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EDITORIAL

Treatment of Urge Urinary Incontinence with Botulinum Toxin A

Urinary incontinence involves the involuntary loss of urine and is widely prevalent in the United States, affecting more than 10 million women. This disorder adversely impacts vulvar and perineal hygiene and can be associated with significant social embarrassment and withdrawal, and can precipitate loss of self esteem. The incidence of urinary incontinence tends to increase as a function of age. Two types predominate: stress and urge, though some women can present with a combination of the two disorders known as mixed urinary incontinence.

The act of micturition involves a complex interplay between the spinal cord, cerebellum, and the pontine micturition center. The cerebral cortex can transmit inhibitory signals to suppress bladder wall contractions. Patients with stress incontinence tend to lose small amounts of urine in response to increases in intra-abdominal pressure, such as with coughing or sneezing. Urinary loss occurs secondary to an acute rise in intravesical pressure which exceeds urethral closure capacity. Patients with urge incontinence typically experience an intense sudden urge to urinate secondary to detrusor muscle overactivity, typically resulting in a large loss of urine often necessitating the habitual use of pads or even diapers.

The majority of cases of urge incontinence are idiopathic. The diagnosis of urge incontinence can be confirmed by characteristic phase changes on subtracted cystometrograms. Urge incontinence can also be induced by spinal cord injuries, brain tumors, Parkinson's disease, chronic diabetes, cerebrovascular accident, and multiple sclerosis. The latter conditions give rise to detrusor hyperreflexia. Many therapeutic interventions are available for the treatment of urge incontinence and exhibit variable success rates. The parasympathetic innervation modulating the micturition reflex utilizes acetylcholine for impulse transmission. At the level of the endplate, acetylcholine binds to muscarinic receptors. Anticholinergic agents such as oxybutynin, oxytrol, tolterodine, and solifenacin succinate are often used to inhibit detrusor muscle contraction. However, because of a fairly high incidence of xerostomia, dry eyes, and constipation, many patients do not tolerate

these medications. Antispasmodics (eg, flavoxate) and tricyclic antidepressants have also been used with limited efficacy. Physical therapy directed at strengthening the levator ani complex of muscles (Kegel exercises and weighted vaginal cone therapy) have demonstrated some therapeutic efficacy. Other approaches include bladder retraining, the use of implanted electrodes for the modulation of sacral nerve function and pelvic floor muscle stimulation, and surgical revision of the bladder with a technique known as augmentation cystoplasty.

In this issue of the *Journal of Applied Research*, Brubaker and coworkers present the design of the Refractory Urge Urinary Incontinence and Botulinum A Injection (RUBI) trial, a prospective, randomized, placebo-controlled trial evaluating the efficacy of intravesical Botulinum A toxin (Botox; Allergan, Inc., Irvine, CA) injection for treating idiopathic detrusor overactivity urge incontinence in women. A number of studies have examined the effect of Botox on detrusor overactivity. This study will be the first to do so in a randomized, placebo-controlled fashion. The primary endpoint is time to failure after the initial Botox injection. Prespecified secondary endpoints include change in frequency of incontinence, improvements in symptom measures and quality of life, and risk for voiding dysfunction necessitating bladder catheterization. A single Botox injection is not expected to be curative as ultimately reinnervation will reestablish the neuronal connections within the detrusor muscle that are etiologic for this disorder.

If successful and if Botox injection is not associated with undo toxicity and adverse event rates, this study may provide a more rigorous and convincing demonstration of the capacity for Botox to at least temporarily reestablish a normal or near normal micturition reflex. Much interest will focus on the magnitude and durability of symptom relief. Additional study will be required to ascertain long-term safety, efficacy, dosing frequency, additive or synergistic benefit when coadministered with other therapies, and whether or not any form of tolerance to repetitive injection develops. It is hoped that this intervention will provide a meaningful alternative to the many women who suffer from urge incontinence that is refractory or incompletely responsive to other interventions. I wish the investigators of the Pelvic Floor Disorders Network much success with this important, well-designed clinical trial.