**EXPLORING THE PATHOPHYSIOLOGY OF URGENCY**

William D. Steers, MD, FACS

---

**ABSTRACT**

Although urgency is the hallmark symptom of overactive bladder (OAB), urgency remains imprecisely characterized and incompletely understood with respect to the underlying pathophysiology and its role in diagnosis of OAB. Antimuscarinic, or anticholinergic, agents have been the mainstay of therapy and historically have been associated with reduced frequency and urge incontinence. However, recent evidence suggests that antimuscarinics also increase warning time and reduce urgency. The central role of the urothelium has become increasingly clear. Additionally, cognitive function related to stress and altered mood might play a role in OAB, and corticotropin-releasing factor might have modulatory effects.


---

**QUALITY OF LIFE OUTCOME MEASURES INDICATE THAT URINARY URGENCY REPRESENTS THE MOST BOTHERSOME COMPLAINT FOR PATIENTS WITH OVERACTIVE BLADDER (OAB). YET, CLINICIANS OFTEN FEEL HELPLESS WHEN TRYING TO ERADICATE THIS SYMPTOM. MUCH OF THE SENSE OF CLINICAL FUTILITY DERIVES FROM A LACK OF UNDERSTANDING OF THE UNDERLYING PATHOPHYSIOLOGY OF URGENCY, BEGINNING WITH THE DEFINITION OF URGENCY.**

Authors have ascribed various terms to the definition of urgency, but the definitions have in common the fact that they were written by individuals who most likely never experienced this sensation. As a result, definitions have suffered from a lack of precision. Urge is a normal sensation, which begs the question of whether urgency is pathologic. The sensation that the bladder is beyond normal full capacity might be considered uncomfortable urgency. When queried, many patients state that their discomfort differs from the normal sensation of a very full bladder. On the other hand, dysuria is the complaint of burning during urination and not with filling. Moreover, does the discomfort emanate from the distended bladder or is it a completely different sensation, such as vaginal or suprapubic pain? This is not a moot point because the different types of pain or discomfort might be mediated by different pathways of perception in the brain. The concept of urgency as being related to a full bladder also begs the question of whether urgency truly occurs when the bladder is not full.

Recent studies have provided insights into the pathophysiology of urgency and the recognition that 3 key components influence what patients perceive as urinary urgency. Understanding urgency requires an appreciation of the factors that generate the sensation of urgency, the processes by which the sensation is transmitted to the brain, and the manner in which the brain interprets the sensation. A fourth component may be factors that maintain this symptom beyond the inciting pathology, such as inflammation.

Studies examining urgency are hindered by the lack of consensus about the best measurement of this symptom. Some investigators and clinicians prefer the urinary diary. Others support use of a Likert scale analogous to the scales used to assess pain. In all probability, urgency does not reflect just a reduction in the warning time that precedes the need to void.

---

*Based on a presentation given by Dr Steers at an industry-sponsored satellite symposium held in conjunction with the American Urogynecologic Society/Society of Gynecologic Surgeons 2004 Joint Scientific Meeting.
†Hovey Dabney Professor of Urology, Chair, Department of Urology, University of Virginia Health System, Charlottesville, Virginia.
Address correspondence to: William D. Steers, MD, FACS, University of Virginia School of Medicine, Box 800422, Charlottesville, VA 22908. Email: wds6t@virginia.edu.
THE MICTURITION PROCESS: NORMAL AND IN OAB

During normal micturition, the desire to void increases along a linear slope as the bladder fills toward capacity. The bladder can be emptied at any point along the slope, but the individual maintains the ability to suppress the need to void without great difficulty or discomfort until the bladder reaches capacity. The desire is not associated with an uncontrolled need to urinate. In contrast, the OAB patient with urgency has a reduced intervoid interval and a desperate need to urinate in order to avoid accidental loss of urine. The need to void arises suddenly and unexpectedly and is associated with considerable anxiety. The OAB patient has a need to void that occurs well before that of the individual with normal micturition and well before the bladder has reached capacity for urine storage.

THE PHARMACOLOGY OF URGENCY

Anticholinergics are the most widely prescribed drugs for OAB. The agents have a well-established ability to reduce frequency. However, only recently has evidence accumulated to demonstrate that anticholinergics also have the ability to reduce the pathologic symptom of urgency. Recent studies have shown that anticholinergics can increase the warning time before the desperate need to void arises in a patient with OAB and urgency. In the process, urgency itself is reduced by the treatment.

How anticholinergic, or antimuscarinic, drugs reduce urgency is not entirely understood, but several possible explanations exist. Anticholinergics may act directly on the urothelium to antagonize M3 muscarinic receptors and stimulate the release of nitric oxide, a potent vasorelaxant. An indirect influence on afferent neurons is another possibility. Anticholinergics might also influence basal detrusor smooth muscle activity, supported by evidence that physostigmine (an acetylcholinesterase inhibitor) reduces the volume threshold during filling. The drugs also might exert an effect through the central nervous system (CNS), although agents that do not access the CNS are still effective, making a CNS explanation for the anticholinergics’ activity unlikely, as compared with other possibilities.

STORAGE-PHASE EFFECTS

As recently reviewed by Andersson, antimuscarinics have a variety of storage-phase effects that could influence micturition frequency and urgency. Anticholinergic agents have been shown to reduce bladder tone during storage, and they increase bladder filling capacity as documented by cystometry. Basal release of acetylcholine from non-neuronal (urothelial) sources has been documented. The release of acetylcholine during filling increases bladder afferent activity, which might be the principal contributor to OAB.

The urothelium has emerged as a central player because of its chemo- and mechanosensor activities. The urothelium expresses both muscarinic and beta-3 receptors, which influence the activity of nitric oxide synthase. The urothelium also generates signaling activity to afferent nerves in response to distention or luminal content. During the signaling, adenosine triphosphate is released from the urothelium in response to hypo-osmolar urine, irritation, or cellular depolarization, activating purinergic P2x2/3 and/or vanilloid TRPV1 receptors on afferent neurons. Moreover, norepinephrine and capsaicin stimulate release of nitric oxide from the urothelium to modulate detrusor contractility. Finally, stretch induces the release of an inhibitory factor from the urothelium, causing detrusor relaxation.

Collectively, the data indicate that the urothelium is more complex than originally thought. Multiple transmitters, mediators, inhibitors, and receptor systems might be involved in the response to bladder filling. The data suggest that the urothelium is intimately involved in the generation of the sensation of urgency.

TRANSMISSION OF URGENCY SENSATION

Upon generation of the sensation of urgency, transmission of urgency sensation appears to be accomplished by 2 likely suspects: A-delta myelinated fibers and C fibers. In particular, the potential role of C fibers has attracted considerable interest. The adverse effects associated with a severed spinal cord include bladder obstruction and inflammation, both of which are associated with activation of C fibers. Within the context of bladder irritation or obstruction, C fibers are silently recruited. They sprout within the lower sacral spinal cord and form new synaptic connections. The result is a lower threshold for the micturition reflex.

PERCEPTION OF URGE

With respect to perception of urge, brain areas that modulate the perception are distinctly different from
those that lead to appreciation of bladder fullness.\(^9\) Positron emission tomography (PET) scans of healthy individuals show that increased bladder volume is associated with activation of the periaqueductal gray matter, the midline pons, mid-cingulate cortex, and the frontal lobe area. In contrast, increased brain activity related to decreased need to void was associated with activation in a different section of the cingulate cortex, in the premotor cortex, and in the hypothalamus. With both types of activation, the effects could not be attributed to the presence of a urinary catheter. However, in some patients who reported uncomfortable sensations from the catheter, a discrepancy was seen between filling volume and urge, such that they reported high degrees of urge with low bladder volumes. The findings provide fodder for hypothesis generation about the origins of perception in patients with urgency.

**Sensation of Pathologic Urgency**

Electrophysiologic, pharmacologic, and immunohistochemical studies have provided evidence of at least 2 general categories of afferents. These afferents have different encoding of frequency or amplitude for firing. They are also under the control of different transmitters, peptidergic versus nonpeptidergic. The observations raise the question of whether the pathologic sensation of urgency is relayed by different afferents or via different mechanisms.

In our laboratory, we have shown that nerve growth factor (NGF) influences the activity of visceral afferents with respect to sodium channels. An increase or decrease in NGF may alter sodium expression and/or function, based on findings in models of neuropathic pain, denervation, and inflammation. NGF increases expression of the TTX-R sodium channel by C-fiber afferents. Indeed, antibodies to NGF or its receptors reduce bladder overactivity in models of cystitis and obstruction. Resistance of sodium channels to TTX (TTX-R) is conferred by a 2 amino acid mutation in one of 3 alpha subunits. Expression of TTX-R causes lowering of the threshold for afferent firing, burst, and spontaneous (tonic) firing. Thus far, no antagonist selective for the TTX-R channel has been developed. However, antiserum oligodeoxynucleotides blocking the cDNA for the Nav1.8 alpha subunit of one type of TTX-R sodium channel increase bladder capacity and reduce bladder overactivity in models of cystitis and obstruction, each associated in humans with urgency.

**Emotional Stress and Incontinence**

Stress is well known as a trigger for mood disorders. However, stress also can trigger or exacerbate urgency and pelvic pain disorders. Psychologic stress is associated with irritable bowel syndrome, pelvic pain syndromes (including interstitial cystitis and male pelvic pain), and overactive bladder.

Recent studies have helped provide insights into the role the stress might play in OAB. PET studies have shown that the brain areas activated by emotions and pain are also turned on during activation of bladder C fibers.\(^10\) Cognitive and emotional stress signals are known to converge on the central nucleus of the amygdala. The amygdala, hippocampus, and prefrontal cortex demonstrated activation of cFos in response to induced cystitis and when stimulated evoked bladder activity.\(^11\) All of the sites respond to glucocorticoids and contain corticotropin-releasing factor (CRF) nerves.\(^14\) The CRF system is linked to chronic anxiety, melancholic and atypical depression, sleep disorders, addictive behavior, acute and chronic neurodegeneration, and allergic and autoimmune inflammatory disorders.

**Interstitial Cells**

Interstitial cells might also play a role in pathologic urgency. Interstitial cells are not contractile in nature but might act as pacemakers and propagate signals associated with urgency. Interstitial cells are known to respond to cholinergic agonists that are blocked by atropine. Interstitial cells also can induce spontaneous contractions, but whether induction of these contractions is muscarinic in origin has not yet been determined.\(^15\)

**Myofibroblasts**

Finally, myofibroblasts have arisen as potential contributors to urgency. They appear as spindle-shaped, vimentin-positive suburothelial cells in the lamina propria of the bladder. They have close appositions with bare nerve endings. They have been shown to be functionally connected via gap junctions consisting of connexon 43.\(^16,17\)

**Summary**

Conventional wisdom has held that antimuscarinic agents affect OAB by blocking the action of those
efferent nerves that trigger a detrusor contraction. Contemporary thinking now focuses on the interactions between urothelium and smooth muscle and afferent nerves. Multiple mechanisms are likely involving the generation (urothelium, smooth muscle, myofibroblasts, interstitial cells), propagation (afferents), interpretation (CNS), and maintenance (urothelium, interstitial cells) of signals that result in the abnormal perception of bladder discomfort termed urgency.

REFERENCES