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ORIGINAL RESEARCH ARTICLE

Impact of Loss of Work Productivity in Patients with Overactive Bladder Treated with Antimuscarinics in Spain: Study in Routine Clinical Practice Conditions

Antoni Sicras-Mainar[1] · Ruth Navarro-Artieda[2] · Amador Ruiz-Torrejón[3] · Marc Sáez-Zafra[4] · Gabriel Coll-de Tuero[5]

Abstract

Background Overactive bladder (OAB) is a syndrome characterized by presenting symptoms of urgency, with or without urge incontinence, and normally accompanied by day and night frequency.

Objective The aim of this study was to evaluate the impact of lost work productivity [number of days of sick leave] in patients treated with fesoterodine versus tolterodine and solifenacin to treat OAB in Spain.

Methods A retrospective, observational study was carried out using the records (digital databases) of actively working patients (2008–2013). The study population comprised of patients from two autonomous communities; 31 primary care centres agreed to participate. Patients who began first treatment with antimuscarinics (fesoterodine, solifenacin or tolterodine) and who met certain inclusion/exclusion criteria were included in the study. Follow-up lasted for 1 year. The main outcome measures were comorbidity, medication possession ratio (MPR), treatment persistence, and number of days of sick leave and associated costs. Indirect costs were considered to be those related to lost work productivity (number of days of sick leave, exclusively), (1) due to OAB and (2) overall total. The cost was expressed as the average cost per patient (cost/unit). Multivariate analyses (Cox, ANCOVA) were used to correct the models.

Results A total of 3094 patients were recruited into the study; 43.0 % were treated with solifenacin, 29.2 % with tolterodine, and 27.8 % with fesoterodine. The average age of patients was 54 years (standard deviation 9.2), and 62.2 % were women. The comparison of fesoterodine versus solifenacin and tolterodine showed a higher MPR (90.0 vs. 87.0 and 86.1 %, respectively), higher treatment persistence (40.2 vs. 34.7 and 33.6 %), lower use of sick leave (22.8 vs. 52.9 and 36.7 %), total number of days of sick leave (5.1 vs. 9.7 and 9.3 days) and costs corrected for covariates (€371 vs. €703 and €683); $p < 0.05$.

Conclusions Despite the possible limitations of this study, active patients who began treatment with fesoterodine to treat OAB (compared with solifenacin or tolterodine) had fewer days of sick leave, resulting in lower costs due to lost productivity.

Key Points

Overactive bladder (OAB) is a syndrome characterized by presenting symptoms of urgency, with or without urge incontinence, and normally accompanied by day and night frequency.

Some available evidence shows that OAB is associated with higher health costs, both direct and indirect (mostly resulting from work absenteeism and decreased performance during work hours).

Active patients who began treatment with fesoterodine to treat OAB (compared with solifenacin or tolterodine) had fewer days of sick leave, resulting in lower costs due to lost productivity.

✉ Antoni Sicras-Mainar
asicras@bsa.cat

[1] Badalona Serveis Assistencials, Calle Gaietà Soler, 6-8 entlo, 08911 Badalona, Barcelona, Spain

[2] Medical Documentation, Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain

[3] ib-Salut, Majorca, Spain

[4] GRECS, Universitat de Girona, Girona, Spain

[5] Research Unit, IAS, Girona, Spain

1 Introduction

Overactive bladder (OAB) is a syndrome characterized by presenting symptoms of urgency, with or without urge incontinence, and normally accompanied by day and night frequency. It consists of detrusor muscle hyperactivity and may be accompanied by neurological disorders [1, 2]. The prevalence of OAB in adults varies between 10 and 20 %, increasing with age, and is more frequent in older men [3, 4]. In the European population, it is estimated that the symptoms of OAB affect 16 % of men older than 40 years of age and 41 % older than 75 years of age, while the prevalence in the general population older than 18 years of age is 11.8 %, similar for men and women [5]. In Spain, according to the results of the Prevalence, Cost and Burden Study of Urinary Incontinence carried out in population groups, it was shown that the prevalence of OAB in adults ≥40 years of age was 21.5 and 38.5 % in people over 65 years of age who have been hospitalized [6, 7].

OAB affects patients' quality of life, due to both the storage symptoms that characterize it and the strategies that patients adopt to be able to live with this condition [8]. In this sense, many patients take extreme measures to avoid frequency and incontinence episodes, which have a significant impact on their physical state, vitality, social life, emotional state, and function [9, 10]. Not all patients seek professional help for this problem and only one-quarter receive treatment. In addition, patients with OAB often do not respond adequately to treatment with drugs, not only because of lack of adherence to that treatment but also because of a lack of effectiveness or tolerability [11, 12].

The goal of treating OAB with drugs is to inhibit the involuntary contractions of the detrusor muscle in the bladder. Since bladder contraction occurs as a result of acetylcholine-mediated activation of the muscarinic receptors, treatment is essentially based on blocking those receptors with antimuscarinic or anticholinergic drugs [13, 14]. In this sense, fesoterodine (an antimuscarinic) has been shown to be safe and effective, with several clinical studies showing an acceptable tolerance for treating OAB [15–17]. Fesoterodine has also been demonstrated to improve quality of life in several studies, being a cost-effective alternative, from a social perspective, for treating OAB compared with tolterodine and solifenacin [18, 19]. However, using drugs in clinical studies limits the generalizability of the results for a more heterogeneous population and in treatment conditions in clinical practice.

Some available evidence shows that OAB is associated with higher health costs, both direct and indirect (mostly resulting from work absenteeism and decreased performance during work hours) [20, 21]. In addition, limited studies are available comparing antimuscarinics for treating OAB with regard to lost productivity in our healthcare environment. Moreover, there are few studies that comprehensively evaluate these variables. However, there is a growing need to carry out naturalistic studies that are representative of real clinical conditions in which medications and health interventions are used. The objective of this study was to evaluate the impact of lost work productivity, in terms of the number of days of sick leave, in patients treated with fesoterodine compared with tolterodine and solifenacin (antimuscarinics) for treating OAB, under routine medical practice conditions in the Spanish population.

2 Methods

2.1 Design and Study Population

A phase IV, multicentre, longitudinal, retrospective, observational design was carried out by reviewing existing medical records (digital databases, with existing and anonymized data) from patients seen on an outpatient and inpatient basis. The study population comprised of patients from two autonomous communities (Catalonia and the Balearic Islands) belonging to three cities [Badalona (Barcelona), Girona and Majorca]. Thirty-one primary care (PC) centres, selected based on their acceptance and the quality of their records, agreed to participate in the study. The population assigned to the centres was mainly urban and lower middle class, and mostly industrial.

2.2 Inclusion and Exclusion Criteria

All patients who began first treatment with antimuscarinics (fesoterodine, solifenacin or tolterodine) between 1 January 2008 and 31 March 2013 (recruitment period) and who met the following inclusion criteria were included in the study: (1) between 20 and 64 years of age; (2) active workers; (3) able to guarantee patient follow-up for a duration of at least 1 year starting from the start date, regardless of continuing or suspending use of the medication; (4) in the prescription programme to obtain prescriptions, with a verified record of the daily dose, time interval and duration of each treatment received; and (5) no prior exposure to these drugs in the 12 months before the start date. Subjects who were excluded were (1) those transferred to other PC centres or who moved, or were outside of the area; (2) patients treated simultaneously with two or more antimuscarinics during the study period; and (3) patients permanently hospitalized.

2.3 Study Groups

A non-intervention study was carried out in which the number of days of sick leave was compared for patients

treated with fesoterodine versus tolterodine and solifenacin (three study groups). Patient follow-up was for 1 year starting from the treatment start date.

2.4 Description of Treatment, Treatment Adherence/Compliance and Persistence

Pharmacological data from patients treated with solifenacin or tolterodine were obtained from the same computer system and according to the Anatomical Therapeutic Chemical (ATC) classification system [22]. The medication chosen for a specific patient was at the discretion of the doctor (clinical practice). The doses of medications taken were obtained (fesoterodine 4 and 8 mg, solifenacin 5 and 10 mg, and tolterodine 2 and 4 mg), as were the time intervals when the medications were taken during the follow-up period. Fesoterodine, solifenacin and tolterodine were the only antimuscarinics selected for this study since they share a similar mechanism of action and because they are the most widely prescribed in Spain. Compliance was defined according to the criteria from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and was calculated based on the medication possession ratio (MPR) [23], which was evaluated from the first to the last prescription and represented the number of days of medication taken over the number of days in treatment (commencing from the start date) [24]. Persistence was defined as the time, measured in months, without stopping the initial treatment or switching to another medication at least 30 days after the initial prescription. The number of incontinent patients, i.e. those using absorbents for urinary incontinence, was quantified.

2.5 Sample Size Calculation

This was a population study. Approximately 906 patients were expected to be recruited for each antimuscarinic ($\alpha < 0.05$; 80 % statistical power, comparing the number of days of sick leave due to illness). The hypotheses were made on the basis of an annual mean difference between groups of at least 1.57 (standard deviation 15.1 days). Despite all this, in two groups the required sample size was not reached, for which it was necessary to recalculate the study power with the differences observed in sick leave due to genitourinary causes. The power was at least 83 % in the comparisons of fesoterodine versus solifenacin and fesoterodine versus tolterodine. However, all records available for the study were obtained. Medical records of patients included in this study were extracted consecutively from various databases, from the total included in those databases until the total number of records for the study was reached.

2.6 Selection of Patients with Overactive Bladder

A diagnosis of OAB was made based on the International Classification of Primary Care (ICPC-2) in component 7 (diseases and health problems) [25] (U13), and based on the codes for hospital and emergency admissions, according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) [596.51].

2.7 Sociodemographic and Comorbidity Variables

Study variables were age (continuous and by range), sex, time since diagnosis to start of treatment, body mass index (BMI; kg/m^2) and medical history (ICPC-2) [25]: hypertension (K86, K87), diabetes mellitus (T89,T90), dyslipidaemia (T93), ischaemic cardiomyopathy (K74, K75), stroke (K90, K91, K93), chronic obstructive pulmonary disease (R95, chronic obstruction of the airways), asthma (R96), dementia or memory disturbances (P70, P20), depression (P76) and malignant tumours (all types).

As a summary variable for general comorbidity, for each patient seen we used (1) the Charlson comorbidity index [26] as an approximate indication of the seriousness of the patient's condition, and (2) the individual case index, obtained from the Adjusted Clinical Groups (ACG), a system that classifies patients by utilization/consumption of resources [27]. The algorithm from the Grouper ACG® Case Mix System is comprised of a series of consecutive steps until the 106 mutually exclusive ACG groups are reached, one for each patient seen. The ACG application provides the resource utilization bands (RUBs), with which each patient is grouped into one of the five mutually exclusive categories based on his/her morbidity: (1) healthy or very low morbidity; (2) low morbidity; (3) moderate morbidity; (4) high morbidity; and (5) very high morbidity).

2.8 Indirect Costs and Sick Leave

Indirect costs are considered to be those related to lost work productivity [number of days of sick leave, exclusively], (1) due to OAB (and/or urinary incontinence) and (2) overall total. Cost (€2014) was expressed as the average cost per patient (cost/unit), by treatment with fesoterodine, tolterodine and solifenacin. The number of days of sick leave or lost productivity was quantified according to the average interprofessional work cost, corresponding to €79.1 per day of sick leave [source: Instituto Nacional de Estadística (INE)] [28].

2.9 Information Confidentiality

Confidentiality of the records was respected (anonymous and dissociated) according to the Personal Data Protection Act (Law 15/1999 of 13 December). This study was classified by the Spanish Agency of Medicines and Medical Devices (Non Interventional Post-Authorization Study-other designs: post-authorization observational study) and was subsequently approved by the Independent Ethics Committee of the Hospital Universitari Germans Trias i Pujol, Badalona.

2.10 Statistical Analysis

Prior to analysis, particularly to the information source belonging to the digital clinical records, the data were carefully reviewed through an exploratory analysis and data preparation, observing the frequency distributions and searching for possible recording or coding errors. A descriptive univariate statistical analysis was carried out, with 95 % confidence intervals (CIs). The normality of the distribution was proven using the Kolmogorov–Smirnov test. Bivariate analysis was carried out using ANOVA tests, Chi-square, Pearson linear correlation and comparison of means for paired groups, according to data distribution. The a posteriori contrasts were carried out using Scheffé's test.

To quantify the median persistence time of the drugs, Kaplan–Meier survival curves were used (comparisons: log-rank test). The treatment persistence time was analysed using a Cox proportional hazards model, corrected for the possible covariates or confounding variables (age, sex, time since diagnosis, MPR, treatment persistence, location and comorbidity—Charlson index and RUB).

Comparison of the number of days of sick leave and their corresponding costs was carried out according to the recommendations of Thompson and Barber [29], using a general linear model (ANCOVA covariate analysis), corrected for the covariates described above (procedure: estimated marginal means, Bonferroni correction). The SPSS WIN program, version 17 (SPSS Inc., Chicago, IL, USA) was used, establishing statistical significance for p values <0.05.

3 Results

Of 490,100 subjects ≥20 years of age assigned and regularly seen at centres in the three geographic areas or cities, 4281 patients started a new treatment for OAB. A total of 3094 patients were selected for inclusion in this study (Fig. 1). Mean age was 54.0 (9.2) years and 62.2 % were women. The general characteristics of the studied series, by city, are detailed in Table 1.

The number of patients included in the study was as follows: Badalona: $N = 497$, 16.1 %; Girona: $N = 489$, 15.8 %; and Majorca $N = 2{,}108$, 68.1 %. The mean age of patients was 53.9 (9.1) versus 53.0 (9.5) and 54.3 (9.1) years ($p = 0.020$), and the percentage of women was 60.6 versus 61.6 and 62.7 %, respectively ($p = 0.641$).

Comparing the cities included in the analysis, the general and specific morbidity burden (88.0 vs. 87.7 and 87.5 %; $p = 0.886$), persistence at 12 months (37.2 vs. 35.6 and 35.6 %; $p = 0.792$), general use of the concomitant medication, consumption of absorbents for urinary incontinence (both in the initial period as well as in the final period) and the number of days of sick leave for all causes (7.3 vs. 7.3 and 8.8 days; $p = 0.300$), respectively, were similar between the groups studied (see Table 1). However, a higher proportion was observed in terms of use of antibiotics/antiseptics in Majorca (15.5 vs. 15.5 and 19.2 %; $p = 0.048$) and dermatologic drugs in Girona (11.3 vs. 17.8 and 12.7 %; $p = 0.004$). The largest discrepancies were observed in the use of antimuscarinics, given that the most widely prescribed drug in Majorca was solifenacin (35.8 vs. 35.6 and 46.4 %; $p < 0.001$), respectively, compared with the other cities studied.

Table 2 shows the demographic characteristics and comorbidities for each type of antimuscarinic. By study group, 43.0 % ($N = 1{,}330$) were treated with solifenacin, 29.3 % ($N = 905$) with tolterodine and 27.8 % ($N = 859$) with fesoterodine ($p < 0.001$). Patients treated with solifenacin showed a higher average age compared with fesoterodine and solifenacin (53.9 vs. 53.0 and 54.3 years; $p = 0.023$). Distribution by sex and morbidity burden was similar in the three groups studied.

Table 3 details the adherence/compliance and the descriptive and corrected persistence, by antimuscarinic use. The MPR with fesoterodine was higher compared with solifenacin and tolterodine (90.0 vs. 87.0 and 86.1 %; $p < 0.001$). In general, patients treated with fesoterodine showed greater treatment persistence compared with solifenacin and tolterodine, both in the descriptive and corrected data (Cox proportional risk models) (see Fig. 2).

This situation is particularly evident at 6 and 9 months, and at 12 months it was (40.2 vs. 34.7 and 33.6 %; $p = 0.008$), respectively, while at 3 months no conclusive results were observed. The medication doses most commonly prescribed were fesoterodine 8 mg ($N = 467$, 54.4 %), solifenacin 5 mg ($N = 944$, 71.0 %) and tolterodine 4 mg ($N = 621$, 68.6 %). Fesoterodine also showed a lower proportion of patients using sick leave compared with solifenacin and tolterodine (22.8 vs. 52.9 and 36.7 %;

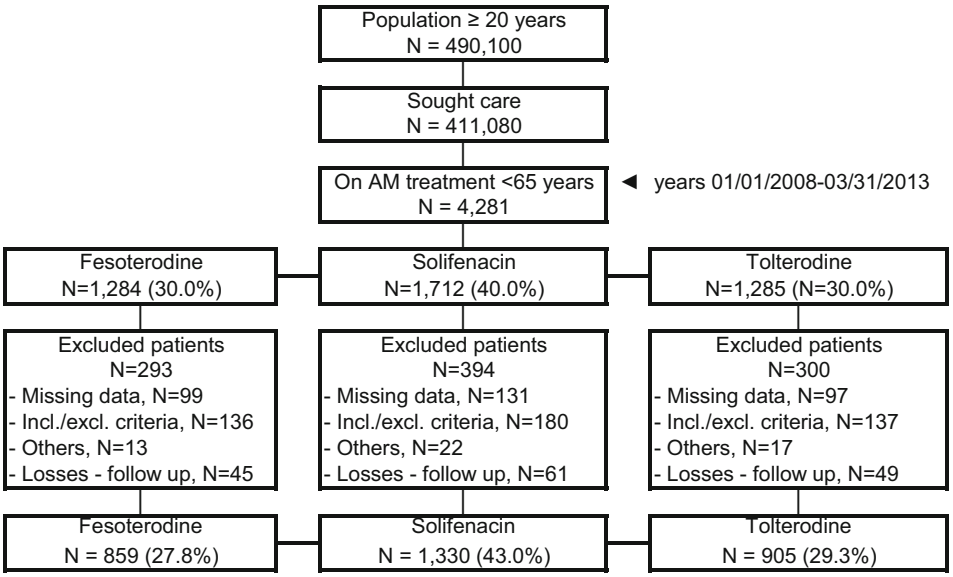

Fig. 1 General study diagram. A phase IV, multicentre, longitudinal, retrospective, observational design was used, carried out based on reviewing existing medical records (computerized databases, with anonymized data) from patients followed up on an outpatient or inpatient basis. *AM* antimuscarinics, *Incl.* inclusion, *excl.* exclusion

$p < 0.001$); the averages/total units were 5.1 versus 9.7 and 9.3 days of leave ($p < 0.001$). These differences were maintained both in number of days of sick leave for genitourinary causes as well as for other reasons (Table 3).

As a result, the indirect cost (total number of days of sick leave) of fesoterodine compared with solifenacin and tolterodine was lower (€402.8 vs. €768.3 and €739.3; $p < 0.001$). These differences were also observed according to the causes/reasons for sick leave (genitourinary and other), and in the raw data as well as in the data corrected for covariates (ANCOVA model, total days: €371 [CI €211–€532] vs. €703 [CI €549–€856] and €683 [CI €517–€849]; $p = 0.006$) (Table 3). Figure 3 shows the average number of days of sick leave (total and from urinary causes) by medication taken according to the presence/absence of urinary incontinence. The differences were less with fesoterodine.

4 Discussion

This study clearly shows that patients in active employment treated with fesoterodine for the treatment of OAB, compared with solifenacin and tolterodine, had fewer days of lost work productivity (number of days of sick leave), resulting in lower costs (average/unit per year) for the employer. It is worth pointing out that there are few observational studies that detail the use of these drugs in real conditions, which makes it difficult to compare results [30]; however, this should be interpreted as a strength of the study. This study was carried out with a broad, representative sample of patients and, moreover, there was an acceptable initial comparability regarding the sociodemographic characteristics and comorbidity in the three drug groups studied. In addition, the data by geographic area (location) were similar. This homogeneity could explain the external validity or generalization of these results in our country since three different geographic areas were represented.

In the references consulted, different studies evaluated the economic burden of OAB, although the differences regarding the methodology used, population characteristics, different cost components and unequal prevalence that exists require caution when generalizing the results [20, 21]. However, the available evidence indicates that OAB is a considerable economic burden for society and will continue increasing over the coming decades (progressive ageing of the population) [31]. In the US, it is estimated that the direct costs of OAB in adults ≥25 years of age could result in an annual national cost of $82.6 billion in 2020, with an annual cost per patient of $1925 ($1433 in direct costs, $66 in direct non-medical costs, and $426 in indirect costs) [32]. In this sense, the lack of studies detailing the cost in number of days of sick leave is notable for both patients and their caregivers, but it is undeniable that the first-line drug treatment (antimuscarinics) improves symptoms (frequency of incontinence episodes) [33]. The study by Balkrishnan et al. [34], to cite an example, shows that increase in adherence to antimuscarinic treatment was the best predictor for reducing healthcare cost. In general, our results are consistent with these data.

The study results show that patients treated with fesoterodine versus solifenacin and tolterodine show greater

Table 1 General characteristics and main variables of the series (by location)

Number of patients (%)	Badalona $N = 497$ (16.1)	Girona $N = 489$ (15.8)	Majorca $N = 2108$ (68.1)	Total $N = 3094$ (100)	p value
Antimuscarinics (%)					
Fesoterodine	31.8	32.9	25.6**,†	27.8	
Solifenacin	35.8	35.6	46.4**,†	43.0	
Tolterodine	32.4	31.5	28.0**,†	29.3	<0.001
Demographic characteristics					
Age, years [mean (SD)]	53.9 (9.1)	53.0 (9.5)	54.3 (9.1)*	54.0 (9.2)	0.020
Age ranges (years) (%)					
20–44	17.5	19.4	19.9	19.5	
45–64	82.5	80.6	80.1	80.5	0.472
Female sex (%)	60.6	61.6	62.7	62.2	0.641
General comorbidity [mean (SD)]					
Charlson index	0.8 (1.3)	0.9 (1.3)	0.9 (1.1)	0.9 (1.1)	0.056
RUB	2.3 (0.9)	2.5 (1)	2.5 (1.5)	2.5 (1.4)	0.111
Associated comorbidities (%)					
Arterial hypertension	30.4	30.5	32.6	31.9	0.469
Diabetes mellitus	10.9	13.9	12.0	12.1	0.324
Dyslipidaemia	41.0	42.9	42.9	42.6	0.738
Ischaemic cardiomyopathy	8.2	9.0	10.0	9.5	0.458
Stroke	6.0	7.8	7.5	7.3	0.472
Bronchial asthma	7.0	8.2	8.0	7.9	0.755
COPD	7.8	9.0	9.4	9.1	0.557
Dementia (all types)	2.2	2.7	2.0	2.2	0.696
Depression	28.2	31.1	29.0	29.2	0.570
Malignant tumours	8.7	12.7	10.5	10.5	0.119
Other variables [mean (SD)]					
Time since diagnosis (years)	2.0 (1.0)	2.0 (1.0)	2.0 (1.0)	2.0 (1.0)	0.987
BMI (kg/m^2)	28.2 (5.2)	28.1 (5.2)	28.2 (5.2)	28.2 (5.2)	0.930
Related to medication					
Treatment possession (months) [mean (SD)]	7.0 (6.1)	6.7 (3.9)	6.8 (3.4)	6.8 (4.1)	0.450
Treatment duration (months) [mean (SD)]	7.9 (4.1)	7.7 (4.2)	7.9 (3.8)	7.9 (3.9)	0.505
MPR (%)	88.0	87.7	87.5	87.7	0.886
Persistence with treatment (months) (%)					
3	82.7	80.0	88.5**,†	86.2	<0.001
6	67.6	65.8	68.0	67.6	0.651
9	51.7	49.9	47.2	48.4	0.147
12	37.2	35.6	35.6	35.9	0.792
Use of concomitant medication					
Total number of medications [mean (SD)]	1.1 (1.2)	1.2 (1.1)	1.2 (1.2)	1.2 (1.2)	0.499
Antidepressants (%)	31.6	32.1	33.1	32.7	0.785
Anxiolytics/hypnotics (%)	37.8	37.0	37.9	37.7	0.941
Antibiotics/antiseptics (%)	15.5	15.5	19.2*	18.0	0.048
Laxatives (%)	14.7	15.1	15.6	15.4	0.880
Dermatologic drugs (%)	11.3	17.8**	12.7	13.3	0.004
Absorbents for incontinence (%)					
Initial period	16.9	17.0	17.0	17.0	0.999
Number of days of sick leave [mean (SD)]					
All causes (total)	7.3 (25.7)	7.3 (18.0)	8.8 (25.9)	8.3 (24.8)	0.300
Due to genitourinary causes	2.6 (10.8)	2.8 (12.6)	3.5 (12.4)	3.2 (12.2)	0.227
Other causes/reasons	4.8 (23.2)	4.5 (13.1)	5.3 (22.0)	5.1 (21.1)	0.680

RUB resource utilization band, *COPD* chronic obstructive pulmonary disease, *BMI* body mass index, *MPR* medication possession ratio, *SD* standard deviation

* $p < 0.001$, ** $p < 0.01$, *** $p < 0.05$ compared with Badalona, † $p < 0.01$ compared with Girona; results that were not statistically significant between the pairwise comparison were not included

Table 2 Baseline characteristics of the series (by use of antimuscarinics)

Study groups Number of patients (%)	Fesoterodine $N = 859$ (27.8)	Solifenacin $N = 1330$ (43.0)	Tolterodine $N = 905$ (29.3)	p value
Locations (%)				
Badalona	18.4	13.4**	17.8	
Girona	18.7	13.1**	17.0	
Majorca	62.9	73.5***	65.2	<0.001
Demographic characteristics				
Age, years [mean (SD)]	53.4 (9.1)	54.5 (9.0)**	53.9 (9.5)	0.023
Age ranges, years (%)				
20–44	21.5	17.9	19.8	
45–64	78.5	82.1	80.2	0.105
Female sex (%)	61.7	62.2	62.7	0.919
General comorbidity				
Charlson index [mean (SD)]	0.8 (1.1)	0.9 (1.2)	0.9 (1.1)	0.559
RUB [mean (SD)]	2.4 (1.3)	2.5 (1.4)	2.5 (1.4)	0.412
RUB-1 (very low morbidity) (%)	31.2	27.8	29.6	
RUB-2 (low morbidity) (%)	31.7	35.2	34.4	
RUB-3 (moderate morbidity) (%)	13.5	10.8	11.5	
RUB-4 (high morbidity) (%)	12.2	12.8	10.3	
RUB-5 (very high morbidity) (%)	11.4	13.5	14.3	0.138
Associated comorbidities (%)				
Arterial hypertension	31.3	32.9	31.0	0.581
Diabetes mellitus	11.5	12.9	11.4	0.455
Dyslipidaemia	41.4	43.3	42.8	0.687
Ischaemic cardiomyopathy	8.7	9.8	9.8	0.641
Stroke	7.3	7.6	7.0	0.853
Bronchial asthma	7.3	8.2	7.8	0.765
COPD	9.1	8.9	9.3	0.964
Dementia (all types)	2.2	2.2	2.1	0.986
Depression	28.1	29.6	29.7	0.677
Malignant tumours	10.1	10.8	10.5	0.873
Other variables [mean (SD)]				
Time since diagnosis (years)	2.0 (1.0)	2.0 (1.1)	1.9 (1.1)	0.228
BMI (kg/m^2)	28.1 (4.9)	28.2 (5.2)	28.3 (5.4)	0.673

RUB resource utilization band, *COPD* chronic obstructive pulmonary disorder, *BMI* body mass index, *SD* standard deviation

* $p < 0.001$, ** $p < 0.01$ compared with fesoterodine; results that were not statistically significant between pairwise comparisons were not included

treatment persistence, resulting in fewer days of missed work. It is also associated with less use of concomitant medication. These data (corrected for covariates) suggest an approximate annual saving of €332 compared with solifenacin and €312 compared with tolterodine. It is our understanding that these reductions in cost/unit are significant, from an efficiency point of view, in the clinical management of this group of patients, given the high prevalence of OAB. The differences in indirect costs for fesoterodine versus tolterodine and solifenacin can be explained by its different pharmacokinetic profile [35]. Fesoterodine is a prodrug, 5-hydroximethyl tolterodine, which is also the active metabolite of tolterodine, and it presents an independent exposure to the genetic polymorphisms of cytochrome P450 2D6 genotype (CYP2D6), with a higher possibility of having therapeutic effects [22]. This has been shown in clinical trials [36] and observational studies [37]. It seems that our results, carried out in routine clinical practice conditions, are consistent with those from some clinical trials, where it was demonstrated that 8 mg

Table 3 Treatment adherence/compliance and persistence. Number of days of sick leave and cost (by use of antimuscarinics)

Study groups Number of patients (%)	Fesoterodine $N = 859$ (27.8)	Solifenacin $N = 1330$ (43.0)	Tolterodine $N = 905$ (29.3)	p value
Treatment adherence/compliance				
Treatment possession (months)				
Mean (SD)	7.1 (5.1)	6.7 (3.5)**	6.6 (3.7)**	0.007
Median (IQR)	7.0 (4.0–9.0)	6.0 (4.0–10.0)	6.0 (3.0–11.0)	
Treatment duration (months)				
Mean (SD)	8.1 (3.9)	7.8 (3.9)	7.7 (3.9)	0.090
Median (IQR)	9.0 (5.0–12.0)	8.0 (4.0–12.0)	8.0 (4.0–12.0)	
Medication possession ratio				
Average (%)	90.0	87.0***	86.1**	<0.001
95 % CI	88.0–92.0	85.2–88.8	83.8–88.4	
Antimuscarinic dose (mg) [*N* (%)]				
4	392 (45.6)	–	621 (68.6)	
8	467 (54.4)	–	–	
5	–	944 (71.0)	–	
10	–	386 (29.0)	–	
2	–	–	284 (31.4)	
Treatment persistence, corrected[a]				
3 months (%)	86.1	86.6	85.6	0.803
OR relative to fesoterodine (95 % CI)	–	1.06 (0.83–1.34)	1.11 (0.86–1.42)	
		$p = 0.646$	$p = 0.436$	
6 months (%)	71.4	67.1	64.8***	0.011
OR relative to fesoterodine (95 % CI)	–	1.21 (1.04–1.42)	1.30 (1.10–1.54)	
		$p = 0.016$	$p = 0.002$	
9 months (%)	52.2	48.0	45.3**	0.015
OR relative to fesoterodine (95 % CI)	–	1.15 (1.02–1.30)	1.21 (1.06–1.38)	
		$p = 0.026$	$p = 0.004$	
12 months (%)	40.2	34.7**	33.6***	0.008
OR relative to fesoterodine (95 % CI)	–	1.16 (1.04–1.30)	1.19 (1.05–1.34)	
		$p = 0.008$	$p = 0.004$	
Patients who had at least 1 day of leave from work [*N* (%)]				
Due to all causes (total)	196 (22.8)	454 (52.9)***	315 (36.7)**,†	<0.001
Due to genitourinary causes	96 (10.6)	272 (30.1)**	214 (23.6)**,†	<0.001
Other causes/reasons	125 (9.4)	283 (21.3)**	220 (16.5)**,†	<0.001
Ranges, days of leave from work [*N* (%)]				
All causes, days (total)				
<30	152 (77.6)	339 (74.7)	238 (75.5)	
31–60	22 (11.2)	58 (12.8)	48 (15.2)	
>60	22 (11.2)	57 (12.6)	29 (9.3)	0.224
Due to genitourinary causes (days)				
<30	76 (79.2)	230 (84.6)	196 (91.6)**,†	
31–60	14 (14.6)	31 (11.4)	9 (4.2)	
>60	6 (6.3)	11 (4.1)	9 (4.2)	0.028
Other causes/reasons (days)				
<30	99 (79.2)	215 (75.9)**	178 (80.9)	
31–60	12 (9.6)	27 (9.6)	24 (10.9)	
>60	14 (11.2)	41 (14.5)	18 (8.2)	0.009
Number of days of sick leave [mean (SD)]				
All causes (total)	5.1 (16.4)	9.7 (27.3)***	9.3 (27.3)**	<0.001

Table 3 continued

Study groups Number of patients (%)	Fesoterodine $N = 859$ (27.8)	Solifenacin $N = 1330$ (43.0)	Tolterodine $N = 905$ (29.3)	p value
Due to genitourinary causes	2.1 (9.3)	3.6 (13.0)**	3.8 (13.2)**	0.003
Other causes/reasons	3.0 (12.9)	6.1 (23.3)**	5.6 (23.5)**	0.003
ANCOVA covariate analysis—cost				
All causes (95 % CI)	371 (211–532)	703** (549–856)	683** (517–849)	0.006
Due to genitourinary causes (95 % CI)	231 (94–367)	445*** (314–575)	428*** (287–570)	0.042
Other causes/reasons (95 % CI)	140 (62–219)	258*** (183–333)	254*** (173–336)	0.045

IQR interquartile range, *CI* confidence interval, *OR* odds ratio, *ANCOVA* analysis of covariance, *persistence* was defined as the time, measured in months, without stopping the initial treatment or switching to another medication at least 30 days after the initial prescription

* $p < 0.001$, ** $p < 0.01$, *** $p < 0.05$ compared with fesoterodine; † $p < 0.05$ compared with solifenacin; results that were not statistically significant between pairwise comparisons were not included

[a] Cox proportional hazards regression (corrected for location, age, sex, time since diagnosis, comorbidity, and medication possession ratio). Reference antimuscarinic: fesoterodine

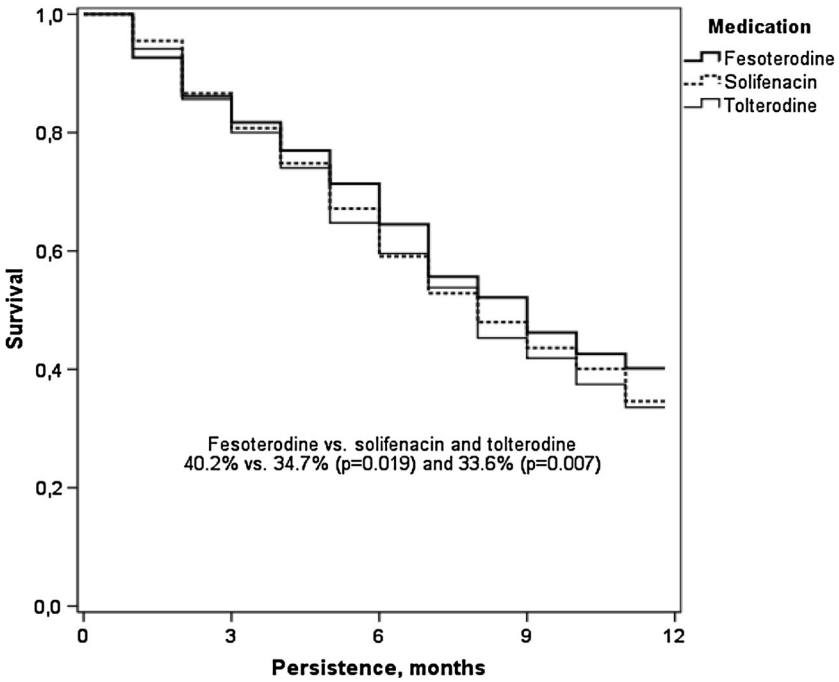

Fig. 2 Persistence curve (by use of antimuscarinic medication). Kaplan–Meier analysis (estimated median treatment persistence time). Comparisons by antimuscarinic treatment: fesoterodine compared with solifenacin (log-rank Mantel–Cox test: 5.456; $p = 0.019$) and tolterodine (log-rank Mantel–Cox test: 7.205; $p = 0.007$)

of fesoterodine was more effective than 4 mg of tolterodine extended release, with significant decreases in episodes of urgency and incontinence [9]. Similarly, clinical trials comparing solifenacin versus tolterodine indicated its similarity regarding efficacy in treating the symptoms of OAB. Our results are consistent with some observational studies published in routine clinical practice [38–40].

The possible limitations of this study are the same as those for all retrospective studies, e.g. underreporting of the disease or the possible variability of professionals and patients, as the study was an observational design. In this aspect, the possible inaccuracy of the diagnostic coding regarding diagnosis and other comorbidities, or the lack of some variable that could influence the final results (socioeconomic class of patients, work exposure, change in prescribed drug dose, type of work, etc.) could be considered a limitation of this study. However, the most important limitation relates to quantifying sick leave, which only corresponds to temporary sick leave, not including permanent disability or lost productivity while present, since only the number of days of sick leave recorded in the databases were quantified. In all cases of these potential biases, it is likely that they affected the three study drugs equally.

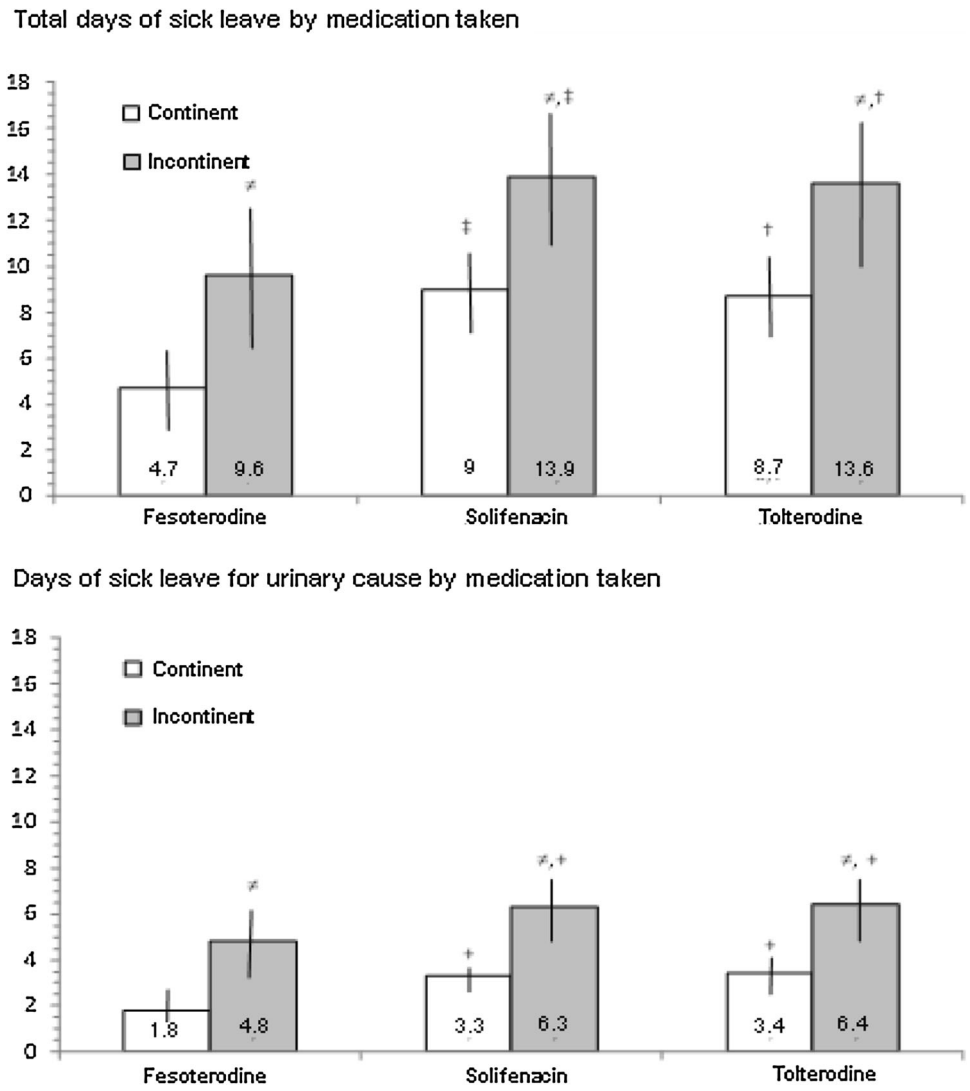

Fig. 3 Total number of days of sick leave (by medication taken) and number of days of sick leave for urinary cause (by medication taken). Values expressed as mean (95 % confidence intervals), corrected for age, sex, and general comorbidity. $^{\dagger}p < 0.001$ compared with continent patients, $^{*}p < 0.001$, $p < 0.05$ compared with fesoterodine

The future prospects offered by this study are focused on replicating it in other healthcare institutions and promoting intervention strategies to encourage self-care in patients.

5 Conclusions

The use of fesoterodine to treat OAB (compared with solifenacin or tolterodine) is associated with lower indirect costs (number of days of sick leave). More studies reinforcing the consistency of these results are required.

Compliance with ethical standards

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Conflict of interest Antoni Sicras-Mainar, Ruth Navarro-Artieda, Amador Ruiz-Torrejón, Marc Sáez-Zafra and Gabriel Coll-de Tuero have no conflicts of interest to declare.

Author contributions Antoni Sicras-Mainar contributed to the planning and design of the manuscript, as well as data collection and statistical analysis. All authors contributed to the data interpretation, and writing, review and approval of the submitted manuscript.

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