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- О ВОЗМОЖНОСТЯХ СОВМЕЩЕНИЯ АНАЛИЗА «ВЛИЯНИЯ НА БЮДЖЕТ» И АНАЛИЗА «ЗАТРАТЫ-ЭФФЕКТИВНОСТЬ» - СОЗДАНИЕ «3D» ФАРМАКОЭКОНОМИЧЕСКОЙ МОДЕЛИ
- ФАРМАКОЭКОНОМИКА САХАРНОГО ДИАБЕТА, РАКА ПОЧКИ, ПОСТИНСУЛЬТНОЙ СПАСТИЧНОСТИ
- СОЦИАЛЬНЫЕ АСПЕКТЫ ТАБАКОКУРЕНИЯ
PHARMACOECONOMIC STUDY OF BOTULINUM TOXIN TYPE A IN TREATMENT OF POST-STROKE SPASTICITY IN THE UPPER LIMB

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Abstract:
According to the World Health Organization, the prevalence of post-stroke spasticity is 200 people per 100 thousand inhabitants and the total number of patients in the world exceeds 12 million people. Approximately 450 000 people have a cerebrovascular accident (CVA) annually in the Russian Federation and the post-stroke spasticity is developed in about one third of the survivors. The main goal of this study is to conduct pharmacoeconomic analysis of three best-selling in the Russian Federation botulinum toxin type A preparations - Dysport®, Botox®, Xeomin compared with standard therapy without botulinum toxin type A. According to the conducted cost-effectiveness analysis where Modified Ashworth scale score is used as a main outcome Dysport® is a dominated alternative compared with other studied therapy schemes. What is more, budget impact analysis shows that therapy with Dysport® during one year leads to the saving of 45 563 rubles compared with Botox® and saving of 44 408 rubles compared with Xeomin per one patient.

Key words: pharmacoeconomics, health economic analysis, effectiveness analysis, cost analysis, cost-effectiveness analysis, budget impact analysis, post-stroke spasticity, cerebrovascular accident, botulinum toxin type A, dysport, botox, xeomin, disability, neurology, muscular hypertonia, health technology assessment.

Introduction:
The main goal of post-stroke spasticity therapy (PSS) is to improve the motor functionality of the paretic limbs, walking and self-care ability of patients. Unfortunately, in the majority cases, treatment options of PSS result only in pain and discomfort reduction associated with high muscle tone, alleviation of care for a paralyzed patient or the elimination of existing cosmetic defect caused by PSS [4],[6].

The constant increase in the number of patients with stroke and patients with PSS, as well as a significant cost of therapy necessitates the conduct of pharmacoeconomic analysis of preparations of botulinum toxin (BTA) registered in Russia with the main goal to reduce the cost of healthcare budget and optimize existing treatment regimens [31],[35],[36].

During information retrieval, it was found that up to the present time international and national experience of providing care to patients with post-stroke spasticity is studied. At the second stage epidemiological and clinical aspects of PPS treatment analysis, an the disability level and the degree of spasticity reduction assessment is performed as well as epidemiological data is collected. At the third stage the direct medical, non-medical costs and indirect costs during PPS therapy are estimated. At the fourth stage comparative pharmacoeconomic analysis with usage of four methods is performed: budget impact analysis, cost-effectiveness analysis, sensitivity analysis, modeling.

The pharmacoeconomic model in Microsoft Excel 2013 designed during this study allows to conduct modeling of clinical economic consequences of taken decisions on PPS treatment schemes and making budget prognosis for three months and one year both at the federal and regional level, using relevant and reliable data.

Data and materials
Effectiveness analysis.

Four treatment schemes are assessed in this study: Dysport® (1000 U), Botox® (240 U), Xeomin (320 U) and standard therapy. Standard therapy does not include administration of botulinum toxin. Authors admit an assumption to Botox® during calculation of treatment costs connected with the maximum recommended dosage of 240 U in the Russian Federation as in the same time effectiveness of Botox® is evaluated using the dosage of 360 U according to the data of clinical trials with consideration of the same amount of injected muscles for unification of conducted analysis.

Patients in all observed groups get physotherapy. Standard therapy is based on the clinical guidelines by the professors Kadykov and Chernikova [5], on the data from the clinical guidelines of patient and outpatient care «The consequences of cerebrovascular accident with severe motor and/or speech impairments» [43].

At the first stage of this research the information retrieval of randomized clinical trials is conducted using the data from major bibliographic databases: Medline, Medscape, PubMed, Cochrane Library, also the world database of open clinical trials - clinicaltrials.gov is used.

Results of information retrieval are summarized in Table 1.
<table>
<thead>
<tr>
<th>The authors of the study</th>
<th>Sample, duration of illness</th>
<th>Compared alternatives</th>
<th>Endpoints (primary, secondary) and outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bakheit et al, 2001 [15]</td>
<td>59, more than 3 months</td>
<td>Dysport® 1000 U or placebo</td>
<td>A significant reduction of spasticity by Modified Ashworth scale (Modified Ashworth scale - MAS) in week 4. 1 – Reduction of spasticity in week 4 2 – Range of Motion (ROM) of joint, pain intensity, functionality</td>
</tr>
<tr>
<td>Bhakta et al, 2000 [17]</td>
<td>40, more than 6 months</td>
<td>Dysport® 1000 U or placebo</td>
<td>The decrease on the Modified Ashworth scale, positive changes in Disability Assessment Scale - DAS.</td>
</tr>
<tr>
<td>Bakheit et al, 2000 [14]</td>
<td>82, more than 3 months</td>
<td>Dysport® 500, 1000, 1500 U or placebo</td>
<td>Changes in ROM in elbow, wrist, finger joints in week 4 and 16. Positive changes in active or passive ROM, joint pain, improvement in limbs functionality in week 4. 1 – All groups demonstrated improvement compared with placebo according to MAS 2 – No significant changes in hand functionality</td>
</tr>
<tr>
<td>Smith et al, 2000 [33]</td>
<td>21, more than 12 months</td>
<td>Dysport® 500, 1000, 1500 U or placebo</td>
<td>Reducing spasticity in the wrist and fingers muscles on the MAS. 1. The effect decreased in week 12, in addition to minor improvements in passive ROM of the elbow for patients taking 1500 U 2 – Non-significant improvement in Frenchay Arm Test</td>
</tr>
<tr>
<td>Hesse et al, 1998 [22]</td>
<td>24, 6-12 months after stroke</td>
<td>Group A: Dysport® 1000 U + electrical muscle stimulation Group B: Dysport® 1000 U Group C: placebo + electrical muscle stimulation Group D: placebo</td>
<td>MAS, limb position at rest, difficulties in activities of daily living 1 – Greatest improvement in group A. Pairwise comparison showed that group A vary from group B and D, but does not vary from group C</td>
</tr>
<tr>
<td>Barnes, 2009 [19]</td>
<td>192, more than 3 months</td>
<td>Xeomin 20 U и 50 U</td>
<td>Ashworth scale, improvement in 1 point and more according to DAS: 63 % in 20 U group, 52,4% in 50 U group</td>
</tr>
<tr>
<td>Kanovsky, 2009 [25]</td>
<td>148, more than 3 months</td>
<td>Xeomin 320 U or placebo</td>
<td>68,5% people who took Xeomin demonstrated improvement in MAS. DAS and Carer Burden scale are also used</td>
</tr>
<tr>
<td>Brashear, 2002 [18]</td>
<td>126, more than 6 months</td>
<td>Botox® 200-240 U</td>
<td>A significant decrease in Ashworth scale and improvement in at least one item in DAS.CGI scale</td>
</tr>
<tr>
<td>Richardson, 2000 [29]</td>
<td>52, from 3 months to 22 years</td>
<td>Botox® 50 U</td>
<td>A significant decrease of spasticity in Modified Ashworth scale</td>
</tr>
<tr>
<td>Kaji, 2010 [24]</td>
<td>109, more than 6 months</td>
<td>Botox® 120-150 U and 200-240 U, or placebo</td>
<td>Spasticity reduction in MAS in week 4, 8 and 12 after injection in 200-240 U group</td>
</tr>
<tr>
<td>D. Simpson, 1996 [30]</td>
<td>39</td>
<td>Botox® 75, 150, 300 U or placebo</td>
<td>A significant decrease of spasticity in Modified Ashworth scale under 300 U of BTA</td>
</tr>
<tr>
<td>B. Bhakta, 1996 [17]</td>
<td>17, 1,5 year</td>
<td>Botox® 100-200 U и Dysport® 400-1000 U</td>
<td>Improvement in range of passive motions in shoulder, wrist and elbow</td>
</tr>
<tr>
<td>Jahangir, 2007 [23]</td>
<td>27</td>
<td>Botox® 50 U, placebo</td>
<td>Improvement in spasticity of the wrist and fingers on the MAS scale, improving the quality of life on EQ-5D and EQ VAS, no major change in the Barthel Index</td>
</tr>
<tr>
<td>G. Lagalla, 2000 [26]</td>
<td>28</td>
<td>Botox® median dose 128 U</td>
<td>A significant reduction in Ashworth scale, the decrease in ROM</td>
</tr>
<tr>
<td>G. Francisco, 2002 [21]</td>
<td>13</td>
<td>Botox® 60 U</td>
<td>Reduction of spasticity according to MAS in week 4, 8 and 12 weeks after injection</td>
</tr>
<tr>
<td>M. Childers, 2004 [20]</td>
<td>91, more than 3 months</td>
<td>Botox® 90, 180, 360 U</td>
<td>Reduction of spasticity according to MAS, improvement in the quality of life on SF-36</td>
</tr>
<tr>
<td>Meythaler, 2009 [27]</td>
<td>21, more than 6 months</td>
<td>Botox® 100 U, placebo</td>
<td>Primal outcome – Reduction of Motor Activity Lag – MAL, reduction in spasticity according to Ashworth scale</td>
</tr>
</tbody>
</table>
During standardization of clinical studies authors used criteria of inclusion and exclusion of clinical studies in the results of effectiveness analysis of this pharmacoeconomic study.

Inclusion criteria:

- Spasticity was assessed using Modified Ashworth scale
- Patients were recruited at least 3 months after the onset of the cerebrovascular event.
- BTA was injected in the same muscles (elbow: biceps brachii, wrist: flexor carpi ulnaris, flexor carpi radialis, finger: flexor digitorum profundus, flexor digitorum superficialis)
- There are results of MAS changing at Week 4 compared with the baseline
- Modified Ashworth Scale score of 2 or higher in patients’ wrist, elbow and fingers muscles at the baseline

Exclusion criteria:

- There are contractures in observed muscle
- Patients were not treated with phenol or alcohol nerve blocks, neurolytic agents during study

Only three clinical studies of BTA therapy from the Table 1 met the proposed requirements:


Data on the reduction of spasticity according to the Disability Assessment Scale was obtained from the clinical trials protocols from the registry and results database clinical studies of human participants conducted around the world - clinicaltrials.gov [41,42], and from the study by Bipin B Bhakta, J Alastair Cozens Anne Chamberlain, John M Bamford - Impact of botulinum toxin type A on disability and carer burden due to arm spasticity after stroke: a randomised double blind placebo controlled trial. (2000).

Modified Ashworth scale is the most commonly used measure of spasticity according to many specialists, as it provides the most accurate comparison of the spasticity degree during treatment regimens [19,20].

Table 2. Modified Ashworth Scale

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No increase in muscle tone</td>
</tr>
<tr>
<td>1</td>
<td>Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end range of motion when the affected parties moved in flexion or extension</td>
</tr>
<tr>
<td>1+</td>
<td>Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the range of motion</td>
</tr>
<tr>
<td>2</td>
<td>More marked increase in muscle tone through most of the range of motion, but the affected part is easily moved</td>
</tr>
<tr>
<td>3</td>
<td>Considerable increase in muscle tone, passive movement is difficult</td>
</tr>
<tr>
<td>4</td>
<td>Affected part is rigid in flexion or extension</td>
</tr>
</tbody>
</table>

Figure 1 Results of Botulinum toxin type A therapy effectiveness according to Modified Ashworth scale

Results of BTA therapy and standard therapy comparison using Modified Ashworth Scale

- Dysport®
- Botox®
- Xeomin
- Standard therapy without BTA
According to the analysis of the results of three randomized clinical trials on the 4th week after the injection of botulinum toxin the following results of the Modified Ashworth score change have been identified: Dysport® - 1.67, Botox® - 1.17, Xeomin - 0.87. If the standard therapy was continued this change in MAS scores equaled 0.67. As a result Dysport® therapy results in more prominent decrease in MAS score compared with Botox®, Xeomin and standard therapy without BTA. It means that Dysport® decreases spasticity more effectively compared with other alternatives: compared with Botox® – by 30%, compared with Xeomin – by 48%, compared with standard therapy – by 60%.

Disability assessment BTA therapy and standard therapy at the 4th week was also conducted using Disability Assessment Scale (DAS).

Disability Assessment Scale (DAS) consists of 4 items:

- Hand hygiene: The rater assesses the extent of palm maceration, ulceration, or infection; cleanliness of the palm, ease of cleaning, and nail trimming; and the effect of hygiene-related disability on other areas of functioning
- Dressing: The rater assesses the patient’s ability to dress and the effect of dressing-related disability on other areas of functioning
- Limb position: The rater assesses the amount of abnormal position of the limb
- Pain: The rater assesses the intensity of pain or discomfort related to upper-limb spasticity and interference with activities of daily living

The DAS Scale uses a 4-point rating scale according to the following criteria:
- 0 – no disability
- 1 – mild disability (noticeable but does not interfere significantly with normal activities)
- 2 – moderate disability (normal activities require increased effort and/or assistance)
- 3 – severe disability (normal activities limited) [19]

An arithmetic value of these four indicators is taken as the value of the disability degree. The results of this analysis were included in the subsequent calculation of indirect costs.

Results: Dysport® therapy – 0.50, Botox® therapy – 0.38, Xeomin – 0.37, standard therapy – 0.1. The comparison showed that Dysport® treatment scheme results in a disability decrease 5 times better than standard therapy without BTA.

Summarizing the obtained data, it should be noted that Dysport® treatment scheme results in more prominent decrease in MAS score compared with other BTA drugs and standard therapy without BTA.

Costs analysis

Direct and indirect costs were considered during this pharmacoeconomic analysis:

- Cost of botulinum toxin type A therapy
- Costs of inpatient medical care (up to 12 months)
- Costs of outpatient medical care (12 months and more)
- Disability pensions
- Temporary disability benefit
- GDP loss due to post-stroke spasticity
- Costs of adverse events

During the calculation of the costs of botulinum toxin therapy price of each drug was taken from the price list of the vital and essential drugs in Russia [49]. Authors took the following time horizon: three months and one year. Three months are explained by the duration of treatment of three months and one year is explained with duration that is more appropriate from the perspective of healthcare budget making. [3]. For standard therapy without BTA this indicator is not calculated.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Costs for three months, rubles.</th>
<th>Costs for one year, rubles.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysport® (1000 U)</td>
<td>28 778</td>
<td>115 112</td>
</tr>
<tr>
<td>Botox® (240 U)</td>
<td>47 620</td>
<td>190 480</td>
</tr>
<tr>
<td>Xeomin (320 U)</td>
<td>34 976</td>
<td>139 904</td>
</tr>
</tbody>
</table>

The main therapeutic interventions and non-medical costs associated with inpatient and outpatient treatment of post-stroke spasticity were taken from the draft of standard of medical care «The consequences of cerebrovascular accident with severe motor and/or speech impairments» (period before 3 months) [43] and the draft of standard for provision of outpatient care «Conditions in patients suffered from a cerebrovascular accident (period after 12 months) with mild and moderate disabilities» [43].

These standards are the most up-to-date ones of inpatient and outpatient medical care for patients suffered from CVA not later than 3 months (e.g late recovery period) at the moment of 02.05.14 according to the The order of the health Committee of the government of St. Petersburg dated 05.10.2010 N 502-R «On approval of the preliminary medical-economic standards» [41].

The price lists of medical services of I.M. Sechenov diagnostic and treatment center were used for the calculations of inpatient care and outpatient care costs [3]. The choice of the price list explained by the fact that it reflects most accurately the actual cost of medical services.

Costs were calculated using the formula:

\[ \text{Total cost} = \text{CS} \times \text{FSP} \times \text{RA} \]

- CS – cost of service
- FSP - frequency of service provision
- RA – rate of application

During the calculation of the costs of drug therapy price of each drug was taken from the price list of the vital and essential drugs in Russia [49]. The list of drugs was taken from the draft of standard of medical care «The consequences of cerebrovascular accident with severe motor and/or speech impairments» (period before 3 months). During the calculation authors admitted the assumption that all assigned courses of therapy had been completed fully regardless of the fact if they had ended the course during inpatient treatment, or the patient had had to continue drug therapy after the end of the inpatient treatment. It was admitted that drug price had been the same before and after the treatment end.

Summarized cost was calculated using the formula:

\[ \text{Total cost} = \frac{\text{FI} \times \text{EDD} \times \text{DT}}{\text{Dosage of 1 drug unit} \times \text{Number of drug units in package}} \]

- FI – frequency of indication
- EDD – estimated daily dose
- DT – duration of treatment
- Dosage of 1 drug unit
- Number of drug units in package

The cost of the correction of side effects was calculated based on the frequency of their occurrence according to the drug labels and according to the standards and clinical guidelines [51].

Indirect costs consisted of the disability pensions and the temporary disability benefit. Disability pensions and monthly monetary payments were calculated using the data of The Russian Pension Fund for 2014. Calculation of the monthly monetary payments was performed according to the mean salary in the Russian Federation for 2013 and 2012 divided into the number of months when a person was disabled.

<table>
<thead>
<tr>
<th>Disability Class 1</th>
<th>7220</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disability Class 2</td>
<td>3610</td>
</tr>
<tr>
<td>Disability Class 3</td>
<td>1805</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disability Class 1</th>
<th>2832</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disability Class 2</td>
<td>2022</td>
</tr>
<tr>
<td>Disability Class 3</td>
<td>1619</td>
</tr>
</tbody>
</table>
The total monthly monetary payments were multiplied by the number of patients with PSS and the proportion of patients belonging to disability groups 1,2 and 3. Then this number was multiplied by the share of disability reduction according to the Disability Assessment Scale (DAS).

The percentage of reductions was calculated based on the comparison of disability changes in BTA group and in standard therapy without BTA group to the week 4 on Disability Assessment Scale (DAS) according to the results of three clinical studies [12],[41],[42]. The results of the comparison: for Dysport® - 0.50, for Botox® - 0.38, Xeomin - 0.37, standard therapy - 0.1.

According to the done comparison, Dysport® therapy results in reduction of disability cases by 17%, Botox® - 12.7 %, Xeomin – 12.3 %, standard therapy – by 3.3 %. As a result, total benefits connected with disability (Disability pensions + Monthly monetary payment) per one patient 1 year were 42 858 rubles for Dysport®, 45 078 rubles – for Botox®, 45 269 rubles – for Xeomin, 49 916 rubles – for standard therapy. In case of treatment during 3 months total benefits connected with disability were 10 714 rubles for Dysport®, 11 269 rubles –for Botox®, 11 317 rubles – for Xeomin, 12 479 rubles – for standard therapy.

Temporary disability benefit was calculated basing on the fact that patient suffered from disease first time in 2014. Calculation of the monthly monetary payments was performed according to the mean salary in the Russian Federation for 2013 in 2012 divided into the number of months when a person was disabled.

Mean salary in Russia in 2012 was 23369 rubles, the one in 2013 was 26628 rubles. It was admitted that patient had worked from 5 to 8 years earlier, was insured, and afterwards was disabled for 5 years. Consequently, 3 months therapy costs for temporary disability benefits per one patient with the consideration of disability reduction on DAS were 49 797 rubles for Dysport®, 52 377 rubles – for Botox®, 52 599 rubles – for Xeomin, 57 999 rubles – for standard therapy.

1 year therapy costs for temporary disability benefits per one patient with the consideration of disability reduction on DAS were 82 995 rubles for Dysport®, 87 295 rubles – for Botox®, 87 665 rubles – for Xeomin, 96 664 rubles – for standard therapy.

GDP loss due to post-stroke spasticity was also calculated. It is calculated by multiplication of GDP per capita (520 547 rubles according to IMF [40]) by the proportion of patients with spasticity with disability level 1 and 2 (e.g. can not work in working age) and by the proportion of disability reduction on DAS.

Results of costs comparison for 3 months and 1 year are given below.

**Table 6. Structure of total costs per 1 patient with post-stroke spasticity in the Russian Federation for 1 year**

<table>
<thead>
<tr>
<th></th>
<th>DYSSPORT®</th>
<th>BOTOX®</th>
<th>XEOMIN</th>
<th>STANDARD THERAPY WITHOUT BTA</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDP loss, rubles.</td>
<td>196 153</td>
<td>206 315</td>
<td>207 189</td>
<td>207 189</td>
</tr>
<tr>
<td>Costs of adverse events, rubles.</td>
<td>3 308</td>
<td>4 441</td>
<td>4 806</td>
<td>0</td>
</tr>
<tr>
<td>Cost of botulinum toxin type A therapy, rubles.</td>
<td>115 112</td>
<td>142 860</td>
<td>139 904</td>
<td>0</td>
</tr>
<tr>
<td>Costs for post-stroke spasticity treatment, rubles.</td>
<td>210 080</td>
<td>210 080</td>
<td>210 080</td>
<td>210 080</td>
</tr>
<tr>
<td>Disability pensions, rubles.</td>
<td>42 858</td>
<td>45 078</td>
<td>45 269</td>
<td>49 916</td>
</tr>
<tr>
<td>Temporary disability benefit, rubles.</td>
<td>82 995</td>
<td>87 295</td>
<td>87 665</td>
<td>96 664</td>
</tr>
<tr>
<td>Total costs, rubles.</td>
<td>650 505</td>
<td>696 068</td>
<td>694 913</td>
<td>585 119</td>
</tr>
</tbody>
</table>

**Table 7. Structure of total costs for whole population with post-stroke spasticity in the Russian Federation for 1 year**

<table>
<thead>
<tr>
<th></th>
<th>DYSSPORT®</th>
<th>BOTOX®</th>
<th>XEOMIN</th>
<th>STANDARD THERAPY WITHOUT BTA</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDP loss, rubles.</td>
<td>41 608 965 261</td>
<td>43 764 610 449</td>
<td>43 950 096 198</td>
<td>48 461 911 708</td>
</tr>
<tr>
<td>Costs of adverse events, rubles.</td>
<td>701 637 680</td>
<td>942 038 842</td>
<td>1 019 450 488</td>
<td>0</td>
</tr>
<tr>
<td>Cost of botulinum toxin type A therapy, rubles.</td>
<td>24 418 198 634</td>
<td>30 304 258 955</td>
<td>29 677 215 770</td>
<td>0</td>
</tr>
<tr>
<td>Costs for post-stroke spasticity treatment, rubles.</td>
<td>44 563 361 772</td>
<td>44 563 361 772</td>
<td>44 563 361 772</td>
<td>44 563 361 772</td>
</tr>
<tr>
<td>Disability pensions, rubles.</td>
<td>9 091 193 074</td>
<td>9 562 182 595</td>
<td>9 602 709 600</td>
<td>9 602 709 600</td>
</tr>
<tr>
<td>Temporary disability benefit, rubles.</td>
<td>88 026 829 696</td>
<td>92 587 255 813</td>
<td>92 979 664 572</td>
<td>102 524 742 491</td>
</tr>
<tr>
<td>Total costs, rubles.</td>
<td>166 801 220 855</td>
<td>177 959 097 977</td>
<td>177 842 402 202</td>
<td>156 690 813 862</td>
</tr>
</tbody>
</table>
According to the results of budget impact analysis it was found that Dysport® therapy for 1 year leads to 45,563 rubles monetary economy compared with Botox® treatment and 44,408 rubles compared with Xeomin per 1 patient. Dysport® therapy is 65,386 rubles more expensive per 1 patient for 1 year compared with standard therapy.

Dysport® therapy results in 23,058 rubles economy compared with Botox®, 23,773 rubles economy compared with Xeomin and 20,744 rubles economy compared with standard therapy without BTA for 3 months treatment per one patient, as well as effectiveness of Dysport® therapy is 60% compared with standard therapy.

Dysport® treatment in whole population of PPS patients in Russia will result in 11,16 billion rubles economy for 1 year compared with Botox®, 11,04 billion rubles economy compared with Xeomin and requires additional financing in 10,11 billion compared with standard therapy without BTA.

Dysport® treatment of 1 PPS patient in Russia will result in 1,63 billion rubles economy for 1 year compared with Botox®, 1,57 billion rubles compared with Xeomin and requires additional financing in 3,09 billion rubles compared with standard therapy without BTA.

Cost-effectiveness analysis
Comparative cost-effectiveness analysis Botulinum toxin A treatment and standard therapy was performed. The results are presented in table 3. Dysport® therapy was more costly compared with standard therapy by 65,386 rubles (by 10.1%). At the same time efficacy of Dysport®, therapy grew by 60% according to the results of spasticity changes on Modified Ashworth scale. Cost-effectiveness ratio for Dysport® was 389,524 rubles and it is more cost-effective compared with standard therapy for 1 year. Botox® and Xeomin are also more cost-effective alternatives compared with standard therapy 594,930 rubles and 798,750 rubles respectively, but they are less cost-effective compared with Dysport®. Results of cost-effectiveness analysis are presented in table 9 and in figures 4 and 5.

Budget impact analysis
Approximately 450,000 people have a cerebrovascular accident (CVA) annually in the Russian Federation [39]. Survival rate for ischemic stroke patients is 60% and for the hemorrhagic ones – 38% at the end of the first year. [34] Five-year survival rate after ischemic stroke is 50% [2], this rate after hemorrhagic stroke is 24% [31]. Ten-year survival rate after ischemic stroke is 25% [2], this one after hemorrhagic stroke is 18%. [15]. The ratio of cases of ischemic and hemorrhagic stroke is 4:1 [1]. One third of the patients survived after CVA suffer from the spasticity [4]. Based on the data of Ministry of labour and social development in 2014 the proportion of stroke survivors with disability class 1 are 15.9%, ones with disability class 2 are 40.9%, ones with disability class 3 are 43.2% and about 20% of stroke survivors have no disabling conditions, authors conclude that there are 12.7% of PSS patients with disability class 1, 32.7% of PSS patients with disability class 24, and 34.6% of PSS patients with disability class 3 [47].
Figure 3. Results of cost-effectiveness ratio comparison in post-stroke spasticity therapy for 1 year.

Figure 4. Results of comparison of cost-effectiveness ratio for post-stroke spasticity treatment schemes for 3 months.
According to the obtained data, the treatment of post-stroke spasticity with Dysport® is a dominated alternative compared with any other PSS treatment scheme from the perspective of the health economics and preferable from the pharmacoeconomic analysis perspective.

Sensitivity analysis

Sensitivity analysis was performed during this pharmacoeconomic study. Its aim was to determine the robustness of the obtained results during its changing. Price of BTA was taken as a changing parameter. Single-factor sensitivity analysis was performed by assessment of costs for all types of treatment in case of changes of variable from -100% to 100%.

Thus, sensitivity analysis demonstrated the robustness of the results obtained in this pharmacoeconomic study. Dysport® therapy compared with Botox®, Xeomin or standard therapy without BTA is a dominated alternative even under significant changes of initial parameters of studied drug prices.

Results

1. Data on effectiveness, safety and therapy costs of BTA (Dysport®, Botox®, Xeomin) and standard therapy without BTA is collected based on the information of retrieval. On the basis of obtained data and materials on methodology of pharmacoeconomic analysis the following types of analyses were chosen: modeling, budget impact analysis, cost-effectiveness analysis, sensitivity analysis.

2. The costs of Dysport®, Botox®, Xeomin therapy and standard treatment in two treatment groups at 3 months and 1 year per patient, cost of PSS treatment, cost of botulin toxin type A therapy and costs for the correction of side effects, costs including temporary disability benefit, disability pensions, the loss of GDP of botulinum toxin type A therapy and costs for the correction of side effects, treatment groups at 3 months and 1 year per patient, cost of PSS treatment, cost for 1 year lead to 45 563 rubles monetary economy compared with Botox® treatment.

3. According to the obtained data, the treatment of post-stroke spasticity with Dysport® is a dominated alternative compared with other BTA drugs and slight increase of costs compared with standard therapy.

4. According to the results of budget impact analysis it is found that Dysport® therapy results in 23 058 rubles economy compared with Botox®, 23 773 rubles more expensive per 1 patient for 1 year compared with standard therapy. Dysport® therapy results in 23 058 rubles economy compared with Botox®, 23 773 rubles economy compared with Xeomin and 20 744 rubles economy compared with standard therapy without BTA for 3 months treatment per one patient.

5. The treatment of post-stroke spasticity with Dysport® is a dominated alternative compared with any other PSS treatment scheme from the perspective of the health economics and preferable from the pharmacoeconomic analysis perspective. It allows to decrease spasticity degree and to lower disability level compared with any other PSS treatment scheme combined with the reduction of costs compared with other BTA drugs and slight increase of costs compared with standard therapy.

6. According to the obtained data, the treatment of post-stroke spasticity with Dysport® is a dominated alternative compared with any other PSS treatment scheme from the perspective of the health economics and preferable from the pharmacoeconomic analysis perspective. It allows to decrease spasticity degree and to lower disability level compared with any other PSS treatment scheme combined with the reduction of costs compared with other BTA drugs and slight increase of costs compared with standard therapy.

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Table 9. Results of comparison of cost-effectiveness ratio for post-stroke spasticity treatment schemes for 3 months, 1 year.

<table>
<thead>
<tr>
<th>Medication</th>
<th>CER for 3 months, rubles</th>
<th>CER for 1 year, rubles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysport®</td>
<td>326 579</td>
<td>389 524</td>
</tr>
<tr>
<td>Botox®</td>
<td>485 850</td>
<td>594 930</td>
</tr>
<tr>
<td>Xeomin</td>
<td>654 207</td>
<td>798 750</td>
</tr>
<tr>
<td>Standard therapy without BTA</td>
<td>844 972</td>
<td>873 312</td>
</tr>
</tbody>
</table>

Table 10. Single-factor sensitivity analysis of CER in case of the change in the price of BTA for 1 year therapy.

<table>
<thead>
<tr>
<th>Price range</th>
<th>-100%</th>
<th>-50%</th>
<th>-10%</th>
<th>0%</th>
<th>10%</th>
<th>50%</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysport®</td>
<td>320 595</td>
<td>355 095</td>
<td>382 631</td>
<td>398 524</td>
<td>396 417</td>
<td>423 989</td>
<td>458 453</td>
</tr>
<tr>
<td>Botox®</td>
<td>472 828</td>
<td>533 879</td>
<td>582 720</td>
<td>594 930</td>
<td>607 141</td>
<td>655 982</td>
<td>717 033</td>
</tr>
<tr>
<td>Xeomin</td>
<td>637 941</td>
<td>716 346</td>
<td>782 669</td>
<td>798 750</td>
<td>814 831</td>
<td>879 155</td>
<td>959 560</td>
</tr>
<tr>
<td>Standard therapy without BTA</td>
<td>873 312</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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