№3 Том3 2015

Фармакоэкономика
теория и практика

Pharmacoeconomics
theory and practice

№3 Volume3 2015

- ОПРЕДЕЛЕНИЕ ПОРОГА «ГОТОВНОСТИ ПЛАТИТЬ» ПРИ ОДОБРЕНИИ МЕДИЦИНСКИХ ТЕХНОЛОГИЙ В УСЛОВИЯХ РОССИЙСКОГО ЗДРАВООХРАНЕНИЯ, РАССЧИТАННОГО НА ОСНОВЕ ПАРИТЕТА ПОКУПАТЕЛЬНОЙ СПОСОБНОСТИ
- ОРИГИНАЛЬНЫЕ РОССИЙСКИЕ ФАРМАКОЭКОНОМИЧЕСКИЕ ИССЛЕДОВАНИЯ

www.pharmacoeconom.com

PHARMACOECONOMIC ANALYSIS OF DIFFERENT TYPES OF TREATMENT FOR SPASTIC FORMS OF CEREBRAL PALSY

Ugrekhelidze D.T., Kulikov A.Yu.

Department of organization of medicinal provision and pharmacoeconomics, I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation

Abstract:
Pharmacoeconomic study of different preparations of botulinum toxin type A used for the treatment of cerebral palsy in terms of health of the Russian Federation was conducted. The aim of this study was to determine the most appropriate therapy of cerebral palsy from the pharmacoeconomic point of view. We compared three regimens: botulinum toxin type A - Dysport® in combination with standard therapy, botulinum toxin type A - Botox® in combination with standard therapy and standard therapy without the use of botulinum toxin. It should be noted that centrally acting muscle relaxant (Baclofen) was used in standard therapy, but BTA in this treatment scheme is not used to eliminate unwanted relaxation of the muscles. As a result, it was found that the regimen Dysport®+standard therapy has the lowest cost-effectiveness ratio (11 608 rubles) in comparison with drug therapy Botox®+standard therapy (12 879 rubles) and standard therapy with a centrally acting muscle relaxant without BTA (25 222 rubles) by the end of 2 years of treatment. According to the budget impact analysis at the end of 2 years for 1 patient the scheme Dysport®+standard therapy was the least expensive form of therapy (1 079 500 rubles) in comparison with therapy Botox®+standard therapy (1 159 085 rubles) and standard therapy with a centrally acting muscle relaxant without BTA (1 210 678 rubles).

Key words: *pharmacoeconomics, clinical and economic analysis, efficiency analysis, cost analysis, cost-effectiveness analysis, budget impact analysis, cerebral palsy, botulinum toxin type A, Dysport®, Botox®, health technologies assessment.*

Cerebral palsy (CP) is one of the most widespread and socially significant neurological diseases that affect as various aspects of physical and psychoverbal development of children from birth and the as stages of their personal development and adaptation in society. [1] In the last years there is a clear trend in the increasing of number of children with disabilities in Russia and it should be noted that CP takes first place in the structure of infant neurological disability. Given the lifetime course of this disease, there is a huge medical and socio - economic importance of CP.

The prevalence of CP in the Russian Federation according to the Ministry of Health is 2.5 cases per 1000 births, and the total number of patients among the child population is equal to 74 532. [2] It should be noted that the most frequent type of SP are spastic forms, namely 75 % of children. [3]

The high cost of the complex therapy of patients with CP and social significance of this disease causes the necessity of pharmacoeconomic analysis of registered in Russia botulinum toxin (BTA) preparations with the aim of reducing costs in the health budget and optimizing existing treatment regimens.

Preparations of botulinum toxin type A are included in the basic treatment of local spasticity in CP in the world practice for over 15 years. Timely, targeted correction of muscle tone helps to change the pattern of walking, verticalization and supporting ability of the lower limbs, learn new movement skills and provide substantial improvement in the quality of life of patients [4].

It should be noted that the formation of contractures and deformities of the extremities in children with CP often cause the need for surgical correction. It is shown that in the long term, multi-stage orthopedic surgery in older children with cerebral palsy have lower risk of recurrence than surgery carried out in the period of active growth. In this regard, there is a particular value of the kinds of therapy helping to avoid surgery or permitting operation at a later period. [5]

The aim of this study was to determine the most appropriate integrated scheme of CP therapy from the pharmacoeconomic perspective in the healthcare system of the Russian Federation for the period of 4 months, 1 year and 2 years. Study period of 4 months is explained with the duration of one course of treatment, and the period of study 1 year is the most acceptable from the point of view of budget formation of the healthcare system. The data for 2 years are particularly important, since they allow to evaluate the influence of different types of therapy in the long term.

To achieve this goal the following tasks were consistently performed:

1. Information retrieval and examination of international and national experience of care for patients with cerebral palsy.
2. Efficiency analysis, including the selection of performance criteria of studied therapy of the spastic forms of CP.
3. Cost analysis using compared treatment regimens for cerebral palsy.
4. Conduct of pharmacoeconomic research analyses: budget impact, cost-effectiveness analysis and sensitivity analysis.

Built as a result of research, model in Microsoft Excel 2013 allows both at the federal and regional level computer simulation of the clinical and economic consequences of decisions regarding the choice of medicines for the treatment of CP using modern methods of pharmacoeconomic analysis, as well as making a prognosis of the budget within 4 months, 1 year and 2 years, using valid epidemiological and clinical data. [6]

Ugrekhelidze D.T. tel.: 8(916) 298 70 31, e-mail: dtu1992@gmail.com

Materials and data

Efficacy analysis

In this study we considered three alternative treatment schemes: Dysport® (450-500 U)+standard therapy, Botox®(120-200 U)+standard therapy and standard therapy without the use of preparations of botulinum toxin (BTA). During calculation of dosages the study authors were guided by clinical guidelines authored by leading experts in the field of botulinum toxin therapy «ABC of botulinum toxin therapy [7]», and considered that the average weight of patients in the studies used in this pharmacoeconomic analysis was 25 kg. The assumption is made that in a simulated population of patients with prevalent cases of spastic diplegia, as this form of the disease is the most common among all the spastic forms of cerebral palsy. [40] Standard therapy did not include the use of botulinum toxin, in this cohort, patients received a centrally acting muscle relaxants (Baclofen). Patients in all groups of patients was conducted physiotherapy, also in all the groups, if necessary, was conducted casting. Standard therapy is based on the standard of providing inpatient and outpatient medical care «Standard of primary health care in children with cerebral palsy» and «Standard of specialized medical care in children with cerebral palsy» [8,9]. The study took into account the population of children population of the Russian Federation with spastic forms of cerebral palsy aged 2 to 14.

During the first phase of this research an information retrieval of RCT using data from major bibliographic databases: Medline, Medscape, PubMed, Cochrane Library, and the search was conducted according to the world database of open clinical trials clinicaltrials.gov was conducted. [35-38]. During the information retrieval domestic pharmacoeconomic study «Pharmacoeconomics of botulinum toxin in complex therapy of cerebral palsy», [10] devoted to the problem of pharmacoeconomics of CP of the Russian Federation was found. Noteworthy that during the cost analysis the dose of Dysport® 1000 U was used different from the dosages described in the table of studies authored by M. W. Baird et al 2010, Baker R et al 2002, Ubhi T. et al 2000. [11-13] and in none of the studies used as a basis for evaluating the efficacy of the drug Dysport® are not described using the maximum permitted doses according to the instructions for medical use of the drug in quantities of 1,000 U of the drug on the treatment cycle. Thus, the choice of 1000 U dose had a significant impact on the final result of cost-effectiveness analysis and budget impact analysis. It should be noted that proper selection of dosages of compared drugs and calculations according to the standards of the Ministry of Health «Standard of primary health care in children with cerebral palsy» and «Standard of specialized medical care in children with cerebral palsy» will give a more accurate pharmacoeconomic evaluation of therapy of the spastic forms of CP in healthcare conditions of the Russian Federation.

During standardization of studies, the authors made the criteria of RCT in efficacy analysis.

Inclusion criteria:

- Age of patients ranged from 2 to 14 years
- Absence of contractures in spastic muscles of the lower limbs
- Patients not previously endured surgery on the studied muscles
- Patients were not taking the centrally acting muscle relaxant during the BTA treatment and did not receive the blockade with phenol and ethanol
- BTA was injected in the same muscle
- Equinus gait: m.Gastrocnemius, m. Soleus
- Equinovarus gait: m.Gastrocnemius, m. Soleus, posterior Tibialis
- At the beginning of the study, the degree of spasticity in the studied muscles above 2 points on the Modified Ashworth Scale
- All patients are able to walk by themselves or using walking aids

As a result of information retrieval, we selected two clinical studies of the efficacy and safety of the botulinum toxin (Dysport® and Botox®) administration with the use of standard therapy, where clinical indicator used was the proportion of patients who avoided surgery on the 1st and 2nd year of therapy.

- Kanovský P., Bares M., Severa, S., Richardson A. Long-term efficacy and tolerability of 4-monthly versus yearly botulinum toxin type A treatment for lower-limb spasticity in children with cerebral palsy. Dev Med Child Neurol 2009; 51: 6: 436-445 - (International multicenter, randomized, blinded for the expert evaluators data to study the efficacy and safety of the drug Dysport® in parallel groups at a dosage of 25-30 U/kg with the participation of 104 patients.) [14]
- Molenaers G1, Desloovere K, Fabry G, De Cock P. The effects of quantitative gait assessment and botulinum toxin a on musculoskeletal surgery in children with cerebral palsy. J Bone Joint Surg Am. 2006 Jan;88(1):161-70. (Retrospective study of efficacy and safety of the drug Botox® in parallel groups in the dosage of 14-31 U/kg involving 424 patients.) [15]

Efficacy analysis

In the efficacy analysis authors considered such indicators as decreased muscle tone according to the Modified Ashworth Scale, the change in global motor function scale GMFM-88, the proportion of patients who avoided surgery on the 1st and 2nd year of therapy.

According to clinical recommendations Modified Ashworth Scale is the most widely used method of measuring muscle tone in patients with neurological disorders at the present time. The advantages of using this scale are reliability, ease of processing of the results, correlation with the scales of disability. To assess muscle tone, the doctor slowly passively flexes or extends a limb of a patient in a particular segment and assesses the degree of resistance of this muscle tension in the scores on the MAS.

Table 1. 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 [16].

So, as a result of indirect comparison it can be seen that by the end of year 1 therapy with botulinum toxin Dysport®+standard therapy reduces muscle tone by 1.2 points, the scheme Botox®+standard therapy by 0.5 points, and standard therapy without BTA by 0.2 points. [31-33] It should be noted that if necessary, casting was conducted in all studied groups conducted. [17]

To assess the change in global motor function by the end of 4 months international randomized trials data on the Gross Motor Function Measure scale with 88 item to was used. The scale was created by the «Centre for childhood disability research» of the Canadian McMaster University and it is an international standard for the evaluation of motor skills of patients with cerebral palsy, representing a detailed list of 88 of assignments in large items: displacement in the supine position, sitting, crawling, walking, running and jumping. Possession of the child each skill is evaluated on a four point system:

0 – does not initiate,
1 – initiate.
2 – partially completes;
3 – completes.

The resulting scores are added together and using a special formula of quantitative measure of motor development is calculated. Often in clinical trials indicated a change in the target item, which can be expressed in percent of the maximum value. In particular, in this pharmacoeconomic study compared data on the improvement in the item «Walk» as a percentage on a 4 month therapy. [11]

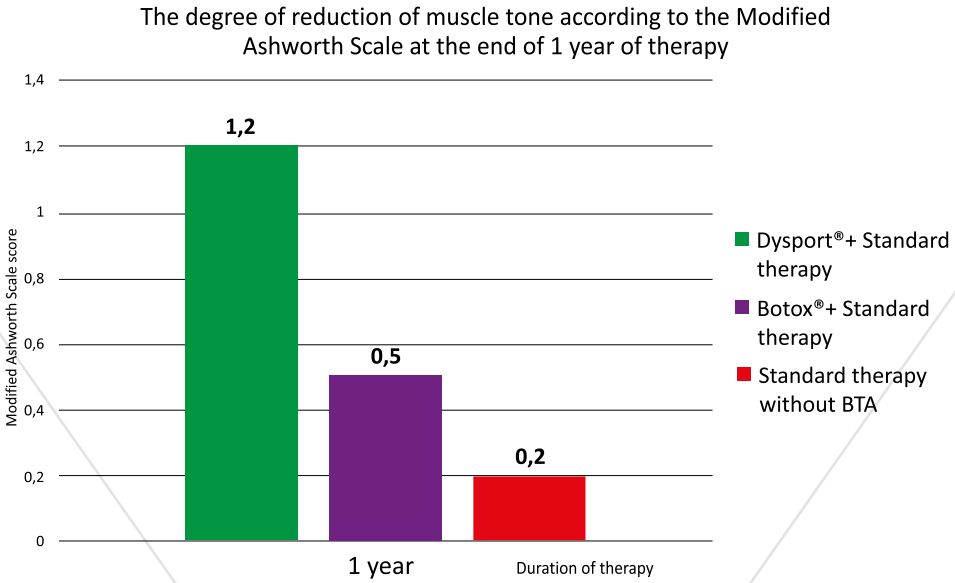

Figure 1. The degree of reduction of muscle tone according to the Modified Ashworth scale at the end of 1 year of therapy.

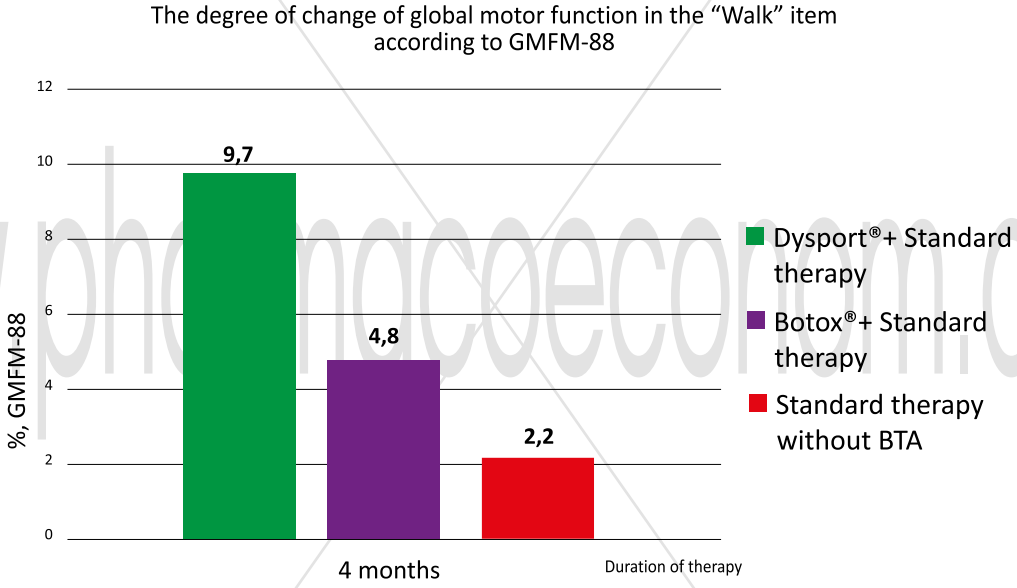

Figure 2. The degree of change of global motor function in the «Walk» item according to Gross Motor Function Measure - 88 in percentage terms.

So, as a result of indirect comparison, a 4 month therapy with botulinum toxin Dysport®+standard therapy provides improvement in the «Walk» item by 9.7% on a scale GMFM-88, drug therapy Botox® + standard therapy and standard therapy without BTA provide an improvement of 4.8% and 2.2% respectively. [11,34]

The formation of contractures and deformities of the extremities in children with cerebral palsy often causes the need for surgical correction. In the long term, surgery in older children with cerebral palsy have lower risk of recurrence compared with the operations carried out in early childhood. In this regard, there is a particular importance of botulinum toxin therapy effect on the likelihood of reducing the frequency of the orthopedic surgeries or postponing them at a later period by reducing spasticity and prevent contractures. [15,16]

For this purpose, it was conducted an indirect comparison for estimating the share of patients avoided surgery.

As a result of indirect comparison it was revealed that the therapy with botulinum toxin Dysport®+standard therapy helps to avoid surgical intervention in 93% of patients compared to 90% of patients during the treatment regimen Botox®+standard therapy and for 48% of patients with standard therapy. By the end of year 1 of 97.5% do not undergo surgery using the treatment Dysport®+standard therapy, in the treatment group of Botox®+standard therapy – 93% avoid surgery, in the group with standard therapy there were 56% ones.

The proportion of patients who avoided surgery on the 1st and 2nd year of therapy is the basic criterion of efficacy in this pharmacoeconomic study, because in addition to its clinical importance, this criterion of efficacy is the most suitable from the point of view of pharmacoeconomic analysis, allowing to calculate the impact of reducing the frequency of operations on the health budget.

Summarizing the obtained data, we can say that the therapy with botulinum toxin Dysport® is more effective from the viewpoint of reducing the frequency of surgical interventions [14,15], reduction of spasticity [31-33], changes of gross motor functions compared with other drugs BTA and standard therapy without BTA [11,34].

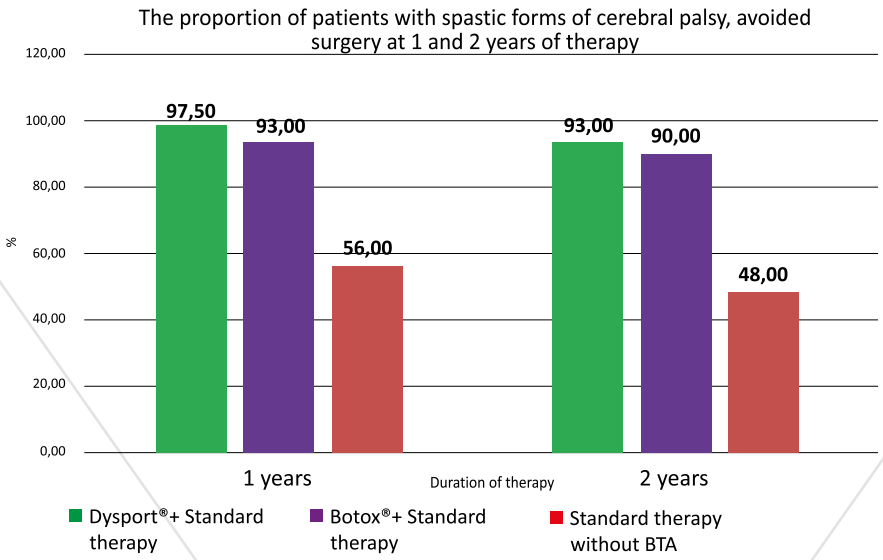

Figure 3. The proportion of patients with spastic forms of cerebral palsy, avoided surgery at 1 and 2 years of therapy

Cost analysis

Direct and indirect costs were taken into account during this pharmacoeconomic study:

Direct costs:

- Cost of BTA therapy
- The cost of correction of side effects of therapy BTA
- Costs for inpatient and outpatient medical care
- Costs for sanatorium-resort medical care
- Costs for casting
- Costs for orthopedic interventions

Indirect costs:

- Disability pensions
- Disable child care benefit

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 [18]. On 29.04.2015 year manufacturer's price for 1 vial of the drug Dysport® volume of 500 U is 14389 rubles, the manufacturer's price for 1 vial of the drug Botox® volume 100 U equals 11905 rubles. Focusing on the range of doses taken during the performance review when calculating the cost of botulinum therapy, the authors proceeded from the fact that during treatment course the patient received either 1 vial of Dysport® 500 U + standard therapy or 2 vials Botox® + standard therapy. In the calculations the authors assumed time horizon 4 months, 1 year and 2 years and frequency of taking the drug 3 times a year, which is the most frequently used treatment regimen in accordance with the recommendations of the clinical management of patients with cerebral palsy [1].

The cost of medical care consisted of expenditures on primary health care on an outpatient basis and expenses on specialised medical care in a hospital environment. [20] The cost of sanatorium care were calculated Separately. Medical services for disease diagnosis, treatment of disease, condition and treatment control, and also the list of medicinal products for medical use for the treatment of this disease indicating the average daily and course doses were taken from the two projects of standards of the Ministry of Health: «Draft standard for primary health care in children with cerebral palsy» and «Draft standard of specialized medical care in children with cerebral palsy». [21] These standards are the most modern ones of medical aid to children with cerebral palsy on 29.04.2015. The cost of sanatorium care was calculated on the basis of the Order of the health Ministry of the Russian Federation No. 213, dated 22.11.2004 g «On approval of the standard sanatorium-resort care for cerebral palsy patients»[19]

Costs were calculated using the following formula [21]:

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

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

The costs of diagnostic and therapeutic procedures have been calculated on the basis of prices provided in the tariffs of the Federal mandatory health insurance Fund of Moscow. [22] In the calculation of the cost of pharmacotherapy of patients as the source of prices price list of the vital and essential drugs in Russia was used in the absence of the drug in this list, the information was taken from the database of prices of medicines www.pharmindex.ru/. [23] It should be noted that the study took into account the prices of the manufacturer, as the study was conducted from the perspective of a public health professional.

Costs were calculated using formula:

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

FI – frequency of indication
EDD – estimated daily dose
DT – duration of treatment

The cost of correction of side effects was calculated as follows: the frequency and pattern of side effects were determined based on data from randomized clinical trials and guidelines regarding the use of drugs BTA and the muscle relaxant Baclofen [28-30], as well as standards of medical care, and the cost of therapy was derived from the rates of the Federal mandatory health insurance Fund Moscow, the category of «Cost per completed case.»

The cost of casting was taken from national pharmacoeconomic studies «Pharmacoeconomics of botulinum toxin in complex therapy of cerebral palsy» authored by Professor A.S.Kolbin and colleagues.

The cost of orthopedic operations was calculated on the basis of the Decree of the RF Government dated 28 November 2014 No. 1273 «On the programme of state guarantees of free rendering to citizens of medical care for 2015 and on planning period 2016 and 2017».

According to the clinical studies used in the efficacy analysis under orthopedic surgeries in this pharmacoeconomic study was determined the standard single-level orthopedic intervention (lengthening of the Achilles tendon) and multi-level single-stage orthopaedic surgery. The list of possible multilevel orthopaedic surgery was taken from the study Molenaers et al.,2006, interventions on soft tissues included: lengthening of the psoas, adductor longus (and brevis) and medial hamstrings; transfer of the rectus femoris to either the gracilis or semitendinosus muscles; procedures involving the gastrocnemius, including Achilles tendon lengthening; peroneal muscle lengthening; tibialis posterior lengthening or split transfer; tibialis anterior split transfer; and flexor halluces longus and abductor hallucis lengthening. Osseous deformities were corrected by means of acetabular procedures (acetabuloplasty), proximal femoral varus derotation osteotomy, distal tibial derotation osteotomy, and foot stabilization surgery (calcaneus lengthening combined with medial soft-tissue shortening, or subtalar arthrodesis). It should be noted that the amount of multi-level single-stage orthopaedic surgery conducted in the Russian Federation is significantly lower compared with Western healthcare systems.

In particular, we used the data about Standards of financial costs per unit of volume rendering high-tech medical care.

Costs in this document include:

- The cost of surgery
- The cost of anesthetics
- The cost of hospitalization
- Wage costs and accruals for wages
- Acquisition costs of drugs, consumables, food, soft equipment, medical instruments, reagents and chemicals
- The cost value of laboratory and instrumental research conducted at other institutions (with no medical organization in laboratory and diagnostic equipment)
- The cost of catering (in the absence organized nutrition in medical organization)
- The cost of communication services, transport services, utilities, works and services for asset maintenance
- Rent expenses for the use of property, payment software and other services
- Social security of employees of medical organizations, established by the legislation of the Russian Federation
- The cost of acquisition of fixed assets (equipment, fixtures and fittings) value to one hundred thousand per unit.[25]

Calculation of standard orthopaedic surgeries was carried out according to section «Removal of defects and deformations by skin and tendon-muscle surgeries» of the Program of state guarantees, the amount of expenses amounted to 164 112 rubles per unit volume of high-tech medical care. The list of interventions included in multi-level single-stage operations was taken from the article by D. A. Popkov and co-authors [41]. For multi-level one-stage operations were taken into account the costs of such interventions, as corrective osteotomy of the bones of the lower limbs (112 515 rbl.) and reconstructive surgery on the bones of the foot, with the use of auto - and allografts,implants,of osteogenesis materials, metal products (164 112 rubles) and elimination of defects and deformations by skin and muscle-tendon surgeries, bone autoplastic and alloplastic using external and internal fixator (164 112 rbl.) Overall costs of single-stage multilevel surgery amount 440 739 rubles. In this study, the assumption was made that the standard orthopedic operations account are 95% of all surgeries and singe-stage multilevel intervention – 5%.

Indirect costs were also calculated. In this study, the following costs were included: disability pension and care allowance for disabled children. During calculation of indirect costs information retrieval of main legislative acts relating to social welfare payments for patients with cerebral palsy and their families was conducted. [39] Consequently, in accordance with article 18 of the Federal law of 15 December 2001 No. 166-FZ «On state pensions in the Russian Federation» pensions for disabled children in 2015 are 11 618 rubles a month. [26] The amount of care allowance for disabled children in 5500 rubles was determined according to the presidential Decree of 26 February 2013 № 175 «On monthly cash payments to unemployed able-bodied persons caring for a disabled child under the age of 18 or a disabled person since the childhood of I group». [27]

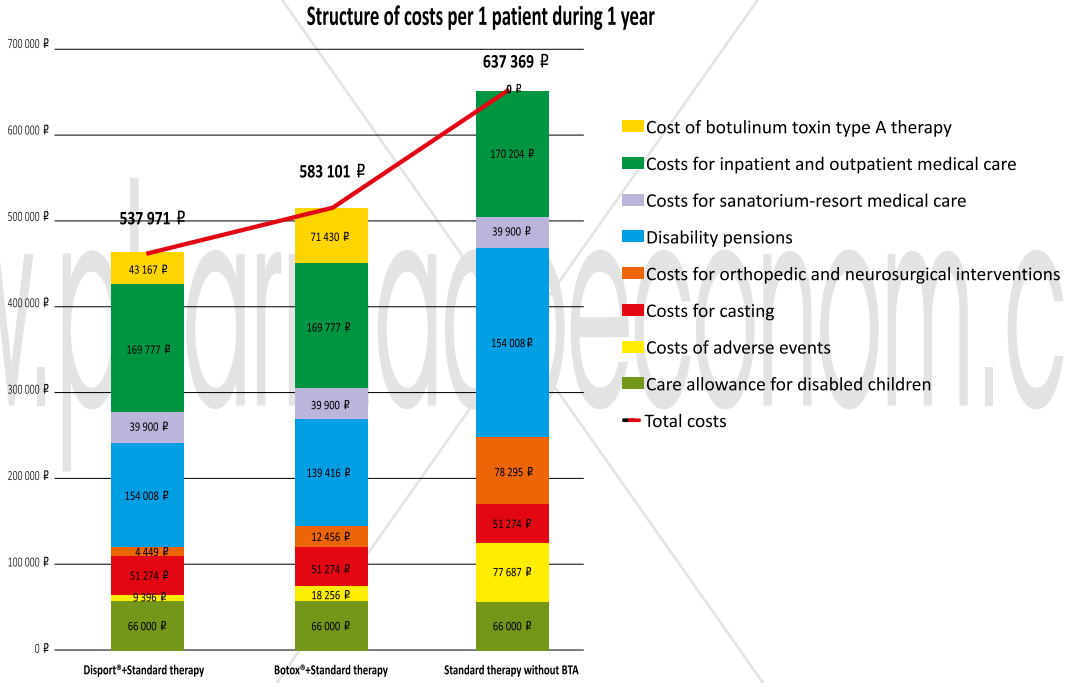

Figure 4. The structure of costs per patient with spastic forms of cerebral palsy for 1 year.

Table 2. The cost structure for the entire population of patients with spastic forms of cerebral palsy by the end of 2 years.

	DYSPORT® + standard therapy	BOTOX® + standard therapy	Standard therapy without BTA
Cost of botulinum toxin type A therapy, rubles.	4 825 984 266	7 985 771 387	0
Costs for inpatient and outpatient medical care	18 980 759 531	18 980 759 531	19 028 492 268
Costs for sanatorium-resort medical care	4 460 740 200	4 460 740 200	4 460 740 200
Disability benefit, rubles	15 586 429 968	15 586 429 968	15 586 429 968
Care allowance for disabled children, rubles	7 378 668 000	7 378 668 000	7 378 668 000
Costs of adverse events, rubles	1 050 441 095	2 040 956 003	8 685 304 229
Costs for casting, rubles	5 732 330 652	5 732 330 652	5 732 330 652
Costs for orthopedic interventions, rubles	696 279 873	994 685 532	5 172 364 767
Total costs	**60 342 990 001**	**64 791 697 689**	**67 675 686 501**

Table 3. The cost structure for 1 patient with spastic forms of cerebral palsy by the end of 2 years.

	DYSPORT® + standard therapy	BOTOX® + standard therapy	Standard therapy without BTA
Cost of botulinum toxin type A therapy, rubles.	86 334	142 861	0
Costs for inpatient and outpatient medical care	339 555	339 555	340 408
Costs for sanatorium-resort medical care	79 800	79 800	79 800
Disability benefit, rubles	278 832	278 832	278 832
Care allowance for disabled children, rubles	132 000	132 000	132 000
Costs of adverse events, rubles	18 792	36 511	155 375
Costs for casting, rubles	102 548	102 548	102 548
Costs for orthopedic and neurosurgical interventions, rubles	12 456	17 794	92 531
Total costs	**1 079 500**	**1 159 085**	**1 210 678**

Cost-effectiveness analysis

Cost-effectiveness analysis is used to estimate the cost of the efficiency unit of compared health technologies [23]. Thus, this type of pharmacoeconomic analysis allows to compare the studied technologies not only on the basis of the final values of the cost analysis, but also by calculating cost-effectiveness ratio.

Cost-effectiveness ratio is calculated using formula:

$$CER = \frac{Cost}{Ef}$$

CER – cost-effectiveness ratio»; Cost – costs for studied health technology, rubles.; Ef – efficacy of studied technology. This type of pharmacoeconomic analysis allows to determine how the costs and efficacy correspond with each other, and using these data choose the most appropriate health technology.

As it was described above, the percent of patients avoided surgery by the 1st and 2nd year of therapy was chosen as efficacy criteria. Results of cost-effectiveness analysis are presented in table 4.

Total costs by the end of 2nd year using Dysport®+standard therapy were lower than using standard therapy by 259 983 rubles (19,5%). Efficacy of treatment was 45% higher.

CER of Dysport® by the second year was 11 608 rubles per efficacy unit compared with standard therapy (25 222 rubles) for 2nd year. Botox® is also more cost-effective compared with standard therapy having CER 12 879 rubles but less than Dysport®+standard therapy. Results of cost-effectiveness analysis are presented in table 4 and figure 5.

Table 4. The results of the cost-effectiveness ratio comparison in the treatment of spastic forms of cerebral palsy at 1 year, 2 years.

Treatment scheme	CER for 1 year, rubles	CER for 2 years, rubles
Dysport®+standard therapy	5518	11608
Botox®+standard therapy	6270	12879
Standard therapy without BTA	11382	25222

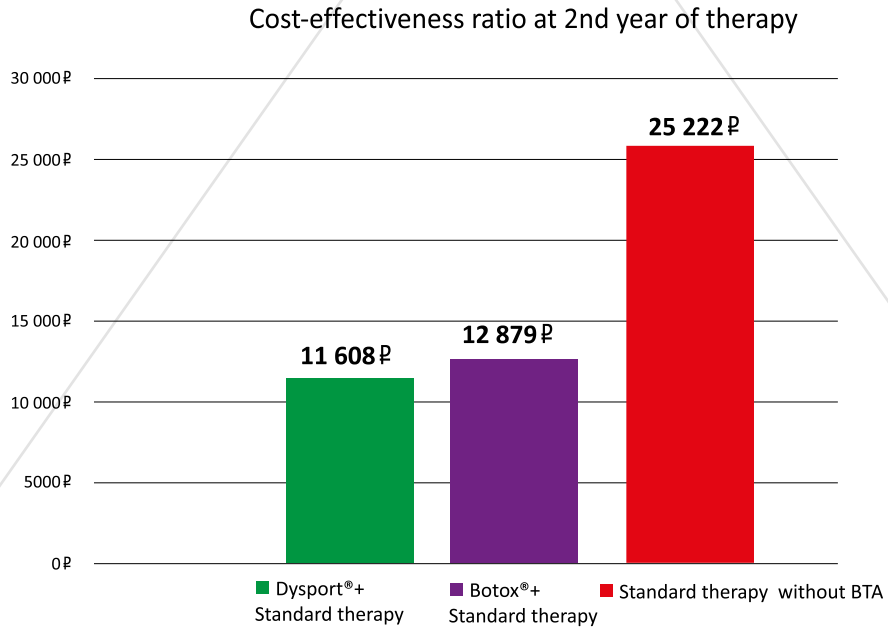

Figure 5. Results of cost-effectiveness ratio comparison in cerebral palsy treatment by the end of 1st and 2nd year.

On the basis of obtained results it can be concluded that treatment with Dysport®+standard therapy is a dominant alternative to any other therapy spastic forms of cerebral palsy and strictly preferable from the point of view of pharmacoeconomic analysis.

Budget impact analysis

The use of the budget impact analysis means an estimate of all costs associated with the implementation of the new scheme of treatment of all kinds of expenses existing regimens [22].

The calculation of costs is made by using the formula:

$$BIA = Cost^1 - Cost^2 ,$$

Cost1 – total cost of health technology, rubles;
Cost2 – total cost of health technology, rubles;
BIA - budget impact analysis result in rubles.

As a result of budget impact analysis it was found that the use of Dysport®+standard therapy for 2 year therapy would save 7 332 696 500 rubles compared with standard therapy, and there are savings 4 448 707 689 rubles compared with the scheme Botox®+standard therapy in the calculations to the entire population. As for 1 patient Dysport®+standard therapy for 2 year therapy would save 131 178 rubles compared with standard therapy, and there are savings 79 585 rubles compared with the scheme Botox®+standard therapy

For the least expensive therapy, an analysis of missed opportunities was conducted, it's aim to calculate the number of potential patients who could be further to provide medical care when changing treatment. We performed a simulation involving a potential change in the distribution of treatment regimens with 100% standard therapy without BTA scheme Dysport®+standard therapy in two versions (30% and 70%). As a result it is calculated that if the ratio is «30% Dysport®+standard therapy and 70% standard therapy without BTA» additional number of children who received treatment were 2,037, while in the scheme «70% of botulinum toxin Dysport® + standard therapy and 30% standard therapy without BTA additional number of children who received treatment were law 4,754.

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 and centrally acting miorelaxant Baclofen 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 -50% to 100%.

Table 5. Single- factor sensitivity analysis of CER in case of the change in the price of BTA in for 1-year therapy

Price range	-50%	0%	50%	100%
Dysport®+standard therapy	5 296	5 960	5 739	5 960
Botox®+standard therapy	5 886	7 038	6 654	7 038
Standard therapy without BTA	11 378	11 389	11 385	11 389

During single-factor sensitivity analysis it was determined that all parameters in -50% to 100% change did not demonstrate dominative character of Dysport®+standard therapy compared with alternatives: CER in Dysport® +standard therapy remained lower in all conditions.

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

Conclusion

From the perspective of pharmacoeconomic analysis of drug therapy Dysport® in combination with standard therapy is preferable for use, as this scheme allows to minimize the possibility of surgery or postpone it to a later date, can reduce the degree of spasticity and improves gross motor function in patients with spastic forms of cerebral palsy with lower costs compared with other medication botulinum toxin – Botox®+standard therapy and compared with standard therapy without BTA with the use of a Central action muscle relaxant Baclofen.

References

1. T. T. Batysheva. Treatment of spasticity in children with cerebral palsy. Guidelines No. 15.Moscow, 2011
2. General morbidity of children population of Russia (0 — 14 years) in 2012 year. The statistical material. The fgbi «Central scientific-research Institute of organization and Informatization of health»
Ministry Of Health Of Russia. Moscow 2013 [Electronic resource]. URL: http://www.rosminzdrav.ru/docs/mzsr/stat/47.
3. Dutikova E. M., Lilin E. T. botulinum toxin type a (Dysport) in the treatment of of cerebral palsy. Farmateka 2007; 7: 142: 37-42.
4. Heinen F, Desloovere K, Schroeder AS, et al. (January 2010). «The updated European Consensus 2009 on the use of Botulinum toxin for children with cerebral palsy». Eur. J. Paediatr. Neurol. 14 (1): 45–66.
5. BZmanovskaya V. A., Levitina E. V., D. A. Popkov, M. N. Butorina, O. L. Pavlova. Prolonged use of the drug botulinum toxin type A: Dysport® in the complex rehabilitation of children with spastic form- mi cerebral palsy. Journal of neurology and psychiatry. S. S. Korsakova 2014; 7: 33-36
6. Khabriev R.U., Kulikov A.Yu., Arinina E.E. Methodological basis of pharmacoeconomic analysis. Moscow: publisher "Medicine", 2011. – 128 pages.
7. The team of authors under the editorship of S. L. Timerbaeva. The ABCs of the botulinum toxin therapy. M.: Practical medicine. 2014. 416 p
8. The draft departmental order «On approval of the standard of primary health care in children with cerebral palsy»
9. Departmental order «On approval of the standard of specialized medical care in children with cerebral palsy»
10. Kolbin, A. S. Pharmacoeconomics of the use of botulinum toxin in the complex therapy of cerebral palsy / A. S. Kolbin, I. A. Vilum,M. A. Proskurin. - P. 14-23
11. Ubhi T, Bhakta BB, Ives HL, Allgar V, Roussounis SH. Randomised double blind placebo controlled trial of the effect of Botulinum toxin on walking in cerebral palsy. Arch Dis Child 2000;83(6):481–7.
12. Baker R., Jasinski M., Maciag-Tymecka I. et al. Botulinum toxin treatment of spasticity in diplegic cerebral palsy: a randomized, double-blind, placebocontrolled,dose-ranging study. // Dev Med Child Neurol 2002; 44: 666—75.
13. Baird M.W., Vargus-Adams J. Outcome measures used in studies of botulinum toxin in childhood cerebral palsy: a systematic review. // J Child Neurol.
14. Kanovský P., Bares M., Severa S., Richardson A. Long-term efficacy and tolerability of 4-monthly versus yearly botulinum toxin type A treatment for lower-limb spasticity in children with cerebral palsy. Dev Med Child Neurol 2009; 51: 6: 436-445
15. Molenaers G1, Desloovere K, Fabry G, De Cock P. The effects of quantitative gait assessment and botulinum toxin a on musculoskeletal surgery in children with cerebral palsy. J Bone Joint Surg Am. 2006 Jan;88(1):161-70.
16. Love S.C., Novak I., Kentish M., Desloovere K., Heinen F., Molenaers G., O'Flanerty S., Graham Y.K. Botulinum toxin assessment, intervention and after-care for lower limb spasticity in children with cerebral palsy: international consensus statement. European Journal of Neurology 2010; 17: Suppl 2: 9-37.
17. Koman L.A., Mooney J.F., Smith B.P., et al. Botulinum toxin type A neuromuscular blockade in the treatment of lower limb spasticity in cerebral palsy: a randomized double-blind placebo controlled trial. // J Pediatr Orthop 2000; 20: 108-115.
18. Data about the maximum selling prices of manufacturers on vital and essential drugs http://grls.rosminzdrav.ru (accessed 11.04.2015)
19. The order of the health Ministry of the Russian Federation No. 213, dated 22.11.2004 «On approval of the standard of the sanatorium help children with cerebral palsy»
20. Yagudina R.I., Serpik V.G. On the possibilities of combining budget impact analysis and cost-effectiveness analysis - development of «3D» pharmacoeconomic model // Pharmacoeconomics: theory and practice. - 2014. - Vol.2, №3. - P.9-13
21. Kulikov A.Yu., Ugrekhelidze D.T. Pharmacoeconomic study of botulinum toxin type A in treatment of post-strok e spasticity in the upper limb // Pharmacoeconomics: theory and practice. - 2014. - Vol.2, №3. - P.38-46
22. Information resource http://pharmindex.ru (accessed 11.02.2015)

23. The rates of the Federal Fund of obligatory medical insurance 2015
24. The branch standard «Clinico - economic studies. General provisions» (OST 91500.14.0001-2002))
25. The RF Government decree dated 28 November 2014 No. 1273 «About the programme of state guarantees of free rendering to citizens medical care for 2015 and on planning period 2016 and 2017 years.».
26.Article 18 of the Federal law of 15 December 2001 № 166-FZ «On state pensions in the Russian Federation»
27. The decree of the President of the Russian Federation from February 26, 2013 № 175 «On monthly cash payments to the idle able-bodied persons caring for a disabled child under 18 years or disabled with childhood of I group».
28. Leaflet of the drug Dysport. The state register of medicines. http://grls.rosminzdrav.ru/grls.aspx
29. Leaflet of the drug Botox. State register medicines. http://grls.rosminzdrav.ru/grls.aspx
30. nstructions for use of the drug Baclosan. State register of medicines. http://grls.rosminzdrav.ru/grls.aspx
31. Ackman JD, Russman BS, Thomas SS, Buckon CE, Sussman MD, Masso P, et al. Comparing Botulinum toxin A with casting for treatment of dynamic equinus in children with cerebral palsy. Dev Med Child Neurol 2005;47(9):620–7.
32. Bottos M1, Benedetti MG, Salucci P, Gasparroni V, Giannini S/Botulinum toxin with and without casting in ambulant children with spastic diplegia: a clinical and functional assessment.Developmental Medicine & Child Neurology 2003, 45: 758–762
33. A. Leland Albright. Topical Review: Baclofen in the Treatment of Cerebral Palsy. J Child Neurol 1996 11: 77
34. Love SC, Valentine JP, Blair EM, Price CJ, Cole JH, Chauvel PJ. The effect of botulinum toxin type A on the functional ability of the child with spastic hemiplegia a randomized controlled trial. Eur J Neurol 8 (Suppl. 5): 50–58. 97.
35. Mall V, Heinen F, Siebel A, Bertram C, Hafkemeyer U, Wissel J, et al. Treatment of adductor spasticity with BTX-A in children with CP: a randomized, double-blind, placebocontrolled study. Dev Med Child Neurol 2006;48(1):10–3.
36. Russo RN, Crotty M, Miller MD, Murchland S, Flett P, Haan E.Upper-limb Botulinum toxin A injection and occupational therapy in children with hemiplegic cerebral palsy identified from a population register: a single-blind, randomized, controlled trial. Pediatrics 2007;119(5):e1149–58.
37. Scholtes VA, Dallmeijer AJ, Knol DL, Speth LA, Maathuis CG,JongeriusPH,et al.The combined effect of lower-limb multilevelBotulinumtoxin type a and comprehensive rehabilitation onmobility in children with cerebral palsy: a randomized clinicaltrial. Arch Phys Med Rehabil 2006;87(12):1551–8.
38. Sutherland DH, Kaufman KR, Wyatt MP, Chambers HG, Mubarak SJ. Double-blind study of botulinum A toxin injections into the gastrocnemius muscle in patients with cerebral palsy. Gait Posture. 1999 Sep;10(1):1-9.
39. An informational resource. Website for people with disabilities http://doorinworld.ru/stati/ (date accessed – 04.06.2015)