

# Drug Consumption And Treatment Costs of The Glaucoma Therapy in The Republic of Serbia

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## SUMMARY

**Introduction:** Glaucoma is the leading cause of the irreversible blindness, affecting more than 70 million people worldwide. Drug therapy is the primary treatment for glaucoma due to its effectiveness, safety, practicality, and cost-effectiveness.

**Aim:** The aim of this study is the analysis of the consumption and costs of the medication therapy for glaucoma on a monthly and annual basis per patient in the Republic of Serbia in the period from 2015 to 2020.

**Material and Methods:** This study employs a retrospective analysis of data collected from the official websites of the Agency for Medicines and Medical Devices of Serbia and the Institute of Public Health of Serbia „Dr Milan Jovanovic Batut” for the period from 2015 to 2020. to examine the consumption and costs of antiglaucoma medicines in the Republic of Serbia.

**Results:** The data on the consumption of the local antiglaucoma therapy, as well as the price of monthly and annual therapy per patient in the period from 2015 to 2020 is shown. Drugs that are consumed the most were prostaglandin analogues (latanoprost) and beta-blockers (timolol). The most frequently prescribed among the fixed combinations were timolol-dorzolamide and timolol-latanoprost. The number of glaucoma patients fluctuated over a five-year period in the Republic of Serbia.

**Conclusion:** Based on the research, latanoprost is the most commonly used medicine in antiglaucoma therapy, followed by timolol and fixed combination of timolol-dorzolamide. Between 2015 and 2020, prices for all medications generally decreased and the most affordable choice was timolol.

**Keywords:** Glaucoma, Antiglaucoma Drugs, Consumption, Intraocular Pressure

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## INTRODUCTION

Glaucoma is the leading cause of blindness worldwide, with an estimated 70 million people affected by this disease. In 2020, 4.13 million people over the age of 50 had moderate to severe visual impairment, and 3.16 million people were blind due to glaucoma. That same year, glaucoma accounted for 11% of global blindness in the world in the population older than 50 years, so it is of great importance to influence the reduction of the prevalence of vision loss due to this disease. The prevalence of glaucoma is highest in people of African origin (6.5-7.3%), followed by the East Asian population (2.59-3.54%), while in Europe the prevalence is below 2%. In the US, Europe, and Australia, 75% to 95% of glaucoma in Caucasians is primary open-angle glaucoma. The largest number of glaucoma patients in Japan also have open-angle glaucoma, while angle-closure glaucoma is very rare in all populations [1-3].

Glaucoma is a group of progressive optic neuropathies characterized by degeneration of retinal ganglion cells and consequent changes in the optic nerve head. Ganglion cell loss is associated with intraocular pressure (IOP) levels, but other factors may also play a role [2,4]. It can be classified into open-angle glaucoma and angle-closure glaucoma, based on the condition of the angle of the anterior chamber. Each type is further divided into primary and secondary, depending on whether the cause that led to the glaucoma is known [2,5].

The most significant risk factor for the development of primary open-angle glaucoma is elevated intraocular pressure. Other risk factors include high myopia, eyes with wider and deeper physiological excavations, people with arterial hypotension and vasospastic changes in blood vessels, as well as members of the black race, are more likely to get sick [6]. For primary angle-closure glaucoma, contributing factors include a shallow anterior chamber, short axial length of the eye, increased lens thickness or forward displacement, and elevated IOP [6].

The primary goal of glaucoma therapy is to preserve sufficient visual function and the patient's quality of life. Key to achieving this is maintaining the target IOP, which is the highest value of intraocular pressure, which is expected to prevent further damage due to

glaucoma or slow the progression of the disease. The target pressure values are individual for each patient and depend on: the IOP value at the beginning of therapy, the stage of glaucoma, the degree of progression during follow-up, years of life and life expectancy, and the presence of other risk factors [1,7].

Drug therapy remains the mainstay of glaucoma treatment due to its effectiveness, safety, practicality, and affordability. At the onset of treatment, it is crucial to explain to the patient the importance of long-term, often life-long therapy and the potential possibility of blindness [1]. Most of these drugs are prescribed locally, in the form of eye drops [1]. The main drug classes used in glaucoma therapy include: adrenergic agonists, beta adrenergic blockers, carbonic anhydrase inhibitors, prostaglandin analogues, cholinergic drugs and hyperosmotic agents, as well as fixed combinations of these drugs [6, 8]. Fixed combinations of drugs are more suitable for use, have greater compliance and better tolerance compared to non-fixed combinations of drugs. They offer advantages such as reduced dosing frequency, minimized washout effects by reducing the number of eye drops, decreased exposure to preservatives and a lower overall number of medication bottles used [8].

## AIM

The aim of the research was to conduct a consumption and financial analysis of the use of anti-glaucoma drugs on the market of the Republic of Serbia in the period from 2015 to 2020 on a monthly and annual usage per patient. This analysis also takes into account the fact that local anti-glaucoma preparations are typically only viable for 28 days after opening the package.

## MATERIAL AND METHODS

This observational, retrospective, academic (non-commercial) phase IV study analyzes data collected from 2015 to 2020 to assess the consumption and costs of glaucoma medications in the Republic of Serbia. Data on consumption and prices of drugs for glaucoma therapy in the Republic of Serbia for five-year period were taken from the official website of the Medicines and Medical Devices Agency of Serbia – ALIMIS [9-25]. Data on glaucoma patients were taken from the official website of

| ATC (INN)                           | Pack<br>[ml] | Year                          |         |         |         |         |         |
|-------------------------------------|--------------|-------------------------------|---------|---------|---------|---------|---------|
|                                     |              | 2015                          | 2016    | 2017    | 2018    | 2019    | 2020    |
|                                     |              | Number of dispensed medicines |         |         |         |         |         |
| S01EA05 (brimonidine)               | 5            | 94,761                        | 113,881 | 128,420 | 143,756 | 172,107 | 174,308 |
|                                     | 10           | 14,476                        | 13,561  | 12,605  | 14,869  | 3,292   | 9,321   |
| S01EB01 (pilocarpine)               | 10           | 35,976                        | 31,155  | 8,988   | 8,107   | 7,455   | 6,385   |
| S01EC03 (dorzolamide)               | 5            | 21,269                        | 31,711  | 14,043  | 30,090  | 31,527  | 29,326  |
| S01EC04 (brinzolamide)              | 5            | 48,532                        | 66,388  | 63,229  | 9,838   | 77,240  | 69,680  |
| S01ED01 (timolol)                   | 5            | 317,023                       | 391,390 | 312,039 | 105,100 | 216,280 | 319,280 |
|                                     | 10           | 22,271                        | 18,798  | 19,187  | 11,756  | 2,727   | 5,927   |
| S01ED02 (betaxolol)                 | 5            | 3,239                         | 3,804   | 3,467   | -       | -       | -       |
| S01EE01 (latanoprost)               | 2.5          | 401,748                       | 310,189 | 317,103 | 373,474 | 399,317 | 405,373 |
| S01EE04 (travoprost)                | 2.5          | 20,713                        | 25,088  | 26,105  | 11,410  | 23,650  | 31,340  |
| S01EE03 (bimatoprost)               | 3            | 28,468                        | 42,465  | 53,753  | 61,568  | 49,411  | 43,640  |
| S01EE05 (tafluprost)                | 30x0.3       | 11,090                        | 13,406  | 19,065  | 37,498  | 57,300  | 65,812  |
| S01ED51 (timolol, bimatoprost)      | 3            | 27,669                        | 36,420  | 40,403  | 47,269  | 40,019  | 36,329  |
| S01ED51 (timolol, latanoprost)      | 2.5          | 41,411                        | 51,511  | 38,898  | 52,632  | 51,841  | 53,708  |
| S01ED51 (timolol, travoprost)       | 2.5          | 894                           | 752     | 1,966   | 60      | 6,750   | 10,530  |
| S01ED51 (timolol, dorzolamide)      | 5            | 343,393                       | 305,230 | 112,507 | 336,880 | 409,419 | 382,005 |
| S01ED51 (timolol, brinzolamide)     | 5            | 2,395                         | 5,826   | 31,306  | 7,940   | 52,945  | 59,540  |
| S01ED51 (timolol, brimonidine)      | 5            | -                             | 1,304   | 3,937   | 2,876   | 1,803   | 1,459   |
| S01EC54 (brimonidine, brinzolamide) | 5            | -                             | -       | -       | -       | 870     | 8,160   |

**Table 1.** Annual consumption of drugs in glaucoma therapy in the Republic of Serbia in the period 2015-2020.

the Institute for Public Health of Serbia „Dr. Milan Jovanović Batul” [26-31].

To analyze drug consumption, internationally recognized and widely accepted methodologies based on the concept of anatomical-therapeutic-chemical drug classification (ATC) and defined daily dose (DDD) were used. The consumption of finished pharmaceutical products is calculated using the DDD methodology according to the ATC classification, where DDD represents a statistical unit of measure of drug use, that is, the average daily dose of drug use in an adult that does not depend on the price, shape, size and packaging of the drug. Drug consumption is expressed as the number of packages used, and the results of this analysis are presented in tabular form in the „Results” section, alongside the costs of monthly and annual glaucoma therapy per patient [34].

For drugs like brimonidine (10 ml) and timolol (10 ml) the price of monthly therapy corresponds to the cost of one package, as all local anti-glaucoma medications must be discarded 28 days after opening the package [9, 10].

For other drugs, including bimatoprost (3 ml), tafluprost (30 x 0.3 ml), and the

fixed combination of timolol and bimatoprost (3 ml), the price of monthly therapy also reflects the cost of one package, as the amount of drug in one package corresponds to the monthly dosage.

For additional local anti-glaucoma preparations, the price of monthly therapy is calculated proportionally, in relation to the price of one package of a certain amount of medicine and the monthly consumption of that medicine.

## RESULTS

The annual consumption of all antiglaucoma drugs in the Republic of Serbia in the period from 2015-2020 is presented on the Table 1. For drugs that are not in fixed combinations, the highest consumption was of drug from the group of prostaglandin analogues (latanoprost), followed by drug from the group of beta blockers (timolol). On the other hand, betaxolol consumption was lowest, as well as brimonidine (10 ml bottle) and pilocarpine.

The most frequently used fixed combination of drugs was timolol-dorzolamide, while the least used were timolol-brimonidine and brimonidine-brinzolamide.

**Table 2.** Costs of glaucoma therapy with individual drugs per patient on a monthly and annual basis in the Republic of Serbia in the period 2015-2020

DDD - Defined daily dose  
MDC - Monthly drug consumption  
P - Package  
MT - Monthly treatment  
AT - Annually treatment  
\* - product with more than one marketing authorisation holder

| INN (pack)            | DDD | MDC (ml) | Price (RSD) | Year                 |                      |                      |                     |                     |                     |
|-----------------------|-----|----------|-------------|----------------------|----------------------|----------------------|---------------------|---------------------|---------------------|
|                       |     |          |             | 2015                 | 2016                 | 2017                 | 2018                | 2019                | 2020                |
| brimonidine (5 ml)    | 0.2 | 6        | P           | 639.80               | 639.80               | 639.80               | 568.50              | 563.57              | 563.57              |
|                       |     |          | 1 DDD       | 25.59                | 25.59                | 25.59                | 22.74               | 22.54               | 22.54               |
|                       |     |          | MT          | 767.76               | 767.76               | 767.76               | 682.2               | 676.28              | 676.28              |
|                       |     |          | AT          | 9,213.12             | 9,213.12             | 9,213.12             | 8,186.40            | 8,115.36            | 8,115.36            |
| brimonidine (10 ml)   | 0.2 | 6        | P           | 566.40               | 566.40               | 566.40               | 562.00              | 557.20              | 557.20              |
|                       |     |          | 1 DDD       | -                    | -                    | -                    | -                   | -                   | -                   |
|                       |     |          | MT          | 566.40               | 566.40               | 566.40               | 562.00              | 557.20              | 557.20              |
|                       |     |          | AT          | 6,796.80             | 6,796.80             | 6,796.80             | 4,744.00            | 6,686.40            | 6,686.40            |
| pilocarpine (12 ml)   | 0.4 | 12       | P           | 155.7                | 155.7                | 155.7                | 154.5               | 153.17              | 153.17              |
|                       |     |          | 1 DDD       | 6.23                 | 6.23                 | 6.23                 | 6.18                | 6.13                | 6.13                |
|                       |     |          | MT          | 186.84               | 186.84               | 186.84               | 185.4               | 183.8               | 183.8               |
|                       |     |          | AT          | 2,242.08             | 2,242.08             | 2,242.08             | 2,224.80            | 2,205.60            | 2,205.60            |
| dorzolamide (5 ml)*   | 0.3 | 9        | P           | 588.90; 464.40       | 588.90; 464.40       | 588.90; 464.40       | 584.30; 431.40      | 579.30; 427.70      | 579.30; 427.70      |
|                       |     |          | 1 DDD       | 35.33; 27.86         | 35.33; 27.86         | 35.33; 27.86         | 35.05; 25.88        | 34.75; 25.66        | 34.75; 25.66        |
|                       |     |          | MT          | 1,059.81; 835.75     | 1,059.81; 835.75     | 1,059.81; 835.75     | 1,051.53; 776.36    | 1,042.53; 769.71    | 1,042.53; 769.71    |
|                       |     |          | AT          | 13,917.72; 10,029.00 | 13,917.72; 10,029.00 | 13,917.72; 10,029.00 | 12,618.36; 9,316.32 | 12,510.36; 9,236.52 | 12,510.36; 9,236.52 |
| brinzolamide (5 ml)   | 0.2 | 6        | P           | 848.20               | 848.20               | 848.20               | 748.80              | 647.90              | 647.90              |
|                       |     |          | 1 DDD       | 33.93                | 33.93                | 33.93                | 29.95               | 25.92               | 25.92               |
|                       |     |          | MT          | 1,017.84             | 1 017.84             | 1 017.84             | 898.56              | 777.48              | 777.48              |
|                       |     |          | AT          | 12,214.08            | 12,214.08            | 12,214.08            | 10,782.72           | 9,329.76            | 9,329.76            |
| timolol (5 ml)        | 0.2 | 6        | P           | 242.00               | 242.00               | 242.00               | 240.10              | 237.97              | 237.97              |
|                       |     |          | 1 DDD       | 10.08                | 10.08                | 10.08                | 9.60                | 9.52                | 9.52                |
|                       |     |          | MT          | 302.40               | 302.40               | 302.40               | 288.12              | 285.56              | 285.56              |
|                       |     |          | AT          | 3,628.80             | 3,628.80             | 3,628.80             | 3,547.44            | 3,426.72            | 3,426.72            |
| timolol (10 ml)       | 0.2 | 6        | P           | 353.40               | 353.40               | 353.40               | 350.60              | 347.60              | 347.60              |
|                       |     |          | 1 DDD       | -                    | -                    | -                    | -                   | -                   | -                   |
|                       |     |          | MT          | 353.40               | 353.40               | 353.40               | 350.60              | 347.60              | 347.60              |
|                       |     |          | AT          | 4,240.80             | 4,240.80             | 4,240.80             | 4,207.20            | 4,171.20            | 4,171.20            |
| betaxolol (5 ml)      | 0.2 | 6        | P           | 270.40               | 270.40               | 270.40               | -                   | -                   | -                   |
|                       |     |          | 1 DDD       | 10.82                | 10.82                | 10.82                | -                   | -                   | -                   |
|                       |     |          | MT          | 324.48               | 324.48               | 324.48               | -                   | -                   | -                   |
|                       |     |          | AT          | 3,893.76             | 3,893.76             | 3,893.76             | -                   | -                   | -                   |
| latanoprost (2.5 ml)* | 0.1 | 3        | P           | 554.60; 638.40       | 554.60; 638.40       | 554.60; 638.40       | 530.10; 609.40      | 525.50; 604.10      | 525.50; 604.10      |
|                       |     |          | 1 DDD       | 22.18; 25.54         | 22.18; 25.54         | 22.18; 25.54         | 21.20; 24.38        | 21.02; 24.16        | 21.02; 24.16        |
|                       |     |          | MT          | 665.52; 766.08       | 665.52; 766.08       | 665.52; 766.08       | 636.12; 731.28      | 630.60; 724.92      | 630.60; 724.92      |
|                       |     |          | AT          | 7,986.24; 9,192.96   | 7,986.24; 9,192.96   | 7,986.24; 9,192.96   | 7,633.44; 8,775.36  | 7,567.20; 8,699.04  | 7,567.20; 8,699.04  |
| bimatoprost (3 ml)    | 0.1 | 3        | P           | 1,419.90             | 1,419.90             | 1,419.90             | 1,408.80            | 1,396.67            | 1,396.67            |
|                       |     |          | 1 DDD       | 47.33                | 47.33                | 47.33                | 46.96               | 46.55               | -                   |
|                       |     |          | MT          | 1,419.90             | 1,419.90             | 1,419.90             | 1,408.80            | 1,396.67            | 1,396.67            |
|                       |     |          | AT          | 17,038. 80           | 17,038. 80           | 17,038. 80           | 16,905.60           | 16,760.04           | 16,760.04           |

|                           |     |   |       |           |           |           |           |           |           |
|---------------------------|-----|---|-------|-----------|-----------|-----------|-----------|-----------|-----------|
| travoprost<br>(3 ml)      | 0.1 | 3 | P     | 1,464.20  | 1,464.20  | 1,464.20  | 1,122.20  | 1,018.50  | 1,018.50  |
|                           |     |   | 1 DDD | 58.57     | 58.57     | 58.57     | 44.89     | 40.74     | 40.74     |
|                           |     |   | MT    | 1,787.04  | 1,787.04  | 1,787.04  | 1,346.64  | 1,222.20  | 1,222.20  |
|                           |     |   | AT    | 21,084.48 | 21,084.48 | 21,084.48 | 16,159.68 | 14,666.40 | 14,666.40 |
| tafluprost<br>(30x0.3 ml) | 0.1 | 3 | P     | 1,657.50  | 1,657.50  | 1,657.50  | 1,644.60  | 1,631.87  | 1,631.87  |
|                           |     |   | 1 DDD | -         | -         | -         | -         | -         | -         |
|                           |     |   | MT    | 1,657.50  | 1,657.50  | 1,657.50  | 1,644.60  | 1,631.87  | 1,631.87  |
|                           |     |   | AT    | 19,890.00 | 19,890.00 | 19,890.00 | 19,732.20 | 19,582.44 | 19,582.44 |

A review of the costs of antiglaucoma drug therapy per patient on a monthly and annual basis in the Republic of Serbia over a five-year period (Table 2) reveals that latanoprost

is the drug with the lowest price for monthly and annual therapy. In addition, timolol also had a lower price compared to other drugs in glaucoma therapy. The price of the monthly

| INN<br>(pack)                          | DDD | MDC<br>(ml) | Price<br>(RSD) | Year                  |                       |                       |                       |                       |                       |
|----------------------------------------|-----|-------------|----------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
|                                        |     |             |                | 2015                  | 2016                  | 2017                  | 2018                  | 2019                  | 2020                  |
| timolol,<br>dorzolamide<br>(5 ml)*     | 0.2 | 6           | P              | 531.00;<br>638.40     | 531.00;<br>638.40     | 531.00;<br>638.40     | 526.90;<br>633.40     | 522.40;<br>629.37     | 522.40;<br>629.37     |
|                                        |     |             | 1 DDD          | 21.24;<br>25.54       | 21.24;<br>25.54       | 21.24;<br>25.54       | 21.08;<br>25.34       | 20.90;<br>25.17       | 20.90;<br>25.17       |
|                                        |     |             | MT             | 637.20;<br>766.08     | 637.20;<br>766.08     | 637.20;<br>766.08     | 632.28;<br>760.08     | 626.88;<br>755.24     | 626.88;<br>755.24     |
|                                        |     |             | AT             | 7,646.40;<br>9,192.96 | 7,646.40;<br>9,192.96 | 7,646.40;<br>9,192.96 | 7,587.36;<br>9,120.96 | 7,522.56;<br>9,062.88 | 7,522.56;<br>9,062.88 |
| timolol,<br>brinzolamide<br>(5 ml)     | 0.2 | 6           | P              | 1,187.40              | 1,187.40              | 1,187.40              | 1,178.10              | 1,168.00              | 1,168.00              |
|                                        |     |             | 1 DDD          | 47.50                 | 47.50                 | 47.50                 | 47.12                 | 46.72                 | 46.72                 |
|                                        |     |             | MT             | 1,424.88              | 1,424.88              | 1,424.88              | 1,413.72              | 1,401.60              | 1,401.60              |
|                                        |     |             | AT             | 17,098.56             | 17,098.56             | 17,098.56             | 16,964.64             | 16,819.20             | 16,819.20             |
| timolol,<br>latanoprost<br>(3 ml)*     | 0.1 | 3           | P              | 598.90                | 598.90;<br>638.40     | 598.90;<br>638.40     | 575.90;<br>628.00     | 575.90;<br>628.00     | 577.27;<br>628.00     |
|                                        |     |             | 1 DDD          | 23.96                 | 23.96;<br>25.54       | 23.04;<br>25.12       | 23.04;<br>25.12       | 23.04;<br>25.12       | 23.09;<br>25.12       |
|                                        |     |             | MT             | 718.68                | 718.68;<br>766.08     | 718.68;<br>766.08     | 691.08;<br>753.60     | 691.08;<br>753.60     | 692.72;<br>753.60     |
|                                        |     |             | AT             | 8,624.16              | 8,624.16;<br>9,192.96 | 8,624.16;<br>9,192.96 | 8,292.96;<br>9,043.20 | 8,292.96;<br>9,043.20 | 8,312.64;<br>9,043.20 |
| timolol,<br>bimatoprost<br>(3 ml)      | 0.1 | 3           | P              | 1,581.40              | 1,581.40              | 1,581.40              | 1,569.10              | 1,555.57              | 1,555.57              |
|                                        |     |             | 1 DDD          | -                     | -                     | -                     | -                     | -                     | -                     |
|                                        |     |             | MT             | 1,581.40              | 1,581.40              | 1,581.40              | 1,569.10              | 1,555.57              | 1,555.57              |
|                                        |     |             | AT             | 18,976.80             | 18,976.80             | 18,976.80             | 18,829.20             | 18,666.84             | 18,666.84             |
| timolol,<br>travoprost<br>(3 ml)       | 0.1 | 3           | P              | 1,695.80              | 1,695.80              | 1,695.80              | 1,682.60              | 1,493.10              | 1,493.10              |
|                                        |     |             | 1 DDD          | 67.83                 | 67.83                 | 67.83                 | 67.30                 | 59.72                 | 59.72                 |
|                                        |     |             | MT             | 2,034.96              | 2,034.96              | 2,034.96              | 2,019.12              | 1,791.72              | 1,791.72              |
|                                        |     |             | AT             | 24,419.52             | 24,419.52             | 24,419.52             | 24,229.44             | 21,500.64             | 21,500.64             |
| timolol,<br>brimonidine<br>(5 ml)      | 0.2 | 6           | P              | -                     | 1,175.00              | 1,175.00              | 1,165.80              | 1,155.57              | 1,155.57              |
|                                        |     |             | 1 DDD          | -                     | 47.00                 | 47.00                 | 46.63                 | 46.22                 | 46.22                 |
|                                        |     |             | MT             | -                     | 1,410.00              | 1,410.00              | 1,398.96              | 1,386.68              | 1,386.68              |
|                                        |     |             | AT             | -                     | 16,920.00             | 16,920.00             | 16,787.52             | 16,640.16             | 16,640.16             |
| brimonidine,<br>brinzolamide<br>(5 ml) | 0.2 | 6           | P              | -                     | -                     | -                     | -                     | 1,329.00              | 1,329.00              |
|                                        |     |             | 1 DDD          | -                     | -                     | -                     | -                     | 53.16                 | 53.16                 |
|                                        |     |             | MT             | -                     | -                     | -                     | -                     | 1,594.80              | 1,594.80              |
|                                        |     |             | AT             | -                     | -                     | -                     | -                     | 19,137.60             | 19,137.60             |

**Table 3.** Costs of glaucoma therapy with fixed drug combinations per patient on a monthly and annual basis in the Republic of Serbia in the period 2015-2020

DDD - Defined daily dose  
MDC - Monthly drug consumption  
P - Package  
MT - Monthly treatment  
AT - Annually treatment  
\* - product with more than one marketing authorisation holder

**Table 4.** The number of newly diagnosed glaucoma patients on an annual basis in the period 2015-2020. taken from the official website of the Institute for Public Health of Serbia „Dr. Milan Jovanović Batut”

| Year | The number of glaucoma patients |
|------|---------------------------------|
| 2015 | 45,669                          |
| 2016 | 48,819                          |
| 2017 | 45,545                          |
| 2018 | 49,506                          |
| 2019 | 50,604                          |
| 2020 | 42,726                          |

therapy of the fixed combination of timolol-dorzolamide as well as the combination of timolol-latanoprost was lower than the price of the monthly therapy of other drug combinations (Table 3).

According to data from the Institute for Public Health of Serbia „Dr. Milan Jovanović Batut” on the number of glaucoma patients in the Republic of Serbia between 2015 and 2020, an increase in the number of patients in 2016 is observed, and then a decrease in the number of patients in 2017. Another sharp increase in the number of patients during 2018 and 2019, and then a significant decrease in the number of patients during 2020, which is shown in Table 4.

## DISCUSSION

Glaucoma with all its consequences, is a significant problem today. It is crucial to identify patients with an increased risk of the disease and refer them to detailed ophthalmological examinations. Damage and loss of vision caused by glaucoma greatly reduces the patient's quality of life and performance of daily activities.

The use of local antiglaucoma preparations is the main form of glaucoma treatment and can adequately regulate IOP in most patients [1]. However, due to numerous side effects of local preparations, their use is limited.

According to the Terminology and guidelines of the European Glaucoma Society, prostaglandin analogues are recommended as the first line of therapy and are the most prescribed drug for the initial treatment of glaucoma in the United Kingdom, the United States of America, China, Australia and Japan [33-36]. As first-choice drugs, prostaglandin analogues have the least side effects, and they are local, which are manifested most often in the form of scratching, burning of the eye, increased pigmentation of the iris and eyelashes [8].

Timolol, a drug from group of the

adrenergic beta blockers, can rarely cause local side effects, however due to systemic side effects resulting from absorption through the conjunctiva or nasolacrimal system, it is contraindicated to patients with chronic obstructive pulmonary diseases, bradycardia and AV block [8,10].

Brimonidine often causes local side effects in the form of eye allergy and is contraindicated in infants, patients on therapy with monoamine oxidase inhibitors and tricyclic antidepressants [9]. Local carbonic anhydrase inhibitors are used as monotherapy in patients who are allergic to other drugs in glaucoma therapy, and their disadvantages are small effect of lowering IOP and dosing three times a day. Among side effects, they can cause dryness and eye irritation, burning sensation, blurred vision, polyuria and paraesthesias [13,14]. Pilocarpine is used less frequently in glaucoma treatment due to its systemic side effects, which result from increased parasympathetic stimulation. These side effects make the drug intolerable for some patients.

Based on the results of the conducted research, with reference to Tables 1-3, which present data on the consumption of medicines in glaucoma therapy in the time period of 2015-2020. in the Republic of Serbia, it is concluded that drugs from the group of prostaglandin analogues are the most frequently used, with latanoprost being the most common. Latanoprost also has the lowest monthly therapy price of all drugs from this group. According to the Table 2, the price of monthly therapy shows a slight decrease from 2015, when it amounted to 665.52-766.08 dinars, to 2020, when it amounted to 630.60-724.92 dinars. The frequency of use of these drugs is justified by the fact that prostaglandin analogues are precisely the drugs with the least side effects and the most convenient dosing regimen, because they are used only once a day, in the evening.

The second most commonly used drug in this period was timolol (Table 1), a drug from the group of beta-adrenergic blockers, with an average consumption of about 300,000 packs per year. The price of monthly therapy in 2015 was 302.40-353.40 dinars, depending on the milliliter size of the purchased package, and by 2020 the price of monthly therapy shows a slight decrease and amounts to 285.56-347.60 dinars (Table 2). Also, timolol has a convenient dosing regimen, twice a

day for 12 hours, and is well tolerated by patients, which, along with its low price, justifies the frequency of its use. In some developing countries, such as India, timolol is the most prescribed drug, with a share of up to 90% compared to other antiglaucoma drugs, but in the world, together with prostaglandin analogues, it represents the gold standard in glaucoma therapy [35, 37].

Of the fixed combinations of drugs, the timolol-dorzolamide combination had the highest consumption in the Republic of Serbia. The cost of monthly therapy ranged from 637.20-766.08 dinars in 2015, and by 2020 it will decrease to 626.88-755.24 dinars (Table 3). The consumption of the fixed combination of timolol and brinzolamide is significantly lower, with its cost nearly twice as high. However, comparative studies conducted in India, which compared the efficacy and safety of these two fixed drug combinations, show that the fixed combination of timolol and brinzolamide is a preferable and more effective therapeutic option in lowering IOP compared to the fixed combination of timolol and dorzolamide. Also, the fixed combination of timolol-brinzolamide causes fewer ocular side effects and is more comfortable to use [7, 8].

A significant increase in the consumption of fixed combinations of timolol with prostaglandin analogues was observed, particularly with the timolol-travoprost combination. The number of packages increased from 894 in 2015 to 10,530 in 2020. The increase in consumption was accompanied by a decrease in the price of the drug, which in 2015 amounted to 2034.96 dinars on a monthly basis, and in 2020 it amounted to 1791.72 dinars. Studies show that a fixed combination of travoprost and timolol is more effective in lowering IOP than a fixed combination of latanoprost and timolol. The average reduction of IOP in 24 hours in patients on therapy with the first combination was 2.6 mmHg, and in patients on therapy with the second combination was 2.2 mmHg. The mean value of IOP reduction compared to initial values for 12 weeks in patients on the first combination therapy was significantly higher ( $2.4 \pm 2.3$  mmHg) compared to the values in patients on the second combination therapy ( $1.1 \pm 2.3$  mmHg). No significant difference in the incidence of side effects was observed between patients using either of these two fixed combinations. A comparative study between the

fixed combinations of bimatoprost-timolol and travoprost-timolol showed a greater average reduction in IOP during the application of the first combination, namely 11.7 mmHg, compared to the reduction during the application of the second combination, which was 7.89 mmHg. However, another study conducted in patients in whom the fixed bimatoprost-timolol combination did not give a satisfactory effect showed an additional 16.5% reduction in IOP at week 8 after switching to the fixed travoprost-timolol combination therapy and 69.2% of patients achieved the target IOP, so this fixed combination of travoprost-timolol proved to be very effective and this justifies the increased frequency of prescription during the observed 5 years [8].

Brimonidine (bottle of 5 ml) follows in terms of consumption, with 94,761 packs sold in 2015 and 174,308 packs sold in 2020. The increase in brimonidine consumption was accompanied by a drop in the price of the drug, which amounted to 767.76 dinars in 2015, and 676.28 dinars in 2020, on a monthly basis. According to the results of comparative studies conducted in America, brimonidine is the drug that has shown the greatest effectiveness in lowering IOP after prostaglandin analogues and timolol. Also, research on the trend of prescribing drugs in Japan shows that the most prescribed drugs in the elderly population were prostaglandin analogues, adrenergic alpha-2 agonists and carbonic anhydrase inhibitors [35, 38].

On the other hand, local carbonic anhydrase inhibitors and pilocarpine are the least used IOP-lowering drugs according to these statistics, which is shown in tables 1 and 2, but this is supported by their unfavorable dosing method, several times a day, as well as numerous side effects of pilocarpine. Pilocarpine shows the biggest drop in consumption, from 2015, when 35,976 packages of the drug were sold, to 2020, when 6,385 packages were sold. According to British studies, carbonic anhydrase inhibitors and alpha-2 agonists are being considered as third-line glaucoma therapy, after prostaglandin analogues and beta-blockers. The declining prescription rates for pilocarpine are likely due to the increasing acceptance of newer drugs, such as alpha-agonists and carbonic anhydrase inhibitors, as confirmed by studies conducted in Australia [37, 39].

## CONCLUSION

Based on the above data and discussion, it is concluded that the highest consumption in the Republic of Serbia was recorded by latanoprost, followed by timolol and in third place a fixed combination of timolol and dorzolamide. In the five-year period, a downward trend in price was observed for each of the mentioned medicines. Of all medicines, brimonidine had the most pronounced drop in price and timolol was the most affordable one. The lowest monthly price of therapy, as well as the biggest drop in consumption was noticed on pilocarpine.

## CONFLICT OF INTEREST

All authors declare no conflict of interest.

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## Potrošnja lekova i troškovi lečenja u terapiji glaukoma u Republici Srbiji

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### KRATAK SADRŽAJ

**Uvod:** Glaukom je vodeći uzrok ireverzibilnog slepila, koji pogađa više od 70 miliona ljudi širom sveta. Zbog efikasnosti, bezbednosti, praktičnosti i niske cene, terapija lekovima predstavlja glavni vid lečenja glaukoma.

**Cilj:** Cilj ove studije je analiza potrošnje i troškova terapije lekovima za glaukom na mesečnom i godišnjem nivou po pacijentu u Republici Srbiji u periodu od 2015. do 2020. godine.

**Materijal i metode:** Metodologija istraživanja zasnovana je na retrospektivnoj analizi prikupljenih podataka za period od 2015. do 2020. godine sa zvaničnih sajtova Agencije za lekove i medicinska sredstva Srbije i Instituta za javno zdravlje Srbije „Dr. Milan Jovanović Batut” za ispitivanje potrošnje i troškova lekova u Republici Srbiji.

**Rezultati:** Prikazani su podaci o potrošnji lokalne antiglaukomske terapije, kao i cena mesečne i godišnje terapije po pacijentu u periodu od 2015. do 2020. godine. Lekovi koji su se najviše konzumirali bili su analozi prostaglandina (latanoprost) i beta-blokatori (timolol). Među fiksnim kombinacijama najčešće su propisivane timolol-dorzolamid i timolol-latanoprost. Broj obolelih od glaukoma je fluktuirao tokom petogodišnjeg perioda u Republici Srbiji.

**Zaključak:** Na osnovu istraživanja, latanoprost je najčešće korišćen lek u terapiji glaukoma, zatim timolol i fiksna kombinacija timolol-dorzolamid. Između 2015. i 2020. cene svih lekova su generalno opadale, a najpristupačniji izbor bio je timolol. Takođe, pilokarpin je imao najveće smanjenje potrošnje za petogodišnji period.

**Ključne reči:** glaukom, antiglaukomski lekovi, potrošnja, intraokularni pritisak

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