Trends-in-Medicine

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SUMMARY

Lilly's duloxetine will require PK, preclinical (in vitro and in vivo) and clinical testing before approval for the treatment of incontinence. The concern appears to be drug-drug interactions because of the way the drug is metabolized – CPY450, particularly the 2D6 and 1A2 pathways. ♦ Johnson & Johnson/Gynecare's TVT remains the most popular vaginal sling system for stress incontinence. Ob-gyns have little interest in newer systems, none of which appears to be gaining much traction in the market. ♦ Ob-gyns are very interested in Watson's Oxytrol patch, and sources predicted that their usage would double to ~38% of their overactive bladder (OAB) patients within a year. ♦ Johnson & Johnson reportedly is exploring the idea of taking regular Ditropan (oxybutynin) over-the-counter.

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AMERICAN UROGYNECOLOGIC SOCIETY
Hollywood, Florida
September 11-13, 2003

Among the topics covered at this meeting were overactive bladder, stress incontinence and vaginal slings.

OVERACTIVE BLADDER
(URGE INCONTINENCE)

Some of the risk factors for overactive bladder (OAB) are:

- Bladder problems in children give them a 10 to 20 times higher risk of OAB in later life.
- ADHD patients 2.7 times more likely than age- and sex-matched controls to have enuresis and 4.5 times more likely to have daytime incontinence.
- There are a few studies suggesting a genetic risk for OAB, enuresis and urge incontinence.

The leading medications for OAB are Pfizer's Detrol and Detrol LA (~53% of the market) and Johnson & Johnson's Ditropan XL (~33% of the market). The newest entry is Watson's Oxytrol (oxybutynin patch). FDA approval is expected shortly for two other drugs: Novartis' darifenacin and Aventis/Yamanouchi's solifenacin. Next year, Indevus is hoping for approval of its trospium chloride (the PDUFA data is February 28, 2004).

According to an industry source, "Urologists write numerically more prescriptions for incontinence medications, but ob-gyns write more in percentage terms. General practitioners write 52% of OAB scripts."

Comparison of Pharmacologic Agents for OAB

	Oxybutynin (e.g., Oxytrol, Ditropan XL)	Tolterodine (Detrol)	Trospium
Metabolizing enzyme	CYP3A4	CYP2D6	Negligible
Hepatic Metabolism	Extensive	Extensive	Low
Active metabolites	M6	DD01	None
Drug interactions	Possible	Possible	Minimal
Active compound in urine	Low	<5%	77%
Blood-brain diffusion	Possible	Minimal (?)	Minimal
Half life	12-16 h	2.1-2.9 h	5-21 h

AVENTIS/YAMANOUCHI'S solifenacin (YM-905)

Comments made about this agent include:

- It has a long half-life.
- It is a bladder-selective anti-muscarinic.
- There is no good dose response curve, but the 10 mg appears to work.
- Dry mouth and constipation are comparable to Detrol.

INDEVUS' trospium chloride

Trospium has been sold in Europe for many years by Madaus, and Indevus submitted it to the FDA on April 28, 2003. A speaker discussed the Phase III data that was presented at the American Urologic Association meeting in April 2003. He noted that trospium:

- Is not metabolized by the liver – 80% of the drug appears in the bladder, unmetabolized.
- Has no metabolites – no breakdown products
- No drug-drug interactions.
- Is hydrophilic, so it does not easily cross the blood brain barrier.
- Is not easily absorbed from the GI tract.
- Has a low incidence of side effects.
- Had a low trial drop-out rate – 83.6%, compared to 83.5% with placebo – but also had a high placebo effect (~40%) in the Phase III trial.
- Is not associated with alpha wave changes, which are observed in patients taking oxybutynin (but not tolterodine).

A once-a-day formulation of trospium is in development. An active clinical trial of QD dosing is underway.

The 20 mg dose appears to be the best dose for trospium. A speaker said, "We don't have data on 30 mg, but the therapeutic benefit is probably better at 20 mg." Another speaker said, "There is data on 40 mg trospium in Germany, and there is no question that if you are going to see a QD formulation, you probably want two different doses to get the right therapeutic index."

Studies Comparing Trospium and Tolterodine

Measurement	Trospium 20 mg BID n=57	Detrol 2 mg BID n=63	Placebo n=60
Study 1			
Change in episode frequency	-3.4% (p<.05 vs. pbo)	-2.6% (p=nss)	-1.9%
Study 2			
UI/24 h	-73%	-67%	---
Frequency/24 h	-28%	-23%	---
Volume void	+33%	+39%	---
Dry Mouth	33%	33%	---

NOVARTIS' darifenacin

A source said darifenacin causes more constipation than Detrol.

WATSON'S Oxytrol (oxybutynin patch)

Doctors questioned at the meeting are using Oxytrol patches for an average of 15% of their OAB patients. Of course, there were wide variations in current usage, but three quarter of the doctors questioned have started prescribing Oxytrol, and all but one of the others plan to do so.

Over the next 12 months, doctors predicted that their use of Oxytrol would increase to an average of 31% of their OAB patients. Their comments included:

- Texas: "Currently, we are prescribing Oxytrol for 25% of our OAB patients, and by next year that probably will increase to 50%, depending on advertising to physicians and direct-to-consumer advertising."
- New York: "About a third of my (OAB) patients are on Oxytrol. Local irritation occurs in a lot of patients – about 46% -- and I've had to stop it in a couple of patients. I don't use it first-lien, but if patients have side effects with Ditropan XL or Detrol, then I try Oxytrol. The doctor issue with Oxytrol is lack of comfort with patches. The patient issues are contact dermatitis, visibility and the patch concept."
- Florida: "The contraceptive patch has done very well. Young women all want it, though they don't always stick with it. So, I'll try Oxytrol because there will be patients who will want it. I don't want to be first, but I will try it. However, patient demand is critical, and no patients are asking for it yet."
- California: "I haven't tried the patch yet, but I will because a lot of patients are already on too many medications. In a year, 25% of my OAB patients could be on it."
- Wisconsin: "I haven't started using the patch because I don't have any samples yet, but I will be telling my patients about it. It is a nice alternative, and I can see 40%-50% of my (OAB) patients being on it in a year. Women love the (Johnson & Johnson/Ortho-McNeil) Evra birth control patch; they ask for that."
- Idaho: "I've tried the patch for a few patients, and it has been pretty good so far. I expect my use to increase, but it will stay less than 30% of my OAB patients."

Watson reportedly was holding a sales meeting in another Florida city about the same time as the AUGS meeting. The company also hired an outside sales force to sell Oxytrol to primary care physicians. Watson sales reps predicted these efforts will give further impetus to Oxytrol sales.

STRESS INCONTINENCE

Stress incontinence, which is almost twice as common as urge incontinence, affects about 30 million American women over the age of 18. It is caused by a decreased urethral sphincter muscle function at the bladder outlet, resulting in accidental urine leakage. Thus, normal activities such as coughing, sneezing, lifting or exercising can lead to an episode of incontinence.

Non-surgical options for stress urinary incontinence (SUI) include:

1. Alterations in the magnitude of intra-abdominal pressure (i.e., "stress") on bladder – cough control, weight loss, reduce heavy lifting, etc.
2. Alterations of fluid and voiding habits (drink less, not more, water).
3. Devices – intravaginal support or urethral occlusive/ obstructive devices (tampon, tampon-like devices, continence rings, pessaries, urethral patches, intraurethral plugs, etc.)
4. Behavioral therapy – bladder retraining, pelvic muscle exercise.
5. Medications – No drugs are currently FDA approved, but a few drugs (e.g., estrogen, ephedrine, etc.) are being used off-label.

LILLY'S duloxetine (Yentreve for incontinence and Cymbalta for depression)

Duloxetine is a dual reuptake inhibitor of the neurotransmitters serotonin and norepinephrine (an SNRI). Serotonin and norepinephrine are believed to play key roles in the normal closure of muscle at the base of the bladder. Increased neurotransmitter concentration in turn stimulates increased activity of the nerve that stimulates the urethral sphincter. This stimulation is believed to increase the tone of the urethral sphincter at the exit of the bladder, thereby helping prevent accidental urine leakage due to physical activity.

On September 3, 2003, the FDA issued an approvable letter for duloxetine for the treatment of SUI. Final FDA approval is contingent upon:

- Successful completion of additional acute pre-clinical and clinical pharmacology studies.
- Satisfactory resolution of manufacturing issues at Lilly's Indianapolis manufacturing facilities, including the satisfactory completion of a pre-approval site inspection.
- Completion of label negotiations.

Sources indicated duloxetine will require PK, preclinical (in vitro and in vivo) and clinical pharmacology testing before approval for the treatment incontinence. The concern appears to be drug-drug interactions because of the way the drug is metabolized – CPY450, particularly the 2D6 and 1A2 pathways. A speaker said that 5% of all people (and 10% of Caucasians) are 2D6 sensitive.

This means that drugs with a narrow therapeutic window which are also metabolized by those pathways would need to have their dosage watched or adjusted; their efficacy could be inhibited. A speaker said, "You would have to be careful using this with drugs metabolized in a similar way. For instance, the effects of valium can be increased, but there are not that many drugs with clinically significant (interaction) problems."

Detrol also affects the 2D6 pathway, but not the 1A2 pathway. Oxybutynin is metabolized by CYP450/3A4. An expert said, "Approximately 50% of drugs metabolized by the CYP enzymes are metabolized by CYP3A3/4 and 25% by CYP2D6."

Drugs Metabolized by CPY450

2D6	1A2 Substrates	1A2 Inducers	1A2 Inhibitors
Cimetidine	Clozapine	Carbamazepine	Amiodarone
Codeine	Olanzapine	Cigarette smoke	Cimetidine
Erythromycin	Estradiol	Omeprazole	Diltiazem
Fluoxetine	Acetaminophen	Phenobarbital	Estradiol
Haloperidol	Imipramine	Phenytoin	Fluvoxamine
Itraconazole	Desipramine	Rifampin	Fluoroquinolones
Ketoconazole	Nortriptyline		Isoniazid
Macrolides	Warfarin		Ketoconazole
Methadone			
Metropolol			
Paroxetine			
Verapamil			

With respect to duloxetine interaction with other concurrent medications:

- **MAO inhibitors.** These also are contraindicated with duloxetine, but a source said that these are a "standard contraindication."
- **SSRIs.** Naturalistic studies are being conducted in which doctors have no limit on concurrent SSRI use. The studies reportedly are large enough that conclusions may be able to be drawn about the safety and efficacy of combining duloxetine with SSRIs. These studies are not yet complete.

Efficacy does not appear to be the issue with duloxetine. A researcher commented, "It is not a question of efficacy, and the studies being requested should be routine." However, several doctors at the meeting commented that duloxetine does not appear to be much better than imipramine in efficacy, though there have been no head-to-head studies of duloxetine and imipramine – yet.

It is not clear yet whether the FDA's Division of Neuro-pharmacologic Drug Products, which is considering the depression indication, will have the same issues as Division of Reproductive and Urologic Drug Products (DRUDP), which is considering duloxetine for incontinence. However, recent

discussions with the FDA would suggest that the drug-drug problems may apply to both indications.

The day before AUGS started, September 10, 2003, the ***Journal of Urology*** published results of a Phase III study of 40 mg duloxetine BID in 683 women. That study found:

- The frequency of incontinence episodes was reduced by 50% with duloxetine, vs. 27% with placebo.
- Average time between voiding increased by 20 minutes with duloxetine vs. two minutes with placebo.
- Women with severe incontinence at baseline experienced a similar reduction in leakages as women with less severe incontinence.
- On the Patient Global Impression of Improvement (PGI-I) scale, 62% of women rated their condition improved with duloxetine compared with 39.6% on placebo.

Lilly had a fairly big presence at the AUGS meeting, though there was a sparse turnout for a Lilly-sponsored session on stress incontinence, probably due to the 6 a.m. start time. There was very little new information at the meeting, but researchers reported that:

➢ **Duloxetine works better in severe incontinence.** Less severe patients have the same proportional decrease in incontinence episodes as most severe patients, but the improvement in quality of life is not as much with severe patients.

➢ **Women may reconsider undergoing surgery after trying duloxetine**. A speaker said, "There is some evidence of increased response and efficacy with dose escalation (from 80 mg/day to 120 mg/day)."

Data was presented from a 109-patient, double-blind, randomized, parallel, placebo-controlled, multi-center study of women with severe stress incontinence (≥14 episodes/week) who were on a waiting list for incontinence surgery in Australia, Canada, the Netherlands, and the U.K. The women were started on duloxetine 80 mg/day and escalated to 120 mg/day for eight weeks. About a third of women dropped out between initial randomization and up-titration, and an investigator said this was due to women moving, deciding they preferred an operation or some protocol violation. "Most did not discontinue for adverse events," she noted.

Duloxetine in Women Waiting for Incontinence Surgery

Measurement	Duloxetine n=55	Placebo n=54	p-value
Completors	64%	78%	---
Adverse Events			
At least one AE	92.7%	72.2%	---
Discontinuation for adverse events	32.7%	5.6%	---
Nausea	45.5%	13.0%	---
Constipation	27.3%	5.6%	---
Dry mouth	21.8%	9.3%	---
Headache	27.3%	9.3%	---
Primary Endpoint: % change in pooled IEF			
Week 4	-60%	-27%	p=<.001
Week 6	-55%	-26%	---
Week 8	-64%	N/A	---
Secondary Endpoint: I-QOL total score	10.6	2.4	p=.003
Pads used	-34.5%	-4.8%	p=.008
Willingness to reconsider surgery	22%	N/A	---

Other sources noted that there is a substantial degree of nausea with duloxetine, though speakers offered several arguments that this is not clinically significant, including:

- **Transient nature.** The nausea is mostly mild-moderate and transient. A speaker said, "The nausea is similar to that seen with other antidepressants. Only a small number of women (slightly more than 6%) stopped secondary to nausea."
- **Lack of titration.** A speaker explained, "The difficulty with the duloxetine studies is that we were recording side effects, not necessarily managing them. With other antidepressants, typically the medication is initiated at a lower dose, so the patient has time to adjust to nausea or may be given something for nausea which was not allowed in these studies.
- **Dose dependent.** The degree of nausea appears to be dose-dependent.
- **New studies ongoing.** A more "naturalistic" study is ongoing where doctors can alter the dosage or offer nausea treatment, but that data is not yet available.

Doctors doubted that Lilly's stress incontinence medication, duloxetine, would have much impact on the sling market when it is launched. Most doubted that there would be even a brief lull in surgeries. An Alabama doctor commented, "I have 60 women on a waiting list for duloxetine. They refuse to have surgery, so they are waiting for duloxetine."

VAGINAL SLINGS

The surgical treatment for stress incontinence is a pubovaginal fascial sling. In these operations, doctors attach a piece of autologous or cadaver fascia (a flat, tough tendon-like material) around the neck of the bladder to keep urine in, even under stress. Several companies also offer sling materials and systems.

JOHNSON & JOHNSON/GYNECARE'S TVT (transvaginal tension-free) sling was the first synthetic system, and it remains the market leader. A J&J official said the company's current TVT focus is on educating doctors about stress urinary incontinence.

Every doctor questioned at the meeting is doing slings, and all use at least one commercial sling system. In most cases, this is TVT. A Florida doctor said, "I've done 40-45 TVTs. I think some of the other systems look interesting, but TVT is already very safe and successful, so I'm not going to change. Doctors are slow to change if they are doing something and it is successful." A Georgia doctor said, "I'm looking at the newer slings, but there is little incentive to change. If I did try something, it would be the Cook system because the mesh is not synthetic." A California doctor said, "I tried Uretex but I've gone back to TVT. There is just more data on TVT."

LBC vs. TVT

Measurement	LBC	TVT	p-value
Cost	$6,368	$6,059	Nss
Hospital time	33 hours	29 hours	Nss
Adhesiolysis	32%	11%	P<.05
Conversion to laparotomy	9%	0	---
Cystomatomy	0	6%	---
Tansfusion	0	3%	---
Bladder suture	3%	0	---
Bowel laceration	3%	0	---
Leaks per week	0.4 post 1 year 0.3 post 2 years	18 post 1 year 0 post 2 years	---

A 69-patient, single-center study was discussed comparing Burch colposuspension (LBC) to TVT. The study was stopped early due to slow recruitment and lack of funding. However, the researchers found that LBC and TVT both significantly improved patient-reported outcomes, but TVT resulted in significantly greater objective improvement.

A Canadian doctor reported on a prospective, randomized study of 50 patients, half who got TVT and half with a modified TVT utilizing a reusable device plus strips cut from sheets of polypropylene mesh. However, few doctors expressed much interest in trying this.

Measurement	TVT	Modified TVT	p-value
Operative time	27 minutes	25 minutes	P=.042
Voiding time	.6 days	.45 days	P=.054
Hospital stay	.84 days	.72 days	P=.70
"Cure" rate	84%	88%	P=1.0
Kit cost	$675	$10	P<.001
Total cost	$1,712	$997	P=.01

AMERICAN MEDICAL SYSTEMS has a TVT-like sling, Sparc, and it introduced the first trans-obturator system in the U.S., Monarc; but **MENTOR** now also has a trans-obturator system as well, the ObTape. Both Monarc and ObTape use fairly similar corkscrew-like needles that go through the obturator

Comparison of Commercial Sling Systems

Brand	Approx. cost	Advantages	Approach	Material
AMS Sparc	$795	Top-down approach	Top-down	Polypropylene mesh
AMS Monarc	$995	Can do repeat procedure; maybe fewer complications	Trans-obturator	Polypropylene mesh
Bard Uretex	$595	Self-anchoring	Either top-down or bottom-up	Monofilament polypropylene mesh
Boston Scientific Advantage	N/A	Pre-packaged, no assembly required, ability to rotate tape, heat sealed edges to tape in area near urethra	Bottom up (but a top-down version is planned)	Polypropylene mesh
Caldera T-sling	N/A	N/A	N/A	Polypropylene mesh with PDS center
Cook Stratasis TF	$695	Only FDA-approved biomaterial; natural, not synthetic material	Either top-down or bottom-up	Natural: porcine small intestinal submucosal
J&J TVT	$795	Easier than Sparc in obese women	Bottom-up	Polypropylene mesh
Mentor Axis	N/A	N/A	N/A	Specially processed human tissue
Mentor Sabre	~$795	Only self-anchoring	Top-down (superpubic)	Bioresorbable synthetic polymer
Mentor ObTape	N/A	Smooth edge to the tape	N/A	Polypropylene mesh
Tyco IVS Tunneler	N/A	No rough edges to tape, no fray, no sheath covering	N/A	Multilayer polypropylene mesh

foramen on each side, avoiding the retropubic space. Doctors need to take a class to learn the procedure, but officials of both companies insisted their system is easy to learn.

An AMS official said 6,000 cases have been performed in Europe with Monarc, but there were no clinical or safety studies done for the 510K submission to the FDA, so the company can't prove there are less complications with Monarc than TVT. The theoretical advantages of the trans-obturator approach include: (1) fewer complications and (2) the ability to do a repeat procedure on a woman who had a previous sling.

Doctors are interested in these devices, but they really want more data before trying them. In fact, the lack of enthusiasm for trying the latest new "gadget" was surprising. A Wisconsin doctor said, "I use TVT. I haven't tried the others, but they are just variations on a theme. The trans obturators are interesting, but they are new, and there is no five-year data on them." An Idaho doctor said, "I've used TVT for three years. I'm interested in the trans-obturator approach, but TVT is so good, that there's no reason to change." A Louisiana doctor said, "I've done a couple of Monarc procedures, and I'll do more, but initially only in thin patients because bladder perforation is more frequent in thin patients than in obese ones. The Mentor system is similar but I don't like the mesh."

BARD'S Uretex sling system was re-launched in January 2003. An official said sales are 30% above the forecast for 2003. He also indicated most sales are to doctors who previously were using TVT rather than doctors just starting use of synthetic sling systems. The company expects to have data at AUGS 2004.

BOSTON SCIENTIFIC launched its new Advantage system just before the AUGS meeting, and it did generated some interest at the meeting. This is a new and improved version of the sling that Boston Scientific introduced last fall (2002) but quickly withdrew after doctors evaluating it in pre-launch tests warned that "the bells and whistles are nice but it could cause some problems and needed a redesign."

Sales reps said the advantages of Advantage over other sling systems include:

- It comes pre-packaged, with no assembly required.
- The dilators allow rotation of the tape after it is put in but before the procedure is finished.
- The edges of the tape that are designed to lie near the urethra are heat-sealed to prevent fraying.

Reportedly, the company is doing a "limited launch" -- very slow, controlled roll-out of this product. Sources said this is not due to inventory problems.

A source said **TYCO'S** IVS Tunneler (formerly U.S. Surgical) has been used in about 55,000 patients world-wide. Data is expected at AUGS 2004, and a head-to-head vs. TVT is expected "soon" in the International Urogynecology Journal.

MISCELLANEOUS

Another item which seemed to garner attention at the meeting was **Boston Scientific's Durasphere EXP** injectable bulking agent. It is composed of circonia beads suspended in a water-based carrier gel. ♦