Economic evaluation of Suboxone® for substitution treatment of opioid drug dependence in Portugal

Miguel Gouveia[1], Rita Sousa[2], João Costa[2,3], and Margarida Borges[2]

1 Católica Lisbon School of Business and Economics, Lisbon, Portugal, EU
2 Centre for Evidence Based Medicine, Faculty of Medicine, University of Lisbon, Portugal, EU
3 Clinical Pharmacology Unit of the Institute of Molecular Medicine, Lisbon, Portugal, EU

Summary

Background: According to a recent Portuguese study the prevalence of lifetime consumption of heroin in the global population (age range: 15-74 years) is 0.5%. Methadone is the standard pharmacological treatment, while buprenorphine has been available since 1999 as an alternative treatment. Nevertheless, no comparative economic evaluation of the cost-effectiveness of these therapies has been made available. Aim: This study estimates the cost-effectiveness and cost-utility of a fixed dose combination of buprenorphine-naloxone (B/N) versus methadone as substitution treatments for opioid drug dependence from the Portuguese social perspective. Material and Methods: The comparator for B/N was methadone treatment, which is the most common pharmacological therapy and current clinical practice in Portugal. Health gains were measured using the number of heroin-free days per year (indicator of effectiveness) and quality-adjusted life years (QALYs) associated with each treatment. Estimated costs included acquisition, preparation and transport of medication; costs of dispensing and supervision of administration; costs arising from the periodic monitoring of patients and the non-medical direct costs of crime associated with drug addiction. Results: The B/N combination is associated with an incremental cost-utility ratio of €5,914 per QALY gained. The B/N combination is dominant when the analysis includes costs of crime associated with drug addiction. Conclusions: The results suggest that this combination is cost-effective and has the potential to generate health gains in the target population at a low cost.

Key Words: Cost-effectiveness; cost-utility; opioid dependence; suboxone; methadone

1. Introduction

Opioid use disorder is a worldwide health problem with major individual, economic and public health consequences [36, 37]. Opioid addiction is also related to severe health problems, including an increased risk of contracting HIV and/or viral hepatitis C and B infections, as a possible consequence of intravenous drug use [6]. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) estimates that there are 1.3 million problematic opioid users in Europe, of which about 700,000 received medically assisted treatment in 2012 [6]. Recent data have shown that in the 15-64 year age range of its population, Portugal has one of the lowest prevalence rates of drug abuse in Europe, with the exception of

heroin, which has presented a more regular consumption pattern than several other European countries. Among heroin users, almost 40% reported daily use and about 30% reported consuming it four or more times per week [1-2,6]. Portuguese data from the European Drug Report 2014 show that, considering the total demand for drug abuse treatment, opioid users correspond to 70.1% of all entrants and 54.4% of first-time entrants [6].

Opioid addiction should be considered a disease that can be successfully treated, especially by comparison with other substance use disorders, and several effective treatment strategies are currently available. Opioid agonist treatment (whether relying on methadone, buprenorphine or buprenorphine/naloxone) has become the most common treatment in

Corresponding author: Miguel Gouveia, PhD, Católica Lisbon School of Business and Economics, Palma de Cima 1649-023 Lisbon Portugal, EU
E-mail: mig@ucp.pt

controlling the effects of illicit drug use [33].

Methadone, first used in Portugal in 1978, is a full opioid agonist and is currently the most widely used pharmacological treatment. However, due to its safety profile and compliance requirements, most patients have a supervised intake, which may be difficult to manage, due to the interference of the dispensing schedules with other daily activities.

Buprenorphine, an opioid partial agonist, was authorized in Portugal in 1999. Buprenorphine prescribed at fixed doses (above 7 mg per day) did not differ from methadone in its capacity to retain patients in treatment and suppress illicit opioid use [25]. It has also broadened access to patient care and may satisfy unmet needs in the opioid-dependent population [21]. The literature has documented the fact that methadone and buprenorphine are the most effective treatments for patients dependent on heroin [8, 18, 19, 31]. On the other hand, the risk of misuse and diversion to the illicit market associated with methadone and buprenorphine has proven to be a difficult problem to solve. With the aim of preventing the misuse of the drug, a buprenorphine/naloxone (B/N) combination (Suboxone®) was developed. The presence of naloxone, an opioid antagonist, prevents the attainment of the desired effects when B/N is injected. The B/N combination was approved by the European Medicines Agency (EMA) in September 2006 as an oral substitution treatment for opioid drug dependence within a framework of medical, social and psychological treatments [34].

In contrast to methadone, which is given free of charge to patients in Portugal, formulations of buprenorphine (whether prescribed alone or in combination with naloxone) are subject to a co-payment of 63% by patients, which can severely limit access to its benefits.

This study presents a pharmacoeconomic evaluation of the B/N combination in mainland Portugal, adding to previous work related to Southern European countries [9, 24]. It estimates the cost-effectiveness and cost-utility of the B/N combination vs methadone from a social perspective, including the costs and consequences for all the parties concerned.

2. Methods

2.1. Model overview

This analysis is based on a cost-utility model created by the York Health Economics Consortium [38]. The model used data reported by Marino and Lazzaro [23], because of the lack of information published in Portugal on resource consumption in the treatment of opioid dependence. The study used by Marino and Lazzaro had been carried out by the Department of Addictions of the Local Health Authority in Varese, Italy. The study included 512 patients on maintenance therapy with methadone, and 211 with the B/N combination.

The timeframe for the economic evaluation was one year. In this way the study did not include discount rates that might have been subject to possible exceptions to be presented later on.

2.2. Treatment comparator

For the B/N combination an average daily dose of 8 mg was considered. Methadone was selected as comparator, since, besides being the most common therapeutic therapy, it also reflects current clinical practice according to the National Drug and Addiction Institute (Instituto da Droga e Toxicodependência - IDT). The standard programme defined by IDT targets abstinence from heroin and other psychoactive substances, and is part of a broader programme of medical, psychological and social intervention [12]. According to IDT, the average daily dose of methadone is 75 mg.

2.3. Effectiveness and Quality of Life Inputs

The measure of effectiveness used was the number of heroin-free days, estimated from the percentage of time in which urine tests undertaken by patients revealed no illegal opioids [23]. Utilities associated to heroin-free days and heroin-using days were used as a measure of health-related quality of life. A conservative assumption whereby possible effects on quality of life related to the convenience, autonomy or adverse effects associated with the different treatments was ignored.

Utilities related to heroin-free day and heroin-using day were computed by adjusting values from the literature. The utility of a heroin-free day was calculated from the study of Harris et al. [13]. In this study patients who were on methadone had a utility value of 0.59 (CI: 95% from 0.54 to 0.65) and on buprenorphine of 0.62 (CI 95% 0.56 to 0.68). Conservatively, it was considered that the utility deriving from a heroin-free day was independent of treatment, so that the average of both values for utility (0.605) was used in the model.

Given that heroin addiction is associated with

multiple negative health consequences [7, 26, 28-30], the quality of life of a heroin-use day was calculated by adjusting estimates from Barnett et al. [3]. In that study, the utility for patients not using heroin was 0.9 and for those using heroin was 0.8. The absolute values are debatable, but it was assumed that the relative values were accurate. Thus, the utility per heroin-free day (0.605) was multiplied by the ratio between the two utility values (0.8/ 0.9), to reach the value 0.538 for a heroin-use day [23].

The number of days spent in each state was estimated for both treatments. According to Marino and Lazzaro the proportion of heroin-free days was 0.677 with methadone and 0.779 with the B/N combination [23]. These annual estimates correspond to 247 heroin-free days with methadone and 284 heroin-free days with B/N.

The overall value for utility was calculated by aggregating total days and their respective utility value. According to this methodology, improvements in quality of life can be achieved by increasing the number of heroin-free days.

Even though the time horizon of the analysis was restricted to one year, it was still necessary to include the effect of mortality on treatment. In order to estimate the QALYs lost by premature deaths attributable to treatment, the life expectancy of an average patient was calculated. The average mortality rate for opioid addicts is 1.84% according to Oppenheimer et al. [28]. By combining these data with the mortality rates provided by the Portuguese National Statistics Institute (INE) for 2009-2011, a composite mortality table was estimated for the opioid-dependent population [17]. The mean patient age was 37.7 years [23]. The mean estimated life expectancy at 38, adjusted for quality of life related to opioid dependence and discounted at a 5% rate, was 4.56 years. This is the only situation where a discount rate has been used in this study. The value of 5% is a mandatory rate according to the Portuguese Health Technology assessment guidelines [15].

These are the QALYs lost when there is a premature death attributable to treatment. According to Gibson et al., the mortality rate for methadone was 2.75 (per 1,000 patients in treatment) [10]. Information for the B/N combination was not available, so the rate for buprenorphine was used (0.02 per 1,000 patients in treatment). The QALYs lost due to annual premature mortality related to treatment can be calculated by multiplying the 4.56 QALYs by the probabilities of death according to each type of treatment. Overall, annual estimated QALYs for the treat-

ment with the B/N combination were 0.590 (whether with or without mortality), as against 0.583 (without mortality) and 0.570 (with mortality) for the treatment with methadone.

2.4. Costs data

2.4.1. Drug treatment of heroin addiction
Cost estimates for the B/N combination were based on data from the National Authority for Medicines and Health Products (INFARMED) [14]. An average daily dose of 8 mg per patient was considered for the B/N combination as established by the World Health Organization [36]. The estimated cost per year per patient was €1,011. This cost is partly paid by the patients themselves.

Cost estimates for methadone were based on the information provided by IDT, since its acquisition, production and distribution occurs completely within public sector institutions. As stated above, the average daily dose of methadone is 75 mg and it is available in three different formats: oral solution, tablets of 10 mg and of 40 mg. In 2012 IDT acquired 540 kg of powder for oral solution (€161,028), tablets of 10 mg (€51,348) and tablets of 40 mg (€65,438).

Numbers of patients in treatment with methadone (oral solution and tablets) were based on the 2011 IDT report [16]. According to this source, as of December 31st of that year, 16,561 individuals were enrolled in methadone treatment in mainland Portugal. As this value corresponds to a likely estimate of the average number of individuals under treatment at any given moment, it was considered as the number of methadone treatment years provided by IDT.

Part of the methadone acquired by IDT is sent to the Madeira and Azores islands. To estimate the additional treatments provided in these islands, the ratio between treatments and population in the islands and those in mainland Portugal was calculated, resulting in 848 additional years of treatment. Estimates of years of treatment with methadone took into account the amount sent to the islands, the number of years of treatment in the format of methadone tablets (1,065) and assumptions about powder and tablet losses. The final results for mainland Portugal, the object of this study, were a total of 15,496 treatment years with oral solution.

Cost estimate for methadone included preparation of the oral solution by the Military Laboratory, with a unit cost of €4 per litre container, provided by IDT. An estimate was also made for the distribution to each treatment centre, based on: the number of cen-

Table 1. Health- and social care-related costs

Resources	B/N combination (€ /patient/year)	Methadone (€ /patient/year)
Psychiatric follow-up visit	252.45	340.58
Interview for psychological follow-up	216.68	207.16
Toxicology drug tests (urine, breath and saliva)	188.20	188.90
Medication and vaccine administrations	26.00	641.92
Individual psychotherapy	22.62	28.53
Family psychoeducational group sessions	0.24	1.68
Psychological tests	32.18	14.36
Social worker visit	1.38	3.21
Drug Monitoring visit	328.44	430.97
B/N: Buprenorphine and naloxone.		

tres; mean distance of each Centre from Regional Offices; and mean cost per kilometer using Portuguese legislation (Decree-Law 137/2010 of 28 December). An average of 12 minutes for the preparation and dispensing of each methadone dose was considered for the purpose of estimating nursing labour costs (Ordinance 1553D December 31, 2008). This estimate took into account administrative and general costs (including energy, and security), too.

2.4.2. Health- and social care-related costs

Health- and social care-related costs included physicians' visits, psychotherapeutic evaluations and interventions, toxicology drug tests and visits by social workers.

The resource consumption pattern was based on Marino and Lazzaro study [23]. Resource unit costs were obtained from Portuguese legislation (Ordinance 839-A/2009). For patients on methadone treatment, costs associated with the administration of vaccines and other medicines were included. For the B/N combination the dispensing cost is included in the overall medication cost, as this medicine is available in a community pharmacy context. Toxicology drug test unit costs (covering urine, breath and saliva) were estimated on the basis of information provided by the IDT. The estimated average cost per patient per year

was €22.91 (Table 1).

2.5. Sensitivity analysis

The robustness of the results was evaluated without the component of premature mortality associated with opioid substitution therapy.

The impact on the results of opioid addiction crime-related costs was evaluated, too. The patterns of criminal activity for a period of one year associated with each treatment were taken from Taylor et al. [35]. The adjustment from British to Portuguese costs assumed the proportionality to the gross domestic product (GDP) per capita in 2011 for both countries, using market exchange rates as established by Eurostat [32].

The costs related to violations of the 'Illicit Substances Law' were estimated on the basis of data from the Portuguese study "Droga e Propinas – Avaliações de impacto legislativo" [11]. According to this source, public expenditure for incarceration based on these violations reached 35 million Euros in 2010. Costs of courts associated with criminal offenses related to the laws on illicit substances were estimated at about 3 million Euros in 2010. Lastly, the estimated costs associated with law enforcement against violations of the 'Illicit Substances Law' were approximately

Table 2. Costs of crime

Type of crime	B/N combination (€ /patient/year)	Methadone (€ /patient/year)
Home robbery	€ -	€ 208.0
Non-car robbery	€ 213.2	€ 3,087.4
Car robbery	€ -	€ 131.6
Other crimes related to property	€ 29.1	€ 27.6
Violations of law on illicit substances	€ 27.5	€ 41.3
B/N: Buprenorphine and naloxone.		

Table 3. Average annual cost of treatment for opiate dependence

Resources	B/N combination (€ /patient/year)	Methadone (€ /patient/year)	Incremental (€)
Drug treatment of heroin addiction	1,011.13	107.70	903.43
Health- and social care-related costs	1,068.18	1,857.31	-789.13
Total cost	2,079.31	1,965.01	114.30

B/N: Buprenorphine and naloxone.

Table 4. Results for Baseline Scenario

	B/N combination (€ /patient)	Methadone (€ /patient)	Incremental
Total Costs	€2,079.3	€1,965.0	€114.3
Total QALYs	0.5901	0.5707	0.0193
Heroin-free days	284	247	37
Incremental Ratios:			
ICUR (€/QALY)			€5,914.1*
ICER (€/Heroin-free day)			€3.06*

B/N: Buprenorphine and naloxone. *Exact values of ratios reported.

26 million Euros in 2010. For 2010, these costs totalled 64 million Euros, arising from 13,500 offences, which corresponds to an average cost of €4,741 per offence. Table 2 shows the annual costs per patient, with variations generated by treatment-related differences in the frequencies of crimes.

3. Results

3.1. Baseline scenario

Table 3 summarizes the average annual costs per patient for the two types of treatment.

In Table 4 baseline incremental cost-effectiveness and cost-utility ratios per patient in the case of treatments based on the B/N combination are compared with those where methadone therapy was used. Treatment with the B/N combination was more costly (€2,079 vs. €1,965) and more effective (0.59 vs. 0.57 QALY) compared with methadone treatment. Overall, B/N treatment exhibits an incremental cost per QALY gain of €5,914 and an incremental cost per heroin-free day of €3.1.

3.2 Sensitivity Analyses

3.2.1. No premature death

In this subsection the advantage of the B/N combination in having lower treatment-related mortality has not been included in the analysis. Results in Table 5 show that premature mortality has a non-negligible impact in contributing to the Incremental Cost-Utility

Ratio (ICUR). Despite these results, the level of the incremental cost-utility ratio remains below standard thresholds, with the outcome that the B/N combination is still cost-effective.

3.2.2. Inclusion of costs of crime

The baseline scenario did not include the crime-related costs. If these are included in the analysis, the results change. In this case the B/N combination acquires the status of the dominant intervention, because of lower costs and higher QALY. More specifically, treatment with B/N was associated with cost savings of €3,112 and a figure of 0.02 for incremental QALY (Table 5). If the costs of crime and the absence of premature deaths are considered jointly, the dominance of the B/N combination is preserved.

4. Discussion

Given the limitations of the study, these estimates followed a conservative approach. First, indirect costs were not included in the analysis. According to the 2011 IDT Report, 93.9% of drug users were 20 to 54 years old. From a societal perspective, therefore, values linked with changes in employment rates would have to rank as important parameters influencing overall cost-effectiveness. Data from the EQUATOR study [4] showed that employment status varied according to treatment. In that study a higher proportion of patients receiving mono-buprenorphine or the B/N combination were employed compared to patients receiving methadone or slow-release oral

Table 5. Results for sensitivity analysis

	B/N combination (€ /patient)	Methadone (€ /patient)	Incremental
No premature death			
Total Cost	€2,079.3	€1,965.0	€114.3
QALYs	0.5902	0.5833	0.0069
ICUR (€/QALY)			€16,604*
Inclusion of costs of crime			
Total Cost	€2,349.2	€5,461.0	€- 3,112
QALYs	0.5901	0.5707	0.0193
ICUR (€/QALY)			Dominant

B/N: Buprenorphine and naloxone. *Exact values of ratios reported.

morphine. According to the authors of that study, daily clinical attendance and supervised dosing may act as barriers to getting and keeping a job [4].

It seemed reasonable to assume that treatment with the B/N combination would be beneficial compared with methadone treatment. However, no reliable data on Portuguese patients' participation in the labour market by type of treatment were available.

The second limitation of this study relates to the role of the Military Laboratory in the processing of methadone. The costs used in the analysis may be underestimated, as the fixed price charged by the Military Laboratory (€4 per bottle) includes storage, manufacturing, primary packaging, transport and security services. Considering the set of services provided – in particular transport and security – this value seems to be, implicitly, heavily subsidized.

In addition, it should be noted that, given the absence of reliable information, some important issues could not be quantified. The role of opioid substitution treatment in reducing the transmission of infectious diseases (hepatitis B, hepatitis C and HIV) was not taken into account. This is of special importance in Portugal due to the high prevalence of these diseases among injecting drug users. The prevalence of HIV in this population is 5.3 per million individuals (well above the European Union average of 3.5) [6], of hepatitis C antibodies (anti-HCV) is 83.1% and of hepatitis B core antibodies (anti-HBc) is 53.7% [27].

According to a recent meta-analysis, treatment with methadone was associated with health gains related to these infectious diseases [20]. Thus it is plausible that treatment with the B/N combination could generate further health gains by increasing compliance with the therapy prescribed and, therefore, by reducing injection drug use.

One further limitation of this study comes from the use of data reported by Marino and Lazzaro [23].

Patients treated with methadone could present characteristics different from those of patients treated with B/N, so biasing the results. On the other hand, Marino and Lazzaro [22] state explicitly that there was no heterogeneity or sample selection bias between treatment groups, so leading one to expect that the potential for bias in the cost-effectiveness results was minimal.

Another limitation of the analysis is that the utility measures only reflect heroin-free days. There are other ways by which different treatments lead to differences in the quality of life, such as effects on mood, side-effects and the burden associated with the dispensing schedules. It is likely that this limitation leads to an underestimate of the cost-effectiveness of using B/N.

The results are in line with those available in the international literature – in particular, studies on the cost-effectiveness of B/N in Italy [22-23], Greece [9] and Australia [5]. All these studies have shown that B/N is cost-effective when compared to methadone, so indicating that the economic advantages of B/N appear to have the some robustness across different health systems.

5. Conclusions

Results of the economic evaluation of the B/N combination for opioid substitution treatment versus methadone, in Portugal, showed an incremental cost of €5,914 per QALY and €3.06 per heroin-free day. If the analysis is broadened to include the costs of crime associated with drug addiction, these estimates improve so much that the B/N combination becomes dominant. Overall, the results suggest that the B/N combination is cost-effective and has the potential to generate substantial health gains at low costs for the Portuguese health system. This implies that improv-

ing access is desirable, particularly when it is considered that methadone treatment is free of charge to patients in Portugal, whereas treatment with the B/N combination is not.

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