URINARY INCONTINENCE

Things go better with Burch . . . 3 more drugs for overactive bladder . . . First-line OAB therapy for elderly women . . . Urethral injection of muscle-derived cells

Although urinary incontinence is one of the most common chronic diseases in women, we still don’t understand its pathophysiology, and treatments have been, of necessity, empiric rather than directed at a specific cause. Fortunately, this bleak scenario may be changing, and I think that is the most exciting news about urinary incontinence in 2005.

Urethral deficiency by any name is still a deficiency

Ironically, the most basic description of urinary incontinence may be the most revealing: Incontinence occurs when the urethra cannot stay closed and fails to hold urine in the bladder, where it should be stored until the “right” time and place for emptying. This description applies equally well to women with stress or urge symptoms, but let’s focus on stress incontinence for now.

By that line of thinking, the urethra is deficient in all women with stress incontinence. I believe this to be true, despite the arbitrary label—intrinsic sphincter deficiency, or ISD—that we apply to women with only the most severe symptoms of stress incontinence.

Surgery does not end the quest

Because surgery focuses on eliminating symptoms, it should come as no surprise that incontinence procedures continue to proliferate while we search for the Holy Grail: the perfect surgery that will effectively and durably “fix” the problem without complications or side effects. However, unless we find and correct the underlying problem that gave rise to the incontinence in the first place, we are doomed to fail in our search.

Doom? Failure? Where is the exciting news I promised?

CARE trial underscores efficacy of Burch procedure


If you have an exceptional memory, you will recall that, in this Update on Urinary Incontinence last year, results from the CARE trial were promised in 2006. Good news! Early results are available now, at least a year before expected.
Superior results with Burch changed the course of the CARE study

The CARE trial (Colpopexy And Urinary Reduction Efforts) was designed to
determine the effect of Burch versus no Burch in
women without stress incontinence symptoms but with advanced prolapse who
were undergoing abdominal sacrocolpopexy. The trial was sponsored by the
National Institute of Child Health and Human Development (NICHD) and per-
formed by the Pelvic Floor Disorders Network of investigators from 7 clinical
sites and a central coordinating center.

The original sample size was set at 480
women, to be randomized equally to
Burch or no Burch, with the primary stress
outcome at 3 months after surgery. However, at the first interim analysis,
when about half the sample (232 women) had reached the primary outcome, the
results showed such a striking benefit in the Burch group that the Data and Safety
Monitoring Board for the Pelvic Floor Disorders Network recommended that
enrollment be halted while all women continued to receive scheduled
follow-up. Therefore, in February 2005, enrollment in the trial was closed, with 322 women
randomized to 1 of the 2 arms.

The following results were presented at the annual meeting of the American
Urogynecologic Society in September:

• **Stress incontinence symptoms were reduced** by about half in women after
abdominal sacrocolpopexy (from 44% in the no-Burch group to 24% in the
Burch group).

• **Stress symptom severity improved with Burch.** More women (62%) in the
no-Burch stress incontinence group were bothered by their symptoms, compared to
32% of women in the Burch group.

• **Urge symptoms were no different with Burch.** More surprising, women in both
groups had similar levels of symptoms measured as the urge endpoint, which
included urge incontinence, urgency, frequency, nocturia, or enuresis; or treat-
ment for any of those 5 symptoms. Almost 33% of women in the Burch
group met the urge endpoint, compared with 38% in the no-Burch group (dif-
ference not statistically significant).

• **Serious adverse events were not significantly different** between the 2 groups.

Many more questions will be
addressed with further analysis of CARE
trial data, such as results of urodynamic
testing with and without prolapse reduc-
tion, and the potential for predicting which
subgroup benefits most when Burch is per-
formed. Long-term follow-up data will
address durability of results related to
incontinence and prolapse. Follow-up is
scheduled for 2 years in the CARE trial,
and for up to 10 years in the Extended-
CARE trial.

Efficacy of anticholinergics

_Trospium chloride (Sanctura): another anticholinergic for overactive bladder. The Medical
Letter. 2004;46(1188):63–64._


Three more drugs for overactive bladder
won FDA approval in 2004 and 2005:

• trospium chloride (Sanctura)
• solifenacin succinate (Vesicare)
• darifenacin hydrobromide (Enablex)

According to The Medical Letter, none
appears to offer an advantage over long-acting anticholinergics for overactive bladder.

Despite the proliferation of anticholinerg-
ic drugs for overactive bladder symp-
toms—or perhaps because of it—one
suspects that these medications are not
achieving substantial, long-lasting relief of
symptoms. One study reported that two
thirds of women discontinued therapy
within 4 months. A comprehensive
review of placebo-controlled trials of anticholinergic drugs for overactive bladder estimated that, as a class, even long-acting agents have a very limited effect on symptoms, with approximately 1 fewer incontinent episode and 1 fewer voiding episode per 48 hours.²

Do anticholinergics and dementia drugs mix?


Treatment recommendations

As ObGyns become more active in evaluating and treating women with urinary incontinence, we must stay alert for potential adverse drug interactions.

Ideally, behavioral treatment (scheduled voiding, fluid management, bedside commode) and pelvic muscle training should be first-line therapies in elderly women with overactive bladder.

Anticholinergic drugs should be used with caution, if at all, in women taking cholinesterase-inhibiting drugs for dementia.

3 studies involving the elderly

Cognitive impairment

Observing a population of older adults with dementia, about half treated with cholinesterase inhibitors for their Alzheimer symptoms, Gill et al found that the patients on cholinesterase inhibitors were more likely to start treatment with an anticholinergic drug for incontinence within a year. They theorized that the cholinesterase-inhibiting drugs possibly contribute to new-onset or worsening urinary incontinence, which in turn leads to treatment with anticholinergic agents.

Jewart and colleagues found better performance in patients with Alzheimer disease who were not taking anticholinergic medication for incontinence.

No or mild cognitive impairment

Lipton et al tested cognitive function with darifenacin for 2 weeks and found no difference between immediate- or controlled-release forms of the drug and placebo. However, the study population consisted of volunteers 65 and older with no or mild cognitive impairment and no use of cholinesterase-inhibiting drugs.
IN THE PIPELINE

Urethral injection of muscle-derived cells may restore function


Some exciting news: Dr. Michael Chancellor and colleagues at the University of Pittsburgh and at Cook MyoSite in Pittsburgh are working to bring stem cell research to the clinician’s office, with their studies of muscle-derived cells that can be injected into the urethra. (This technique is well-established and currently used for injection of synthetic or biologic material such as bovine collagen.)

What is remarkable about this type of injection is that the muscle cells not only stay put in the urethra, they appear to integrate into the muscle of the urethral sphincter and differentiate into cells that produce new muscle fibers. Newly functioning muscle improves urethral function and, ideally, will be able to restore continence in women with incontinence.

Technique’s success in rats
Could the same be accomplished with muscle-derived stem cells from humans? At the 2005 meeting of the International Continence Society, Chancellor and colleagues described how they injected human muscle-derived stem cells into the urethras of a nude rat model of stress incontinence (via nerve transection). In the injected rats, leak-point pressure measurements were restored to levels similar to those in a control group of rats.

In addition, immunohistochemistry and histology showed persistence of the human muscle-derived stem cells in the injected rats, versus periurethral muscle atrophy in the rats that had nerve transection but no injection.

Clinical testing underway
Clinical trials of this technology in women are now being performed in Toronto. It will be necessary to show safety and efficacy before the stem cell therapy is made available clinically, but there are a couple of factors in its favor:

• In terms of safety, the risks associated with the current crop of injectable mate-
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