СРПСКИ АРХИВ
ЗА ЦЕЛОКУПНО ЛЕКАРСТВО
SERBIAN ARCHIVES
OF MEDICINE

Address: 1 Kraljice Natalije Street, Belgrade 11000, Serbia
☏ +381 11 4092 776, Fax: +381 11 3348 653
E-mail: office@srpskiarhiv.rs, Web address: www.srpskiarhiv.rs

Paper Accepted*

ISSN Online 2406-0895

Original Article/ Оригинални рад

Aleksandra Dutina[1], Ivana Stašević-Karličić[1,2], Nikola Pandrc[3], Anđelka Prokić[4], Slobodan M. Janković[4,†]

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

Однос трошкова и ефикасности ариприпразола насупрот оланзапину код дуготрајног лечења схизофреније

[1]Dr. Laza Lazarević Clinic for Mental Disorders, Belgrade, Serbia;
[2]University of Priština – Kosovska Mitrovica, Faculty of Medicine, Kosovska Mitrovica, Serbia;
[3]Ministry of Health of the Republic of Serbia, Belgrade, Serbia;
[4]University of Kragujevac, Faculty of Medical Sciences, Kragujevac, Serbia

Received: October 12, 2018
Revised: January 18, 2019
Accepted: May 27, 2019
Online First: June 19, 2019
DOI: https://doi.org/10.2298/SARH181012065D

*__Accepted papers__ are articles in press that have gone through due peer review process and have been accepted for publication by the Editorial Board of the *Serbian Archives of Medicine*. They have not yet been copy edited and/or formatted in the publication house style, and the text may be changed before the final publication.

Although accepted papers do not yet have all the accompanying bibliographic details available, they can already be cited using the year of online publication and the DOI, as follows: the author's last name and initial of the first name, article title, journal title, online first publication month and year, and the DOI; e.g.: Petrović P, Jovanović J. The title of the article. Srp Arh Celok Lek. Online First, February 2017.

When the final article is assigned to volumes/issues of the journal, the Article in Press version will be removed and the final version will appear in the associated published volumes/issues of the journal. The date the article was made available online first will be carried over.

†**Correspondence to:**
Slobodan M. JANKOVIĆ
University of Kragujevac, Faculty of Medical Sciences, Svetozara Markovića 69, 34000 Kragujevac, Serbia
E-mail: **nensi.lalic@mf.uns.ac.rs**

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

Однос трошкова и ефикасности ариприпразола насупрот оланзапину код дуготрајног лечења схизофреније

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 either aripiprazole and olanzapine are further treated with clozapine. The perspective of Republic 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 were 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 1 Serbian gross national product per capita per quality-adjusted life (QALY) year 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

САЖЕТАК

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

Методи Урађен је модел по Маркову са тромесечним циклусима и четири стања, да би се упоредили ариприпразол и оланзапин. Модел је подразумевао да пацијенти код којих дође до погоршања здравственог стања после употребе или ариприпразола 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 Монте Карло микросимулације на узорку од 1000 виртуелних пацијената. Урађене су мултипла једносмерна и пробабилистичка анализа сензитивности.

Резултати Након анализе случајева оланзапин је био доминантан у односу на ариприпразол, јер је нето монетарни бенефит био негативан (-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 пацијената са схизофренијом у Србији помоћу оланзапина је јефтинија и нешто делотворнија од терапије ариприпразолом.

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

INTRODUCTION

Schizophrenia is a chronic, hard 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 a behaviour dangerous for themselves or the others, endangering their personal relationships, their education or their employment status, relapse also leads to rehospitalizations, which significantly increases the cost of treatment. According to various studies, from 20 to more than 90% of the patients with the first episode of schizophrenia are relapsed within 2 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 5HT2A receptors. Thisdrugwas 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 sedative antipsychotic, which often leads to increase in both body weight and cardiometabolic risk. On the other hand, aripiprazole is not sedative, leads to almost no increase in either body weight or cardiometabolic risk, and it does not cause the appearance of metabolic syndrome (insulin resistency, dislipidemia, increased level of triglycerides), but in some patients it could cause a slight agitation, akathisia or problems with the control of impulses. As far as the efficiency of these two antipsychotics is concerned, some researches have shown that there were no differences, while others favoured olanzapine [6].

If we take into consideration limited efficiency of antipsychotics, which is often closely related to the termination of the treatmen, relapses and rehospitalizations, and thus, increases the treatment costs, it is obvious that we need to evaluate a cost effectiveness profile of antipsychotics to be able to make an adequate choice of antipsychotics for the treatment of schizophrenia while being in accordance with the financial reality of the health system. 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 haven't been any cost/effectiveness or cost/utility studies that would compare olanzapine and aripiprazole (two atypical antipsychotics currently highly utilized for treatment of scizophrenia) in the health and economic milieu of the countries of Southeast 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 with olanzapine for long-term treatment of patients with schizophrenia. Markov model owe its name to Andrey Andreyevich Markov (1856 – 1922), Russian mathematician who first described chronic processes (like schozophrenia is) through chain of interconnected states. 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 sex residing in Serbia who are in the second epizode schizophrenia (any type), and are about to receive for the second-line treatment with oral antipsychotics. The population chosen was that for which both aripiprazole and olanzapine received approved indication: treatment of schizophrenia in adults and in adolescents aged 15 years and older. The setting for the analysis was healthcare system of Republic of Serbia, which consists of state-owned health care facilities and is funded by Republic Health Insurance Fund (RHIF), based on obligatory health insurance contributions from all employed adults in Serbia. Prices of drugs and health care services are controled by RHIF and Government of Republic of Serbia.

The perspective for this economic analysis was that of the RHIF, 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 daily, and olanzapine 5-20 mg once daily, 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 Referrent annual interest rate

of National Bank of Serbia [8]. The main outcome of the study were 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 ot 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 RHIF through its legal acts [9, 10] or when unavailable, taken from producers. The dates of estimated resource quantities depended on the dates of published studies, but as a rule, the most recent studies were favored; the unit costs were taken for year 2018. All costs were reported in Serbian dinars (RSD).

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 (remission without adverse effects, remission with adverse effects, relapse, 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) and death, according to descriptions of natural course of the disease [11], and 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. 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 comparatory table (base case *vs.* PSA), respectively.

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 1000 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) and (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) and (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 was131,417.69 ± 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 the Figure 3, one may learn that 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 RHIF is willing to pay for one more QALY gained with aripiprazole (again in comparison with olanzapine). If willingness of RHIF 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. probability that aripiprazole is cost/effective in comparison to olanzapine) could be read from the acceptability curve. From the Figure 4 one may see that probability of aripiprazole being cost/effective is about 13% only if the RHIF is willing to pay one to nine GDPs per capita for a QALY gained (634.156 RSD).

One-way sensitivity analysis

Within the framework of one-way sensitivity analysis values of input variables were varied ± 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 most 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 the Table 2. With supra-treshold 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 aripripazole 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 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 1 Serbian gross national product per capita per quality-adjusted life (QALY) year 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, 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 risperidon, quetiapine and ziprasidone, as well [12]. In another model done in the United States as well, olanzapine was also 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 conclusion of the study from Singapore, too, where olanzapine also proved to be more cost/effective antipsychotic than aripiprazole [14]. The same conclusion about the superiority of a pharmacoeconimic profile of olanzapine was reached in the study by Obradovic et al, the focus of which was compliance rate, rehospitalization rate for compliant and non-compliant patients, duration and frequency of hospitalization, and adverse event rate [15].

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 years of age) 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, e.g.), 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 wasn't long enough to capture the long term outcomes in the treatment of schizophrenia. In general, the studies did not account for patient heterogeneity, which imply 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 the patient files and database of the RHIF, the costs of health states were estimated from published resource utilization studies, multiplying presented figures with unit costs set by the RHIF. 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.

CONCLUSION

According to this study, olanzapine has more beneficial cost/effectiveness ratio than aripiprazole for long-term treatment of schizophrenia in 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 arripiprazole's cost/effectiveness.

ACKNOWLEDGEMENT

The study was partially funded by grant No. 175007 given by the Ministry of Education, Science and Technological Development of the Republic of Serbia.

The authors comply with the International Committee of Medical Journal Editors recommendations.

Conflict of Interest: None declared.

REFERENCES

1. Simeone JC, Ward AJ, Rotella P, Collins J, Windisch R. An evaluation of variation in published estimates of schizophrenia prevalence from 1990─2013: a systematic literature review. BMC Psychiatry. 2015; 15:193. PMID: 26263900 DOI: 10.1186/s12888-015-0578-7
2. Zipursky RB, Menezes NM, Streiner DL. Risk of symptom recurrence with medication discontinuation in first-episode psychosis: a systematic review. Schizophr Res. 2014; 152(2–3):408–414. PMID: 23972821 DOI: 10.1016/j.schres.2013.08.001
3. Emsley R, Chiliza B, Asmal L, Harvey B. The nature of relapse in schizophrenia. BMC Psychiatry. 2013; 13:50. PMID: 23394123 DOI: 10.1186/1471-244X-13-50
4. Karson C, Duffy RA, Eramo A, Nylander AG, Offord SJ.Long-term outcomes of antipsychotic treatment in patients with first-episode schizophrenia: a systematic review.Neuropsychiatr Dis Treat. 2016; 12:57–67. PMID: 26792993 DOI: 10.2147/NDT.S96392
5. Santos A, Godói I, Vidal C, Ruas C. Economic evaluation of antipsychotics for the treatment of schizophrenia: a systematic review. J Bras Econ Saúde. 2017; 9:207–28. DOI: 10.21115/JBES.v9.n2.p207-28
6. Stahl SM. Prescriber's Guide: Stahl's Essential Psychopharmacology. 6 edition. Cambridge, United Kingdom ; New York, NY: Cambridge University Press; 2017. 890 p.
7. Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet Lond Engl. 2013; 14;382(9896):951–62. PMID: 23810019 DOI: 10.1016/S0140-6736(13)60733-3
8. NBS | Kamatne stope Narodne banke Srbije [Internet]. [cited 2018 Sep 9]. Available from: http://www.nbs.rs/internet/latinica/30/30_4/30_4_5/
9. Act regulating prices of laboratory services at primary, secondary and tertiary health care level. Offiicial Gazette of Republic of Serbia. 2014; 36(14).
10. Act regulating prices of healthcare services at secondary and tertiary healthcare level. Official Gazette of Republic of Serbia. 37/14. Official Gazette of Republic of Serbia. 2014;
11. Zeidler J, Mahlich J, Greiner W, Heres S. Cost effectiveness of paliperidone palmitate for the treatment of schizophrenia in Germany. Appl Health Econ Health Policy. 2013; 11(5):509–21. PMID: 23975630 DOI: 10.1007/s40258-013-0050-0
12. Furiak NM, Ascher-Svanum H, Klein RW, Smolen LJ, Lawson AH, Conley RR, et al. Cost-effectiveness model comparing olanzapine and other oral atypical antipsychotics in the treatment of schizophrenia in the United States. Cost Eff Resour Alloc CE. 2009; 7:4. PMID: 19351408 DOI: 10.1186/1478-7547-7-4
13. Ascher-Svanum H, Stensland MD, Peng X, Faries DE, Stauffer VL, Osuntokun OO, et al. Cost-effectiveness of olanzapine vs. aripiprazole in the treatment of schizophrenia. Curr Med Res Opin. 2011; 27(1):115–22. PMID: 21110749 DOI: 10.1185/03007995.2010.537594
14. Lin L, Zhao YJ, Zhou HJ, Khoo AL, Teng M, Soh LB, et al. Comparative cost-effectiveness of 11 oral antipsychotics for relapse prevention in schizophrenia within Singapore using effectiveness estimates from a network meta-analysis. Int Clin Psychopharmacol. 2016; 31(2):84–92. PMID: 26619182 DOI: 10.1097/YIC.0000000000000111
15. Obradovic M, Mrhar A, Kos M. Cost-effectiveness of antipsychotics for outpatients with chronic schizophrenia. Int J Clin Pract. 2007; 61(12):1979–88. PMID: 17997804 DOI: 10.1111/j.1742-1241.2007.01431.x
16. Colombo GL, Caruggi M, Di Matteo S, Rossi A. An economic evaluation of aripiprazole vs olanzapine adapted to the Italian setting using outcomes of metabolic syndrome and risk for diabetes in patients with schizophrenia. Neuropsychiatr Dis Treat. 2008; 4(5):967–76. PMID: 19183788 DOI: 10.2147/NDT.S5342
17. Kasteng F, Eriksson J, Sennfält K, Lindgren P. Metabolic effects and cost-effectiveness of aripiprazole versus olanzapine in schizophrenia and bipolar disorder. Acta Psychiatr Scand. 2011; 124(3):214–25. PMID: 21609324 DOI: 10.1111/j.1600-0447.2011.01716.x
18. L P, Dudley E, M L, Bentley A, McAllister R. The cost effectiveness of aripiprazole for the treatment of adolescents with schizophrenia. Eur Neuropsychopharmacol. 2010;20:S626. DOI: 10.1016/S0924-977X(10)70959-7

19. Tandon R, Marcus RN, Stock EG, Riera LC, Kostic D, Pans M, et al. A prospective, multicenter, randomized, parallel-group, open-label study of aripiprazole in the management of patients with schizophrenia or schizoaffective disorder in general psychiatric practice: Broad Effectiveness Trial With Aripiprazole (BETA). Schizophr Res. 2006; 84(1):77–89. PMID: 16483745 DOI: 10.1016/j.schres.2005.12.857
20. Schneider-Thoma J, Efthimiou O, Huhn M, Krause M, Reichelt L, Röder H, et al. Second-generation antipsychotic drugs and short-term mortality: a systematic review and meta-analysis of placebo-controlled randomised controlled trials. Lancet Psychiatry. 2018;5(8):653–63. PMID: 30042077 DOI: 10.1016/S2215-0366(18)30177-9
21. Siskind D, Siskind V, Kisely S. Clozapine Response Rates among People with Treatment-Resistant Schizophrenia: Data from a Systematic Review and Meta-Analysis. Can J Psychiatry Rev Can Psychiatr. 2017; 62(11):772–7. PMID: 28655284 DOI: 10.1177/0706743717718167
22. Fakra E, Azorin J-M. Clozapine for the treatment of schizophrenia. Expert Opin Pharmacother. 2012; 13(13):1923–35. PMID: 22803789 DOI: 10.1517/14656566.2012.709235
23. Inada K, Oshibuchi H, Ishigooka J, Nishimura K. Analysis of Clozapine Use and Safety by Using Comprehensive National Data From the Japanese Clozapine Patient Monitoring Service. J Clin Psychopharmacol. 2018; 38(4):302–6. PMID: 29912802 DOI: 10.1097/JCP.0000000000000904
24. Briggs A, Wild D, Lees M, Reaney M, Dursun S, Parry D, et al. Impact of schizophrenia and schizophrenia treatment-related adverse events on quality of life: direct utility elicitation. Health Qual Life Outcomes. 2008; 6:105. PMID: 19040721 DOI: 10.1186/1477-7525-6-105
25. Toševski DL, Vojislav Ćurčić, Grbeša G, Veronika Išpanović Radojković, Jović V, Gordana Kokora, et al. Protection of mental health in Serbia: challenges and solutions. Psihijatrija danas. 2005;37(1).
26. Olanzapine 5 mg tablets - Summary of Product Characteristics (SmPC) - (eMC) [Internet]. [cited 2018 Sep 11]. Available from: https://www.medicines.org.uk/emc/product/3071/smpc
27. Aripiprazole 10mg tablets - Summary of Product Characteristics (SmPC) - (eMC) [Internet]. [cited 2018 Sep 11]. Available from: https://www.medicines.org.uk/emc/product/3544/smpc
28. Clozaril 25mg and 100mg Tablets - Summary of Product Characteristics (SmPC) - (eMC) [Internet]. [cited 2018 Sep 11]. Available from: https://www.medicines.org.uk/emc/product/4411/smpc
29. Neupogen Singleject 30 MU (0.6 mg/ml) - Summary of Product Characteristics (SmPC) - (eMC) [Internet]. [cited 2018 Sep 11]. Available from: https://www.medicines.org.uk/emc/product/608/smpc
30. Detke HC, Weiden PJ, Llorca P-M, Choukour M, Watson SB, Brunner E, et al. Comparison of olanzapine long-acting injection and oral olanzapine: a 2-year, randomized, open-label study in outpatients with schizophrenia. J Clin Psychopharmacol. 2014;34(4):426–34.PMID: 24781441 DOI: 10.1097/JCP.0000000000000140

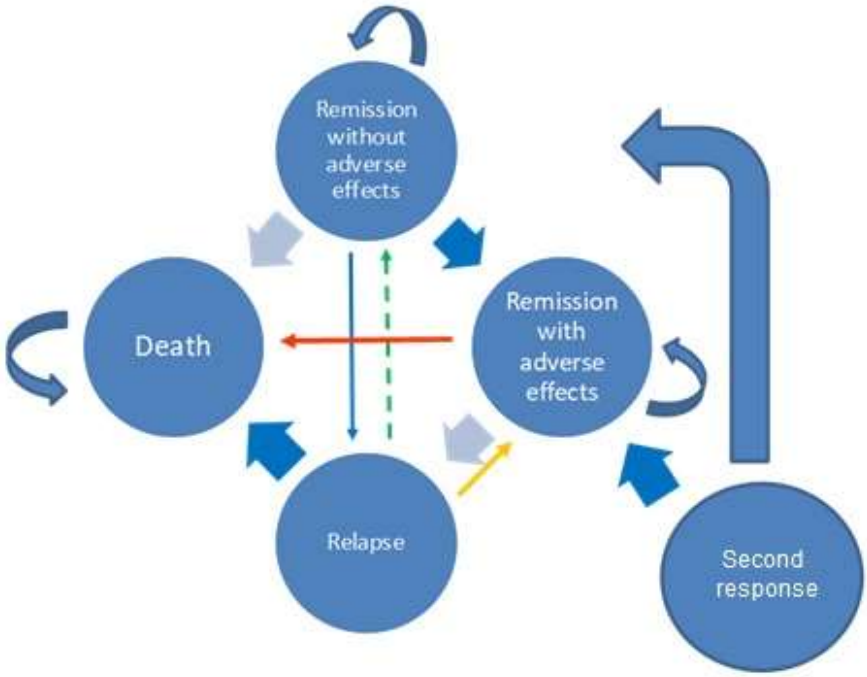

Figure 1. Graphic representation of the Markov model used in the study, with health states and possible transitions

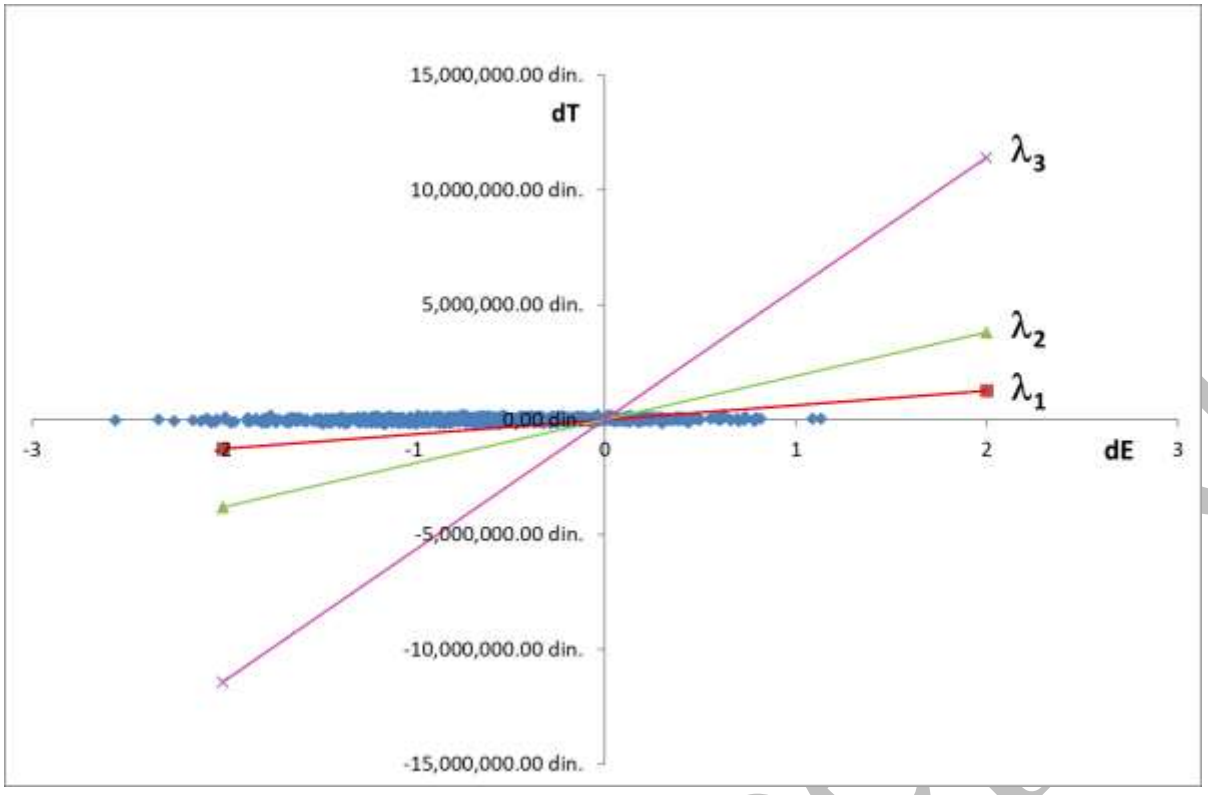

Figure 2. Base case incremental cost/effectiveness ratio for each virtual patient in the model: long-term treatment of schizophrenia with aripiprazole *vs.* olanzapine; the effect is on the scale marked as number of quality-adjusted life years gained

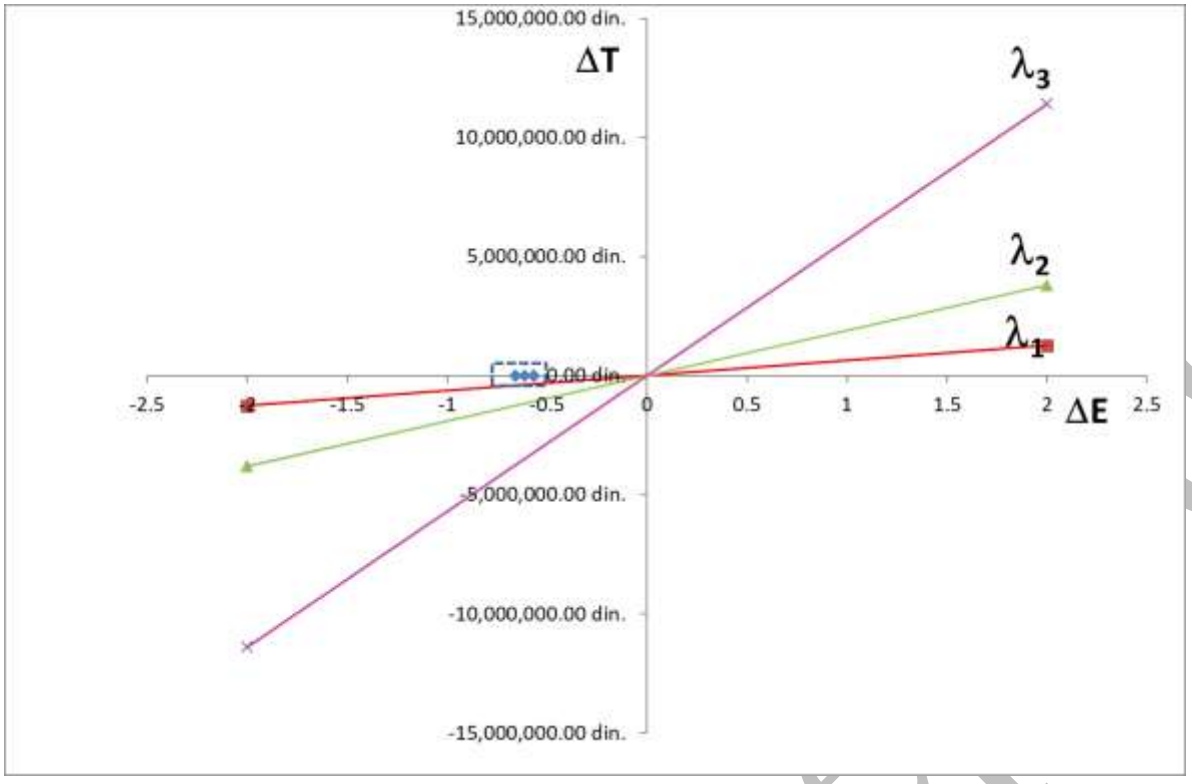

Figure 3. Base case average incremental cost/effectiveness ratio with 99% confidence intervals: long-term treatment of schizophrenia with aripiprazole *vs.* olanzapine; the effect is on the scale marked as number of quality-adjusted life years gained

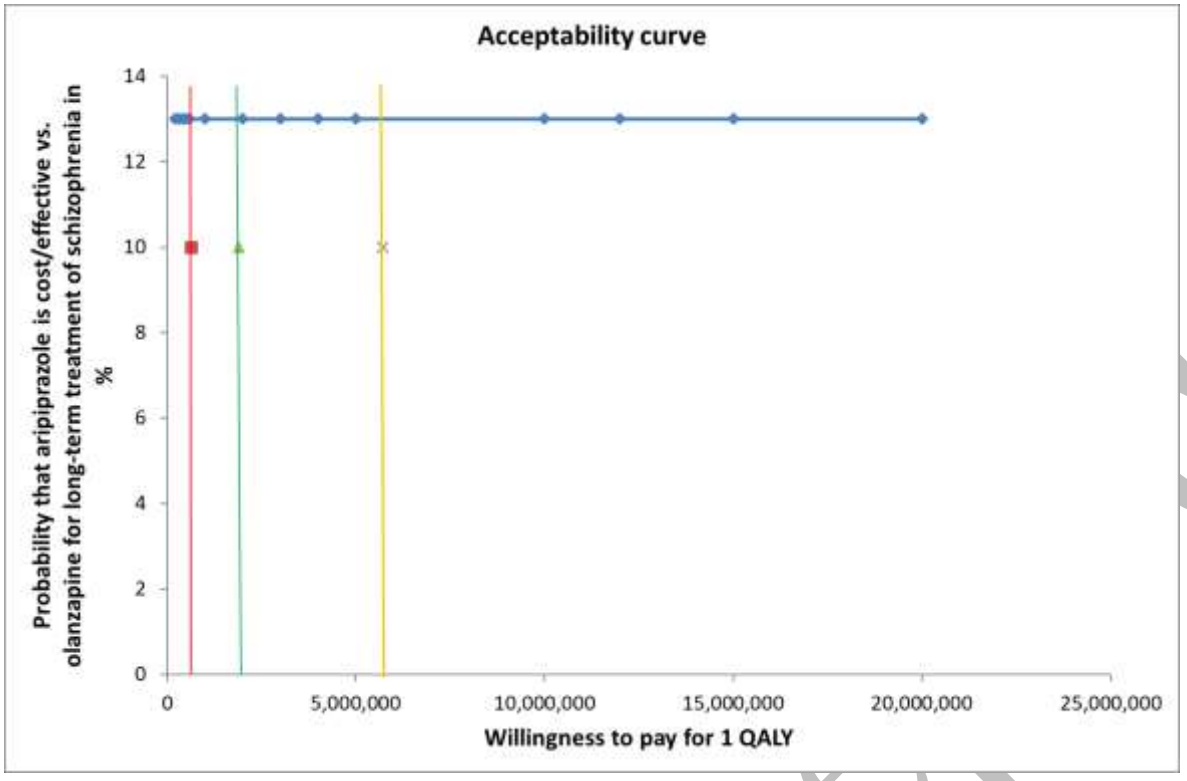

Figure 4. Acceptability curve

Red vertical line – one GDP/capita for a QALY gained; green vertical line – three GDPs/capita for a QALY gained; yellow vertical line – nine GDPs/capita for a QALY gained

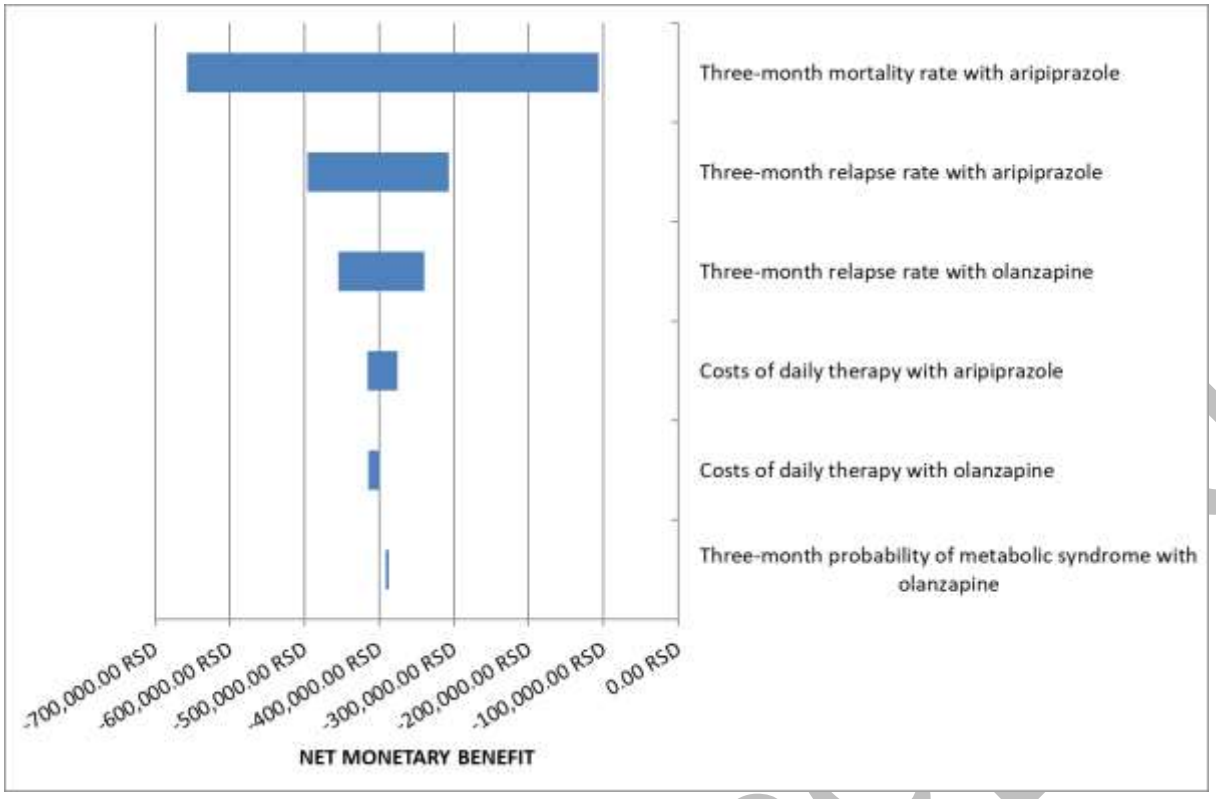

Figure 5. Tornado diagram

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 α=53, β=47	[19]
Three-month probability of relapse in patients taking aripiprazole	0.0473	Beta distribution α=5, β=95	[19]
Three-month probability of extrapyramidal syndrome in patients taking aripiprazole	0.0325	Beta distribution α=3, β=97	[19]
Three-month probability of metabolic syndrome in patients taking aripiprazole	0.0025	Beta distribution α=0.25, β=99.75	[19]
Three-month mortality rate in patients taking aripiprazole	0.0088	Beta distribution α=0.88, β=99.12	[20]
Three-month probability of treatment response with clozapine	0.401	Beta distribution α=40.1, β=59.9	[21]
Three-month probability of extrapyramidal syndrome in patients taking clozapine	0.0368	Beta distribution α=3.7, β=96.3	[22]
Three-month probability of metabolic syndrome in patients taking clozapine	0.0049	Beta distribution α=0.49, β=99.51	[23]
Three-month probability of neutropenia in patients taking clozapine	0.0021	Beta distribution α=0.21, β=99.79	[23]
Three-month mortality rate in patients taking olanzapine or clozapine	0.004	Beta distribution α=0.4, β=99.6	[20]
Utility of schizophrenia remission	0.919	Beta distribution α=92, β=8	[24]
Utility of schizophrenia relapse	0.604	Beta distribution α=60.4, β=39.6	[24]
Utility decrease due to metabolic syndrome	0.132	Beta distribution α=13.2, β=86.8	[24]
Utility decrease due to extrapyramidal syndrome	0.256	Beta distribution α=25.6, β=74.4	[24]
Costs of hospitalization	52,465.28 RSD	Gamma distribution α=16, β=3279.08	[25]
Costs of daily treatment with olanzapine (5-20 mg daily)	25–122 RSD	Gamma distribution α=16, β=5.87	[26]
Costs of 3-months treatment of stable schizophrenia	5,693.14 RSD	Gamma distribution α=16, β=335.82	[10, 25],

Costs treating relapse of schizophrenia for 3 months	11,142.43 RSD	Gamma distribution α=16, β=696.40	[10, 25]
Costs of daily therapy with aripiprazole (15mg)	54.68 RSD	Gamma distribution α=16, β=3.42	[27]
Costs of daily therapy with clozapine (200-400mg)	35–70 RSD	Gamma distribution α=16, β=3.25	[28]
Costs of treating neutropenia	53,000.99 RSD	Gamma distribution α=16, β=3.312.56	[29]
Three-month relapse rate of schizophrenia with olanzapine	2.28%	Beta distribution α=2, β=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

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

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

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

