

Perspectives on overactive bladder in the elderly population

Masaki Yoshida

Received: 22 April 2009 / Accepted: 26 October 2009 / Published online: 11 November 2009
© Springer-Verlag 2009

Abstract

Introduction Overactive bladder (OAB) represents a disruption in the storage function of the lower urinary tract. This bothersome condition occurs more commonly in the elderly. Since population forecasts predict a worldwide increase in the proportion of people aged over 65 years, it is reasonable to expect that the healthcare burden associated with OAB will also increase. The pathophysiology of OAB in the elderly is thought to be multifactorial, with an abnormality occurring in the nervous supply and/or the structure/function of the urothelium or bladder smooth muscle, leading to bladder hypersensitivity, abnormalities in bladder sensation (urgency) and involuntary detrusor contraction.

Methods A review of some of the key aspects relating to management of this growing population was undertaken.

Results The potential for an elderly patient to present with a number of concomitant conditions means that careful characterization of their overall status is required before deciding on the most appropriate management option for their urinary tract pathology. Lifestyle interventions and pharmacological agents have shown success in treating OAB in the elderly, but as this patient group often has many concomitant conditions they are more likely to be seen by a non-urology specialist.

Conclusions It is therefore important to raise awareness of the condition and an appreciation of its impact among healthcare professionals to ensure the most appropriate care.

Keywords Lower urinary tract symptoms · Overactive bladder · Elderly

Characteristics of overactive bladder in the elderly population

The overactive bladder (OAB) symptom complex represents the bothersome disruption of storage symptoms affecting the lower urinary tract [1]. OAB comprises urinary urgency, with or without urgency incontinence, usually with frequency and nocturia in the absence of other pathologies and occurs with a higher incidence in the elderly. Current population forecasts predict a worldwide increase in the proportion of people aged over 65 years, with the greatest rise being in those aged over 80 [2]. With this in mind, it is reasonable to expect that the healthcare burden associated with OAB and lower urinary tract symptoms (LUTS) will also increase.

The NOBLE study estimated the overall prevalence of this condition in the US population at 16.0% in men and 16.9% in women [3]. As the population ages there is an overall increase in prevalence of both OAB with urgency incontinence (wet) and OAB without urgency incontinence (dry), as shown in Fig. 1. However, there are notable sex-specific differences in the prevalence of the different symptoms: OAB dry is more prevalent in men than women (13.6 vs. 7.6%; $P < 0.0001$) and OAB wet is more prevalent in women than men (9.3 vs. 2.6%; $P < 0.0001$) with notable changes in the patterns associated with aging in both sexes. When considering the elderly population (>65 years) the prevalence of both OAB “wet” and “dry” further increases in the male population but not the female population.

The most recent international population-based survey, the EPIC study [4], was conducted in five countries. This survey assessed LUTS in 19,165 men and women and determined the prevalence of OAB at 11.8%. This study used the 2002 ICS definitions [5] for the first time and confirmed previous findings that OAB was equally common in

M. Yoshida (✉)
Department of Urology, Kumamoto Hospital of Japan
Labor Health and Welfare Organization,
3-30-34-1402 Suizenji, Kumamoto 862-0950, Japan
e-mail: akko-maki@umin.net; akkomaki@kumamoto-u.ac.jp

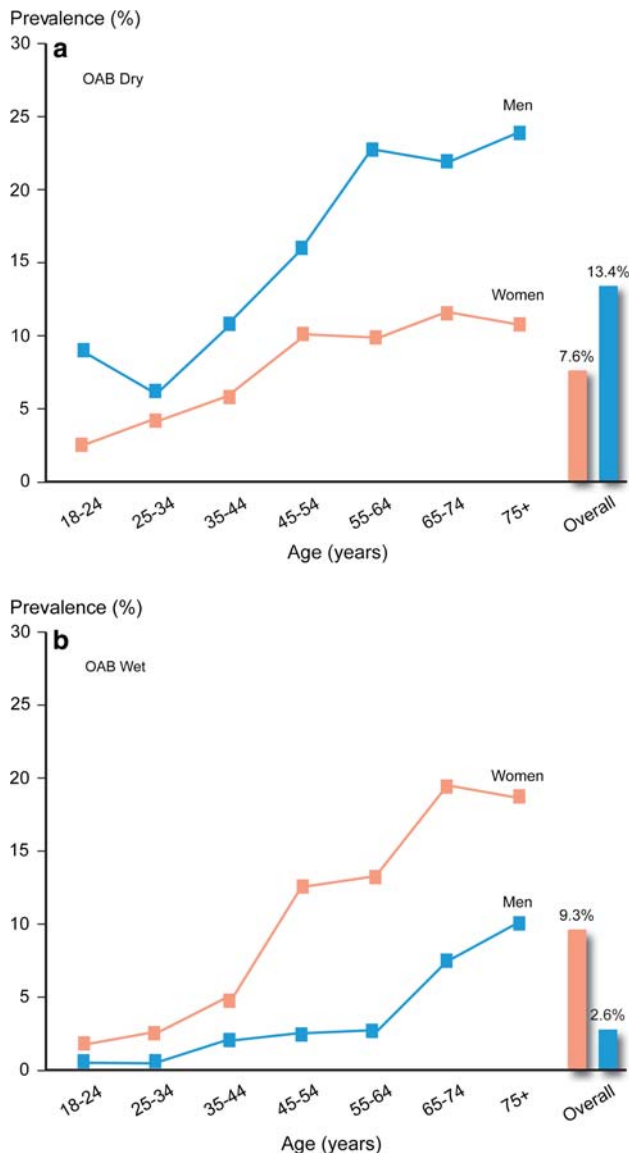


Fig. 1 Prevalence of overactive bladder. Prevalence of OAB “dry” and OAB “wet” with increasing age in men and women (adapted from Stewart et al. [3])

men and women and that its prevalence increased with age, although men have a higher prevalence of OAB symptoms compared with women over 60 years of age.

Epidemiological studies are essential to delineate both medical and social aspects of disease. Homma et al. [6] reported a survey on LUTS in 10,096 Japanese respondents and estimated the incidence of OAB as 12.4% in the general population aged over 40; the prevalence increased with age but there were noticeable differences again by gender and age. The findings from this study are therefore consistent with the other US and European studies. However, the study further reported that health-related quality of life (HRQoL) was compromised in more than half (53%) of respondents. OAB notably affected emotions (42%), sleep/

vitality (37%) and physical capability (34%), but less than one quarter (23%) had visited a medical institution because of their urinary problems.

The occurrence of OAB in the aging population therefore has important quality of life and economic consequences [7–9]. Urinary incontinence, in addition to urgency, may be one of the most relevant symptoms given that other comorbidities may also limit the ability to remain dry [10]. The impact on the quality of life in this population is vast; incontinence remains a risk factor for nursing home placement [11, 12], and links with other conditions, including an increased risk of falls and fractures [13], sleep disorders and depression [14, 15]. The factor of age is in itself likely to exacerbate the problem as elderly men with LUTS report a poorer quality of life than younger men with the same condition [16].

Studies [17–19] have repeatedly shown that although patients consider their daily life to be affected by OAB, few actively seek and hence receive treatment. Furthermore, several factors related to both the patient (low motivation and acceptance) and the physician (lack of time and knowledge) have been reported to compromise the management of urinary tract conditions in the elderly [20].

Bridging the gap between physician and patient

The SURPRISE (*Survey on the Gap in Perception for Overactive Bladder between Primary Care Physician and the Female Patient with Chronic Disease*) survey [21] was initiated on the supposition that many female patients attending primary care clinics for chronic diseases remain untreated for OAB symptoms. The study aimed to: evaluate the present status of OAB symptoms and treatment in patients attending primary care for chronic diseases; determine differences in perception of the condition between doctors and patients; and promote primary care and, thereby, help improve quality of life in patients with OAB.

When primary care doctors in the study were surveyed they estimated the prevalence of OAB to be 9.5%—in stark contrast to the 22.4% prevalence rate derived from patient responses. The rate of OAB increased in older patients with a prevalence of 29.7% being reported for the over 70 years age group. As primary care doctors underestimate the prevalence of OAB so dramatically, this is likely to result in a considerable treatment gap. The study confirmed that less than half of patients with symptoms receive treatment in the primary care setting across all the age ranges surveyed. These data have been validated elsewhere [22].

The SURPRISE study also showed that primary care clinicians’ perception of OAB is at variance with the patient experience; doctors anticipated that nocturia would be the most bothersome symptom, whereas patients considered all

symptoms to be equally problematical. Previous works [8, 9] have suggested that the lack of ability to control urgency and the bother associated with this problem may have a substantial negative impact on QOL. As bother is a patient-specific issue, many factors, including cultural backgrounds and lifestyle may affect “bothersomeness” of individual OAB symptoms.

Approximately 25% of all patients expressed dissatisfaction with their urinary condition in the SURPRISE study rising to 30% of the elderly group. When patient tolerance of their urinary condition was correlated with specific symptoms, urgency was most closely associated with reports of dissatisfaction. This was particularly the case in elderly patients where incontinence and nocturia also showed an increasing association with dissatisfaction rates. When assessed in terms of treatment satisfaction, a lower level of urgency symptoms was strongly related to patients’ perception of treatment benefit. Clearly, initiatives such as this study are needed to inform on how best to promote treatment and thereby improve quality of life for elderly patients.

In the management of OAB, it is important to evaluate which urinary symptoms are particularly bothersome and what degree of resolution of these symptoms is perceived as an acceptable outcome by physicians and by patients. Robinson et al. [23] demonstrated that when considering the acceptability of residual symptoms, following treatment for lower urinary tract dysfunction, there appears to be relatively poor agreement between the views of patients and clinicians. Nevertheless, storage symptoms of urgency and urgency incontinence were felt to be unacceptable by both clinicians and patients, in keeping with previous studies demonstrating a significant impact of detrusor overactivity (DO) on patient quality of life [24].

These data suggest that, in the elderly patient, management of urgency and urgency incontinence are especially important for perception of cure and satisfaction with the management of urinary tract conditions.

The pathophysiology of lower urinary tract function in the elderly

The impact of age is multifactorial

Normal bladder function involves a complex interplay between the urinary tract and nervous system. During filling, the healthy bladder functions as a compliant structure which is capable of relaxation with pressure in the bladder remaining lower than urethral resistance. Normal micturition is initiated by a decrease in urethral resistance and tonic contraction of the detrusor smooth muscle. Symptoms of OAB are frequently attributable to detrusor overactivity

(DO) causing involuntary contraction, which can result from neurogenic or idiopathic alterations in bladder physiology; alterations in the properties of the smooth muscle itself may also result in DO and the associated symptoms of OAB [25]. In contrast, detrusor underactivity may cause incomplete emptying and increased post-void residual urine, and may lead to lower urinary tract symptoms, including urinary incontinence. A combination of detrusor overactivity during the filling phase and detrusor underactivity during voiding is termed as detrusor hyperactivity with impaired contractile function (DHIC) [26]. This condition was reported to occur in one-third of institutionalized elderly patients—being the second most common cause of incontinence in this setting [26]. Therefore, DHIC may have important pathophysiological and therapeutic implications in the elderly.

The pathophysiology of OAB in the elderly is thought to be multifactorial in nature (comorbid medical illness, neurological and psychiatric conditions, medications, functional impairments and environmental factors; Table 1); however, this review concentrates on abnormality occurring in the nervous supply and/or the structure/function of the urothelium or bladder smooth muscle. These changes can lead to bladder hypersensitivity, abnormalities in bladder sensation (urgency) and DO. A number of lines of evidence indicate that age-related physiological changes may lead to the development of OAB.

Age-related changes in bladder physiology

In the elderly, the boundaries between neurogenic and non-neurogenic are uncertain, since age-associated neurogenic diseases such as subclinical cerebrovascular disorders, autonomic neuropathy and chronic brain failure commonly occur. Computerized tomography, magnetic resonance imaging or functional brain imaging sometimes can detect the presence of cerebral lesions in elderly patients with detrusor overactivity [27, 28]. This may distinguish neurogenic from idiopathic detrusor overactivity in a considerable number of older patients.

With regard to age-related detrusor overactivity in humans, Elbadawi et al. [29–31] have proposed a possible explanation based on detailed ultrastructural study. Electron microscopic findings of human detrusor biopsies have revealed a characteristic structural pattern in specimens from the elderly with detrusor overactivity. The main ultrastructural features of this dysfunctional pattern were abundant distinctive protrusion junctions and abutments which it was proposed mediated electrical coupling between the muscle cells and were involved in generation of myogenic contraction in the overactive bladder. In addition, if the patients had impaired detrusor contractility, there was superimposed widespread degeneration of muscle cells and

Table 1 Co-morbid conditions that can cause or contribute to UI in frail elderly persons

Co-morbid medical illnesses	Neurological and psychiatric conditions	Medications	Functional impairments	Environmental factors
Diabetes mellitus	Stroke	Alpha adrenergic agonists	Impaired mobility	Inaccessible toilets
Degenerative joint disease	Parkinson's disease	Alpha adrenergic antagonists	Impaired cognition	Unsafe toilet facilities
Chronic pulmonary disease	Normal pressure hydrocephalus	Angiotensin converting enzyme inhibitors		Unavailable caregivers for toileting assistance
Congestive heart failure	Dementia (Alzheimer's, multi-infarct, others)	Anticholinergics		
Lower extremity venous insufficiency				
Sleep apnea	Depression	Calcium channel blockers		
Severe constipation or fecal impaction		Cholinesterase inhibitors		
		Diuretics		
		Lithium		
		Opioid analgesics		
		Psychotropic drugs		
		Selective serotonin re-uptake inhibitors		

Reproduced in part from 4th international consultation on incontinence; Incontinence in the frail elderly; C. DuBeau (Table 2)

nerve axons, which matched the special group of elderly patients with DO (detrusor overactivity) [26]. However, a subsequent publication failed to show any such association [32].

Age-dependent alterations in detrusor function have also been evaluated. Cystometry in conscious rats shows that bladder compliance decreases with aging [33].

Using animal and human bladder, there are many in vitro studies regarding the effects of age on bladder physiology and pharmacology. Although there were several differences among species, the overall bladder contractile machinery appears intact in the aged bladder; at least in Wistar rats and humans no evidence for specific alterations of contractile responses to muscarinic receptor stimulation has been reported [34–46]. It has been investigated on the possible changes in the roles of M_2 and M_3 receptors subtypes with aging [47, 48]. A study showed no shift in the relative roles of M_2 and M_3 receptors in old as compared to young adult Wistar rat bladders [44]. Similar findings were obtained in both male and female Fisher 344 rats and in female Sprague–Dawley rats, whereas a shift from M_3 to M_2 receptors was reported in male Sprague–Dawley rats [49].

Several studies have explored possible alterations in muscarinic receptor expression or function at a biochemical level. Receptor expression was unchanged in the bladder of aged rabbits [50], whereas it was decreased in those of Wistar rats [44] or humans [51]. In humans, a selective downregulation of M_3 but not M_2 receptors was reported at the mRNA level in the aged bladder, but corresponding protein data were not reported [45, 51].

Change in α_1 -adrenergic receptors have been also studied in animals. The overall data suggest that aging has no major effect on α_1 -adrenergic receptor function in the bladder [36, 39, 40, 50, 52, 53].

Studies on the effect of aging on bladder relaxation by β -adrenergic agonists have yielded inconsistent results. One study reported reduced maximum relaxation by norepinephrine, isoproterenol and forskolin but not by dibutyryl-cAMP against KCl-induced tone in the old animals [54]. Another study detected no alteration in the potency or efficacy of isoproterenol to relax isolated bladder strips [36]. Similar concentration-dependent bladder strip relaxation by isoproterenol, norepinephrine and the β_3 -adrenergic agonists BRL 37,344 and CGP 12,177 in young and old age groups [34] was reported. In human bladder, it has been reported that bladder relaxation responses to isoproterenol and BRL 37,344 and also receptor independently to forskolin and dibutyryl-cAMP were lower in a group of subjects in their mid-sixties than in those in their late twenties [55], indicating that the data may at least partly relate to an overall reduced ability to relax rather than a specific β -adrenergic receptor desensitization.

A binding study reported that the number of β -adrenergic receptors increased in rabbit bladder dome and base with age [50]. In contrast, a study using male Fischer 344 rats reported a decrease in receptor in aged rats [54]. A similar decrease was also reported for human bladder [55].

Taken together these data, the age-related change of autonomic responsiveness (muscarinic or α_1 -adrenergic receptor-mediated contractility or of β -adrenergic relaxation

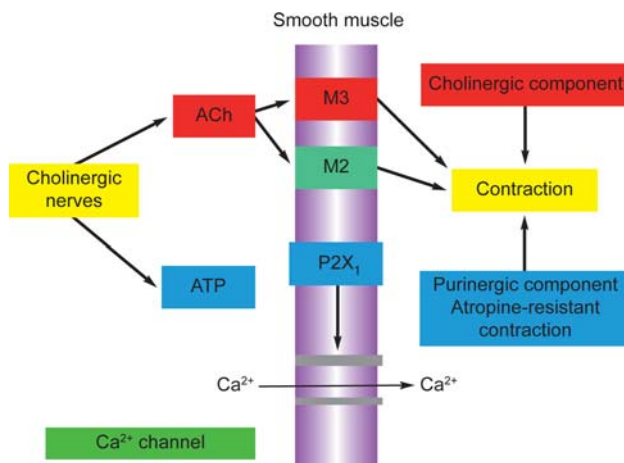


Fig. 2 Neurotransmitter induction of bladder smooth muscle contraction. Stimulation of cholinergic nerves releases both acetylcholine (ACh) and adenosine triphosphate (ATP). ACh will act on muscarinic M₃ and M₂ receptors. ATP will act to increase intracellular calcium that gives rise to the purinergic, atropine-resistant contraction of the detrusor smooth muscle (Adapted from information in Bayliss et al. [57])

of the urinary bladder) may have some contribution to detrusor overactivity and urgency in the elderly.

We previously demonstrated that age-related changes may occur in the neuronal transmissions that modulate bladder function [56]. In general, stimulation of cholinergic nerves leads to the release of both acetylcholine and ATP. Neuronal acetylcholine stimulates the M₃ and M₂ muscarinic receptors, leading to contraction of detrusor smooth muscle and the bladder as summarized in Fig. 2 [57].

In addition there is likely to be an atropine-resistant (purinergic) component to bladder smooth muscle contraction, whereby ATP causes stimulation of P2X₁ receptors that activate calcium channels and cause calcium influx into smooth muscle cells. It has been suggested that purinergic neurotransmission triggers bladder contraction, with cholinergic neurotransmission mediating urinary emptying. In the normal bladder it is estimated that the ATP-induced, purinergic component is responsible for less than 10% of bladder contractions.

Our own in vitro studies with human bladder tissue have shown that cholinergic bladder contraction decreases with age, while purinergic contraction increases [57]. Increased purinergic activity in the elderly may be related to symptoms of urgency and the other components of OAB and DO, whereas decreased cholinergic activity may contribute to detrusor weakness. These changes in neurotransmission may be the mechanism behind the combined picture of DO with impaired contraction seen in the aging bladder.

According to these findings, it could be anticipated that age-related changes in bladder physiological pro-

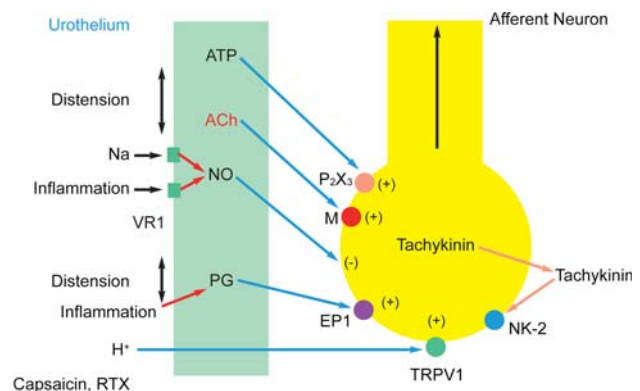


Fig. 3 Bladder urothelial mechano-afferent transduction. (adapted from Yoshida M et al. [62])

cesses may affect the efficacy of OAB treatments in elderly patients; however, the data do not support this hypothesis. A study by Zinner et al. [58] evaluated the use of the muscarinic receptor antagonist tolterodine (targeting M₂ and M₃ receptor types) and showed no significant difference in the mean reduction in incontinence episodes per week or symptoms of urgency when comparing older (≥ 65) and younger (< 65) patients. Comparable efficacy in older and younger patients has also been demonstrated for the muscarinic receptor antagonists darifenacin [59] and solifenacin [60, 61]. Clinical findings have shown solifenacin to be effective in reducing the incidence of urgency, incontinence, micturition symptoms and to increase voided volume in the elderly. These studies indicate that age-related physiological changes in the bladder do not compromise the efficacy of antimuscarinic agents at ameliorating the symptoms associated with this condition.

The relevance of the bladder urothelium

Recently, important functions of the bladder urothelium have been brought to light. The urothelium releases a variety of chemical mediators (ATP, prostaglandins, tachykinins, vasoactive intestinal polypeptide and nitric oxide) following bladder distension or other stimuli, which modulate signaling through afferent C neurons as summarized in Fig. 3 [62]. In particular, a non-neuronal cholinergic system present in the urothelium/suburothelium has been shown to mediate acetylcholine release from stretched human bladder tissue (non-neuronal ACh) [63].

Recent reports had demonstrated that non-neuronal ACh release may contribute to various pathophysiologic conditions. In our study, non-neuronal ACh release increased and was significantly greater in stretched bladder strips with intact urothelium when compared with those without urothelium. The release was also related to the degree of stretch (elevation of resting tension) and age of the bladder

tissue donor. We hypothesize that an increase in the resting tension of bladder strips represents a condition similar to the distension of the bladder wall during the storage phase of the micturition cycle. Thus, it could be postulated that during the storage phase there is ongoing stimulation of detrusor tone due to ACh release from non-neuronal sources such as the urothelium.

Non-neuronal ACh from the urothelium may subsequently enhance the muscarinic receptor-mediated myogenic contractile activity of the detrusor, which may already be increased in patients with DO [62]. This increased myogenic activity may, in turn, increase the firing of afferent nerves and contribute to OAB symptoms. It is also possible that non-neuronal ACh directly acts on afferent nerves to activate bladder sensation.

There is limited evidence to suggest that muscarinic receptors are present on the urothelium, suburothelium and afferent terminals that supply the bladder. Hawthorn et al. [64] reported a 1.5 times greater number of muscarinic receptors in the urothelium than in the smooth muscle layer in the pig bladder. A recent publication by Mansfield et al. [65] also demonstrated a high density of M₂ muscarinic receptors in the human bladder mucosa. Furthermore, Mukerji et al. [66] reported that M₂ and M₃ immunoreactive staining was present in human detrusor, myofibroblast-like cells, the nerve fiber bundle, and the dorsal root ganglion of small and medium sensory neurons in the suburothelium. These muscarinic receptors could be targets for non-neuronal ACh produced by the urothelium.

Detrusor overactivity and treatment mechanisms

DO, the prevalence of which increases with age, is the main underlying cause of OAB symptoms. However, in older individuals sphincter function, urine output and sensation may modify the clinical manifestations of DO. Certainly, DO is linked with a decrease in bladder capacity and increased bladder sensation [67, 68].

Muscarinic receptor activation is involved in DO and is, therefore, the most common drug treatment target for OAB. It is supposed that antimuscarinic drugs act mainly during the storage phase of the micturition cycle, by increasing bladder capacity and decreasing urgency [69, 70]. During the storage phase, there is normally no parasympathetic nerve activity [71]. However, increased non-neuronal ACh release during storage is thought to stimulate DO and thereby contribute to OAB. It is, therefore, possible that antimuscarinic drugs have inhibitory effects on muscarinic receptors activated by non-neuronal ACh. Our studies [63] may also provide useful information about the mechanism of action of antimuscarinic drugs during the storage phase.

Considerations for the management of overactive bladder in the elderly

A number of factors complicate both the diagnosis and management of OAB in the elderly; therefore, a clear evaluation process to achieve a differential diagnosis is important. These factors are associated with a general deterioration in physical and cognitive function and the requirement for medications to treat concomitant conditions. Coexisting conditions that need consideration during the management of OAB are numerous and include (but are not limited to) cardiovascular conditions, neurological disease, dementia and sleep disorders. Cognitive impairment is an important issue when considering the use of pharmacological treatment of OAB, particularly as there is a spectrum of disability that can range from age-related cognitive impairment to true dementia which increases with age [72].

The potential for an elderly patient to present with a number of concomitant conditions means that careful characterization of their overall status is required before deciding on the most appropriate management option for their urinary tract pathology. As elderly patients often have many concomitant conditions they are more likely to be seen by a non-urology specialist. It is, therefore, more important to increase the awareness and depth of understanding of OAB in this growing patient group.

Maximizing treatment options

Effective OAB management in older patients, using a combination of non-pharmacological and pharmacological approaches, is dependent on an accurate diagnosis with a comprehensive medical history and medical/neurological examinations, including urinalysis, use of a voiding diary, details of current drug regimen along with additional special assessments in certain patient groups.

Non-pharmacological therapies, such as behavioral modification [73], may offer some symptomatic benefit and should be implemented in all patients with OAB. The older patient or their healthcare provider should also be encouraged to implement strategies such as fluid management and alterations in diet, avoidance of bladder irritants alongside bladder retraining, pelvic floor exercises and where appropriate pre-emptive or prompted voiding. The author of a recent review [74] also suggested that, in his opinion, care should be taken to ensure older patients do not reduce their fluid intake excessively, as chronic dehydration and increased urine concentration can irritate the bladder wall and worsen symptoms.

Antimuscarinic therapy, with or without behavioral therapy, currently represents the standard of care for patients with OAB [75]. Data have been presented on the efficacy and tolerability of some therapeutic agents in older patients,

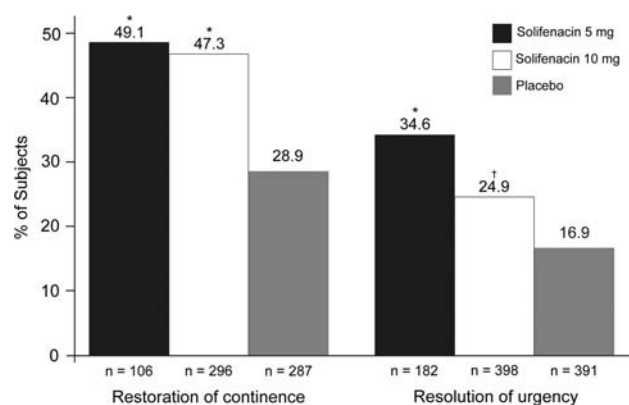


Fig. 4 Resolution of urgency and restoration of continence of the elderly in the treatment with solifenacin. Proportion of elderly subjects with overactive bladder syndrome achieving restoration of continence or resolution of urgency at the end of the 12-week, double-blind studies of solifenacin 5–10 mg. * $P < 0.001$ versus placebo; † $P < 0.01$ versus placebo. (adapted from Wagg et al. [61])

including tolterodine [58], darifenacin [59], solifenacin [60, 61], trospium [76] and transdermal oxybutynin [77]. Pooled analysis of data from over a thousand patients with a mean age over 70 years using solifenacin shows a clear link between the resolution of urgency and restoration of continence (Fig. 4) [61].

When selecting an antimuscarinic agent for the management of OAB in an older patient, consideration should be given to: evidence of clinical efficacy; the frequency of anticholinergic adverse events such as dry mouth; the likelihood of detrimental CNS effects (including cognitive impairment [78] and sleep disturbance); and the potential for interaction with ongoing pharmacotherapies. In higher-functioning nursing home residents, recent evidence on dual use of anticholinergics and cholinesterase inhibitors has suggested some functional decline with combined treatment compared with the use of cholinesterase inhibitors only [79]. Many medications have anticholinergic properties, and thus the potential for additive effects must be taken into account. Biotransformation by the cytochrome P450 (CYP450) system is an important step in the elimination of a large number of agents, although the extensive literature base of this is outside the scope of this article. Critical also are the pharmacokinetic changes in older persons in drug absorption, distribution, metabolism and clearance which must be taken into consideration for a patient on polypharmacy.

Conclusion

The prevalence of OAB, and hence urgency, increases with age, with urgency incontinence being a proportionately

greater problem in the elderly population. United Nations estimates indicate that the proportion of individuals aged over 65 years is likely to increase in developed countries from 15% of the population in 2005 to about 26% in 2050 [2]. In certain countries such as Japan this ratio will increase even more dramatically (from 20 to 38%). Hence, in the future, the effective management of conditions such as overactive bladder in the elderly will be a major issue. Better understanding of the pathological changes associated with such conditions will be key to optimizing treatment in this growing patient group.

Conflict of interest statement MY has received support from and participated in studies with Astellas.

References

- Abrams P, Cardozo L, Fall M et al (2002) The standardisation of terminology of lower urinary tract function: report from the Standardisation Subcommittee of the International Continence Society. *Neurourol Urodyn* 21:167–178
- United Nations World Population Prospects, 2006 Revision. <http://esa.un.org/unpp/index.asp>
- Stewart WF, Van Rooyen JB, Cundiff GW et al (2003) Prevalence and burden of overactive bladder in the United States. *World J Urol* 20(6):327–336
- Irwin DE, Milsom I, Hunskaar S et al (2006) Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. *Eur Urol* 50(6):1306–1315
- Abrams P, Cardozo L, Fall M et al (2003) The standardisation of terminology in lower urinary tract function: report from the Standardisation Sub-Committee of the International Continence Society. *Urology* 61(1):37–49
- Homma Y, Yamaguchi O, Hayashi K et al (2005) An epidemiologic survey of overactive bladder symptoms in Japan. *BJU Int* 96:1314–1318
- Abrams P, Kelleher CJ, Kerr LA et al (2000) Overactive bladder significantly affects quality of life. *Am J Manage Care* 6(Suppl 11):S580–S590
- Coyne KS, Payne C, Bhattacharyya SK et al (2004) The impact of urinary urgency and frequency on health related quality of life in overactive bladder: results from a national community survey. *Value Health* 7:455–463
- Currie CJ, McEwan P, Poole CD et al (2006) The impact of the overactive bladder on health-related utility and quality of life. *BJU Int* 97:1267–1272
- Wagg A, Cohen M (2002) Medical therapy for the overactive bladder in the elderly. *Age Ageing* 31:241–246
- Thom DH, Haan MN, Van Den Eeden SK (1997) Medically recognised urinary incontinence and risks of hospitalisation, nursing home admission and mortality. *Age Ageing* 26:367–374
- DuBeau C (2008) 4th international consultation on incontinence 2008; incontinence in the frail elderly
- Wagner TH, Hu TW, Bentkover J et al (2002) Health related consequences of overactive bladder. *Am J Manage Care* 6(Suppl 19):S598–S607
- Brown JS, McGhan WF, Chokroverty S (2000) Comorbidities associated with overactive bladder. *Am J Manage Care* 6(Suppl 1):S574–S579

15. Wong SYS, Hong A, Leung J et al (2006) Lower urinary tract symptoms and depressive symptoms in elderly men. *J Affect Disord* 96:83–88
16. Engstrom G, Henningssohn L, Walker-Engstrom ML et al (2006) Impact on quality of life of different lower urinary tract symptoms in men measured by the short form SF-36 questionnaire. *Scan J Urol Nephrol* 40:485–494
17. Homma Y, Yamaguchi O, Hayashi K, the members of the Neurogenic Bladder Society committee (2006) Epidemiologic survey of lower urinary tract symptoms in Japan. *Urology* 68:560–564
18. Milsom I, Abrams P, Cardozo L et al (2001) How widespread are the symptoms of overactive bladder and how are they managed? A population based prevalence study. *BJU Int* 87:760–766
19. Shaw C, Tansey R, Jackson C et al (2001) Barriers to help seeking in people with urinary symptoms. *Fam Pract* 18:48–52
20. Teunissen D, van den Bosch W, van Weel C et al (2006) Urinary incontinence in the elderly: attitudes and experiences of general practitioners. *Scan J Prim Health Care* 24:56–61
21. Yoshida M, Inadome A, Matsumoto K et al (2009) Overactive bladder in female patients with chronic diseases visiting primary care doctors: effect of age on prevalence and bothersomeness. *LUTS* 1:45–50
22. McGrother CW, Donaldson MMK, Shaw C, Matthews RJ, Hayward TA, Dallosso HM et al (2004) Storage symptoms of the bladder: prevalence, incidence and need for services in the UK. *BJU Int* 93:763–769
23. Robinson D, Anders K, Cardozo L et al (2007) Outcome measures in urogynecology: the clinician's perspective. *Int Urogynecol J* 18:273–279
24. Kelleher CJ, Cardozo LD, Khullar V et al (1997) A new questionnaire to assess the quality of life of urinary incontinent women. *Br J Obstet Gynaecol* 104:1374–1379
25. Brading AF (1997) A myogenic basis for the overactive bladder. *Urology* 50:57–67
26. Resnick NM, Yalla SV (1987) Detrusor hyperactivity with impaired contractile function. An unrecognized but common source of incontinence in elderly patients. *JAMA* 257:3076–3081
27. Griffiths DJ et al (1994) Cerebral aetiology of urinary urge incontinence in elderly people. *Age Ageing* 23:246–250
28. Kitada S et al (1992) Bladder function in elderly men with subclinical brain magnetic resonance imaging lesions. *J Urol* 147:1507–1509
29. Elbadawi A, Yalla SV, Resnick NM (1993) Structural basis of geriatric voiding dysfunction. II. Aging detrusor: normal versus impaired contractility. *J Urol* 150:1657–1667
30. Elbadawi A, Yalla SV, Resnick NM (1993) Structural basis of geriatric voiding dysfunction. III. Detrusor overactivity. *J Urol* 150:1668–1680
31. Elbadawi A, Yalla SV, Resnick NM (1993) Structural basis of geriatric voiding dysfunction. IV. Bladder outlet obstruction. *J Urol* 150:1681–1695
32. Carey MP, de Jong S, Dwyer P et al (1998) Impaired detrusor contractility in women—is there a morphological basis? *Neurourol Urodyn* 17:308–309
33. Kohan AD et al (2000) Effect of aging on bladder function and the response to outlet obstruction in female rats. *Urol Res* 28:33–37
34. Frazier EP, Schneider T, Michel MC (2006) Effects of gender, age and hypertension on β -adrenergic receptor function in rat urinary bladder. *Naunyn Schmiedeberg's Arch Pharmacol* 373:300–309
35. Hegde SS, Mandel DA, Wilford MR et al (1998) Evidence for purinergic neurotransmission in the urinary bladder of pithed rats. *Eur J Pharmacol* 349:75–82
36. Kolta MG, Wallace LJ, Gerald MC (1984) Age-related changes in sensitivity of rat urinary bladder to autonomic agents. *Mech Ageing Dev* 27:183–188
37. Lagou M, Gillespie J, Kirkwood T et al (2006) Muscarinic stimulation of the mouse isolated whole bladder: physiological responses in young and ageing mice. *Auton Autacoid Pharmacol* 26:253–260
38. Lai HH, Bonne TB, Thompson TC et al (2007) Using caveolin-1 knockout mouse to study impaired detrusor contractility and disrupted muscarinic activity in the aging bladder. *Urology* 69:407–411
39. Lluet P, Deplanne V, Heudes D, Bruneval P, Palea S (2003) Age related changes in urethrovessical coordination in male rats: Relationship with bladder instability? *Am J Physiol Regul Integr Comp Physiol* 284:R1287–R1295
40. Lluet P, Palea S, Barras M et al (2000) Functional and morphological modifications of the urinary bladder in aging female rats. *Am J Physiol* 278:R964–R972
41. Ordway GA, Esbenshade TA, Kolta MG et al (1986) Effect of age on cholinergic muscarinic responsiveness and receptors in the rat urinary bladder. *J Urol* 136:492–496
42. Ordway GA, Kolta MG, Gerald MC et al (1986) Age-related change in α -adrenergic responsiveness of the urinary bladder of the rat is regionally specific. *Neuropharmacol* 25:1335–1340
43. Pagala MK, Tetsoti L, Nagpal D et al (2001) Aging effects on contractility of longitudinal and circular detrusor and trigone of rat bladder. *J Urol* 166:721–727
44. Schneider T, Hein P, Michel-Reher M et al (2005) Effects of ageing on muscarinic receptor subtypes and function in rat urinary bladder. *Naunyn Schmiedeberg's Arch Pharmacol* 372:71–78
45. Wuest M, Morgenstern K, Graf EM et al (2005) Cholinergic and purinergic responses in isolated human detrusor in relation to age. *J Urol* 173:2182–2189
46. Yu HJ, Wein AJ, Levin RM (1997) Contractile responses and calcium mobilization induced by muscarinic agonists in the rat urinary bladder: effects of age. *Gen Pharmacol* 28:623–628
47. Braverman AS, Luthin GR, Ruggieri MR (1998) M_2 muscarinic receptor contributes to contraction of the denervated rat urinary bladder. *Am J Physiol* 275:R1654–R1660
48. Braverman AS, Legos JJ, Young W et al (1999) M_2 receptors in genito-urinary smooth muscle pathology. *Life Sci* 64:429–436
49. Ruggieri MR Sr, Braverman AS (2006) Regulation of bladder muscarinic receptor subtypes by experimental pathologies. *Auton Autacoid Pharmacol* 26:311–325
50. Latifpour J, Kondo S, O'Hollaren B et al (1990) Autonomic receptors in urinary tract: sex and age differences. *J Pharmacol Exp Ther* 253:661–667
51. Mansfield KJ, Liu L, Mitchelson FJ et al (2005) Muscarinic receptor subtypes in human bladder detrusor and mucosa, studied by radioligand binding and quantitative competitive RT-PCR: changes in ageing. *Br J Pharmacol* 144:1089–1099
52. Lluet P, Salea S, Rbiere P et al (2003) Increased adrenergic contractility and decreased mRNA expression of NOS III in aging rat urinary bladders. *Fundam Clin Pharmacol* 17:633–641
53. Takahashi S, Moriyama N, Yamazaki R et al (1996) Urodynamic analysis of age-related changes of 1-adrenoceptor responsiveness in female beagle dogs. *J Urol* 156:1485–1488
54. Nishimoto T, Latifpour J, Wheeler MA et al (1995) Age-dependent alterations in b-adrenergic responsiveness of rat detrusor smooth muscle. *J Urol* 153:1701–1705
55. Li G, Li K, Li Z et al (2003) Age-dependent changes in β -adrenoceptor function in human detrusor and possible mechanisms. *Chin Med J* 116:1511–1514
56. Yoshida M, Homma Y, Inadome A et al (2001) Age-related changes in cholinergic and purinergic neurotransmission in human isolated bladder smooth muscles. *Exp Gerontol* 36:99–109
57. Bayliss M, Wu C, Newgreen D et al (1999) A quantitative study of atropine-resistant contractile responses in human detrusor smooth

- muscle, from stable, unstable and obstructed bladders. *J Urol* 162:1833
58. Zinner NR, Mattiasson A, Stanton SL (2002) Efficacy, safety, and tolerability of extended-release once-daily tolterodine treatment for overactive bladder in older versus younger patients. *J Am Geriatr Soc* 50:799–807
 59. Foote JE (2004) Darifenacin, an M_3 selective receptor antagonist (M_3 SRA), is effective and well tolerated in elderly patients with overactive bladder. *J Am Geriatr Soc* 52(S1):A321
 60. Chapple CR, Cardozo L, Steers WD et al (2006) Solifenacin significantly improves all symptoms of overactive bladder syndrome. *Int J Clin Pract* 60:959–966
 61. Wagg A, Wyndaele JJ, Sieber P (2006) Efficacy and tolerability of solifenacin in elderly subjects with overactive bladder syndrome: a pooled analysis. *Am J Geriatr Pharmacother* 4:14–24
 62. Yoshida M et al (2007) Treatment of overactive bladder: Pharmacological treatment (in Japanese). *Jap J Clin Urol* 61:611
 63. Yoshida M, Inadome A, Maeda Y et al (2006) Non-neuronal cholinergic system in human bladder urothelium. *Urology* 67:425–430
 64. Hawthorn MH, Chapple CR, Cock M et al (2000) Urothelium derived inhibitory factor(s) influences on detrusor muscle contractility in vitro. *Br J Pharmacol* 129:416–419
 65. Mansfield KJ, Liu L, Mitchelson FJ et al (2005) Muscarinic receptor subtypes in human bladder detrusor and mucosa, studies by radioligand binding and quantitative competitive RT-PCR: changes in ageing. *Br J Pharmacol* 144:1089–1099
 66. Mukerji G, Yiangou Y, Grogono J et al (2006) Localisation of M_2 and M_3 muscarinic receptors in human bladder disorders and their clinical correlations. *J Urol* 176:367–373
 67. Griffiths DJ, McCracken PN, Harrison GM et al (2002) Urge incontinence and impaired detrusor contractility in the elderly. *Neurourol Urodyn* 21:126–131
 68. Pfisterer MHD, Griffiths DJ, Rosenberg L et al (2006) The impact of detrusor overactivity on bladder function in younger and older women. *J Urology* 175:1777–1783
 69. Andersson KE, Chapple C, Wein A (2001) The basis for drug treatment of the overactive bladder. *World J Urol* 19:294–298
 70. Andersson K-E, Appell R, Cardozo L et al (2005) In: Abrams P, Cardozo L, Khoury S, Wein A (eds) 3rd international consultation on incontinence, Monaco, June 26–29, 2005, chap 14, Health Publications Ltd
 71. de Groat WC, Downie JW, Levin RM et al (1999) Basic neurophysiology and neuropharmacology. In: Abrams P, Khoury S, Wein A (eds) Incontinence, 1st international consultation on incontinence, Plymouth, Plymbridge Distributors Ltd, pp 105–154
 72. Matthews F, Brayne C (2005) The incidence of dementia in England and Wales; Findings from the five identical sites of the MRC CFA study. *PLoS Med* 2:753–763
 73. Erdem N, Chu FM (2006) Management of overactive bladder and urge urinary incontinence in the elderly patient. *Am J Med* 119(3A):295–365
 74. MacDiarmid SA (2008) Maximising the treatment of overactive bladder in the elderly. *Rev Urol* 10:6–13
 75. Staskin DR (2005) Overactive bladder in the elderly—a guide to pharmacological management. *Drugs Aging* 22:1013–1028
 76. Zinner N, Gittelman M, Harris R et al, for the Trospium Study Group (2004) Trospium chloride improves overactive bladder symptoms: a multicentre phase III trial. *J Urol* 171:2311–2315
 77. Sand P, Zinner N, Newman D et al (2007) Oxybutynin transdermal system improves the quality of life in adults with overactive bladder: a multicentre, community based, randomized study. *BJU Int* 99:836–844
 78. Kay GG, Granville LJ (2005) Antimuscarinic agents: Implications and concerns in the management of overactive bladder in the elderly. *Clin Therapeutics* 27:127–136
 79. Sink KM, Thomas J, Xu H et al (2008) Dual use of bladder anticholinergics and cholinesterase inhibitors: long terms functional and cognitive outcomes. *J Am Geriatr Soc* 56:847–853