

OVERVIEW CONSENSUS STATEMENT

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The first international conference on New Perspectives on the Overactive Bladder, co-chaired by David R. Staskin, MD, and Alan J. Wein, MD, was held in Cambridge, Massachusetts, March 8 to 9, 2002. Conference participants were selected based on their contributions to the basic or clinical understanding of overactive bladder (OAB) and included internationally recognized specialists in urology, urologic surgery, urogynecology, urodynamics, geriatrics, pediatrics, clinical pharmacology, and behavioral science.

The conference was organized with the objective of sharing data and perspectives on new advances in evaluating the pharmacology of treating OAB. The conference format combined brief scientific reports with extended periods of open discussion. Throughout, the conference chairs asked the participants to provide insight on the following key questions:

- Given that there are multiple causes for OAB symptoms, is there a preferred way to define the condition?
- Is OAB a different condition in different patients (eg, children, men, or women, or in those with and without obstruction)?
- What does the sensation of urgency mean?
- Is OAB a myogenic or neurogenic disease?
- How should we diagnose and categorize OAB, both for reversible and irreversible treatment, given its multiple origins and limited diagnostic sensitivity and specificity?
- Is it important to differentiate the type of OAB based on its cause, given that today treatments are similar, regardless of cause?
- Are combination therapies effective in the treatment of OAB?
- What are the other promising therapies for investigation?
- How can we best clinically study new agents to compare and contrast them with existing choices?
- How should other forms of therapy be used?

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At the conclusion of the conference, an executive committee met in a special session to review what had been learned and to formulate a consensus on the directions of future research in OAB.

CONFERENCE SUMMARY

OAB is a highly prevalent disorder that affects the lives of millions of people worldwide. Prevalence of OAB, as distinct from urinary incontinence, is now the subject of well-performed studies through which physicians are beginning to be able to characterize the disorder by various demographic features. Unfortunately, there are few data on the effects of OAB on patient quality of life, the economic burden of OAB treatment, and the effects of various treatments on patients with OAB. An important challenge in treating OAB is to increase awareness of this significant problem worldwide and to impress on other specialists and primary

care physicians the importance of identifying this clinical problem and of managing it in a way that will maximize quality-of-life improvement while minimizing morbidity.

DEFINING OVERACTIVE BLADDER

The Standardization Subcommittee of the International Continence Society (ICS) now recognizes OAB as a "symptom syndrome suggestive of lower urinary tract dysfunction." It is specifically defined as "urgency, with or without urge incontinence, usually with frequency and nocturia . . . if there is no proven infection or other obvious pathology."¹ Much debate surrounds the use of the term *OAB*. There are 2 schools of thought: (1) the term is too general to be used, and (2) the term is a useful symptom syndrome because it is familiar and easy to use for patients, the public, and primary care physicians. The Executive Committee members differed in their opinions on the use of the term *OAB*. Some members believed that the term should be used more inconclusively and others thought the term should be abolished in scientific communications. However, there was consensus among the Executive Committee members that the ICS terms *associated pathology* and *urgency* need to be further defined.

EPIDEMIOLOGY

Little definite epidemiologic information was available on the prevalence of OAB until recently. Nearly all epidemiologic studies in this area have previously focused on urinary incontinence. To determine the prevalence of OAB, investigators in these past studies estimated the number of patients who had urge or mixed incontinence, then, figuring that these patients constituted 33% of the patients with OAB, calculated a number.^{2,3} Estimates using this technique ranged anywhere from 10 million to 20 million in the United States. There are, however, 2 recently completed studies whose methods suggest that they have developed a more accurate estimate of OAB prevalence.^{4,5} In these studies, OAB was defined as a symptomatic diagnosis composed of the symptoms of frequency, urgency, and urge incontinence, occurring singly or in combination, and not explained by metabolic or local pathologic factors. Both these studies found a prevalence of OAB of approximately 16% in adult men and 17% in adult women.

PHYSIOLOGY

Both storage and evacuation of urine from the bladder require coordination of the smooth muscles of the bladder and urethra, and of the striated muscles of the outflow region and pelvic floor, by a

complex neural control system. Immunocytochemical and tracing studies⁶⁻⁸ have revealed that numerous peptides, including substance P, calcitonin gene-related peptide, vasoactive intestinal polypeptide, enkephalins, and cholecystokinin, are localized either alone or in combination in afferent pathways of the bladder and urethra. The receptors on these nerves include vanilloid receptors, purinoceptors, tachykinin receptors, and prostanoid receptors. Extracellular adenosine triphosphate (ATP) has been found to mediate excitation of small-diameter sensory neurons via P2X₃ receptors, and it has been proposed that in the bladder, distension causes the release of ATP from the urothelium.⁹ In turn, ATP can activate P2X₃ receptors on suburothelial afferent nerve terminals to evoke a neural discharge. The clinical implications of signaling both via P2X₃ receptors on suburothelial nerves and via P2X₁ receptors on detrusor smooth muscle remain to be established. However, both P2X₃ and P2X₁ might be targets for pharmacologic intervention.

The central nervous control of micturition also involves many transmitter systems that may be suitable targets for pharmacologic intervention. γ -Aminobutyric acid, dopamine, enkephalin, serotonin, and noradrenaline receptors and mechanisms are known to influence micturition, and potentially drugs that affect these systems could be developed for clinical use. However, a selective action on the lower urinary tract may be difficult to obtain. Traditionally, drugs used for treatment of bladder overactivity have had a peripheral site of action, mainly the efferent (cholinergic) neurotransmission or the detrusor muscle itself. In the normal bladder, muscarinic receptor stimulation produces the main part of detrusor contraction. However, evidence is accumulating that in disease states, such as neurogenic bladders, outflow obstruction, idiopathic detrusor instability, and interstitial cystitis, and in the aging bladder, a noncholinergic activation via purinergic receptors may occur.¹⁰⁻¹² If this component of activation is responsible not only for part of the bladder contractions, but also for the symptoms of OAB, it should also be considered an important target for therapeutic interventions.

PATHOPHYSIOLOGY

OAB is associated with the effects on neurologic control or myogenic activity by a variety of conditions, including (1) neurologic illness or injury, most commonly spinal cord injury, stroke, Parkinson disease, Alzheimer disease, diabetes, spinal stenosis, and multiple sclerosis and similar demyelinating diseases; (2) bladder outlet obstruction that affects sensory and motor aspects of voiding re-

flexes and leads to changes in bladder muscle structure and function; (3) urethral weakness associated with intrinsic sphincter deficiency and pelvic relaxation in middle-aged and elderly women; (4) detrusor hyperactivity and impaired contractility in elderly patients; (5) emergence of new voiding reflexes mediated by unmyelinated capsaicin-sensitive C-afferents, leading to hypersensitivity-induced overactivity; and (6) so-called idiopathic bladder overactivity, which may be caused by some parts of all these categories or factors not yet discovered.

Currently, it is difficult to consolidate our knowledge about OAB and its causes into a single theory. There are simply too many observations that do not easily fit together. It has also been difficult to integrate experimental results on changes in bladder muscle with changes seen in afferent nerve activity after bladder outlet obstruction. Although these changes may occur concurrently in humans and other animals, it is not clear how to integrate our knowledge about them. Additional research into the etiology of OAB is needed.

TREATMENT OF OVERACTIVE BLADDER

Most clinicians would agree that effective treatment of OAB symptoms should be guided by a basic assessment of patients for factors that contribute to the OAB. A particular type of treatment that has been used for decades to treat urge incontinence and other symptoms of OAB is behavioral modification. Perhaps the earliest form of behavioral modification was the bladder drill, an intensive intervention that was usually conducted on an inpatient basis. Bladder drill procedures imposed a lengthened interval between voids to establish a normal frequency of urination and were purported to result in normalization of bladder function. Bladder training is a modification of bladder drill that is conducted more gradually on an outpatient basis and has resulted in significant reduction of incontinence in older, community-dwelling women. Multicomponent behavioral training is another form of behavioral treatment that includes pelvic floor muscle rehabilitation, and focuses less on voiding habits and more on altering the physiologic responses of the bladder and pelvic floor muscles. Biofeedback or other teaching methods can help patients learn to inhibit bladder contraction using pelvic floor muscle contraction and other urge suppression strategies.

There are also pharmacologic agents for the treatment of OAB, including darifenacin (clinical trials are currently under way to determine the effectiveness of darifenacin in treating OAB), hyoscyamine oxybutynin, propiverine, propantheline, solifenacin (in development Phase III), tolterodine, and trospium. Pharmacologic therapy is currently based on the use

of muscarinic receptor antagonists. Bladder contraction is largely regulated by the stimulation of muscarinic receptors. Hence, blocking these receptor sites will cause less frequent and forceful bladder contractions, allowing improved bladder filling and reduced urge incontinence. Although M₂-muscarinic receptors are the predominant cholinoreceptor present in urinary bladder, the smaller population of M₃-receptors appears to be the most functionally important because they mediate direct contraction of the detrusor muscle. M₂-receptors may modulate detrusor contraction by several mechanisms and may contribute more to contraction of the bladder in pathologic states, such as bladder denervation or spinal cord injury. Prejunctional inhibitory M₂- or M₄-receptors and prejunctional facilitatory M₁-muscarinic receptors in the bladder have also been reported, but their relevance to the clinical effectiveness of muscarinic antagonists is unknown.¹³⁻¹⁵ Future research is necessary to determine whether subtype-selective or nonselective muscarinic antagonists will be more clinically effective in treating OAB. The holy grail of treatment for antimuscarinics and all other therapy is uroselectivity.

Pharmacologic agents may be affected by the mode of delivery. Drug delivery systems can enhance or improve the therapeutic index of an agent by altering the pharmacokinetic properties and bioavailability of the drug. In the case of antimuscarinic agents, oral, transdermal, and alternative systems have been used to modify pharmacokinetic properties so that bladder contractility is reduced and adverse events are minimized. Currently, extended-release formulations of oxybutynin and tolterodine provide convenient, once-daily dosing and treat OAB effectively with fewer adverse effects than immediate-release formulations. Other drug delivery systems and agents, such as the S-isomer of oxybutynin, may also provide new treatments for OAB.

In addition, the effect of the gastrointestinal tract on absorption and bioavailability, as well as the relation between the parent drug and the metabolic products, may have a significant effect on the therapeutic index of various compounds. Once-daily products are important for both patient compliance and the regulation of serum levels to avoid the peaks and troughs associated with multiple-dose therapy. Clinical studies—but to date not in vitro binding studies—may support the benefits of altering parent-metabolite ratios for some compounds by avoiding drug absorption in the proximal aspect of the gut.

Additional research also needs to explore whether single-form therapies or combination therapies are more effective in treating OAB. The ubiquity of lower urinary tract symptoms might suggest that these symptoms are caused by similar mechanisms and, theoretically at least, would be

amenable to a single form of therapy. Conversely, the limited kinds and number of lower urinary tract symptoms, and the limited representation of lower urinary tract structures in the central nervous system may mean that several different causes produce similar symptoms, but these are not amenable to a single form of therapy. In addition, although the mechanisms by which behavioral treatments work have not been established, there is some evidence that behavioral and drug interventions may operate by different mechanisms, suggesting that they may have additive effects and combining them may result in better outcomes.¹⁶

Regardless of what treatment is used, the key questions physicians should ask their patients are, "How do you feel," and "Do you wish to continue the treatment?" Admittedly, there are multiple reasons why a patient might feel better or worse. However, overall, patient responses to these questions should serve as the overriding considerations for determining treatment of OAB in the absence of any evidence that would suggest progression from the point of presentation to a more severe form.

CONSIDERATIONS IN SPECIAL POPULATIONS

ELDERLY PATIENTS

The most rapidly growing segment of society in industrial nations is people >85 years of age, and the prevalence of OAB symptoms increases in this age group. Numerous considerations affect the diagnosis and management of OAB in older patients, including neurologic and cardiovascular disorders, musculoskeletal conditions, diabetes, and psychiatric disorders. When treating geriatric patients, clinicians should keep in mind the following: (1) geriatric patients are a heterogeneous group (some are healthy and functional, and some are frail and impaired); (2) comorbid conditions are common and can affect diagnosis and management; (3) factors other than lower urinary tract symptoms often play a role in OAB symptoms and treatment; (4) polypharmacy is common and can contribute to OAB symptoms and/or interact with drug treatment; (5) multiple lower urinary tract conditions may be present in older patients with OAB symptoms; (6) urodynamics, cystoscopy, and other procedures are generally unnecessary in assessing older patients with OAB symptoms, but in patients with hematuria or those who have undergone previous ineffective medical therapy, the level of diagnostic studies should be elevated; (7) treatment choice depends on numerous patient factors and preferences; (8) family and other caregivers are often critical for successful treatment; and (9) the adverse effects of bladder relaxant medication, such as constipation, impaired bladder contractil-

ity, and increased or decreased outlet resistance, can exacerbate underlying geriatric conditions. It is most important to remember that in treating geriatric patients the goals of treatment must be realistic and communicated clearly. In these patients, improvement in quality of life is usually more important than complete cure.

CHILDREN

OAB in children has 3 origins: neurologic, anatomic, and functional. The neurologic causes stem predominantly from a group of spinal abnormalities, collectively called *myelodysplasia*, that affect lower urinary tract function. Anatomic lesions that produce an obstruction at the bladder outlet (ie, posterior urethral valves) will often result in a hyperactive bladder. However, the most common cause of OAB in children is a functional problem. In addition to the underlying functional problem, this condition may be exacerbated by a recurrent urinary tract infection (without an anatomic cause) that initiates inflammatory changes in the detrusor wall, which triggers premature contractions.

The basis for treatment of OAB in children depends on its presentation, underlying cause, status of the kidneys and bladder, and future effects it may have on the upper and lower urinary tract. Early identification of the condition in neurogenic bladder dysfunction, and proactive treatment with antimuscarinic medication and clean intermittent catheterization are warranted to prevent upper and lower urinary tract deterioration. Detrusor hyperactivity in occult spinal dysraphisms suggests an upper motor neuron lesion and the need for early neurosurgical intervention. If acted on early enough, the hyperactivity can diminish postoperatively or at least not get any worse. In addition, the risk of later neurologic deterioration is minimized when spinal cord untethering is undertaken at an early age. Detrusor hyperactivity in patients with sacral agenesis is managed with antimuscarinic medication and clean intermittent catheterization to ensure continence and complete bladder emptying. When treating children with cerebral palsy and detrusor hyperactivity, which occurs only rarely, the amount of anticholinergic medication must be titrated slowly to balance the child's ability to continue to empty the bladder completely with each voluntary void while simultaneously minimizing the premature contractions. Antimuscarinic agents can suppress, to some extent, detrusor contractility attributed to C-fiber stimulation in patients with spinal cord injury, but the most effective therapy is direct inhibition of the fibers with capsaicinlike substances.¹⁷ Treating the hyperactivity in functional disorders requires the judicious use of anticholinergic agents, biofeedback training,

and behavioral modification along with antibiotics in those children who have exhibited urinary infection. Bowel management programs to ensure regular and complete emptying are also needed, when indicated, to help control the detrusor hyperactivity.

MEN

Lower urinary tract symptoms in men may be primarily emptying, filling/storage, or both. Lower urinary tract symptoms may arise from a variety of underlying causes, including benign prostatic hyperplasia, primary bladder neck dysfunction, or abnormal voiding dynamics, and may have a significant component of storage symptoms at presentation. The evaluation and treatment of men with OAB symptoms, including urinary urgency, frequency, and urge urinary incontinence, hinge on the identification and assessment of the magnitude of concomitant lower urinary tract obstruction that may coexist with and be a cause of the presenting symptoms. The complexity of the presenting symptoms and the variety of entities that exist as possible differential diagnostic entities mandate a thorough and diligent evaluation of the lower urinary tract in men so that an optimal therapeutic intervention can be planned. Evaluation is predicated on a complete assessment of voiding dynamics and is best accomplished with urodynamic studies. These studies should provide a complete representation of filling characteristics, pressure and flow criteria, sphincteric activity, and postvoid residual determination. Optimal therapy for these patients may rely on bladder outlet, bladder storage, or a combination of outlet and storage therapy to achieve optimal symptomatic response. Patients with coexistent OAB and benign prostatic obstruction must be carefully managed. There was a consensus that anticholinergic therapy can be used in such patients, although most would choose to address the outlet obstruction first (either by ablation or with drug therapy) and use anticholinergics for residual filling/storage symptoms.

WOMEN

In women of all ages, lower urinary tract infection is the most common cause of irritative urinary symptoms, and midstream urine microscopy and culture should be performed. A chronic problem with residual urine secondary to voiding may also result in symptoms of frequency and overflow incontinence and may be diagnosed using a postmicturition ultrasound scan. In premenopausal women, pregnancy should be excluded. In postmenopausal women, urogenital atrophy can cause lower urinary tract symptoms that may be improved with hormone replacement therapy although there are currently no consensus or a pleth-

ora of data to support this concept. Vaginal administration of estrogen has been shown to be most effective and may be used to supplement systemic replacement therapy. In addition, estrogen replacement may be beneficial in the management of the urge symptoms of OAB as an adjunct to anticholinergic therapy. When investigating elderly women with OAB, special consideration should be given to constipation and fecal impaction, mobility problems, and the loss of independence. Use of concomitant medications, such as diuretics and α -adrenergic blockers, should also be noted and the need for therapy reviewed. In all women, it is mandatory to exclude other causes of lower urinary tract dysfunction before beginning treatment with anticholinergic therapy. Failure to take into account concomitant pathologic conditions, such as poorly controlled diabetes mellitus, congestive cardiac failure, urethritis, or urethral syndrome, will lead to overdiagnosis, overtreatment, and, most likely, increased morbidity.

FUTURE STUDY DESIGNS

The Executive Committee firmly believes that pharmacologic studies require precise planning, strict adherence to study design, meticulous attention to study conduct and statistical methods, and straightforward and highly directed formulation of the conclusions that are derived expressly from the data that have been collected. The exact method to achieve this end is often debated among statisticians and experts in study design and by clinicians who interpret the clinical implications. The Executive Committee recommends the following areas be considered in the design of future clinical trials:

- Because previous studies have often excluded the type of patients that geriatricians treat on a daily basis, future studies should be conducted using standard definitions and clearly specified outcome measures that are particularly relevant to the geriatric population.
- Future trials of the functional causes of OAB in children need to take into account the neural maturation process over bladder control.
- Future clinical trials should examine the effectiveness of combining treatment approaches (eg, behavior modification and drug therapy).
- New anatomic targets for therapy need to be explored, with emphasis on how the micturition reflex is initiated, how the afferent information is controlled at the central level, and how we can control the efferent part of the micturition reflex.

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