Estimating economic efficiency of preclinical diagnostics of Parkinson's disease with cost-utility approach

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Abstract

Neurodegenerative diseases, Parkinson's disease among them, set challenges to modern societies both in terms of premature deaths and resources spent on treatment of the diseases. At that, preventive care and early diagnostics in particular are potential directions towards higher economic efficiency of healthcare interventions in this area. Authors of this paper suggest a modification of the cost-utility approach to evaluate economic efficiency of an early diagnostics at the presymptomatic (prodromal) stage of PD, when its symptoms do not appear clinically yet. Such diagnostics, in combination with neuroprotective therapy for persons at high risk of PD, allows postponing its development until later years, and thereby ensuring an improvement in the quality of life of the population, as well as saving resources of the healthcare system and society as a whole. The authors rely on the diagnostic approach proposed by the research group headed by M. Ugryumov, which is currently at the stage of laboratory testing. Its implementation potentially leads to savings in both direct and indirect costs for PD treatment compared to the traditional approach, but increases testing costs, and also requires the development of new neuroprotective therapy for identified risk groups. The authors propose a modification of the cost-benefit assessment procedure to take into account the uncertainty associated with the lack of a final understanding of the scope and composition of the testing group at the preclinical stage. The condition for the economic efficiency of the preclinical diagnostic method in the developed procedure is the minimum permissible probability of detecting an increased risk of PD in the test group. To test their algorithm, the authors carry out calculations basing on the Russian data.

Introduction

In modern society Parkinson's disease (hereinafter referred to as PD) poses a serious challenge since it is one of the most common neurodegenerative disorders with high comorbidity and mortality rates. Besides, quite difficult to diagnose, the disease is usually detected already after the onset of the symptoms (Beitz 2014). The number of patients with PD is growing quickly across the globe, with the highest rates of increase occurring in developed nations since the disorder mostly affects people in the older age cohorts, who are most likely to develop the disease (Bovolenta et al. 2017). Thereby, the task of optimizing the care of these patients and improving their quality of life requires a better knowledge of the symptoms of PD, its treatment methods and prospects thereof, as well as the related costs.

Studies show that the costs of treating PD grow as the disease progresses from an early to a late stage, when the symptoms become more severe. The development of new life-sustaining measures, adding years to life and, accordingly, the treatment period, also contributes to cost increases. Consequently, a great deal of attention is being paid not only to early diagnostics, which usually means diagnosing at a clinical stage, when the symptoms of PD are already obvious and the irreversible loss of dopaminergic innervation is in progress, but also to the disease detection at an earlier, presymptomatic stage. Presently neurobiologists discuss prospects of the development of an innovative technology of presymptomatic diagnostics of PD – at a prodromal stage, before clinical phase; such technology, when applied to at-risk individuals in combination with the subsequent neuroprotective therapy, is bound to add years to the patients' lives and improve their quality of life (Ugrumov 2020). The disease detection at that stage would slow down its progress while also reducing the costs related to the treatment and rehabilitation. The issue of preclinical diagnosis is undoubtedly relevant for other conditions as well, but it is especially important with relation to neurodegenerative diseases, including PD and Alzheimer's. The distinctive characteristic of these diseases is that pathologies start developing long before clinical symptoms appear, at which stage the progress of the disease can be only slowed down. In view of this, the preclinical diagnosis would allow to delay the onset of symptoms and, therefore, make active life expectancy longer, enhance the quality of life and reduce the costs, which grow as the disease progresses. In the case we discuss within this paper, putting into practice the new method of PD's presymptomatic diagnostics will have not only important clinical implications but also the economic significance.

The objective of this study is to propose a method for estimating the efficiency of the preclinical (presymptomatic) diagnostics of PD and, when needed, the subsequent neuroprotective therapy in a situation when major economic parameters are uncertain; and this method is a part of the complex economic study of the innovative methods of PD's preclinical diagnostics, which is currently under development.

Our review of literature, including both Russian and international sources, identified methods of estimating healthcare costs currently in use and their distinctive features. In

this paper we mostly apply the cost-utility approach to evaluate the economic effect of the introduction of the presymptomatic diagnostics of PD and the concomitant neuroprotective therapy. We adjusted this method in terms both of estimating costs and evaluating effects (utility) because the new methods of presymptomatic diagnostics are still under development and some of the economic parameters, therefore, cannot be assessed not only through the use of statistical data but even by expert opinion. We propose a modified method of the cost / utility assessment that accounts for this uncertainty.

The lack of clear understanding of what the size and composition of the preclinical stage testing group should be is the most serious obstacle to estimating the economic effects of early diagnosis at a presymptomatic stage of PD. Relatively small costs of testing per one individual included into the test group can swell into huge expenses *per one case of detected PD*, if the criteria for inclusion into this test group are too broadly defined (for instance, all population older than 45 years). Compared to this, the lack of precision in expert estimates of the other economic parameters, which is inevitable at an innovative approach's development stage, produces a relatively small margin of error. We, therefore, propose to evaluate the economic efficiency of the presymptomatic diagnostics applying such indicator as the minimally acceptable probability of identifying individuals at risk of PD in a test population.

We tried the elaborated algorithm using data from Russia. This study relies on the methodology of diagnosing PD at prodromal phase proposed by the academician M.V. Ugrumov's group (Kim et al. 2020; Ugrumov 2020), the development of which, at the time of this study, is yet at a preclinical stage. The new methods involve tests, including the ones to detect specific blood markers, that would allow to identify risks of developing PD at a presymptomatic phase. The medical and economic data related to the preclinical detection of PD and to the concomitant therapy were obtained, as part of this project, from the leading group of experts on PD (hereinafter referred to as expert opinion)[1].

The findings allow for cautionary conclusions about the economic efficiency of the introduction of the innovative method of presymptomatic diagnostics and concomitant therapy for PD currently in development.

1. Literature review

Reviewing international and Russian publications on pharmaco-economic aspects of PD, we did not find examples of quantitative research into *preclinical diagnostics*, although some studies address the subject of economic efficiency of the introduction of new drugs or technologies for clinical phase of PD.

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1 Data related to medical and economic parameters of the preclinical testing was provided by the group of experts on PD working on the project "Development of the Early Diagnosis Method of Parkinson's Disease (PD) and Comprehensive Economic Analysis of the Impact of Its Introduction," sponsored by the Russian Foundation for Basic Research (RFBR). The group is led by V.G. Kucheryanu (Doctor Sci. (Med.), chief researcher at the laboratory of general pathology of the nervous system at the Russian Academy of Sciences' Institute of General Pathology and Pathophysiology) and Ye.A. Katunina (Doctor Sci. (Med.), full professor, director of postgraduate instruction of doctors at the department of neurology, neurosurgery and medical genetics of the Pirogov Medical University, executive secretary of the panel of experts on neuropsychiatry of the Central Certification Commission of Russia's health ministry).

Outside Russia, research into economic aspects of PD produced quite a lot of studies employing an array of methods, including the cost-utility approach, which is a "golden standard" for evaluating efficiency of healthcare interventions (Beitz 2014; Bovolenta et al. 2017). Employed to assess economic effects of medical interventions, this method measures costs against health effects applying QALY (Quality-Adjusted Life Year) – the tool used in healthcare economics to measure benefits in the form of added years of life adjusted to the quality of life (Neumann 2005). To measure cost-effectiveness in terms of QALY, scholars rely on such criterion as society's willingness to pay for a unit of effect – this approach establishes a threshold of economic efficiency (cost-utility ratio) for any healthcare interventions (Gosse 2008; Munoz et al. 2017).

Since PD is a progressive disorder, causing a deterioration of the patient's health as it progresses, it arguably has five phases: (1) unilateral involvement; (2) bilateral involvement; (3) loss of balance; (4) significant and then (5) full physical incapacitation, when the patient is wheelchair- or bed-ridden (Hoehn, Yahr 1998). The median length of PD's first stage is approximately 20 months; the second, 87 months; the third, 24 months; the fourth, 26 months (Zhao et al. 2010). This means that the average time it takes for PD to develop from the first to the fifth stage is 13-15 years. The average age of the disease onset, by different estimations, varies between 55 and 65 (Zhao et al. 2010; Munoz et al. 2017). The quality-of-life estimates for each of the five stages of PD provided in international literature differ depending on the assessment methods. Thus, according to (Munoz et al. 2017), who used the EQ-5D tool, the quality of life is 0.9 during the first phase; 0.4, during the second; 0.25 during the third; 0.2, during the fourth; and close to 0 (0.02), during the fifth. According to (Siderowf et al. 2002), the quality of life at the first stage is 0.84; 0.81 at the second; 0.79 at the third; 0.65 at the fourth; and 0.45 at the fifth, where quality of life goes from 0 (the lowest) to 1 (the highest)..

The studies address different treatment methods, drugs and surgical interventions, as well as different stages of PD. For instance, recent years have seen the publication of several studies on the effectiveness of deep brain stimulation (DBS) (Fann et al. 2020) and a number of works addressing separate stages of PD, mostly the early phase or, to the contrary, the advanced one (Findley et al. 2011). However, although the costs grow as the disease progresses (Tinelli et al. 2016), examining the costs of individual stages of PD is not a universally used research approach.

As was noted by (Bovolenta et al. 2017), authors of the pharmaco-economic studies, depending on the data available to them, apply different PD cost estimation methods, which makes comparison difficult.

One of the factors accounting for the differences is small sizes of patient populations in most studies, with some patients receiving medical services in ambulatory settings, and others, at inpatient facilities. One of the typical examples is a study conducted in Australia (Bohingamu Mudiyanselage et al. 2017). "The study is based on monitoring 87 participants over 12 months. The researchers concluded that PD has sizable costs to both individuals and society, with the main reasons being universal healthcare coverage and population aging responsible for the increasing disease prevalence. The mean annual healthcare cost is estimated to amount to $32,556 AUD per one PD patient, with hospitalization accounting for 69% of total costs. On top of this, there are $45,000 AUD of other annual costs per one PD case added to the social costs of PD. The scholars also point out that the costs of moderate and severe PD cases are 4 times higher than those of mild PD ($63,569 AUD versus $17,537 AUD)." An additional factor worthy of note is a tendency to recruit for field studies patients with lighter forms of PD, which can produce unrealistically low figures.

Another cause of the divergences is differences in healthcare cost estimates for PD arising from different characteristics of national healthcare and nursing systems and the inclusion of different components into the cost estimates. The economic estimates usually include direct costs (first of all costs of healthcare services and drugs), but in some cases, also indirect costs, such as income loss or, less frequently, home nursing care (Céu, Coloma 2013). For instance, Yang 2017 reports that the average annual cost per PD patient in China is $3,225.94, with $2,503.46 direct and $722.48 indirect costs. Direct costs comprise of $556.27 costs of surgery, $44.67 appointment fees, $605.67 costs of drugs, $460.29 hospitalization costs, $71.03 auxiliary examination costs, $35.64 transportation costs, $10.39 special equipment costs, and $719.50 formal care costs (Yang 2017). The methodologies of estimating total costs are informed by the type of cost bearer in focus: it can be society, insurance companies, or patients and their families. The choice of a particular viewpoint is often conditioned by the way the assistance to population with PD is organized and financed (Kowal et al. 2013).

Yet, there are some comparative studies as well. An example is the study (von Campenhausen et al. 2010) based on surveying PD patients in six European countries, including Russia, for 6 months. According to the estimates, in Russia the costs totaled €2,620 per patient; in Portugal, €3,000; in the Czech Republic, €5,510; in Italy, €8,340; in Germany, €8,610; in Austria, €9,820. The authors of the study note that in all countries surveyed direct costs were on the average 20%-40% higher than indirect costs, accounting for 70% of the total costs in Germany and Italy, 69% in Portugal, 67% in Russia, 60% in Austria and the Czech Republic. The share of direct costs covered by a state-run healthcare system is lower in Eastern European countries (49% in the Czech Republic and 47% in Russia) than in Western Europe (59%–89%). The authors also notice that the costs increase with severity of disease, with Portugal being the only exception.

In Russia the scope of economic assessments of PD is limited to pharmaco-economic aspect, and researchers, applying a limited array of analytical tools, mostly address the subject of effects of various PD-related medicines and compare their effectiveness levels. In general terms, there are two types of Russian publications on the subject.

Studies in the first group provide concrete calculations and compare costs and efficiency or, less frequently, costs and utility in the application of various PD-related medicines (Levin, Vasenina, Gankina 2015; Belousov, Afanasieva 2015). Costs estimates mostly include direct healthcare costs such as medicines and therapies. A good case in point is Yagudina et al.'s study (2010), which provides the most thorough cost estimate for the Stalevo drug: as of 2009, the costs per patient amounted to ₽158,938. Besides, Russian researchers calculate treatment costs using data from Russia (Belousov, Afanasieva 2015), whereas QALY-related data is mostly taken from non-Russian sources or gathered from a small sample of patients (Shindryaeva 2011).

The second group arguably includes papers addressing issues of methodology, such as components of the costs, discounting tools, the substance of cost-utility approach, etc. (Yagudina et al 2010; Strachunskaya 2008).

We have not found any Russian studies on preclinical diagnostics that would include calculations of any sort, despite the fact that early diagnosis has, inter alia, economic effects. Thus, (Goncharova et al. 2014), highlighting the importance of preclinical diagnostics, puts forward general considerations: an optimal compensation of the shortage of dopaminergic input can have a long-term impact on the subsequent progress of PD, slowing down the transition to the more severe and costly phases.

2. Methodology of the assessment of economic efficiency

Assessing the efficiency of the preclinical diagnostics of PD in comparison to the standard treatments, we applied the cost-utility approach, where utility is measured by QALY, and costs include both direct and indirect components. In international research practice, this approach involves comparison of both costs and effects with a certain alternative – usually this alternative is the absence of any healthcare assistance. In some studies, the baseline for comparison is an existing treatment. A comparative analysis of two treatment methods helps researchers select the best one, whereas comparison of each of the methods – the old and the new ones – with the situation of complete absence of a treatment allows researchers to compare the efficiency of each treatment with all others healthcare interventions. The latter approach is preferable because it shows advantages society stands to gain from the application of either method during a certain transition period. Because of the shortage of data, we compare the new method in development with the one applied in practice. Although updated every now and then, the standard treatments for PD include a number of tried and tested methods combining drug and non-drug interventions that bring relief to patients and enhance their quality of life. In this case researchers can produce relatively objective assessments of both costs and effects. Since the new methods are still in development, their efficiency can be measured only by expert opinion (details of the methodology, including parameters needed for measuring economic effects, are discussed in paragraphs 3-5).

In this paper we engage with an evolving innovative method of preclinical diagnosis of PD, which consists, first, in searching for biomarkers in body fluids, mostly blood, of patients with premotor symptoms included into the group at risk of PD at prodromal phase and, second, in prescribing them neuroprotective therapy (Ugrumov 2020; Kim et al. 2020).

The proposed average age for the study population is 45. The creators of this innovative method estimate that in 80% of cases neuroprotective therapy would prevent the disease from progressing to the clinical phase during 30 years after the intervention. In 20% of cases therapy can fail to prevent the progress to the clinical phase. In these cases patients are offered the standard treatment for PD. If neuroprotective therapy at a presymptomatic stage is not administered to at-risk individuals, 10 years later in 80% of them PD will reach the clinical phase and in 20% of them, it won't.

Because the costs and benefits are distributed over time, they should be compared using discounting tools[1]. Researchers have used a wide range of discounting rates, from 1% to 8% (see an overview in Smith, Gravelle 2001). The most often used values are 3% and 5% (Smith, Gravelle 2001; Brouwer et al. 2000). Given stable low interest rates in the last decade (in real terms, that is inflation adjusted), in this study we apply nearly the lowest value of the range: 2%. The application of a higher discount rate will give more weight to costs and benefits at the initial stage of PD compared to later stages. Variations in the range between 2% and 5%, however, are not critical for our estimates. The present value of both costs and benefits is calculated at the time when PD's clinical phase starts (i.e. at age 55, the median age of the PD patient with the first clinical symptoms).

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1 Comparing costs at different points in time, one cannot ignore the question of accounting for inflation. In studies on economic efficiency in healthcare this question is largely left unaddressed (see Turner et al. 2019), and this lack of attention is justified by low inflation levels in developed nations, on the one hand, and the use of the real interest rate as the discount rate, on the other.

A presymptomatic diagnostics is efficient if the ratio of the incremental costs to the incremental QALYs is below a certain critical level – a sum that society is willing to pay for a unit of effect (QALY), see the formula (1) (Munoz et al. 2017).

$$\frac{C_{\text{early diagnosis}} - C_{\text{traditional treatment}}}{QALY_{\text{early diagnosis}} - QALY_{\text{traditional treatment}}} < critical\ value \qquad (1)$$

In this formula C stands for costs of the respective treatment method and C = $= C_{\text{direct medical costs}} + C_{\text{indirect costs}}$.

Testing this assumption requires estimating all of the formula's components, and further in the paper we discuss the calculations step by step: chapter 3 describes the selection of the threshold value; chapter 4 deals with calculation of additional benefits of the early diagnosis and the concomitant therapy as compared to the traditional treatment; chapter 5, relying on Russian data, calculates costs of the traditional treatment and costs of the early diagnosis and concomitant therapy.

3. Calculating the threshold value

Russia does not have a ready estimate of how much its society is willing to pay for a QALY, so we use for reference relevant figures calculated for the USA and the UK, adjusting them for the cost of living (based on the purchasing power parity – PPP). Using the estimates from the USA and the UK as points of reference is a standard approach employed in healthcare costs and benefits research because this approach is used in these two countries much more widely than elsewhere.

In the USA, $20,000 per a QALY is the cost deemed by American society as absolutely acceptable (treatments with such cost of a QALY are regarded as economically efficient). Treatments costing between $20,000 and $40,000 are regarded in the USA as acceptable (this is the cost range of most treatments); costs between $40,000 and $60,000 are borderline acceptable; $60,000-$100,000, expensive; and costs higher than that, too expensive (Vorobiev et al. 2004; Afentou et al. 2019). The corresponding acceptable cost range for the UK is £20,000-£30,000 (NICE 2008; Shiroiwa et al. 2010) – adjusting the figures for differences in these countries' per-capita GDP in 2019, we come up with $21,600 as the upper value of the range. If we use the acceptable costs range $21,600-$40,000 as a point of reference and adjust it for differences in the cost of living in Russia and the USA (according to the IMF, in 2019 the ratio of these countries' per capita GDPs, measured at PPP, was 0.418), the acceptable costs range in Russia would be between $9.02K-$16.72K. In rubles, therefore, the acceptable costs range would be ₽584K-₽1,178.8K (at the average weighted exchange rate of ₽64.74 for $1 in 2019) for a QALY. So, the estimated upper threshold of acceptable costs of a QALY would be ₽1.18M[1], if the point of reference is the corresponding figure for the USA, and ₽0.59M, if the point of reference is the corresponding figure for the UK. These are the figures we use as the threshold values in the formula (1). Let us notice that $40,000 is the upper acceptability threshold for the costs per a QALY, quality-adjusted life-year, used by the USA's healthcare. Please note that $40,000 is

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1 A similar calculation using the ₽-to-$ exchange rate in terms of PPP for 2019, based on the OECD data (https://data.oecd.org/conversion/purchasing-power-parities-ppp.htm), produces a similar figure: ₽1.028M.

the upper acceptability threshold for the costs per a QALY, quality-adjusted life-year, used by the USA's healthcare. This assessment is different from the assessments of American society's willingness to pay for a year of healthy life, which, in turn, vary significantly as well. There are studies (such as (Gyrd-Hansen 2003; Shiroiwa et al. 2010), for instance) that discuss differences in the estimates of the value of life produced by different methods and used in research and actuarial models, as well as for establishing healthcare costs efficiency thresholds. The value-of-life estimates for Russia vary widely from ₽40M to ₽70M, and our estimate of the threshold of acceptable costs per a QALY is close to the highest value of this range.

4. Calculating the utility (benefits)

Calculating the utility / benefits of treatments for PD requires information about the number of years each of these treatments adds to life and about the quality of life during these added years. Since PD progresses in stages, estimating utility in terms of QALY requires the application of discount rates to estimate a present value of utility, and quality of life should be evaluated separately for each stage. This paper applies two versions of quality-of-life assessments for PD: (Munoz et al. 2017) as the view "from below" and (Siderowf et al. 2002) as the view "from above".

Benefits, in terms of QALY, of the presymptomatic diagnostics compared to the traditional treatment for PD (the denominator in formula (1)) are calculated using the formula (2):

Discounted utility (benefit) of the presymptomatic diagnostics, compared to the traditional approach,

$$QALYs = \sum_{t=d}^{d+LE^{\text{early diagnostics}}} \frac{Q_t^{\text{early diagnostics}}}{(1+r)^t} - \sum_{t=d}^{d+LE^{\text{traditional}}} \frac{Q_t^{\text{traditional}}}{(1+r)^t}. \qquad (2)$$

where Q_t is an assessment of the quality of life at the moment T, on a (0-1) scale; r is the discount rate (assuming r = 0,02); d is the mean or median age when PD starts or is identified; LE is the average length of life of PD patients receiving different therapies.

Please note that the discounted utility formula accounts for variations in both the length and the quality of life that may be caused by different treatment methods.

The presymptomatic diagnostics and concomitant neuroprotective therapy reduce the probability of the disease among the at-risk population, which is a potential benefit, in terms of the quality and length of life, for those who would have become ill otherwise.

The quality-of-life benefit consists of two elements. For people who do not develop PD due to neuroprotective therapy (80% of the at-risk group, according to the expert opinion of the creators of the innovative approach), the quality of life is rated 0.98 (the decrease is caused by the necessity to consume neuroprotective drugs) during 30 years after the testing. Assuming that the median age of the tested population would be 45 years and taking into account the Rosstat estimates of the life expectancy for 45-year-olds in Russia at 30.8 years (in 2019), we conclude that PD in these patients would not reach a clinical stage before the age of 75 years. And in case of the traditional approach to PD, the median age when DP reaches a clinical stage is 55 years. For this group, thus, the presymptomatic diagnostics at preclinical stage improves the quality of life between 55 and 75 years of age but slightly reduces it between 45 and 54 years of age.

The creators of the innovative approach claim that for those 20% whom neuroprotective therapy fails to help, the presymptomatic diagnostics does not slow down the disease's progress or influence the quality of life if the disease develops. For this group, after the onset of the disease, there is zero difference in utility levels between the presymptomatic diagnostics and therapy, on the one hand, and the traditional diagnostics and therapy, on the other.

The benefit in terms of the length of life, in case of the preclinical diagnosis and subsequent neuroprotective therapy, is the difference between the length of life in the country and the average length of life for people with PD. Given the absence of data on life expectancy for people with PD, this difference can be estimated only approximately. If 55 years is the average age when a person starts receiving a treatment for PD (when PD is detected), life expectancy for the cohort of 55-year-olds in Russia is 24.3 years (2019), and the average duration of the disease is 15 years, then people diagnosed with PD live 9.3 years less than the average Russian. Applying the discount rate, we come up with a benefit of 6.06 additional years of life.

Calculated with the formula (2), the estimated combined discounted QALY benefit from the combination of the presymptomatic diagnostics and neuroprotective therapy, as against the traditional treatment, represents a wide range of values from 9.08 to 12.4 QALYs per patient – this reflects the large differences in quality-of-life estimates at the late stages of PD, as well as sensitivity of the gains estimates to methods of quality-of-life assessment.

5. Calculating the costs

Assessing the efficiency requires assessing the costs of the traditional treatments for PD as well as the costs of the treatment with the preclinical diagnosis.

5.1. Costs of the traditional approach

In this study, estimates of the costs include both direct and indirect costs. Direct costs include medical expenditures: initial diagnostics, therapies, and medicines. Indirect costs consist of income loss for patients with PD caused by their unfitness for work and the costs of home nursing care (provided by family members or a hired nurse). Because the costs are spread over time, we calculate the present value of the costs spread over time (factoring in the phase and the duration of each phase) (Bovolenta et al. 2017).

5.1.1. Direct medical costs

Estimating direct medical costs of the traditional treatment for PD, we applied the standards developed on the basis of medical experts' recommendations and approved by Russia's health ministry[1]. These standards use the average patient as the point of reference and calculate the average frequency of the provision of particular healthcare services, as well

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1 Order of Russia's health ministry No. 1574н, dated December 28, 2012, "On Approving Standards of Primary Healthcare Services for Patients with Parkinson's Disease." The order details primary healthcare services in ambulatory settings for PD patients at the early, middle and advanced stages of the disease, irrespective of the complications, as per 365 days; Order of Russia's ministry of health No. 1583н, issued on December 28, 2012, "On Approving the Standards of Specialized Healthcare for Patients with Parkinson's Disease in Need of Inpatient Care on Account of Unstable Reactions to Anti-PD Medicines," which details the provision of specialized outpatient care at the early, middle and advanced stages of PD in case of the complications (acquired cognitive, vegetative and mental disorders), as per 30 days.

as the index of multiplicity thereof. Probabilities of the provision of a healthcare service or prescription of a drug included into the healthcare standards range from 0 to 1: 1 means that a given intervention is provided for 100% of patients and lower values indicate that the intervention is provided only when medically warranted (Starodubov et al. 2015). Such approach to calculating costs is different from the one normally used by researchers. Usually, PD costs are estimated based on the experience of treating a particular group of patients during a certain observation period (1-2 years as a rule) (Bovolenta et al. 2017). However, as mentioned above, such estimates can be not without a bias. Besides, the use of the standards is warranted by the fact that it is the frame of reference for the provision of PD-related treatments under the mandatory health insurance plan (OMS: *obyazatel'noe meditsinskoe strakhovanie*), as well as for tariffs for healthcare services and purchases of drugs by Russia's healthcare institutions.

Initial diagnostic procedures for PD, as per the standards, involve primary consultations by specialty doctors (geneticist, neurologist, ophthalmologist, psychiatrist, endocrinologist), blood and urine tests, posturography. Given Moscow OMS tariffs for 2019, the array of diagnostic services would cost ₽885 per patient. When administered as a part of the regular physical examinations, the tariffs for which, depending on the examined person's age, are set at ₽1,570–₽3,323 for women and ₽1,409–₽2,659 for men, the costs of primary diagnostic procedures for PD can be slightly higher. We proceed with our estimation using ₽885 as the baseline. So, the combined costs of ambulatory care and health monitoring, if we apply the current standards and OMS tariffs, total ₽15,543 per person per year (the discounted value, assuming the average duration of PD is 15 years).

At different stages of PD, when a patient experiences a flare-up of the condition, (s)he may need inpatient care – usually for 30 days. Under the OMS, inpatient care services are paid for per a completed case. In 2019 the costs of a PD treatment totaled ₽26,655.14 (disease ID: 66090). If inpatient care is to be correctly accounted for in direct medical costs, we need information about the probability of flare-ups which require inpatient care at different stages of PD. Dr.hab. Ye.A.Katunina estimates that at the phases 3, 4 and 5 the probability of annual hospitalization is 30%. This means that the combined inpatient care costs during the phases 3-5, whose average duration is 6 years, total ₽79,965.42 (= 30% * ₽26,655.14 * 6 years), or ₽3,199 per annum (a discounted figure, assuming that the average duration of PD is 15 years).

Besides, at late stages of PD some patients undergo surgical interventions, such as neurostimulation, thalamotomy, pallidotomy. Such interventions are warranted in case of insufficient effectiveness of a pharmacotherapy, incapacitation and loss of vital force, as well as in case of certain forms of the disease that are best treated by surgery[1]. In the absence of precise statistical data[2] related to this component, we likewise relied on an expert opinion, according to which the probability of a deep brain stimulation surgery is 1%-2% (we apply the upper threshold of 2%). When adjusted to such low probability rate, the surgery costs amount to ₽7,858.4 (=392,920*0.02) per one patient with PD.

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1 http://www.gofn.su/bolezn-parkinsona.html

2 Information about frequency of such surgical interventions in relation to PD patients is scarce, which confirms the expert's claim that they are resorted to very rarely. We did not find official statistics on thalamotomy in Russia. The Institute of Neurology claims that only 42 thalamotomies were performed in 1987-2006 (Shirshov 2010). Only a handful of pallidotomies were carried out at the Research Center of Neurology (Tyurnikov et al., 2017). In 1987-2010 the institution performed 87 destructive surgeries on 78 patients with PD. Neurostimulation interventions are performed at the Research Center of Neurology, the Burdenko Neurosurgery Institute, and the Treatment and Rehabilitation Center of the Health Ministry (Illarioshkin 2011).

Standard drug therapies for PD include combinations of two main types of drugs: medicines against PD as such and additional medicines to treat nonmotor symptoms associated with PD. We calculated the combined costs of drugs relying on retail prices at online pharmacies for medicines listed in the standards of care. We analyzed the prices as of August 2019 on the sites of pharmacies with the largest online reach and the biggest number of offline outlets in Moscow[1]. The prices were recalculated to show the cost (in rubles) of a unit of an active ingredient, in order to compare drugs with different content of an active ingredient and sold in packages of different sizes and volumes. These calculations produced an average cost of the drug treatment for PD per one patient using outpatient care services in Moscow as of August 2019. So, the cost is ₽80,131 per annum, and with the complementary medicines factored in, ₽148,723 per annum.

So, for a patient with PD receiving the traditional treatment, the overall direct healthcare costs (diagnosis, therapy, and medicines), based on the standards of care, stand at ₽176K per annum or ₽2.26M for the entire duration of treatment (at a 2% discount rate, assuming that the average duration of PD is 15 years).

One of the limitations of the above method is the application of OMS tariffs for calculating the costs of diagnosing and therapies along with the application of retail prices for medicines, which reduces the share of diagnosing and therapy costs and increases the share of medicine costs in the outpatient care costs.

5.1.2. Estimating indirect costs

Indirect costs include estimates of income loss of the patient and/or member of his/her family caused by the disease.

₽686K per annum is the estimated social losses, per a patient with PD, caused by the loss of fitness for work at late stages of PD, assuming that the average salary in 2019 was ₽44K and factoring in the 30% payroll tax. The patient becomes unfit for work already at the third phase of PD, that is approximately 8 years after the disease onset. Assuming the median age when PD starts is 55 years, the losses caused by unfitness for work amount to 9 years (72 years was for a long time a generally agreed limit of working age in Russia – and minus 63 years). Assuming that society's losses caused by one PD patient's unfitness for work amount to ₽686K per annum, the indirect losses from such patient (with the discount applied) total ₽5.4M. Please note that estimating societal losses we apply the conservative upper limit of working age: 72 years. Statistical data released in and after 2015 does not use the notion of the upper age limit for working age.

Estimating the home care costs, we factored in the cost of a nurse's services: ₽40K per month. Assuming that home nursing care becomes necessary beginning from the third phase of PD, its average cost per patient would be ₽192K per annum or ₽2.5M (with the discount applied) overall.

The overall (discounted) indirect costs thus amount to ₽7.9M per one patient. Under the standard treatment scheme, the overall normalized direct medical costs and indirect costs, such as the PD patient's income loss caused by premature unfitness for work and home care costs, amount to ₽10.16M per one patient.

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1 The sample included the following pharmacy chains: Internet Pharmacy No. 1 (OOO Parus-Invest, Moscow); the federal online pharmacy apteka.ru (AO NP Katren, medicines are delivered at offline outlets of partner pharmacies); Zdravcity; Stolichka pharmacies (OOO NEO-PHARM), in Moscow and Moscow region; Apteki GORZDRAV (OOO APTEKA-A.v.e-1, Moscow); Rigla (OOO Rigla, Moscow); chain of pharmacies 36.6 (OOO APTEKA-A.v.e., a part of the group of companies PAO Aptechnaya set 36.6).

5.2. Costs of the innovative approach

As noted above, the costs estimate for the innovative method is based on an expert opinion of the method's creators. Diagnostics costs (in particular, the blood test) would amount to ₽20K *per tested individual* in the (broadly defined) at-risk group, whereas neuroprotective therapy would cost ₽80 per diem per one patient whose blood test identifies him/her as being at risk of PD.

Precision of the costs assessment depends on the number of tested persons in the at-risk group. The costs per one tested person are not very great but they can become quite substantial per one patient identified as being at risk of PD, if the criteria for inclusion into the at-risk population are broad. The costs of medical examinations *per one person identified as being at risk* can be as high as ₽2M, if the probability of identifying the heightened risk of PD in this broad group is 1%, and ₽20M, if the probability is 0.1%. It is this lack of certainty that complicates the task of estimating the *per-patient* costs of detecting the heightened risk of PD at presymptomatic stage (and per-patient costs are precisely the "metric" of estimates under the traditional treatment scheme). We, therefore, evaluate the new method's efficiency in terms of maximally acceptable costs or, to use an equivalent measure, in terms of minimally acceptable probability of detecting individuals at risk of PD among a tested population.

Persons at risk of PD will receive neuroprotective therapy costing (by expert opinion) ₽80 per diem, or ₽880K during 30 years (the predicted duration period of the effect of neuroprotective therapy) *per one at-risk person*. This is an equivalent of ₽751.6K in normalized prices (the prices are adjusted to the median age of PD's onset in the absence of the preclinical diagnosis and concomitant therapy, that is 55 years).

In the population that undergoes the test and is identified as at-risk, 20% will not develop PD even in the absence of therapy, so 20% of neuroprotective therapy costs should be considered as excessive – this increases the *per-patient* costs of neuroprotective therapy by 20%, so now the figure is ₽901.9K.

At the same time, the method's developers believe that in 20% of cases either the test gives false negative results or neuroprotective therapy does not work, and this group of persons will receive the traditional treatment. The costs of their treatment, which stand at 0.2*₽2.26M = = ₽0.45M per patient, should be added to the overall costs of the innovative method. The total discounted costs of the innovative method thus would amount to ₽1.352M.

Additionally, these 20% of cases of PD would also entail indirect costs of home nursing care and societal losses caused by early unfitness for work – according to our estimates, these losses would total ₽0.2 * 7.9M = ₽1.58M.

Therefore, the combined medical and indirect costs *per one patient* with PD who receives the innovative treatment would amount to about ₽2.932M.

The estimated costs of diagnosing for patients receiving the innovative treatment remain uncertain and below we estimate the threshold of economic acceptability for these costs.

6. Estimating economic efficiency

Considering that at the early stage of the new method's development there is great uncertainty as to the criteria for including individuals into the PD risk testing group and, consequently, as to estimating the probability of identifying at-risk persons among the tested populations or total costs of diagnosing, it is impossible to make a definite conclusion about

the proposed method's economic efficiency or the lack thereof. What appears possible in such situation, however, is estimating threshold values for economic efficiency (acceptability) of the presymptomatic diagnostics and subsequent neuroprotective therapy, that is establishing maximally acceptable diagnosis costs (let's denote it by X) and, so, a minimally acceptable probability of identifying at-risk persons in the tested population.

We applied the formula (1) and took as a basis the efficiency level of ₽1.18 per a QALY, the new method's benefit of 9.08–12.4 QALYs per patient, the traditional method's estimated discounted per-patient costs ₽10.16M and the new method's per-patient costs ₽(2.932 + *X*) M, and thus we established that the range of acceptable costs of diagnosing related to the new treatment were ₽17.9M–₽21.9M ($276K-338K) *per one patient*, given the upper limit of acceptability for the USA (see formula (3)). If we likewise apply the UK's upper limit of acceptability (₽0.59M), the range of acceptable costs of diagnosing related to the new technology is ₽12.6M–15.4M *per one patient*.

$$X < 1.18 * 9.08 + 10.16 - 2.932 = 17.942 \ \left(\text{based on the lower bound estimate of QALY}\right)$$

$$\text{or} \qquad\qquad\qquad\qquad\qquad\qquad (3)$$

$$X < 1.18 * 12.4 + 10.16 - 2.932 = 21.86 \ \left(\text{based on the upper bound estimate of QALY}\right)$$

Let's assume the per-capita costs of diagnosing are ₽Y and the probability that a tested individual identified as at risk indeed develops PD is 80%. To ensure that the per-patient costs of diagnosing fits the inequality (3), the probability of prescribing the prodromal therapy in the initial at-risk group needs to be in the range of a_1-a_2 in the formula (4)

$$a_i = 100Y/0{,}8X_i, \qquad\qquad\qquad\qquad (4)$$

where a_i, i =1.2 are the lower and upper bounds of the estimated probability, as a percentage, and X_i, i=1.2 are the upper and lower bounds of the acceptable costs (in rubles).

Assuming that Y = ₽20K, the innovative approach is economically efficient if the probability of prescribing the prodromal therapy in the initial at-risk group is in the range of 0.114%–0.139%, given the USA's economic acceptability threshold, and in the range of 0.162%–0.198%, given the UK's economic acceptability threshold. This means that in a conservative estimate of economic efficiency (applying an upper bound estimate of quality of life component in QALY at PD's clinical stage and the UK's economic acceptability threshold), the probability of prescribing the prodromal therapy in the initial tested at-risk population should be at least 0.2%.

Conclusions

This paper proposes a method of estimating economic efficiency of the early (preclinical) diagnosis of PD and subsequent therapy applying the cost-utility method in a situation when not all economic parameters of early diagnosis can be calculated or estimated by expert opinion. The lack of clear understanding of the size and composition of the tested population at a preclinical phase of the disease is the most serious challenge for estimating costs of the early diagnosis at the prodromal (presymptomatic) stage of PD. The relatively small per capita testing costs in the tested population can grow into a significant cost *per one identified individual with PD* if criteria for inclusion into the tested population are too broadly defined.

In this study, we established thresholds of economic efficiency of the innovative method of early diagnosis, which is presently at an experimental stage, in terms of minimally acceptable probability of identifying at-risk individuals in the tested population.

Estimating costs of the traditional PD treatment, we for the first time used Russia's official standards of care for the disease, preventing the bias typical for the small-sized samples on which the existing estimates are based and reflecting the fact that the coverage of PD under OMS, as well as the tariffs for healthcare services and the purchase of drugs by healthcare providers, are pegged to these standards. Moreover, unlike most other studies, this one factors in the costs of primary diagnosis and subsequent home nursing care provided by household members, as well as income losses due to the patient's unfitness for work. The estimates of income losses are based on wage amounts with relevant taxes: this approach reveals societal costs. The modified methodology of estimating the costs proposed by us makes it possible to establish a range of acceptable costs for the innovative technology of preclinical diagnosis of PD currently in development. A comparison of the efficiency of the new technology in the making to the traditional approach, even if it is approximate, is necessary for evaluating the prospects of this technology's practical use, including its inclusion into the OMS scheme. Besides, the proposed method of estimating economic efficiency is important for fine-tuning the new technology when it progresses from an experimental stage to a stage of clinical trial.

According to our estimates, the innovative method of using blood markers to identify prodromal PD patients and treating them, when necessary, with neuroprotective therapy is efficient when the probability of identifying at-risk individuals in the tested group is higher than 0.2%. Considering that PD's prevalence level in a population, on the average, is 0.3%, reaching 1% among people aged 60+ years and 4% among people aged 75+ years (Levin 2011; Muangpaisan et al. 2011), the efficiency threshold appears achievable but requires carefully thought-out rules for including individuals into the at-risk groups to be tested.

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