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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 local comparative pharmacoeconomic studies of botulinum toxin preparations and standard therapy of PSS have not been conducted.
The main goal of this study is to perform a pharmacoeconomic evaluation of three-months and one-year botulinum toxin type A preparations treatment scheme (Dysport®, Botox®, Xeomin) compared with standard therapy of post-stroke spasticity in the Russian Federation. Length of study is explained by the duration of treatment of three months and one year length is explained with more appropriate duration from the perspective of healthcare budget making.
The study is performed gradually. At the first stage an information retrieval is performed, an 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 physiotherapy. 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.

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Table 1. Results of information retrieval.

The authors of the study	Sample, duration of illness	Compared alternatives	Endpoints (primary, secondary) and outcomes
DYSPORT®			
Bakheit et al, 2001 [15]	59, more than 3 months	Dysport® 1000 U or placebo	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
Bhakta et al,2000 [17]	40, more than 6 months	Dysport® 1000 U or placebo	The decrease on the Modified Ashworth scale, positive changes in Disability Assessment Scale - DAS.
Bakheit et al,2000 [14]	82, more than 3 months	Dysport® 500,1000,1500 U or placebo	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
Smith et al,2000 [33]	21, more than 12 months	Dysport® 500,1000,1500 U or placebo	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
Hesse et al,1998 [22]	24, 6-12 months after stroke	Group A: Dysport® 1000 U+ electrical muscle stimulation Group B: Dysport® 1000 U Group C: placebo + electrical muscle stimulation Group D: placebo	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
XEOMIN			
Barnes, 2009 [19]	192, more than 3 months	Xeomin 20 U и 50 U	Ashworth scale, improvement in 1 point and more according to DAS: 63 % in 20 U group; 52,4% in 50 U group
Kanovsky 2009 [25]	148, more than 3 months	Xeomin 320 U or placebo	68,5% people who took Xeomin demonstrated improvement in MAS. DAS and Carer Burden scale are also used
BOTOX®			
Brashear,2002 [18]	126, more than 6 months	Botox® 200-240 U	A significant decrease in Ashworth scale and improvement in at least one item in DAS.CGI scale
Richardson,2000 [29]	52, from 3 months to 22 years	Botox® 50 U	A significant decrease of spasticity in Modified Ashworth scale
Kaji, 2010 [24]	109, more than 6 months	Botox® 120-150 U and 200-240 U, or placebo	Spasticity reduction in MAS in week 4,8 and 12 after injection in 200-240 U group
D.Simpson, 1996 [30]	39	Botox® 75,150,300 U or placebo	A significant decrease of spasticity in Modified Ashworth scale under 300 U of BTA
B.Bhakta 1996 [17]	17, 1,5 year	Botox® 100-200 U и Dysport® 400-1000 U	Improvement in range of passive motions in shoulder, wrist and elbow
Jahangir 2007 [23]	27	Botox® 50 U, placebo	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 Bartel Index
G.Lagalla,2000 [26]	28	Botox®, median dose 128 U	A significant reduction in Ashworth scale, the decrease in ROM
G.Francisco,2002 [21]	13	Botox® 60 U	Reduction of spasticity according to MAS in week 4,8 and 12 weeks after injection
M.Childers,2004 [20]	91, more than 3 months	Botox® 90,180,360 U	Reduction of spasticity according to MAS, improvement in the quality of life on SF-36
Meythayler, 2009 [27]	21, more than 6 months	Botox® 100 U, placebo	Primal outcome – Reduction of Motor Activity Lag – MAL, reduction in spasticity according to Ashworth scale

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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:

- Bakheit A.M.O, Pittock S, Moore AP, et al. A randomized, double-blind, placebo-controlled study of the efficacy and safety of botulinum toxin type A in upper limb spasticity in patients with stroke (2001). [15]
- Childers M.K, Brashear A, Jozefczyk P, et al. Dose-dependent response to intramuscular botulinum toxin type A for upper-limb spasticity in patients after a stroke. (2004). [20]
- Kanovsky P., Slawek J., Denes Z., Platz T., Sassin I., Comes G., Grafe S. Efficacy and safety of botulinum neurotoxin NT 201 in post stroke upper limb spasticity. (2009). [25], [42]

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 - clinicaltrails.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).

Reliable data allowing to compare in an unbiased way clinical economic effectiveness of therapy with BTA and standard therapy was collected through proper information retrieval and the choice of clear and accurate clinical trials' criteria.

Effectiveness analysis

According to clinical guidelines, Modified Ashworth Scale is the most widely used method of measuring spasticity in patients with neurological disorders at the present time. This is a standard method for all patients with the post-stroke spasticity.

The advantages of this scale are reliability, simplicity of processing results and correlation with the disability scales. Therefore, change of Modified Ashworth Scale scores at the 4th week compared with baseline was chosen as an effectiveness criterion.

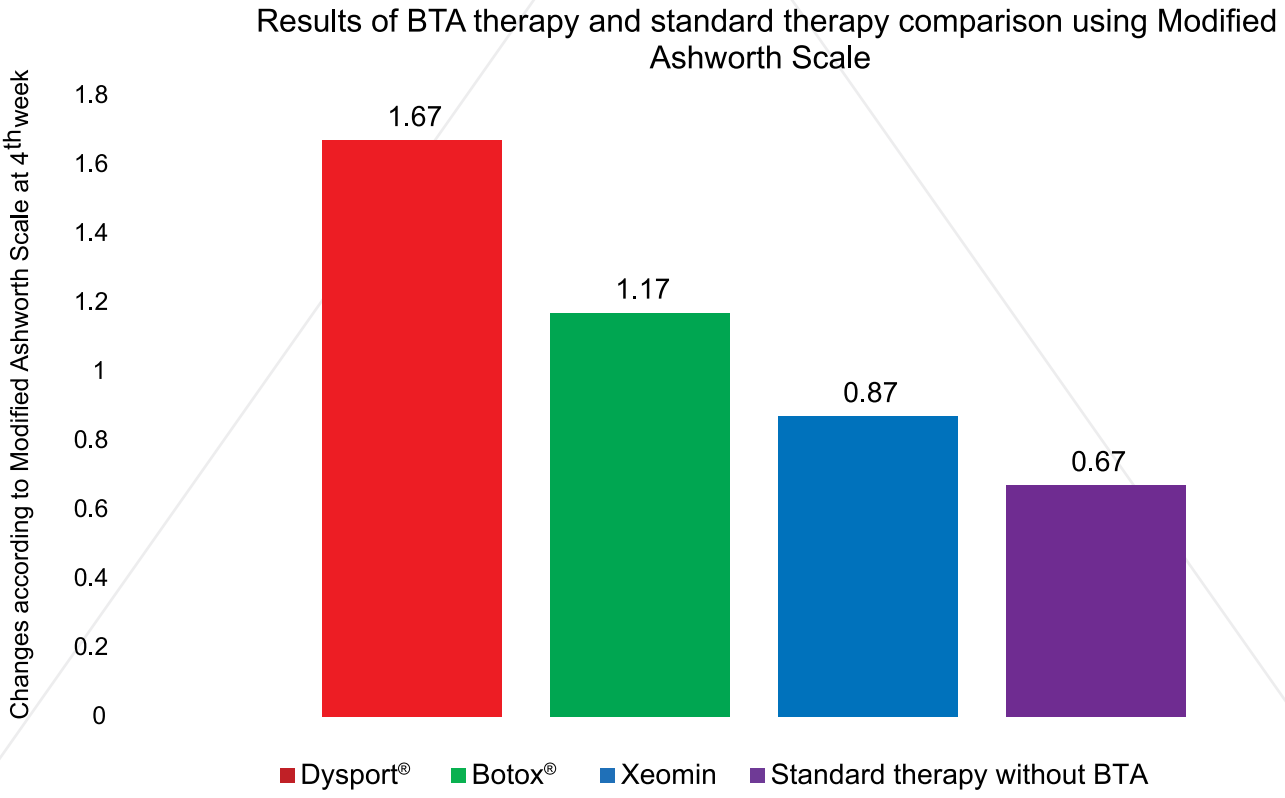
To assess muscle tone the examiner slowly passively flexes or extends the limb of the patient in a certain segment and assesses the degree of muscle resistance using MAS.

Table 2. Modified Ashworth Scale

Grade	Description
0	No increase in muscle tone
1	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
1 +	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the range of motion
2	More marked increase in muscle tone through most of the range of motion, but the affected part is easily moved
3	Considerable increase in muscle tone, passive movement is difficult
4	Affected part is rigid in flexion or extension

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].

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



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 is more efficient from the point of view of reducing spasticity and reducing the disability rate 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 3. Cost of botulinum toxin type A therapy per 1 patient

Medication	Costs for three months, rubles.	Costs for one year, rubles.
Dysport® (1000 U)	28 778	115 112
Botox® (240 U)	47 620	190 480
Xeomin (320 U)	34 976	139 904

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:

$$\text{Total cost} = CS \times FSP \times RA$$

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:

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

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 и 2012 divided into the number of months when a person was disabled.

Table 4. Calculation of disability pensions according to the data of the Pension Fund of the Russian Federation for 2014.

Disability pensions, rubles.	
Disability Class 1	7220
Disability Class 2	3610
Disability Class 3	1805

Table 5. Monthly monetary payment за 2014 year

Monthly monetary payment, rubles.	
Disability Class 1	2832
Disability Class 2	2022
Disability Class 3	1619

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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 и 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

	DYSPORT®	BOTOX®	XEOMIN	STANDARD THERAPY WTHOUT BTA
GDP loss, rubles.	196 153	206 315	207 189	207 189
Costs of adverse events, rubles.	3 308	4 441	4 806	0
Cost of botulinum toxin type A therapy, rubles.	115 112	142 860	139 904	0
Costs for post-stroke spasticity treatment, rubles.	210 080	210 080	210 080	210 080
Disability pensions, rubles.	42 858	45 078	45 269	49 916
Temporary disability benefit, rubles.	82 995	87 295	87 665	96 664
Total costs, rubles.	650 505	696 068	694 913	585 119

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

	DYSPORT®	BOTOX®	XEOMIN	STANDARD THERAPY WTHOUT BTA
GDP loss, rubles.	41 608 965 261	43 764 610 449	43 950 096 198	48 461 911 708
Costs of adverse events, rubles.	701 637 680	942 038 842	1 019 450 488	0
Cost of botulinum toxin type A therapy, rubles.	24 418 198 634	30 304 258 955	29 677 215 770	0
Costs for post-stroke spasticity treatment, rubles.	44 563 361 772	44 563 361 772	44 563 361 772	44 563 361 772
Disability pensions, rubles.	9 091 193 074	9 562 182 595	9 602 709 600	9 602 709 600
Temporary disability benefit, rubles.	88 026 829 696	92 587 255 813	92 979 664 572	102 524 742 491
Total costs, rubles.	166 801 220 855	177 959 097 977	177 842 402 202	156 690 813 862

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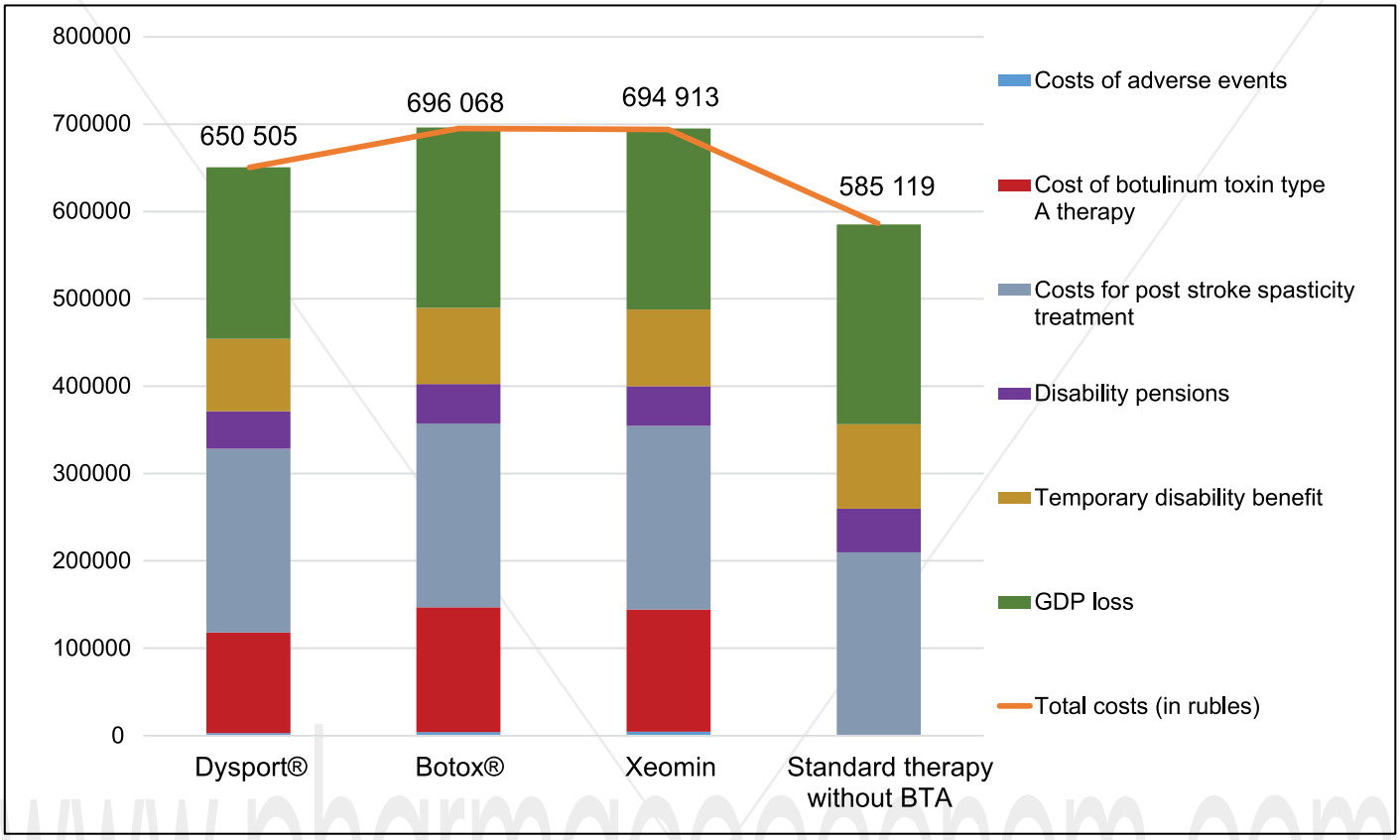
Figure 2. **Structure of total costs per 1 patient with PSS for 1 year in the Russian Federation in graphic display**



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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].

Table 8. Survival rate of different types of stroke.

Time horizon	Ischemic stroke	Hemorrhagic stroke
8 years	25%	18%
5 years	50%	24%
1 year	60%	38%
3 months	80%	62,5%

[2], [31],[35], [44]

According to the results of the modeling the total number of PSS patients after 3 months will be 157 404, at the end of 1 year of PSS will be 212 117 people.

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 popualtion of PPS patients in Russia will result in 11,16 billion rubles economy for 1 year compared with Botox®ом, 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.

Figure 3. **Results of cost-effectiveness ratio comparison in post-stroke spasticity therapy for 1 year**

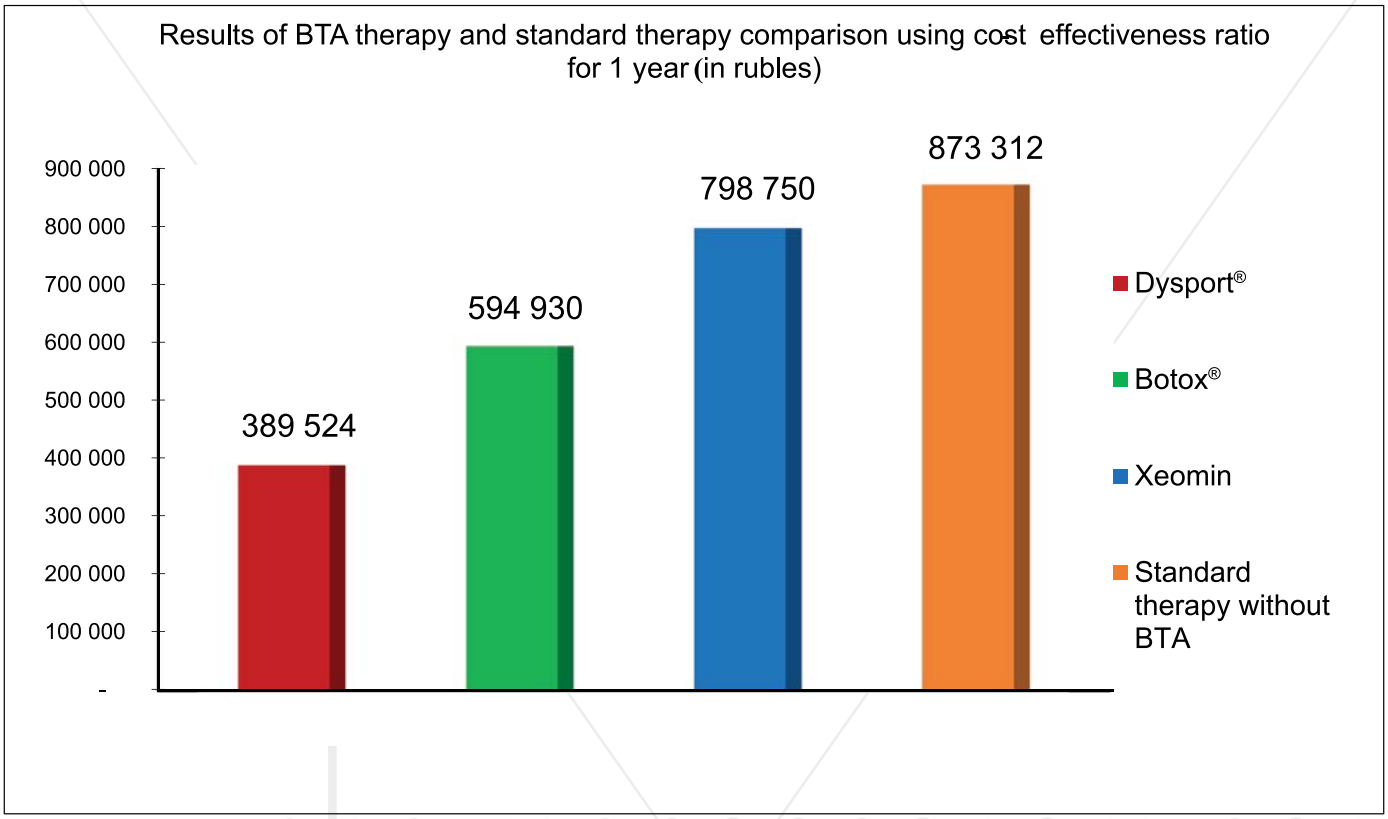

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Figure 4. **Results of comparison of cost-effectiveness ratio for post-stroke spasticity treatment schemes for 3 months.**

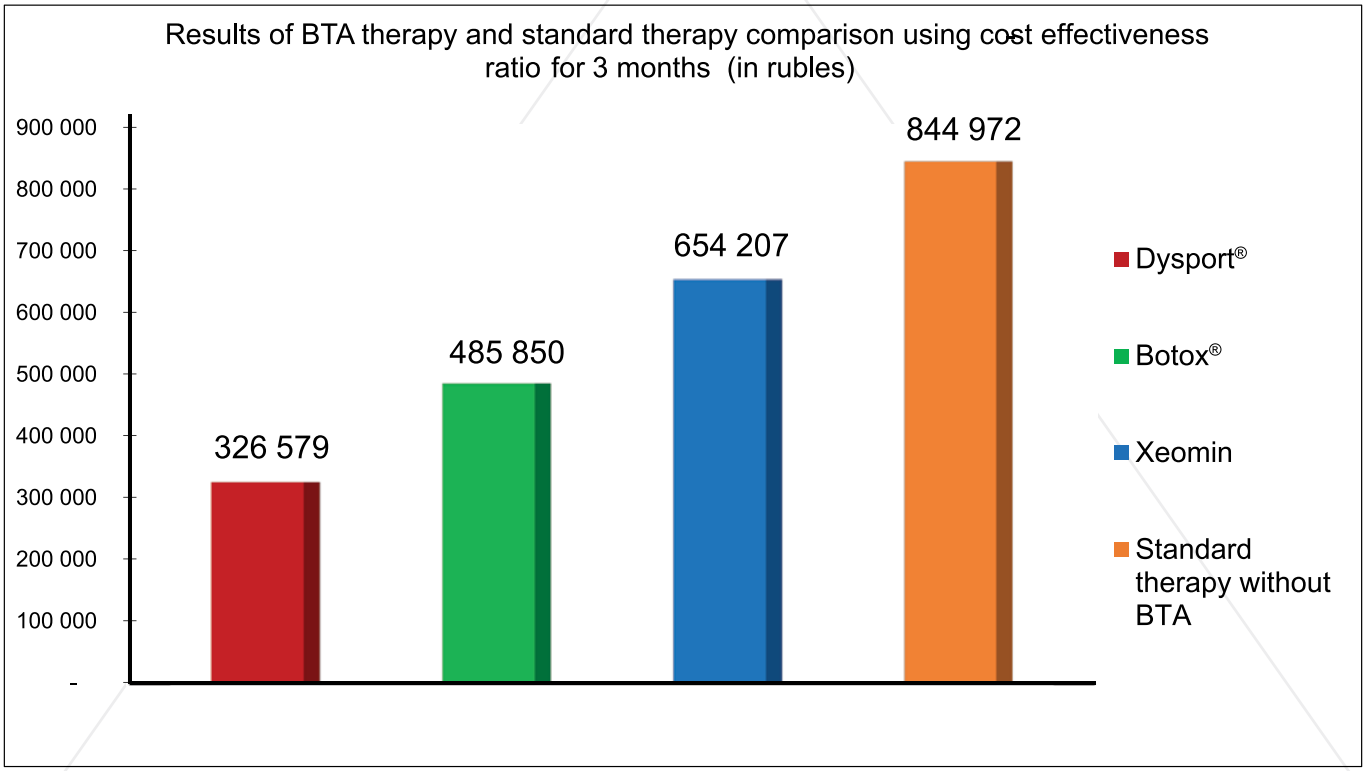

Table 9. Results of comparison of cost-effectiveness ratio for post-stroke spasticity treatment schemes for 3 months,1 year.

Medication	CER for 3 months, rubles	CER for 1 year, rubles
Dysport®	326 579	389 524
Botox®	485 850	594 930
Xeomin	654 207	798 750
Standard therapy without BTA	844 972	873 312

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%.

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

Price range	-100%	-50%	-10%	0%	10%	50%	100%
Dyspor®®	320 595	355 059	382 631	389 524	396 417	423 989	458 453
Botox®	472 828	533 879	582 720	594 930	607 141	655 982	717 033
Xeomin	637 941	718 346	782 669	798 750	814 831	879 155	959 560
Standard therapy without BTA	873 312						

During single-factor sensitivity analysis it was determined that all parameters in -100% to 100% change did not demonstrate dominative character of Dysport® therapy compared with alternatives: CER in Dysport® therapy remained lower in all conditions.

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 drugs 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 analysis 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 botulinum toxin type A therapy and costs for the correction of side effects, costs including temporary disability benefit, disability pensions, the loss of GDP were calculated using pharmacoeconomic model.
3. Cost-effectiveness analysis shows that Dysport® therapy has more dominated (lower) cost-effectiveness ratio with higher effectiveness compared with Botox®, Xeomin and standard therapy, therefore Dysport® is a dominated alternative.
4. According to the results of budget impact analysis it is found that Dysport® therapy for 1 year lead 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.
5. Integration of performed analysis results allows to make a choice in favour to Dysport® in three-month post-stroke spasticity patients.

Conclusion

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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