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Клинико-экономический анализ современной тактики лечения больных с метаболическим синдромом

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Цель исследования. *Определить пути оптимизации тактики ведения пациентов с метаболическим синдромом (МС) на основании комплексного клинико-экономического анализа.*

Материалы и методы. *В исследование включено 60 пациентов с МС. Пациенты из основной группы (30 человек в возрасте 41,0±11 лет, из них 23 (76,7%) женщины) помимо рекомендаций по изменению образа жизни получали медикаментозную терапию ожирения (орлистат) и инсулинорезистентности (ИР) (метформин), а также гиполипидемическую и антигипертензивную терапию при необходимости. Больные из группы контроля (30 пациентов в возрасте 43,4±9,5 лет, из них 26 (86,7%) женщин) получали рекомендации по изменению образа жизни и, при необходимости, гиполипидемическую и антигипертензивную терапию. На этапе включения в исследование и через 6 месяцев терапии всем пациентам проводилось клинико-лабораторное исследование, оценка по Шкале депрессии Бека и качества жизни по данным опросника SF-36. На основании полученных результатов исследования проведен комплексный клинико-экономический анализ с расчетом показателей «затраты-эффективность» (CER), «приращения эффективности затрат» (ICER), «затраты-полезность» (CUR), «добавленные годы жизни» (LYG), «годы жизни с поправкой на качество» (QALY) и «чистая денежная выгода» (NMB).*

Результаты. *В основной группе отмечалось достоверно более выраженное улучшение клинико-лабораторных показателей и качества жизни пациентов по сравнению с контрольной. Прямые медицинские затраты на лечение пациентов с МС в основной группе составили 33 440,4 руб. за 6 мес терапии, в контрольной группе – 18 878,5 руб. за 6 мес терапии. CER для контрольной группы составил 4016,7, для основной группы – 3125,3; ICER – 2430,9 руб. Показатель LYG для контрольной группы равен 0,7 года, для основной – 2,3 года. NNT составил 16,7 для контрольной группы и 6,3 для основной группы. Показатель QALY для контрольной группы составил 8,63, для основной – 9,45. Суммарные средневзвешенные затраты за предполагаемый период дожития в контрольной группе равны 498 745 руб., основной группе – 457 866 руб. CUR в контрольной группе равен 57 792 руб./QALY без дисконтирования и 54 902 руб./QALY с дисконтированием, в основной – 48 451 и 46 029 руб./QALY соответственно. Показатель NMB в контрольной группе составил 10 790 910 руб. без дисконтирования, 10 815 840 руб. с дисконтированием, в основной группе – 11 904 500 и 11 927 390 руб. соответственно.*

Заключение. *Тактика ведения пациентов с МС, включающая фармакотерапию ожирения и ИР, является приоритетной как с клинической, так и с экономической точки зрения, по сравнению с консультированием и обучением пациентов по изменению образа жизни.*

Ключевые слова: *метаболический синдром; клинико-экономический анализ; абдоминальное ожирение; инсулинорезистентность; качество жизни; метформин; орлистат*

Clinical and economic analysis of the modern strategies for treating metabolic syndrome

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Objective. *The objective of this study was to identify the ways to optimize therapy for metabolic syndrome through complex clinical and economic analysis.*

Methods. *Sixty patients with metabolic syndrome were included in the study. The study group (30 subjects with the mean age of 41.0±11 years, 23 females (76.7%), 7 males (23.3%)) received pharmacotherapy for obesity (orlistat) and insulin resistance (metformin), lipid-lowering therapy and antihypertensive therapy, if needed. The control group (30 patients with the mean age of 43.4±9.5 years, 26 females (86.7%), 4 males (13.3%)) received lipid-lowering and antihypertensive therapy, if needed. All patients underwent clinical and laboratory examination, assessment of depression (Beck Depression Inventory) and evaluation of the quality of life using the SF-36 questionnaire at admission to the study and after 6 months of therapy. Complex clinical and economic analyses, including cost-effectiveness and cost-utility analyses and calculation of such indices as "the incremental cost-effectiveness ratio" (ICER), LYG, QALY and "net monetary benefit" (NMB), were conducted based on the results obtained.*

Results. *Improvement of clinical and laboratory indicators and quality of life in the study group was more significant than that in the control group. The direct medical costs were 33,440.40 RUB for the study group and 18,878.50 RUB for the control group (for 6 months of therapy). The control group CER was 4,016.70, while the study group CER was 3,125.30; ICER was 2,430.90 RUB. LYG was equal*

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to 0.7 and 2.3 years for the control and the study groups, respectively. The QALY measure for the control and study groups was 8.63 and 9.45, respectively. The weighted average total costs for the intended period of living was 498,745.00 RUB for the control group and 457,866.00 RUB for the study group. The control group CUR was 57,792.00 and 54,902.00 RUB/QALY without and with discounting, respectively, while in the study group they were 48,451.00 and 46,029.00 RUB/QALY, respectively. The NMB for the control group amounted to 10,790,910.00 and 10,815,840.00 RUB without and with discounting, respectively, while for the study group the values were 11,904,500.00 and 11,927,390.00 RUB.

Conclusions. *The results of clinical and economic analysis show that treatment of the metabolic syndrome, including pharmacotherapy of obesity and insulin resistance, should be prioritized over mere medical advisory and lifestyle modifications.*

Keywords: *metabolic syndrome; clinical and economic analysis; abdominal obesity; insulin resistance; quality of life; metformin; orlistat*

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The main outcomes of metabolic syndrome (MS) are ischaemic heart disease (IHD) and type 2 diabetes mellitus (T2DM), which are the leading causes of death in the Russian Federation and among the most serious medical and social challenges that confront society. The economic burden of MS on national healthcare systems results from the high costs of therapeutic interventions aimed at attenuating the diverse clinical manifestations of MS. Moreover, the chronic and progressive nature of diseases associated with MS, the high incidence of cardiovascular diseases (CVDs) and their complications that cause disabilities require new strategic approaches.

There is no standard strategy for treating MS. Patients are affected by both modifiable and non-modifiable risk factors, which generate the numerous phenotypes of MS. These, in turn, require personalised approaches to the selection of an appropriate therapy for each individual component. For example, clinically significant weight loss is associated with lower insulin resistance, improved parameters of carbohydrate metabolism and lipid profile, positive changes in haemostatic systems and lower blood pressure (BP) [1, 2]. An overwhelming majority of specialists agree that lifestyle modifications are the first-choice therapies for treating MS. However, the Cochrane Review published in 2011 showed that counselling and education designed to change behaviour do not reduce overall mortality or mortality associated with coronary heart disease in the total population [3]. Changing lifestyle is challenging for most patients and the achieved weight loss is not maintained in the long run, indicating that the overall efficiency of this therapeutic strategy is rather low. Maintaining the achieved weight loss is crucial for gaining long-term benefits. Orlistat (Xenical®) effectively achieves and maintains the desired weight loss [4] and reduces lipid levels, which is very important for patients with MS because 50% of them initially suffer from hypertension as well.

Most patients with MS are insulin resistant and require early diagnosis of prediabetic states [impaired fasting glucose (IFG) and impaired glucose tolerance (IGT)]. The consensus statement issued by the American College of Endocrinology and the American Association of Clinical Endocrinologists released in 2008 recommends prescribing metformin to patients at a high risk of T2DM with IFG, IGT and/or MS as well as for patients with a history of gestational DM, non-alcoholic fatty liver disease or polycystic ovary syndrome [5].

To our knowledge, there are no published studies in Russia that provide complex combined clinical and economic analyses of MS treatment strategies (including lifestyle modification and pharmacotherapy for obesity and insulin resistance as well as the interplay between clinical benefits and economic costs).

AIM

The objective of the present study was to identify strategies to optimise treatment of MS based on the results of combined complex clinical and economic analyses.

METHODS

This open, prospective, randomised clinical study included 60 patients who provided their informed consent and were eligible according to the diagnostic criteria for MS approved by the International Diabetes Federation in 2005. We used a block randomisation procedure to divide the patients into 2 groups of 30 subjects each. Patients in the study group were prescribed combined therapy for MS aimed at attenuating its components, including pharmacotherapy for obesity (orlistat) and insulin resistance (metformin, Glucophage®). Patients in the control group did not receive these drugs. Upon admission to the study, both groups underwent individual training in a school for patients with obesity and were advised to convert to a hypocaloric diet and become more physically active. The patients then underwent monthly counselling with correction of their diet according to their individual diet diaries. If necessary, patients received individually tailored lipid-lowering and antihypertensive drug therapies.

The baseline clinical and laboratory parameters were comparable in both groups (Table 1). Patients were observed for 6 months. Upon admission to the study and after 6 months of therapy, patients underwent physical examination, laboratory tests and evaluation of their quality of life using the SF-36 questionnaire. We developed a mathematical model according to the results of international and national clinical studies [6–17] (Fig. 1) to determine the dynamics of well-being of patients with MS. We defined the condition of patients by assigning them to one of several discrete states with specified transition probabilities.

Transition probabilities between these health states were determined from the results of national and clinical studies

Table 1

Clinical characteristics of patients			
Group	Study	Control	Significance level
	M±σ	M±σ	p
Age, years	41,0±11,0	43,4±9,5	0,379
Height, m	1,68±0,1	1,68±0,1	0,789
Weight, kg	107,9±17,4	101,9±14,9	0,157
BMI, kg/m^2	38,21±5,4	36,22±4,16	0,115
WL, cm	115,6±10,5	110,4±11,8	0,078
SBP, mm Hg	139,2±11,9	132,1±13,8	0,042
DBP, mm Hg	88,2±10,1	85,4±7,9	0,247
HR, bpm	78,3±9,5	77,3±10,0	0,704
FPG, mmol/L	5,2±0,5	5,4±0,6	0,373
IRI, μU/mL	24,01±7,34	18,69±8,57	0,013
HOMA-IR	5,55±1,70	4,67±2,14	0,083
TC, mmol/L	6,2±1,1	6,1±1,5	0,665
LDL, mmol/L	4,0±1,0	4,1±1,2	0,636
HDL, mmol/L	1,0±0,3	1,1±0,3	0,421
TG, mmol/L	2,6±2,7	1,9±0,9	0,256*
AST, U/L	29,0±19,4	27,8±13,9	0,791*
ALT, U/L	37,5±27,6	36,3±23,7	0,868

p – values were calculated using analysis of variance
* Mann–Whitney test was used for parameters with non-normal distributions.

conducted in other countries (Table 2).

The reduction of the risk of MS complications in the control group was calculated according to data showing that minor weight loss leads to a moderate decrease in the risk of onset of T2DM [31% over 3 years, Diabetes Prevention Program (DPP) study results [18]] and T2DM-associated mortality (32% over 12 years, American Cancer Society's Cancer Prevention Study I [19]) but does not affect CVD prognosis [19–21].The reduction of the risk of MS complications in the study group was calculated according

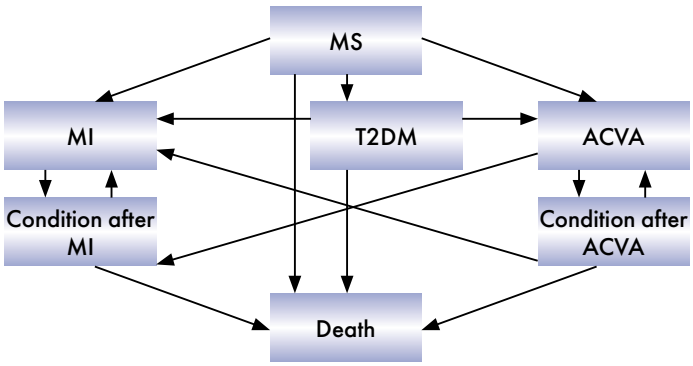

Figure 1. Model of metabolic syndrome outcomes
Note: myocardial infarction (MI), acute cerebrovascular accident (ACVA), metabolic syndrome (MS), type 2 diabetes mellitus (T2DM)

to the results of the study, clinically significant reduction in body mass and BP (Table 3).

This model does not differentiate between patients with one or multiple complications; therefore, only the most recent complication was defined as current. We used a modified model with 17 possible states for in-depth analysis, which takes into account the possibility of several complications for 1 patient. Analysis was performed to estimate patients' survival. Based on the results of modelling, the value of life-years gained (LYGs) was calculated for various treatment options according to the results of this modelling, and the value of weighted average quality-adjusted life years (QALYs) for each year of life was calculated as follows:

weighted average QALYs = IIQOL1 for state 1 × probability of state 1 + IIQOL2 for state 2 × probability of state 2 + ... + IIQOLn for state n × probability of state n,

where IIQOL is the integral indicator of quality of life evaluated using the SF-36 questionnaire (based on our

Table 2

Transition probabilities between various health states of patients with MS				
Data source	Transition from one state to another	Observation period, years	Transition probability over the entire observation period	Transition probability over 1 year
Botnia study [6]	MS→ACVA	6,9	0,048	0,007104
Botnia study [6]	MS→MI	6,9	0,09	0,013575
San Antonio Heart Study [7]	MS→T2DM	7,0	0,5	0,094276
UKPDS [8]	T2DM→ACVA	8,3	0,132	0,016911
Russian Stroke Register [9]	ACVA→Death	2001 r.	0,4037	0,4037
KAPS [10]	T2DM→MI	7,0	0,202	0,031721
KAPS [11]	Recurrent MI	7,0	0,319	0,053406
Denmark population study [12]	T2DM→Death	5,0	0,225	0,049701
Botnia study [6]	MS→Death	6,9	0,18	0,028351
PROGRESS [12]	Consistent after ACVA →MI	3,9	0,0517	0,013528
Swedish Registers [13]	Consistent after MI →ACVA	1	0,041	0,041
Data of national studies [14]	MI→Death	1	0,5	0,5
Göteborg Metoprolol Trial [15]	Consistent after MI →Death	5	0,425	0,104772
MOSES [16]	Consistent after ACVA →Death	2,5	0,0806	0,033055

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Table 3

Risk of MS complications following treatment					
Data source	Health status	Observation period, years	Clinical outcome responsible for reduction of transition probability	Reduction of transition probability over the entire observation period	Reduction of transition probability (into this state) over 1 year
Meta-analysis of 7 RCTs [22]	Recurrent ACVA	3,5	10 mmHg reduction of SBP and 5 mmHg reduction of DBP	0,24	0,075415
Meta-analysis of 14 RCTs [23]	MI	5,0	10–12 mmHg reduction of SBP and 5–6 mmHg reduction of DBP	0,38	0,112644
American Cancer Society's Cancer Prevention Study I [19]	Overall mortality	12,0	Weight loss of >9.1 kg	0,2	0,018423
American Cancer Society's Cancer Prevention Study I [19]	DM-associated mortality	12,0	Weight loss of >9.1 kg	0,36	0,036508
Meta-analysis of 7 RCTs [22]	Recurrent MI	3,5	10 mmHg reduction of SBP and 5 mmHg reduction of DBP	0,21	0,065131
Meta-analysis of 7 RCTs [22]	CV-associated mortality	3,5	10 mmHg reduction of SBP and 5 mmHg reduction of DBP	0,14	0,042177
Meta-analysis of 37 studies [24]	ACVA	7,0	10 mmHg reduction of SBP and 5 mmHg reduction of DBP	0,54	0,105001
Diabetes Prevention Program (DPP) [18]	T2DM	3,0	Weight loss of >7%	0,58	0,251113

results and those of national RCTs [25–28]). The overall QALY equals the sum of weighted average QALY values for each year of treatment.

The total cost of treatment of patients with MS included the direct medical cost for standard medical services and the cost of prescribed medications. The prices of counselling, laboratory and diagnostic services were acquired from the price list of paid medical services at the I.M. Sechenov First Moscow State Medical University (as of 1 March 2012). The prices of medications were the average Moscow retail prices (as of 13 November 2012) based on the data available at www.medlux.ru as well as data of the State Register of the prices of pharmaceuticals included in the List of Vital and Essential Medicines (VAEML). The cost of treatment of complications was determined from the results of national pharmacoeconomic studies [29–30]. All costs were estimated per capita.

Clinical and economic analyses included calculation of cost-effectiveness and cost-utility parameters as well as indices such as the incremental cost-effectiveness ratio (ICER), LYGs, QALYs, net monetary benefit (NMB) and number needed to treat (NNT). The fixed 'society's willingness-to-pay' (WTP) threshold was used to compare the economic efficiency of 2 different approaches to treatment and was defined as 3 times GDP per capita. The efficiency of treatment of patients with MS was defined as weight loss in kg as well as the proportion of patients who achieved a clinically significant weight loss of >5% of baseline. A discount of 5% per year was applied to the calculated weighted average costs.

To determine the sensitivity of the results to changes in input parameters, sensitivity analysis was performed for changes in prices of medications from maximum to minimum retail price, costs of treatment of complications between ±37% and QOL of patients with MS and its complications within a range of ±10%. The price range for the treatment of MS complications was calculated according to the difference in prices between day 1 of hospitalisation stated in the programme of State Guarantees for the City of Moscow in 2012 and the average price of hospitalisation for a day in 10 randomly selected hospitals, taking into account the features of MS complications. The QOL range was selected on the basis of the difference in the IIQOL values obtained by 2 different methods.

Statistical analysis was performed using Portable PASW Statistic and Microsoft Excel 2010 software. The results are presented as the mean ± standard deviation ($M \pm \sigma$). Analysis of variance was used to evaluate quantitative parameters. The Mann–Whitney test was used for data with non-normal distribution. Differences were considered statistically significant if $p < 0.05$.

RESULTS AND DISCUSSION

The reduction in body mass, BMI, WL and BP levels as well as improvement in carbohydrate and lipid metabolism parameters were significantly more pronounced in the study group than in the control group (Table 4), indicating that a combination of treatment of obesity with orlistat and attenuation of insulin resistance with metformin is significantly more effective than counselling and education.

The average value of the direct medical cost of examination and treatment of 1 patient with MS for 6 months in the control group was 18,878.50 ± 4,689.40 RUB, including 5,328.50 ± 4,689.40 RUB for therapy and 13,550.00 RUB for diagnostics and professional medical advice. The direct medical cost of examination and treatment of 1 patient with MS, including pharmacotherapy for obesity (orlistat) and insulin resistance (metformin), was 33,440.40 ± 2,304.70 RUB, including 22,826.60 ± 4,622.10 RUB and

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Table 4

Changes in anthropometric, clinical and laboratory parameters during therapy

Group	Study	Control	Significance level
	M±σ	M±σ	p
Δ Weight, kg	10,7±6,9	4,7±7,1	0,002
Δ BMI, kg/m^2	4,05±2,62	1,66±2,49	0,001
Δ WL, cm	10,0±6,4	3,4±6,9	<0,001
Δ SBP, mm Hg	12,7±11,4	1,2±10,6	<0,001
Δ DBP, mm Hg	8,0±8,7	2,1±7,5	0,007
Δ HR, bpm	4,3±8,3	0,9±4,4	0,057
Δ FPG, mmol/L	0,24±0,64	0,08±0,56	0,234
Δ glycaemia 2 h after OGTT, mmol/L	0,63±1,53	-0,44±1,09	0,005*
Δ IRI, μU/mL	9,65±9,28	2,94±8,77	0,006
Δ HOMA, points	2,32±2,19	0,91±2,35	0,019
Δ TC, mmol/L	1,1±1,1	0,4±0,9	0,006
Δ LDL, mmol/L	0,8±1,2	0,5±0,8	0,199
Δ HDL, mmol/L	-0,03±0,27	0,01±0,21	0,448
Δ TG, mmol/L	0,9±2,3	-0,01±0,8	0,057*
Δ AST, U/L	7,1±16,2	2,8±10,1	0,260*
Δ ALT, U/L	13,0±23,1	2,6±14,1	0,040

p – values were calculated using analysis of variance
p* Mann–Whitney test for parameters with non-normal distribution.

13,550.00 RUB for therapy and diagnostics and professional medical advice, respectively (Table 5).

Efficiency was defined as weight loss in kg as well as the proportion of patients who achieved clinically significant weight loss (≥5% of baseline).

If efficiency was defined as weight loss in kg, the cost-effectiveness ratios for the control and study groups were 18,878.50/4.7 = 4,016.70 RUB and 33,440.40/10.7 = 3,125.30 RUB, respectively. Therefore, a weight loss of 1 kg costed 4,016.70 RUB and 3,125.30 RUB for a patient in the control and study groups, respectively. If defined as the proportion of patients who achieved clinically significant weight loss (≥5% of baseline), the efficiency rates were 0.37 (37%) and 0.77 (77%) for the control and study groups, respectively, and the cost-effectiveness ratio was 18,878.50/0.37 = 51,023.00 RUB for the control group and 33,440.40/0.77 = 43,429.10 RUB for patients who received metformin and orlistat with standard therapy. Therefore, the cost-effectiveness ratio calculated using 2 different approaches was lower in the study group despite its higher direct cost of treatment (Table 5). Because the more efficient therapy option was more expensive, ICER was calculated. When efficiency was defined as weight loss in kg, ICER was (33,787.00 – 19,201.80)/(10.7 – 4.7) = 2,430.90 RUB. The calculated indicator shows the investment required to lose an extra 1 kg with metformin and orlistat treatment.

Numerous RCTs [2, 20, 22, 23] demonstrate that a weight loss of ≥10 kg or 5%–10% of baseline significantly decreases the risk of T2DM and CVDs. Here the average weight loss in patients treated with metformin and orlistat was 10.7 ± 6.9 kg (10.0% ± 6.4%) compared with 4.7 ± 7.1 kg (4.6% ± 6.7%) in the controls. These data indicate that patients in the study group achieved the weight loss required for preventing MS complications, whereas it is likely that the preventive effect of the weight loss achieved in the control group was not significant.

The results of a meta-analysis performed by the National Institute of Health and Care Excellence (NICE) show that weight loss maintenance was achieved significantly more often in patients who received orlistat than in those who received placebo [34% vs. 18% achieved a sustained weight loss of ≥5% over 2 years (p = 0.02) and 28% vs. 19% achieved a sustained weight loss of ≥10% over 2 years (p <0.05)] [31]. During the second year of treatment, 35.2% patients receiving orlistat gained weight (average = 3.2 kg), whereas 63.4% patients in the control group gained an average of 5.6 kg [4]. Thus, if a weight loss of 1 kg in the study group requires 2,430.90 RUB, then losing 10 kg would require 24,309.00 RUB, which can be considered as the cost of preventing MS complications.

To illustrate this point, let us present examples of treatment costs in cases of disorders accompanying MS.

Analysis of the State Registry of Patients with Diabetes Mellitus showed that the average direct medical cost per T2DM patient is $853 (25,590.00 RUB) per year, which increases with complications to $1,786.00 (53,580.00 RUB) per year; if a patient suffers from severe complications such as CRD, detached retina, blindness, myocardial infarction (MI) and acute cardiovascular accident (ACVA), the cost increases to $8,630.00 (258,900.00 RUB) per year [30]. Based on the summarised CVD treatment costs, the costs of therapy for a patient with AMI are 223,803.00 RUB and 9,424.00 RUB for the first and second years, respectively. The costs of ACVA therapy are 300,802.00 and 7,658.00 RUB for the first and second years, respectively [29]. When these values are compared with the cost of treating complications,

Table 5

Cost-effectiveness ratio for different therapies

	Counselling and education	Pharmacotherapy for insulin resistance and obesity
Direct cost, RUB	18 878,5±4689,4	33 440,4±2304,7
Efficiency index 1 (weight loss), kg	4,7	10,7
Efficiency index 2 (proportion of patients with a weight loss of ≥5%), %	37	77
Cost-effectiveness 1	4016,7	3125,3
Cost-effectiveness 2	51 023	43 429

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we suggest that 24,309.00 RUB for preventing complications is definitely lower.

The results of our modelling show that life expectancy (LE) is 21.8 years for untreated patients with MS, 22.5 years for those who undergo counselling and education and 24.1 years for those treated with metformin and orlistat. These LE values were used to estimate LYGs for both groups.

LYGs (control group): 22.5 – 21.8 = 0.7 years.

LYGs (study group): 24.1 – 21.8 = 2.3 years.

These data indicate that pharmacotherapy combined with changes in lifestyle extend the lives of patients with MS by at least 2 years.

The present results are further supported by those of a similar study conducted in another country showing that the LE of patients aged 51–52 years who achieve clinically significant results from treatment for obesity increases by 0.85 years. Clinically significant results achieved by treating hypertension and T2DM add 2.05 and 3.17 years, respectively. Despite an increased LE, the expenses are lower for patients who receive efficient and adequate treatment of complications ($7,168.00 for obese patients, $13,702.00 for patients with hypertension and $34,483.00 for patients with DM) [33].

The modelling results suggest that treatment with pharmacotherapy for obesity and insulin resistance prevents 4 deaths, 3 MIs, 1 ACVA and 8 cases of T2DM (16 adverse consequences of MS over 20 years). The NNT values for the study and control groups were 6.25 and 16.67, respectively, indicating lower efficiency of counselling and education compared with pharmacotherapy for obesity and insulin resistance. The IIQOL values after 6 months of treatment were 0.71 and 0.76 in the control and study groups, respectively. The overall weighted average QALY values were 8.63 for 22.5 years and 9.45 for 24.1 years, respectively. The indices show that treatment incorporating pharmacotherapy for obesity and insulin resistance provides patients with an increased LE and higher quality of life compared with standard therapy.

Further, we used the probabilities of MS complications generated with our model to calculate the weighted average costs of alternative scenarios. The overall weighted average of expenses for 22.5 years for a control group patient who received counselling and education regarding weight loss was 498,745.00 RUB. The corresponding expense for a study group patient who received treatment with metformin and orlistat was 457,866.00 RUB, i.e. 40,879.00 RUB fewer than that for a patient in the control group despite an increased LE of 24.1 years.

The costs of medication and medical services were discounted by 5% per year for 22.5 and 24.1 years for the control and study groups, respectively (according to the average LEs of patients calculated using our model). After discounting, the weighted average costs were 473,808.00 RUB and 434,973.00 RUB for the control and study groups, respectively. Cost-utility analysis was performed using the QALY values. The cost-utility ratios for the control group were 498,745.00/8.63 = 57,792.00 RUB/QALY and 473,808.00/8.63 = 54,902.00 RUB/ QALY before and after discounting, respectively. The cost-utility ratios for the study group were 457,866.00/9.45 = 48,451.00 RUB/ QALY and 434,973.00/9.45 = 46,029.00 RUB/QALY before and after discounting, respectively. These results show that incorporating pharmacotherapy for insulin resistance and obesity was more beneficial for LE and quality of life as well as more profitable. The acceptable price for 1 QALY is represented as the WTP threshold. This value varies significantly for different countries and depends on the national wealth. Taking this into consideration, the WTP ratio can be considered to be equal to 3 times GDP per capita [34]. The ratio can be interpreted as follows: if the result expressed as a cost of 1 QALY is lower than the WTP threshold, the technology is considered as cost-efficient; if it exceeds 2 WTP thresholds, it is considered acceptable; 2–3 WTP thresholds is borderline acceptable and >3 WTP thresholds is unacceptable. According to the data of the Federal State Statistics Service, in 2012, GDP per capita in Russia was 436,062.20 RUB; therefore, the WTP ratio is 1,308,186.70 RUB. The 'cost-utility' index values, which do not exceed the WTP threshold, show that both treatment options are cost efficient in the Russian Federation.

The NMB was calculated according to the cost-utility score of both treatment options and the WTP threshold.

NMB (control group) = 8.63 × 1,308,186.70 – 498,745.00 = 10,790,910.00 RUB before discounting and 8.63 × 1,308,186.70 – 346,748.20 = 10,815,840.00 RUB after discounting.

NMB (study group) = 9.45 × 1,308,186.70 – 510,795.70 = 11,904,500.00 RUB before discounting and 9.45 × 1,308,186.70 – 485,255.90 = 11,927,390.00 RUB after discounting.

An NMB of >0 indicates that both approaches to MS treatment assessed here are economically viable. Moreover, the NMB was higher for patients in the study group than for those in the control group, indicating the advantages of the former strategy.

Table 6 summarises the results of clinical and economic analysis of the 2 treatment options.

To determine the sensitivity of the results to the changes in the input parameters, sensitivity analysis was performed for changes in metformin and orlistat prices, changes in the cost of treatment of complications as well as changes in quality of life in patients with MS and its complications. The minimum and maximum retail prices of metformin and orlistat were used as medication price changes. The cost range for treatment of complications was defined as ±37% according to the differences in the cost of 1 day of hospitalisation according to the State Guarantee Program in Moscow and an average cost of a day of hospitalisation in 10 randomly selected hospitals, taking into account the features of MS complications. Changes in quality of life in patients with MS and its complications were ±10% according to the differences in IIQOL values using different calculation methods. The maximum retail price of metformin (Glucophage, 850 mg) is 7.67 RUB, whereas that of orlistat (Xenical, 120 mg) is 52.38 RUB. If the price of these medications are increased to the maximum retail price and the cost of treatment of MS complications is increased by 37%, the weighted average

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Table 6

Results of clinical and economic analyses of MS treatment.		
	Counselling and education	Pharmacotherapy for insulin resistance and obesity
QALY	8,63	9,45
Cost-utility ratio	57,792.00 RUB/QALY before discounting	48,451.00 RUB/QALY before discounting
	54,902.00 RUB/QALY after discounting	46,029.00 RUB/QALY after discounting
NMB	10,790,910.00 RUB before discounting	11,904,500.00 RUB before discounting
	10,815,840.00 RUB after discounting	11,927,390.00 RUB after discounting

Table 7

Results of sensitivity analysis		
	Counselling and education	Pharmacotherapy for insulin resistance and obesity
Weighted average expenses	360,080.00–646,435.00 RUB	317,676.00–569,625.00 RUB
Cost-effectiveness ratio	37,943.00–83,196.00 RUB/QALY	30,546.00–70,542.00 RUB/QALY
NMB	9,518,176.00–12,054,610.00 RUB	10,519,980.00–13,287,470.00 RUB

cost of the standard MS treatment increases to 646,435.00 RUB and that of metformin and orlistat treatment increases to 599,606.00 RUB. The minimum retail price of 850 mg of metformin is 3.23 RUB, whereas that of 120 mg of orlistat is 5.95 RUB. If the price of medication is decreased to the minimum retail price and the cost of treatment of MS complications is decreased by 37%, the weighted average cost of standard MS treatment decreases to 360,080.00 RUB and that of the scheme with metformin and orlistat decreases to 317,676.00 RUB. In both cases, therapy with metformin and orlistat is preferable because it is both more efficient and less expensive.

Because the QOL data for MS complications were obtained from different studies, this parameter was also modified by ±10%. In the best-case scenario (minimal cost with maximum efficiency), the cost-utility ratio was 360,080.00/9.49 = 37,943.00 RUB/QALY for the standard therapy and 317,676.00/10.4 = 30,546.00 RUB/QALY for the therapy with metformin and orlistat. The NMB was 12,054,610.00 RUB for the standard therapy and 13,287,470.00 RUB for the therapy with metformin and orlistat. In the worst-case scenario (maximum cost with minimal efficiency), the cost-utility ratio was 646,435.00/7.77 = 83,196.00 RUB/QALY for the standard therapy and 599,606.00/8.5 = 70,542.00 RUB/QALY for the therapy with metformin and orlistat. The NMB was 9,518,176.00 RUB for the standard therapy and 10,519,980.00 RUB for the therapy with metformin and orlistat. Table 7 summarises the results of sensitivity analysis.

The results show that regardless of the fluctuations in the prices of medications, costs of treatment of complications and changes in quality of life in patients with MS and its complications, the MS treatment option including pharmacotherapy for insulin resistance and obesity is preferable to the standard treatment option.

CONCLUSIONS

1. The results of the present complex clinical and economic analyses show that active prevention of MS complications, including pharmacotherapy for obesity (orlistat) and insulin resistance (metformin), is efficient from clinical and economic considerations, because a patient's LE is increased without adverse effects on QOL. Further, it reduces the risk of onset of MS complications and is characterised by better cost-effectiveness and cost-utility ratios as well as by better NNT and NMB values.
2. The economic viability of the proposed therapy was confirmed by demonstrating that the cost of 1 QALY is significantly lower than the WTP threshold, whereas the NMB is considerably greater than 0.
3. When choosing the best approach to treat patients with abdominal obesity and insulin resistance (the main components of MS), the results of clinical and economic analyses should be considered.

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The authors declare that there is no potential or current conflict of interest related to the conduct of this research and publication of its results.

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