

Management of opioid-dependent patients: comparison of the cost associated with use of buprenorphine/naloxone or methadone, and their interactions with concomitant treatments for infectious or psychiatric comorbidities

Manejo de pacientes dependientes de opiáceos: Comparación del coste asociado al uso de buprenorfina/naloxona o metadona, y sus interacciones con tratamientos concomitantes para comorbilidades infecciosas o psiquiátricas

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Abstract

The objective was to estimate the annual interaction management cost of agonist opioid treatment (AOT) for opioid-dependent (OD) patients with buprenorphine-naloxone (Suboxone®) (B/N) or methadone associated with concomitant treatments for infectious (HIV) or psychiatric comorbidities. A costs analysis model was developed to calculate the associated cost of AOT and interaction management. The AOT cost included pharmaceutical costs, drug preparation, distribution and dispensing, based on intake regimen (healthcare center or take-home) and type and frequency of dispensing (healthcare center or pharmacy), and medical visits. The cost of methadone also included single-dose bottles, monthly costs of custody at pharmacy, urine toxicology drug screenings and nursing visits. Potential interactions between AOT and concomitant treatments (antivirals, antibacterials/antifungals, antipsychotics, anxiolytics, antidepressants and anticonvulsants), were identified to determine the additional use of healthcare resources for each interaction management. The annual cost per patient of AOT was €1,525.97 for B/N and €1,467.29 for methadone. The average annual cost per patient of interaction management was €257.07 (infectious comorbidities), €114.03 (psychiatric comorbidities) and €185.55 (double comorbidity) with methadone and €7.90 with B/N in psychiatric comorbidities. Total annual costs of B/N were €1,525.97, €1,533.87 and €1,533.87 compared to €1,724.35, €1,581.32 and €1,652.84 for methadone per patient with infectious, psychiatric or double comorbidity respectively. Compared to methadone, the total cost per patient with OD was lower with B/N (€47.45-€198.38 per year). This is due to the differences in interaction management costs associated with the concomitant treatment of infectious and/or psychiatric comorbidities.

Key Words: costs analysis, buprenorphine-naloxone, methadone, comorbidities, opioid dependence.

Resumen

El objetivo fue estimar en pacientes con dependencia a opiáceos (DO), el coste anual del manejo de interacciones del tratamiento sustitutivo con buprenorfina/naloxona (Suboxone®) (B/N) o metadona, asociado con tratamientos concomitantes por comorbilidades infecciosas (VIH) o psiquiátricas. Se realizó un análisis de costes (€, 2013), del tratamiento sustitutivo y del manejo de interacciones. El coste del tratamiento de B/N incluyó costes farmacológicos, elaboración, distribución y dispensación, en función del régimen de administración (centro asistencial o domiciliaria) y del tipo y frecuencia de dispensación (centro asistencial o farmacia), y visitas al especialista para prescripción. El coste de tratamiento con metadona incluyó, además, frascos monodosis, coste de custodia en farmacia, determinación en orina y visitas a enfermería. Se identificaron las interacciones para determinar los recursos sanitarios adicionales consumidos por la administración conjunta del tratamiento sustitutivo y concomitante (antirretrovirales, bactericidas/antifúngicos, antipsicóticos, ansiolíticos, antidepresivos y anticonvulsivos). El coste anual/paciente estimado del tratamiento sustitutivo fue de 1.525,97€ (B/N) y 1.467,29€ (metadona). El coste promedio anual/paciente estimado del manejo de interacciones fue de 257,07€ (infecciosas), 114,03€ (psiquiátricas) y 185,55€ (ambas) con metadona, y de 7,90€ con B/N por comorbilidades psiquiátricas. El coste total anual/paciente estimado de B/N fue 1.525,97€, 1.533,87€ y 1.533,87€ comparado con 1.724,35€, 1.581,32€ y 1.652,84€ de metadona, en pacientes que presentan comorbilidad infecciosa, psiquiátrica o ambas, respectivamente. Comparado con metadona, el coste total por paciente con DO de B/N fue menor (47,45€-198,38€ anuales) derivado de la diferencia del coste por manejo de interacciones del tratamiento concomitante de las comorbilidades infecciosas y/o psiquiátricas.

Palabras clave: análisis de costes, dependencia de opiáceos, buprenorfina/naloxona, metadona, comorbilidades.

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Addiction to opioids such as heroin can pose significant medical, social and economic problems for both the individual and society (Canadian Agency for Drugs and Technologies in Health, 2013). Different therapies are currently in use to combat opioid dependence, with methadone and buprenorphine-naloxone (Suboxone®) (B/N) being the most widespread therapeutic alternatives in agonist opioid treatments in Spain. In 2011, 76,263 people aged 15 to 64 were treated in opioid replacement programs, of which 97.29% were attended to in programs administering methadone while 2.71% used B/N (Ministerio de Sanidad, Servicios Sociales e Igualdad, 2011).

Methadone is the most widely used opioid agonist in the treatment of heroin addiction, and is dispensed in health care centers. In pill form and taken sublingually, B/N has proven to be an effective treatment for heroin addicts and can be used by outpatients, thus making life easier for them (Sittambalam, Vij, & Ferguson, 2014).

Patients usually remain in maintenance treatment for long periods (Roncero et al., 2011), the average duration being 26 months (Observatorio Vasco de Drogodependencias, 2004). This period is typically divided into three phases: induction, maintenance and dose reduction. The induction phase lasts three days, during which time the opioid previously consumed by the patient is substituted and the dosage is adjusted based on the clinical response of the patient. In the maintenance phase, which lasts for months and even years, a dosage is established to prevent withdrawal symptoms. The dose reduction phase is implemented when the patient reaches and maintains clinical stability over time, and is typically initiated after a year of treatment (Terán, 2010).

Patients with opioid dependence (OD) present high clinical comorbidity, most commonly with infectious diseases and psychiatric disorders. The most frequent infectious comorbidities are those related to the human immunodeficiency virus (HIV), the hepatitis C virus (HCV) and co-infections of both HCV/HIV with a prevalence between 21%-53%, 47%-73% and 14% respectively (González-Saiz et al., 2011; Roncero et al., 2011; Sanvisens et al., 2014). Based on the classification of psychiatric disorders in accordance with DSM-IV-TR axes I and II (American Psychiatric Association, 2000), the prevalence of psychiatric comorbidity is between 25%-78% (Pereiro, Pino, Flórez, Arrojo, & Becoña, 2013; Roncero et al., 2011; Sanvisens et al., 2014). The majority of these patients receive concomitant treatment for their different illnesses, with 30.6% being treated for infectious disease and 21.6% for psychiatric disorders (Roncero et al., 2011). Patients frequently receive such treatment since the presence of some mental disorders is associated with a greater likelihood of engaging in behaviour with risks

of contracting infectious diseases (Cervera, Valderrama, Bolinches, Salazar, & Martínez, 1998).

The administration of opioid replacement treatment together with other pharmaceutical drugs can lead to side effects (Haro, 2012) as well as pharmacological interactions (pharmacogenetic or pharmacodynamic) which can bring about modifications in plasma concentrations or affect the efficacy and safety of the drugs involved (Sociodrogoalcohol, 2010). To prevent possible withdrawal symptoms or overdose caused by such interaction, it is necessary to adjust dosage and patient monitoring (Puche, Faus, Soler, & Blasco, 2000). This can provoke an increase in the use of health resources with a resulting rise in the costs of treating the illness. Not many economic assessments have been published regarding rehabilitation programs. While the majority focus on the costs of drugs and care incurred by methadone maintenance programs (Cobacho, López, & Ramos, 2011; Del Pozo, Soldevilla, Murga, & Antoñanzas, 2012; Puigdollersa, Cotsa, Brugal, Torralba, & Domingo-Salvany, 2003) only a very few investigate B/N programs (Martínez-Raga, González-Saiz, Pascual, Casado, & Sabater, 2010; Martínez-Raga et al., 2012). Today it is essential that all costs associated with or complementary to the different treatments received by the patients are taken into account with the aim of seeking out those which are most effective and efficient (Bernal-Delgado, Campillo-Artero, & García-Armesto, 2014; López-Bastida et al., 2010). Nevertheless, it is difficult to calculate such costs given the variations between the different care centers which can attend to these patients, the manner in which the opioid pharmaceutical is prescribed and dispensed, the monitoring of patients depending on the type of center in the different communities and because of the variability associated with how comorbidity is managed. Despite the widespread presence of medical comorbidity and dual pathology in opioid dependents on opioid maintenance programs (González-Saiz et al., 2011; Roncero et al., 2011; Sanvisens et al., 2014; Szman et al., 2014), and studies assessing the interactions occurring due to concomitant medication, there is no information available about the additional costs produced by managing the pharmacological interactions in everyday clinical practice with this type of patient.

The present analysis attempts to estimate and compare the annual costs of replacement therapy with B/N or methadone in OD patients, together with the costs of dealing with the potential interactions caused by the co-administration of the opiate drug with the medication for infectious and psychiatric comorbidity, and study if there are significant differences between both treatments.

Method

Study design

A cost analysis was designed based on a decision-making tree representing clinical practice (Figure 1) to calculate the annual cost of replacement treatment in OD patients and the cost of managing interactions caused by the co-administration of drugs in patients with at least one infectious and/or psychiatric comorbidity.

The analysis was carried out with Microsoft Excel® 2010 and included all costs of the replacement treatment with the alternatives in question (B/N and methadone) as well as the costs associated with the presence of infectious and psychiatric comorbidity.

The identification of health resources was carried out through a questionnaire sent to a panel of experts (PE) consisting of a group of seven clinicians expert in the care of OD patients from different parts of Spain. The questionnaire included data obtained from the literature on therapeutic management and physical and psychiatric comorbidity, and questions about information not found in the bibliography but necessary for this study. The results of the questionnaires were unified and filtered so that the PE was able to reach a consensus on the clinical management of OD patients undergoing replacement treatment and associated comorbidities in clinical practice in different health centers throughout Spain.

The analysis was carried out from a Spanish National Health System (SNHS) perspective, following national and international recommendations for this type of study (López-Bastida et al., 2010; Prieto et al., 2004). The time horizon was one year and for this reason no discount was applied.

The results were expressed as average cost per patient.

Resources and costs

The total estimated cost per patient for each of the alternatives included the cost of the replacement treatment on the one hand, which included the cost of the drug, preparation, distribution and dispensing, and the

cost of managing the interactions on the other, taking into account the consumption of additional healthcare resources (increase or decrease in the opioid drug, psychiatrist or medical visits, electrocardiograms, blood and urine toxicology screening, and single-dose bottles for dispensing methadone) associated with this issue in everyday clinical practice.

Replacement therapy. The dosage used to estimate the cost of drugs involved in replacement therapy included the daily average doses in the induction and maintenance phases, i.e. 10mg for 3 days and 8 mg for 362 days for B/N and 50.45 mg for 14 days and 61.52 mg for 351 days for methadone (Roncero et al., 2011). To calculate the cost of B/N, the retail price (RP+VAT) was used (Consejo General de Colegios Oficiales de Farmacéuticos, 2013). The cost of drugs finally included in the analysis was that incurred by the financing body (the Spanish National Health System). The estimated annual drugs cost of B/N incurred by the financing body (€1,461.43) took into account the employment situation of the OD patients (Roncero et al., 2011), as well as the distribution of income levels across three groups (<€18,000, €18,000-€100,000, >€100,000) (Instituto Nacional de Estadística, 2013), the co-payment percentage for each type of patient and the maximum monthly contribution (Real Decreto-ley 16/2012) (Table 1).

Methadone is a pharmaceutical drug which is centrally produced and then distributed under security to the different autonomous communities, which are responsible for distributing them to the dispensing centers and authorized pharmacies (Cobacho et al., 2011). In the present study, the costs associated with the preparation (€378.57), distribution (€258.31) and purchase of methadone (wholesale price per kg) were obtained from the literature (Martínez-Raga et al., 2012), and were updated to 2013 by applying the rate of change in the Consumer Price Index of the Spanish Statistical Office (Instituto Nacional de Estadística, 2011).

Regarding dispensing, two groups of patients were differentiated in terms of how the dose was administered

Table 1
Number of patients by employment situation and income.

GROUP	RETIRED			WORKING			UNEMPLOYED
	<18,000	18,000-100,000	>100,000	<18,000	18,000-100,000	>100,000	-----
Income							
Roncero et al., 2013		21.00%			24.50%		52.00%
Co-payment (%)	10%	10%	60%	40%	50%	60%	0
Maximum monthly contribution per patient	8.14€	12.18€	61.08€	N/A	N/A	N/A	N/A
Patients by income (%)	84.16%	15.57%	0.18%	58.19%	40.97%	0.84%	100.00%

Note. N/A: not applicable

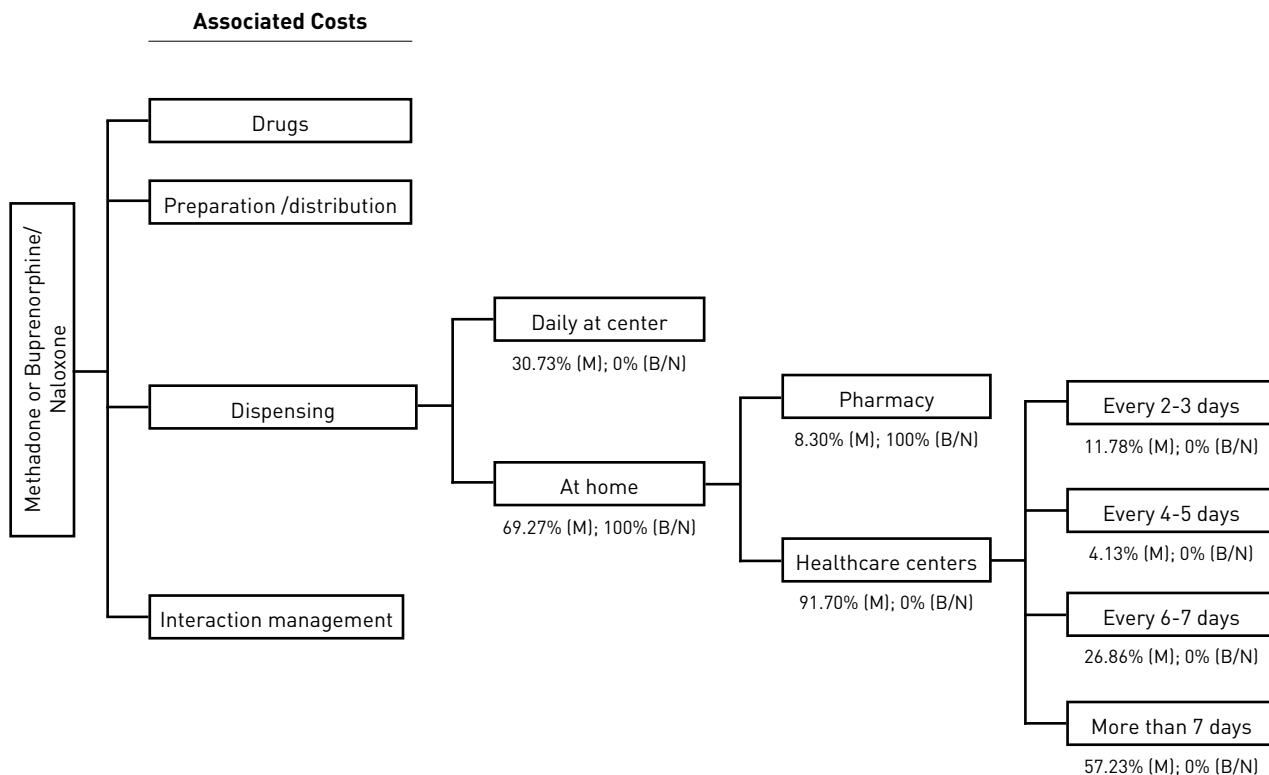


Figure 1. Study design. Patient distribution.

and dispensed. For methadone, the dose was administered daily at the healthcare center or at home. For those patients on a take-home regimen, the drug was dispensed at the healthcare center every 2-3 days, 4-5 days, 6-7 days or more than 7 days, or through the pharmacy. The distribution of patients assigned to each group was taken from an observational study carried out in Spain (Roncero et al., 2011) (Figure 1).

The resources calculated per patient were: 5 minutes of nurse time when dispensed at the health center or custody at pharmacy if dispensed there, and a single-dose bottle per day. In addition, a 50% increase in bottles was calculated for fast-metabolising patients (10%) for whom the bottle is divided into several doses (Instituto de Adicciones Madrid, 2008). Reuse of the single-dose bottle was not considered in the calculations. Quarterly urine toxicology screening was included. A medical appointment every 6 weeks for the prescription was included in both treatments.

Interaction management. When different drugs are taken together, the possible pharmacological interactions require closer control of the patient (Bruce, Moody, Altice, Gourevitch, & Friedland, 2013). For this reason, additional costs associated with the use of resources for managing the interactions caused by the co-administration of drugs were analyzed. The pharmacological treatment groups included were antivirals, antibacterials/

antifungals, antipsychotics, anxiolytics, antidepressants and anticonvulsants (McCance-Katz, Sullivan, & Nallani, 2010; McCance-Katz, 2012). Based on the information found in the literature (Amariles, Giraldo, & Faus, 2007; Bruce, Altice, Gourevitch, & Friedland, 2006; Gallego, Barreiro, & López-Ibor, 2012; McCance-Katz et al. 2010; McCance-Katz, 2012; Pérez, Jornet, & Bonet, 2002; Puche et al., 2000; Serrano, 2011) and provided by the panel of experts, the drugs from each group to be included in the study due to their potential interaction with B/N or methadone and their use in everyday clinical practice were identified. At the same time, in order to estimate the costs of an average patient, the panel of experts, estimated the disaggregated additional consumption of healthcare resources generated by the interaction, and the frequency and percentage of patients using each resource for each of the treatment options. In the case of B/N, the drugs examined for their interaction potential and for the variation from the norm generated in patient management were citalopram and escitalopram (Table 2). The interaction between drugs included as concomitant medication and their dosage variations were not examined. The costs of using drugs which are not normally administered due to the seriousness of the interaction were also not analyzed. The increase in dose of the opioid was included when occasioned by the clinical manifestation of withdrawal symptoms. A rise in the number of specialist

and medical visits was associated with greater monitoring and a variation in the treatment regimen. Blood toxicology screening was associated with methadone doses above 100 mg per day, with antiretroviral treatments, and medication liable to interfere with methadone metabolism (Instituto de Adicciones Madrid, 2008). Electrocardiograms were linked to drugs which can cause prolongation of the QT-interval, and the increase in the number of bottles was linked to those drugs which increased methadone metabolism and caused dose fractionation. To determine total infectious or psychiatric comorbidity costs, an average of the cost of drugs with interaction potential in each comorbidity was calculated.

In order to estimate the monthly frequency of each resource, an average month length of 30.4 days was applied. All costs included in the analysis were direct healthcare costs in 2013 and quoted in Euros (Table 3).

Table 3
Unit costs of drugs and healthcare resources (€, 2013).

	Unit cost
Drug	
Methadone	0.0006€/kg (Wholesale)
Buprenorphine/naloxona (Suboxone®)	0.50€/mg (Retail+VAT)
Healthcare resources	
Specialist visits	46.22€ ^a
Medical visits (cost per minute)	0.34€ ^a
Custody of methadone per patient	69€/mes ^b
Bottle for dispensing	0.45€ ^c
Urine toxicology screening	12.03€ ^a
Electrocardiogram	33.90€ ^a
Test of plasma levels	115.04€ ^a

Note. ^ae-Health Database. ^bAgreement between Comunidad de Madrid and the Professional Association of Pharmacists in Madrid (COFM), ^cPanel of experts.

Sensitivity analysis

To determine the stability of the results, univariate sensitivity analyses (SA) were carried out with the highest uncertainty values of the analysis. The variables included were minutes of nurse time, from 4 to 6 minutes, and the cost of single-dose bottles within a $\pm 20\%$ range.

Results

Replacement therapy with B/N generated an annual per-patient cost of €1,525.97, of which 75.77% corresponded to pharmaceutical costs and 24.23% to dispensing. The annual cost of methadone treatment was €1,467.29, with the pharmaceutical cost making up 0.86%, preparation and distribution 43.41% and dispensing 55.73% (Table 4).

Table 4
Total annual cost of therapy with B/N or methadone per patient with infectious or psychiatric comorbidity (€, 2013).

Cost type	B/N (Suboxone®)	Methadone
Replacement therapy		
Drugs	1,156.25€	12.58€
Preparation and distribution	0.00€	636.98€
Dispensing	369.72€	817.73€
Interaction management		
Infectious	0.00€	257.07€
Psychiatric	7.90€	114.03€
Both	7.90€	185.55€
TOTAL ANNUAL PER PATIENT		
Infectious Comorbidity	1,525.97€	1,724.35€
Psychiatric Comorbidity	1,533.87€	1,581.32€
Both Comorbidities	1,533.87€	1,652.84€

The annual per-patient costs of interaction management for infectious and psychiatric comorbidity for methadone were €257.07 and €114.03 respectively. B/N generated costs of €7.90, associated solely with the average costs incurred in the interaction management of psychiatric comorbidity. To avoid duplication of resources, the cost of a patient with both comorbidities was calculated by taking an average of the two: €185.55 (methadone) and €7.90 (B/N).

The annual total costs per OD patient in replacement treatment with infectious or psychiatric comorbidity or both were €1,525.97, €1,533.87 and €1,533.87 respectively for B/N and €1,724.35, €1,581.32 and €1,625.84 for methadone (Figure 2).

The SAs showed that variations in minutes of nurse time spent on dispensing the drug, or in the cost of the single-dose bottle of $\pm 20\%$, can generate savings of €6.90-€242.54.

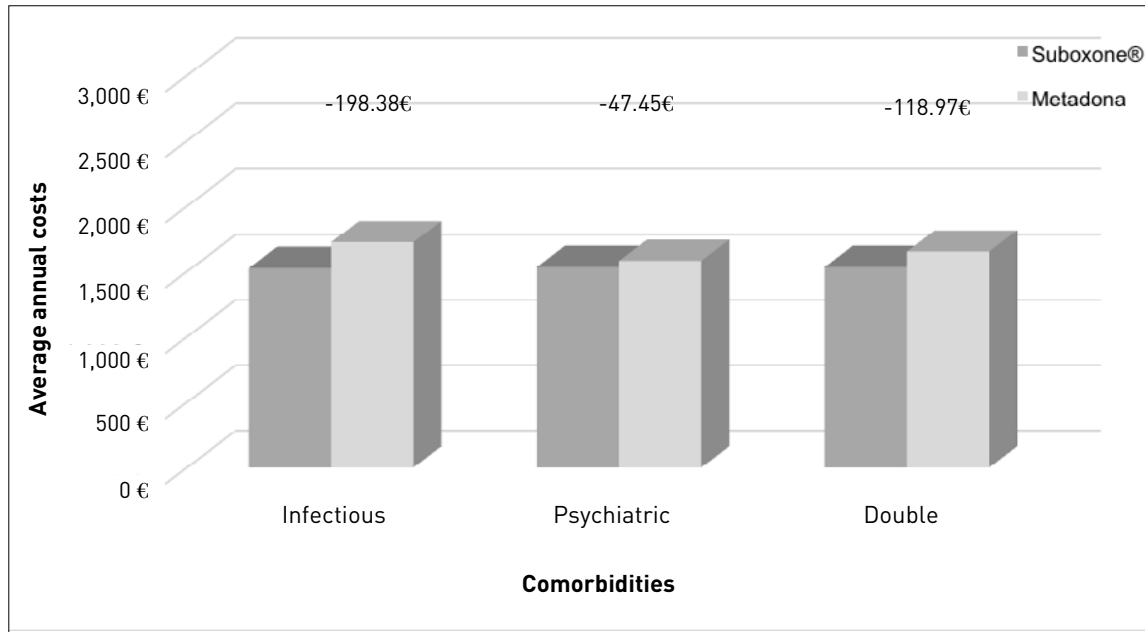


Figure 2. Results per patient.

Discussion

The study of medical or psychiatric comorbidity in OD patients is important for several reasons. Its frequent occurrence (González-Saiz et al., 2011; Pereiro et al., 2013; Roncero et al., 2011) means that different aspects of patients' lives, such as driving, can be affected (Roncero et al., 2013). Furthermore, pharmacological interactions caused by the co-administration of other drugs, especially antiretrovirals, with methadone and buprenorfina can have clinical consequences which necessitate closer patient monitoring (Bruce et al., 2013) and generate a change in total treatment cost, as demonstrated by this study.

Today it is necessary to implement strategic plans to optimize existing resources dedicated to patients with addictions (Ministerio de Sanidad, Servicios Sociales e Igualdad, 2013) and dual patients (Arias et al., 2013; Roncero et al., 2014; Szman et al., 2014), and to carry out more studies which evaluate the direct and indirect costs of the pathology to the healthcare system. For these reasons, apart from analyzing the direct costs of B/N and methadone treatment, it is important to account for the costs generated by the co-administration of drugs which can cause changes in the monitoring of patients leading to increases in the consumption of resources and thus a rise in costs.

This study calculates treatment and interaction costs for both therapies. Results are quoted in terms of total cost per OD patient in replacement treatment with infectious and psychiatric morbidity. This information can be useful in decision making if we are interested in making better use of healthcare resources dedicated to replacement therapy programs.

Studies published in Spain of the costs involved in opioid replacement therapies are few and far between. Almost all of them focus on the costs of RTPs with methadone and only a few compare these with B/N (Martínez-Raga et al., 2010; Martínez-Raga et al., 2012). The results of a recent study comparing the budgetary impact of introducing B/N as a treatment for OD as opposed to methadone showed that B/N carried an additional cost of €9 (in 2007) per patient. Costs included in the study were medication, logistics, dispensing, medical and social services staff and toxicology tests (Martínez-Raga et al., 2010). On updating the study in 2012, the use of B/N was found to have an additional per-patient cost of €10.58 in the first year, €6.58 in the second and €7.34 in the third (costs in 2010) (Martínez-Raga et al., 2012).

Although there are numerous studies of the interaction caused by the use of opioids alongside other medication, the authors believe that the present study is the first to analyze the costs of comorbidity in OD patients in clinical practice in Spain or other countries. For this reason, it was not possible to compare our results with those of other studies.

It is important to point out that psychiatric comorbidity management is rather variable and depends on both the characteristics of each patient as well as on the psychotherapeutic measures employed simultaneously, which means that the analysis of all the costs associated with the comorbidity can be complex. At the same time, this type of patient can be attended to in a variety of settings, such as healthcare centers, official opioid prescription centers, primary healthcare, and regional HIV programs (Roncero et al., 2011). Prescription and dis-

dispensing of the drug and monitoring of the patient takes on different forms depending on the center and the autonomous community (Torrens, Fonseca, Castillo, & Domingo-Salvany, 2013). This makes it difficult to determine the cost of resources per OD patient exactly, which in turn accounts for the diversity of results in previous studies. In the present study, the costs associated with both the therapy and interaction management represent the average use of resources of a standard OD patient. This may not be representative of clinical practice and could have an influence on the results.

Although the pharmaceutical cost of B/N in this analysis was higher than that of methadone, when taking into account the preparation, distribution and dispensing costs the difference is significantly reduced. Nevertheless, it must be pointed out that there are a number of costs associated with methadone maintenance programs (depreciation of equipment, glass crushers, security staff at the centers, mobile units) which were not considered in this study (Cobacho et al., 2011; Del Pozo et al., 2012; Pellín, Gimeno, Barril, Climent, & Vilanova, 2000; Puigdollersa et al., 2003). The inclusion of these variable costs could raise the cost of methadone treatment, which would alter the difference between the two strategies analyzed.

There are a number of limitations to be taken into account in this study. The most important is the lack of scientific evidence regarding the interaction of B/N with other medication. For this reason, the same interactions as for buprenorphine alone are considered here. The list of pharmaceuticals which interact with methadone or buprenorphine is longer, but in this study only those most frequently used in clinical practice are taken into account. It can be pointed out that buprenorphine is associated with fewer pharmacological interactions than methadone (McCance-Katz, 2012; Terán, 2010), thereby reducing management costs.

The analysis did not account for the possible interactions among the drugs included as concomitant medication, nor the costs associated with them, since these were not the goal of the study. Also excluded were the costs of drugs which are contraindicated as well as those for HCV, given that the most frequently used (interferon and ribavirin) do not interact at all with opioids (Panel de expertos de Gesida, 2010). The administration of methadone in beveled tablet form, as carried out in some autonomous communities, was also excluded because it is not standard clinical practice in Spain and there is a lack of available data.

A variation of $\pm 20\%$ was assumed in the SA parameters (minutes of nurse time and single-dose bottles) because no more data were available for analysis.

In costs analyses comparing more than one alternative therapy, it is important that as well as the pharmaceutical

costs, the patient management costs of clinical practice are also assessed.

One study comparing the total cost of OD patients treated with and without B/N concluded that although the medication costs of B/N were higher, when considering the costs associated with the care of these patients, the total costs of B/N therapy was lower than for those not treated (Kharitonova, Aballéa, Clay, Ruby, & Azh, 2014).

The present study has shown that the choice of B/N or methadone has economic implications when treating patients with infectious and psychiatric comorbidities. B/N is associated with fewer pharmaceutical interactions, which means that there is no increase in the consumption of resources caused by interaction management and therefore no increase in cost. Given the frequent presence of these comorbidities in OD patients (González-Saiz et al., 2011; Roncero et al., 2011; Sanvisens et al., 2014; Szerman et al., 2014), the choice of one or the other drug can generate substantial savings for the national health system.

Finally, the results of this analysis indicate that, compared to methadone, the total cost per OD patient was lower with B/N due to the difference in interaction management costs regarding concomitant treatments of infectious and/or psychiatric comorbidities.

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Conflict of interests

Carlos Roncero has received fees for taking part as a speaker in the educational activities of Janssen-Cilag, Bristol-Mayers Squibb, Ferrer-Brainfarma, Pfizer, Reckitt Benckiser Pharmaceuticals, Lundbeck, Otsuka, Servier, Lilly, Shire, GSK, Rovi. He has also received payment for participating in meetings with Janssen-Cilag, Lilly, and Shire. He has developed the PROTEUS project with the support of a grant from Reckitt Benckiser Pharmaceuticals.

Tomás Díaz has taken part as a speaker in the educational activities of Pfizer, Reckitt Benckiser Pharmaceuticals, and Janssen-Cilag.

José Manuel Forcada has not received fees from other entities.

Rafael Forcada has taken part as a speaker in the educational activities of Janssen-Cilag, and Bristol-Mayers Squibb.

José Manuel Martínez has taken part as a speaker in the educational activities of Reckitt Benckiser Pharmaceuticals, Janssen-Cilag, Bioclever 2005 SL, Pfizer, Brinpharma, and Laboratorios Estévez.

Pedro Seijo has taken part as a speaker in the educational activities of Reckitt Benckiser Pharmaceuticals, Janssen-Cilag, Pfizer, Otsuka and Astrazeneca.

Antonio Terán has received fees for speaking in educational activities of Janssen-Cilag, Pfizer, Lundbeck, Otsuka, Lilly, Shire, and Reckitt Benckiser Pharmaceuticals, and for participating in meetings of Janssen-Cilag, Lilly, and Shire.

None of the authors report other relevant affiliations or have economic interests in any organization or entity with an economic interest in or in conflict with the subject or materials discussed in the manuscript, other than those described.

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