

Overactive Bladder: Defining the Disease

Alan J. Wein, MD

This Special Report supplement to *The American Journal of Managed Care* features proceedings from the workshop, "Overactive Bladder: Examining the Burden of Disease," held December 11 and 12, 1999, in New York, New York and supported by Pharmacia Corporation. The panel included experts and researchers in urology, gynecology, urogynecology, geriatrics, economics, epidemiology, and nursing from the United States and Europe. The panel was convened to discuss available data, both published and unpublished, on the economic, societal, and humanistic burden of overactive bladder (OAB), and to identify areas in which further research is needed.

The need to better establish OAB as a disease entity is clear, because it is a highly prevalent disorder that affects millions of people worldwide. Unfortunately, data regarding the prevalence, economic burden, and quality-of-life aspects of OAB and its treatment are scarce, largely because the current definition of the disease is limited.

Patients who experience involuntary or uninhibited contractions of the detrusor muscle during the storage phase of the micturition cycle are considered to have OAB. The condition is characterized by the symptoms of an increased number of micturitions (frequency), a strong desire to void (urgency), or in its most severe form, urge incontinence. The amount of urine loss may be large, because the bladder often empties completely.

Etiology of Overactive Bladder

To begin to understand the pathology of OAB, it is necessary to review the normal physiologic functioning of the lower urinary tract, which is composed of the bladder, urethra, and the supporting muscles and ligaments. The bladder is a highly elastic structure that is maintained under relatively low pressure, even as it fills with increasing amounts of urine. The wall of the bladder consists predominantly of detrusor muscle bundles that form a complex network of smooth muscle fibers interspersed with areas of connective tissue. When the bladder is empty, the muscle bundles have no specific orientation, but as the bladder fills, the detrusor muscle bundles stretch and become reoriented, contributing to the bladder's elastic properties.

Nerve fibers from the parasympathetic and sympathetic nervous systems innervate the detrusor muscle. Activation of the parasympathetic nervous system results in detrusor muscle contraction, promoting micturition. In contrast, sympathetic activation results in inhibition of detrusor contraction and an increase in tension in the smooth muscle of the bladder neck and proximal urethra, thereby preventing micturition (Figure 1).¹

The flow of urine through the urethra is controlled by muscle fibers in the bladder neck and by the internal and external urethral sphincters. A longitudinally arranged layer of smooth muscle stretches from the

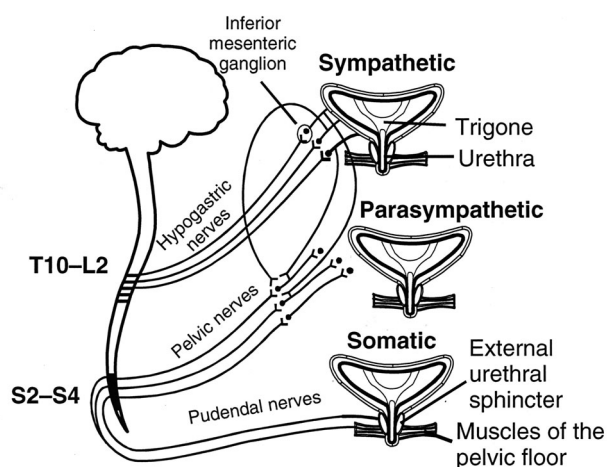
bladder neck to below the external sphincter, which is a highly specialized muscle that contains the highest proportion of slow-twitch fibers of any striated muscle in the body, making it

capable of maintaining sphincteric tone for long periods of time. Although the external sphincter muscle is supported by the muscles in the pelvic floor, pelvic floor muscles alone can only maintain continence for relatively short (ie, 5- to 20-second) periods of time. Nerve fibers from the somatic nervous system innervate the external urethral sphincter (Figure 1). The internal sphincter, which is not a true anatomic sphincter but rather a physiologic and functional one, consists of the smooth muscle of the bladder neck and the proximal urethra. This striated sphincter has 2 parts: the first is the striated muscle, which is concentrated around the proximal portion of the urethra, and the second is the striated muscle that forms part of the outer wall of the urethra extending from this maximal concentration for various lengths to the bladder neck.

In men and women, continence is maintained as a result of the low pressure in the bladder during the storage of urine and the higher pressure of the sphincter at the bladder outlet. Conversely, incontinence occurs when detrusor pressure in the bladder exceeds that in the urethra as the bladder fills with urine.

Neural control of micturition is a complex process, involving communication between many parts of the central and peripheral nervous systems (Figure 1).¹ Motor innervation of the bladder, pelvic floor, and urethral sphincter arises from segments S2 to S4 of the spinal cord, which contain the parasympathetic nuclei responsible for the contraction of the bladder. Sensations of stretch or bladder fullness are conveyed through long neurons from the spinal cord to the pons. Spinal reflex pathways, which are active during bladder filling, facilitate the storage of urine. When the volume of urine in the bladder has reached about half its physiologic capacity, the first sensation of bladder fullness reaches the central nervous system. When the bladder is filled to 75% of

Figure 1. Neural Control and Regulation of the Micturition Cycle at the Lower Urinary Tract Level



Source: Adapted and reprinted with permission from *The Overactive Bladder: A Widespread but Treatable Condition*. Stockholm, Sweden: Sparre Medical Group; 1998.

Table 1. Proposed Factors Involved in the Pathogenesis of OAB

| | |
|--|--|
| Aging | |
| Bladder outlet obstruction | Prostate enlargement |
| Neurogenic | |
| Suprapontine lesions | Dementia, stroke, Parkinson's disease |
| Spinal cord lesions | Multiple sclerosis, spina bifida, diabetic neuropathy |
| Spinal cord injury | |
| Myogenic | |
| Partial denervation of the detrusor muscle | Advanced age, chronic bladder outlet obstruction, idiopathic instability |
| Smooth muscle dysfunction | Bladder outlet obstruction, diabetes |

capacity, the normal desire to urinate is triggered. The ultimate control of micturition, which allows the individual to voluntarily choose an appropriate social setting for voiding, is exerted by the cerebral cortex of the brain and is achieved only during early childhood.

One of the possible causes of the symptoms characteristic of OAB is the inappropriate contraction of the detrusor muscle during the filling phase. Other possible causes of these symptoms include pelvic floor or urethral abnormalities, but the causal relationship has not been clearly defined and the etiology of OAB remains largely unknown. The mechanisms for chronic detrusor overactivity may occur at the neuronal or muscular levels or may be a result of a combination of factors (Table 1).

Certain central pathways may be damaged by neurologic conditions such as Parkinson's disease, multiple sclerosis, spinal cord injury, or stroke and therefore may be responsible for some cases of detrusor overactivity. Dr. William DeGroat, of the University of Pittsburgh School of Medicine, has researched neurologic factors contributing to the pathogenesis of OAB, using experimental models of neural injury, including spinal cord transection, cerebral infarction, and localized brain lesions.² Although the details of his research are beyond the scope of this presentation, they are reviewed elsewhere.²

The myogenic theory of OAB hypothesizes that alterations in the properties of the detrusor myocytes are responsible for unstable increases in detrusor pressure.³ Certain precipitating factors, such as bladder outlet obstruction, can cause a partial denervation of smooth muscle, leading to increased excitability between cells and resulting in coordinated myogenic contractions of the whole detrusor muscle.^{3,4}

Because the possible causative factors are interconnected and no single

theory can account for all instances of OAB, it is most likely that a combination of factors is responsible for the development of the disease.

Workshop colleague Dr. Walter Artibani has shared results from his recent study, which show that age may be an important factor in the progression of OAB (unpublished observations). In a retrospective chart review with corresponding personal interviews conducted at the Institute of Urology in Padova, Italy, 52 patients ranging in age from 5 to 78 years who had urodynamically defined OAB received oral pharmacotherapy for OAB for 8 to 17 months and were followed for a mean of 9 years. The results are summarized in Table 2. In younger patients (ie, those 5 to 20 years of age), 92% were cured and 8% improved with no cases remaining the same or worse. With increasing age, there was a tendency for symptoms to remain stable, with some worsening in patients older than 40 years of age. Dr. Artibani has suggested that in younger patients the

Table 2. Results of a Long-Term (9-year) Follow-up in 52 Patients With Urodynamically Defined OAB

| Outcome | Number (%) of Patients Achieving Result in Indicated Age Range (years) | | | | Total Number of Patients (%) |
|-----------|--|---------|--------|--------|------------------------------|
| | 5-20 | 21-40 | 41-60 | > 60 | |
| | n = 26 | n = 10 | n = 12 | n = 4 | N = 52 |
| Cured | 24 (92) | 5 (50) | 1 (8) | - | 30 (58) |
| Improved | 2 (8) | 1 (10) | 4 (33) | 1 (25) | 8 (15) |
| Unchanged | - | 4 (40)* | 4 (33) | 2 (50) | 10 (19) |
| Worsened | - | - | 3 (25) | 1 (25) | 4 (8) |

Source: W. Artibani, unpublished observations.

*Two women were diagnosed with multiple sclerosis during the follow-up period.

regression of disease may be spontaneous, and pharmacotherapy may possibly shorten the time to regression. In adults, spontaneous regression is not evident; rather, the disease tends to remain stable and symptoms may wax and wane over time, but they generally reappear or progress with age. He also has noted that multiple sclerosis was diagnosed in 2 women whose symptoms remained unchanged after pharmacotherapy, illustrating the probable neurogenic cause of OAB in these patients. Dr. Artibani acknowledges that the small patient population and the retrospective nature of this study limit its conclusions but stresses the need to further evaluate disease progression and the impact of treatment on the long-term outcome.

The Need to Redefine the Disease

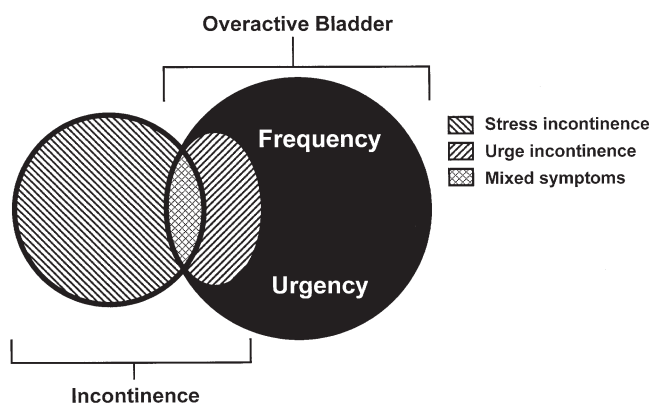
In 1988, the International Continence Society (ICS) defined OAB as “a disorder of bladder filling and urine storage characterized by the presence of involuntary bladder contractions while the patient is attempting to inhibit urination.” This definition subdivides OAB into 2 subtypes,

based on results obtained from urodynamic (cystometric) testing. The causative factors are detrusor hyperreflexia (if the condition is the result of neurologic disease such as multiple sclerosis, stroke, or Parkinson’s disease) and detrusor instability (if no neurologic disease exists). Based on this definition, patients who have symptoms of OAB but no cystometrically observed evidence of detrusor instability during the storage phase are said to have sensory urgency.

There are several reasons why the ICS definition of OAB is not adequate for use in clinical practice. First and foremost is the requirement, based on this definition, for the use of cystometry to make the diagnosis of OAB. Cystometry is an invasive diagnostic test that requires administration and evaluation by skilled and trained specialists. Because of the high worldwide prevalence of patients with symptoms of OAB, it is neither necessary nor economically feasible for all patients to be initially evaluated by specialists using cystometry.⁵ In addition, as the technical sophistication required to perform cystometry increases so does the ability to measure involuntary bladder contractions. In fact, with ambulatory urodynamic studies, approximately 60% of patients tested will have involuntary bladder contractions, regardless of the presence of symptoms. However, only those with symptoms of frequency, urgency, or urge incontinence that occur singly or in combination would receive a diagnosis of OAB.

Symptoms of frequency and urgency that occur in the absence of urge incontinence are very common, accounting for approximately two thirds of those reported by patients with OAB. According to a survey conducted by SIFO Research and Consulting AB in 6 European countries, 85% with OAB symptoms reported frequency as a bothersome symptom, whereas 54% reported urgency and only 36% reported urge

Figure 2. Mixed Symptoms in OAB



incontinence as the bothersome symptoms.⁶ Patients with symptoms of urgency and/or frequency in the absence of incontinence have not been considered to have a genuine medical condition, and they are not referred to a specialist for diagnosis. As a result, they rarely receive treatment. However, even without experiencing incontinence, many people are negatively affected by symptoms of frequency and urgency. Symptoms can be associated with discomfort, embarrassment, and loss of confidence, causing its sufferers to withdraw from social and physical activities. Consequently, these symptoms, even in the absence of leakage, can significantly impair a person's quality of life and therefore mandate treatment.

Furthermore, there is no clinical relevance for distinguishing between neurogenic and non-neurogenic etiologies when defining OAB, because most treatment approaches would not differ on the basis of etiology. In addition, the current definition does not address how the pelvic floor or urethral behavior may contribute to the problem.

Alternatively, OAB can be defined on the basis of symptomology, making the disease and its treatment more patient- and primary care-friendly. As a result, a reasonable definition of OAB is that it is a chronic condition comprised of the symptoms of frequency, urgency, and urge incontinence that occur either singly or in combination, which are not explained by local pathologic or metabolic factors. To further characterize the symptoms, *frequency* is defined as emptying the bladder more often than 8 times per day, and *urgency* is defined as a sudden, strong desire to urinate. Incontinence that occurs after the sensation of impending leakage of urine is termed *urge incontinence*, whereas bladder contraction

that occurs without warning or sensation (eg, as in a patient with a spinal cord injury) is considered *reflex incontinence*. *Stress incontinence*, or leakage of urine as a result of increased intra-abdominal pressure such as lifting, sneezing, or running, may occur in combination with other OAB symptoms, but it is not part of the definition of OAB (Figure 2). Symptoms of other conditions that may be mistaken for OAB, such as urinary tract infection and bladder outlet obstruction, can be ruled out

ACRONYM LIST

The following acronyms appear in the pages of this Special Report Supplement:

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|-----------------|---|
| DALY | Disability-adjusted life years |
| Euro-QoL | European Quality of Life (scale) |
| ICD | International Classification of Diseases |
| ICS | International Continence Society |
| KHQ | King's Health Questionnaire |
| MOS SF | Medical Outcome Study Short Form |
| MRI | Magnetic resonance imaging |
| NAFC | National Association for Continence |
| NOBLE | National Overactive BLadder Evaluation (Program) |
| OAB | Overactive bladder |
| PFD | Pelvic Floor Disease |
| PISQ | Pelvic Organ Prolapse/Incontinence Sexual Questionnaire |
| QALY | Quality-adjusted life-years |
| SF-36 | Short Form 36 |
| SHF-12 | Sexual History Form-12 |
| UTI | Urinary tract infection |

by a thorough physical examination by the primary care physician prior to initiating therapy.

A definition based on presenting symptoms of OAB provides a framework to facilitate diagnosis and treatment of it in the primary care setting. By making OAB a more "patient-friendly" disease, primary care (and specialty) physicians and patients can communicate more effectively about what most people consider an embarrassing condition. The availability of a symptom-based definition makes it possible to obtain an *International Classification of Diseases, Revision 10* (ICD-10) classification, which makes reimbursement for healthcare costs, including those for pharmacotherapy, easier to accomplish.

This new symptom-based definition also will be used to evaluate the true epidemiology of OAB. Because most epidemiologic studies have assessed urge incontinence while ignoring symptoms of frequency and urgency, the true prevalence of OAB, when considering all symptoms, is

probably much higher than estimated by previous studies. A urodynamic definition will continue to be necessary for scientific study and to provide specialists with definitive diagnoses in difficult cases.

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