Adherence to fesoterodine in women with overactive bladder in routine clinical practice

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KEYWORDS
Overactive bladder; Adherence; Fesoterodine

Abstract
Objectives: To assess the short-term compliance with fesoterodine treatment and to identify the reasons for lack of adherence and discontinuation in routine clinical practice. The secondary aim was to estimate the patient-reported outcomes.
Methods: This was an observational retrospective, multicenter study conducted in a sample of women with overactive bladder on fesoterodine treatment for at least three months. Adherence to medication was assessed using the Morisky–Green test. Patient-reported outcomes were assessed using the Incontinence Questionnaire Short Form (ICIQ-SF), Overactive Bladder Questionnaire Short Form (OAB-qSF), and Treatment Benefit Scale (TBS).
Results: One hundred and twenty women with a mean age [standard deviation (SD)] of 62.2 (12.0) years with severe OAB [mean (SD) ICIQ-SF score 13.2 (4.0)] were included. 42.1% of the patients were considered compliant with fesoterodine treatment. The main causes for non-compliance/discontinuation stated by the remaining 57.9% of the patients were adverse events (62.2%) and lack of clinical benefits (20.0%). The illness status as well as the patient-perceived bother occasioned by the OAB symptoms and their impact on the quality of life improved significantly after three months on fesoterodine treatment (p < 0.0001). Most of the patients stated that the current state of their urinary problems had greatly improved/improved.

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Adherencia a fesoterodina en mujeres con vejiga hiperactiva en la práctica clínica diaria

Resumen

Objetivos: Valorar a corto plazo la adherencia al tratamiento con fesoterodina e identificar las causas de la falta de adherencia o abandono en la práctica clínica diaria. El objetivo secundario fue estimar los resultados desde el punto de vista del paciente.

Métodos: Este fue un estudio observacional, retrospectivo, y multicéntrico, llevado a cabo en una muestra poblacional de mujeres con vejiga hiperactiva (VH), en tratamiento con fesoterodina durante al menos 3 meses. La adherencia a la medicación se valoró mediante el test Morisky-Green. Los resultados desde el punto de vista del paciente fueron valorados empleando los cuestionarios cortos de incontinencia (ICIQ-SF) y vejiga hiperactiva (OAB-qSF) y la escala del beneficio del tratamiento (TBS).

Resultados: Se incluyeron 120 mujeres con una edad media (desviación estándar [DE]) de 62,2 (12,0) años con VH grave según la puntuación media (DE) del ICIQ-SF (13,2 [4,0]). El 42,1% de las pacientes fueron consideradas cumplidoras con el tratamiento de fesoterodina. Las principales causas de incumplimiento/abandono indicadas por el 57,9% restantes fueron los efectos adversos (62,2%) y la falta de beneficio clínico (20,0%). Tanto el grado de enfermedad como las molestias debidas a los síntomas de la VH percibidas por los pacientes y el impacto en su calidad de vida mejoraron significativamente después de 3 meses del tratamiento con fesoterodina (p < 0,0001). La mayoría de los pacientes indicaron que sus problemas urinarios habían sufrido una gran mejora o habían mejorado.

Conclusión: En la práctica clínica diaria un elevado porcentaje de pacientes fueron considerados cumplidores con el tratamiento de fesoterodina y percibieron los beneficios que dicho tratamiento proporcionaba después de 3 meses de iniciarla. Sin embargo, más de la mitad de la población de estudio no cumplió o abandonó el tratamiento debido principalmente a intolerancia o falta de eficacia.

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Introduction

Overactive bladder (OAB) is a common chronic condition, characterized by urinary urgency with or without urge incontinence, often with increased daytime frequency and nocturia.1 In Spain, OAB prevalence rates of 5.9–11.8% have been reported for women.2,3

The symptoms associated with OAB have an adverse impact on several aspects of health-related quality of life (HRQL) in adult women of all ages,4 including physical function, emotional well-being, sexual relationship, and work productivity.5

Antimuscarinic agents are the pharmacological mainstay of OAB treatment.6 Fesoterodine, a nonselective oral antimuscarinic agent, has shown to be effective and well tolerated.7 In addition, the availability of two doses of fesoterodine provides an opportunity to establish an optimal balance between efficacy and tolerability in individual patients.8,9

For pharmaceutical therapy to be beneficial, good persistence and adherence are essential. Poor persistence with long-term medication in chronic diseases is common.10 For overactive bladder, however, medication persistence is lower than average.11 In studies that have a 6-month follow-up, antimuscarinic persistence rates of 11–30% have been reported and in studies with at least 1 year’s follow-up, persistence rates range from 8% to 29%.12 Persistence may vary among antimuscarinic agents.12,13 A retrospective study, carried out with medical records from Spanish primary healthcare centers, reported a cumulative probability of persisting with initial therapy significantly higher for fesoterodine than for solifenacin or tolterodine.13

On the other hand, clinical practice suggests that adherence rates reported in clinical trials are much higher than in real practice.12 Trial subjects receive intensive follow-up and incentives which encourage adherence, so they might not be representative of the general population treated in normal clinical practice.14 Non-interventional studies, as the one we present here, may therefore provide complementary information to clinical trials.

Despite well-established efficacy of fesoterodine in clinical trials, treatment non-compliance is a major obstacle.
to its effectiveness in clinical practice. Identification of reasons for non-compliance/discontinuation of fesoterodine medication provides an opportunity to tailor strategies aimed at improving patient compliance with treatment.

We carried out a study aimed at evaluating the short-term adherence to fesoterodine treatment among women diagnosed with overactive bladder (OAB) and identifying the reasons for lack of adherence and the potential factors influencing adherence. The secondary aim was to assess the short-term patient-reported outcomes in routine clinical practice.

Patients and methods

Study design and patients

This is an observational and retrospective study conducted at six hospitals and one primary care center of Barcelona, Spain. Eligibility criteria included adult women diagnosed with OAB according to the International Continence Society (ICS) definition, without pelvic organ prolapse (< stage II Baden-Walker), with absence of symptoms or signs of urinary tract infection, new users of fesoterodine 4 mg without dose-escalation to 8 mg, and on treatment for at least three months.

The study was of a non-intervention nature, and the OAB treatment prescribed was determined by the clinical judgment of the doctor responsible for the patient’s management. At the time of diagnosis, as in routine clinical practice, patients completed the validated Spanish version of the International Consultation on Incontinence Questionnaire Short Form (ICIQ-UI-SF)\(^\text{15}\) to assess OAB severity and the Overactive Bladder Questionnaire Short Form (OAB-qSF)\(^\text{16}\) to evaluate impact of OAB on their lives. Clinical examination was performed and urinary tract infection was ruled out using a urine test strip. After diagnosis, antimuscarinic treatment for OAB was prescribed and a follow-up visit was scheduled.

At the scheduled first follow-up visit, three months after time of diagnosis and start of treatment, those patients who fulfilled the selection criteria stated above were included. Adherence to fesoterodine treatment was measured using the Morisky–Green test\(^\text{17}\) adapted and validated for the Spanish language.\(^\text{18}\) In addition, patients were asked how many pills they had taken. The main reasons for lack of adherence or treatment discontinuation and potential factors influencing adherence were also recorded at the only study visit. Patient-Reported-Treatment benefit [Treatment Benefit Scale (TBS)],\(^\text{19}\) OAB-qSF and ICIQ-UI-SF were recorded to assess the patient-reported outcomes after three months of therapy.

All study participants provided their written informed consent. In accordance with the Spanish recommendations, the study was approved by the Clinical Research Ethics Committee of Hospital de la Santa Creu i Sant Pau, Barcelona, Spain.

Measurements and instruments

The Morisky–Green questionnaire\(^\text{17,18}\) is a four-question survey to assess the patient’s treatment adherence. A person was considered to be non-adherent if they responded affirmatively to at least one question. In addition, patients who declared forgetting to take medication were asked what the proportion of drug they did not take (>75%; 75–50%; 50–25%; <25%).

The TBS\(^\text{19}\) is a self-administered single-item instrument, used to compare the current state of their urinary problems with their state before the start of the treatment. It is scored from 1 to 4 (1 = greatly improved, 2 = improved, 3 = no change, 4 = worsened during the treatment).

The OAB-qSF\(^\text{16}\) evaluates patient-perceived bother occasioned by the symptoms and their impact on health-related quality of life (HR-QOL). It consists of a 6-item symptom bother scale and a 13-item quality of life scale. The total score on the symptom bother scale ranges from 0 (not at all) to 100 (a very great deal). The total score on the quality of life scale ranges from 0 to 100; the higher the score, the better the quality of life.

ICIQ-UI-SF\(^\text{15}\) is a four-question survey to assess the urinary incontinence severity. Total scores range from 0 to 21 (1–5 mild; 6–12 moderate; 13–21 severe).

Statistical analysis

The descriptive analysis included demographic and clinical characteristics of patients. Quantitative and qualitative variables were analyzed using measurements of central tendency (mean, median) and of dispersion (95% confidence interval [CI]). Student’s t-test or Mann–Whitney U test were used to compare quantitative variables and Pearson’s Chi-square or Fisher exact tests for qualitative variables. Variables: age, educational level, place of residence (urban, rural), number of concomitant drugs, place of healthcare attention (primary care, hospital setting), ICIQ-UI-SF and OABqSF scores at prescription time, were screened as potential factors influencing adherence using univariate analysis and then assessed using logistic regression. Tests were two-tailed with a significance level of 5%. Data were analyzed using SPSS V17.0 statistical software.

Results

One hundred and twenty patients who suffered from severe OAB at diagnosis according to the ICIQ-SF [mean (SD) score 13.2 (± 4.0)] were included in the study. Table 1 summarizes the baseline patient characteristics at the time of initiation of the OAB therapy.

Of the total patients, 107 women who answered the Morisky–Green test were included in adherence analysis. According to the Morisky–Green test, 42.1% of the patients (n = 45) were classified as compliant or adherent, while the remaining 57.9% of the patients (n = 62) were considered non-compliant with the treatment.

Compliant patients took a mean (SD) of 87.0 (39.5) fesoterodine tablets compared with the 62.7 (60.5) taken by non-compliant patients (p < 0.05). 30 of the 62 non-compliant patients indicated the proportion of drug they forgot to take: most women (63.3%, 19/30) forgot to take less than 25% of their prescribed drug, 2 (6.7%) 25–50%, 4 (13.3%) did not take 50–75%, and 5 (16.7%) more than 75%.
Reasons for lack of compliance or discontinuation with fesoterodine treatment were available on 45 of 62 non-compliant women; some patients reported more than one reason. Side effects were the main cause (62.2%), followed by lack of clinical benefits (20.0%; Table 2). Among the other causes stated, patient’s neglect (11.1%) and clinical improvement (6.6%) were the most frequent (Table 2). The main side effects reported (>10% patients) as the reason for lack of adherence included dry mouth (10/27; 37.0%) and constipation (3/27; 11.1%).

No significant differences were observed between patients with and without adherence to treatment regarding any of the potential factors influencing adherence analyzed (age, educational level, place of residence, number of concomitant drugs, place of healthcare attention, ICIQ-UI-SF and OABqSF scores at prescription time; Table 3). Therefore, subsequent logistic regression analysis was not performed.

Table 4 summarizes the patient-reported outcomes. The proportion of patients who reported improvement (greatly improved/improved) according to TBS was greater among compliant patients (73.3%) compared with non-compliant (62.9%); however, no significant inter-group differences were observed (p > 0.05). At the time of diagnosis, significant differences in total ICIQ-SF and OAB-qSF scores were not observed between compliant and non-compliant patients (p > 0.05). Three months after fesoterodine prescription, patient-perceived bother occasioned by the OAB symptoms and their impact on health-related quality of life as well as OAB severity showed a significant improvement (p < 0.0001, Table 4). Significant differences were not observed amongst compliant and non-compliant patients after three months of treatment (p > 0.05).

Discussion

Medication adherence plays a key role in patients with OAB. OAB patients who discontinue treatment prematurely are unable to obtain the full benefit of therapy. As seen with patients with other chronic conditions, adherence and persistence to antimuscarinic therapy is very poor.

Several reports have assessed adherence rates to different antimuscarinic therapies, but only a few include real-world fesoterodine data, one of the most widely used antimuscarinic drugs in Spain, together with tolterodine and solifenacin.

Definitions and calculation of adherence are not uniform across the literature. The present report shows a high short-term adherence rate of 42% in a sample of new users of fesoterodine with severe OAB. In a post hoc analysis from the IMPACTA study, Castro-Díaz et al. reported a two-month fesoterodine adherence measured also by the Morisky–Green test of 31%. A Norwegian retrospective analysis of a pharmacy claims database evaluated adherence to tolterodine, solifenacin, darifenacin, and fesoterodine using the medication possession rate (MPR); the new users of fesoterodine were the most adherent with an annual adherence rate of 38.5% for MPR ≥ 0.8.

Adherence to treatment is achieved when a good balance exists between tolerability, efficacy, and cost of treatment. In contrast to previous studies where lack of efficacy was the most frequent cause of discontinuation, in our study, in agreement with Dmochowski et al., lack of compliance or discontinuation was more often due to intolerance than inefficacy. In line with several previous studies, the main side effects here reported were dry mouth (25.0%) and constipation (11.1%). Thus, actions aimed at offsetting these common side effects such as providing adequate information that will allow the patients to have a more realistic view of the treatment tolerance, an early detection of AEs, and an effective implementation of management strategies that can reduce patient discomfort might improve patient compliance and support optimal clinical outcomes.

We believe, as other authors have reported, that inadequate symptom control, unmet or unrealistic expectations and inadequate follow-up after initiation of therapy could be other important factors influencing adherence to medication. Therefore, a better patient–physician communication is necessary to improve treatment.
adherence. Recently, the Global Development of Self-Assessment Goal Achieved (SAGA) questionnaire, which provides a basis for the patients and physicians to discuss realistic treatment expectations, has been reported. A mismatch between treatment expectations and outcomes can lead to patients’ dissatisfaction and discontinuation of medication of which the physician may be unaware. Physicians must provide good information about OAB treatment that will allow the patients to have realistic expectations about its efficacy and tolerability. A short-time appointment to ensure adequate understanding of instructions and help solve initial problems with medication might be helpful, too.

Table 3  Potential factors influencing to adherence at time of prescription.

<table>
<thead>
<tr>
<th></th>
<th>Compliant (n = 45)</th>
<th>Non-compliant (n = 62)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>62.2 (10.8)</td>
<td>62.2 (12.6)</td>
<td>0.743</td>
</tr>
<tr>
<td>Educational level, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without studies</td>
<td>43</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>18 (41.9)</td>
<td>33 (55.9)</td>
<td>0.585</td>
</tr>
<tr>
<td>Secondary or higher</td>
<td>20 (46.6)</td>
<td>21 (35.6)</td>
<td></td>
</tr>
<tr>
<td>Place of residence, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural (&lt;10,000 inhabitants)</td>
<td>3 (6.7)</td>
<td>7 (11.7)</td>
<td>0.408</td>
</tr>
<tr>
<td>Semi-urban area (10,000–30,000 inhabitants)</td>
<td>6 (13.3)</td>
<td>10 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Urban area (&gt;30,000–200,000 inhabitants)</td>
<td>17 (37.8)</td>
<td>14 (23.3)</td>
<td></td>
</tr>
<tr>
<td>Metropolitan area (&gt;200,000 inhabitants)</td>
<td>19 (42.2)</td>
<td>29 (48.3)</td>
<td></td>
</tr>
<tr>
<td>Place of health care attention, n (%)</td>
<td>44</td>
<td>61</td>
<td>0.274</td>
</tr>
<tr>
<td>Primary care</td>
<td>3 (6.8)</td>
<td>8 (13.1)</td>
<td></td>
</tr>
<tr>
<td>Hospital setting</td>
<td>41 (93.2)</td>
<td>53 (86.9)</td>
<td></td>
</tr>
<tr>
<td>Number of concomitant treatments, mean (SD)</td>
<td>2.48 (2.3)</td>
<td>2.8 (2.4)</td>
<td>0.436</td>
</tr>
<tr>
<td>OABqSF score, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OAB bother severity scale</td>
<td>56.6 (15.7)</td>
<td>53.1 (18.5)</td>
<td>0.397</td>
</tr>
<tr>
<td>Quality of life scale</td>
<td>62.6 (20.4)</td>
<td>63.4 (20.0)</td>
<td>0.870</td>
</tr>
<tr>
<td>ICIQ-SF score, mean (SD)</td>
<td>13.3 (4.1)</td>
<td>12.7 (4.7)</td>
<td>0.685</td>
</tr>
</tbody>
</table>

SD: standard deviation. OABqSF: OAB Questionnaire Short Form (range 0–100). ICIQ-SF: International Consultation on Incontinence Questionnaire Short Form (range 0–21).

Establishing factors that predispose patients to be compliant with their medication is also crucial for effective OAB therapy. Several retrospective studies have found that rates of adherence were higher in patients taking extended-release formulations and in older people. Poor compliance can be attributed to other factors, including low levels of formal education, cultural factors, side effects, and financial barriers. In the present study, contrary to what was expected, associations were not observed between the demographic/clinical factors analyzed and compliance with treatment.

Fesoterodine has shown significantly improved OAB symptoms and health-related quality of life of OAB patients in

Table 4  Patient-reported outcomes.

<table>
<thead>
<tr>
<th></th>
<th>At time of diagnosis</th>
<th>3 months after prescription</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Compliant (n = 45)</td>
<td>Non-compliant (n = 62)</td>
</tr>
<tr>
<td>TBS, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greatly improved</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Improved</td>
<td>24 (53.3)</td>
<td>22 (35.5)</td>
</tr>
<tr>
<td>No change</td>
<td>12 (26.7)</td>
<td>23 (37.1)</td>
</tr>
<tr>
<td>Worsened</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>OAB-qSF score, mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bother scale</td>
<td>56.0 (15.7)</td>
<td>53.1 (18.5)</td>
</tr>
<tr>
<td>Quality of life scale</td>
<td>62.6 (20.4)</td>
<td>63.4 (20.0)</td>
</tr>
<tr>
<td>ICIQ-SF, mean score (SD)</td>
<td>13.3 (4.1)</td>
<td>12.7 (4.7)</td>
</tr>
</tbody>
</table>

SD: standard deviation; TBS: Treatment Benefit Scale; OABqSF: Overactive Bladder Questionnaire Short Form (range 0–100); ICIQ-SF: International Consultation on Incontinence Questionnaire Short Form (range 0–21).

*p intra-group at time of diagnosis vs. months after prescription <0.0001.
several clinical trials.31 The patient’s perception of treatment benefit and the effects on their quality of life often impacts on whether or not a patient will continue with OAB therapy.30 In consonance with the results reported in other real-life studies,9,32 in the present study, where a high adherence rate was achieved, the illness status as well as the patient-perceived bother occasioned by the symptoms and the impact on their quality of life improved significantly three months after starting fesoterodine treatment. Furthermore, according to TBS, most compliant patients (73.3%) reported an improvement of their urinary symptoms when compared to their baseline status before the start of treatment.

Nevertheless, non-compliant patients in the present study reported having achieved similar therapeutic benefit to those observed in compliant patients. Choo et al. indicated that although four weeks after discontinuing treatment all the voiding parameters decreased significantly, these remained improved compared with baseline.33 Therefore, it could be possible that this group of patients with a drug intake of nearly 70% of the total prescribed treatment discontinued at dates close to the inclusion visit, so they retained the benefit of the medication taken.

Some limitations in our analysis must be considered. The Morisky–Green test was fulfilled by the patients in the presence of the attending physician or therapist. It is known that patients may not answer truthfully under these circumstances. However, the subjective nature of this test allows for the obtaining of qualitative data of the reasons for discontinuation, which is one of the strengths of the present study. Furthermore, we used a validated Spanish version of the test. Another limitation of our study was that adherence was measured 12 weeks after prescription which precludes further conclusions regarding adherence in the long-term. However, a dramatic fall in adherence is observed during the first three months after drug prescription. Shaya et al. in a large medicaid population study30 showed that 56% of patients abandoned antimuscarinic treatment during the first month after prescription. In addition, Chancellor et al.34 showed that about 33% of patients fail early to comply with treatment (within the first 30 days). Therefore, research is needed to understand the reasons for low persistence during this initial period, so that interventions can be developed to improve persistence and compliance. Lastly, in this study the time in which treatment discontinuation occurred was not recorded.

Conclusions

This study has shown that adherence to fesoterodine treatment at three months of prescription was 42% in routine clinical practice. The main reasons for non-compliance were side effects (dry mouth and constipation), followed by lack of efficacy. Amongst those who discontinued or did not comply with treatment, nearly three quarters had completed more than half the total treatment prescribed.

Conflict of interest

All authors declare that they have no competing interests.

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