

Cost-effectiveness analysis of fesoterodine flexible dose in newly diagnosed patients with overactive bladder in routine clinical practice in Spain

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Objective: To carry out cost-effectiveness analysis from the Spanish National Health System perspective, of treating overactive bladder (OAB), in newly diagnosed patients with two flexible doses of fesoterodine in routine clinical practice.

Patients and methods: Economic evaluation of flexible-dose fesoterodine in newly diagnosed patients, including two treatment groups: standard escalating from 4 to 8 mg or fast escalating to 8 mg. Costs were estimated from health care resources utilization related to OAB, and were expressed in 2015 Euros. Quality-adjusted life-years (QALYs) were obtained from overactive bladder questionnaire-short form. Univariate and probabilistic sensitivity analyses were carried out.

Results: Three hundred and ninety symptomatic OAB patients treated with fesoterodine and newly diagnosed (141 in fast escalating group and 249 in standard escalating) were analyzed. Adjusted health care total costs were not statistically different; difference −€4.1 (confidence interval: −153.3; 25.1) $P=0.842$. QALYs were higher in fast escalating to high dose vs standard escalating group, resulting in a cost of −€16,020/QALY gained for fast escalating vs standard escalating group.

Conclusion: When the cost-effectiveness threshold is set at a maximum value of €30,000/QALY gained, fesoterodine fast escalating group was cost-effective vs standard escalating group 67.6% of the time. The treatment with fesoterodine, in female patients newly diagnosed, fast escalating to 8 mg was a cost-effective option relative to escalating traditionally from 4 to 8 mg, in the management of OAB in routine clinical practice, from the Spanish National Health System perspective.

Keywords: antimuscarinic, fesoterodine, flexible dose, overactive bladder, cost-effectiveness

Introduction

Overactive bladder (OAB) is characterized by symptoms of urinary urgency with or without incontinence, often accompanied by daytime and nighttime frequency.¹ It is caused by an overactive detrusor muscle, in many cases with no apparent cause, although a significant proportion of cases may be accompanied by a neurogenic dysfunction.¹ The prevalence of OAB in the general adult population ranges from 14% to 16%,² usually associated with other health problems, such as sleep disorders, anxiety and/or depression, urinary tract and skin infections, etc, that not only lead to a considerable use of health care resources, but also affect the general well-being, activities of daily living, and health-related quality of life.³⁻⁷

Antimuscarinics are the primary drugs used for the treatment of OAB,³ but response and tolerability vary among patients. Flexible doses have become increasingly important in society, especially among elderly patients and children.⁸ The use of flexible doses

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allows treatment to be better adapted to the patient's needs, by determining the most favorable balance for patients.⁸ Approximately 60% of patients with OAB choose to have the dose of their antimuscarinic increased, resulting in a favorable response in terms of disease management without increasing adverse effects.⁸ Flexible doses are defined as the capacity of a treatment to shift within a certain range, in which the drug is shown to be safe, while still exerting the desired therapeutic effect.^{9,10} Many conditions and needs of the patient may affect the treatment and benefit from the use of flexible doses, such as tolerability, safety, severity, and other clinical and demographic characteristics that the patients may present. The possibilities offered by the use of flexible doses directly affect how doctors and patients adjust treatment to maximize therapeutic response while controlling the occurrence of adverse effects.¹¹

Fesoterodine is an antimuscarinic indicated for the symptomatic treatment of OAB and can be given in flexible doses.^{11–14} In a study based on the analysis of data from two flexible-dose clinical trials of fesoterodine, Cardozo et al¹⁵ observed that the highest dose of the drug was more effective in patients with more severe OAB symptoms, that is, those who had at least two episodes a day of urinary incontinence with urgency. However, dose escalation can lead to increased use of health care resources (medical visits, use of pads, or concomitant drugs) because of a delay in achieving greater effectiveness in symptom control.¹¹ Therefore, in routine clinical practice, some clinicians prescribe high doses of fesoterodine, from the time of first treatment in newly diagnosed patients (<12 months).¹⁶

Given the limited health care resources of the National Health Service (NHS), economic evaluations of cost-effectiveness provide evidence for deciding on the most appropriate use of resources. To date, economic evaluations with antimuscarinic drugs have not addressed the cost-effectiveness of flexible doses,^{17–19} despite this being a routine practice in the treatment of these patients in real life.¹⁶ Therefore, the purpose of this study is to conduct a cost-effectiveness analysis (CEA) from the perspective of Spain's NHS. This analysis considers patients newly diagnosed (<12 months of history) with symptomatic OAB, who are on treatment with flexible doses of fesoterodine, scaling from the traditional 4 to 8 mg, compared with fast escalation to 8 mg.

Patients and methods

Economic model

To carry out this economic evaluation, a decision tree model was designed that reflects the titration or escalation of the

fesoterodine dose from the start of the treatment (Figure 1). Each branch of the model represents a type of regimen followed by the clinician treating the OAB with fesoterodine, depending on the starting dose and the changes in symptoms and tolerability of the antimuscarinic. However, the economic analysis compares a starting regimen with a fast escalation to high dose versus a regimen with standard scaling both from low doses of fesoterodine 4 mg.

Following the product characteristics, the recommended starting dose of Fesoterodine is 4 mg once daily. Based upon individual response and tolerability, the dose may be increased to 8 mg once daily, with a maximum daily dose of 8 mg. The total treatment effect was between 2 and 8 weeks. Therefore, it is recommended by evaluating the efficacy in each individual patient after 8 weeks of treatment.

Taking this into account and based upon individual response, two groups were compared; the traditional escalating group and the fast escalation to 8 mg group.

Source data

To populate the economic model, use of health care resources and effectiveness – expressed in terms of quality-adjusted life-years (QALYs) gained – were analyzed from an observational, cross-sectional/retrospective, multicenter study involving specialists in urology and gynecology from 88 private and public centers, representative of Spain as a whole according to geographical density.¹⁶ The sampling of centers was done randomly, without replacement based on the census available in urology and gynecology clinics, whereas the patients included were selected through a systematic sampling procedure from those who met the following screening criteria: patients of both sexes, aged ≥18 years, diagnosed with OAB according to routine clinical practice, and who had started treatment with an antimuscarinic that might allow for dose titration (flexible doses; Figure 1). Patients undergoing any type of surgery on the lower urinary tract, who had given birth in the previous year, were unable to complete health questionnaires in Spanish, were excluded. All patients had to give their informed consent in writing. The study was approved by the ethics committee of the Hospital General Universitario de Valencia, and was conducted in compliance with the principles established in the Declaration of Helsinki for studies in humans.

All patients must have had two visits prior to the study visit, with information on the titration of the antimuscarinic drug with which they were being treated. The time between the study visit and the previous visits must have been at

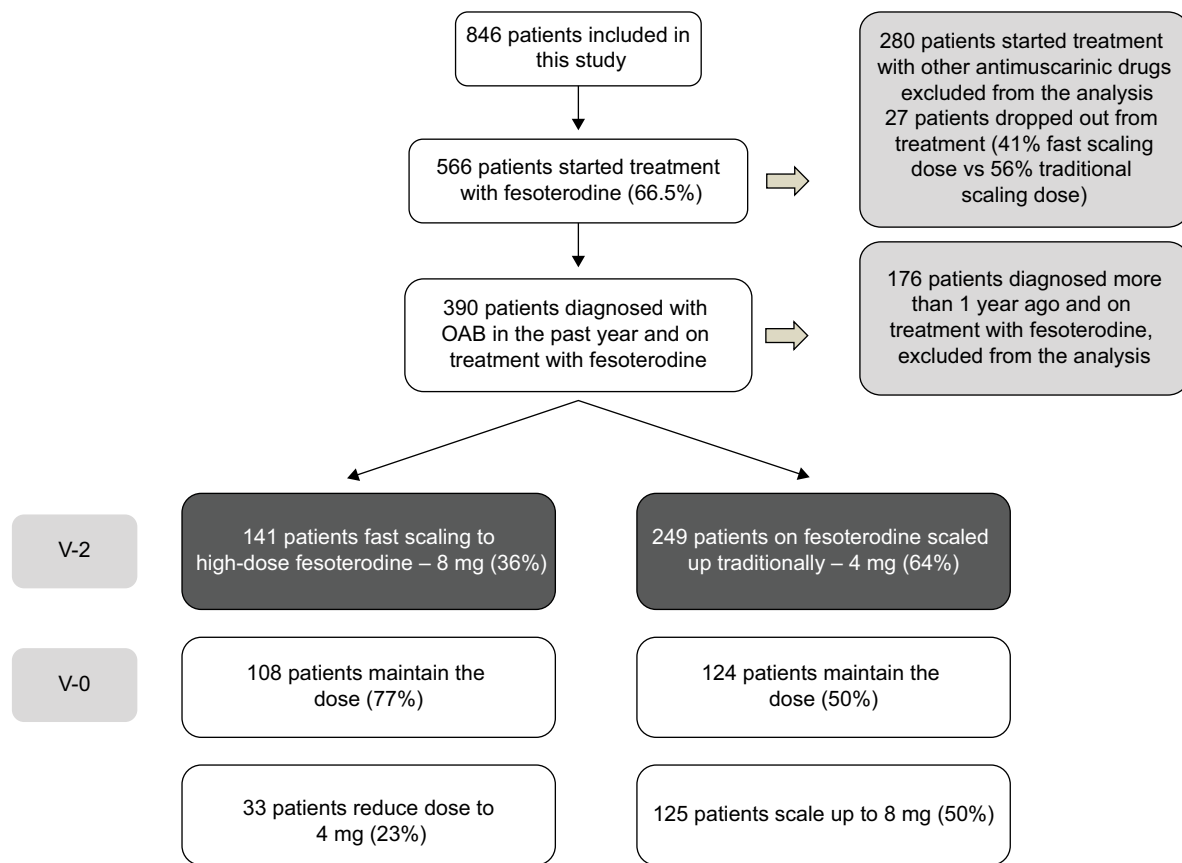


Figure 1 Flow chart showing the change of treatment during the study.

Notes: V-2: Baseline visit. V-0: Study visit. Prescribed regimens during the study are shown; from the baseline visit, showing the number of patients who entered the study with the inclusion criteria; and at the study visit, showing the flows of patients who maintained their original treatments, changed the dose, or changed treatment.

Abbreviation: OAB, overactive bladder.

least 8 weeks. During the visit at which the treatment was started, the following were collected: demographic data, comorbidities, clinical history of the OAB, and treatment prescribed for the OAB and doses. In the first follow-up visit after the start of treatment, the following, if available, were collected: data on change of doses, reason for change (side effects, lack of clinical benefit, lack of treatment compliance or other), and who requested the change. During the study visit, the following, if available, were collected again: data on change of doses and/or treatment, reason for change and who requested it, and concomitant medication. During the study visit, the use of health care resources due to OAB from the start of treatment was evaluated. In addition to the dose and days of treatment with the antimuscarinic drug, information on the number of absorbents used daily, visits to primary care doctors and specialists, and visits to hospital outpatient clinics and emergency rooms were also collected.

In order to evaluate treatment adherence, during the study visit, patients were given the Spanish (Spain) version of the Morisky–Green Medication Adherence Scale.²⁰

For this economic evaluation, patients with a recent diagnosis of OAB were selected; patients' OAB could not exceed 12 months of history and they had to be on treatment with a fast scaling to high-dose fesoterodine or have their doses scaled up in the standard way, so that dose flexibility could be analyzed. In addition, fesoterodine was chosen to be the single drug in order to avoid any confusion that might arise from including two drugs which, though similar, have different pharmacokinetic properties. Fesoterodine was chosen because its numerical representation was more in the study sample.

Costs and use of resources

The costs included in this study, from the perspective of the Spanish NHS, were related to the antimuscarinic drug based on dose and days of treatment, public selling price + VAT and after deducting 7.5% of the price according to the corresponding royal decree (8/2010), use of health care resources (visits to primary care doctors and to specialists, hospital outpatient visits and emergency room visits), and use of absorbents and concomitant medication for comorbidities directly associated with OAB (Table 1). The costs were expressed in 2015 Euros.^{21,22}

Table 1 Unit costs in 2015 Euros

	Unit costs in €	References
Costs for antimuscarinic drugs*		18
Fesoterodine 4 mg	€1.57	
Fesoterodine 4+4 mg	€3.15	
Fesoterodine 8 mg	€2.52	
Health care resources**	First visit	Subsequent visits 21
Visits to primary care	€66.32	€36.73
Visits to specialists	€156.34	€86.83
Visits to emergency rooms	€194.66	–
Hospital visits	€156.34	€86.83
Absorbents funded	€0.59	22
Concomitant medication (daily drug cost)***		
Depression	€1.11	
Skin infections	€0.93	
Urinary tract infections	€1.87	
Insomnia (hypnotics or sedatives)	€0.06	

Notes: *Public selling price, VAT (–7.5% as per RD 8/2010). **Updated mean cost of rates published by the following autonomous communities: Andalusia, Asturias, Canary Islands, Cantabria, Castile and León, Extremadura, Galicia, Community of Madrid, Basque Country, La Rioja, Ceuta, and Melilla. ***Mean cost: IMS data.

Abbreviations: IMS, Intercontinental Marketing Services; RD, Royal Decree; VAT, valued added tax

CEA

The economic evaluation consisted of a cost–utility analysis with a time horizon equal to the duration of the retrospective study. The costs were computed from the perspective of the Spanish NHS, as mentioned above, and effectiveness was expressed in terms of QALYs gained. For this economic evaluation, to compute the QALYs gained by cohort and to calculate the difference between the two interventions studied, utility values were allocated individually to each patient, both at the initial visit of the start of treatment with fesoterodine, as well as at the end-of-study visit. Utility values for each patient were derived from the responses obtained from patients on the overactive bladder questionnaire-short form (OAB-q SF) health-related quality-of-life questionnaire.²³ To derive the utility values of the EQ-5D (EuroQoL five dimensions) questionnaire from OAB-q SF, the algorithm developed by Ruiz et al²⁴ was used with a multilevel regression model which, through mapping techniques, allowed for obtaining the above values. As the OAB-q SF was given only at the study visit, the utility values that might correspond to the baseline visit were obtained by a predictive algorithm based on a linear regression model (backward elimination, the variables of which were: presence of urinary incontinence and number of comorbidities, and corrected R^2 : 0.183; $P=0.001$; U : $0.828-0.003 \times$ number of comorbidities -0.052 , in the case of urinary incontinence), developed in the subsample of patients who, according to the doctor, had no change in OAB symptoms at the study visit after antimuscarinic treatment.

Once the costs and effectiveness had been computed (QALYs gained), with both interventions evaluated, the incremental cost-effectiveness ratio (ICER) per QALY gained was estimated with the following formula: $ICER = (\text{difference in costs between fast escalation and standard scaling}) / (\text{difference in QALYs between fast escalation and standard scaling interventions})$. The value of the ICER represents the extra cost (if the value was >0) for each additional unit of health benefit, expressed in QALYs (QALYs gained). The incremental costs and the QALYs were calculated as the difference between the values for the fesoterodine fast scaling to high-dose group minus the values for the dose-scaling traditional group. In Spain, the cost-effectiveness threshold at which a health intervention may be financed by the NHS is usually around an $ICER <€30,000$.²⁵

The uncertainty surrounding the parameters estimated in the results from the model was measured.^{26,27} This uncertainty analysis was carried out by using three types of sensitivity analysis. First, a deterministic univariate sensitivity analysis of extreme values was performed; the model's parameters that were considered to have greater uncertainty, and which may have changed the results of the ICER significantly, varied by $\pm 25\%$. These parameters were treatment costs for each group, QALYs gained and individualized disaggregated costs, analyzed both simultaneously and in an isolated manner in each group. Tornado charts were used for graphical representations. Another sensitivity analysis consisted of repeating the CEA of the base case in a series of subgroups (subgroup analysis). These included the following: females, males, <65 years, ≥ 65 years, vulnerable individuals (>75 years), by number of comorbidities, with or without urine leakage, and patients with OAB for >12 months. Last, a third uncertainty analysis of the model included a probabilistic sensitivity analysis (PSA) with nonparametric repeated sampling (bootstrapping). The PSA was performed by using nonparametric resampling methods (bootstrapping), consisting of empirically studying the behavior of the ICER through a large number of subsamples (simulations) obtained by randomly selecting samples of the same size as the study samples.^{26,27} In this study, 5,000 simulations were performed.

Statistical analysis

The cost comparison was done by following Thompson and Barber's recommendations,²⁸ using a general linear model (analysis of covariance), and adjusted for the following covariates: sex, history of OAB, total days of treatment, and the following comorbidities: perineal surgery, perineal aortic surgery, stroke, cardiovascular disease, angina and disc

diseases, spinal stenosis, and spine surgery. In addition, a multiple linear regression analysis was carried out to observe the associated variables (adjusted for covariates).

A descriptive and univariate statistical analysis was performed with the mean and median values, the standard deviation and 95% confidence intervals in parametric variables and median and interquartile ranges in nonparametric variables, after verifying the normality of the distribution with the Kolmogorov–Smirnov test. In the bivariate analysis the following tests were used: analysis of variance, chi-squared, Pearson correlation coefficient, and paired sample *t*-test, according to the data distribution. The confidence interval of the mean differences was calculated by resampling (bootstrapping) with 1,000 iterations. SPSS for Windows, version 19 (IBM Corporation, Armonk, NY, USA), was used to establish the statistical significance for *P*-values at <0.05.

Results

A total of 390 patients with newly diagnosed OAB (141 in the fast scaling high-dose group and 249 in the traditional dose-scaling group), who received antimuscarinic treatment with fesoterodine, were drawn from the study to carry out this economic analysis. A significantly higher percentage of patients remained on the fast scaling high dose of 8 mg throughout the study, compared with those who started with the dose of 4 mg (traditional dose-scaling group) (chi-squared =25.7; *P*<0.001).

Table 2 shows the sociodemographic characteristics of the groups analyzed. The group that started treatment with fast scaling high doses not only had a higher proportion of females but also had fewer months of diagnosed OAB than the standard dose-scaling group (Table 2). Significant differences were observed in the mean duration of treatment with fesoterodine: 157.2 days (high-dose group) compared with 180.8 days (standard dose-scaling group); *P*=0.005. However, there were no significant differences in the level of adherence as assessed by the Morisky–Green Medication Adherence Scale: 58.2% vs 52.6%; *P*=0.341.

The difference in adjusted overall health care costs was not statistically significant between fesoterodine regimens (Table 3): difference of –€64.1 (confidence interval: –153.3; 25.1); *P*=0.842. However, the disaggregated cost analysis showed statistically significant differences in accumulated cost for primary care visits (€53.4 vs €81.9; *P*=0.002), cost for absorbents (€59.9 vs €100.0; *P*=0.014) and concomitant medication (€70.1 vs €110.8; *P*=0.016), which offset the significantly higher cost for antimuscarinic medication in the fast scaling high-dose fesoterodine group; €419.2 vs €325.2; *P*<0.001 (Table 3). These differences in cost factors were due to a different frequency in the use of health care resources between groups. Thus, a lower number of visits to primary care doctors (1.1 vs 1.7; *P*=0.05) or to the specialist (2.1 vs 2.4; *P*=0.030) was observed, in favor of the fast scaling high-dose fesoterodine group compared with

Table 2 Sociodemographic characteristics of patients with both treatments included in the study

Sociodemographic characteristics	Fesoterodine: fast dose scaling to 8 mg (n=141)	Fesoterodine: standard dose scaling (n=249)	* <i>P</i> -value
Age, years	61.9 (12.9) [59.8; 64.1]	61.1 (11.5) [59.6; 62.5]	0.520
Sex (%), females	87.9%	67.5%	<0.001
BMI (kg/m ²)	26.0 (5.6) [25.1; 27.0]	26.3 (3.6) [25.9; 26.8]	0.606
History of OAB	5.6 (2.4) [5.2; 6.0]	6.1 (2.2) [5.9; 6.4]	0.029
Number of comorbidities	2.7 (2.8) [2.2; 3.2]	2.5 (2.2) [2.2; 2.8]	0.468
Hypertension	31.2%	38.2%	0.205
Common urinary tract infections	34.8%	30.5%	0.455
Insomnia	22.7%	20.1%	0.632
Depression	19.1%	16.5%	0.595
Diabetes mellitus	15.6%	14.1%	0.790
Obesity	14.9%	16.1%	0.872
Rheumatic diseases	11.3%	12.4%	0.873
Cardiovascular diseases	10.6%	4.4%	0.031
Osteoarthritis	8.5%	10.0%	0.752
Perineal surgery	6.4%	2.8%	0.080
Stroke/TIA	6.4%	2.4%	0.092
Angina	5.0%	0.4%	0.007
Abdominal aorta	3.5%	0.8%	0.050
Chronic pelvic pain	2.1%	3.2%	0.761
Disc diseases, spinal stenosis, spine surgery	0.7%	4.4%	0.042

Note: **P*-value between groups; values expressed as mean (SD) or as a %. [Upper and lower range.]

Abbreviations: BMI, body mass index; OAB, overactive bladder; SD, standard deviation; TIA, transient ischemic attack.

Table 3 Use of resources and costs (2015 Euros) by treatment group

Use of resources	Fesoterodine: baseline fast dose scaling (n=141)	Fesoterodine: standard dose scaling (n=249)	Mean difference	P-value*
Medical care (mean number of visits)				
Primary care visits	1.1 (0.8; 1.4)	1.7 (1.4; 2.0)		0.005
Specialist outpatient visits	2.1 (1.8; 2.4)	2.4 (2.3; 2.6)		0.030
Emergency room visits	0.0 (-0.0; 0.1)	0.2 (0.1; 0.3)		0.083
Specialist hospital visits	0.5 (0.3; 0.8)	0.7 (0.5; 0.9)		0.193
% Patients using absorbents	39.0	5.0		0.299
% Concomitant medication used	23.0	18.0		0.332
Costs € (mean cost per patient)				
Total costs, €	840.7 (770.9; 910.4)	904.7 (853.1; 956.3)	-64.1 (-153.3; 25.1)	0.842
Medical care, €	351.3 (295.7; 406.9)	468.7 (427.5; 509.8)	-117.3 (-118.4; -46.2)	0.001
Primary care visits	53.4 (39.1; 67.7)	81.9 (71.4; 92.5)	-28.5 (-45.3; -9.7)	0.002
Specialist outpatient visits	233.7 (209.2; 258.1)	275.6 (257.5; 293.7)	-41.9 (-77.4; -8.2)	0.009
Emergency room visits	8.5 (-13.3; 30.2)	32.7 (16.6; 48.9)	-24.3 (-52.1; 3.6)	0.087
Specialist hospital visits	55.8 (31.8; 79.8)	8.4 (60.6; 96.2)	-22.6 (-53.3; 8.1)	0.149
Absorbents funded, €	59.9 (35.0; 84.8)	100.0 (81.6; 118.4)	-40.1 (-71.9; -8.2)	0.014
Antimuscarinic drugs, €	419.2 (407.3; 431.1)	325.2 (316.4; 334.0)	94.0 (78.8; 109.2)	<0.001
Concomitant medication, €**	70.1 (44.1; 96.0)	110.8 (91.6; 130.0)	-40.7 (-72.9; -10.0)	0.016

Notes: *P-value between groups. **Drug treatment for comorbidities associated with OAB (depression, skin infections, urinary tract infections, insomnia, and others) (cost for drug only). Values and differences are adjusted for covariates: sex, history of OAB, total days of treatment, and the following comorbidities: perineal surgery, perineal aortic surgery, stroke, cardiovascular disease, angina, and disc diseases, spinal stenosis, and spine surgery. Data are presented as mean values (95% confidence interval)

Abbreviation: OAB, overactive bladder.

Table 4 Base case scenario in the cost-effectiveness analysis of fesoterodine in flexible doses

	Fesoterodine: fast dose scaling	Fesoterodine: standard dose scaling	Difference
QALYs	0.013 (0.010; 0.016)	0.009 (0.006; 0.011)	0.004
Total costs, €	840.7 (770.9; 910.4)	904.7 (853.1; 956.3)	-€64.08
ICER for fast dose-scaling fesoterodine vs standard dose scaling	-	-	-€16,020

Note: Data are presented as mean values (95% confidence interval).

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.

the dose-scaling group (Table 3). In the base case scenario, the QALYs gained were higher in the fast scaling high-dose group vs the dose-scaling group (0.013 vs 0.009), although the differences were not statistically significant. The ICER per QALY gained in the fast scaling high-dose group versus dose-scaling group was negative (-€16,020), as a result of the ratio of a negative difference in costs (-€64) divided by a positive gain in QALYs in the fast scaling high-dose group (Table 4).

Sensitivity analysis

The univariate sensitivity analysis of extreme values, in which the model's parameters that were considered the most sensitive varied by $\pm 25\%$, showed that the option of starting

treatment with fast scaling high doses of fesoterodine for OAB was dominant for most of the modified parameters related to treatment costs (fewer costs and more health effects; see the tornado chart). This shows the potential savings for the Spanish NHS (Figure 2), as the threshold of the ability to pay €30,000/QALY gained was cost-effective in the other parameters where it was nondominant. Further, the subgroup sensitivity analysis confirmed the robustness of the base case in most subgroups analyzed, showing a dominant or cost-effective ICER (with the threshold of €30,000 per QALY gained) in the fast escalating high-dose group versus the dose-scaling group, except in the subgroups of males with OAB and in patients with OAB with >12 months of history (Table 5).

The PSA with 5,000 simulations showed that, in 5.5% of the iterations, the ICER of the fast escalating high-dose group was in the upper right quadrant of the cost-effectiveness graph (Figure 3A), indicating greater effectiveness, albeit with a higher cost; whereas for 4.0% of the time, the fast scaling high-dose group was less effective and with higher costs than the dose-scaling group (dominated option). Overall, 47.2% in the fast scaling high-dose group was dominant (more effective with lower costs) and for 43.4% of the time, it was less effective but with lower costs. The PSA showed that when the cost-effectiveness threshold was set at a maximum of €30,000 per QALY gained, the fast scaling high-dose group proved to be cost-effective vs the dose-scaling group in 67.6% of simulations performed with the ICER (Figure 3B).

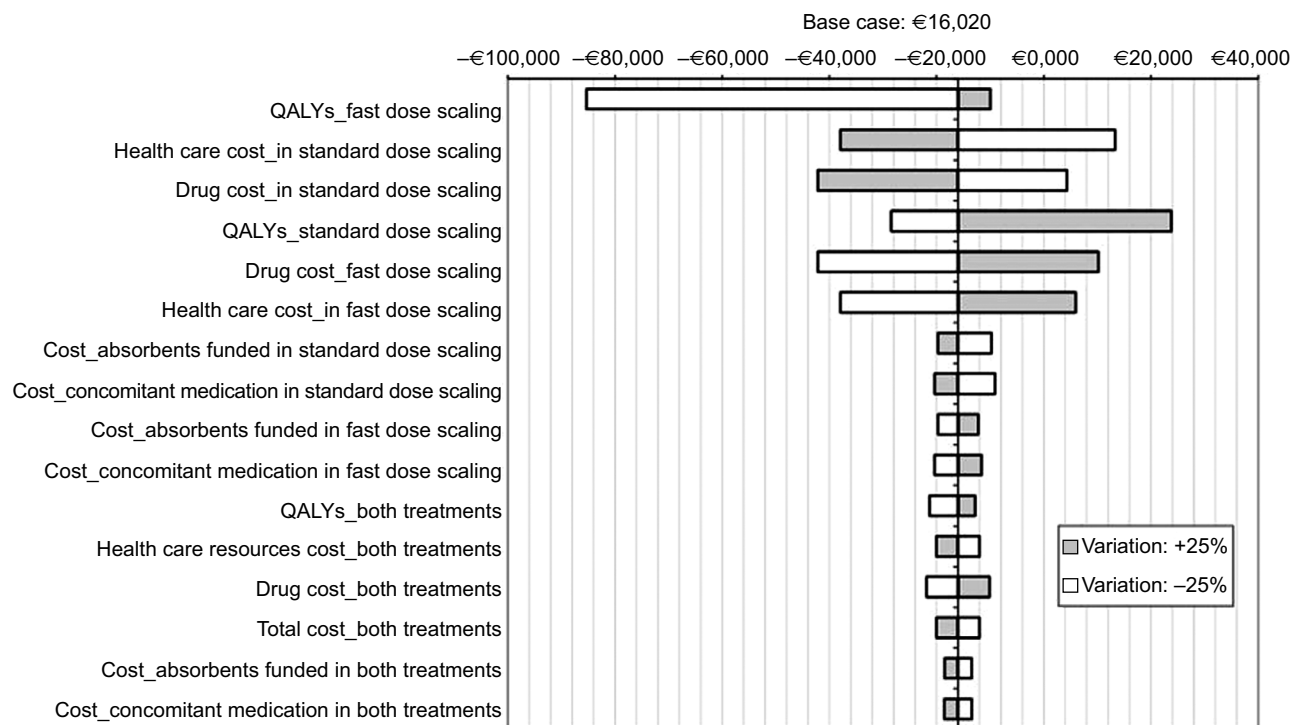


Figure 2 Univariate sensitivity analysis: tornado chart.
Note: Each variable is changed independently, by $\pm 25\%$.
Abbreviation: QALYs, quality-adjusted life-years

Table 5 Sensitivity analysis in subgroups

	Difference in QALYs	Difference in total costs	ICER	Change from base case
Base case	0.004	-€64.08	-€16,020	-
Females	0.005	-€93.49	-€18,697	-17%
Males	-0.001	€72.26	-€72,263	Dominated
Patients <65 years	0.006	-€35.68	-€5,946	63%
Patients ≥ 65 years	0.001	€15.01	€15,010	194%
Vulnerable patients >75 years	0.004	-€118.51	-€29,629	-85%
No comorbidity associated with OAB	0.002	-€36.48	-€18,239	-14%
Patients with I+ comorbidity associated with OAB	0.002	€9.98	€4,989	131%
Patients with no urine leakage	0.003	€53.72	€17,908	212%
Patients with urine leakage	0.002	-€212.95	-€106,474	-565%
Patients >1 year of history of OAB	-0.004	€111.67	-€27,917	Dominated

Note: The differences in QALYs and costs represent the differences observed between fast dose-scaling fesoterodine vs standard dose scaling.
Abbreviations: ICER, incremental cost-effectiveness ratio; OAB, overactive bladder; QALYs, quality-adjusted life-years.

Discussion

This study comprised an economic evaluation of the use of an antimuscarinic drug (fesoterodine), given in flexible doses, in patients newly diagnosed with OAB, in daily clinical practice in Spain, using flexible doses to prescribe two different dosages. In this way, its relative efficiency was estimated in routine clinical practice conditions. Numerous clinical studies have shown the effectiveness of using flexible doses of antimuscarinic drugs to treat symptomatic OAB.^{8-12,14,15} Data from observational studies, such as the

study presented here,¹⁶ which give a more realistic view of daily practice, may also help to develop better therapeutic strategies, which complement those obtained in traditional clinical trials, and therefore it is also interesting to estimate effectiveness of drug use in these conditions.²⁹

In different economic evaluations with fesoterodine published in Spain, where a CEA has been performed, the superiority of fesoterodine has been shown, compared with other drugs for the symptomatic treatment of OAB.¹⁷⁻¹⁹ These economic evaluations have shown that, compared

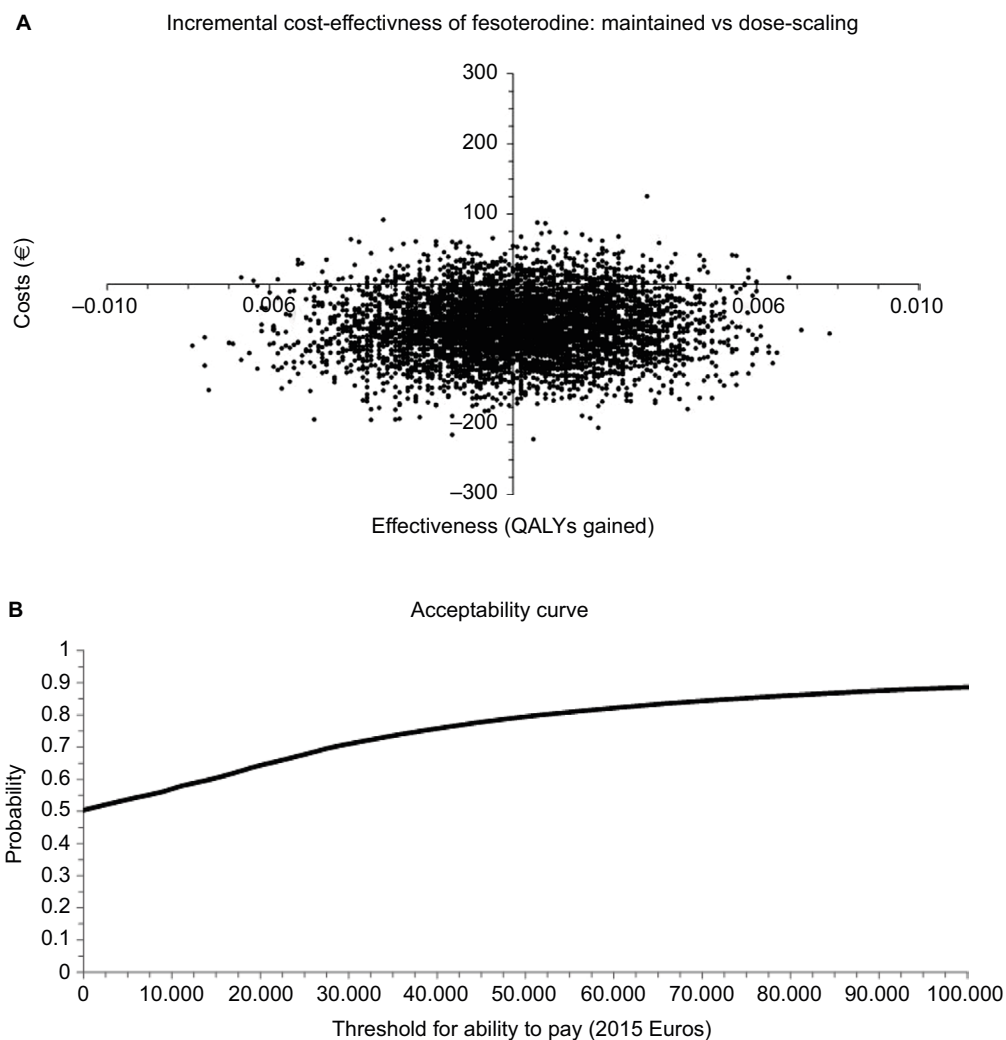


Figure 3 (A) Incremental cost-effectiveness graph and (B) acceptability curve.

Note: The acceptability curve shows the probability of fast-scaling fesoterodine being cost-effective vs standard dose scaling.

Abbreviation: QALYs: quality-adjusted life-years.

with solifenacin, tolterodine or mirabegron, fesoterodine has an ICER under the cost-effectiveness threshold normally accepted in Spain for inclusion in the pharmaceutical services of NHS.²⁵ The economic superiority of fesoterodine compared with other antimuscarinic drugs available in our health care setting has also been shown in conditions of routine or real-life practice, indicating that fesoterodine can lead to health care savings in the treatment of OAB, which is NHS-funded, and offsetting its higher pharmacological cost with less use of health care resources, such as medical visits, absorbents, or concomitant medication related to OAB (antidepressants, anxiolytics, etc), in patients of any age and in vulnerable subjects.^{30–32} However, none of the above economic evaluations has addressed the cost-effectiveness of fesoterodine in flexible doses, which allows for two different dosages: a rapid scaling to high doses or the standard scaling according with the recommendation in the fesoterodine sum-

mary of product characteristics. In our study, when flexible doses of fesoterodine were used in newly diagnosed patients, fast scaling to high doses proved to be a cost-effective treatment option in most of the situations analyzed according to the current recommendations in our health care setting.^{25,33}

This economic evaluation has confirmed the findings of other economic evaluations with fesoterodine, which show that its biggest pharmacological cost (in this case due to the use of fast scaling to high doses versus conventional titration) comes with savings in other components of NHS-funded health care costs, namely, cost for absorbents, concomitant medication related to OAB, and health care costs for medical visits to primary care and to specialists, which fully offset additional pharmacological costs. These results have been able to be replicated in various alternative scenarios and subgroups of patients, which fully justify this economic evaluation, although it may be considered unusual to compare

two doses of the same drug, because it is rare to find similar economic evaluations in the scientific literature.³⁴ One of the most sensitive factors in this economic evaluation was time since diagnosis of OAB. Thus, the results show that high doses of fesoterodine turn out to be cost-effective when the diagnosis of OAB is recent, that is, <1 year. But they are not cost-effective when patients have had OAB for >12 months, from the current perspective in Spain for the ability to pay per QALY gained, according to current recommendations.^{25,33} This suggests that clinicians should consider escalating fast to high doses of fesoterodine only if patients have had OAB for <12 months, because only in these circumstances is the greater pharmaceutical cost offset by savings in other components of health care costs, while there are more QALYs gained.

The findings of this economic evaluation could help health authorities and decision makers in health care in the process of making decisions that entail improvements in daily clinical practice (real world), although this study is not without its limitations. First, due to the study design, no data are available on the severity of the OAB at the start of treatment or on dose escalation, because doing this evaluation required bladder diaries that the patients had to complete over several days, tasks that are often used in clinical trials but not in routine practice. This has prevented us from knowing whether the groups were completely homogeneous at the start of treatment with fesoterodine. However, the advantage of pragmatic studies such as this one, which represent routine or real-life medical practice, may lie in their utility in health care decision making. Another possible limitation revolves around the costs used, since in this study no information on hospitalizations, cost per protocol (cost of side effects or switching), or additional testing (urodynamics, cultures, etc) was collected. Still, it should be noted that these patients usually do not require hospitalization, and this cost component might not be expected to change the results of the economic study. Further, the impact of possible fractures produced, particularly in vulnerable patients, on the use of health care resources, was not collected. However, this might not be a significant problem from an economic point of view, as has been observed in other economic evaluations carried out in our health care setting with antimuscarinic drugs.^{17–19} Finally, this evaluation was not performed from the society's perspective, because this study did not take into account variables such as payment for absorbents by the patient, travel costs, losses in productivity, or their impact on indirect costs.

With increasing pressure on payers and prescribers to make economic decisions regarding patients, data on cost-effectiveness should be taken into account more often in decision making. This is the first study to carry out an

analysis of fesoterodine with different treatment regimens and show that treatment with fesoterodine scaling fast to high doses involves savings and more clinical benefits (in terms of QALYs gained) versus the standard titration of this drug.

Conclusion

According to the results from this study, treatment with fesoterodine fast scaling to 8 mg may be considered a cost-effective alternative for the Spanish NHS, compared with the traditional titration of this drug, from 4 to 8 mg, in the treatment of OAB in females who have had OAB for <12 months, in routine clinical practice.

Author contributions

FS-B and JMG-M contributed to the study conceptualization and design. CP, JR, and JR contributed to study conceptualization, methodology plan, and performed the analysis. All authors listed made substantial contributions to the study in conceptualization and/or study design, analysis and/or data interpretation, and manuscript preparation and/or review. All authors read, edited, and approved the final manuscript.

Disclosure

Carmen Peral and Javier Rejas are employees of Pfizer. Jaime Ramos is a former employee of Pfizer. The other authors report no conflicts of interest in this work.

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