Suboxone® (Buprenorphine/Naloxone) as an Agonist Opioid Treatment in Spain: A Budgetary Impact Analysis

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Key Words

Buprenorphine/naloxone • Methadone • Opiate dependence • Maintenance treatment • Budgetary impact analysis

Abstract

Objective: To evaluate the economic impact of buprenorphine/naloxone (B/N) as an agonist opioid treatment for opiate dependence. **Methods:** A budgetary impact analysis model was designed to calculate the annual costs (drugs and associated costs) to the Spanish National Healthcare System of methadone versus B/N. Data for the model were obtained from official databases and expert panel opinion. **Results:** It was estimated that 86,017 patients would be in an agonist opioid treatment program each of the 3 years of the study. No increase in the number of patients is expected with the introduction of B/N combination. The budgetary impact (drugs and associated costs) for agonist opiate treatment in the first year of the study would be 89.53 million EUR. In the first year of B/N use, the budgetary impact would rise by 4.39 million EUR (4.6% of the total impact), with an incremental cost of 0.79 million EUR (0.9% of the total impact). The budgetary increase would be 0.6% (0.48 million EUR increase) and 0.6% (0.49 million EUR increase) in the second and third years of use, respectively. The mean cost per patient in the

first year with and without B/N would be EUR 1,050 and 1,041, respectively. The most influential variables in the sensitivity analysis were logistics and production costs of methadone and the percentage use of B/N. **Conclusion:** With an additional cost of only EUR 9 per patient, B/N is an efficient addition to the therapeutic arsenal in the drug treatment of opiate dependence, particularly when considering clinical aspects of novel pharmacotherapy.

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Introduction

Opiate addiction is a chronic relapsing disorder associated with significant morbidity and mortality as well as with severe psychosocial complications and which requires long-term care and management strategies [1]. It is estimated that there are 12.9 million problem opiate users worldwide including 9.2 million heroin abusers [2]. European estimates for 2004 indicated that opiates, primarily heroin, remained the principal drugs for which patients sought treatment, and accounted for about 60% of all treatment requests [3]. The annual prevalence of opiate abuse among individuals aged between 15 and 64 years over the period 2000–2004 ranged from 0.2% in Greece, Czech Republic, Germany, and The Netherlands

to 0.8% in Italy, Luxembourg and the United Kingdom, whereas in Spain it was similar to the average worldwide annual prevalence of approximately 0.4%.

There are a number of efficacious pharmacological treatment strategies available for the management of opiate withdrawal and to facilitate the safe transition to a relapse prevention program [4, 5]. Long-term relapse prevention in opiate-dependent patients is primarily based on agonist opioid therapy aimed at stabilizing the individuals within the community while helping them to avoid returning to their previous pattern of drug abuse. Methadone, a full μ -opioid receptor agonist that is taken orally once a day, is the most widely used and most extensively studied pharmacological treatment for opiate dependence. At sufficient doses as part of a maintenance program, it suppresses withdrawal symptoms and craving, blocks the effects of other opiates, and is a highly effective pharmacotherapeutic aid in retaining patients in treatment. It is effective in suppressing heroin use and in reducing addiction-associated crime [6, 7]. In Spain, methadone maintenance (MM) treatment is widely available although, as is the case in other countries, there are substantial regional differences with respect to the nature and quantity of additional psychosocial support delivered, the degree of supervision of methadone administration, the regulatory guidelines, and the restrictions on dispensing facilities [8–10].

Despite availability, increasingly easy access, popularity, and the well-documented effectiveness of MM programs, many patients fail to improve and are unable to achieve and to maintain abstinence while on methadone. In addition, the regulated environment in which methadone is generally dispensed (often at clinics serving large numbers of patients at different stages of change with limited provision for take-at-home dosing) frequently deters patients from entering MM treatment. Buprenorphine, a partial μ -opioid receptor agonist and a κ -opioid receptor antagonist with low intrinsic agonist activity (prescribed alone or in a combination tablet with naloxone), has emerged as an alternative to methadone in the treatment of heroin addiction. Its effectiveness and tolerability profile has been established in several placebo-controlled clinical trials [11–14]. According to the most recent Cochrane reviews, both methadone and buprenorphine are effective for maintenance treatment, provided that adequate dosages are prescribed [15, 16]. Buprenorphine is licensed in many countries for the treatment of moderate-to-severe pain. It is long-acting and, consequently, can be administered every 1, 2, or 3 days [17, 18]. Buprenorphine has a relatively good safety profile and,

compared to methadone, rarely results in clinically significant respiratory depression in cases of overdose. This is probably due to its partial μ -agonist activity [19]. In addition, buprenorphine is associated with a comparatively mild withdrawal syndrome [5]. Like methadone, buprenorphine can suppress opioid withdrawal effects and block the effects of other opiates. The buprenorphine/naloxone (B/N) combination (Suboxone®, Schering-Plough Corp.) was introduced in the United States in 2000 and was approved by the European Medicines Agency (EMA) in September 2006 for 'substitution treatment for opioid drug dependence within a framework of medical, social and psychological treatment' [20]. The rationale for its development was to minimize the need for intravenous administration and, because there is less need for direct observation during agonist opioid treatment (AOT), the treatment becomes more accessible and less expensive [9, 21]. Taken sublingually, the opioid antagonist naloxone has negligible bioavailability [22]. Hence, when used as prescribed, the preparation produces effects of buprenorphine alone. However, if injected, naloxone would precipitate opioid withdrawal in opiate-dependent patients [22, 23].

In the current scenario of rising healthcare costs and limited resources, managers, public-health administrators and clinicians are increasingly concerned about the costs versus potential benefits of any given treatment. This becomes particularly relevant when a novel treatment is being assessed by regulatory agencies or health administrations for approval and funding. This is currently the case for the B/N combination for opiate dependence in Spain. Since buprenorphine alone has not been available previously for the treatment of opiate-dependent individuals, this would be a good opportunity to have an efficacious alternative of maintenance programs for this complex addiction. The primary objective of the present study was to conduct pharmacoeconomic modeling of the B/N combination in the management of opiate-dependent individuals. The results would help in estimating the economic impact of its introduction not only into the Spanish National Health System (NHS) but also in other countries with a public NHS.

Methods

Budgetary Impact Analysis Model

An interactive model of budgetary impact analysis (BIA) based on international recommendations [24–27] was developed using Microsoft Excel 2003 for Windows to calculate the annual healthcare costs (pharmacological treatment and associated

costs) that the introduction of B/N combination would have in the Spanish NHS. A decision tree describing progress-over-time of patients in AOT as a function of the transition probabilities between the different model stages was incorporated into this model. The following variables were included in the model: (1) number of dependent patients in AOT programs in Spain; (2) use of resources, cost of pharmacotherapies, logistics (preparation and distribution), treatment and patient supervision, and urine drug monitoring; (3) rates of the different medications used in AOT; (4) probability of annual transition between the stages of the decision tree.

Two scenarios were evaluated in the BIA: (1) scenario 1: the scenario currently implemented in Spain in which 100% of patients in AOT take methadone, and (2) scenario 2: an analysis projected over 3 years with an estimation of the percentage use of methadone and B/N following the gradual introduction of B/N into the therapeutic arsenal. Consequently, a proportion of patients in AOT will be taking methadone and another proportion will be taking B/N.

The BIA is performed with a 3-year time projection with 3 cycles of 1 year each. The perspective of the final funders of the resources associated with AOT was assumed to be the Spanish Regional Healthcare System. This system is core-funded by the NHS with additional funding generated from regional (autonomous governmental) taxes and budgets.

Target Population

The population most likely to be eligible for one of the two treatment alternatives assessed in the model was estimated from the following sources: (1) *Plan Nacional sobre Drogas* (National Program on Drugs, Spanish Ministry of Health; available at <http://www.pnsd.msc.es/>), or (2) expert opinion of a working group consensus panel (WGCP).

Three likely target population groups were considered: (1) patients in medically assisted withdrawal (MAW) programs (patients undergoing a MAW prior to entering a relapse prevention program, not in AOT); (2) high-threshold programs (HTP) (patients with no physical or psychological impairment, but with difficulty in remaining abstinent; these patients generally show good adherence to AOT, they should require intermediate or high methadone doses, and need a high level of supervision), and (3) low-intermediate-threshold programs (LITP) (patients with physical and/or psychological impairment and with poor treatment adherence to AOT; these patients have less supervision, should require higher doses of methadone and the majority are poly-substance (e.g., cocaine, alcohol, ...) abusers).

It was assumed that introduction of B/N into the therapeutic arsenal would not cause an annual increase in the population in AOT and that the incidence of new cases in AOT was irrelevant to the objectives of the present study. Given the high accessibility to the program, these assumptions are based on the elevated healthcare coverage for the target population.

Pharmacological Treatment Options: Estimate of Resource Use

Two pharmacotherapies were considered in the present analysis: methadone, the medication widely used in AOT in Spain, and the alternative of B/N. Naltrexone, an opioid antagonist also licensed to reduce heroin relapse as part of a maintenance treatment program, was excluded from the analysis due its limited acceptance among both patients and clinicians [28] and because

of insufficient evidence supporting its use in maintenance treatment for opioid dependence [29]. The doses of the two medications were based on the approved prescribing information together with the opinions of the WGCP. As such, an average daily dose of 60 mg of methadone (WGCP expert opinion) was used independently of whether they were HTP or ILTP, while B/N was used at an average daily dose of 8 mg. These doses were the *defined daily dose* established by the World Health Organization. The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults (DDD; details available at: <http://www.whocc.no/atcddd/>).

The following resources and treatment components were identified, quantified and their assigned costs included in the analysis (unit costs, expressed in EUR 2007):

(1) *Medication*: Costs of producing methadone (EUR 636.36/kg) or B/N (EUR 23/7 tablet pack) combination for use in AOT.

(2) *Logistics*: Cost involved in a series of procedures, generally performed by an accredited pharmacist, including collection of methadone with appropriate safety measures; transfer to the central pharmacies where individual doses of methadone hydrochloride are prepared, as a magistral formulation from the methadone solution; distribution to the dispensing centers, and collection of unused doses. The distribution and production of the final methadone dose is considered to have a cost of EUR 0.16 and EUR 0.47/min, respectively.

(3) *Dispensing*: Costs of dispensing methadone to patients, generally by nursing staff, was considered to be EUR 0.26/min. The costs of methadone dispensers (such as MDS4 or Methadone Dispensing System) were not included.

(4) *Medical and pharmacy personnel*: Costs of clinicians involved in medical supervision of patients in MM treatment; psychiatric care and administrative costs of registry control of the methadone used by each patient in AOT in each of the dispensing centers (tasks performed by pharmacists). Both costs were assumed to be EUR 0.47/min.

(5) *Counseling*: Costs assigned to specialist addiction psychologists; additional social and employment rehabilitation care provided by social workers for individuals in AOT. Psychiatric care and psychologists counseling costs were assumed to be EUR 0.47/min, and social and employment rehabilitation cost assumed to be EUR 0.26/min.

(6) Urine toxicology drug screenings at a cost of EUR 3.59 per test.

Percentage Use of Each Pharmacotherapy in AOT

The WGCP considered that the B/N combination would reach a percentage of market share of 10, 15 and 20% of the total of HTP in the first, second and third years, respectively. Similarly, the consensus was that all LITP would remain on their usual treatment with methadone.

Description of the Decision Tree of Methadone versus B/N

Using the effectiveness data of the two treatments being compared and considering that the probabilities of the different events are fixed and determined variables, a deterministic model was devised using a decision-tree analysis. The decision tree, which was designed based on the opinions of the WGCP, represents with the highest precision possible for simulating the events and outcomes occurring with methadone or B/N in daily clinical practice during AOT in the 3 cycles analyzed (corresponding to the first,

Fig. 1. Decision tree of methadone versus B/N: methadone branch.

second and third years of B/N use). There were as many branches in the decision tree as the possible different options: patients in MAW, HTP, and LITP. For each possible outcome or decision-tree branch and for each treatment option (methadone or B/N), the corresponding probabilities of transition were estimated. Data on the different treatment options considered in the model were ob-

tained from a literature review and, where the information needed was missing or controversial, the opinions of the WGCP were sought.

Figures 1 and 2 show the structure of the decision tree for each of the treatments assessed in the analysis, and the probabilities of annual transition between the stages and the sources considered

Fig. 2. Decision tree of methadone versus B/N: B/N branch.

in the study. The initial probabilities used in the first year were maintained in subsequent cycles.

For the modeling, a base case was defined using the data available and the following univariate sensitivity analyses were performed to assess the robustness of the scenarios of the model:

(1) Increase in the number of individuals in the AOT program to 100,000 per year.

(2) Leveling in the probabilities of transition between stages in the branches of methadone and of B/N; considering that the probabilities for B/N were the same as those for methadone in the base case.

Table 1. Annual projection (at the start of the year) of the number of patients (and percentages) in MAW or treated with methadone and B/N in scenario 1 (without the introduction of B/N) and scenario 2 (with the incorporation of B/N) from the first to the third year of B/N use in AOT

Treatment	First year, patients (%)			Second year, patients (%)			Third year, patients (%)		
	scenario 1	scenario 2	scenarios 2 – 1	scenario 1	scenario 2	scenarios 2 – 1	scenario 1	scenario 2	scenarios 2 – 1
No treatment – MAW ¹	0 (0)	0 (0)	0	1,290 (1.5)	1,621 (1.9)	330	1,763 (2.1)	2,337 (2.7)	573
Methadone	86,017 (100)	83,436 (97.0)	–2,581	86,017 (100)	81,087 (94.3)	–3,639	86,017 (100)	79,712 (92.7)	–4,541
B/N	0 (0)	2,581 (3.0)	2,581	0 (0)	3,309 (3.8)	3,309	0 (0)	3,968 (4.6)	3,968
Total	86,017 (100)	86,017 (100)	0	86,017 (100)	86,017 (100)	0	86,017 (100)	86,017 (100)	0

¹ Patients without methadone or B/N treatment in MAW.

(3) The logistic costs such as preparation and distribution of methadone are zero.

(4) Leveling of the percentage of B/N use in HTP and LITP. In this analysis, the initial treatment arm with B/N was considered to have the same percentage of use in HTP and LITP (10, 15 and 20% in both groups in the first, second and third years of B/N use).

Results

Treatment Population: Patients on Each of the AOT Programs

Based on data from the Spanish *Plan Nacional sobre Drogas*, 86,017 patients are expected to be included in methadone program during the first year. This number of patients is expected to remain unchanged throughout the study.

Table 1 shows the change in the percentage of expected use for the different medications within AOT in scenarios 1 and 2 (following the introduction of B/N). In scenario 1, all patients receive methadone in the 3 cycles of treatment. In scenario 2, the overall percentage of patients treated with B/N varies from 3.0% in the first year to 4.6% in the third year. The number of patients treated with each medication was based on the number of patients in AOT and according to the projection of the percentage use expected in the 3 years of the study. Thus, with B/N, 2,581, 3,309 and 3,968 patients would be treated during the first, second, and third year, respectively. The remaining patients in scenario 2 would continue with methadone.

Estimation of Resource Use

Table 2 summarizes the total annual cost of each of the stages in the model. The cost per cycle varies between

EUR 672 per individual in MAW and EUR 1,701 for HTP treated with B/N.

Budgetary Impact Analysis

In scenario 1 the overall budgetary impact during the first year will be 89.53 million EUR (table 3), considering in the analysis all 86,017 patients included in AOT in Spain and all treatment-related costs (medication, production, logistics, dispensing, medical and pharmaceutical supervision, counseling, social worker input and psychiatric care) and the estimated percentage of use of each medication.

In scenario 2, during the first year of B/N use, the total budgetary impact of the two medications used in AOT in Spain and the treatment-associated costs will be 90.32 million EUR. During this year, the budgetary impact of B/N will rise to 4.39 million EUR (4.9% of the total budgetary impact), i.e. the introduction of B/N in the first year will increase the NHS budget by 0.79 million EUR (0.9% of the total impact). The budgetary cost of distribution for each of the products in the first year appears in table 4.

Comparing scenario 2 with scenario 1, each year has an increase in the total budgetary impact. This increase will be 0.6% (0.48 million EUR) and 0.6% (0.49 million EUR) in the second and third years, respectively, of the B/N use in scenario 2 (table 4). During the first year, the average cost per patient in AOT in Spain will be EUR 1,041 in scenario 1 and EUR 1,050 in scenario 2 (EUR 9 increase per subject per year following the introduction of B/N) (table 4).

The increase in the budgetary impact over the cycles of the study in scenario 2 relative to scenario 1 is associated with an increase in the number of patients in MAW. Thus, using the strategy in scenario 2 in place of sce-

Table 2. Annual cost per patient, according to the resource consumption at each stage, in patients in MAW or in those treated with methadone or B/N (values are expressed in EUR updated to 2007)

	MAW	HTP				LITP	
		methadone		B/N		methadone	B/N
		first year	second and third years	first year	second and third years	first year	first year
Methadone – B/N ¹	0.00	13.94 ²	13.94 ²	1,199.29 ³	1,199.29 ³	13.94 ²	1,199.29 ³
Logistics/distribution	0.00	231.67	231.67	0.00	0.00	231.67	0.00
Production of methadone	0.00	339.61	339.61	0.00	0.00	339.61	0.00
Prescription	47.62	137.58	68.79	0.00	0.00	68.79	0.00
Drug supervision	16.75	169.80	169.80	0.00	0.00	169.80	0.00
Clinical supervision	69.78	69.78	69.78	69.78	69.78	41.87	41.87
Psychological supervision	232.61	232.61	116.30	232.61	58.15	0.00	0.00
Psychiatric supervision	116.30	116.30	116.30	116.30	58.15	0.00	0.00
Social worker supervision	59.53	39.69	39.69	39.69	19.84	23.81	23.81
Monitoring	129.24	43.08	43.08	43.08	0.00	0.00	0.00
Total	671.83	1,394.05	1,208.96	1,700.74	1,405.21	889.49	1,264.97

¹ Based on official technical data and the opinion of the Expert Panel. ² 60 mg/day. ³ 8 mg/day.

Table 3. Budgetary impact (in EUR 2007, and %) for patients in MAW or for those treated with methadone and B/N in scenario 1 (without the introduction of B/N) and scenario 2 (with the introduction of B/N) and average annual cost per patient (in EUR 2007) from the first to the third year of B/N use in opiate substitution treatment

Treatment	Impact first year (%)			Impact second year (%)			Impact third year (%)		
	scenario 1	scenario 2	scenarios 2 – 1	scenario 1	scenario 2	scenarios 2 – 1	scenario 1	scenario 2	scenarios 2 – 1
Without treatment – MAW ¹	0 (0)	0 (0)	0	866,836 (1.0)	1,088,746 (1.3)	221,910	1,184,676 (1.4)	1,569,957 (1.9)	385,281
Methadone	89,531,424 (100)	85,934,053 (95.1)	–3,597,371	82,508,214 (99.0)	78,116,692 (93.2)	–4,391,522	81,441,618 (98.6)	75,973,538 (91.4)	–5,468,080
B/N	0 (0)	4,388,789 (4.9)	4,388,789	0 (0)	4,649,838 (5.5)	4,649,838	0 (0)	5,575,470 (6.7)	5,575,470
Total	89,531,424 (100)	90,322,842 (100)	791,418	83,375,050 (100)	83,855,276 (100)	480,226	82,626,294 (100)	83,118,965 (100)	492,671
Cost per patient	1,041	1,050	9	969	975	6	961	966	5

¹ Patients without methadone or B/N treatment in the MAW program.

nario 1, there are 331, 574 and 769 additional patients in MAW by the end of first, second and third years, respectively. By the end of the first year, the cost per patient in MAW at the end of each cycle will be EUR 1,394 and 1,481 in scenarios 1 and 2, respectively (table 4).

Sensitivity Analysis

To assess the robustness of the results of the BIA model, the values of relevant parameters in the analysis

were modified, and the influence of the modification on the following variables on the final outcomes was assessed:

(1) *With 100,000 persons per year in AOT:* The budgetary impact increases in both scenarios, but the percentage increase in the overall budgetary impact in scenario 2 compared to scenario 1 is the same as in the base case (0.9, 0.6 and 0.6% in the first, second and third years, respectively).

Table 4. Budgetary impact (in EUR 2007) and patients in MAW, HTP and LITP in scenario 1 (without the introduction of B/N) and scenario 2 (with the introduction of B/N) from the end of the first year to the end of the third year of B/N use in opiate substitution treatment

Stages	End first year; impact (patients)			End second year; impact (patients)			End third year; impact (patients)		
	scenario 1	scenario 2	scenarios 2 – 1	scenario 1	scenario 2	scenarios 2 – 1	scenario 1	scenario 2	scenarios 2 – 1
MAW	1,798,686 (1,290)	2,400,022 (1,621)	601,336 (331)	1,785,304 (1,763)	2,505,502 (2,337)	720,198 (574)	1,822,035 (1,899)	2,736,772 (2,668)	914,737 (769)
HTP	29,658,170 (22,364)	29,733,857 (22,060)	75,686 (–304)	23,355,213 (20,343)	23,094,005 (19,839)	–261,208 (–510)	21,702,471 (19,070)	21,302,893 (18,421)	–399,578 (–649)
LITP	58,074,568 (62,362)	58,188,964 (62,337)	114,396 (–25)	58,234,533 (63,911)	58,255,769 (63,842)	21,236 (–69)	59,101,789 (65,048)	59,079,300 (64,928)	–22,488 (–120)
Total	89,531,424 (86,017)	90,322,842 (86,017)	791,418 (0)	83,375,050 (86,017)	83,855,276 (86,017)	480,226 (0)	82,626,294 (86,017)	83,118,965 (86,017)	492,671 (0)
Cost per patient in MAW	1,394	1,481	87	1,012	1,072	60	960	1,026	66

Table 5. Budgetary impact (in EUR 2007) of methadone and B/N to AOT from the first to the third year of B/N use; sensitivity analysis

First year			Second year			Third year		
scenario 1	scenario 2	scenarios 2 – 1	scenario 1	scenario 2	scenarios 2 – 1	scenario 1	scenario 2	scenarios 2 – 1
Base case								
89,531,424	90,322,842	791,418	83,375,050	83,855,276	480,226	82,626,294	83,118,965	492,671
Increase in the number of subjects in AOT program: 100,000 per year								
104,085,732	105,005,804	920,071	96,928,573	97,486,864	558,292	96,058,098	96,630,858	572,761
Equal transition probabilities of methadone and B/N								
89,531,424	90,322,842	791,418	83,375,050	84,033,412	658,362	82,626,294	83,424,769	798,475
Logistics and production costs of methadone = 0								
40,391,837	42,657,443	2,265,605	34,972,557	37,531,830	2,559,273	34,494,069	37,581,014	3,086,945
Equal use of B/N in HTP and in LITP								
89,531,424	92,583,675	3,052,251	83,375,050	87,420,162	4,045,111	82,626,294	88,027,529	5,401,235

(2) *If the probabilities of transition between stages in methadone and in B/N become level:* The increment in the budgetary impact in scenario 2 versus scenario 1 increases sensibly relatively to the base case in the second and third years to 0.8 and 1%, respectively.

(3) *If logistics and production costs of methadone are zero:* The total budgetary impact in the 2 scenarios decreases significantly. Further, the percentage increase in the total budgetary impact in scenario 2 relative to scenario 1 rises to 5.6 and 8.9% in the first and third years, respectively.

(4) *If in scenario 2 the percentage of B/N used is the same in HTP and ILTP:* The number of patients treated with B/N increases in the first, second and third years to 8,602,

12,650 and 16,708, respectively. Therefore, the budgetary impact of scenario 2 versus scenario 1 is increased by 3.05, 4.05 and 5.40 million EUR per year, respectively.

The different scenarios considered in the sensitivity analysis are summarized in table 5.

Discussion

Research into health outcomes involves a combination of techniques and methods of a multidimensional character and includes studies of effectiveness, evaluation of the quality-of-life assessment, patient satisfaction and preferences, as well as measurement of economic impact

of healthcare interventions. To analyze the clinical and economic impact of a clinical decision, one must rely on data derived from different sources. When this information is insufficient or too dispersed for global conclusions to be drawn, it becomes necessary to employ mathematical models that enable us to integrate, adapt and extrapolate pharmacoeconomic data [24]. The present document constitutes the first analysis conducted in Spain of budgetary impact of the costs associated with the management and supervision of patients in AOT, and its results could be extrapolated to other European countries with a public NHS.

This study reveals that the introduction of B/N combination to the therapeutic arsenal as compared to the only AOT currently available in Spain will be associated with an important cost increase of the pharmacological treatment, but will be accompanied by a gradual decrease in costs related to logistics/distribution, production, delivery, supervision and monitoring. Thus, the present results indicate that with the percentage of use of B/N referred to in the model, there will be an increase in the budgetary impact of the Spanish NHS of 1.45 million EUR during the first year after the introduction of B/N. This value will increase slightly to values ranging between 1.90 and 2.49 million EUR for the second and third years of use of this medication. In addition, a rise in the number of patients in MAW, of 331, 574 and 769, at the end of the first, second and third years following the introduction of B/N, respectively, was projected. The results of the sensitivity analysis of the model indicate that the factors with greatest influence on the final outcomes would be those associated with the production and logistics of methadone, and the percentage of B/N use in AOT.

The model has several advantages. It is a transparent model in that the variables included (unit costs, probabilities of transition, etc.) and the assumptions of the study are presented in sufficient detail to allow for the study to be replicated. In addition, the perspective used is that of the funding body or the administration; the key agents in budgetary decision-making. Finally, as it is an interactive computer model, it is easily reproducible and adaptable by those performing economic analyses to enable the recalculation of the budgetary impact (and obtain 'tailor-made' results) when there are changes in the major parameters considered in the study.

There are a number of limitations to be considered in this study, as well. Firstly, there are currently no studies comparing methadone versus B/N in standard clinical practice with respect to the resources used in the model.

Consequently, we had to rely on WGCP. To improve decision-making it would be essential to conduct a pragmatic or naturalistic prospective study to assess the effectiveness and safety of both medications under conditions of standard clinical practice, and which would include those resources and costs associated with treatment [30]. The model does not consider other patient costs such as the social costs derived from the administration regimes of B/N; savings derived from patient travel costs, both in terms of time and money, and costs of office space and equipment [9]. Another potential limitation of the study refers to the assumption made in the model that introduction of B/N into the therapeutic arsenal would not cause a significant increase in the population entering AOT. It is possible that the number of patients in AOT could increase as reported when buprenorphine was launched in the UK in 1999 [31], or with the emergence of new types of patients entering into treatment resulting from establishing office-based treatment [32]. However, in the first months of B/N in Spain in those health departments where the medication was approved for funding for a limited number of opiate-dependent patients, contrary to what would have been expected, the target number of funded patients was not reached. Therefore, to avoid confounding factors regarding the final budgetary increase, we decided to maintain constant the number of patients in AOT. Another aspect not included in the model is the potential for improvements in quality of life, or the potential benefits resulting from a better integration at a social level. Indeed, some studies have shown an improvement in the psychological, medical, family, work status, use of alcohol and other illegal drugs in patients treated with buprenorphine compared to previous treatments [33]. Another consideration relates to the rather conservative approach we have used in some aspects of the model. For example, whilst it is plausible that the clinical practice of performing frequent or routine toxicology drug screening may remain unchanged, it is possible that introduction of B/N may also result in a reduction in the frequency of urine screenings, with a concomitant reduction in associated costs [21].

As argued by other authors [31, 34], when available resources are limited, prescription of buprenorphine and methadone in AOT should be rationalized based on both pharmacoeconomic and clinical evidence. In addition to costs, a pharmacoeconomic evaluation must address a number of clinical issues not solely in terms of the efficacy and effectiveness of the new medication compared to the best currently available pharmacotherapy but also in terms of the differential clinical profile and potential ben-

efits of the new medication. Opioid-dependent patients are often prescribed other medications for comorbid medical or psychiatric conditions, and have a high prevalence of cocaine or other substance abuse while in MM. However, a rate-corrected QT (QTc) interval prolongation and, consequently, a higher risk of developing the potentially life-threatening torsade de pointes (TdP) ventricular tachycardia in methadone-treated patients has been reported in reports of single cases [35, 36], retrospective case series [37–39], and in cross-sectional, prospective, controlled clinical trials [40–44]. In contrast, buprenorphine was associated with less QTc prolongation compared to equally effective doses of methadone or levomethadyl acetate (LAAM; now withdrawn from the market due to an associated risk of cardiac arrhythmias) in a 17-week, double-blind, randomized, controlled, clinical trial that analyzed 12-lead electrocardiograms collected at baseline and every 4 weeks from 154 opioid-addicted patients [43]. Patients receiving LAAM and methadone were significantly more likely to show a QTc >470 ms if male or >490 ms if female (28% for the levomethadyl group vs. 23% for the methadone group vs. 0% for the buprenorphine group; $p < 0.001$). Similarly, in a large cross-sectional study, 28% male and 32% female heroin addicts on MM treatment had prolonged QTc interval, whilst none of the subjects treated with buprenorphine had QTc interval >440 ms [40]. Of note is the report of the safe and successful induction onto buprenorphine of a patient who developed TdP while receiving high-dose methadone [45].

Up to 60% of patients entering AOT and up to 60% of patients in MM have been found to be abusing cocaine as well [46–48]. Although increasing the dose of methadone could be a useful strategy to significantly reduce cocaine use in heroin- and cocaine-dependent patients as reported in a prospective study with 421 methadone-maintained patients [55], methadone and MM do not seem intrinsically efficacious for the treatment of cocaine addiction in dual-opiate-dependent patients. Moreover, there are important and complex pharmacokinetic interactions between cocaine and methadone; cocaine abuse has been described as decreasing methadone blood concentrations, possibly by inducing CYP3A4 and by accelerating methadone elimination [49–51]. Consequently, the greater efficacy of methadone for concurrent opiate and cocaine dependence reported in some clinical trials could be explained by the increase in daily methadone dosage administered but may also favor the likelihood of cardiovascular adverse events in cocaine abusers taking high doses of methadone.

As evidenced in preclinical studies, buprenorphine could have the potential to reduce cocaine use in comorbid opiate and cocaine dependence. Several studies have described a dose-dependent reduction of cocaine self-administration by rhesus monkeys, with no effects on food self-administration, after short-term treatment with buprenorphine [52–55] and for periods of up to 120 days of daily buprenorphine treatment [56]. Similarly, a human laboratory study with 12 methadone-maintained individuals who had concurrent cocaine abuse showed that, compared with methadone, buprenorphine maintenance decreased cocaine self-administration [57]. Results from other clinical studies are less consistent. Initial reports showed daily buprenorphine dosing for one month decreased cocaine-positive urine screens significantly more than methadone treatment, in a sample of individuals with concurrent opiate and cocaine addiction [58, 59]. Some subsequent studies failed to show a significant reduction of cocaine abuse when receiving buprenorphine [60–63]. Characteristically, methadone administration failed to show a significant effect on cocaine use in dual-opiate-dependent patients; daily buprenorphine doses ranged from 4 mg to an average of 11.2 mg, while doses of methadone ranged between 20 mg to an average of 66.6 mg [59, 60, 62]. Similarly, a recent double-blind, 6-month follow-up, randomized, controlled trial with patients maintained either with 65 mg/day of methadone or 12 mg/day of buprenorphine plus contingency management or performance feedback found that subjects who received methadone remained in treatment significantly longer and achieved significantly longer periods of sustained abstinence than individuals receiving buprenorphine [61]. In contrast, other studies [64, 65] including a recent, large, randomized, placebo-controlled, double-blind, clinical trial [66] with patients with dual dependence on heroin and cocaine showed a reduction in cocaine use associated with buprenorphine treatment. The doses of buprenorphine in these latter studies were up to 16 mg/day; the largest reductions of cocaine use were at the higher doses of buprenorphine. This may help explain, at least in part, the inconsistencies in the results between trials.

The theoretical increase in costs of AOT to be expected in Spain when B/N becomes commercially available would not only seem reasonable, but also justified because of the limited treatment options currently available for opiate-dependent individuals. This is particularly apparent in Spain where methadone and naltrexone, in oral formulations, are the only compounds approved for preventing relapse in individuals with opiate dependence.

Having more efficacious medications available would enable clinicians to meet the needs of patients with broad-spectrum characteristics. Even if methadone and buprenorphine are equally effective in specific patient populations with dual addiction to heroin and cocaine, it appears reasonable that B/N combination is at least a safe

er treatment choice. Empirical data from further studies, particularly from controlled trials, are required in order to validate our BIA model and to identify factors affecting the economic impact of B/N in different treatment settings, and involving different opiate-dependent patient subgroups.

References

- 1 Hser YI, Huang D, Chou CP, Anglin MD: Trajectories of heroin addiction: growth mixture modeling results based on a 33-year follow-up study. *Eval Rev* 2007;31:548–563.
- 2 United Nations Office for Drug Control and Crime Prevention (UNODCCP), 2002. *Global Illicit Drug Trends*. New York, United Nations Publications, 2002.
- 3 European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). *Annual Report 2007. The state of the drugs problem in Europe*. Luxembourg, Office for Official Publications of the European Communities, 2007.
- 4 Gowing LR, Farrell M, Ali RL, White JM: Alpha-2-adrenergic agonists in opioid withdrawal. *Addiction* 2002;97:49–58.
- 5 Kosten TR, O'Connor PG: Management of drug and alcohol withdrawal. *N Engl J Med* 2003;348:1786–1795.
- 6 Amato L, Davoli M, Perucci CA, Ferri M, Faggiano F, Mattick RP: An overview of systematic reviews of the effectiveness of opiate maintenance therapies: available evidence to inform clinical practice and research. *J Subst Abuse Treat* 2005;28:321–329.
- 7 Vocci FJ, Acri J, Elkashef A: Medication development for addictive disorders: the state of the science. *Am J Psychiatry* 2005;162:1432–1440.
- 8 De la Fuente L, Brugal MT, Domingo-Salvany A, Bravo MJ, Neira-León M, Barrio G: More than thirty years of illicit drugs in Spain: a bitter story with some messages for the future. *Rev Esp Salud Publica* 2006;80:505–520.
- 9 Rosenheck R, Kosten T: Buprenorphine for opiate addiction: potential economic impact. *Drug Alcohol Depend* 2001;63:253–262.
- 10 Tober G, Strang J: *Methadone Matters: Evolving Practice of Community Methadone Treatment of Opiate Addiction*. New York, Taylor & Francis, 2003.
- 11 Fiellin DA, Pantalon MV, Chawarski MC, Moore BA, Sullivan LE, O'Connor PG, Schottenfeld RS: Counseling plus buprenorphine-naloxone maintenance therapy for opioid dependence. *N Engl J Med* 2006;355:365–374.
- 12 Fudala PJ, Bridge TP, Herbert S, Willford WO, Chiang CN, Jones K, Collins J, Raisch D, Casadonte P, Goldsmith RJ, Ling W, Malkerneker U, McNicholas L, Renner J, Stine S, Tusel D, for the Buprenorphine/Naloxone Collaborative Study Group: Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine-naloxone. *N Engl J Med* 2003;349:949–958.
- 13 Johnson RE, Eissenberg T, Stitzer ML, Strain EC, Liebson IA, Bigelow GE: A placebo-controlled trial of buprenorphine as a treatment for opioid dependence. *Drug Alcohol Depend* 1995;40:17–25.
- 14 Kakko J, Svanborg KD, Kreek MJ, Heilig M: One-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden; a randomised, placebo-controlled trial. *Lancet* 2003;361:662–668.
- 15 Mattick RP, Breen C, Kimber J, Davoli M: Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database Syst Rev* 2003;2:CD002209.
- 16 Mattick RP, Kimber J, Breen C, Davoli M: Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev* 2004;3:CD002207.
- 17 Amass L, Kamien JB, Mikulich SK: Efficacy of daily and alternate-day dosing regimens with the combination buprenorphine-naloxone tablet. *Drug Alcohol Depend* 2000;58:143–152.
- 18 Schottenfeld RS, Pakes J, O'Connor P, Chawarski M, Oliveto A, Kosten TR: Thrice-weekly versus daily buprenorphine maintenance. *Biol Psychiatry* 2000;47:1072–1079.
- 19 Davids E, Gastpar M: Buprenorphine in the treatment of opioid dependence. *Eur Neuropsychopharmacol* 2004;14:209–216.
- 20 European Medicines Agency (EMA) European Public Assessment Report 2006. Suboxone H-C-697. <http://www.emea.europa.eu/humandocs/Humans/EPAR/suboxone/suboxone.htm> (accessed 3 April 2008).
- 21 Mintzer IL, Eisenberg M, Terra M, MacVane C, Himmelstein DU, Woolhandler S: Treating opioid addiction with buprenorphine-naloxone in community-based primary care settings. *Ann Fam Med* 2007;5:146–150.
- 22 Preston KL, Bigelow GE, Liebson IA: Effects of sublingually given naloxone in opioid-dependent human volunteers. *Drug Alcohol Depend* 1990;25:27–34.
- 23 Stoller KB, Bigelow GE, Walsh SL, Strain EC: Effects of buprenorphine/naloxone in opioid-dependent humans. *Psychopharmacology* 2001;154:230–242.
- 24 Brosa M, Gisbert R, Rodríguez JM, Soto J: Principles, methods and applications of budgetary impact analysis in the health sector. *Pharmacoeconomics – Spanish Research Articles* 2005;2:65–79.
- 25 Mauskopf JA, Sullivan SD, Annemans L, Caro J, Mullins D, Nuijten M, Orlewska E, Trueman P, Watkins J: Principles of Good Practice for Budget Impact Analysis: Report of the ISPOR Task Force on Good Research Practices – Budget Impact Analysis. *Value Health* 2006;10 (available in http://www.ispor.org/workpaper/budget_impact.asp).
- 26 Orlewska E, Mierzejewski P: Proposal of Polish guidelines for conducting financial analysis and their comparison to existing guidance on budget impact in other countries. *Value Health* 2004;7:1–10.
- 27 Trueman P, Drummond M, Hutton J: Developing guidance for budget impact analysis. *Pharmacoeconomics* 2001;19:855–867.
- 28 Sullivan MA, Garawi F, Bisaga A, Comer SD, Carpenter K, Raby WN, Anen SJ, Brooks AC, Jiang H, Akerele E, Nunes EV: Management of relapse in naltrexone maintenance for heroin dependence. *Drug Alcohol Depend* 2007;91:289–292.
- 29 Kirchmayer U, Davoli M, Verster AD, Amato L, Ferri A, Perucci CA: A systematic review on the efficacy of naltrexone maintenance treatment in opioid dependence. *Addiction* 2002;97:1241–1249.
- 30 Soto J, Sacristán JA, Galende I: Naturalistic studies to evaluate the effectiveness of medications following their commercialization: Why? When? How? *Aten Primaria* 1998;22:182–185.
- 31 De Wet CJ, Reed LJ, Bearn J: The rise of buprenorphine prescribing in England: analysis of NHS regional data, 2001–03. *Addiction* 2005;100:495–499.

- 32 Sullivan LE, Chawarski M, O'Connor PG, Schottenfeld RS, Fiellin DA: The practice of office-based buprenorphine treatment of opioid dependence: is it associated with new patients entering into treatment? *Drug Alcohol Depend* 2005;79:113–116.
- 33 Auriacombe M, Tignol J, Picard G: Buprenorphine use in France: quality of life and conditions for treatment success. *Res Clin Forums* 1997;19:25–32.
- 34 Alvarez FJ, Gonzalez-Saiz F: Buprenorphine prescription and the increased relative cost. *Addiction* 2005;100:1373–1374.
- 35 Lamont P, Hunt SC: A twist on torsade: a prolonged QT interval on methadone. *J Gen Intern Med* 2006;21:C9–C12.
- 36 Routhier DD, Katz KD, Brooks DE: QTc prolongation and torsades de pointes associated with methadone therapy. *J Emerg Med* 2007;32:275–278.
- 37 Krantz MJ, Lewkowicz L, Hays H, Woodroffe MA, Robertson AD, Mehler PS: Torsade de pointes associated with very-high-dose methadone. *Ann Intern Med* 2002;137:501–504.
- 38 Krantz MJ, Kutinsky IB, Robertson AD, Mehler PS: Dose-related effects of methadone on QT prolongation in a series of patients with torsade de pointes. *Pharmacotherapy* 2003;23:802–805.
- 39 Sanchez Hernandez AM, Atienza Fernandez F, Arenal Maiz A, Gonzalez Torrecilla E, Puchol Calderon A, Almendral Garrote J: Torsades de pointes during methadone treatment. *Rev Esp Cardiol* 2005;58:1230–1232.
- 40 Ehret GB, Voide C, Gex-Fabry M, Chabert J, Shah D, Broers B, Piguet V, Musset T, Gaspoz JM, Perrier A, Dayer P, Desmeules JA: Drug-induced long QT syndrome in injection drug users receiving methadone: high frequency in hospitalized patients and risk factors. *Arch Intern Med* 2006;166:1280–1287.
- 41 Fanoe S, Hvidt C, Ege P, Jensen GB: Syncope and QT prolongation among patients treated with methadone for heroin dependence in the city of Copenhagen. *Heart* 2007;93:1051–1055.
- 42 Maremmanni I, Pacini M, Cesaroni C, Lovrecic M, Perugi G, Tagliamonte A: QTc interval prolongation in patients on long-term methadone maintenance therapy. *Eur Addict Res* 2005;11:44–49.
- 43 Peles E, Bodner G, Kreek MJ, Rados V, Adelson M: Corrected QT intervals as related to methadone dose and serum level in methadone maintenance treatment patients: a cross-sectional study. *Addiction* 2007;102:289–300.
- 44 Wedam EF, Bigelow GE, Johnson RE, Nuzzo PA, Haigney MC: QT-interval effects of methadone, levomethadyl, and buprenorphine in a randomized trial. *Arch Intern Med* 2007;167:2469–2475.
- 45 Krantz MJ, Garcia JA, Mehler PS: Effects of buprenorphine on cardiac repolarization in a patient with methadone-related torsade de pointes. *Pharmacotherapy* 2005;25:611–614.
- 46 Haasen C, Prinzleve M, Zurhold H, Rehm J, Güttinger F, Fischer G, Jagsch R, Olsson B, Ekendahl M, Verster A, Camposeragna A, Pezous AM, Gossop M, Manning V, Cox G, Ryder N, Gerevich J, Bácskai E, Casas M, Matalli JL, Krausz M: Cocaine use in Europe – a multi-centre study methodology and prevalence estimates. *Eur Addict Res* 2004;10:139–146.
- 47 Peles E, Kreek MJ, Kellogg S, Adelson M: High methadone dose significantly reduces cocaine use in methadone maintenance treatment patients. *J Addict Dis* 2006;25:43–50.
- 48 Schwartz RP, Highfield DA, Jaffe JH, Brady JV, Butler CB, Rouse CO, Callaman JM, O'Grady KE, Battjes RJ: A randomized controlled trial of interim methadone maintenance. *Arch Gen Psychiatry* 2006;63:102–109.
- 49 Moolchan ET, Umbricht A, Epstein D: Therapeutic drug monitoring in methadone maintenance: choosing a matrix. *J Addict Dis* 2001;20:55–73.
- 50 Quinn DI, Wodak A, Day RO: Pharmacokinetic and pharmacodynamic principles of illicit drug use and treatment of illicit drug users. *Clin Pharmacokinet* 1997;33:344–400.
- 51 Tennant F, Shannon J: Cocaine abuse in methadone maintenance patients is associated with low serum methadone concentrations. *J Addict Dis* 1995;14:67–74.
- 52 Mello NK, Mendelson JH, Bree MP, Lukas SE: Buprenorphine suppresses cocaine self-administration by rhesus monkeys. *Science* 1989;245:859–862.
- 53 Mello NK, Negus SS: The effects of buprenorphine on self-administration of cocaine and heroin 'speedball' combinations and heroin alone by rhesus monkeys. *J Pharmacol Exp Ther* 1998;285:444–456.
- 54 Mello NK, Mendelson JH: Buprenorphine treatment of cocaine and heroin abuse; in Cowan A, Lewis JW (eds): *Buprenorphine: Combating Drug Abuse with a Unique Opioid*. New York, Wiley, 1995, pp 241–287.
- 55 Rodefer JS, Mattox AJ, Thompson SS, Carroll ME: Effects of buprenorphine and an alternative nondrug reinforcer, alone and in combination on smoked cocaine self-administration in monkeys. *Drug Alcohol Depend* 1997;45:21–29.
- 56 Mello NK, Lukas SE, Kamien JB, Mendelson JH, Drieze J, Cone EJ: The effects of chronic buprenorphine treatment on cocaine and food self-administration by rhesus monkeys. *J Pharmacol Exp Ther* 1992;260:1185–1193.
- 57 Foltin RW, Fischman MW: Effects of methadone or buprenorphine maintenance on the subjective and reinforcing effects of intravenous cocaine in humans. *J Pharmacol Exp Ther* 1996;278:1153–1164.
- 58 Kosten TR, Kleber HD, Morgan C: Role of opioid antagonists in treating intravenous cocaine abuse. *Life Sci* 1989;44:887–892.
- 59 Kosten TR, Kleber HD, Morgan C: Treatment of cocaine abuse with buprenorphine. *Biol Psychiatry* 1989;26:637–639.
- 60 Oliveto AH, Kosten TR, Schottenfeld RS, Ziedonis D, Falcioni J: Cocaine use in buprenorphine- vs. methadone-maintained patients. *Am J Addict* 1994;4:43–48.
- 61 Schottenfeld RS, Pakes JR, Oliveto A, Ziedonis D, Kosten TR: Buprenorphine vs. methadone maintenance treatment for concurrent opioid dependence and cocaine abuse. *Arch Gen Psychiatry* 1997;54:713–720.
- 62 Schottenfeld RS, Chawarski MC, Pakes JR, Pantalon MV, Carroll KM, Kosten TR: Methadone versus buprenorphine with contingency management or performance feedback for cocaine and opioid dependence. *Am J Psychiatry* 2005;162:340–349.
- 63 Strain EC, Stitzer ML, Liebson IA, Bigelow GE: Buprenorphine versus methadone in the treatment of opioid-dependent cocaine users. *Psychopharmacology* 1994;116:401–406.
- 64 Gastfriend DR, Wapler M, Teoh SK, Reif JH, Mendelson JH, Mello NK: Effects of buprenorphine on needle sharing, drug use and drug craving in men with combined heroin and cocaine dependence; in Harris LS (ed): *Problems of Drug Dependence*. 1992 NIDA Res Monogr 132. Washington, US Government Printing Office, 1993, p 312.
- 65 Schottenfeld RS, Pakes J, Ziedonis D, Kosten TR: Buprenorphine: dose-related effects on cocaine and opioid use in cocaine-abusing opioid-dependent humans. *Biol Psychiatry* 1993;34:66–74.
- 66 Montoya ID, Gorelick DA, Preston KL, Schroeder JR, Umbricht A, Cheskin LJ, Lange WR, Contoreggi C, Johnson RE, Fudala PJ: Randomized trial of buprenorphine for treatment of concurrent opiate and cocaine dependence. *Clin Pharmacol Ther* 2004;75:34–48.