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Cost-utility analysis of methadone maintenance treatment in Lithuania

Giedrius Vanagas[1], Žilvinas Padaiga[1], Eugenijus Bagdonas[2]
[1]Department of Preventive Medicine, Kaunas University of Medicine,
[2]Department of Health Care Management, Kaunas University of Medicine, Lithuania

Key words: *economic evaluation; cost-utility analysis; methadone maintenance treatment; drug addiction; Lithuania.*

Summary. *Background. Economic evaluations in health care involve the identification, measurement, valuation, and then comparison of the costs (inputs) and outcomes of treatments or preventive activities.*

The aim was to analyze the cost-utility of six-month methadone maintenance treatment program in a Lithuanian primary health care setting.

Methods. A prospective study design was used. All the information was obtained through the validated questionnaires at the baseline and 3- and 6-month follow-ups. WHOQOL-BREF was used to assess the quality of life; the costs were assessed using the DATCAP methodology from the perspective of a patient and outpatient clinic during follow-up period.

Results. A total of 102 opioid-dependent patients were recruited in the study; 512 follow-up patient-months were obtained. The methadone maintenance treatment has significantly improved physical, psychological, and environmental components of quality of life during follow-up. Total program costs were 61 288.87 EUR. Cost paid by a patient comprised about 31% of total program costs. Cost per quality-adjusted life-month (QALM) for physical domain was 2227.55 EUR; for psychological domain, 1879.50 EUR; for social domain, 5467.64 EUR; and for environmental domain, 4626.47 EUR. Costs per QALM and quality-adjusted life-year (QALY) for total quality of life in the maintenance program were 2864.00 EUR and 34 368.00 EUR, respectively.

Conclusions. Our results showed that 6-month methadone maintenance program was effective in the terms of quality-of-life improvement. Methadone maintenance treatment program was less effective in terms of cost per QALY.

Introduction

Lithuania is one of the Baltic States, which reestablished independence from the Soviet Union in 1990. Illegal drug use was already a known problem in Soviet times as many of the World War II veterans were addicted to opiates. The practice of obtaining and injecting poppy milk opioids still exists as the main source of drugs in Lithuania (1).

During the 10-year period, the prevalence of substance abuse increased from 34.0 in 1995 to 164.2 cases per 100 000 population in 2005. In 2005, 79.7% of addictions were attributed to opioids (2). Considering epidemiological situation in the country, it is necessary to develop cost-effective substitution treatment program, as allocated facilities and resources are scarce and should be used in an effective way.

Methadone has been used as a successful pharmacologic intervention for the treatment of heroin dependence and acute and chronic pain. This treatment is effective in opiate addiction, reducing morbidity and mortality associated with heroin use. However, methadone overdosing and abuse is one of the shortcomings of this treatment (3, 4). In economic evaluations, the costs and the consequences (positive and negative) of interventions should be compared in order to examine the effective use of the scarce resources. In health care, it involves the identification, measurement, valuation, and then comparison of the costs (inputs) and outcomes of treatments or preventive activities (4). The conceptual framework of economic evaluation differs according to the type of decisions or to what is evaluated. Also it is attributed to methodology and instruments used in economic evaluations (5).

Cost-utility analysis allows us to compare the outcomes of treatment by evaluation of changes in quality of life (QoL) before and after treatment (4, 6, 7). This type of analysis in maintenance treatment can be regarded as the most valuable type of economic analysis, exploring improvement of quality of life for drug-addicted persons (4).

Correspondence to G. Vanagas, Department of Preventive Medicine, Kaunas University of Medicine, Eivenių 4, 50009 Kaunas, Lithuania. E-mail: giedrius.vanagas@kmu.lt

Adresas susirašinėti: G. Vanagas, KMU Profilaktinės medicinos katedra, Eivenių 4, 50009 Kaunas
El. paštas: giedrius.vanagas@kmu.lt

We aimed to analyze cost-utility of the six-month methadone maintenance treatment program in a Lithuanian primary care setting.
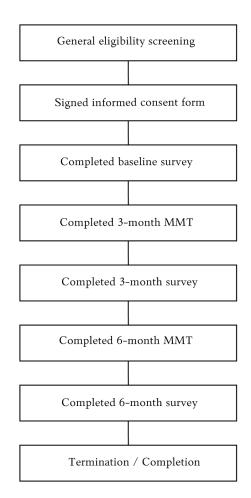
Material and methods

Setting. Methadone maintenance outpatient clinics (centers of addiction diseases in Vilnius, Kaunas, and Klaipėda) in a primary care setting in Lithuania.

Participants. All opioid-addicted persons for the first time involved into the outpatient methadone maintenance program from January 1, 2004, to June 30, 2004, and meeting eligibility criteria for the study were enrolled into the study.

Ethical considerations. Study protocol was approved by the decision of the Lithuanian Bioethics Committee meeting (June 3, 2003; case No. 53). Each study participant was informed on study objectives and signed an informed consent form.

Study design. A prospective study design was developed according to the Substitution Therapy of Opioid Dependence and HIV/AIDS program. All the information was obtained using validated questionnaires at baseline and at the 3- and 6-month follow-ups (Fig. 1).

Fig. 1. Study design used to assess the impact of methadone maintenance treatment program

Quality of life. The WHOQOL-BREF (8, 9) is the shorter 26-item version of the WHOQOL-100. It was used to assess the QoL at the baseline and after 3-month and 6-month follow-ups. According to the WHOQOL-BREF, one-month period before the study is evaluated. At the baseline, this refers to the month before the involvement to the treatment.

The WHOQOL-BREF defines the QoL as the participants' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns. This definition describes QoL as a subjective parameter of evaluation, which is embedded in a cultural, social, and environmental context. Because this definition of QoL focuses on respondents' "perceived" QoL, it is expected to provide a means of measuring effects of the disease and health interventions on QoL. The recognition of the multidimensional nature of QoL is reflected in the WHOQOL-BREF structure and is based on a four-domain structure:

1. Physical health activities of daily living,
2. Psychological body image and appearance,
3. Social and personal relationships,
4. Environment of financial resources.

After completion of the study, question scores for each domain were summed up, and the mean score was calculated. The multiplication of the mean score by 4 in order to transform domain scores comparable with the scores used in the WHOQOL-100 with a range of 4 and 20 was performed. Summing up the domain scores, the total QoL score was obtained. Domain scores and total QoL score were converted to 0–100 scale using the WHOQOL-BREF transformation table (8, 9), and finally scores were divided by 100 to get 0–1 scale, in which 0 represents the worst health status and 1 represents the best health status of study participants.

Costs. In the study, we used the Drug Abuse Treatment Cost Analysis Program (DATCAP) methodology, which is a cost data collection instrument and can be used in mental health clinics, day treatment centers for alcoholism, outpatient drug abuse treatment programs, and employee assistance programs (10–12). This instrument is intended to collect and organize detailed information on the resources used in service delivery and associated costs. Resource categories include personnel, supplies and materials, contracted services, buildings and facilities, equipment, and miscellaneous items (7, 10–12). All costs in this study were collected in national currency litas (LTL) and then converted to Euro (EUR) by fixed currency exchange rate of the Lithuanian Central Bank, when 1 EUR is equal to 3.4528 LTL.

Statistical analysis. Anticipating relatively small sample and that scores would not necessarily be

normally distributed, nonparametric statistics was used. The Friedman test, also known as Friedman two-way analysis of variance, tests the null hypothesis that measures from k-dependent samples come from the same population (13). The Friedman test allows us to show the difference among more than 2 measurements in the same population. It is based on the rationale that if the groups do not differ by the criterion variable, then the rankings of each subject will be random and there will be no difference in mean ranks between groups by the criterion variable. If the significance of Friedman chi-square was less than $P<0.05$, it meant that the groups differed by the criterion variable.

The aim of the cost-utility analysis was to compare different interventions in the terms of both quantity and QoL, as we express them as costs for gaining one full healthy month in terms of a specific QoL measure (e.g. cost per QALM) (6, 14). When the QoL score is expressed from 0 to 1, we can calculate expected quality-adjusted survival time adjusted for a specific QoL domain. Let $Q_S(t)$ be the average score or utility of those subjects who were followed up to time t and still alive, and $S(t)$ be the survival function for the cohort. Hwang and Wang (14) showed that the expected quality-adjusted survival time adjusted for a specific QoL domain or utility over a time period [a, b] can be obtained from the formula:

$$E[QAS]_{[a,b]} = \int_a^b Q_S(t)S(t)dt + \delta \int_a^b (1 - S(t))dt,$$

where δ is a score value or utility assigned to the death in the time period. In the 6-month follow-up study, we can calculate the average domain scores $Q_S(t)$ at $t=0$, 3, and 6 month for the treated cohort. In forming a hypothetical untreated group for comparison, we assume the domain scores of a subject at month 3 and 6 are the same as his/her scores at time 0, if the subject has not been treated. That is $Q_S(6)=Q_S(3)=Q_S(0)$ for the hypothetical untreated group. We were obliged to use mortality rates from other studies as our study was too short to get annual mortality rates, and we do not had deaths during follow-up period attributed to MMT program. The literature suggests that annual mortality is about 3% for the untreated subjects and 1% among those in the methadone treatment group (15–19). Hence, we may assume that survival rates are $S(t)=(1-q/12)^t$ at $t=0$, 3 and 6 month, where q is the annual mortality rate. If we further assume that score for the death is $\delta=0$, the expected quality-adjusted survival time adjusted for a specific QoL domain over the 6 months can be estimated, using a trapezoidal approximation, by:

$$0.5 \times (Q_S(0)S(0) + Q_S(3)S(3)) \times 3 + 0.5 \times (Q_S(3)S(3) + Q_S(6)S(6)) \times 3.$$

Since the time unit is a month, the unit of these estimates can be domain score-month or quality-adjusted life-month (QALM) adjusted for a specific domain, which is a month of being perfect in the specific QoL domain. The gain of the treatment in terms of each QoL domain over the 6 months is the difference between expected quality-adjusted survival estimates for the treated and untreated groups. The average total extra costs of treated subjects over the 6 months divided by the gain with respective to a QoL domain over the same time period can be interpreted as the cost to gain one QALM.

The costs per QALM to a full healthy month and costs per QALY to a full healthy year in terms of a specific QoL domain and total QoL can be obtained from formulas:

Cost per QALM = $Cost_6/QALM_6$
Cost per QALY = $Cost_6/QALM_6 \times 12$,

where, $Cost_6$ is the average total costs per patient in the MMT program during 6 months; $QALM_6$ is the total QALM gain per patient over 6-month MMT program.

Cost-per-QALM value used in the study could be regarded as a ratio, which shows us costs per 1 month of survival gain adjusted to full QoL improvement.

Results
A total of 102 opioid-dependent patients were recruited for the study. During the follow-up period, 30.4% (N=31) of patients dropped out; 71 patients completed the full six-month methadone maintenance program.

Participants. The mean age of study participants was 32.6 years (SD, 9.2). The mean age at onset of regular drug use was 19.9 years (SD, 4.5). The mean number of days of opioid use during the last 30 days was 26.6 (SD, 3.7) days. The mean methadone dose for substitution treatment from the beginning of MMT was 52±18 mg.

No significant differences were found between groups for all sociodemographic characteristics (Table 1).

Changes in quality of life. The 6-month follow-up survey showed that methadone maintenance treatment has a potency to improve QoL and health of opioid-addicted study participants (Fig. 2). The methadone maintenance treatment significantly improved physical ($\chi^2=11.0$; $P=0.004$), psychological ($\chi^2=11.0$; $P=0.004$), and environmental ($\chi^2=6.1$; $P=0.048$) components of QoL; regarding social component of WHOQOL-BREF, there was no significant improvement ($\chi^2=2.0$; $P=0.362$).

Program costs. Six-month methadone maintenance program involved 512 patient-months of

Table 1. Descriptive characteristics of the study participants who completed the full methadone maintenance program

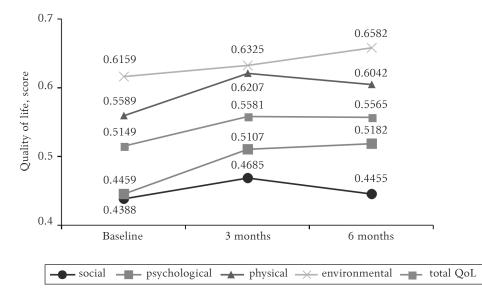| Variable	Completed study (N=71)		Terminated study (N=31)	
	N	Frequency (%)	N	Frequency (%)
Gender				
Male	55	77.5	27	87.1
Female	16	22.5	4	12.9
Age, years				
<24	21	29.6	7	22.6
25–32	20	28.2	7	22.6
33–40	11	15.5	12	38.7
41>	19	26.7	5	16.1
Marital status				
Married	8	11.3	2	6.4
Cohabiting	11	15.5	5	16.1
Widowed	4	5.6	–	–
Divorced	16	22.5	6	19.4
Never been married	32	45.1	18	58.1
Education years completed				
⩽10 years	30	42.3	10	32.3
11–12	29	40.8	11	35.4
13 and >	12	16.9	10	32.3
Graduated the last school				
No	26	36.6	10	32.3
Yes	45	63.4	21	67.7

Fig. 2. Quality-of-life changes during 6-month methadone maintenance program

follow-up period. The average costs per patient-month and patient-year in methadone maintenance program were 119.82 EUR and 1437.84 EU, respectively.

Staff costs. Because of concerns about medication diversion, dispensing methadone is strictly regulated. A typical outpatient MMT program covers 6 days per week. Average salary costs per visit were 2.76 EUR (Table 2). Salary costs for medical staff in the 6-month MMT program comprised 64.78% of all program costs (Table 3). To these costs, we included salary costs of personnel directly (nurse, medical doctor, etc.) and indirectly involved (administration, registrar, etc.) in the program. These

Table 2. Index of price unit costs

Costs	Units	Unit costs, EUR
Health care		
Salary	Visit	2.76
Building and maintenance	1 m²/month	1.83
Other	Patient/month	2.27
Patient		
Methadone	100 mg	0.90
Transportation	Visit	0.68
Other	Visit	0.19

costs were allocated proportionally to the registered visits during project period in the outpatient clinic.

Office space and equipment maintenance. The space was allocated directly by office space used by

Table 3. Costs of methadone maintenance treatment program

Costs	Allocation units	Quantity allocated to MMT program	Total allocated MMT program costs, EUR
Health care			
Salary	Visit	14 385	39 702.60
Buildings and maintenance	1 m²/month	856.02	1566.52
Others	Patient/month	512	1162.24
Patient			
Medications	Average dose	13 494.8	6342.56
Transportation	Visit	14 385	9781.80
Others	Visit	14 385	2733.15
Total costs, EUR			61 288.87

the methadone maintenance program, and indirectly we allocated 10% of all general-purpose space in the participating institutions. Total allocated space in all outpatient clinics was 142.67 m², and all costs allocated to office space maintenance were 1566.52 EUR during whole maintenance program period or 1.83 EUR per m²/month. Other costs were allocated to telecommunications, personnel training, services and tests, other equipment by the number of treated patients (1162.24 EUR).

Patient costs. Using the DATCAP methodology and questionnaire, we collected data on costs covered by patients who completed the MMT program. Costs covered by patients made up 31% of all program costs, and during 6-month program period, they were 18 857.51 EUR or 184.88 EUR per patient (Tables 2 and 3). These costs were composed of methadone, transportation costs and other costs related to the program.

Medication costs. All costs for medications during 6-month program period for all participants were 6342.56 EUR. The cost of methadone at a mean dose of 50.9 mg per day is about 0.47 EUR. Using the mean dose 7 days per week, costs per patient per year should be 171.55 EUR.

Cost-utility of the program. During six-month MMT program from the baseline, each study participant in average gained 0.27 QALM in physical domain, 0.32 QALM in psychological domain, 0.11 QALM in social domain, and 0.13 QALM in environmental domain. After rescaling the WHOQOL-BREF domains to one general QoL scale, the average 6-month QALM gain per patient for MMT program was 0.21 QALM. Applying cost-utility analysis, costs per QALM for physical domain were 2662.67 EUR; for psychological domain, 2246.63 EUR; for social domain, 6535.64 EUR; and for environmental domain, 5530.15 EUR. Costs per QALM and QALY for total QoL in the maintenance program were 2864.00 EUR and 34 368.00 EUR, respectively.

Discussion

The outcomes and inputs are recommended measurements to be used for research aimed to estimate economic effectiveness of the treatment (5,

6, 20). As outcome measurement, we used the QoL definition proposed by the WHO that is defined as a holistic approach of physical, psychological, social, and environmental QoL. As inputs to economic analysis, we used an economic definition of costs, which avoid problems associated to financial cost definition.

Our study highlighted better QoL for our study participants at the baseline as it was reported in other studies (21–23), where QoL in different domains was from 0.31 to 0.40 at the baseline and after 6-month follow-up it increased to 0.42–0.60. In our study, QoL was 043–0.62 at the baseline and after 6-month follow-up it increased to 0.45–0.66. Such findings, at first, could be attributed to different inclusion/exclusion criteria. Our study included smaller number of opioid addicts with HIV infection comparing to other studies. Secondly, the lowest QoL gains were seen in the social and environmental domains – this indicates lower availability and accessibility of social care services from social workers in our program. Third, different QoL questionnaires may include different definitions about what health dimensions constitute QoL; different scoring systems may be also important. In our study, we used a validated instrument for our population, which is a generic type of QoL measurement instrument, suitable for addictive diseases and let us compare results across different interventions (24, 25).

Our results highlighted that 6-month methadone maintenance program was effective in terms of QoL improvement with WHOQOL-BREF measures, but the program was less effective in terms of cost per QALY. No threshold value of acceptable cost-utility rate has been established in Lithuania yet. In the United States, 50 000 USD (39 270 EUR) per QALY is the threshold value below which medical technologies are informally but widely considered to be cost-effective (26). Although the United Kingdom does not have a fixed threshold value below which medical technologies are automatically judged as cost effective, the National Institute for Clinical Excellence noticed that a technology with incremental costs greater than 30 000 GBP (43 731 EUR) per QALY would require strong arguments to be accept

ed (27). In many studies, methadone maintenance programs showed high cost–per–QALY values, which ranged from 3300 to 12 800 EUR (15, 28, 29), and this should be regarded as cost-effective to known thresholds; our program was less effective. Our results could be affected by used methadone dosage policy, insufficient availability of psychological and social care, and other supplemental services, which were used in similar studies and had an additional positive effect on the effectiveness of MMT program (30).

Choosing an appropriate study design in economic research and using it in practice can be problematic. For economic evaluation, it is recommended to perform clinical trials or follow-up studies, when values of resources are assigned by defining costs at the same time and with the same degree of accuracy as outcome data (4, 6). We did it in our study, and it could be seen as strength of our study. Our study had several methodological limitations: the measurement of health outcomes was based on self-reports, and due to our study design, extraneous factors may confound our results. It is also important to note that due to the low number of the new participants in the MMT program, it was difficult to get sufficient data on

mortality. Regarding to this, in economic analysis, we used extrapolated data from similar studies, but it is acceptable as it is widely used methodology in recent research (11, 12, 15, 28). The data reported may be important to policy makers, program administrators, and program evaluators as benchmarks. It also can be used as comparisons of generic quality of life and base for economic evaluations and MMT program planning.

Conclusions
Our results highlighted that 6-month methadone maintenance treatment program was effective in the terms of quality-of-life improvement. Methadone maintenance treatment program was less effective in terms of cost per quality-adjusted life-year.

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Pakaitinio gydymo metadonu kaštų ir naudingumo analizė Lietuvoje

Giedrius Vanagas[1], Žilvinas Padaiga[1], Eugenijus Bagdonas[2]
[1]Kauno medicinos universiteto Profilaktinės medicinos katedra, [2]Kauno medicinos universiteto Sveikatos vadybos katedra

Raktažodžiai: ekonominis vertinimas, kaštų ir naudingumo analizė, pakaitinis gydymas metadonu, priklausomybė nuo narkotikų, Lietuva.

Santrauka. *Įvadas.* Sveikatos ekonominiai vertinimai apima gydymo ar profilaktikos programų kaštų ir naudingumo nustatymą, įvertinimą bei palyginimą tarpusavyje.
Tikslas. Įvertinti šešių mėnesių pakaitinio gydymo metadonu pirminėje sveikatos priežiūros grandyje programos kaštus ir naudingumą.
Metodai. Taikytas perspektyvusis tyrimo modelis. Visa informacija rinkta naudojant klausimynus, kurių patikimumas ir validumas buvo įvertintas. Apklausos vykdytos prieš pradedant tyrimą ir praėjus 3 ir 6 mėn. nuo įtraukimo į tyrimą. Gyvenimo kokybė vertinta vadovaujantis WHOQOL-BREF klausimynu; kaštai vertinti taikant DATCAP metodologiją, skirtą pakaitinio gydymo metadonu pirminėje sveikatos priežiūros grandyje kaštams vertinti.
Rezultatai. Į tyrimą įtraukti 102 priklausomi nuo opioidų asmenys, tiriamieji stebėti 512 mėn. Stebėjimo laikotarpiu pakaitinis gydymas metadonu statistiškai reikšmingai pagerino tiriamųjų fizinę, psichologinę ir aplinkos gyvenimo kokybę pagal WHOQOL-BREF skales. Bendrieji programos kaštai sudarė 61288,87eurų. Paciento patirtos sąnaudos sudarė apie 31 proc. visų programos išlaidų. Kokybiško gyvenimo mėnesio kaina atitinkamai fizinio komponento skalėje buvo 2227,55 eurai, psichologinio komponento – 1879,50 eurų, socialinio komponento – 5467,64 eurų, aplinkos komponento – 4626,47 eurų vienam kokybiško gyvenimo mėnesiui. Bendra kokybiško gyvenimo mėnesio kaina buvo 2864,00 eurai, arba atitinkamai laimėtų kokybiškų gyvenimo metų (QALY) kaina buvo 34368,00 eurai.
Išvados. Tyrimo rezultatai rodo, kad 6 mėn. pakaitinio gydymo programa pirminėje sveikatos priežiūros grandyje statistiškai reikšmingai pagerino tiriamųjų gyvenimo kokybę, tačiau, vertinant kokybiškų gyvenimo metų rodikliais, programa nėra pakankamai ekonomiškai efektyvi.

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