

Schmid DM, Sauermann P, Werner M, et al. Experience with 100 cases treated with botulinum-A toxin injections in the detrusor muscle for idiopathic overactive bladder syndrome refractory to anticholinergics. *J Urol.* 2006;176:177-185.

## Q Does Botox relieve urinary urgency and urge incontinence?

**A** Yes, but improvements are time-limited. In this series of 100 cases of idiopathic detrusor overactivity treated with botulinum toxin A (Botox), symptoms resolved in 74% of patients with urge incontinence by 4 weeks after treatment, and in 80% of patients by 12 weeks after treatment. Urgency resolved in 72% at 4 weeks and 66% at 12 weeks.

### EXPERT COMMENTARY

**Anne M. Weber, MD, MS**, Program Officer, Female Pelvic Floor Disorders Program, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Md

This fairly large case series helps clarify the potential of Botox to ease symptoms in patients who do not respond to current therapies for idiopathic detrusor overactivity.

Among the first authors to report successful use of Botox for neurogenic detrusor overactivity was a research team from Switzerland led by Brigitte Schurch—the same group that published this case series. Participants met detailed criteria for “overactive bladder syndrome,” as defined by the International Continence Society, with either (1) urodynamically demonstrated nonneurogenic (idiopathic) detrusor overactivity with or without incontinence or (2) hypersensitive bladder with premature filling sensation (even when maximum bladder capacity was normal) and more than 8 voids per 24 hours (urgency–frequency syndrome with or without incontinence).

Participants included 77 women and 23 men, each of whom received 100 U of

Botox diluted with saline and injected at 30 sites in the bladder under cystoscopic guidance, sparing the trigone.

### Risks versus benefits

Adverse events reported in this study included urinary tract infections in 10 patients (10%) and urinary retention requiring intermittent self-catheterization in 4 patients (4%). However, retention was otherwise not well characterized. Mean postvoid residual did not return to baseline values until 9 months after injection.

### Why these data are imperfect

Although the study included both women and men (ratio about 3:1), data were not reported by sex. Moreover, according to the International Continence Society definition, patients with overactive bladder syndrome constitute a heterogeneous group based on urinary symptoms (which may or may not include urge incontinence) and urodynamic findings (which may or may not include detrusor overactivity).

A small percentage of patients had apparent detrusor hypocontractility or acontractility with elevated postvoid residual urine volumes—a group clinically distinct from patients with otherwise “normal” bladder emptying despite symptoms attributed to the detrusor muscle.

### A robust placebo effect is likely

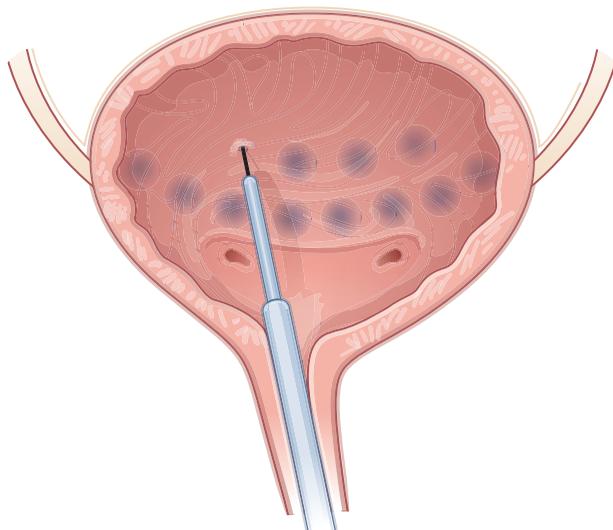
In this open-label series, as in clinical practice, both patients and clinicians expected treatment to be beneficial—raising the possibility of a placebo effect that may explain

### FAST TRACK

**Urgency and urge incontinence resolved in nearly 3/4 of patients 4 weeks after Botox injection**

CONTINUED

## Beyond beauty: Botox for the bladder



Under cystoscopic guidance, Schmid et al injected 100 U of saline-diluted Botox (tinted with indigo carmine to aid in spacing) at 30 sites in the bladder, excluding the trigone. Most women reported temporary relief of symptoms.

IMAGE: RICH LAROCCO

### **FAST TRACK**

**The greatest immediate or short-term risk of Botox for detrusor overactivity incontinence is urinary retention**

part (or most) of the improvement. In many placebo-controlled drug trials involving patients with detrusor overactivity, a relatively large portion of the “treatment effect” may be attributed to the placebo effect; as many as 40% of patients taking placebo report some relief of symptoms.

#### **More data are needed**

To address these gaps in knowledge, especially as use of Botox is being rapidly incorporated into clinical practice, investigators in the NIH-sponsored Pelvic Floor Disorders Network are conducting a randomized, placebo-controlled trial in women with idiopathic detrusor overactivity incontinence. The aim of the trial: to describe the percentage of women whose symptoms resolve, followed by time to recurrence, after treatment with Botox versus placebo, with 1 year of follow-up.

To obtain focused data, inclusion and exclusion criteria were developed to ensure that the population of this triple-blinded study is relatively homogeneous. As the occurrence and consequences of urinary retention have not been well described in prior studies, subjects in the NIH trial are

being carefully assessed for urinary retention. Enrollment should be complete by mid-2007, and follow-up by mid-2008.

#### **Should ObGyns consider Botox for women with intractable symptoms?**

For clinicians experienced with cystoscopically guided injections, Botox might be a reasonable option for highly selected women who are truly refractory to all other treatments for detrusor overactivity incontinence. Such women should understand that Botox is not FDA-approved for this indication and that its use is experimental. No evidence identifies the optimal dose of Botox to be injected cystoscopically for incontinence related to detrusor overactivity. However, dosing information may be forthcoming from a Phase II study being performed by the company that markets Botox (*Allergan*).

#### **Greatest risk is urinary retention**

The most important immediate or short-term risk is probably urinary retention. Although experienced clinicians have estimated a low risk of retention, a much higher rate can be found when the postvoid residual is measured routinely after Botox injection. It still seems likely that Botox-associated retention is temporary, but it may last as long as the effect on symptoms, on the order of several months. Women should be counseled carefully to be sure they understand this.

Further, because urinary sensation may be altered after Botox, women may not experience bothersome symptoms of retention. Nevertheless, more data on possible short- and long-term consequences are needed before changing clinical management of this type of retention (ie, I recommend continuing to treat retention rather than watchful waiting).

Until more data are available on risks versus benefits, I recommend against using Botox in women at high risk for complications associated with partial urinary retention. I would be particularly concerned about elderly women at risk of urinary tract infection that may lead to urosepsis.

CONTINUED

## Q Does prophylactic oophorectomy raise the risk of death?

**A** Maybe. Women who undergo bilateral oophorectomy before the age of 45 have significantly higher mortality, especially when no estrogen is given, than women who do not have their ovaries removed. However, it is unclear whether the relationship between bilateral oophorectomy and increased mortality is causal or merely a marker of underlying risk.

### EXPERT COMMENTARY

**David S. Guzick, MD, PhD**, Dean, University of Rochester School of Medicine and Dentistry, Rochester, NY

A longstanding controversy in gynecologic practice is whether the ovaries should be removed at the time of abdominal hysterectomy. Depending on the patient's age, this question requires the clinician to weigh the risk of subsequent ovarian cancer against the benefit of protection against cardiovascular disease and osteoporosis. During my training in the late 1970s, prophylactic oophorectomy was recommended at the time of hysterectomy if the patient was older than 40 years. The most recent guidelines (1999) from the American College of Obstetricians and Gynecologists<sup>1</sup> state: "The decision to perform prophylactic oophorectomy should not be based only on age; it should be a highly individualized decision that takes into account several patient factors and choices."

#### High risk of heart disease versus low risk of ovarian cancer

Given that the number of women older than 40 who will die of heart disease is vastly greater than the number who will die of ovarian cancer, even a small protective effect against heart disease from the retention of estrogen-producing ovaries might outweigh the potential risk of ovarian cancer. Other variables influence the outcome—eg, ovarian conservation reduces

hip fracture but increases breast cancer—but the main drivers of overall outcome are heart disease and ovarian cancer.

#### How this study explored the issue

One way to address the question of risk is to model various outcomes using simulation methods, as discussed in a recent issue of OBG MANAGEMENT.<sup>2</sup> Another way is to analyze retrospectively the survival across time of women who did or did not undergo oophorectomy. The study by Rocca and colleagues is such an analysis, using data from women residing in Olmstead County, Minnesota, between 1950 and 1987.

Women were included as cases if they had oophorectomy between 40 years and menopause; controls were age-matched women in the database who had survived without oophorectomy to the same index year as the case. Using these criteria, almost 1,100 women were identified who underwent bilateral oophorectomy between 40 years and menopause.

Life-table analysis revealed no difference between cases and controls in survival across time (hazard ratio, 1.05; 95% confidence interval, 0.92–1.20). However, a subgroup of 79 women who had bilateral prophylactic oophorectomy between 40 and 45 years, but who were not given estrogen, were estimated to have twice the mortality of their controls across time. Similarly, a group of 183 women who underwent bilateral oophorectomy for benign disease between 40 and 45 years had a 50% higher mortality. None of the subgroups of women who underwent bilateral oophorectomy after 45 years had increased mortality in comparison with controls.

#### What this means for clinical practice

It is safe to say that data from a randomized, controlled trial will not be forthcoming anytime soon. Therefore, we must rely on the careful analysis of retrospective

Rocca WA, Grossardt BR, de Andrade M, Malkasian GD, Melton LJ III. Survival patterns after oophorectomy in premenopausal women: a population-based cohort study. *Lancet Oncol*. 2006;7:821–828.

### FAST TRACK

**Removing the ovaries before 45 years of age raises mortality—significantly. But why?**

data, as in the study by Rocca et al. From this analysis, 2 recommendations can be drawn:

- **After age 45.** It appears that oophorectomy after age 45 will not alter the subsequent overall mortality risk. For this age group, the decision to remove or retain the ovaries should be made on an individual basis depending on the risk profile and informed patient choice, as suggested by American College of Obstetricians and Gynecologists guidelines.<sup>1</sup>
- **Prior to age 45.** If bilateral oophorectomy is performed, estrogen replacement should be strongly considered. In contemporary practice, if alternatives to estrogen are desired, the patient should be monitored for evidence of preclinical cardiovascular disease and osteoporosis, and appropriate treatment should be initiated, if indicated. ■

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