Overactive Bladder Syndrome: Evaluation and Management

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Abstract
Overactive bladder (OAB) syndrome is a chronic medical condition which has a major influence on the quality of life in a significant amount of the population. OAB affects performance of daily activities and has an estimated prevalence of 16.5%. Many sufferers do not seek medical help. Moreover, many family physicians and even gynecologists are not familiar with this issue. Usually patients suffer from OAB in advanced age. Nocturia is reported as the most bothersome symptom in the elderly population. The aim of our review was to discuss all aspects of this challenging disorder and suggest tools for assessment and management strategies. Practitioners can easily overlook urinary complaints if they not directly queried. We would like to encourage practitioners to give more attention to this issue.

Key Words
Overactive bladder syndrome • Antimuscarinic drugs • Overactive detrusor muscle • Nocturia • Aging

Introduction
Overactive bladder (OAB) syndrome is a chronic medical condition which has a tremendous impact on the quality of life in both men and women [1]. OAB affects performance of daily activities and social function such as work, traveling, physical exercise, sleep, and sexual function. The definition of OAB updated in 2010 by the International Continence Society is: A condition with characteristic symptoms of “urinary urgency, usually accompanied by frequency and nocturia, with or without urgency incontinence, in the absence of urinary tract infection or other obvious pathology” [2].

The National Overactive Bladder Evaluation study found that 16.5% of participants met the criteria for OAB. Although this translates to effect as many as 33 million adult Americans [1] this may be an underestimation, as many patients fail to seek help due to embarrassment or ignorance. Urgency is the key symptom in diagnosing OAB and it is closely associated with frequent daytime desire to urinate, nocturia, and incontinence. Nocturia is reported as the most bothersome symptom [3]. Nocturia was found to be directly related to decreased sleep quality, decreased health-related quality of life, and depression in the elderly population [3–5].

Diagnosis of OAB is considered in the absence of urinary tract infection, metabolic disorders (affecting urination), or urinary stress incontinence (generated by effort or overexertion). Only a third of OAB patients show urge incontinence also called wet OAB. This is different from incontinence due to failure of the urethra and pelvic floor to withstand abdominal pressure that is usually not accompanied by “urgency”. Some patients may have both OAB and urinary stress incontinence symptoms and are diagnosed as having mixed urinary symptoms. This syndrome was shown to be prevalent in some European and American populations 12–17% [1, 6, 7] and significant budgets were allocated for its medical management.
Although OAB can affect children and young adults, this condition is most common in patients over 40 years old [8]. Since the frequency and consequences of OAB is more significant in elderly patients, this group of the population has to be more carefully evaluated for relevant complains. This is a challenging condition since some of the risk factors involved are as yet unknown and suitable treatments need to be further investigated. This review addresses various aspects of diagnosis and clinical management of the OAB syndrome.

Pathophysiology of the OAB syndrome

Various factors may be involved in OAB and the major cause may vary from individual to individual. The etiology of OAB is still under investigation and is not well understood. However, 4 theories have been proposed to explain the pathophysiology of OAB:

1. The neurogenic theory: reduction in the inhibitory neural impulses and increase in the afferent impulses from the bladder trigger the voiding reflex [9].

2. The myogenic theory: the detrusor muscle becomes more sensitive to cholinergic stimulation leading to increased spontaneous activity [10].

3. The autonomous bladder theory: alteration or exacerbation of phasic activity is generated by muscarinic stimulation [11].

4. The afferent signaling theory: spontaneous bladder contractions during filling result in increased afferent output and hence the awareness of bladder filling [12].

All these theories attempt to explain what is referred to as “detrusor overactivity”. The micturition reflex is activated when the detrusor muscle is stretched, while control of the bladder is achieved through a complex of interactions between the central and the peripheral nervous systems. OAB syndrome pathological conditions affect the bladder’s sensory pathway and contribute to the urge to urinate at a low bladder volume. The detrusor muscle is densely innervated and allows synchronous activation and a rise in bladder intra vesicle pressure. A pathological partial denervation of the detrusor may induce muscle contractions leading to an urgency sensation and possible urge of urinary incontinence. Anatomically and functionally the detrusor muscle phasic activity is also controlled by the autonomous nervous system and any imbalance in the excitation or inhibition of smooth muscle modulators may also result in detrusor overactivity [13].

Evaluation of Patients with the OAB Syndrome

There are usually no clinical signs on examination, so a careful history is essential. Table 1 presents the questions a clinician should ask a patient presumed to have OAB. The primary care physician should take a focused history and perform a primary evaluation for urinary tract disorders, such as recurrent urinary tract infections, urinary bladder calculi, and bladder tumors. Such an evaluation is necessary to rule out general conditions and risk factors that cause incontinence such as diabetes mellitus, stroke, lumbar disc disease or spinal cord injury, Parkinson’s disease, multiple sclerosis, pelvic surgery, multiple vaginal deliveries and obstetric history, immobility, dementia, and psychiatric disease.

Current drugs taken by the patient and the patient’s observations as to what makes the symptoms better or worse should also be taken into account. Certain medications may contribute to urinary incontinence through the following mechanisms:

- Decreased urethral pressure (neuroleptics, benzodiazepines, α-adrenergic blockers)
- Excess urine production (diuretics)
- Incomplete bladder emptying (β-blockers, anti-Parkinson agents)
- Drugs with indirect effects such as angiotensin-con-
vertiding enzyme inhibitors which may cause a cough, narcotics which may cause constipation [14], and lithium which may cause excess fluid intake.

Radiotherapy for uterine, colon, rectal, or prostate cancer can also irritate the lining of the bladder wall and muscle wall, leading to decreased bladder compliance and capacity.

The physical examination should begin with observation of the patient and a general assessment should be done with focused examination on the organ systems that may be implicated in urinary incontinence. These assessments include: an abdominal examination for scars, masses such as uterine fibroids, hernias, and distension of the bladder, a neurological screen for upper motor lesions such as Parkinson’s disease, and a neurological screen for lower motor lesions such as sacral-nerve root lesions.

A direct rectal examination can determine the anal sphincter tone. Fecal impaction distends the distal sigmoid and rectum, resulting in inadequate detrusor activity and compromised bladder emptying [15].

A vaginal examination will reveal a prolapse of pelvic organs because both cystocele and rectocele may impair bladder emptying, and show evidence of urine leakage.

A bladder diary which describes the day-to-day bladder habits and patterns related to urination is the simplest and most important initial assessment tool. It can be very helpful in determining the frequency, volume, and pattern of voiding [16]. Three days of a bladder diary provide a stable and reliable measurement of the frequency of incontinent episodes. OAB sufferers may have urgency, frequency (more than 8 voids per 24 hours), or nocturia (one or more voids after falling asleep and a return to sleep after voiding), with or without urge incontinence [17, 18].

Several laboratory tests are recommended in the evaluation of OAB: urine analysis, urinary culture, and blood tests to determine the levels of glycozilated hemoglobin (HbA1C), electrolytes, and levels of creatinine for kidney function evaluation.

Post-void residual urine is measured using ultrasound or a straight catheter. The patient should void immediately before this test if the last void was more than half an hour ago (residual volume measured should be less than 50 ml). If available, perform uroflowmetry before and in sequence with the post-void residual urine test. Look for a maximum urinary flow greater than 15 ml/s, with at least 150 ml voided. Values of < 150 ml may not accurately reflect the patient’s true maximum flow [19, 20].

### Management Strategies

The European Association of Urology and the Japanese Urological Society recommend non-pharmacological and pharmacological treatments for OAB [21, 22].

#### Non-Pharmacological Treatment

The aim of non-pharmacological treatment is to educate patients about OAB and help them to develop strategies to manage urge and urge incontinence. It is important to communicate to the patient that treatment demands patience and motivation otherwise long-term improvements will not be achieved. Life style changes such as cessation of smoking, weight reduction, dietary and fluid intake changes (caffeine, acidic foods, and alcohol), bowel regulation, and exercise are all included in this group and were shown to be effective [23, 24].

Bladder retraining involves urination at regular intervals disregarding the normal urge to void. Initially the voiding intervals may be as short as 30 minutes and training may bring a gradual increase of voiding intervals until the patient can be in control for periods of 3 to 4 hours. This procedure may lead to a slow increase of bladder capacity. In addition, pelvic floor muscle training (with or without biofeedback) is a treatment aimed at reducing detrusor contractions through inhibitory reflexation of the pelvic floor, thus reducing episodes of urgency and urge incontinence [25]. During the training, the patients are taught to tighten their pelvic floor muscles when they experience an involuntary contraction, when sitting up from a prone position and when standing up from a sitting position. Behavioral therapy was found to be most effective when combined with oral drug therapy [26].

Table 2 summaries the options for non-pharmacological treatment.

| Classification   | Treatment                                                                 |
|------------------|---------------------------------------------------------------------------|
| Life style changes | weight loss and exercise, dietary and fluid intake changes (restriction of fluids), bowel regulation, cessation of smoking, bladder training (habit-training schedules) |
| Pelvic floor exercise | Kegel exercises, vaginal weight training, pelvic floor exercise with biofeedback, pelvic-floor electrical stimulation |

Table 2. Non-pharmacological treatment of OAB
Table 3. Drugs for treatment of OAB: characteristic, dosage, side effects, contraindications, and special precautions

| Generic name | Drug classification | Brand name | Common dosage | Significant adverse reactions | Contraindications | Special precaution |
|--------------|---------------------|------------|---------------|-----------------------------|------------------|-------------------|
| Oxybutynin | anticholinergic agent | Gelnique | oral: 4 mg once daily, may be increased to 8 mg once daily | gastrointestinal: xerostomia (19–35%), constipation (4–6%) | pregnancy risk factor C | not recommended for patients with severely impaired renal or hepatic function; patients taking strong CYP3A4 inhibitors; elderly with dementia, delirium; lactation: not recommended. |
| Solifenacin | anticholinergic agent | Vesicare | oral: 5 mg twice daily; maximum: 5 mg 4 times daily | gastrointestinal: xerostomia (11–28%), constipation (5–13%) | pregnancy risk factor C | not recommended for patients with severely impaired renal or hepatic function; patients taking strong CYP3A4 inhibitors; elderly with dementia, delirium; lactation: not recommended. |
| Darifenacin | anticholinergic agent | Detrol | oral: 7.5 mg once daily, may be increased to 30 mg once daily | cardiovascular: hypertension (9–11%) | pregnancy risk factor C | not recommended for patients with severely impaired renal or hepatic function; patients taking strong CYP3A4 inhibitors; elderly with dementia, delirium; lactation: not recommended. |
| Mirabegron | beta3 agonist | Myrbetriq | oral: initial 2.4 mg once daily, efficacy is observed within 8 weeks for 25 mg once daily; may increase to 30 mg once daily | no response after 12 weeks; dosage may be increased to 75 mg once daily | pregnancy risk factor C | not recommended for patients with severely impaired renal or hepatic function; patients taking strong CYP3A4 inhibitors; elderly with dementia, delirium; lactation: not recommended. |
| Tolterodine | antimuscarinic agent | Sanctura | oral: initial 0.4 mg, may be increased to 2.0 mg daily in 0.4 mg increments | gastrointestinal: xerostomia (3%–6%), constipation (1%–6%) | not recommended for patients with severely impaired renal or hepatic function; patients taking strong CYP3A4 inhibitors; elderly with dementia, delirium; lactation: not recommended. |
| Trospium | antimuscarinic agent | Trosec | oral: immediate-release: 20 mg twice daily extended-release: 60 mg once daily | gastrointestinal: xerostomia (1%–5%), constipation (1%–6%) | not recommended for patients with severely impaired renal or hepatic function; patients taking strong CYP3A4 inhibitors; elderly with dementia, delirium; lactation: not recommended. |
| Fesoterodine | antimuscarinic agent | Unidet | oral: 2 mg, may be increased to 4 mg once daily | gastrointestinal: xerostomia (13%–18%), constipation (7%–11%) | not recommended for patients with severely impaired renal or hepatic function; patients taking strong CYP3A4 inhibitors; elderly with dementia, delirium; lactation: not recommended. |
| Mirabegron | beta3 agonist | Myrbetriq | oral: initial 2.4 mg once daily, efficacy is observed within 8 weeks for 25 mg once daily; may increase to 30 mg once daily | no response after 12 weeks; dosage may be increased to 75 mg once daily | pregnancy risk factor C | not recommended for patients with severely impaired renal or hepatic function; patients taking strong CYP3A4 inhibitors; elderly with dementia, delirium; lactation: not recommended. |
Pharmacological Treatment

The state of the art pharmacological treatment for OAB is the use of antimuscarinic (also called anticholinergic) drugs. The intended end result of these drugs is to achieve some relaxation of the detrusor muscle and consequently to improve patient symptoms. This drug family improves the OAB symptoms by 2 mechanisms. The first mechanism of action works at the level of the neuromuscular junction on cholinergic muscarinic receptors producing a competitive inhibition of the process through which parasympathetic stimulation leads to detrusor muscle contractions. In addition, a second mechanism of action may work on urothelial sensory receptors inhibiting afferent nerve activity. Several anticholinergic drugs used today are available and prescribed worldwide and are recommended by the International Consultation on Incontinence (Oxford guidelines) [27].

More recent clinical trials have tried to address this by recruiting greater numbers of subjects and/or more severely affected patients. However, only the former approach is associated with an increased probability of a successful study outcome. Alternative approaches to managing the large and heterogeneous populations of patients characterizing antimuscarinic drug trials in the future might be to develop and/or to explore different trial designs that can reduce population heterogeneity in OAB drug trials and improve the clinical end point result of reducing urgency, urge frequency, and incontinence [31]. This analysis confirms earlier observations in antimuscarinic drug trials for OAB [28–30]. In addition, a meta-analysis of randomized placebo controlled studies indicated that the placebo effect is also substantial and significant in achieving the clinical end point result of reducing urgency, urge frequency, and incontinence [31]. This analysis confirms earlier observations in antimuscarinic drug trials for OAB [28–30]. In addition, a meta-analysis of randomized placebo controlled studies indicated that the placebo effect is also substantial and significant in achieving the clinical end point result of reducing urgency, urge frequency, and incontinence [31]. This analysis confirms earlier observations in antimuscarinic drug trials for OAB [28–30]. In addition, a meta-analysis of randomized placebo controlled studies indicated that the placebo effect is also substantial and significant in achieving the clinical end point result of reducing urgency, urge frequency, and incontinence [31]. This analysis confirms earlier observations in antimuscarinic drug trials for OAB [28–30]. In addition, a meta-analysis of randomized placebo controlled studies indicated that the placebo effect is also substantial and significant in achieving the clinical end point result of reducing urgency, urge frequency, and incontinence [31].

Several reviews of randomized trials concluded that antimuscarinic drugs produced a significant improvement or cure [29–30]. In addition, a meta-analysis of randomized placebo controlled studies indicated that the placebo effect is also substantial and significant in achieving the clinical end point result of reducing urgency, urge frequency, and incontinence [31]. This analysis confirms earlier observations in antimuscarinic drug trials for OAB [28–30]. In addition, a meta-analysis of randomized placebo controlled studies indicated that the placebo effect is also substantial and significant in achieving the clinical end point result of reducing urgency, urge frequency, and incontinence [31].

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However, in many cases drugs resulted in treatment discontinuation due to bothersome adverse effects [31].

In addition, constipation may potentiate symptoms due to the effect of the presence of excessive stool in the rectal ampulla. This may decrease the bladder capacity and therefore, should constipation appear, an early use of fiber and stool softeners is recommended [33].

Precautions

Dry mouth and constipation are the most common and bothersome side effects of antimuscarinic agents. In addition constipation may potentiate symptoms due to the effect of the presence of excessive stool in the rectal ampulla. This may decrease the bladder capacity and therefore, should constipation appear, an early use of fiber and stool softeners is recommended [33].

Side Effects of Antimuscarinic Drugs and Safety

Precautions

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Constipation may lead to the discontinuation of medication in up to 50% of patients [33]. Another reason for not following the recommended oral drug regime during the first 2 to 3 months may be that improvement appears gradually or only to a small degree.

Other common anticholinergic adverse effects associated with antimuscarinic drugs are blurred vision, and somnolence. These are not life threatening, but may be associated with poor compliance and discontinuation of treatment [27]. More serious adverse effects include confusion, cognitive, and cardiac effects, specifically prolongation of the QT interval [34]. These occur particularly in older people [35] who may experience greater central nervous system toxicity secondary to cerebrovascular disease and other conditions that can affect the permeability of the blood-brain barrier [35]. The use of agents with reduced blood-brain barrier penetrance (such as trospium and darifenacin) may prevent the co-vagolytic influence on the cardiovascular system that may lead to alterations in heart rate and blood pressure [36]. Therefore an M3 selective muscarinic receptor agent may be preferable in patients with pre-existing heart disease. Several antimuscarinic drugs are relatively M3 receptor specific, but it is unclear whether they are better than non-selective ones. Elderly patients who receive polypharmacy and/or might have renal and hepatic impairment should receive special attention when antimuscarinics are prescribed, given that these agents may interact with drugs that compete for hepatic metabolism via cytochrome P450 and renal excretion [37].

Contraindications for the use of antimuscarinic agents are patients with closed angle glaucoma, myasthenia gravis, severe ulcerative colitis, a toxic megacolon, or intestinal obstruction because of their anticholinergic effects on the bowel. However, treatment decisions should be individualized and their prescription might need approval from the clinician caring for these disorders.

Compliance in using antimuscarinic may not be sufficient, as shown in a 2011 systematic review of 149 papers that found discontinuation rates of 43–83% in the first 30 days of treatment, and more than half of patients never refilled the initial prescription [38]. Regular follow-ups (every 2–3 month) are important in monitoring treatment effects and adherence. All available antimuscarinic drugs come as an oral preparation.

Oxybutinine has a transdermal preparation (patch and gel). Patients should be advised on common side effects and be aware that the effect may be dose dependent. Precise instructions should be given on the timing and dosing of choice since timing may reduce the occurrence and severity of adverse effects and concomitantly increase the therapeutic effect in accordance with the patients’ individual symptoms.

In general, we recommended starting at a low dose of one of the anticholinergic drugs listed in table 3 and titrating according to efficacy and side effects. We found it practical to allow flexible drug regimens given on alternate days, to stress the importance of adhering to the treatment plan, and allowing reasonable time for a therapeutic effect (between a few days and up to 12 weeks). However, some patients may feel little improvement with one drug and have a significant clinical improvement when switched to another drug within the same group, and thus persistence is needed.

Although several studies concluded that antimuscarinic drugs are safe, tolerable, and efficacious in improving the quality of life of patients with OAB, the evidence comparing different drugs is less robust. Some randomized controlled data suggested that extended release oxybutynine and tolterodine may have superior efficacy to the immediate release preparations. In addition, solifenacin is as effective as extended release tolterodine and fesoterodine is superior to it [39–43]. However, the incidence of adverse effects increases with an increasing dose [27]. Table 3 presents characteristics, dosage, side effects, contraindications, and special precautions for the most useful present pharmacological agents.

**Management of Resilient OAB**

Failure in achieving clinical improvement with antimuscarinic drugs is problematic for the patient and challenging for the physician. We believe that referral to a urologist or urologist should not be delayed when a conservative non-pharmacological treatment has not been beneficial or for patients who have received a full dose of 1 or 2 antimuscarinic drugs without a sufficient clinical improvement or in those who stopped medical therapy due to adverse effects.

There are some minimally-invasive second line treatment options to be considered when antimuscarinic drugs are unsuccessful. These include botulinum toxin injections directly into the detrusor muscle, posterior tibial nerve neuromodulation, and sacral neuromodulation. Recently a new β adrenergic drug has shown some benefit.

Botulin toxin, especially Botox (which does not cross the blood brain barrier), is used by direct cystoscopic multiple injections of the detrusor muscle. This selectively blocks presynaptic release of acetylcholine from
nerve endings and as a result decreases contractility, and muscular atrophy is obtained at the injection site. This treatment can be administered in the clinic with local intravesical anesthesia using viscous lidocaine. In a study of 100 cases from 2006, the efficacy and safety of Botox injections in the detrusor muscle to treat patients with idiopathic OAB was evaluated [44]. After 4 to 12 weeks, 88% of patients showed significant improvement in the bladder function with regard to subjective symptoms, quality of life, and urodynamic parameters. However, the effects of this treatment began to diminish after 6 to 9 months and repeat treatments were necessary. In a prospective cohort study it was shown that after multiple injections the improvement was maintained, although the dropout rate after 2 injections was 37% [45]. The most common reasons for discontinuation were insufficient efficacy (13%) and temporary urinary retention (11%) [45]. Intradetrusor injections of onabotulinumtoxin A were also found to be effective in treatment of OAB [18], in a randomized, double-blind, placebo-controlled trial versus anticholinergics [46]. In 2013 the FDA expanded the approved use of Botox (onabotulinumtoxin A) to treat adults with OAB who cannot use or do not adequately respond to anticholinergics [47].

Another approach to resilient OAB is the use of neuromodulation to regulate bladder and pelvic floor function. There is peripheral tibial nerve stimulation and sacral neuromodulation.

An external electrical signal is sent through the tibial nerve retrograde to the sacral plexus, through a small needle inserted into the lower leg near the ankle. This approach, first described in 1983, has low risk and in a retrospective study was shown to have a 60–80% success rate [48]. This treatment which consists of repeated 30 minutes sessions for 3 months was associated with no serious adverse effects and is used in North America and Europe not only to treat the OAB syndrome but also for fecal incontinence.

In more severe cases, S3 nerve root stimulation by an implanted electrical pulse generator may provide relief from frequency-urgency symptoms in patients with severe symptoms of OAB that are refractory to proven behavioral treatment [49]. Surgical implantation of a pulse generator is performed with electrical probes lying in close proximity to the nerves and provides continuous stimulation. van Kerrebroeck et al. [50] evaluated the long-term safety and efficacy of sacral nerve modulation in patients with refractory urge incontinence, urgency frequency, and retention. For patients with urge incontinence, the mean number of voids per day decreased and the mean volume voided per void increased. The average number of catheterizations per day decreased in the urinary retention group and changes were statistically significant. The most frequently reported therapy-related event was new pain, but no life-threatening or irreversible adverse events occurred. The implanted patients, if successful at 1 year, continued to have a successful outcome at a 5 year follow-up.

As the last resort, surgery to augment the size of the bladder by adding to its intraluminal surface area with the interposition of a 10–15 cm loop of the small bowel or stomach, referred to as an augmentation enterocystoplasty, is also of benefit to some patients [51]. However, these are expensive procedures requiring prolonged convalescence and the benefit of reducing urination urgency may be complicated by incomplete emptying of the new bladder, which may necessitate clean intermittent catheterisation on a temporary to permanent basis. Such procedures can produce resolution in some patients [52]. Unfortunately, bowel problems may also appear after augmentation cystoplasty [53].

A new β3 adrenergic drug (Mirabegron) has recently been introduced and has shown some benefit. A better understanding of the pathophysiological mechanism and approval of newer drugs such as mirabegron which are currently under investigation [53, 54] targeting other pathways will enable us to improve our ability to provide a better quality of life to patients with OAB. A systematic literature search was performed on published peer-reviewed articles from 2000 to 2013. Mirabegron is a first-in-class β3-adrenoceptor agonist licensed for the treatment of OAB and has shown to be well tolerated and effective in the treatment of OAB symptoms. Mirabegron 50 mg had similar efficacy to most antimuscarinics with a lower incidence of dry mouth, the most common adverse event reported with antimuscarinics and one of the main causes of discontinuation of treatment. Further head-to-head comparisons between mirabegron and antimuscarinics should be conducted to confirm these results [55].

Among other investigational therapies, neurokinin receptor antagonists, alpha-adrenoceptor antagonists, nerve growth factor inhibitors, gene therapy, and stem cell-based therapies are of considerable interest. The future development of new modalities in OAB treatment appears promising [56–59].

**Conclusion**

The causes of OAB are not completely understood, and symptoms may differ between patients and may be confusing. A complete cure is rare and the management...
of an OAB is a challenging mission for the physician, with the need to tailor treatment options to the patient’s condition. Patient satisfaction and improvement of 50% of global symptoms are achievable goals in many patients and should be targeted.

Antimuscarinic agents remain the most effective and simple option to treat the complex symptoms of OAB, and their pharmacological profiles have been well studied and recently confirmed by a large scale meta-analysis. Additional secondary treatments for resilient OAB have been described.

There is a significant influence of OAB on health-related quality of life. The importance of diagnoses and proper treatment cannot be overemphasized, especially in elderly patients. Practitioners can easily overlook urinary complaints if they not directly queried. We would like to encourage practitioners to give more attention to this issue. In our opinion, familiarity with this condition and basic knowledge about the diagnoses and treatment options can contribute to the general health, which is especially important in elderly patients.

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