Trends-in-Medicine

June 2004
By Lynne Peterson

SUMMARY

Stress incontinence: Doctors are excited about Lilly's Yentreve (duloxetine), but it is unlikely to find much off-label use for overactive bladder since there are several new therapies on the near horizon for that. ♦ **Urge incontinence:** It may not seem possible but the marketing wars are heating up – and that's about all the difference doctors see among the various agents. ♦ **Vaginal slings:** The transobturator approach is gaining popularity, though Johnson & Johnson's TVT remains the market leader. ♦ **Cancer:** Doctors have little interest in cryotherapy for prostate cancer or RF therapy for renal cell cancer, and vaccines are viewed as futuristic. ♦ **ED:** Doctors are not sure GlaxoSmithKline's Levitra will survive, but Lilly's Cialis has become a strong competitor to Pfizer's Viagra. However, the market is growing very slowly, and Pfizer has begun to fight back.

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Stephen Snyder, Publisher
1879 Avenida Dracaena
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com

AMERICAN UROLOGIC ASSOCIATION (AUA)

May 8-13, 2004
San Francisco, CA

This was a busy meeting this year, and there was news in a number of areas, including:

URINARY INCONTINENCE

According to the Agency for Health Care Policy and Research (AHCPR), 13 million Americans are incontinent and 11 million of these are women. From 15%-30% of the community and up to 50% of long-term care patients are incontinent. By contrast, an estimated 25% of women have hypertension, 20% depression, and 8% diabetes.

Incontinence Drugs

Company	Brand	Chemical	Type of incontinence	Key side effect/ disadvantage	Potential advantages
Pfizer	Detrol	Tolterodine	Urge	Dry mouth	Efficacy; Experience
Johnson & Johnson	Ditropan XL	Oxybutynin	Urge	Dry mouth	Efficacy; Experience
Watson	Oxytrol	Oxybutynin	Urge	Patch; Skin irritation; Lower efficacy	Patch; Less dry mouth
Novartis	Enablex	Darifenacin	Urge	Constipation; Dry mouth	Efficacy; Selectivity
Indevus/ Odyssey	Sanctura	Trospium	Urge	BID dosing	Less dry mouth; No P450 metabolism; Quick onset of action
Lilly	Yentreve	Duloxetine	Stress	23% nausea	M3 selectivity

Types of Urinary Incontinence

Symptom	Description	Prevalence in women >60 years	Prevalence in women <60 years	Incidence among women with incontinence
Stress	Leakage with physical exertion or on sneezing or coughing	30%	5%	49%
Urge	Leakage with a strong and urgent desire to void	35%	20%	22%
Mixed	Combination of stress and urge	35%	25%	29%

STRESS INCONTINENCE

Urinary Stress Incontinence Therapies

Symptom	Goal	Opinion
Colposuspension	Suspending anterior vaginal wall to iliopectineal ligaments	May see resurgence with new technology
Suburethral slings	Places urethra in a sling, suspending it from rectus fascia or pubic bone	Several new products
Bulking agents	Injection of bulking materials about urethra to increase outlet resistance	Good idea but no ideal agent
Medication	None FDA-approved yet; off-label use of tricyclic antidepressants, estrogen and alpha agonist	Preference for American women but off-label products not very effective

LILLY'S Yentreve (duloxetine)

On September 3, 2003, the FDA issued an approvable letter for duloxetine, pending the results of additional pre-clinical and clinical studies on drug-drug interactions, resolution of manufacturing issue, and agreement on labeling. The dose for incontinence is 40 mg, which is lower than for depression (where it will be sold as Cymbalta).

The key issue with duloxetine for doctors and patients will be nausea, which is comparable to that seen with SSRIs – 21% fluoxetine (Lilly's Prozac), 26% sertraline (Pfizer's Zoloft), 26% paroxetine (GlaxoSmithKline's Paxil), 31% venlafaxine XR (Wyeth's Effexor), and 21% citalopram (Forest Labs' Celexa).

Published Phase III Duloxetine Trial Results

Measurement	Duloxetine	Placebo
IEF%	-50	-27
I-QoL increase	+11.0	+6.8
PGI-I % better	62%	40%
MTBV change	+20.0	+2.0
Nausea	26%	N/A
Nausea patients who dropped out	6.4%	N/A

Asked how he will use duloxetine when it is approved, an expert said, "I will offer it as an option to my patients, and I think it will be greeted with at least some level of happiness by patients." Another expert said, "I agree. It works within four weeks and maybe more rapidly, but certainly within one month…And it does appear to have benefit in post-surgical patients." A third expert commented, "The way I would see it used is to try and identify the more prominent component (of the incontinence) and treat that first, and then add a second agent if you need it…If you had a sling patient who still needs one pad a day, you would think this is worthwhile."

The outlook is for Yentreve to be a huge hit in stress incontinence, with rapid uptake. A urologist said, "100% of urologists will try duloxetine if it is approved. Everyone wants a pill. But there will still be a place for slings." A North Carolina doctor said, "Usage will be huge, but off-label use is not likely." However, an AMS official does not think duloxetine will negatively impact vaginal sling procedures. He said, "Duloxetine will be a boon to our business because it will bring new patients into the doctor's office. It is indicated for mildly incontinent patients. If we can get women out of the woodwork and into the doctor's office, that will give them a chance to be presented with alternatives. A lot of women are not aware that a 20-minute outpatient procedure, with little pain, is available.

The downside to duloxetine is nausea, which was described as being similar to being pregnant. However, an expert said the nausea goes away in a week for most patients and in three to four weeks for all patients.

The most negative comment about duloxetine – and it wasn't that negative – came from a New Jersey doctor who participated in duloxetine studies. He said, "I don't think there will be widespread use, but it will have a role. The question is whether 45- to 50-year-old women will want to take it for 20 years vs. a 20-minute (surgical) procedure. Preliminary data indicates the efficacy of duloxetine is 50%-60%."

Yet, sources do not expect significant off-label use of duloxetine for urge incontinence (overactive bladder, OAB). A urologist said, "It probably will work in a subset of OAB patients, but there is no data yet to support that. There is also some speculation that it may be useful in pain. But I think doctors will stick to the stress incontinence indication – but there is a lot of mixed incontinence, and it will be used in that." A New York doctor said, "With the new OAB treatments coming, there will be little off-label use of duloxetine until those have been tried."

There was no information available at AUA on Lilly's manufacturing situation with duloxetine. Lilly is already laying the groundwork for a strong marketing campaign, and speakers were explaining the advantages to an SNRI with good M3 activity. The focus at the booth and at lectures was

on raising awareness of stress incontinence and the expected availability soon of new treatment options.

Data are expected at AUA 2005 on duloxetine use post-prostatectomy.

The impact of duloxetine on sling procedures is unlikely to be significant, sources predicted. A doctor said, "Short-term there may be a 10%-15% slump, but duloxetine actually will increase disease state awareness. This will bring women in and then they will move to other options as they progress."

UROMEDICA'S Adjustable Continence Therapy (ACT)

This new, minimally invasive surgical procedure for recurrent stress urinary incontinence utilizes a device which is implanted next to the patient's bladder. It consists of two silicone balloons that are positioned peri-uretherally at the bladder neck and can be adjusted post-operatively by inflation or deflation in an outpatient setting. The key advantage to ACT is the adjustability of these balloons. Researchers reported an 83% reduction in leakage at six months and 87% at 12 months. The most common adverse events were balloon failure, bladder perforation, balloon or port erosion, vaginal and urethral perforation, balloon migration, and urge.

OVERACTIVE BLADDER (URGE INCONTINENCE)

More than 33 million Americans experience the symptoms of overactive bladder (OAB), the exact number with incontinence is not known. The annual cost of treating women's incontinence is estimated to be $12 billion.

For several years there has been a marketing war raging between Pfizer's Detrol and Johnson & Johnson's Ditropan XL. Last year Watson's Oxytrol patch joined the fray, and not long after AUA, Indevus/Odyssey's Sanctura (trospium chloride) gained FDA approval. Soon, another two agents are expected to be approved for OAB – Novartis's Enablex (darifenacin) and Yamanounchi's Vesicare (solifenacin) – plus there could be off-label use of Lilly's stress incontinence drug Yentreve. Each of these has advantages and disadvantages, and each has its proponents. Most doctors said they are glad to see new options coming, but they consider the drugs fairly comparable. Sources expect the competition to heat up even more with all these players.

Comparison of New Agents

Drug	Advantage	Disadvantage
Yamanouchi's Vesicare (solifenacin)	More volume held with less urge to void	Dry mouth
Novartis's Enablex (darifenacin)	When urge occurs, can wait (warning time is good)	Constipation
Indevus/Odyssey's Sanctura (trospium chloride)	Can hold more urine and lasts longer; less dry mouth; no CYP450 metabolism	BID dosing

How will doctors choose among these agents? Since all are considered relatively comparable in efficacy, sources said their choice will largely depend on weighing (1) side effects, (2) price, and (3) relationships with the sales reps.

WATSON'S Oxytrol (transdermal oxybutynin)

Oxytrol received FDA approval during the AUA meeting in 2003, and doctors questioned at that meeting estimated that within six months, the Oxytrol patch would account for an average of 27% of their OAB patients. Urologists questioned at this year's AUA meeting, said an average of 12% of their OAB patients are now on Oxytrol, which is higher than the company's market share nationally. Thus, sales haven't met predictions. A Watson official said the problem with Oxytrol sales is a lack of sufficient "feet on the ground." The company does not appear to have any particular strategy to correct this.

Doctors speculated that any disappointment in – or flattening of – Oxytrol sales is likely due to one or more of the following factors:

- **Poor marketing to primary care doctors**. An internist said he's never been detailed on Oxytrol but might use it if he were detailed.
- **Disinterest by primary care doctors** who, they said, prefer pills to a patch which takes time to explain. A Maryland doctor said, "When you are prescribing a patch, you have to take the time to explain it to the patient, and PCPs may not want to do that. And PCPs are not used to patches."
- **The tertiary nature of urologists' treatment of urge incontinence**. Sources pointed out that by the time patients get to a urologist, they generally have tried at least one oral medication, so they are more willing to try new options.
- **Twice-a-week dosing.** Sources said this has been confusing to doctors and patients.

On average, sources predicted that their usage of Oxytrol would increase slightly over the next year. Generally, doctors leave the choice of a pill or a patch to patients, but they said patients who opt for the patch generally are satisfied with it. They said Oxytrol appeals more to older patients than younger (40- to 50-year-old) women. A Texas doctor said, "I've had a pretty positive experience with Oxytrol, so my use may go up a little. The company needs to market more to OBs because they are used to patches." A North Carolina doctor said, "About 25% of my OAB patients are on Oxytrol, and that is likely to stay the same or go up slightly over the next year. I leave the choice to patients. But there may be a role for Oxytrol in kids with spina bifida – not yet but perhaps." Another doctor said, "Oxytrol has a niche, but it is a niche. From 10%-15% of my OAB patients are on it, and that should remain pretty steady."

Some patients experience skin reactions, but that hasn't caused many patients to stop using it, and it has not discouraged doctors from offering Oxytrol to patients. A New Jersey urologist said, "Skin irritation is a problem, but it has not caused me to prescribe Oxytrol less. I use it a lot in combination therapy, adding it to Detrol." A New York doctor said, "There is rarely a problem with irritation." However, a competitor commented "Skin reaction is a real problem, and it is showing up at four to five months of usage."

Watson had a big booth at the meeting – larger than last year. However, traffic appeared thin.

Pooled Efficacy Analysis of Darifenacin Phase III Trials

Measurement	Darifenacin 7.5 mg	Placebo	Darifenacin 15 mg	Placebo
Primary endpoint: Incontinence episodes	-68.4%	-53.8%	-76.8% (p<.001)	-58.4%
% of patients achieving reduction from baseline in incontinence episodes	66%	52%	70% (p<.001)	56%
Secondary endpoints				
Number of micturitions per day	-16.6%	-9.1%	-17.4%	-9.9%
Increase in bladder capacity	9.6%	4.9%	17.5%	3.9%
Urgent episodes/day	-29%	-14.3%	-29%	-16.7%
Severity of urgency	-14.2%	-7.8%	-16.1%	-8.0%
Number of leaks/week	-77.1%	-47.7%	-78.6%	-55.1%

INDEVUS'S Sanctura (trospium chloride)

An official said summer is not an ideal time to launch this new product, but the company doesn't want to wait in case one of the other companies with a new product in development gets an approval; Indevus wants to have the first new product this year.

The company had a huge and graphically impressive booth, which was a big change from its presence at AUA 2003. Indevus signed a co-promote agreement with Odyssey (a division of Pliva). An official declined to say how it planned to differentiate Sanctura, but commented, "The 'sea of sameness' is how the others are doing it, and we will do our image differently." Initially, the focus will be on doctors, not direct-to-consumer advertising. Indevus does not plan a segmented launch. The official said, "Primary care doctors write more than 50% of the prescriptions, so we can't wait for our competitors to counter-detail."

NOVARTIS'S Enablex (darifenacin)

Novartis purchased this drug last year from Pfizer. At AUA 2003, it was not clear who would be selling this product, but a Novartis official said the company is building a special U.S. sales force to promote this product. In the meantime, it will be handled by the Novartis GI sales reps.

Pooled Safety Analysis of Darifenacin Phase III Trials

Side Effect	Darifenacin 7.5 mg	Darifenacin 15 mg	Placebo
Dry mouth	20%	35%	8%
Constipation	14.8%	21.0%	5.4%
Dyspnea	1.8%	7.5%	1.5%
≥1 CNS adverse event	1.5%	2.7%	2.3%
Dizziness	0.6%	0.3%	0.5%
Any cardiovascular event	2.1%	0.9%	0.3%
Dropouts due to adverse events	0.6%	2.1%	0.3%
Dropouts due to dry mouth	0.9%	0	0
Dropouts due to constipation	0	0.6%	0

A pooled analysis of 12-week data from Phase III trials of darifenacin was presented. Dr. Christopher Chapple of Royal Hallamshire Hospital in the U.K. concluded, "Both doses QD seem effective and are well tolerated with no CNS or cardiovascular concerns." However, there was a fairly high placebo rate in this analysis.

YAMANOUCHI'S Vesicare (solifenacin succinate, YM-905), to be marketed in the U.S. by GLAXOSMITHKLINE

The company got an approval letter from the FDA in October 2003, but the FDA wants more clinical data. There was no news on Vesicare at this meeting.

Other incontinence therapies in development

➢ **Stem Cell Therapy**. Austrian researchers reported on a one-year trial of stem cell therapy for urge incontinence (OAB) in 20 patients. Two types of stem cells – myoblasts and fibroblasts – were grown under strict cGMP standards, and then administered by ultrasound-guided transurethral injection. A researcher said, "Now, there is clinical proof that stem cell therapy can really cure incontinence…This new modality may represent a major breakthrough."

Among the findings in this trial:

- The rhabdosphincter became thicker and contractile force was markedly improved. Contractility of the rhabdosphincter improved, from 0.5 mm before therapy to about 1.7 mm after treatment.
- Incontinence score improved: 12 women and 4 men became fully continent, and the other four patients (1 woman and 3 men) improved.
- Quality of life markedly improved: a mean score of 60 before and 18 post-therapy.
- Maximal closure pressure was better.
- There were no side effects and no de novo urgency.

The results were better in women than men, and the researcher speculated that this was due to the men having had more prior surgeries. He commented, "We know that patients with a rigid urethra after radical prostatectomy are not good for this therapy…Now, we will try to find in which patients it works and in which it doesn't."

➢ **BOSTON SCIENTIFIC/ADVANCED BIONICS' Bion.** This minimally-invasive pudendal nerve stimulator looks like a tube, and it was described as about half the size of a match-stick. A Dutch researcher reported good results placing it in patients with very refractory urge incontinence – several had failed sacral nerve stimulation (SNS). The average number of leaks dropped 57% (from 6.8/day at baseline to 2.9/day at six months), the average volume voided per micturition increased 11%, and leak severity decreased 60%.

The device looked slick and appears effective. Currently, it cannot be used bilaterally because the device has a unique "address" recognized by the external charging pad, but the investigator believes the company will solve this problem and bilateral use will be possible in the future, but a moderator commented, "I'm not convinced it is more efficacious, but it is an alternative."

VAGINAL SLINGS

The transobturator approach – referred to generically as "TOT," despite Boston Scientific's trademark of the phrase T.O.T. (transobturator technique) – is gaining popularity, though Johnson & Johnson's TVT remains the market leader. Among the comments about TOT and TVT were:

- "I was one of the original TVT investigators, and I've done about 60 TVTs with good results. I'm also doing TOT with J&J. TOT is not replacing TVT, but it is having a definite impact."
- "TVT and (American Medical Systems') Sparc are very similar in short term efficacy and complications."
- "TOT is hot, but several companies offer devices for doing it, and they are all fairly comparable. TOT is easy to do, and a lot of us are trying it. There is no good long-term data, but patients have a reasonable chance of doing well…Most doctors do what they were trained to do, but others are new gadget people who want to try the newest thing. Tertiary care doctors will use more advanced techniques like TOT…There is more data on TVT, but TOT is a little easier on the patient. The question is whether that's worth the unknown. I give most of my patients the choice of TVT or TOT, and some choose TOT…TOT is good for patients who are obese, have had lots of prior surgery, are elderly with concurrent prolapse, or transplant recipients."
- "The early results with transobturator slings are encouraging, but there is no selection criteria as there is for TVT. At this time, I would only consider trans-obturator slings for 'select' cases."

Factors Influencing Choice of Sling Procedure

Condition	Choice
SUI with urethral hypermobility	Mid-urethral synthetic sling*
SUI with no hypermobility	Bladder neck sling
Occult SUI	All types of sling applicable

* most common in speaker's practice

An AMS official cited company training courses for doctors as a key reason for the success of its Sparc and Monarc sling systems. He said, "We run our own training courses…Our philosophy with Monarc – and will be with Prolapse – is to have doctors participate in a cadaveric training program…Our feeling is that if a doctor will dedicate a weekend to do that, they will be very successful in going back and picking it up…We facilitate physician-to-physician training. We've probably trained 2,000 physicians on Monarc…and that model has worked well, and we will continue that. Because these products are so new, there is no way to get in the fellow or residency training programs; We have to train doctors ourselves…But a year from now, fellows may be training on Monarc in some of the (fellowship) programs…Our biggest challenge with Monarc is capacity and training all the people who want to be trained."

CANCER VACCINES

Doctors are not excited about urologic vaccines. A Texas doctor said, "Any interest is market driven because of the increase in prostate cancer. My impression is that vaccine therapy is in the earliest stages. This is a heterogenic disease, and a vaccine effective across the board will be difficult…It may be that one has enough effect that it is effective in a sub-population of prostate cancer patients who have aggressive disease." A New York doctor said, "Vaccines are pretty much in the distant future. They are not specific enough, and some have had complications…If a company doesn't have papers (abstracts) here, it isn't going very far – at least for the near future." A Florida urologist said, "There is no buzz about vaccines. I'm hopeful, but there isn't enough information yet to get excited."

At least three companies have vaccines in development to treat urologic cancers.

ANTIGENICS' Oncophage (HSPPC-96) for kidney cancer.

NORTHWEST BIOTHERAPEUTICS' DCVAX-PROSTATE, a prostate cancer vaccine.

DENDREON'S Provenge (APC-8015) for prostate cancer. The FDA has granted Dendreon a Special Protocol Assessment and fast track status, but that hasn't convinced sources that the vaccine will work. The pivotal Phase III trial is still ongoing, enrolling patients and adding sites. This is a three-year trial, but the company expects to file its BLA on one-year data in 2005, with approval and marketing in 2006.

Experts are not optimistic about Provenge, and clinicians are not excited about it. The big criticism is that the company has not published data from its clinical trials, including a completed Phase III trial – or even presented the data at a major medical conference. There was no new data on Provenge at the AUA meeting. Among the comments about Provenge were:

- "Only one of these vaccines is likely to work, and it isn't Dendreon."
- "You can be ***very*** misled by that company. No one has seen the data. I'm very skeptical…It is the least likely to work."
- "I think we are several years from widespread clinical use. I believe many of the researchers who have done (vaccine research) have been a bit disappointed that the field has not moved along as quickly as we would like. We have not found the silver bullet yet…Vaccines are at least three to five years away, but we've been saying three to five years for several years."

A Dendreon official responded, "There is a broad lack of knowledge about immune therapy for prostate cancer. People will be excited when they hear the data, but they need more education." Dendreon's response to doctors who suggested the company has not been forthcoming with data from its trials was that:

- At ASCO 2003, all available Phase III data from the D9901 Provenge trial was presented.
- In a press release in January 2004, the company released the interim survival data (through December 2003) from the D9901 trial. The manuscript with this data is currently being written and prepared for publication.
- A subset analysis of D9901 interim results was presented at a closed-door session of the Society of Urologic Oncology at this year's AUA meeting.
- The three-year safety follow-up in D9901 will be completed in October 2004.
- Another Phase III Provenge trial (D9902B) is enrolling. D9902B is an event-driven trial, with 203 events the trigger, in asymptomatic prostate cancer patients, and it can be unblinded when it reaches the event point. In D9901, patients reached the event point at 9-12 weeks, so the company expects to reach the unblinding point in 2005. The D9902B trial has two primary endpoints:
  - Time to objective disease progression.
  - Time to onset of disease-related pain.

OTHER CANCER THERAPIES

Researchers at Johns Hopkins and the National Institute on Aging reported at AUA on a 40-year, 759-man study that found high blood levels of free testosterone are associated with an increased risk of prostate cancer, but height, body fat, muscle mass, or levels of DHEAS are not. These findings raise questions about the safety of testosterone replacement therapy. A researcher warned that older men considering or receiving testosterone replacement should be counseled about this association until data from long-term clinical trials becomes available.

DIAGNOCURE

This Canadian company has developed a urine test for detection of prostate cancer. This manually-run test doesn't have FDA approval yet, but it is marketed in the U.S. by Bostwick Laboratories. It was described as good for patients with a rising PSA but negative biopsy, not as a replacement for PSA testing.

ENDOCARE'S cryotherapy for prostate cancer

Urologists definitely were ***not*** enthusiastic about cryotherapy. One doctor commented, "I tried it, but I was not encouraged with the initial results, and I stopped." Another urologist said, "Cryotherapy has gone through several generations, but it is still hard to do." A Maryland doctor said, "There is no interest in cryotherapy, and it is not catching on. The National Comprehensive Cancer Network issues guidelines for prostate cancer, and nowhere does it even mention cryotherapy." A Florida doctor said, "I don't do cryotherapy. It's more for salvage. The data is not there for first-line use, and salvage therapy is for a very select group of patients…A first year failure rate of 25% is pretty high." A California doctor added, "Salvage patients are better off at an academic center…Maybe it's the best we can do, but we need more data."

Prostate cancer experts generally dismissed this therapy and had no interest in it, explaining that there is not sufficient long-term data. A New York doctor said, "I'm not interested in cryotherapy because I've seen some of the horrible complications." A California doctor said, "I had a lot of experience with cryotherapy five to 10 years ago, but there were a lot of side effects, so I moved away from it. I still use it occasionally for small kidney tumors, but the oncologic control is not good enough (for broader use)."

An Endocare source said the company currently has 287 doctors trained on their system and on their referral list, with another 100 in training. The company claims 82% of patients are catheter-free post-procedure. The source said, "Doctors are becoming comfortable using cryotherapy as primary therapy, and with the advent of nerve-sparing approaches, they can offer it to younger men. A Florida doctor has dubbed it

'male lumpectomy.'" A doctor who does cryotherapy said, "95% of my patients are older (age ≥60)."

Yet, there appears to be a ripple – not a wave, but a ripple – of renewed interest in this technology. Among the comments on cryotherapy:

- *California*: "Every few years there is a resurgence in cryotherapy, and it is happening again. Centers that do a lot of cryotherapy will do more, and they will get better at it."
- *Florida*: "Cryotherapy is growing quickly. I'm not doing it yet. Most institutions doing research are still deciding if it is curative. Then I'll decide."
- *Illinois*: "I'm not doing cryotherapy, but I'll start. It is efficacious, and patients are asking for it. It is catching on."
- *Indiana*: "I'm looking at starting cryotherapy. It is controversial, but the safety has improved, and it may have a role."
- *Kentucky*: "The technology has definitely improved. There is a little better temperature control. I tell patients it isn't superior to other therapies like brachytherapy, and it has worse outcomes."
- "I have no interest in cryotherapy, but it may have a role in salvage therapy."
- "Cryotherapy is having a resurgence, but it is still used for a very small percentage of patients."

Two of the challenges facing Endocare are:

- **Reimbursement.** A company official claimed reimbursement is great for doctors and low for Medicare, and hospitals don't have to buy the machine; they can lease it on a per-procedure basis. However, a doctor who does a lot of cryotherapy called reimbursement a big problem. He said, "Cryotherapy is a very labor intensive procedure. I can get $800 for brachytherapy, which takes an hour, but I spend three hours on cryotherapy and only get $1,100…Some hospitals don't allow cryotherapy because of the cost. We had a hard time getting the hospitals in our area to agree and some still don't allow it. Endocare needs to get reimbursement improved."
- **Attracting patients.** An Endocare source said the company relies primarily on:
  - Its website. Apparently this has not been very effective, and it is being revamped. The old website was **www.cryocarepca.org** and the new website is **www.prostatecancer.org**.
  - Direct-to-consumer (DTC) advertising, primarily on television but also in some local publications.

Hormone therapy

The reimbursement for anti-androgen therapy, which has been a big revenue generator for many urologists, is scheduled to drop on January 1, 2005. There has been speculation that this might lead to increased use of longer-acting agents (e.g., Atrix's Eligard). However, a urologist explained why he believes that is unlikely to happen: "The government doesn't want the reimbursement change to affect what drugs patients are given, and the government will be watching for doctors who do that. It will be a red flag for an audit, so I don't think many urologists will do that." Several other urologists predicted that older urologists may simply retire when the new reimbursement goes into effect.

INTUITIVE'S daVinci

This robot for prostate surgery is a very hot technology. Doctors seemed very interested, and the booth was very busy. Among the comments were:

- An official said, "Salesmen – people on 100% commission – really go for this."
- An expert said, "It is good for pediatric cardiology, OB/GYN removal of fibroids, kidney transplants, and pediatric reflux…I believe in the future it will have a tremendous advantage, but currently the benefits are minimal…The robot will be useful when it lets the surgeon do things that can't be done in open surgery – when there is real-time imaging of the neurovascular bundle, and a coagulating laser is added."
- A urologic oncologist predicted that, for now, these robots will be sold primarily to centers of excellence, with perhaps three being able to service a large city, "They are not appropriate for small, rural hospitals that have a low volume of prostatectomies."
- A Maryland doctor said, "I trained on daVinci, but now I'm at a hospital where I can't justify the purchase."
- A California urologist said, "This is the beginning of the future. I'm trying to get one for my hospital. Under the current reimbursement, hospitals can't justify the expense, so some are having benefactors donate the money for it, and that's what we are considering at my hospital…We are good at open prostatectomies, but this is a night-and-day difference. When you see (robot) patients post-op and you work with it, you get sold on it."
- A South Carolina urologist said, "I'm very impressed. I've been doing it for a year, and I'm impressed with the technique and patients' rapid return to normal activity, compared to one month with open prostatectomy."
- Another doctor warned, "Time will tell how useful this is. Every laparascopic study has increased more (missed) margins compared to open prostatectomy, and that is serious…In published laparascopic series, the positive margins are 15 times higher than with a radical prostatectomy at a center of excellence."

RITA MEDICAL SYSTEM

This company has an RF therapy designed for renal cell and other cancers. A doctor said, "We do RF therapy, but for kidney cancer, not prostate cancer. What's nice about RF is that you get to a definite temperature." Another doctor said, "RF may be worth testing in a trial, but it is not ready for prime time. It's at the Wright Brothers stage." Results from a small study (41 tumors in 33 patients) was reported at AUA, and researchers found 98% success with laparascopic RF ablation of small renal tumors at an average follow-up of 16 months.

ERECTILE DYSFUNCTION

The general consensus was that the outlook is only for small growth in the ED drug market, even with three major pharmaceutical companies conducting DTC advertising. Some of the reasons for this are:

- **No perceived need.** Many men don't feel ED needs treatment. As one expert explained, "The estimate that there are 30 million American men with ED comes from the Framingham study, but that study didn't look at whether those men wanted or needed treatment for the condition."
- **Cost.** A New York doctor said, "Cost is holding the ED market back."
- **Poor advertising.** There may be a lot of ads, but they may be going over the head of men. An Illinois doctor said, "Patients don't understand the ads."

Pfizer's Viagra (sildenafil), GlaxoSmithKline's Levitra (vardenafil) , and Lilly's Cialis (tadalafil) tablets all can be – and are – split by patients, which can be a cost-saving strategy for patients since all doses are priced similarly. However, doctors said Levitra and Cialis tablets don't break as easily as Viagra tablets. A California doctor said, "You can't split Levitra because it is not as strong (as the others). Patients don't split Levitra because then there is not enough bang for the buck. Cialis I do split."

ABBOTT'S ABT-724

Sources offered a mixed outlook on this drug. One expert said, "It's promising, and it will be a nice addition for people who can't take a PDE5. It has a faster onset of action than the PDE5s." Others doubted it will ever make it to market.

GLAXOSMITHKLINE/BAYER/ICOS'S Levitra (vardenafil)

Numerous sources speculated that this agent may not survive. The company needs some new marketing approach, but no one could imagine a strategy that would work – except perhaps low, low cost. They also noted that the ban on use with any alpha blocker discourages use. A New York doctor said, "Levitra was never very generous with samples."

PFIZER'S Viagra (sildenafil)

- A Pfizer-sponsored trial of daily Viagra vs. placebo in 400+ patients is planned. An expert quipped, "PDE5 inhibitors may be part of men's health just as statins are today."
- Doctors insisted that the Viagra patients who switch to Cialis, and less frequently, Levitra, are primarily chronic, not intermittent, Viagra users. They explained that even patients who find Viagra effective want to see if they can do better with another agent. However, they are not sure whether these patients will remain on the alternative long-term, so there have been and could be further switches back to Viagra. A California doctor commented, "A lot of switchers are just experimenting. Those who stay on the new agent are mostly chronic Viagra users." A New York doctor said, "Some of the chronic Viagra users who switched felt that Viagra had weakened over time."

PALATIN TECHNOLOGIES' PT-141

Sources all were very positive about this nasally administered peptide. Nausea is an issue, but experts definitely did not think this was a fatal problem for the therapy. As a reminder, here are the Phase IIa side effects reported at AUA 2003.

PT-141 Phase IIa Side Effects in Viagra Responders

Side effect	Placebo	Low dose	High dose
Flushing	1%	12%	24%
Nausea	0	1%	13%
Vomiting	0	0	1%

A researcher from the University of Washington presented the results of a Phase IIb trial of at-home administration of PT-141 in 271 men who had a previous response to Viagra but no prostatectomy or spinal cord injury. This randomized, double-blind, placebo-controlled, parallel group study found no syncope or hypertension, and only one serious adverse event –

Results of 1-Month Phase IIb Trial of PT-141

Measurement	Placebo	5 mg	10 mg	15 mg	20 mg
Primary endpoint: International Index of Erectile Function(IIEF) increase	~1.5	N/A	~5 *	~8 *	~8 *
Global Assessment Questionnaire	~8%	~50%	~70%	~70%	~70%
% of men achieving EF domain ≥26	10%	30%	36% *	53% *	50% *
Improved erections (GAQ)	17%	49%	67%	66%	66%

*p<.05

a prolong, non-painful erection that resolved without treatment. Dropouts due to adverse events were 12.5% across all doses and were mostly due to vomiting or nausea. A "small" percentage of men had side effects related to nasal delivery, and flushing of about 30% occurred across all doses. The researcher said, "Nausea was worse at the highest dose. Many of the reactions were mild or moderate, but some required discontinuation." Dose titration studies are planned to assess PT-141 in the 7.5 mg-15 mg range."

The key advantage of this product over the PDE5s is that it not only facilitates erections but can initiate them. It also reportedly has rapid onset of action and no cardiovascular side effects. Phase I studies found no QT prolongation and no hypotension. The time to peak effect is 30 minutes. A researcher said, "I'm not saying it boosts libido, but if you take it, you may get some erectile activity before the onset of foreplay…We think this goes into the CNS…Men may be able to have multiple episodes of sexual intercourse…We don't have a clear definition of that yet."

WYETH

An official said his company is looking to get into the erectile dysfunction treatment area.

Penile Implants

An Ohio urologist said the rate of penile implants is starting to increase – and injections and vacuum pumps decline – now that men are starting to fail all three PDE5 inhibitors. An American Medical Systems (AMS) official said, "Our penile implants were down 2% in 1Q04…We think that is just a slight downturn and there will be a more positive pickup for 2Q04."

ED Drug Usage Issues

Twenty urologists at the meeting were questioned about trends relating to the ED drugs. Following are the findings from those interviews:

ED Use by Doctors Questioned at AUA

Issue	Average
% of male patients on ED therapy	39%
% of male patients who are candidates for ED therapy	59%
% of patients who try an ED drug and fail within 6-12 months	35%
% of patients who fail one ED drug and then try another	83%
% of patients who respond to a second ED drug after failing a first	28%
Patients who switch from Viagra to Cialis/Levitra are generally	Chronic Viagra users

Which of the three ED drugs (Viagra, Cialis, Levitra) is the most efficacious?

Cialis because there is more spontaneity and it lasts longer. A Texas doctor said, "I've had several patients give unsolicited testimonials. The spontaneity with Cialis is an advantage. It takes away the pressure of needing to perform in a four-hour window." A West Virginia doctor said, "Cialis is the most efficacious because of its prolonged effect. Patients find timing more difficult with the others."

Which of the three ED drugs (Viagra, Cialis, Levitra) is the safest?

There was no consensus on this issue. The longer safety data on Viagra was noted by several doctors, and one commented that Levitra is the least safe because of the contraindication with alpha agonists. However, each had its advocates, and some doctors believe they are all equally safe. A doctor commented, "Viagra is the oldest and best known, but younger men like Cialis because they want the longer duration of action and the spontaneity it affords."

Which of the three ED drugs (Viagra, Cialis, Levitra) is the most preferred by your patients?

Cialis. Doctors said patients are asking for Cialis because of the advertising. Most patients doing well on an agent are not asking to switch, and doctors are not recommending it if patients don't ask, but more than half of new patients are opting for Cialis. A doctor commented, "Patients all have comments about the commercials."

The factors most important to patients in making a decision as to which ED drug to take:

Ranked most to least important: 1) duration of action, 2) time to onset of action, 3) food interaction (though this is not very important), and 4) cost (which is really not an issue at all).

Positive/Negative Attributes of PDE5 Inhibitors

Drug	Biggest Positive	Biggest Negative
Viagra	Data Experience Ability to cut tablets in half	Lack of spontaneity Short duration
Cialis	Duration of action	Newness
Levitra	None	New drug Can't use with alpha agonists

Have you had noticeable stoppages of therapy with any one of the three agents?

No. It is probably too early to tell with the newer agents; they need to be on the market longer before this will be known.

Has sampling increased, decreased, or remained stable in the past few weeks after the initial launches of Cialis and Levitra? Have any of the companies started to curtail their sampling practices?
Sampling has remained stable, and none of the companies has noticeably started to curtail its sampling practices. One doctor reported a decrease in Viagra samples, and another doctor said Levitra sampling has been cut, "GlaxoSmithKline is going to vouchers instead of samples, which makes the Levitra prescriptions look higher than they are."

Have you been involved in the Cialis Challenge program in which Lilly/Icos provides a 5 tablet sample of Cialis and then a voucher for 5 free tablets of any one of the three ED drugs? If so, what has your experience been in terms of the ED drug that patients have chosen with the free voucher?
A few doctors questioned said they have participated in the Cialis Challenge, and all agreed that it worked very well. One commented, "It was a good tactic. Some patients liked it, and some didn't, but the program worked pretty well." Another said, "I just started doing it, and it is working well."

Given the fact that Viagra has lost some share to Cialis and Levitra, how is Pfizer fighting back? Does it have any new strategies to counter-detail Cialis and Levitra? Has Pfizer stepped up (or slowed down) its promotional effort in recent weeks?
Not surprisingly, Pfizer is not going to lie down and let Cialis and Levitra take more market share without a fight.

- Pfizer is countering the Cialis and Levitra marketing by pointing to studies Lilly and Bayer have done – but never published – showing their drugs could not prove non-inferiority to Viagra (implying they are inferior). The existence of those studies was revealed in European filings made by Bayer and Lilly.

- This is from Lilly's scientific discussion of Cialis in its EMEA filing. Obviously, Pfizer is emphasizing the part where highlighting has been added:

  "Comparative efficacy: The comparative efficacy with sildenafil 50 and 100 mg is unclear. Three active comparator trials are submitted one of them with characteristics of a pilot study. In the first well designed placebo controlled trial, **tadalafil 5 or 10 mg appeared superior to placebo, but it did not reach the non-inferiority margin as compared to sildenafil 50 and 100 mg. In another study, tadalafil at the maximum 20 mg is compared to sildenafil 50 and 100 mg but several deficiencies in the design preclude the acceptance of non-inferiority**:

  - As many as half of the patients suffered from mild ED, and it seems that there were patients included that did not suffer from ED according to the baseline IIEF scores. Scores of 27 and 30 are the upper limit of the basal IIEF scores (Normal 26-30).
  - Sildenafil (and tadalafil) was recommended to be taken 1-5 hours before sexual activity. However, SPC recommends that sildenafil should be taken an hour before sexual activity, based on PK/PD and clinical considerations. A window of 5 hours is considered too large and may have resulted in a lack of efficacy with sildenafil."

- This is from Bayer's scientific discussion of Levitra in its EMEA filing.

  "Study 10128, the second pivotal trial, is a randomized, double-blind, placebo-controlled (sildenafil), multicenter, fixed-dose, parallel-group study. Primary analysis was the comparison of vardenafil to placebo…The trial was also designed for testing the non-inferiority of vardenafil 10 mg as compared to sildenafil 50 mg. Some problems in the study design did not allow the conclusions to be considered as reliable."

- Pfizer is bombarding doctors with data, including long-term data, on Viagra.

- One Viagra theme being repeated is: "There when you want it, not there when you don't."

- One doctor said Pfizer reps have responded by citing a German study that found Viagra gives a better quality erection, but he didn't believe the findings. He said, "It was interesting, but it was obvious that the authors were supported by Pfizer, and the findings appeared biased and not well-documented." However, Pfizer officials appeared unaware of this study, and the company was not promoting it at the booth or the meeting.

- A Pennsylvania doctor said, "After the initial hit, Pfizer is retaining its market share because the same sales reps are marketing Detrol (for overactive bladder). They are not cutting our Viagra samples because they want to push Detrol and don't want to anger us…All the companies are doing a fairly good job in marketing."

Before the launch of Cialis and Levitra, the ED market in terms of patients was growing about 5% per year. By what percent do you expect the ED market to grow in terms of patients over the next six, 12, and 24 months?
An average of 10% for the next two years because of all the advertising, then slower growth after that. A West Coast doctor commented, "Levitra marketing is not working – not even the new ads with women."

Is the new market growth we have seen in the early days of the Cialis and Levitra launch coming from former Viagra users or ED drug naive patients?
Some has come from Viagra users, but mostly these have been new patients who expanded the market. A Texas doctor said, "I'm not actively trying to switch patients from Viagra to the newer drugs. One-third of my Cialis patients were on Viagra,

and the others were new to PDE5s. I usually recommend Cialis for new patients." Another doctor commented, "About 30% of Cialis and Levitra patients were on Viagra and wanted to try a new drug, but 70% were new patients."

BENIGN PROSTATE HYPERPLASIA (BPH)

BOSTON SCIENTIFIC'S Prolieve

This was approved by the FDA in February 2004 but officially launched at this meeting. The company claims 82% of patients are catheter-free post-procedure. What makes this microwave system different is:

- A balloon at the end of the catheter that first dilates the prostate, reducing heat sink.
- High wattage (≤50 watts).
- Flow through the catheter at body temperature (thermal dilatation).

However, it appears that Prolieve only improves urine flow by an average of 1.5 cc/second. Normal flow is about 15 cc/sec.

LASERSCOPE'S GreenLight PVP (photoselective vaporization of the prostate)

Among the advantages claimed for this 532 nm laser for therapy for BPH are: less pain, minimal catheterization time, and no limit on gland size. One of the factors driving this hospital outpatient technology may be reimbursement, which reportedly increased on April 1, 2004, from about $1,850 to about $3,750. The company is targeting hospital CEOs and CFOs with its marketing. A Laserscope official said most patient referrals are coming from existing patients and the Internet, "This is a very patient-driven procedure." A South Carolina doctor said, "It's dynamite."

ALLERGAN'S Botox (bolulinum toxin A)

Another new use for Botox was discussed at AUA: treating BPH. Dr. Michael Chancellor of the University of Pittsburgh School of Medicine said, "We have completed a number of studies that have shown Botox injections are a safe and effective treatment for conditions of the lower urinary tract. In this study, we have shown the same may be true for using Botox injections for enlarged prostate." The study included 11 patients. Three to seven days post-injection, the men showed a 62.3% improvement in irritative symptoms and a 56.5% improvement in quality of life. Flow rate also increased, and the men did not experience any significant side effects.

SPECIFIC COMPANIES

GTx

This company has two drugs in development, but sources were not very enthusiastic about either of them:

1. Acapodene (toremifene citrate tablets) – an oral, once-daily SERM (selective estrogen receptor modulator), which was licensed from Orion Corp. Positive results from a 12-month, double-blind, placebo-controlled, Phase IIb trial in 514 men with high risk prostate cancer were released shortly after AUA. The company plans to initiate a pivotal, 1,200-patient, two-year, Phase III U.S. trial of Acapodene to reduce the incidence of skeletal fractures, osteoporosis, and other serious complications of androgen deprivation therapy – with LHRH agonists such as TAP Pharmaceuticals' Lupron (leuprolide acetate) or AstraZeneca's Zoladex (goserelin acetate) – in men with advanced prostate cancer.

2. Andarine – SARM (selective androgen receptor modulator) for "male menopause." This has the potential to treat testosterone deficiency, or andropause, in aging men or related diseases, including male osteoporosis and muscle wasting. Several Phase I trials have been completed, and the company has a marketing agreement with Johnson & Johnson. A Maryland doctor said, "There is a lot of controversy over this now. While we believe a SERM would be good, maybe we should be more careful in males so we don't do more harm than good." However, the company reportedly enrolled PIN patients without a biopsy score, so a source said there could be a lot of noise relating to the entry of patients.

AMERICAN MEDICAL SYSTEMS

AMS reported surprising strong sales for the last quarter, boosted by women's health. Sales increased 25%, with women's health products up 61% year-to-year and male continence up 21% year-to-year. Douglas Kohrs, Chairman of the Board said, "Part of what really propelled our growth is the breadth of our product offering…We sell four different products…and they can really handle any condition – revisions, previous hysterectomy, peri-abdominal surgery… There really is no female incontinence instance that you couldn't treat with our product line. We believe we are the only company that can say that. Most competitors have one or two products…We also sell direct, not through distributors, even outside the U.S. Most companies our size use distribution networks, but we are direct everywhere except Asia, which is a small percentage of our business."

AMS is introducing several new products, including:

- **Sling**. Kohrs said, "This new product will allow doctors to do a sling...But if they are adverse to synthetic materials – if they are purists and want to harvest tissue from the patient – they can do that and still use Monarc…If they are a fan of porcine, they can do that."

- **HerOption,** a cryotherapy system for treating menorrhagia (excessive menstrual bleeding) without requiring a hysterectomy. This product is designed more for gynecologists than urologists.

- **A laparascopic cryotherapy** procedure to treat uterine fibroids. Kohrs said, "We figured a way to do the laparascopic procedure to target the fibroid and freeze it – cryotherapy for fibroids. We are the only people we know taking that tack…The message here is that there are 700,000 hysterectomies a year in the U.S., and with this and HEROption, we think 400,000 of those can be avoided...Many, many more women today want to keep their uterus." A Phase I study (under a PMA) is underway, and a pivotal U.S. study will follow.

- **Apogee and Perigee,** for female pelvic prolapse. Both of these products were submitted to the FDA (as 510K applications) at the same time, but Apogee is on a fast track, so it should be approved first. Kohrs said, "We believe there are 150,000 cystocele repairs done in the U.S. every year…Every one is done differently because there is no product for this repair…Doctors use sutures and all kinds of different meshes and attach them to different locations to get support. We are regimenting that procedure with a fixation method as well as the tissue. We have a patent pending on the procedure itself as well as the device. Apogee is our first product. It's for rectocele and interacele repairs and vault prolapse repairs. Second is Perigee, and that is predominantly for cystocele repair, which is a larger market…The problem with repairs is the high published failure rates. The success rate is about 65%. Our goal is to regiment it, train doctors, provide secure fixation, and get to 90% if we can – which avoids re-operations and associated problems."

- **Invance,** a new version of a male sling. Kohrs said, "We launched this in 1Q04, and it is helping to drive our male continence business."

- **The Tactile pump**, a new penile implant due to launch in 3Q04.

- **Intepro**, a large pore polypropylene mesh used for cystocele and rectocele repairs. It has been sold with the slings, but AMS is now selling it separately.

Other interesting notes about AMS:

- Last year AMS merged its male and female sales forces, and the company is continuing on that path.
- The average ASP for male products is $5,000, and it is ~$900 for female products.
- The make-or-break items for 2004 are, according to Kohrs:
  - Adoption of the Apogee and Perigee
  - Continued penetration of Monarc

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