OBG MANAGEMENT

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Drug therapy for incontinence: New agents, new applications

Profiles and practice recommendations for 3 new drugs for urinary incontinence, plus new potential for an "old" medication

Urinary incontinence is more prevalent with age, but it is never "normal." Every woman with bothersome symptoms deserves evaluation and treatment, which can often proceed without exhaustive testing (**TABLE**). In addition, our arsenal of drugs has expanded over the past year, with 3 new medications for overactive bladder and urge incontinence:

- solifenacin (Vesicare)
- darifenacin hydrobromide (Enablex)
- trospium chloride (Sanctura)

We also have evidence that an antidepressant can improve stress incontinence:

- duloxetine (Cymbalta)

The first 3 agents have FDA approval for treatment of overactive bladder and are similar to 2 older anticholinergics, oxybutynin (Ditropan) and tolterodine (Detrol). The newer drugs reportedly have slightly fewer side effects.

Duloxetine has been effective against stress incontinence in clinical trials, and was approved for this purpose in Europe in 2004. In the United States, duloxetine has FDA approval for the treatment of depression, but it is unclear whether it will be approved for stress incontinence.

Oxybutynin vs tolterodine

The "gold standard" for treatment of urge incontinence has long been oxybutynin, originally trademarked as Ditropan but now available in generic form. It is a short-acting spasmolytic and anticholinergic that works by exerting a direct effect on the contractility of bladder smooth muscle and by blocking acetylcholine at muscarinic parasympathetic receptor sites in the bladder.

Unfortunately, its clinical utility is often limited by side effects arising from its influence on other muscarinic receptors:

- dry mouth, due to its effects on the salivary glands
- increased heart rate, due to its effect on the vagus nerve
- constipation from slowed peristalsis of the gastrointestinal tract
- blurred vision from its interference at high doses with the ciliary muscles of the lens of the eye
- occasional drowsiness or confusion, especially in elderly patients, from effects on the central nervous system[1,2]

The intensity of these side effects is directly related to peak serum levels, due to the short half-life of oxybutynin. Extended-release formulations of oxybutynin were developed to reduce the incidence of these effects, and other anticholinergics, such as tolterodine (Detrol LA), followed suit with long-acting formulations of their own.

Dosage. Extended-release oxybutynin is available in 5-, 10-, and 15-mg preparations for once-daily dosing. There also is a

IN THIS ARTICLE

transdermal patch (Oxytrol) that is changed twice weekly and is equivalent to a 5-mg dose of oxybutynin.

Tolterodine is better tolerated but less effective than oxybutynin

The first major competitor to oxybutynin was tolterodine, an anticholinergic agent with a longer half-life and better selectivity for muscarinic receptors in the bladder.[3]

Dosage. Tolterodine was originally given in 1- or 2-mg doses twice per day. The extended-release preparation is available as a single daily dose of 2 or 4 mg.

OPERA: A head-to-head trial. Long-acting oxybutynin (10 mg daily) was compared with long-acting tolterodine (4 mg daily) in the OPERA trial (Overactive bladder: Performance of Extended Release Agents), a 12-week, double-blind, randomized trial involving 790 women.[4] Both drugs reduced the weekly number of urge incontinence episodes to a similar degree, but oxybutynin was more effective at reducing urinary frequency. A larger percentage of participants taking oxybutynin became completely dry during the study (23% vs 16.8%). However, more women taking oxybutynin had complaints of dry mouth.

My clinical experience coincides with these findings. Long-acting tolterodine appears to be better tolerated than equivalent doses of oxybutynin, but the latter usually controls symptoms more effectively.

If symptoms are controlled, no need to change drugs. If a patient is referred to me with well-controlled symptoms on long-acting tolterodine, I see no reason to change the medication. Conversely, symptoms that are still bothersome often respond to a change to long-acting oxybutynin.

Dose titration is possible with both drugs by using different strengths in combination.

New incontinence drugs

Solifenacin

This muscarinic receptor antagonist with improved bladder selectivity entered the US market in 2005.

TABLE

How to evaluate urinary incontinence

1. **Thorough medical history, including assessment of symptoms**
   - What is the predominant complaint—stress or urge incontinence?
2. **Physical examination**
   - General medical conditions, cardiovascular and pulmonary status
   - Documentation of any stress incontinence with a full bladder
   - Documentation of the state of pelvic support and any pelvic organ prolapse
3. **Urinalysis (chemical and microscopic)**
   - Urine culture if urinalysis is abnormal
   - Urinary cytology in women with irritative symptoms, particularly those over 50, with a smoking history, or with hematuria
4. **Measurement of postvoid residual urine volume**
   - Rule out incomplete bladder emptying
   - Postvoid residual urine volume should be <100 mL
5. **Frequency/volume bladder diary**
   - Document 24-hour urine production, number of voids, average voided volume, functional bladder capacity, number of incontinence episodes
6. **Multichannel urodynamic studies**
   - If surgical intervention is considered
   - In cases of previously failed surgery
   - If symptoms and physical findings are discordant or if additional information is needed

Performance in clinical trials. In a double-blind, placebo-controlled trial of male and female patients with symptoms of overactive bladder (urinary frequency with urgency and/or urge incontinence), solifenacin in doses of 5 or 10 mg was superior to placebo in reducing both daily frequency of micturition and daily episodes of incontinence.[5] At the 10-mg dose, the drug was also effective in reducing nocturia.

Among patients who recorded at least 1 episode of urge incontinence on their 3-day bladder diary at the start of the study, 50% became dry during the study using solifenacin at either dose.

Side effects. Predictably, the patients taking the active drug had significantly more complaints of dry mouth, constipation, and blurred vision than those taking placebo—up to 23% of patients on the higher dose noted dry mouth.

How solifenacin compares. The FDA does not require pharmaceutical companies seeking approval of new medications to demonstrate efficacy in comparison with a

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Both oxybutynin and tolterodine reduced urge incontinence, but oxybutynin also reduced urinary frequency

standard treatment already available (such as oxybutynin or tolterodine)—only their efficacy in comparison with placebo. European countries, however, are increasingly requiring such comparisons:

- **versus tolterodine.** Solifenacin at 5- and 10-mg doses was compared with both placebo and extended-release tolterodine (2 mg) in a randomized, controlled, multicenter trial in Europe.[6] Both dosages of solifenacin reduced urgency episodes by 50% or more, compared with a 38% reduction with tolterodine. Incontinence episodes also decreased to a greater degree with solifenacin. However, a relatively low dose (2 mg) of tolterodine was used as a comparison.

Considerable placebo effect. Both studies involved a substantial placebo response: Placebo treatment alone reduced urgency by 33% and episodes of urge incontinence by 40%.

Darifenacin

Like solifenacin, this new drug is a selective M_3 muscarinic receptor antagonist.

Performance in clinical trials. In an international multicenter, double-blind, placebo-controlled trial,[6] patients (85% female) with overactive bladder who took darifenacin (3.75, 7.5, or 15 mg daily) found the drug superior to placebo in reducing the frequency of micturition, increasing bladder capacity, decreasing urgency, and reducing the number of severe incontinence episodes (ie, those that necessitate a change of clothes or protective pads).

Side effects. Anticholinergic side effects such as dry mouth and constipation were more prevalent among patients taking the active medication.

Placebo effect was substantial.

Increased "warning time." A novel study[8] compared a daily dose of 30 mg of darifenacin with placebo, looking specifically at the time from the first sensation of urgency to either voluntary micturition or incontinence, because urge incontinence can be avoided if patients have adequate time to reach the toilet once the urge to void arises.

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Mean, minimum, and median warning times all increased significantly in patients using darifenacin, compared with placebo. Again, adverse side effects (dry mouth, constipation) were greater in the group taking the active drug.

"Me too"? Not all experts believe solifenacin and darifenacin represent improvements in drug therapy for overactive bladder. In the words of Marcia Angel, MD, they are simply "me too" drugs, competing with each other for the same market niche.[9] According to *The Medical Letter on Drugs and Therapeutics*, an independent not-for-profit clearinghouse for pharmaceutical information, "There is no convincing evidence that either solifenacin or darifenacin offers any advantage in efficacy or tolerability over other long-acting anticholinergics for treatment of overactive bladder. Darifenacin may have more potential for adverse drug interactions, but one short study suggested that it might have less effect on cognitive function than other anticholinergics. All of these drugs are only modestly more effective than placebo for this indication."[10]

Trospium

This anticholinergic has been marketed in Europe for several years and was recently introduced in the United States. It is a quaternary ammonium derivative of nortropanol that exerts predominantly peripheral, nonselective, antimuscarinic anticholinergic effects. As with almost all quaternary amines, it is poorly absorbed from the gastrointestinal tract and has only 10% to 15% bioavailability, with a plasma half-life of 12 to 18 hours.

Dosage. The usual dose is 20 mg twice daily.

Side effects. The quaternary amine structure appears to inhibit passage of the drug across the blood–brain barrier and probably accounts for the relatively low incidence of central nervous system side effects. Unlike solifenacin and darifenacin, it exhibits no selectivity for M_3 receptors in the bladder.

No advantage over long-acting anticholinergics. "Trospium appears to offer no advantage over long-acting anticholinergics for treatment of overactive bladder, and its poor absorption from the gastrointestinal tract could be problematic," *The Medical Letter* concluded.[11]

Performance in clinical trials. For a closer look at 1 of the 2 trials the FDA evaluated in approving trospium chloride for the US market, see page 52. The European experience was recently summarized by Hofner and colleagues.[12]

What's in a name? A review of incontinence terminology

Incontinence is usually classified as one of the following:

- **stress** – leakage of urine with physical activity,
- **urge** – leakage accompanied by a strong urge to void; also known as overactive bladder syndrome,
- **mixed** – containing elements of both stress and urge, or
- **other causes** – neurogenic, overflow, or other factors.

Although behavioral interventions such as bladder "retraining" can improve both urge and stress incontinence, the former is often treated with drugs, the latter with surgery.

For details on a simple test to distinguish between stress and urge incontinence, turn to Examining the Evidence, page 14.

Cost vs side effects for overactive bladder drugs

All of the long-acting preparations for overactive bladder have proven more effective than placebo. However, undesirable side effects have led to high rates of discontinuation over the long term.

The new preparations have a better side-effect profile than older medications such as oxybutynin. Now that oxybutynin is available in generic form, however, the new drugs are usually at least 3 times more expensive than short-acting oxybutynin. Although "none of these drugs are as effective as advertisements to the public have suggested" (*The Medical Letter*[11]), nonetheless, pharmacologic therapy is a useful option for women with symptoms of overactive bladder. Most women on these medications for a long time

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Darifenacin increased mean, minimum, and median "warning times," the interval from first urge to urination

tend to take the drugs intermittently, depending on symptoms, or discontinue them because of side effects.

Use non-drug tactics, too

I recommend a bladder behavioral modification program with fluid management and timed voiding or bladder drills, in addition to the drug regimen, for maximum therapeutic benefit.

Treatment of stress incontinence

Stress incontinence is widespread among women of all ages, due to the vulnerability of the anatomical supports of the female urethra and bladder neck. It occurs when the force to which the sphincter mechanism is subjected during moments of exertion exceeds the sphincter's ability to remain closed ("sphincter strength").

Physical therapy sometimes suffices

A wide variety of treatments have been used for this problem. Because urethral closure depends largely on coordinated contractions of the pelvic floor in synchrony with increased intra-abdominal pressure, rehabilitation of the pelvic muscles through structured, supervised programs of physical therapy improves or cures many women.[13]

How drugs affect the urethra

The urethra and bladder neck contain alpha-adrenergic receptors, stimulation of which can increase urethral tone. Conversely, blockade of these receptors can lead to urinary stress incontinence by reducing urethral outlet resistance.[14]

Alpha-agonist drugs are common components of many over-the-counter cold remedies (eg, pseudoephedrine, ephedrine, phenylpropanolamine, etc) and have been readily available. Besides increasing urethral tone, however, alpha-agonists can also raise blood pressure by constricting arteriolar smooth muscle.

In 2000, an epidemiological study[15] of phenylpropanolamine found that use of

this medication raised the risk for stroke, even in young women, and the drug was later removed from the market by the FDA. These events led to a decline in use of such medications for stress incontinence, even for preparations that remain on the market.

How duloxetine works

It is a selective serotonin and norepinephrine reuptake inhibitor that is FDA-approved for major depressive disorder in adults, and for diabetic peripheral neuropathic pain. Besides inhibiting serotonin and norepinephrine reuptake in the brain, duloxetine inhibits reuptake in the sacral spinal cord, where the drug exerts an interesting effect on Onuf's nucleus, which regulates tone of the urethral striated muscle sphincter through the pudendal nerve.[16] The accumulation of serotonin and norepinephrine at Onuf's nucleus (by reuptake blockade) increases efferent activity to the urethra, improving urethral tone. This is thought to have a therapeutic effect.

Dosage. The usual dose for depression is 20 to 30 mg twice daily or 60 mg once daily.

Contraindications include severe renal impairment and hepatic disease.

Side effects include nausea, dry mouth, constipation, dizziness, fatigue, increased sweating, and somnolence.[17]

Performance in clinical trials. Van Kerrebroeck and colleagues[18] conducted a multicenter, randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of stress incontinence. The trial involved 494 women from 6 European nations and Canada. Episodes of stress incontinence decreased 50% in women taking the drug (40 mg twice daily), compared with 29% among women taking placebo.

Nausea was the main side effect noted in the study and tended to be moderate and transient, rather than progressive. However, 22% of women taking duloxetine discontinued it because of side effects,

INTEGRATING EVIDENCE AND EXPERIENCE

Anatomy of a drug decision: The FDA and trospium chloride

Zinner N, Gittleman M, Harris R, et al. Trospium chloride improves overactive bladder symptoms: a multicenter phase III trial. J Urol. 2004;171:2311–2315

What goes into a drug approval? In weighing the merits of trospium chloride (Sanctura), one of the studies the US Food and Drug Administration considered was a 12-week multicenter, double-blind, parallel, placebo-controlled trial that compared 20 mg of the drug (twice daily) with placebo.

Trospium significantly reduced the frequency of toilet voids and urge incontinence episodes, compared with placebo. It also increased the average volume per void and decreased urge severity and daytime frequency.

However, several factors limited this study's application to "real-life" women with overactive bladder.

1. Most participants were older white women

A total of 523 patients were enrolled, more than 70% of them women. The mean age was over 60 years, and about 80% of participants were white. More than half had already used a drug for overactive bladder.

2. Brief duration did not reflect real life

Most patients with overactive bladder need treatment for much longer than 12 weeks, so this study does not address the long-term efficacy or tolerability of trospium chloride.

3. Placebo response was substantial

Patients in the placebo arm had less frequent urination, decreased nocturia, fewer episodes of urge incontinence in 24 hours, and reduced urgency with voiding. Although these outcomes were statistically significant in the treatment group, were they clinically meaningful?

A difference of 2 tablespoons. The mean increase in average voided volume in the trospium group was 32.1 mL, compared with an increase of 7.7 mL in the placebo group. Although the *P* value was outstanding ($P \leq 0.0001$), one could argue that an increase in bladder capacity of less than 2 tablespoons is clinically meaningless.

Try non-drug measures first

In this study, 54% of patients taking placebo reduced the number of incontinence episodes in 24 hours, compared with 71% on the active drug. In addition, 10% of patients taking placebo became completely dry, compared with 21% on the active drug.

Because the placebo effect in these studies is always strong, focused behavioral therapy ("bladder drill" or bladder retraining) should be the first line of treatment for overactive bladder, reserving drugs for those in whom behavioral treatment is not effective, or as an initial "crutch" to help advance the behavioral program, weaning patients off medications whenever possible.

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In light of the strong placebo effect, start with behavorial therapy for overactive bladder

compared with 5% of the women who were taking placebo.

A multicenter, randomized, double-blind, placebo-controlled trial involving 683 women from the United States and Canada, who took 40 mg of duloxetine twice daily, found a decrease in episodes of stress incontinence similar to that demonstrated by van Kerrebroeck et al,[18] with comparable discontinuation rates.[19]

Cardozo and colleagues[20] compared duloxetine with placebo in patients with stress incontinence symptoms severe enough that they had been placed on a waiting list for surgery. After taking duloxetine, 20% of these women were no longer interested in surgery, compared with none of the women in the placebo group.

Duloxetine may avert surgery. Taken together, these studies indicate that duloxetine is

effective and may improve incontinence enough to render surgery unnecessary. ■

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