysis confirmed results of the base case simulation.

According to the study by Furiak et al. [12], in the United States, where olanzapine has been compared with other oral antipsychotics in the treatment of schizophrenia, it was proved to be the most cost-effective treatment strategy, not only in relation to aripiprazole, but to risperidone, quetiapine and ziprasidone as well. In another model done in the United States, olanzapine was also the dominant cost/effective choice in the treatment of schizophrenia, due to its higher efficiency and lower cost of treatment compared to aripiprazole [13]. Our results are in accordance with the

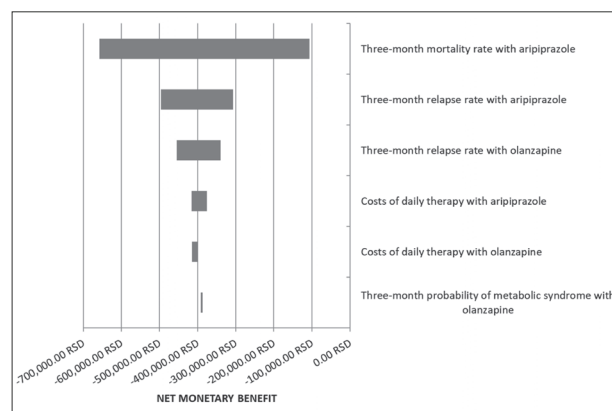


Figure 5. Tornado diagram

Table 2. Values of output variables before and after probabilistic sensitivity analysis (mean \pm 99% CI)

Output variables	Base case	PSA
Costs of aripiprazole treatment per patient	428,082.91 \pm 4,755.66 RSD	435,072.79 \pm 11,077.85 RSD
Costs of olanzapine treatment per patient	426,213.49 \pm 4,186.63 RSD	430,481.08 \pm 9,273.21 RSD
QALYs gained with aripiprazole	6.82 \pm 0.04	6.95 \pm 0.08
QALYs gained with olanzapine	7.43 \pm 0.03	7.51 \pm 0.07
ICER	131,417.69 \pm 127,548.34 RSD	102,750.08 \pm 176,564.03 RSD
Net monetary benefit	-390,341.96 \pm 29,131.53 RSD	-359,894.06 \pm 58,321.83 RSD

PSA – probabilistic sensitivity analysis; QALYs – quality-adjusted life years; ICER – incremental cost/effectiveness ratio

conclusion of the study from Singapore, where olanzapine also proved to be more cost/effective antipsychotic than aripiprazole [14]. The same conclusion about the superiority of a pharmacoeconomic profile of olanzapine was reached in the study by Obradovic et al [15], the focus of which was compliance rate, rehospitalization rate for compliant and non-compliant patients, duration and frequency of hospitalization, and adverse event rate.

On the contrary, economic evaluation of aripiprazole and olanzapine in Italy has shown medical and economic advantage of aripiprazole over olanzapine, in terms of reduced incidence of metabolic syndrome and diabetes, and lower treatment costs [16]. Moreover, according to a cost/effectiveness analysis done in Sweden, with the patients treated with aripiprazole, there was a significantly lower risk of the development of metabolic syndrome, diabetes of cardiovascular morbidity and mortality, which confirmed that there is a superiority of the pharmacoeconomic profile of aripiprazole over olanzapine [17]. In the study with adolescents (15–17-year-olds) in England, aripiprazole was shown to be cost/effective treatment option compared to olanzapine [18].

The differences in cost/effectiveness estimate of aripiprazole vs. olanzapine may probably be attributed to different methods of cost estimation (some of the studies did not take into account all costs incurred by adverse effects of the drugs compared), to variations in socioeconomic milieus, and to variations in adherence rate, as well. In addition,

period covered by the models used in these studies varied, which could support the thesis that in some of these studies period covered by the model was not long enough to capture the long term outcomes in the treatment of schizophrenia. In general, the studies did not account for patient heterogeneity, which implies that different subpopulations of patients were used in various studies.

Our study also has certain limitations, which are in the first place related to source of the cost data. Since we lacked data from patient files and database of the NHIF, the costs of health states were estimated from published resource utilization studies, multiplying presented figures with unit costs set by the NHIF. Estimate of costs based on such method is certainly less reliable than from actual data, but we tried to offset this by wide distributions of cost estimates used in the PSA. Another limitation was certainly imposed by pooling all types of schizophrenia into one population, while there could have been important differences which became obtunded, i.e. some schizophrenia types could have been more responsive to one than another drug, and *vice versa*.

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CONCLUSION

According to this study, olanzapine has more beneficial cost/effectiveness ratio than aripiprazole in long-term treatment of schizophrenia in the Serbian milieu. Treatment with aripiprazole is less effective and somewhat more expensive than treatment with olanzapine, therefore probability of being cost/effective in comparison to olanzapine is less than 15%. Sensitivity analysis shows that variation of input parameters over full range of possible values does not improve estimate of aripiprazole's cost/effectiveness.

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Однос трошкова и ефикасности арипипразола насупрот оланзапину код дуготрајног лечења шизофреније

Александра Дутина¹, Ивана Сташевић-Карличић^{1,2}, Никола Пандрџ³, Анђелка Прокић⁴, Слободан М. Јанковић⁴

¹Клиника за психијатријске болести „Др Лаза Лазаревић“, Београд, Србија;

²Универзитет у Приштини – Косовска Митровица, Медицински факултет, Косовска Митровица, Србија;

³Министарство здравља Републике Србије, Београд, Србија;

⁴Универзитет у Крагујевцу, Факултет медицинских наука, Крагујевац, Србија

САЖЕТАК

Увод/Циљ Мада је ефикасност атипичних антипсихотика код болесника који болују од шизофреније углавном слична, постоје значајне разлике код стопе нежељених реакција и трошкова лечења, што чини поређење односа њихових трошкова и ефикасности кључним за најбољи избор лека. Циљ ове студије је био да се упореде трошак и ефекти арипипразола и оланзапина код дуготрајног лечења шизофреније.

Метод Урађен је модел по Маркову са тромесечним циклусима и четири стања, да би се упоредили арипипразол и оланзапин. Модел је подразумевао да болесници код којих дође до погоршања здравственог стања после употребе или арипипразола или оланзапина буду даље лечени клозапином. Изабран је став Републичког фонда за здравствено осигурање, а временски оквир је био десет година. Резултати

модела су добијени после микросимулације Монте Карло на узорку од 1000 виртуелних болесника. Урађене су мултипла једносмерна и пробабилистичка анализа сензитивности.

Резултати После анализе случајева оланзапин је био доминантан у односу на арипипразол, јер је нето монетарна корист била негативна (-390,341.96 ± 29,131.53 РСД), а прираштај односа исплативости изнад линије спремности да се плати за једну годину кориговану за квалитет у односу на српски бруто домаћи производ по глави становника. Мултипла једносмерна и пробабилистичка анализа сензитивности су потврдиле резултате симулације.

Закључак Дугорочна терапија болесника са шизофренијом у Србији помоћу оланзапина је јефтинија и нешто делотворнија од терапије арипипразолом.

Кључне речи: арипипразол; оланзапин; трошак/ефикасност анализа; Марковљев модел