


Urinary Urgency: A Symptom In Need Of A Cure

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Abstract: Urgency, defined as “a sudden, compelling desire to pass urine which is difficult to defer”, is not always reported by patients with overactive bladder, and is not usually described in these words. Urgency is known to have a strong negative impact on patients’ quality of life and requires attention from healthcare professionals, as they play a key role in establishing the diagnosis and in deciding, together with the patient, the most appropriate treatment. This topic was debated during the symposium “Urinary Urgency: A Symptom in Need of a Cure?”, held at the 11th Annual Meeting of the European Urogynaecology Association (EUGA) in October 2018 in Milan, Italy. The presentation of two clinical cases, those of a young, active woman and a retired teacher, illustrated the importance of this cornerstone symptom and demonstrated how fesoterodine may represent an important option in the management of this condition. The experts concluded that the physician should not leave urgency undeclared or untreated; that the patient should be involved in the choice of treatment; and that fesoterodine, which offers flexible dosing and has proven, consistent positive results on urgency episodes and urgency urinary incontinence, with very low/no risk of impairment of cognitive function, appears to be one of the good choices in the treatment of this symptom.

Keywords: antimuscarinic agents, cognitive function, fesoterodine, incontinence, overactive bladder

Introduction

Urgency, the cornerstone symptom of overactive bladder (OAB) is defined by the International Continence Society (ICS) as “a sudden, compelling desire to pass urine which is difficult to defer”.¹ However, urgency often remains unreported and therefore undiagnosed in clinical practice. Its significant impact on quality of life should motivate health professionals to track this symptom and decide, together with the patient, on the best treatment approach. This topic was debated during the symposium “Urinary Urgency: A Symptom in Need of a Cure?”, held at the 11th annual meeting of the European Urogynaecology Association (EUGA) in October 2018 in Milan, Italy. This article reports on the lectures given at the symposium, which underlined the importance of this symptom through the presentation of two illustrative clinical cases and illustrated how fesoterodine (Toviaz[®], Pierre Fabre Laboratories, Castres, France) could represent a further step toward a cure for this condition.

Urgency: More Than A Symptom

One of the concerns when establishing the diagnosis of OAB is to make the difference between “urge”, a normal feeling experienced by healthy people, and “urgency”, which is always pathological. In the case of urgency, the patient tries to

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cope with the situation by increasing the frequency of micturition, and usually complains about frequency. Consequently, the inter-void interval is decreased and the voided volume per micturition is reduced. OAB cannot be diagnosed in the absence of urgency.² This hallmark symptom is associated with incontinence in the case of failure of voluntary control over urination, and sometimes with nocturia with sleep disturbance.³

The impact of urinary urgency on health-related quality of life (HRQL) was analyzed in a group of 1015 men with storage lower urinary tract symptoms (LUTS). Urgency was found to be an important cause of bother and the number of urgency episodes was inversely correlated with HRQL.⁴ The emotional impact is also important. Urinary urgency triggers emotional responses, as demonstrated by Arya et al⁵ in women with OAB. Using arterial spin labeling, a functional magnetic resonance imaging (fMRI) technique that allows quantitative measurement of cerebral perfusion, the authors found that urinary urgency is associated with quantitative increases in cerebral perfusion in the limbic system known to process emotional response to discomfort.

The sensation of urgency varies between individuals and under various circumstances, such as waking, rising, running water, cold weather, fatigue, or worry. It also differs with the specific context and situation, such as whether toilets are available or not.² To express the burden this causes them, patients use diverse words and expressions, not always related to the feeling of urgency. This response is patient-dependent and fluctuating; some patients do not verbalize any emotional response because they are ashamed, or they consider that it is normal with aging, or that it is not serious, or as a denial of incontinence.

A qualitative study⁶ reports the answers of nine continent OAB patients who answered the question “What words would you use to describe your urge or desire to urinate?”. Patients replied with various terms; for example, “urgent, right now”; “too often”; “frequency of urination, when I have to go, I have to go”.

To conclude, the terms “sudden” and “compelling” of the ICS definition seem highly subjective and difficult to use in consultation. To identify urgency, health care professionals should rather ask a simple question: “do you have trouble getting to the bathroom in time?”

The presentation of two cases of urgency gave the opportunity to discuss how women with OAB can find a cure. Due to time constraints only two cases were presented, one in a young patient and one in an elderly patient. They were chosen to illustrate how urgency alters the daily life

irrespective of the age. The patients corresponding to the two following clinical cases gave their written informed consent for publishing their cases.

First Case

The first case concerns a 42-year-old woman, a divorced mother of two children, six and eight years of age, who is very active as a top manager in a publishing company in the world of fashion. She suffers no comorbidities and does not take any medications. During her consultation with the urogynecologist she complained of urgency, explaining that she has to rush to the bathroom during meetings. She also experiences episodes of urgency urinary incontinence (UUI), which result in embarrassing little spots on her white trousers. She likes light colors and does not want to change her wardrobe. Urgency and UUI episodes also affect her sex life, making intimacy problematic. As a precautionary measure she uses pads and is afraid that this may be noticeable when she wears trousers. The first symptoms occurred months ago; however, her general practitioner (GP) did not consider her situation carefully and had answered that “these things come and go, you know”. She also consulted a gynecologist for advice, who said that her symptoms could be related to stress or urinary infection. Eventually, the patient took the advice of a friend who had the same problem and was under the care of a helpful and supportive urogynecologist. The patient self-referred to a urogynecologist, who performed a thorough evaluation. She complained of typical symptoms of OAB with incontinence, and also of constipation. Her lifestyle as a top-level manager was considered, with her long working days making it difficult to reconcile her professional and personal life, particularly with children. She does not get enough sleep, drinks too much coffee, and moderate quantities of wine almost every day. Physical examination did not reveal any clinical signs. Urinalysis, prescribed by the gynecologist, was normal and urine culture was negative. A conservative management approach was adopted first, with clear advice to reduce her coffee intake, adapt her water intake to 1–1.5 liters/day and begin bladder retraining. Completing a three-day voiding diary before she started treatment was also suggested. The ultrasound measure of post-void residual urine showed complete bladder emptying. With this information, she was prescribed mirabegron 50 mg once a day. Six weeks later, she presented again at the urogynecologist’s office. She had completed a voiding diary, indicating the number of urgency episodes and the number of

incontinence episodes, which confirmed urgency and UUI that had improved slightly but remained bothersome. Therefore, a more flexible approach was desired to better balance efficacy and safety and a switch to fesoterodine 4 mg daily was suggested with instructions to increase to 8 mg daily if required, since fesoterodine 8 mg has proven superiority compared to 4 mg in reducing UUI episodes in a head-to-head comparison in OAB patients.⁷ Fesoterodine has also been demonstrated to have consistent efficacy on urgency in several randomized clinical trials.^{7–11} One month later, her urgency had improved after dose escalation to 8 mg, but her dry mouth symptoms were slightly worse. Therefore, she decided to revert to fesoterodine 4 mg/day for a better risk/benefit ratio, but she kept fesoterodine 8 mg tablets in her briefcase in case her symptoms worsened or she needed better control of her OAB. This clinical case does not intend to compare medical drugs. Efficacy and safety of antimuscarinics and β_3 agonist have been analyzed elsewhere in meta-analyses.^{12–14} Moysen et al reviewing ten meta-analyses and 26 randomized control trials stated that “the choice of use of anticholinergic or mirabegron should be based on the balance of efficacy/tolerance to be estimated for each patient.”¹²

Second Case

The second clinical case reports the story of a 72-year-old retired teacher, who is married, has three daughters and seven grandchildren, and is still active in the local community. She has several comorbidities: hypertension, chronic obstructive pulmonary disease, and atrial fibrillation, for which she is treated with olmesartan 20 mg, amlodipine 10 mg, hydrochlorothiazide 12.5 mg, tiotropium bromide, and rivaroxaban 20 mg. She reports severe urgency with increased daytime frequency, approximately every two hours, and nocturia with three episodes per night, but no UUI. The urgency has negatively affected her social life. She has reduced her fluid intake, which has aggravated her constipation. Although she is dry, she is afraid that one day she may not make it to the toilet in time. Moreover, her nocturia is very bothersome and affects the quality of her sleep. She has almost stopped traveling, her lifelong passion, because of her urgency episodes. Her GP has been very positive, attentive, and sympathetic; she has prescribed local estrogens and suggested a visit to a urologist or a urogynecologist to confirm the diagnosis of OAB. Four weeks later, the urogynecologist confirmed the diagnosis of dry OAB, based on the patient’s clearly described urgency symptoms and history.

He requested urinalysis, bladder diary completion and bladder ultrasonography, and confirmed the prescription of local estrogens. Three months later, her urgency had decreased somewhat, as indicated by the number of urgency and UUI episodes collated in the 3-day diary, but the patient was still very bothered by OAB symptoms, most notably her nocturia, which remained unchanged. She was advised to begin treatment with fesoterodine 4 mg and to continue with local estrogen therapy.

The choice of fesoterodine was justified by the pharmacological properties of this antimuscarinic agent. Fesoterodine is immediately and completely metabolized into its active form, 5-hydroxymethyl tolterodine (5-HMT), by ubiquitous plasma esterases and is therefore not affected by the genetic variability in hepatic enzymes, and thus shows low inter-individual clinical variability.¹⁵ Fesoterodine also has a well-balanced affinity ratio for the detrusor M2 and M3 receptors, reducing parasympathetic activity during the storage phase, which results in an increase in functional bladder capacity.^{16,17} As a result of its prolonged release formulation and its 7–9-hr half-life, fesoterodine can be taken daily as a single dose without the risk of accumulation of the active ingredient.¹⁸ Finally, fesoterodine has a very low risk of crossing the blood-brain barrier¹⁹ and has no significant effect on cognitive function, which has been confirmed in clinical trials.^{10,20,21}

Recently there has been much discussion in the peer-reviewed literature regarding the effects of anticholinergic agents on cognition. Beers Criteria, published by the American Geriatrics Society and a useful tool although not routinely used, indicate that the total anticholinergic load should be considered in elderly patients.²² Richardson et al²³ suggest that the use of urological anticholinergics, notably oxybutynin, may be associated with impairment of cognition and an increased risk of dementia. However, certain factors must be taken into consideration; most notably that the serum anticholinergic activity does not correlate with effects on cognition.²⁴ Moreover, some disorders, such as LUTS, may be early symptoms of neurodegeneration linked to the future onset of dementia, making it difficult to determine whether the increased risk is specific to the anticholinergic action or secondary to underlying conditions. This leads to a possible hypothesis: is OAB an early sign of dementia?

To summarize, it seems that estimated cumulative high levels of anticholinergic burden, as measured by the ACB scale score, may be a minor risk factor for future cognitive impairment that need to be balanced with the unquestionable

benefit of successful treatment of OAB in older persons.²⁵ The blood-brain barrier (BBB) is a dynamic barrier between the circulatory system and the central nervous system that restricts unwanted molecules from entering the brain. Antimuscarinics may cross the BBB via passive diffusion and their crossing will depend on lipophilicity, molecular weight and whether they are a substrate of the permeability glycoprotein (P-gp), a system that actively pumps drugs out of the brain.

Fesoterodine has a high molecular weight, and its active metabolite, 5-HMT, has the lowest lipophilicity of the antimuscarinics (except for trospium, which is a quaternary amine) and is a P-gp substrate.^{19,26} Its low impact on cognitive function has been confirmed in randomized clinical trials, where fesoterodine showed no significant effect on cognitive function in healthy elderly subjects,²¹ appeared to be cognitively safe in a population of older adults,²⁰ triggered no new safety signals and did not decrease the mean minimal state examination scores in study participants.¹⁰

The retired teacher revisited the urogynecologist 12 weeks later, reporting a decrease of urgency episodes with fesoterodine 4 mg, no major adverse events; notably, no constipation and no cognitive impairment. However, her nocturia continued to bother her, despite some improvement. A possible up-titration of fesoterodine to 8 mg was discussed but the patient preferred to keep the lower dose, and both patient and physician agreed with this decision.

Conclusion

Several messages can be drawn from the symposium lectures. First, urgency, a cornerstone symptom of OAB, can go unreported and be confused with other resulting symptoms, such as frequency. Second, the physician should not leave urgency undeclared or untreated. Third, when urgency is diagnosed, consider treatment with antimuscarinic agents, and before switching to another medication consider increasing the dosage. Finally, the patient must be involved in therapeutic education to facilitate disease management, including the choice of treatment.

In this respect, as a result of the combination of four favorable pharmacological properties (well-balanced M2/M3 affinity, limited crossing of the BBB, no first pass hepatic activation and its prolonged release formulation), fesoterodine has demonstrated consistent positive results on urgency episodes and UUI with very low/no risk of impairment of cognitive function. It allows for flexible dosing, with the possibility to increase or reduce the daily dose, and therefore appears to be one of the good choices for the treatment of urgency.

Disclosure

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