Trends-in-Medicine

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By Lynne Peterson

SUMMARY

U.S. urologists view Viagra, Cialis and Levitra as equally safe and "functionally equivalent." Many plan to let patients choose which agent they prefer. European cardiologists are already prescribing Cialis and Viagra equally to new patients or plan to do so.

- Sources all plan to try Watson's Oxytrol patch for OAB, and doctors predicted it would capture 27% of their prescriptions within six months.
- Medicare reimbursement cuts for penile implants will put intense downward pressure on prices soon, but vendors are encouraging doctors to lobby CMS to revoke the change.
- J&J's TVT remains the most popular vaginal sling, but AMS's new Monarc is attracting attention.

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Following is a look at some select topics, drugs, and devices discussed or presented at this meeting, including overactive bladder, erectile dysfunction, penile implants, hormone therapy, vaginal slings, and benign prostate hyperplasia. In addition, 22 urologists were questioned about the outlook for various products.

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OVERACTIVE BLADDER (OAB)

The 12-week, 790-patient OPERA study, which will be published in June 2003, found that Pfizer's Detrol ER 4 mg and Johnson & Johnson's Ditropan XL, the current OAB market leaders, are essentially equivalent in efficacy and tolerability.

OPERA Trial Results

Measurement	Ditropan XL	Detrol	p-value
Primary endpoint: Change from baseline in mean weekly urge incontinence episodes	-26.3%	-25.5%	Nss
Reduction in mean weekly total incontinence episodes	-28.4%	-25.2%	p<.01
Mean weekly voiding frequency	23.0%	16.8%	p<.05
Total dry mouth	29.7%	22.3%	p<.05
Mild dry mouth	22.3%	17.3%	Nss
Moderate/severe dry mouth	7.4%	5.0%	Nss
Dizziness	3.8%	2.5%	---
Somnolence	1.0	2.3%	---

WATSON PHARMACEUTICALS' Oxytrol (oxybutynin patch)

Oxytrol, the newest treatment for OAB (urge incontinence), was approved in February 2003 but not officially launched until the AUA meeting. Most doctors were just starting to hear about it; few were very familiar with it yet. Only two of the 22 urologists interviewed were excited about Oxytrol. Many said they heard about it for the first time at the meeting, often at the Watson booth.

While doctors were not excited about the patch, they were interested in it, and everyone questioned saw a role for it. Some plan to offer patients the option of a pill or a patch, and let the patient choose (but reserving their choice of which pill). Others plan to use the patch for patients who develop a dry mouth problem or other intolerable side effect with Detrol or Ditropan. Most agreed with one doctor who said, "The proof will be in the pudding. I'll try the patch, but it has to perform in clinical practice or I won't keep using it." Another commented, "I will offer it as an option to patients and let them decide. It would be good if I could titrate it up. I've never used a patch yet, but that's not a barrier to my use." A California doctor said, "I'll try a pill first, and if there are too many side effects, then I'll try the patch." A Washington doctor said he is reluctant to try new drugs right away, but he may try Oxytrol "because the drug has been out a long time." Another said, "I'm not excited, but I'm interested."

OAB experts were the most optimistic about the patch. One said, "Americans prefer pills, but the patch really does have less dry mouth. Initially, there will be huge enthusiasm, but in six months, we'll see. I have patients I want to try on it, but I don't know if the lack of dry mouth outweighs the skin irritation with the patch. And I've never prescribed a patch in my life." Another OAB expert said, "I'll try the patch ahead of the pills because phone calls are not from patients complaining of lack of efficacy but from patients with dry mouth." A third said, "There definitely is less dry mouth with the patch. The highest dose right now is 3.9 mg, which is comparable to 8-9 mg Ditropan XL, but the question is whether that is enough to help severe patients. It needs a higher dose, and the company is investigating smaller patches with a double dose. That's what they need…Patches also are gaining popularity because of HRT, so I think this will catch on pretty well."

However, every source plans to try the patch. A New Jersey doctor said, "If it works, it will find a place." A New York doctor said, "I am pretty excited because it is supposed to have less dry mouth. It sounds too good to be true, but it is worth trying." Another doctor said, "I'm not excited about it, but I'll try it. If it works, it will be huge." A Nebraska doctor said, "Oxytrol will be appealing if the side effect profile really is lower. I'll try it."

In six months, urologist predicted an average of 27% of their OAB patients would be using Oxytrol. A New York urologist said, "I'll offer it to all of my patients, and I expect about half of them to choose it." A Michigan doctor said, "It will expand the market." A Utah doctor said, "More than half my patients will be on it in a year, if it really works."

Some doctors said they will use the patch for patients who complain of too much dry mouth from Pfizer's Detrol or Johnson & Johnson's Ditropan XL. A California doctor said, "I'll try Oxytrol in pill failures or if a patient has too many side effects from the pills." A Maryland doctor said, "Initially, I'll reserve Oxytrol for pill failures or patients with too much dry mouth on pills." A New York doctor said, "I'll start it in refractory pill patients."

However, several urologists said they will offer patients Oxytrol as first-line therapy. A Connecticut doctor said, "I'll offer it to patients along with the oral medications, and let them decide." An Oregon doctor said, "How much I use depends on how many samples I get."

Although many urologists already prescribe patches for testosterone therapy, most are less familiar with patches than some other specialists, but that doesn't appear to be a problem for Oxytrol. A New England doctor said, "I've never used a patch yet, but that's not a barrier to use of Oxytrol." A Texas urologist said, "Patches are gaining popularity because of HRT. I think Oxytrol will catch on pretty well…I'll try it before pills. The phone calls doctors get aren't from lack of efficacy of the pills but from the dry mouth side effect." A North Carolina doctor said, "Urologists don't use a lot of patches, not as much as gynecologists, but the patch could be very good – just not in patients with a catheter. I'll try it in patients taking orals who have side effects."

One question raised about Oxytrol is the dosage. Oxytrol delivery 3.9 mg per day of oxybutynin, and the company recommends the patch be changed twice a week. A Texas doctor said, "The question is whether the dose is high enough to help severe patients." A New England doctor said, "If I could titrate the dose up, it would be good."

Watson is pricing Oxytrol about 10% below Detrol and Ditropan XL. Interestingly, most urologists did not cite price as a reason for wanting to try Oxytrol.

INDEVUS'S trospium chloride

Trospium has been sold in Europe for many years by Madaus, and more than 265 million doses reportedly have been given there, and during the AUA meeting – on April 28, 2003 – Indevus filed an NDA for trospium chloride. Experts predicted that Indevus' trospium chloride would succeed because it (1) doesn't cross the blood brain barrier, (2) has comparable efficacy to Ditropan XL, and (3) is better tolerated than Ditropan XL.

An Indevus official said the company hopes to launch trospium in May 2004, and the claims may be:

- Less dry mouth than oxybutynin or Detrol.
- Equal or slightly better efficacy than Detrol.
- No P450 metabolism.
- Concentration in the bladder, which "is where you want an OAB drug to be."
- Quicker onset than other agents (i.e., quicker than four weeks).

Trospium is an anticholinergic as are the other major OAB agents. It hits muscarinic receptors 1-5, and appears to hit them non-selectively. The company has done QT studies and reportedly found no QT issues. Constipation is in the range of 1%-3%, which is similar to the other agents.

Madaus also did two studies of trospium:

- 52-week study of ~360 patients, comparing trospium chloride and oxybutynin. Reportedly, this showed, trospium comparable in efficacy but better tolerated, with less dry mouth. The abstract is in press and will appear soon in the *World Journal of Urology*.
- Small study comparing trospium, Detrol and placebo. This reportedly showed slightly better efficacy with trospium, but it wasn't statistically significant. There was a statistically significant decrease in frequency with trospium over placebo, but Detrol was not statistically significantly lower than placebo in frequency. Thus, an Indevus official said superiority really can't be drawn from this study, though it did show at least comparability, with a hint of superiority.

New Phase III data was presented at the AUA. This 523-patient, double-blind, placebo-controlled trial compared trospium 20 mg BID and placebo over 12 weeks.

12-Week Phase III Trial of Trospium*

Measurement	Trospium 20 mg n=22	Placebo n=261	p-value
Co-primary endpoints			
Change in frequency of voids per 24 hours			
Week 1	-1.3	-0.8	p=0.05
Week 4	-2.2	-1.2	p<0.0001
Week 12	-2.4	-1.5	p<0.0001
Change in frequency of episodes per 24 hours			
Week 1	-40%	-28%	p<0.05
Week 4	-60%	-40%	p<0.05
Week 12	-60%	-45%	p<0.05
Secondary endpoints			
Change in volume voided (ml) per void			
Week 1	20	7	p<0.0001
Week 4	30	9	p<0.0001
Week 12	33	8	p<0.0001
Adverse Events			
Dry mouth	21.7%	6.5%	N/A
Constipation	9.5%	3.8%	N/A
Headache	6.5%	4.6%	N/A
Abdominal pain	3.1%	1.1%	N/A
Diarrhea	3.1%	5.4%	N/A

*All numbers approximations from a bar graph

Urologists interviewed at the meeting predicted that it would be hard for Indevus to market trospium against Detrol and Ditropan XL. The dose also may not be high enough, one expert noted, explaining, "The highest does is 3.9 mg (which is equivalent to 8-9 mg of Ditropan XL in efficacy). The company is working on smaller patches with a double dose, which is what they need." Another expert said, "Trospium is interesting because it is not metabolized by the liver, and that might make a difference."

Indevus wants a partner for this drug, though an official said the company could field a 100-person sales force to sell it to urologists. An official said, "There are a bunch of companies with one urology product, and this would be great for them." Indevus believes OAB is an expanding market and hopes to capture a piece of it.

Pagoclone. Indevus also has an anxiety drug in development. It licensed pagoclone to Pfizer, but got the drug back after one study was positive and another negative. An Indevus official said that there are now three positive studies, and three negative studies with pagoclone, but Indevus is not giving up on this agent. In fact, he said Indevus is in due diligence with two or three companies over this agent.

PFIZER

Pfizer appears to have a CRF-1 (corticotropin-releasing factor) in development and has offered samples to a key research lab to do studies. Pfizer studied a small molecule CRF-1 (CP-154,526) in rats for depression about four years ago, but it was dropped.

Other CRF-1 companies (perhaps Neurocrine Biosciences, Taisho Pharmaceutical Co. of Japan or Merck) declined to provide their drug to this lab, so this would seem to indicate Pfizer has some degree of confidence in its agent. Several other companies have tried unsuccessfully to develop CRF-1s, including Johnson & Johnson's Janssen Division, which reportedly dropped its CRF-1 because of liver toxicity problems.

ALLERGAN'S Botox

Botox kept coming up at sessions – for use in OAB and through direct injection into the prostate to treat benign prost hyperplasia. An expert said, "Botox is beginning to take off as off-label use by general urologists for OAB. It is long lasting – three to six months." Another expert who has started doing Botox said, "It is slowly catching on, but they need randomized studies. Reimbursement is the big problem right now."

Several other urologists expressed interest in Botox, and said they might be interested in using it more often if reimbursement clarifies. Currently, payors will only cover it in rare situations.

Other OAB agents on the near horizon

➢ **LILLY'S duloxetine.** This is for stress incontinence, but it is likely to be used off-label for OAB. An OAB expert predicted that duloxetine would "make a big splash, but a lot of urologists are pooh-poohing it because they don't know a lot about it. Duloxetine is harder to understand than the other OAB drugs. Lilly has more of a track record with OBGYNs than urologists. But the research and the concept are interesting, sound and elegant."

➢ **NOVARTIS'S darifenacin,** which was recently purchased from Pfizer. Sales reps at the Novartis booth said they only just learned about the purchase, and they haven't been told who will sell it since Novartis does not have a urology sales force, though they admitted they (the oncology sales reps) probably could sell it to urologists along with the company's bisphosphenate, Zometa (zoledronic acid). A urologist commented that the drug has a high rate of constipation, adding, "I'm not sure Novartis bought the right drug."

➢ **YAMANOUCHI'S Vesicare (solafenacin, YM-905).** Experts offered contradictory opinions of Vesicare, which will be marketed in the U.S. by Aventis. One said it appears to be more effective than either Detrol or Ditropan XL, "Yamanouchi makes Flomax (Abbott, tamsulosin), and that took down the other alpha blockers because it was a little better. This new OAB drug could do the same." However, another expert said the drug "definitely has a problem."

Phase III Trial Results at 12 Weeks

Measurement	Placebo N=301	Solifenacin 5 mg n=299	Solifenacin 10 mg n=307
Primary endpoint: Change in mean number of micturitions in 24 hours	-13%	-20% *	-23% *
Urgency/24 hours	-35%	-45% *	-53% *
Incontinence/24 hours	-34%	-65% *	-56% *
Urge incontinence/24 hours	-35%	-66% *	-61% *
Volume voided (mL)	-7%	-21% *	-25% *
Nocturia/24 hours	-24%	-30%	-39% *
Nocturnal voids/24 hours	-25%	-28%	-36% *
Adverse Events			
All	38.8%	43.5%	48.2%
Dry mouth	2.3%	7.7%	23.1%
Constipation	2.0%	3.7%	9.1%
Upper abdominal pain	1.0%	2.3%	0.7%
Dyspepsia	1.0%	1.3%	2.3%
Blurred vision	2.3%	4.0%	5.9%
Urinary tract infection	0.3%	3.3%	1.3%
Discontinuation due to side effects	3.0%	2.3%	3.9%

* $p<0.05$

Sources raised several questions about this agent, including:

- It reportedly has an 80 hour half life.
- The 5 mg reportedly is more effective than the 10 mg dose, and this is the dose with which the company appears to be proceeding.

Analysis of Two Pooled Double-Blind, Placebo-Controlled Vesicare Studies

Side Effect	Placebo n=648	Vesicare 10 mg n=658
Dry mouth	4.8%	32.2%
Constipation	3.7%	17.6%
Nausea	2.9%	5.2%
Dyspepsia	1.2%	5.0%

ERECTILE DYSFUNCTION (ED)

Since Pfizer's Viagra (sildenafil) was approved, more than one billion pills have been dispensed. The average age of a man seeking treatment has dropped since the launch of Viagra from 59 to 52, and the average duration of ED before the man-sought treatment has dropped from five years to 18 months.

There are an estimated 30 million men in the U.S. with ED. Only 10-12% of these men are actually using Viagra. Thus, speakers predicted that new agents would not only try to take market share from Viagra but that they also would try to expand the market through direct-to-consumer advertising.

Among the slogans doctors expect:

- "Proven."
- "You know what you get."
- "Don't think about it."
- "Take it every day."
- "Faster."

Urologists aren't treating most of ED today. Eighty-five percent of new prescriptions for Viagra are written by non-urologists. So, the preference of urologist or their planned use of new agents may not reflect what will happen in the marketplace.

What do urologists at the meeting plan to do when all three agents -- Viagra, Lilly/Icos's Cialis (tadalafil) and Bayer/GlaxoSmithKline's Levitra (vardenafil) -- are available? Many said they would give patients a sample of each, let patients try them all and then decide which works best. One speaker said, "We don't have to decide what patients should use. We can make them all available, and let patients decide what is efficacious, as long as patients have informed consent." Another commented, "I may have patients try all three, and see which works best, unless insurance companies bar that. I'll have samples of all of them, and give patients some of each to try."

While there was considerable discussion of the new agents, speakers were generous with their thanks to Pfizer for bringing Viagra to market in the first place. One speaker commented, "Everyone is bashing Viagra, but it basically is a good drug, the gold standard, and has an excellent safety profile…Pfizer deserves credit for bringing us this drug."

Speakers repeatedly emphasized the similarity of Viagra, Levitra and Cialis. One said, "What is striking to me is not the differences between the agents but the similarities."

The one difference that appears to have caught the attention of some urologists is duration of action, which is longest with Cialis. An expert said, "The one difference for me as I look and hear the data is the prolonged half-life of Cialis. A few years ago, I heard about daily Cialis with low toxicity, and I remember thinking…about the idea of being ready every day, of taking an (ED) pill like a vitamin…That won't happen for some time, and Cialis is not being marketed that way, but it is an interesting concept and viable in theory. You couldn't take the others daily and be ready all day long."

Speakers also warned urologists about claims companies may make to try to differentiate their product. One commented, "There are no head-to-head trials published, so be careful of whatever company claims you hear." Another warned against putting too much emphasis on speed of action, "Most men without or with ED take one hour between the first thought of sex and the actual act, most have sex once in 24 hours, and most men are only sexually active once a week." A third said, "Use caution comparing study results. We do not know what the FDA knows, head-to-head comparative trials are lacking, different patient populations were selected for trials which may impact treatment outcomes, and outcomes measures must be the same for comparison." A fourth said, "None of the pills is absorbed in the stomach. They are absorbed in the small intestine, so their action is slowed down by meals, by fatty foods, so there will never be an instant pill."

Potency of PDE5 Inhibitors

Drug	IC50 nm *	K_D nm *
Levitra	.091	.38
Cialis	1.8	2.4
Viagra	3.7	4.8

*** the lower the number, the more potent**

Receptor Binding of PDE5 Inhibitors

Drug	PDE-6	PDE-11
Viagra	10	11
Cialis	1187	780
Levitra	25	1160

The cardiac safety of all these agents was emphasized – and it was described as very similar for all. The nitrate contraindication with Viagra was described as a class effect. There was even a hint that Viagra and Levitra (and maybe Cialis) may be cardioprotective. One said, "(In trials) vardenafil had a favorable cardiovascular safety profile, and the overall incidence of CV-related adverse events was similar to placebo." Another speaker said, "(In five studies) the overall rate of MI with Cialis per 100 patient years was 0.43%

Comparison of PDE-5 Inhibitors

Issues	Viagra	Cialis	Levitra
Food /alcohol interaction	Less efficacious after consumption of high fat meals	None. Can be taken with regard to food, including a high fat meal and alcohol, but less effective when taken with high fat meal	Take 25-60 minutes prior to eating, but little or drop in efficacy by high fat meal
Visual side effects	4%	No	No
Headache	13%	11% - 14%	18%
Myalgia	0.9%	5.7% - 12%	0
Back pain	No	6.5% - 8%	No
PDE-11 inhibition	No	Yes – but meaning unclear (questions raised about lowered sperm count)	No
Half-life	4 hours	17.5 hours	4.5 hours
Cardiac safety	Yes	Yes	FDA Advisory panel to consider QT prolongation on May 29, 2003
Onset of action	30-60 minutes	45-60 minutes	25 minutes
Duration of action	4 hours (label) but in practice often much longer	24-36 hours but bioavailability may decrease sooner	4 hours
Potency	Least	Middle	Highest
Drug-drug interaction	Nitrates Alpha blockers HIV drugs	Nitrates	Nitrates Alpha blockers HIV drugs

vs. 0.6% with placebo." A third said, "Now, there is enormous data that the class does not have cardiac safety issues."

There was no mention by any speaker of a QT issue with any of these agents, and there was no mention whatsoever of the FDA Cardio-Renal Drugs Advisory Committee meeting on May 29, 2003, on the QT prolongation effects with Levitra. An expert said, "The death and MI data on all three are similar to placebo. I don't know what is going on with the FDA in terms of QT. I didn't see any sign of it in any of the data presented." Another commented, "There have been about 17,000 EKGs with that drug, and there was no hint of a problem. I don't know why the FDA has raised questions."

LILLY/ICOS' Cialis (tadalafil)

The Cialis sperm study was formally presented. Two mouse studies and one rat study found no signs of toxicity and no pathological changes to organs, including the testes. However, there were histologic changes in a few beagles, which raised a concern. A double-blind, randomized, placebo controlled trial in men who were healthy or had mild ED was conducted, comparing placebo to 10 mg Cialis and 20 mg Cialis given daily for six months. Patients were all followed for another six months after the Cialis was stopped.

Effect of Cialis on Sperm Count

Measurement	Placebo	10 mg Cialis n=204	20 mg Cialis n=217
Primary endpoint: ≥50% reduction in sperm concentration from baseline	3.4%	2.3%	5.7%
Mean sperm concentration (in millions)	81.5	74.9 (p=.02 vs. pbo)	76.8 (p=.913 vs. pbo)
Sperm count/ejaculate	-22%	-41.7% (p=.089 vs. pbo)	-25%

Numerous experts were asked what this means, and they all focused on the 20 mg dose, which they felt showed the drug is safe. However, most of these same doctors said Cialis might be problematic in men who already had a low sperm count and cared about their reproductive status, and they would not give Cialis to those men – though they estimated this is not a large percentage of men with ED. One said, "The important thing is that you didn't see it (sperm concentration reduction) at the higher dose." Another said, "There is a concern in men with impaired sperm count, subfertile men, but most men using this medication are not concerned about reproduction…But I think Cialis will be asked about QT as well, eventually."

European doctors were generally unfamiliar with the suggestion that Cialis may reduce sperm count, and they all agreed that, even if it does, it is a non-issue. A French doctor said, "These men only care about intercourse, not sperm count." A German doctor said, "Fertility is not an issue." Another German doctor said, "Sperm count is not a concern to men of this age." A Dutch doctor said, "I don't believe it does affect sperm count." Another source said, "If there is a concern about sperm count in the U.S., that would be a cultural issue. It is not an issue for these men in my country."

18-Month OUS Cialis Safety Study

Side Effect	Incidence
Headache	15.8%
Dyspnea	11.8%
Nasopharyngitis	11.4%
Back pain	8.2%
Flu	4.4%
Hypertension	4.1%
Flushing	3.6%
Nasal congestion	3.6%
Arthralgia	3.5%
Cough	3.2%
Flu-like illness	3.2%

American urologists were equally unconcerned about the issue of sperm count, and several commented that they didn't even think competitors would be successful using this issue in counter-marketing. A Nebraska doctor said, "Sperm count is a non-issue." A Utah urologist said, "Doctors will simply explain it to patients if they ask. It is not an issue." A Maryland doctor said, "Sperm count is not a concern. There is no hypothetical mechanism of action that would cause it, and most ED men are beyond wanting kids."

Yet, several doctors commented that they see no reason to change from Viagra to a new ED medication unless the man hasn't responded to Viagra. A Maryland doctor said, "A company needs to show me an advantage to cause me to switch from Viagra. Viagra is sampled in packages of six 50mg pills, and patients can cut the 100 mg pills in half to reduce the cost if the 50 mg works. Cialis might be good if it works longer, but the Viagra brand is recognized like Kleenex for tissue." A Washington urologist said, "I plan to keep on using only Viagra. Years ago, I would have jumped on the bandwagon of a new drug sooner than I will today. Unless something has a really compelling clinical advantage, I prefer to wait and see the safety, especially for drugs in the same class. Something has to be a lot better to get over the long-term data with Viagra."

PDE-11. Questions have been raised about Cialis's inhibition of PDE-11. Cialis is the only one of the PDE-5 inhibitors that also inhibits PDE-11. Speakers generally downplayed any negative effect of this PDE-11 inhibition, but the issue continues to hang over the drug. One expert said, "I don't think it is a problem, and it shouldn't keep Cialis off the market, but we can't say yet that it isn't an issue." Another

commented, "PDE-11 is a potential problem for Cialis." A third commented, "There was a drop in sperm production in beagles, but not in rats. In the six-month study, where patients took the drug daily. There was a decrease in sperm count at 10 mg but not at 20 mg, so it is not a drug effect because there was no dose response curve. This should put the issue to rest." A fourth said, "(A study to be presented at the meeting) shows no effect on motility, sperm count, testicular hormone production, or pituitary function. However, that study was done in healthy men. The question is whether it could have a deleterious effect if the men had a low sperm count to start."

Bioavailability. While Cialis has the longest duration of any of these drugs, a speaker raised questions about the bioavailability of Cialis, saying, "How much is getting to the cell. There is some discrepancy in studies by different labs."

Cumulative effect. An expert said that the cumulative maximum efficacy is reached after five doses, and then the increase stops.

PFIZER'S Viagra (sildenafil)

A 12-week, double-blind study examined whether adding topical testosterone to oral Viagra (100 mg) would boost the performance of Viagra. In this study, 75 Viagra patients with moderate to severe ED either used a placebo gel or Unimed Pharmaceuticals' AndroGel 5 g (testosterone 1%). At week 4, the combination significantly improved erectile function, orgasmic function and sexual satisfaction, but there was only a trend to improvement with the combination at 8 and 12 weeks. The researcher concluded, "Testosterone replacement therapy with AndroGel 5g improves erectile response to Viagra 100 mg and may be considered for the treatment of ED in men with low to low-normal testosterone who have failed prior treatment with Viagra." Asked why there was a benefit at four but not eight or 12 weeks, he said, "We honestly think it was a sample size issue…We believe the sample size was marginal to start, and with the dropouts, it became too small."

Tachyphylaxis. A speaker commented, "Not only does Viagra work, but it keeps on working. Men who respond continue to respond. Any tachyphylaxis is more likely due to progression of the underlying disease."

Possible new indications being explored for Viagra:

- Pulmonary hypertension
- Female sexual arousal disorder
- Prevention of endothelial disease
- Premature ejaculation

Direct-to-Consumer Advertising

With the launch of new ED drugs, direct-to-consumer advertising for ED is expected to increase, so a speaker reviewed DTC advertising. In 2000, pharmaceutical companies spent $2.5 billion on all DTC advertising, compared to $4 billion for office detailing, $765 million for hospital detailing, $484 million for medical journal ads and $8 billion for samples. A speaker pointed out that less than half of the ads in 70 issues of 10 leading consumer magazines in 2000 discussed efficacy – and none mentioned cost.

DTC has caused patients to talk to their physicians earlier and to have more information about their choices, though, a speaker pointed out, that information "comes from a clearly biased source." It has de-stigmatized ED, and it may help improve compliance, though there is no data on that. Academic detailing (academic center doctors educating community doctors) was supposed to be the panacea to counter pharmaceutical detailing, but no one in the audience at this talk on DTC seemed to know what academic detailing was, indicating it hasn't been very effective. A speaker said, "We doctors should be able to advertise our own results as well as pharmas do, but we can't because none of you have heard of this."

What's the answer? The speaker said there wasn't enough data to ban DTC, so physicians needed to be educated about how to respond to inappropriate requests and how to talk to patients about the efficacy of the various drugs.

Future Erectile Dysfunction Therapies

Among the agents under investigation are:

Topicals

- **Nitroglycerin**
- **Alprostadil,** including NexMed's Alprox and MacroChem's Topiglan. These have no serious drug interactions, are very fast acting, have a short half-life, and have a low incidence of systemic side effects. A speaker said, "Patients may prefer this to injection therapy. In our studies there were a number of men who were ecstatically happy with these therapies."

Centrally acting agents

- **Dopamine** – which is approved in Japan.
- **Potassium channel openers** (KCOS). AstraZeneca, Wyeth and Abbott all are working on these. The concern is possible cardiac toxicity. These agents will have to prove they do not cause excessive hypotension, change in QT, etc.
- **Rho-Kinase.** Yoshitomi Pharmaceutical Industries' Y-27632 (azasetron) is in early rat studies have been promising. A speaker said, "The problem is whether it will affect vascular and non-vascular smooth muscles, although intracavernosal delivery, including gene therapy, may be a possibility.
- **Soluble guanylate cyclase (sGC) activators.** Bayer, Abbott and Aventis are working on these.
- **Gene therapy**

- **Melanocortins**:
  - Merck's MT-II, and MCR-4 agonist which acts in the brain and spinal cord to induce erections. Merck's drug is starting a Phase IIb study on April 28, 2003.
  - Palatin Technologies' PT-141, an analog of MT-II. A Phase IIa study of this agent reportedly showed good efficacy. Competitive Technologies licensed this agent, which was invented by researchers at the University of Arizona, to Palatin.

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%

PENILE PROSTHESES

Two companies – Mentor and American Medical Systems (AMS) -- share the penile prosthesis market since Endocare sold its flexible prosthesis line to AMS. Both Mentor and AMS have products designed to reduce infections with penile implants, which occur in 1% - 5% of cases. Infections can occur at any time – immediately after implant or weeks, months or years later.

- **AMS** has the InhibiZone, an antibiotic-coated device.
- **Mentor** has the Titan, which has an anti-adherence coating. Mentor also is touting its lock-out valve modification that a speaker said diminishes the prevalence and severity of auto-inflation.

The big issue in penile implants is Medicare reimbursement. An AMS official said about 60% of implants are in Medicare patients, and on January 1, 2003, CMS cut reimbursement. A typical device costs from $5,300-$6,100, with the average hospital cost ranging from $2,000-$2,500. As part of its new Outpatient Prospective Payment System reimbursement, CMS now pays $4,900 for the combination of device and hospital costs. Thus, hospitals now are reimbursed less than the device costs, leaving nothing to cover their costs for the surgery. This translates to a 33%-43% reduction in total reimbursement. The physician fee is separate.

A coalition has been formed to urge CMS to review and revise this reimbursement. Coalition supporters claim the methodology CMS used was flawed. Hospitals are not involved in the effort, though one expert said they are watching it.

Prior to the reimbursement change, about 7% of urologists did all the penile implant surgery, and urologists who specialize in the surgery predicted this trend would continue. He said, "My concern is that hospitals will say doctors can't do them any more."

Some ED specialists are worried that unless reimbursement is increased, one or both of the companies might decide to exit the business. A source said penile implants are not high margin products, but they are profitable items. Sources insisted no price cutting has occurred – yet – because of the reimbursement change, but they said they expected that in the future, perhaps by next year, hospitals would put pressure on Mentor and AMS to lower prices. That's when sources are worried that one of the companies might choose to exit the business instead of lowering prices significantly.

HORMONE THERAPY

TAP Pharmaceuticals' Lupron (leuprolide acetate) is the top choice for these urologists for anti-androgen therapy, but some prefer AstraZeneca's Zoladex (goserelin acetate), and a few use both Lupron and Zoladex. Not a single source is prescribing any of Sanofi-Synthelabo/Atrix's Eligard (leuprolide acetate) yet, and most have no plans to try it. An Oregon doctor said, "I use Lupron 4-month mostly, and I have no interest in Eligard." A Massachusetts doctor said, "There is no advantage to Eligard." A New York doctor said, "I've never been detailed on Eligard, and I have no interest in it."

However, two doctors plan to try Eligard. A Texas doctor said, "I've been using Lupron, but I'll try Eligard because it's administered subcutaneously." A Nebraska urologist said, "I use Lupron, but Eligard will catch on slowly. The subcutaneous injection in the arm will be nice for some patients. The problem is the cost of stocking more than one product. Doctors have to pay in advance for it, and they get volume discounts, so they don't usually use more than one product."

VAGINAL SLINGS

The surgical treatment for stress incontinence is a pubovaginal fascial sling. In these operations, urologists 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.

Very few urologists questioned at the meeting were using any of these commercial sling products. A urologist who uses the Cook Stratasis said, "I like the idea of TVT, but the Cook Stratasis is not synthetic. I will take a look at the Monarc." A New Jersey doctor said, "Monarc is probably more for OBGYNs." Another doctor said, "I tried TVT, but the erosion rate was too much, so I stopped, and now I do mostly fascia slings." A New York doctor said, "I'm interested in Monarc; it looks like a winner."

Comparison of Commercial Slings

	J&J's TVT	AMS' Sparc	AMS' Monarc	Cook's Stratasis TF	Mentor's Sabre
Approximate cost	$795	$795	$995	$695	~$795
Advantages	Easier than Sparc in obese women	Top-down approach	May appeal to OBGYNs; can do repeat procedure; maybe fewer complications	Only FDA-approved biomaterial; Natural, not synthetic material	Only self-anchoring
Success rate	Good	Good	Good	Good	Good
Approach	Bottom-up	Top-down	Through obturator foramen	Either top-down or bottom-up	Top-down
Material	Polypropylene mesh	Polypropylene mesh	Polypropylene mesh	Natural: porcine small intestinal submucosal	Bioresorbable synthetic polymer

Asked what the impact of Lilly's stress incontinence medication, duloxetine, is likely to have on the sling market when it is launched, an AMS official said, "The PDE5 model will be played out in slings, too, but the effect of duloxetine won't be as much as Viagra. Growth in sales may slow, but it won't decline.

JOHNSON & JOHNSON/GYNECARE'S TVT (transvaginal tension-free) sling. This was the first synthetic system, and it remains the market leader. It uses a "bottom-up" (antegrade) approach to insert a polypropylene mesh sling to support the middle of the urethra .

MENTOR

➢ **Sabre**. This is the only self-anchoring product, and it has a bioresorbable mesh that is incorporated into the body. Mentor also plans to introduced a trans-obturator product to compete with AMS's Monarc sling. Mentor bought Porges, which has had a trans-obturator sling in Europe since 1999, with 9,000 patients treated so far, and this is the product Mentor is bringing to the U.S. A Mentor official said, "We have data, and AMS doesn't. We will be using our bioresorbable material and our trocars."

➢ **Suspend** and **Axis**. These slings are made of specially processed human tissue.

BOSTON SCIENTIFIC'S Advantage. The company launched its new sling last fall but quickly canceled the launch after doctors evaluating in pre-launch tests warned that "the bells and whistles are nice but it could cause some problems and needed a redesign." A Boston Scientific official said the company hopes to bring the revised version out in summer 2003. This will initially be a bottom-up system, but a top-down version is planned for the future.

COOK'S Stratasis TF. This is made out of small intestinal submucosa (SIS), a natural (porcine) biomaterial that supports tissue remodeling. The patient's cells, tissues and blood vessels infiltrate the mesh and, in time, replace it with natural tissues. The needles with this system can be used for their a top-down or bottom-up approach.

AMERICAN MEDICAL SYSTEMS. Penile implants account for a third to half of the company's revenue, and slings for about 20% -25%. A company official said, "One percent of all our procedures used to be in females, but 67% of our procedures will be in females soon."

➢ **Sparc**. This polypropylene mesh sling system is very similar to J&J's TVT except that it is performed "top down" (superpubic) instead of "bottom up." Sparc will continue to be sold even after Monarc is launched. A sales rep said, "The advantage is there is less chance of bladder or bowel perforation with this approach."

➢ **Monarc**. This product received FDA approval in April 2003 and is expected to be launched in the U.S. in mid-2003; it has been available in some European countries since January 2003. An official said 6,000 cases have been performed in Europe, 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.

Monarc uses a very different approach, a trans-obturator approach, using corkscrew-like needles that go through the obturator foramen on each side, avoiding the retropubic space. Doctors need to take a class to learn the procedure, but officials insisted it was easy to learn. A sales rep said, "There have been a lot of complications with both the top-down and bottom-up approaches. That's the reason for Monarc. Among the advantages of Monarc are the thinner, ergonomically designed needles and less cumbersome to use."

Another official said the theoretical advantages of Monarc are: (1) fewer complications and (2) the ability to do a repeat procedure on a woman who had a previous sling.

AMS has merged its sales force for male products with the sales force for female products, so that now all sales reps support all products. The company hopes that will help them increase sling sales. An official offered this message for urologists: "AMS is a company that now has the ability to provide choice for treating the needs of urologists in a way we couldn't before – a full spectrum for females and males." In the future, AMS hopes to combine devices with bioactivity, with a replacement for the polypropylene mesh.

BENIGN PROSTATE HYPERPLASIA

The current market leader is Abbott's Flomax (tamsulosin), but new competitors don't appear to be a major threat to that position. A urologist said, "A lot of men are unhappy with Flomax because of ejaculatory disturbances. They have sex and nothing comes out – retrograde ejaculation – and they are shocked when that happens. I don't think Avodart (GlaxoSmithKline, dutasteride) is likely to catch on. UroXatral (Sanofi, alfuzosin) needs a distinct advantage to sell." Another speaker said studies seem to show a greater effect with Avodart, a dual 5-α reductase inhibitor, than with Merck's Proscar (finasteride), but he did not believe that translated into a better clinical benefit for Avodart. The same speaker described UroXatral as having comparable efficacy to Flomax, but he suggested it may have less sexual dysfunction.

Other agents under investigation include:

- Endothelin receptor antagonists
- NO donors
- PDE inhibitors
- P2X3 inhibitors

LASERSCOPE claims sales are strong for its 532 nm Greenlight PV System, a 532 nm KTP laser for the treatment of benign prostate hyperplasia (BPH). The company claims to have 36 machines in the field now, compared to just six machines a year ago. Six machines were shipped to new customers in 1Q03, and another 20 machines reportedly are on order. The CEO predicted that this laser would account for 10% of the company's business this year.

The positives. A urologist doing this procedure said the advantages of this therapy are:

- Low post-op pain.
- Short post-op catheterization. A user said, From 60-70% of my patients don't require a cath at all."
- Less bleeding than with other procedures.
- Can be done while patients are on anti-coagulants or are in urinary retention.
- Long-term data available: 3 years on 66 patients, showing that the laser is effective and the results are durable.
- Less after hours calls from patients.
- Patients can return to work within two days.
- Relatively short learning curve for doctors.
- High level of patient satisfaction.

The negatives.

- *Cost.* The laser costs $88,000, but doctors also can pay a per-use fee or rent it. A separate company is offering the Laserscope laser on a mobile basis. Thus, doctors can "rent" a mobile laser (similar to the LVCI mobile excimer laser refractive surgery) if they want to try it out or have a low-volume of BPH. Reportedly, 60%-70% of the procedures are being done with mobile lasers. A California doctor who has done about 40 of these procedures said he still uses a mobile laser, and he estimated that a urologist would need 8-10 procedures a month to justify buying a machine. The Chairman of Urology at a major medical center said, "I plan to try a rental Laserscope on an anticoagulant patient and see how it does."

- *Reimbursement.* This is the biggest problem for Laserscope. Reimbursement for lasers is less than for TUMT or TUNA. Average out-of-hospital Medicare reimbursement for lasers is ~$1980, and the in-hospital physician fee is $572. This compares to about $2,700 total reimbursement for the Urologix TUMT, with the physician fee about $1,000 of this. So, doctors make more money doing TUMT or TUNA.

- *Laser history*. Many doctors had a bad experience with earlier lasers and are reluctant to try a laser again. However, five-year data from the Mayo Clinic is being presented at this meeting.

- *Location*. This is not an office-based procedure; it is done as a hospital outpatient procedures or at an ambulatory surgery center, under general anesthesia, a short-acting spinal, MAC with topical lidocaine gel, or a prostatic or pudental block.

- *Length of procedure.* The Greenlight procedure takes from 30-90 minutes, compared to about 6 minutes for the Johnson & Johnson Indigo laser.

The major laser competitors are Lumenis which has a holmium YAG laser, and J&J's Indigo laser (which costs $15,000-$20,000). J&J sources suggested that the Indigo laser is better for small (≤25 cc) prostates and that the Greenlight laser is better for larger glands in lieu of a TURP. The Indigo is minimally invasive, but the Greenlight is not. However, all Indigo patients are cathed, and that appears unnecessary with the Greenlight.

BLADDER CANCER

➢ A U.K. cell-line study suggested that AstraZeneca's Iressa (gefinitib, ZD-1839) may be a good radiosensitizer for subsequent radiotherapy of bladder cancer.

➢ A study suggested Millennium's **Velcade** (bortezomib, PS-341) may be synergistic with gemcitabine in chemo-therapy-resistant bladder cancer. ♦