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The patient pathway for overactive bladder management: A quantitative analysis

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Abstract

Purpose: We aimed to explore the pathways followed by patients with overactive bladder (OAB) from referral to the urologist to final treatment.

Methods: This was a single-center, retrospective cohort study of female patients diagnosed with OAB in a large Dutch nonacademic teaching hospital. The number, sequence, and duration of treatment steps offered were analyzed, and the effectiveness, reasons for discontinuation, and possible case-mix variables influencing OAB treatment were studied.

Results: In total, 120 patients were enrolled and required a median of 2 steps (range, 1–6) of treatment over a median total duration of 28 weeks (range, 5–256). Treatment typically started with drug therapy, including antimuscarinics (38%; 95% CI, 30%–47%), antimuscarinics plus pelvic floor muscle therapy (21%; 95% CI, 15%–29%), or mirabegron (11%; 95% CI, 6%–18%). However, 52% of patients required further treatment, with botulinum toxin A (BoNT-A) injections being most effective (67%; 95% CI, 42%–85%), followed by antimuscarinics plus percutaneous tibial nerve stimulation (50%; 95% CI, 25%–75%), and antimuscarinics plus pelvic floor muscle therapy (36%; 95% CI, 21%–54%). Other therapies showed lower effectiveness. Common reasons for discontinuation were insufficient response and side effects. Overall, 22 patients were lost to follow-up.

Conclusion: Most patients try at least two treatments before they experience satisfactory symptom relief, with treatment evaluations requiring time because therapeutic onsets differ by patient and treatment. Our data can help to manage expectations among urologists and patients when seeking treatment for OAB.

Keywords
real-world data, treatment effectiveness, urgency incontinence
INTRODUCTION

Current treatment guidelines for overactive bladder (OAB) advocate a linear patient pathway based on treatment invasiveness, recommending less invasive treatments before more invasive ones. In the Dutch Healthcare system, patients with OAB first consult their general practitioner (GP) for lifestyle interventions, pelvic floor muscle therapy (PFMT), and medication (restricted to tolterodine or transdermal oxybutynin patches in case of side effects). If symptoms persist, patients are referred to an urologist for alternative medication, percutaneous tibial nerve stimulation (PTNS), or more invasive options, such as intravesical botulinum toxin A (BoNT-A) injection, sacral neuromodulation (SNM), and bladder augmentation or urinary diversion.

Although the efficacy of different treatments has been demonstrated in randomized controlled trials, these have typically had short follow-up periods and have been conducted in highly selected populations (e.g., females with limited comorbidity). Adherence to treatment is a common problem when managing OAB, with common reasons for discontinuation being a lack of effectiveness and the side-effect burden. In daily practice, effectiveness and side-effect tolerance may differ among patients, making outcomes difficult to predict, and this situation is compounded by the fact that it can take weeks to months for the effects of treatment to be evaluated adequately. Together, these features mean that the current treatment algorithm may not produce a quick reduction in symptom severity for many patients, leading to impaired quality of life and additional costs. Existing studies of real-world experience typically describe the efficacy of a single therapy for OAB and the persistence and adherence of patients.

In this study, we aimed to provide real-world data on the OAB patient pathway from referral to a urologist to final treatment with a satisfactory response. Analysis of the overall effectiveness of OAB treatment focused on five questions: (1) which treatments were offered?, (2) how many treatment steps were offered?, (3) what was the duration of each individual treatment step?, (4) which patients achieved satisfactory response to each treatment?, and (5) what led to treatment discontinuation? We also aimed to analyze if case-mix variables can be used to predict the number of treatment steps and the duration of treatment needed to achieve satisfactory symptom reduction.

MATERIALS AND METHODS

2.1 Study design and population

This was a retrospective cohort study of female patients diagnosed with OAB in a large Dutch nonacademic teaching hospital. We enrolled patients referred to the outpatient urology clinic between January 1, 2014, and September 30, 2016. Case identification was by diagnosis treatment combination code (DBC code) “035” or “OAB/urge-incontinence” (i.e., OAB/urge incontinence) in the CTcue® health records search engine (CTcue B.V.). In the Netherlands, a DBC code is applied to the diagnosis given to each patient. Electronic medical records (EMRs) were further checked for exclusion criteria, including age <18 years and other pathology that could explain the OAB symptoms (e.g., urinary tract infection, bladder tumor, bladder stones, or anatomic abnormalities, and neurogenic OAB). Follow-up ended when a patient experienced satisfactory response and did not require further treatment, or on January 1, 2020. Onset of symptoms and prior treatments by the GP were not analyzed, because these treatments (i.e., lifestyle interventions, PFMT, and medication) were not systematically evaluated and/or not reported in the referral letters. The choice of treatment was made by the patient and the urologist from among PFMT, antimuscarinics, mirabegron, PTNS, BoNT-A, and since 2017, SNM. We searched the EMRs to extract data on the provided treatments, the number and duration of treatments, and the reason for discontinuation. We defined successful treatment as the satisfactory reduction of symptoms with no need for further treatment, as evaluated in an outpatient visit or phone call by the treating urologist. Evaluations were conducted at different times depending on the therapy, following our standard institutional practice. PFMT was typically evaluated after 3 months, medication after 4–8 weeks, and PTNS not earlier than 12 weeks. In the case of BoNT-A injection, therapy was expected to start working anywhere between 3 days to 3 weeks, so we asked patients to call when symptoms recurred (this is dose dependent, but typically occurs between 3 and 6 months). Patients with no follow-up records were excluded from the analysis. Treatment duration for PFMT, medication, and PTNS was calculated as the number of weeks from the start of therapy to the first evaluation of its effectiveness, while for BoNT-A injection, this was the number of weeks from primary to repeat injections.

The International Consortium for Health Outcomes Measurement (ICHOM) have defined case-mix variables as those that may influence the outcome of OAB treatment. These included age, body mass index, comorbidities (e.g., bowel disorders or diabetes mellitus), coexisting pelvic organ prolapse symptoms or stress incontinence, estrogen or hormone replacement therapy, or prior pelvic surgery. Treatment combinations offered more than 10 times are reported separately, but those offered less often are reported as “other combined therapy.”
2.2 Measurements and analysis

Baseline characteristics and response are presented as means and standard deviations, percentages and 95% confidence intervals (95% CI), or medians and ranges, depending on the data distribution. To visualize the treatment sequence, which represents the OAB patient pathway, we created a Sankey plot in Display R (www.displayr.com). This was created using data for all participants, including those with no follow-up data. Treatment duration was assessed using only patients with at least one follow-up contact recorded in the EMR after starting treatment. Statistical analysis was done with IBM SPSS version 24 (IBM Corp.).

3 RESULTS

The initial search identified 296 patients, and of these, 120 met the inclusion criteria (Table 1). Figure 1 summarizes the OAB patient pathway in our cohort, including the different treatments offered, the number of steps, and the sequence of steps required before no further treatment was necessary. This includes not only patients with satisfactory response but also patients with no follow-up data.

Medication was the most common treatment option in the first step, including antimuscarinics (38%; 95% CI, 30%–47%), antimuscarinics plus PFMT (21%; 95% CI, 15%–29%), or mirabegron alone (11%; 95% CI, 6%–18%) (Figure 1). Of the 62 patients receiving another treatment and progressing to the second step, antimuscarinics (19%; 95% CI, 11%–31%), mirabegron (21%; 95% CI, 13%–33%), or PTNS (23%; 95% CI, 14%–34%) were typically offered in isolation. Additional steps and details are illustrated in Figure 1.

The median number of steps required by patients to achieve a satisfactory treatment outcome was 2 (range, 1–6). Notably, 52% of patients sought further treatment after the first step, falling to 28% (95% CI, 20%–36%) in the third step, 13% (95% CI, 8%–21%) in the fourth step, 5% (95% CI, 2%–10%) in the fifth step, and 2% (95% CI, 0%–6%) in the sixth step.

The median total treatment duration was 28 weeks (range, 5–256) (Table 2). For the less invasive options, median treatment durations were 19 weeks (range, 5–32) for PFMT, 9 weeks (range, 1–118) for antimuscarinic drugs, 8 weeks (range, 1–74) for mirabegron, and 11 weeks (range, 1–78) for PTNS. For the more invasive options, median treatment durations were 45 weeks (range, 7–200) for intravesical BoNT-A injections, 12 weeks (range, 1–137) for antimuscarinic drugs plus PFMT, 11 weeks (range, 2–67) for antimuscarinic drugs plus PTNS, and 15 weeks (range, 6–131) for other combined treatments.

The most common reasons for discontinuation were insufficient response and side effects. Insufficient response was reported in 45% (95% CI, 26%–66%) after PFMT, 44% (95% CI, 29%–61%) after mirabegron, 64% (95% CI, 49%–77%) after PTNS, 28% (95% CI, 19%–40%) after antimuscarinics, and 26% (95% CI, 11%–52%) after BoNT-A injections (Table 3). Patients who reported side effects as a reason for discontinuation had used antimuscarinics with PFMT (39%; 95% CI, 24%–58%), antimuscarinics alone (36%; 95% CI, 26%–47%), or mirabegron (21%; 95% CI, 10%–37%). No side effects were reported after BoNT-A injections (Table 3). Seven patients stopped treatment for other reasons (one pregnancy and six unknown).

A total of 22 patients were lost to follow-up. The highest rate of loss to follow-up was after PFMT (30%; 95% CI, 15%–52%), followed by other combined therapies (17%; 95% CI, 6%–39%), antimuscarinics (13%; 95% CI, 7%–23%), BoNT-A injections (7%; 95% CI, 1%–30%), mirabegron (6%; 95% CI, 2%–19%), and PFMT plus antimuscarinics (4%; 95% CI, 1%–18%).

Effectiveness is depicted for each treatment in Table 3. BoNT-A injection was the most effective treatment (67%; 95% CI, 42%–85%), followed by PTNS plus antimuscarinics (50%; 95% CI, 25%–75%), and PFMT plus antimuscarinics (35%; 95% CI, 21%–54%). Other therapies were less effective (Table 3).

**TABLE 1 Patient characteristics**

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>n*</th>
<th>% (95% CI)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean ± SD)</td>
<td>120</td>
<td>58 ± 16</td>
</tr>
<tr>
<td>Obesity, BMI &gt; 25</td>
<td>60</td>
<td>67 (54–77)</td>
</tr>
<tr>
<td>Bowel problems, yes</td>
<td>101</td>
<td>36 (27–45)</td>
</tr>
<tr>
<td>Diabetes mellitus, yes</td>
<td>119</td>
<td>17 (11–25)</td>
</tr>
<tr>
<td>Cognitive impairment, yes</td>
<td>116</td>
<td>7 (4–13)</td>
</tr>
<tr>
<td>Coexisting pelvic organ prolapse symptoms, yes</td>
<td>79</td>
<td>33 (24–44)</td>
</tr>
<tr>
<td>Coexisting stress incontinence, yes</td>
<td>102</td>
<td>47 (38–57)</td>
</tr>
<tr>
<td>Use of estrogens or hormone replacement therapy, yes</td>
<td>117</td>
<td>16 (11–24)</td>
</tr>
<tr>
<td>Pelvic surgery in the past, yes</td>
<td>117</td>
<td>49 (40–58)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CI, 95% confidence interval; DM, diabetes mellitus.

*Number of patients for whom data could be retrieved per item.

**% (95% CI) unless otherwise specified.
We detailed the OAB patient pathway from referral to the urologist to a satisfactory final treatment outcome in a large cohort of women over a 6-year follow-up period. The findings indicated that most patients received at least two treatments before achieving a satisfactory result and that this took a median duration of 28 weeks. Insufficient response most often followed PFMT, mirabegron, and PTNS, while discontinuation due to side effects was most often associated with antimuscarinics plus PFMT, antimuscarinic monotherapy, or mirabegron.

To the best of our knowledge, no previous study of the OAB patient pathway has analyzed both the number and the sequence of treatments. Most randomized controlled trials of antimuscarinics and mirabegron to date have provided no information about treatment either before enrolment or after follow-up for the clinical trial. By contrast, trials of BoNT-A and SNM have provided some information about previous treatment because antimuscarinic or conservative therapy will typically have failed (i.e., intolerance or treatment refractory). Long-term studies of persistence and adherence also provide limited or no information about the patient pathway, instead of focusing on antimuscarinic or mirabegron discontinuation and not on what happens to patients thereafter. We provide real-world data confirming the complexity of the OAB patient pathway when seeking to achieve satisfactory symptom relief (Figure 1).

The effectiveness of any OAB treatment is dependent on adequate symptom reduction and tolerance. Reasons for variation in treatment responses among patients are complex and may depend on the case-mix variables defined by the ICHOM. However, we did not perform an analysis of case-mix variables because our sample size was too small for the large number of treatment sequences and combinations. Insufficient response and side effects were the most important reasons for offering alternative treatments (Table 3), consistent with other studies on persistence with, and adherence to, drug therapy. As others have suggested, phenotyping patients with OAB based on their underlying pathophysiology or symptomatology may help to improve treatment outcomes and patient experience.

FIGURE 1 A Sankey plot giving a visual overview of the OAB patient pathway. Steps and sequences are shown. Treatments are color-coded in each step. The graphic shows resolution among most of the population in the first two steps, with less dramatic gains thereafter. In total, 22 patients (18%) were lost to follow-up.

AM, antimuscarinics; BoNT-A, botulin toxin A; NFT, no further treatment; PFMT, pelvic floor muscle therapy; PTNS, percutaneous tibial nerve stimulation.

TABLE 2 Median duration of treatment per type of treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median duration Weeks (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFMT</td>
<td>19 (5–32)</td>
</tr>
<tr>
<td>Antimuscarinics</td>
<td>9 (1–118)</td>
</tr>
<tr>
<td>Mirabegron</td>
<td>8 (1–74)</td>
</tr>
<tr>
<td>PTNS</td>
<td>11 (1–78)</td>
</tr>
<tr>
<td>BoNT-A injections</td>
<td>45 (7–200)</td>
</tr>
<tr>
<td>PFMT + antimuscarinics</td>
<td>12 (1–137)</td>
</tr>
<tr>
<td>PTNS + antimuscarinics</td>
<td>11 (2–67)</td>
</tr>
<tr>
<td>Other combined therapies</td>
<td>15 (6–131)</td>
</tr>
<tr>
<td>Total median treatment duration</td>
<td>28 (5–256)</td>
</tr>
</tbody>
</table>

Abbreviations: BoNT-A, botulin toxin A; PFMT, pelvic floor muscle therapy; PTNS, percutaneous tibial nerve stimulation.
Treatment evaluation was a rate-limiting factor that could take a substantial number of weeks to complete (Table 2). This was partly determined by the expected therapeutic onset, which for example, is typically after 12 weeks for PTNS. However, drug therapy was evaluated for a median duration of 8–9 weeks, which far exceeds the guideline recommendation of 4–6 weeks. Looking forward, new technological developments may enable remote monitoring to provide insight into the moment of onset of the therapeutic effect, thereby helping to shorten the patient pathway. An example might be to include automated bladder diaries with automated reporting of patient-related outcome measures. We are currently conducting a trial to evaluate the effectiveness of one such technology.

This study has some important limitations. First, the study was performed in the Dutch healthcare system, which differs from other international healthcare systems. In the Netherlands, patients first consult their GP, they follow the stepwise approach from the guideline, and are referred to a urologist if symptoms persist. This might imply that patients are referred in a relatively late stage, although we have no solid data to confirm this. Notably, this was a retrospective single-center study that was vulnerable to bias, making it difficult to generalize the results to other populations. In addition, it was not possible to draw firm conclusions about either effectiveness or the role of case-mix variables because of the large number of treatment sequences and combinations. To resolve these limitations, a larger population should be studied prospectively, preferably in a multicenter (pragmatic) trial. This should not only account for the case-mix variables set out by the ICHOM but also identify specific OAB subgroups with shared symptoms (e.g., urgency- or nocturia-dominant OAB). Finally, no side effects were reported after PFMT and BoNT-A injections, which we think was probably due to under-reporting.

5 | CONCLUSIONS

This retrospective study of women with OAB revealed two important conclusions. First, most women need to trial at least two treatments before they experience satisfactory symptom relief. Second, treatment evaluation takes time to allow for different onsets of therapeutic effect, which vary by patient and treatment. We think that these findings are relevant to clinical practice and could help to manage treatment expectations by clinicians and patients alike.

ACKNOWLEDGMENTS

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CONFLICT OF INTERESTS

Lambertus P. W. Witte is speaker for Pierre Fabre. The remaining authors declare that there are no conflict of interests.

ETHICS STATEMENT

The study was submitted to a legally constituted ethics committee, the Medical Ethical Research Committee of Isala Clinics, Zwolle, the Netherlands, which provided an exemption for the need of a waiver for the study.

<table>
<thead>
<tr>
<th>TABLE 3</th>
<th>The success or reasons for unsuccessful treatment of all treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>n</td>
</tr>
<tr>
<td>PFMT</td>
<td>20</td>
</tr>
<tr>
<td>Antimuscarinics</td>
<td>70</td>
</tr>
<tr>
<td>Mirabegron</td>
<td>34</td>
</tr>
<tr>
<td>PTNS</td>
<td>42</td>
</tr>
<tr>
<td>BoNT-A injections</td>
<td>15</td>
</tr>
<tr>
<td>PFMT + antimuscarinics</td>
<td>28</td>
</tr>
<tr>
<td>PTNS + antimuscarinics</td>
<td>12</td>
</tr>
<tr>
<td>Other combined therapies</td>
<td>18</td>
</tr>
</tbody>
</table>

Note: Results are shown as % (95% CI) unless otherwise specified.
Abbreviations: BoNT-A, botulinum toxin A; FU, follow-up; PFMT, pelvic floor muscle therapy; PTNS, percutaneous tibial nerve stimulation; SEs, side-effects; 95% CI, 95% confidence interval.
AUTHOR CONTRIBUTIONS
Data collection, data analysis, drafting of the manuscript, revision of the manuscript: Auke Seinen. Data collection, revision of the manuscript: Rogier Elburg and Lianne Hollegien. Data analysis, revision of the manuscript: Marco Blanker. Study design, data analysis, drafting of the manuscript, revision of the manuscript: Lambertus P. W. Witte.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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REFERENCES