Association of BPH with OAB:
The Plumbing or the Pump?

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Disclosure of Financial Relationships

Ryan P Terlecki, MD, FACS

Has disclosed relationships with an entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients.

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Objectives (in 20 minutes)

- Summarize data on relationship between OAB, urodynamic parameters, and voiding symptomatology in men with LUTS
- Review outcomes data on concomitant pharmacological treatment of OAB and BPE (‘H’ is histological)
- Discuss rates of persistent dysfunction after surgical relief of BOO

Audience Response Question 1

Audience Response Question 2

Overactive Bladder (OAB)

- Urgency +/- UUI, usu w/frequency and nocturia in absence of UTI or obvious pathology (clear overlap with male LUTS in many cases)
- OAB affects about 12-14% men and women >40y (in **52-80% of men with BOO**)
- Men more likely to have urgency, frequency, nocturia (women more UUI)

Abrams PH et al. *J Urol*. 1979;121:640-642.
Chapple CR et al. *BJU Int*. 1994;73:117-123.

Overactive Bladder (OAB)

- LUTS: Storage, Voiding, Post-Void
- Storage: Frequency, Urgency, Nocturia, UI (seen in 51.3% men, 59.2% women)
- Voiding: Slow FOS, Split stream, Intermittency, Hesitancy, Straining (25.7% men, 19.5% women)
- Post-micturition: PVD (16.9% men, 14.2% women)

Moss et al. Curr Urol Rep 2017. 18:1

Male LUTS

- Male LUTS involve **detrusor and outlet**
- BPE +/- BPO managed w/alpha blockers/5ARIs still leaves some men w/bothersome LUTS
- OAB meds **used less in men** despite similar prevalence of storage LUTS as women
- Numerous PCRCTs show antimuscarinics and beta-3 agonists, alone or in combo, improve storage symptoms, **without negative impact** on Qm, PVR, or incidence of retention

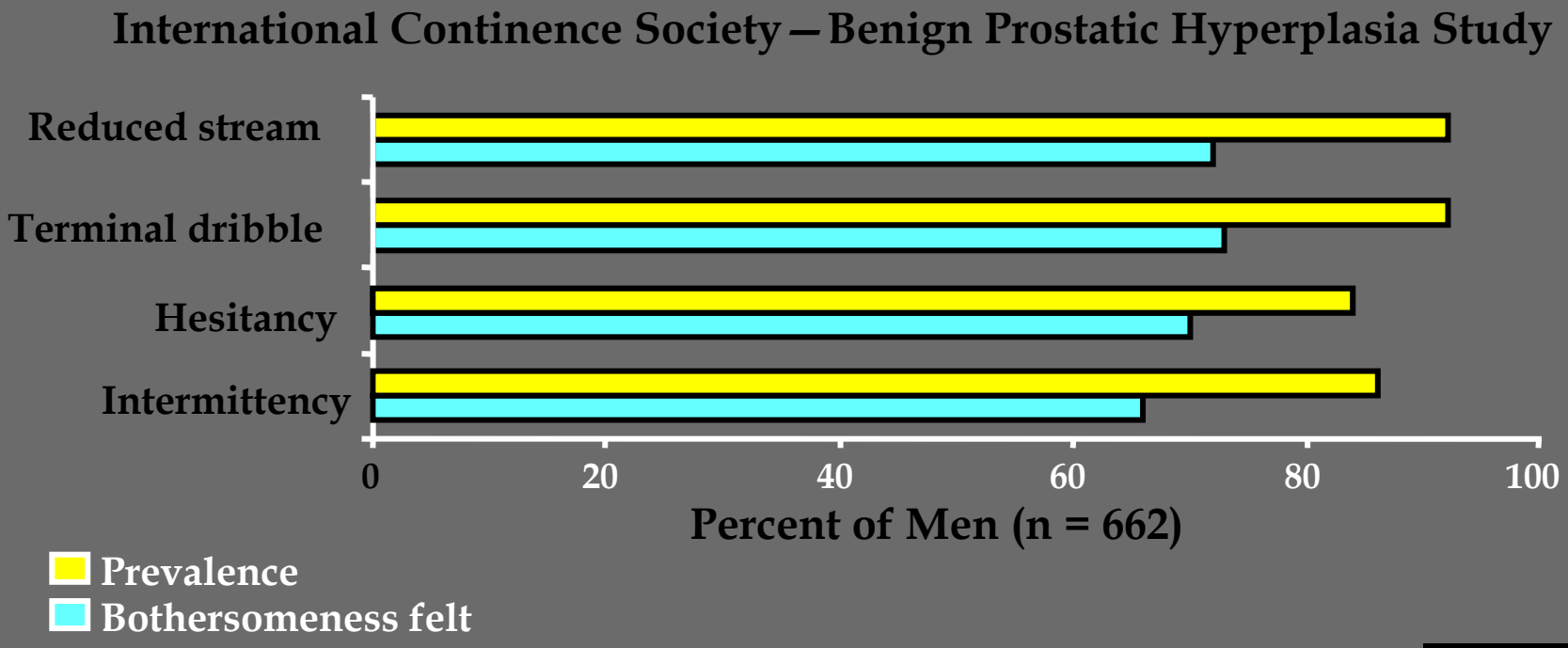
Moss et al. Curr Urol Rep 2017. 18:1

Male LUTS

- LUTS/BPH both increase with age
- Voiding symptoms may be more common, Storage symptoms more bothersome/embarrassing
- Men often first receive alpha blockers to treat storage symptoms (i.e., urgency) due to perception that BPE is cause, but storage LUTS remain bothersome in 2/3 men

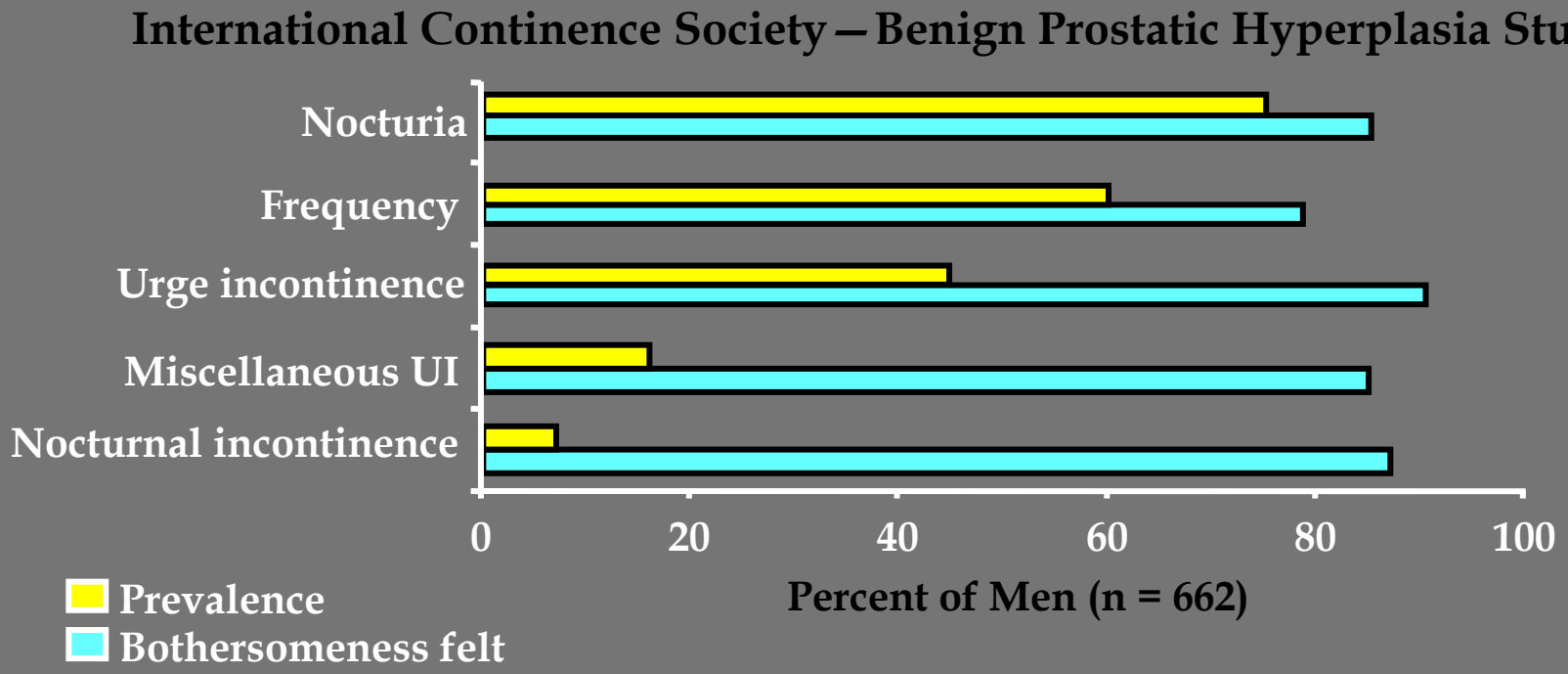
Witjes et al. J Urol. 1997; 157:1295-300
Lee et al. BJU Int 2004; 94:817-20

Obstructive Symptoms Are Most Prevalent in BOO/BPH



Peters TJ et al. *J Urol.* 1997;157:885-889.

Storage Symptoms Are Most Bothersome in BOO/BPH



Peters TJ et al. *J Urol*. 1997;157:885-889.

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Urodynamics

- Not routine in male LUTS; no preop RCT
- Results **poorly correlate** with clinical OAB
- Shows DO in 50% of OAB cases (more when UUI present)
- Severe urgency appears to be a negative predictor for obstruction
- **UDS appears indicated in setting of UUI, extreme ages (>80, <40), or possible neurological disease**

Cornu and Grise. Curr Opin Urol 2016. 26:17-21

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After TURP

- Old data suggests 20% persistence of OAB symptoms
- Recent data on 1y postop outcomes suggest worse outcomes in older patients, those with capacity <250 cc (>83% with persistent DO symptoms at 1 year)
- GOLIATH study showed similar improvement in OAB symptoms between PVP and TURP

Antunes et al. J Urol 2015; 193:2028-32
Thomas et al. Eur Urol 2015

Pathophysiology

- Most data from animal studies
- Obstruction can lead to overactivity and/or decreased compliance
- Initial detrusor hypertrophy (smooth muscle)
- Later increases in ECM (collagen)

Chang et al. Am J Physiol Renal Physiol 2010; 298:F1416-223
Li et al. BJU Int 2008; 101:1588-94
Kim et al. Can Urol Assoc J 2013. 7:E268-274
Song et al. Int J Urol 2013; 20:116-22

Pathophysiology

- Decrease in calcium-activated potassium channels (big potassium; BK)
- Some data suggests ischemic-induced changes in response to neurotransmitters
- Nitric oxide pathway also implicated
- Bladder histology compared between patients undergoing TURP vs controls
  - Significantly increased **Collagen I and III**
  - Significantly increased **M2 and M3** (more so in patients with persistent DO)

Barbosa et al. Urology 2017. 106:167-72

Why is this important?

- Only 50% of men with preop DO have resolution after TURP (20-30% after simple prostatectomy)

Van Venrooj et al. J Urol. 2002; 168:605-9

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Traditional medical therapy (BPE)

- Alpha blockers (tone)
- 5ARIs (size)
- PDE5i (voiding LUTS, not well studied for storage LUTS)
- MTOPS didn’t separate AUASS improvement by voiding vs storage

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Medical therapy for OAB

- Antimuscarinics
- Beta-3 agonists
- Botox (hybrid medicosurgical)

Antimuscarinic monotherapy for BOO

- Blasphemous in past
- Tim Boone's $20 bill
- Tolterodine in UDS-proven BOO didn't significantly alter Qm or voiding pressure compared to placebo; Volume to first contraction and capacity significantly improved
- PVR went up (25 cc vs 0 cc); not meaningful. Only retention case was in placebo arm.

Herschorn et al. Urology 2010. 75:1149-55

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Tolterodine Did Not Increase the Incidence of Urinary Retention in Men With OAB and BOO

OAB/BOO: Abrams et al

Urinary Symptom Adverse Events	Placebo (n = 72)		Tolterodine (n = 149)	
	N	%	N	%
Micturition disorder	2	2.8	7	4.7
Urinary tract infection	3	4.2	6	4.0
Dysuria	1	1.4	3	2.0
Micturition frequency	2	2.8	3	2.0
Micturition urgency	1	1.4	2	1.3
Strangury	0	–	2	1.3
Urinary retention	1	1.4	1	0.7
Bladder discomfort	0	–	1	0.7
Urethral disorder	0	–	1	0.7
Urinary incontinence	2	2.8	0	–
Overall	9	12.5	19	12.8

Abrams P et al. *Neurourol Urodyn*. 2001;20:547-548.

Antimuscarinic monotherapy for BOO

- Risk of retention from ACs in men is **< 1%**
- Most commonly prescribed drug is oxybutynin, likely due to cost/coverage

Kaplan et al. BJU Int 2008;102:1133-39
Anger et al. Neurourol Urodyn 2017. Epub ahead of print

Beta-3 agonist monotherapy

- Nitti looked at studies showing improvement but not stratified by gender
- He performed a PCRCT in 200 men looking at UDS, and non-inferior to placebo, but storage LUTS not evaluated (certainly not a home-run treatment yet)
- Recent analysis of 5 phase III studies showed that mirabegron 50 mg was better than placebo for frequency (BEYOND trial). Similar improvement in urgency, frequency, and UUI as solifenacin 5 mg.

Tubaro et al. Ther Adv Urol 2017. 9(6):137-154
Batista et al. Adv Urol 2015. 7:167-179

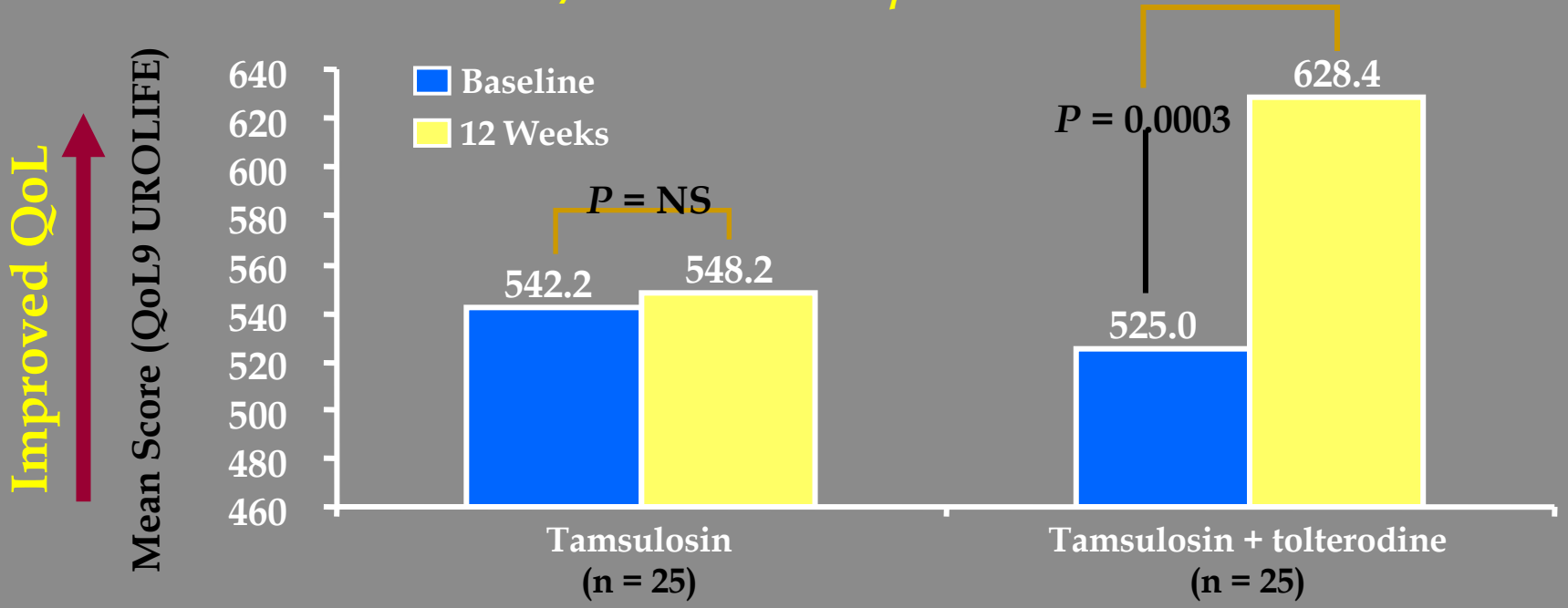
Antimuscarinics + Alpha Blockers

- Several published studies looking at adding tolterodine to alpha blocker
- Improvements in QOL (not seen with tamsulosin alone), Qm, voiding pressures, and AUASS reported with little to no incidence of retention
- Similar findings with tamsulosin in combo with solifenacin or darifenacin

Athanasopoulos et al. J Urol. 2003; 169:2253-6
Lee et al. BJU Int. 2004; 94:817-20
Kaplan et al. J Urol. 2005; 174:2273-6
Drake et al. BJU Int 2016; 117:165-72
Singh et al. J Clin and Diag Res 2015. 9(6):PC08-11

Tolterodine and Tamsulosin Combination Therapy in Men With BOO: Effects on QoL

OAB/BOO: Athanasopoulos et al



Athanasopoulos A et al. *J Urol*. 2003;169:2253-2256.

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Meta-analyses (combo therapy)

- Hao et al reviewed 18 RCTs (1978 men alpha blocker only, 2106 combo w/antimuscarinic). **Combo tx** noted significant improvement in storage IPSS, QoL score, voids/24h, and urgency episodes/24h. No sig diff in Qm, total IPSS, and voiding IPSS

- Gong et al. meta-analysis of studies comparing tamsulosin alone vs combo with solifenacin (7 studies, 3063 men). **Combo** w/sig improvement in storage IPSS, QoL, voids/24h, and urgency episodes/24h. Similar AEs, rare AUR, and no clinically significant change in Qm

Who is a good candidate?

- Some suggest those with good Qm, predominantly storage LUTS, PVR </= 50 cc
- Caution w/antimuscarinics in elderly; beta-3 may be better but more data needed (still not recommended with severe uncontrolled HTN)
- Other options
  - Botox
  - Neuromodulation (results somewhat disappointing in men)
  - NSAIDs/Analgesics (select cases)

Audience Response Question 1

Audience Response Question 2

Conclusions

- Treat most bothersome symptoms first
- Alpha blockers are good first choice for voiding symptoms, but antimuscarinics should be considered when storage symptoms predominate (EAU Guidelines 2013)
- Both mono and combo tx with antimuscarinics are accepted options in men with storage LUTS

Oelke et al. Eur Urol 2013; 64:118-140

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Conclusions

- AE rate (esp AUR) of using anticholinergics in BPH is low and there is minimal negative impact on UDS parameters (PVR, Qm)
- More research is need on beta-3 agonists in men
- Don’t be afraid to try and take men off alpha blockers and 5ARIs if eligible (tx polypharmacy)