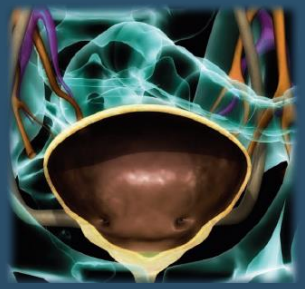
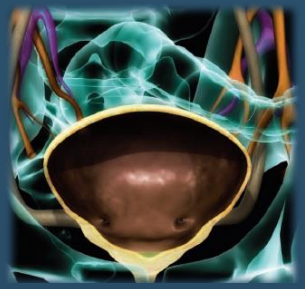


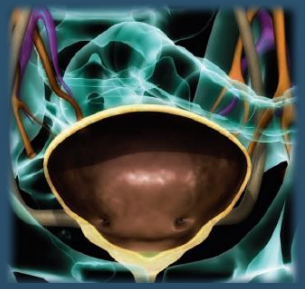
BPH in the Elderly: Beyond Alpha – Blockers and 5 – ARIs: Challenging Our Approach

Steven A. Kaplan, M.D., F.A.C.S.
Professor of Urology
Icahn School of Medicine at Mount Sinai
Director, Men's Health Program
Mount Sinai Health System



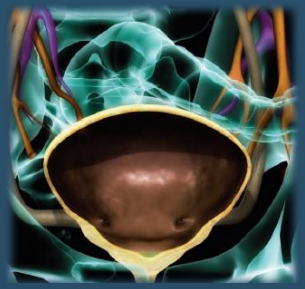
Disclosures

- None



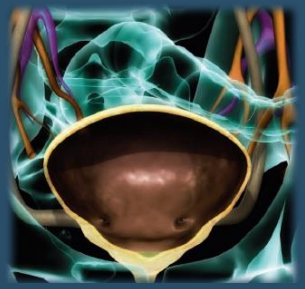
Learning Objectives

- Role of BPH Medical Therapy in the Elderly
- Challenges to Long Term Use
- Alternative Therapies

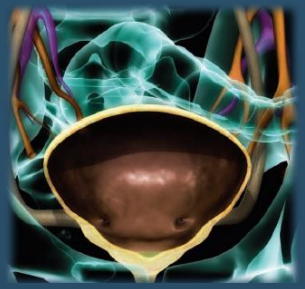


Most people see what they expect to see, what they want to see, what they have been told to see, what conventional wisdom tells them to see – not what is in front of them in its pristine conditions

Vincent Bugliosi



Medical Treatment Failure Depends on Definition



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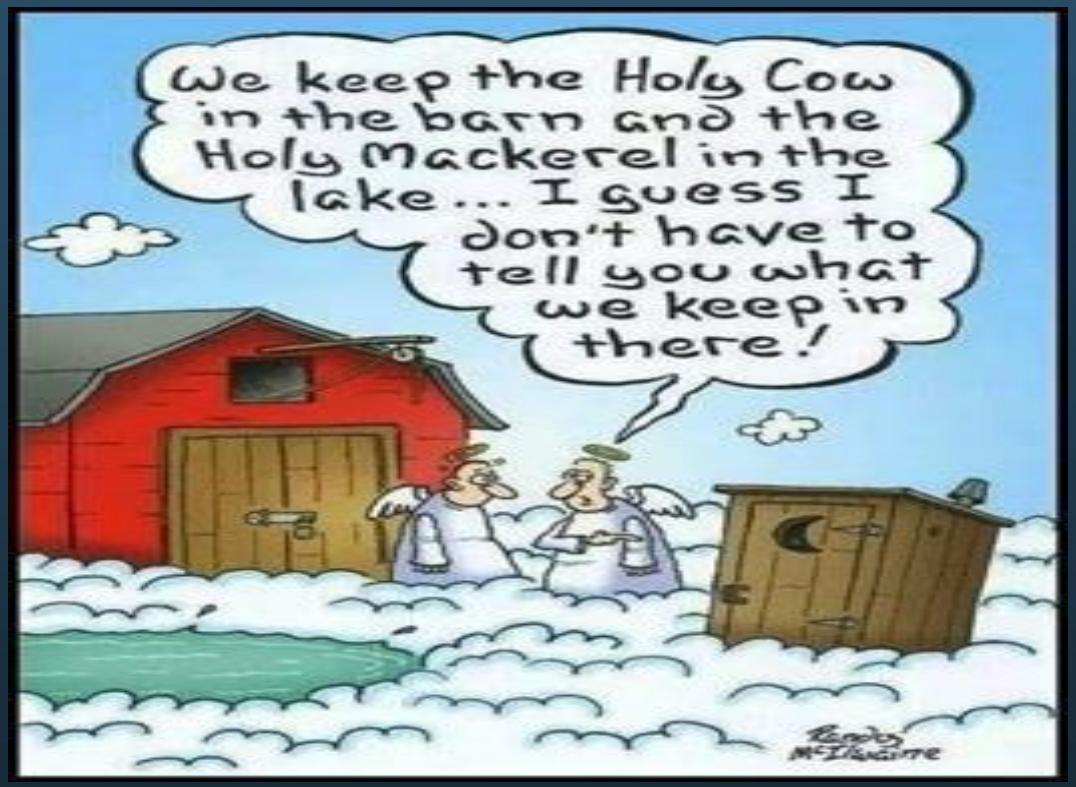
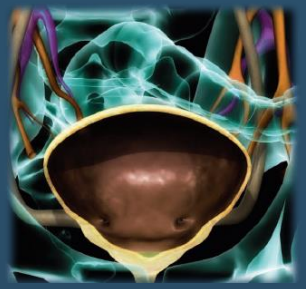
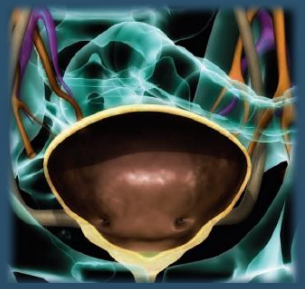




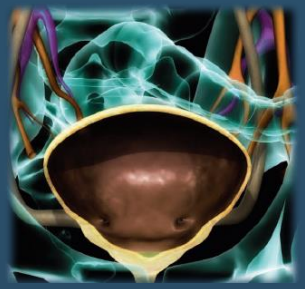
Medical Treatment Failure Traditional Definitions

- Assessed via switch to other therapies
  - Other medications
  - MIST
  - Surgery
  - WAWA



Why Do Patients Fail Medical Therapy?

- Symptoms not relieved
  - Are alpha blockers the same?
  - Differences among 5 ARI's?
- Intolerable side effects
- Progression of Disease
  - Symptom progression
  - Need for surgery
  - Urinary retention



Why Do Patients Fail Medical Therapy?

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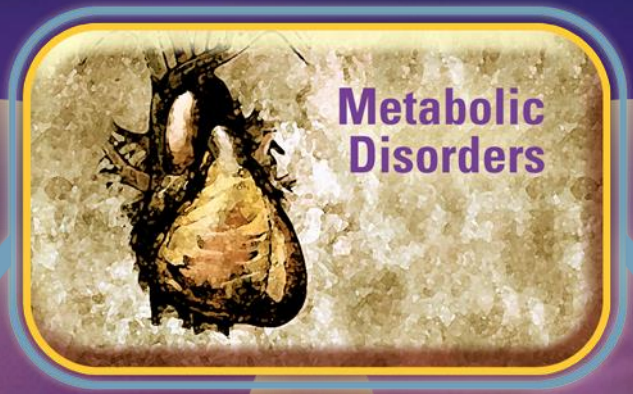
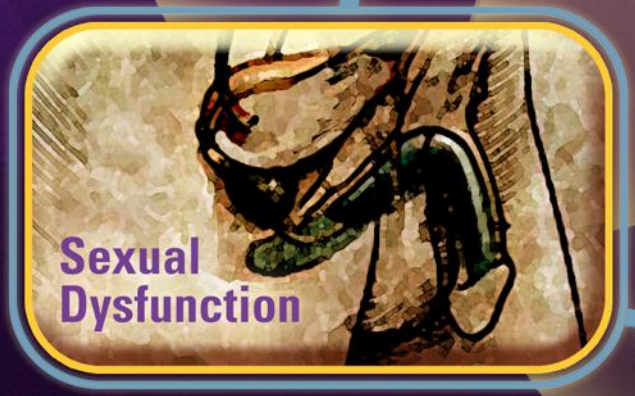
  - **Antimuscarinics / β3 - agonists target the bladder**



PATHOPHYSIOLOGY

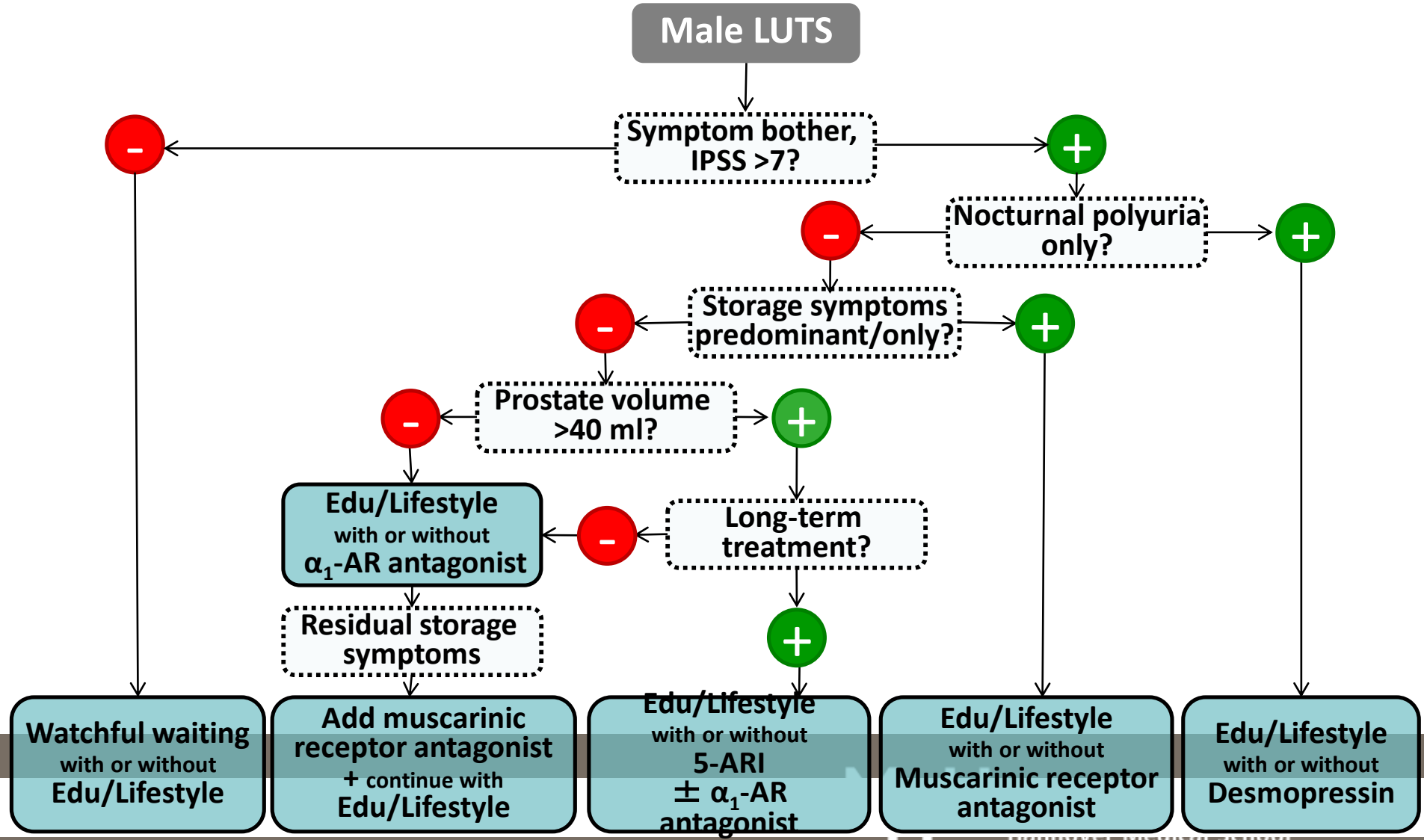
EPIDEMIOLOGY



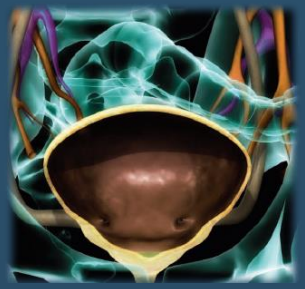
PHARMACOTHERAPY

BPH = benign prostatic hyperplasia; LUTS = lower urinary tract symptoms.

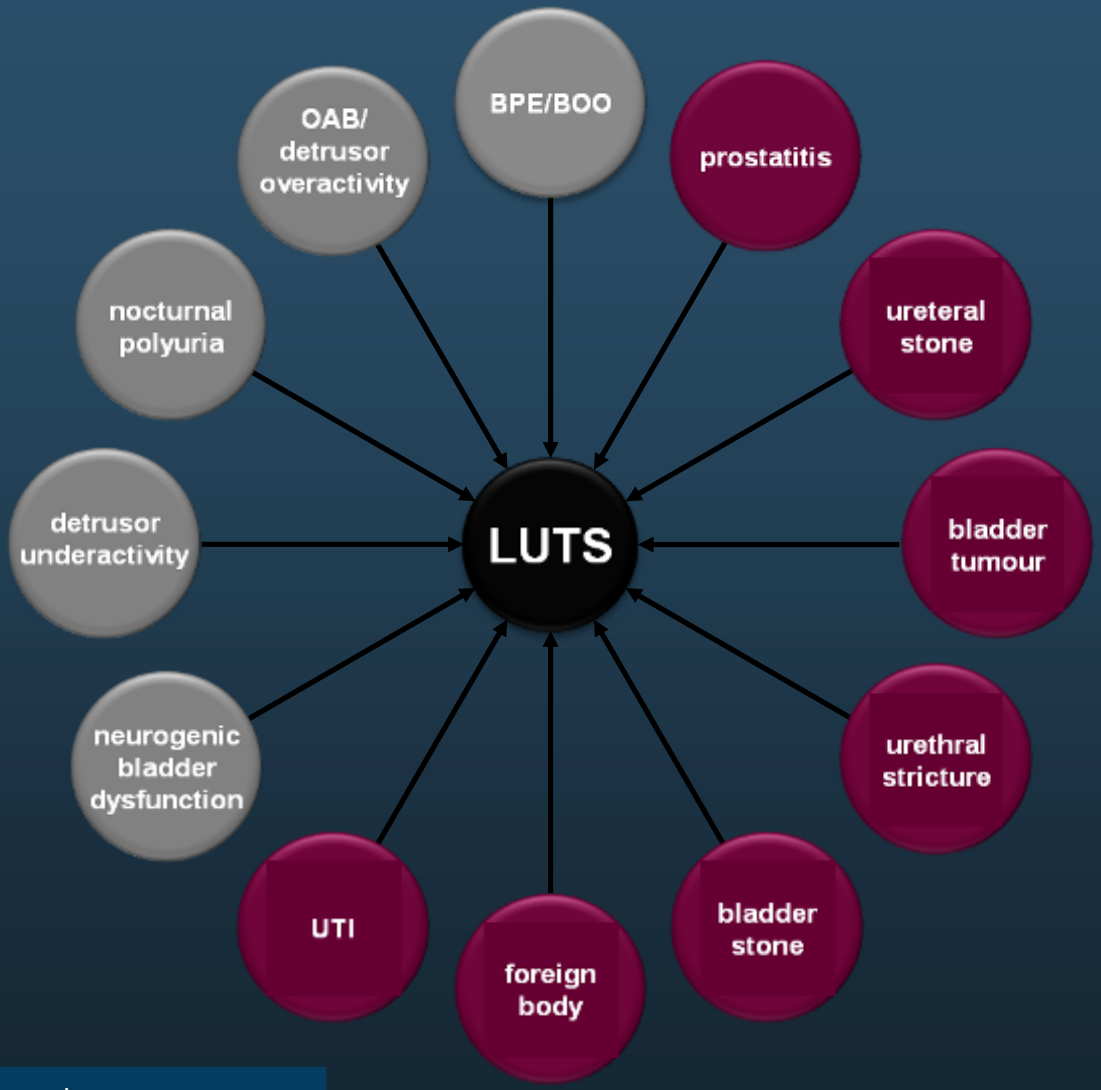
Treatment Algorithm Male LUTS: Drugs



Oelke M et al. Management of Male LUTS. European Association of Urology. 2012
[www.uroweb.org/gls/pdf/12_Male_LUTS_LR%20May%209th%202012.pdf]

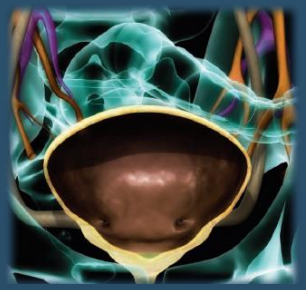


Conditions or diseases behind symptoms



BPE: benign prostatic enlargement;
BOO: bladder outlet obstruction;
OAB: overactive bladder; UTI: urinary tract infection

Oelke M et al. Management of Male LUTS. European Association of Urology. 2012 [www.uroweb.org/gls/pdf/12_Male_LUTS_LR%20May%209th%202012.pdf]



Pharmacological Options

Targeting the bladder

Antimuscarinics

→ Symptom control of OAB (storage) component of LUTS ↓involuntary bladder contractions

PDE5 inhibitors (prostate ± bladder?)

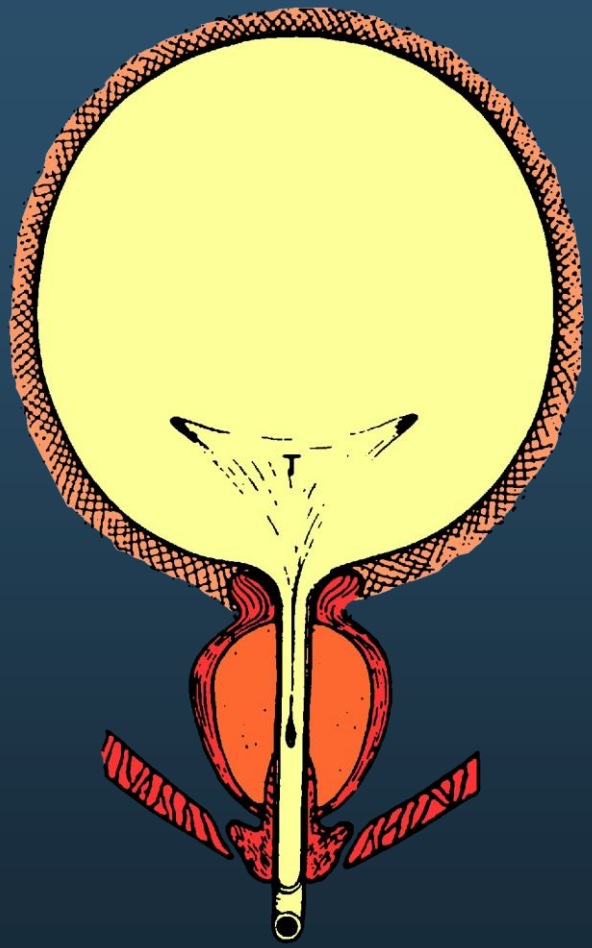
Targeting the prostate

α-blockers

→ Symptom control by relaxation of prostatic and urethral tissue

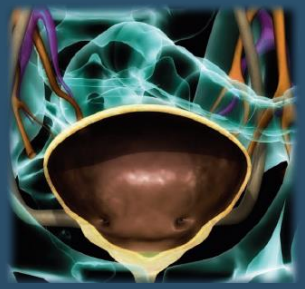
5-ARIs

→ Long-term symptom control and prevention of disease progression by prostatic tissue shrinkage



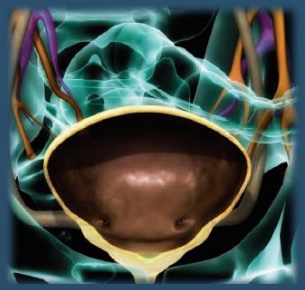
5-ARIs: 5α-reductase inhibitors;
OAB: overactive bladder

Oelke M et al. Management of Male LUTS. European Association of Urology. 2012 [www.uroweb.org/gls/pdf/12_Male_LUTS_LR%20May%209th%202012.pdf]



Surgical Options

- **Minimally invasive options**
  - Office based
  - Ambulatory based
  - Minimal anesthestic
  - High risk patients
  - Low morbidity
- **Advanced Invasive Options**
  - Improved versions of prostatectomy



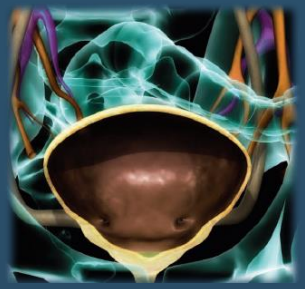
Technology Based Treatment of LUTS related to BPH

- **ALL surgical approaches based on removing bladder outlet obstruction[1] (? Tissue)**

- **Minimally Invasive Therapies[1]**
- **Thermotherapies[1]**
- **Novel hybrid therapies[2]**
- **Surgical Debulking Procedures[1]**
  - Vaporizers and Enucleators[1]
  - Robots Vs. Lasers Vs Electrosurgical Technologies[3]

LUTS: lower urinary tract symptoms
BPH: benign prostatic hypertrophy

1. Kacker R, Williams SB. *J Uro*l 2011: 8; 171-176.
2. Hoffman RM et al. *Cochrane Database Syst Rev* 2009;(1):CD001987
3. Lee N et al. AUA 2011. Abstract 2098.



Minimally Invasive Therapies: Update

FDA APPROVED

- Prostatic Lifts[1]
  - Transurethral Suture Tacking
- Robotic/Laparoscopic Technology
  - Single Port[2] and Transvesical Approaches[3]
- Vapor Ablation (Steam / CONVECTIVE RADIOFREQUENCY)
- AquaBlation
- Prostatic Arterial Embolization

Investigational

- Stents / balloons
- Histotripsy (focused ultrasound)
- Intraprostatic Injections[5]
  - Botox, NX 1207, ethanol and other compounds

1. Woo, H. et al. *BJU Int* 2011;108: 82-8
2. Fareed K, et al. *BJU Int* 2012: DOI: 10.1111/j.1464-410X.2012.10954.x
3. Granberg CF, et al. J Endourol. 2009 May;23(5):747-52
4. Tiwari A, et al. Exp Opin Invest Drugs 2005;
5. Denmeade S, et al. Eur Urol 2011; 59:747-54. Epub 2010 Nov 24.

α-Blockers for Treatment of BPH

- Most commonly used and effective medical therapy for treating LUTS secondary to BPH[1]
- Prevents clinical symptomatic progression of BPH[1]
- Efficacious[2]
- Well tolerated
- Reduce the cost of medical therapy[3]

1. IMS HEALTH NPA 2008.
2. McConnell JD et al. *N Engl J Med*. 2003;349;2387-2398.
3. Naslund M et al. *Am J Manag Care*. 2007;13(suppl 1):S17-S22.

Efficacy of alpha1 - blocker

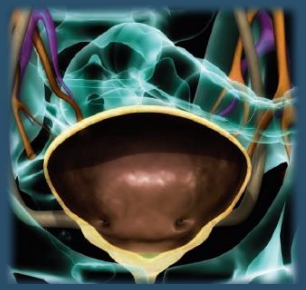
	α_1-AR antagonist
Total IPSS	↓ 35 - 40%
Q_{max}	↑ 20 - 25%
Onset of action	Rapid (days)
Prostate volume	-
Long-term risk of AUR or BPH-related surgery	-

AUR: acute urinary retention;
BPH: benign prostatic hyperplasia;
IPSS: International Prostate Symptom Score;
Q_{max}: maximum urinary flow rate

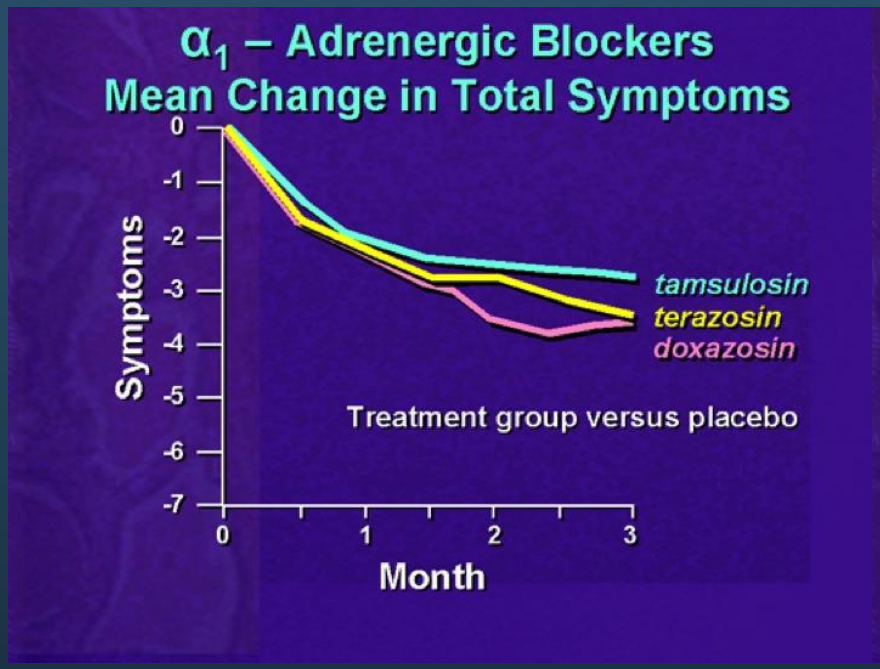
Oelke M et al. Management of Male LUTS. European Association of Urology. 2012 [www.uroweb.org/gls/pdf/12_Male_LUTS_LR%20May%209th%202012.pdf]

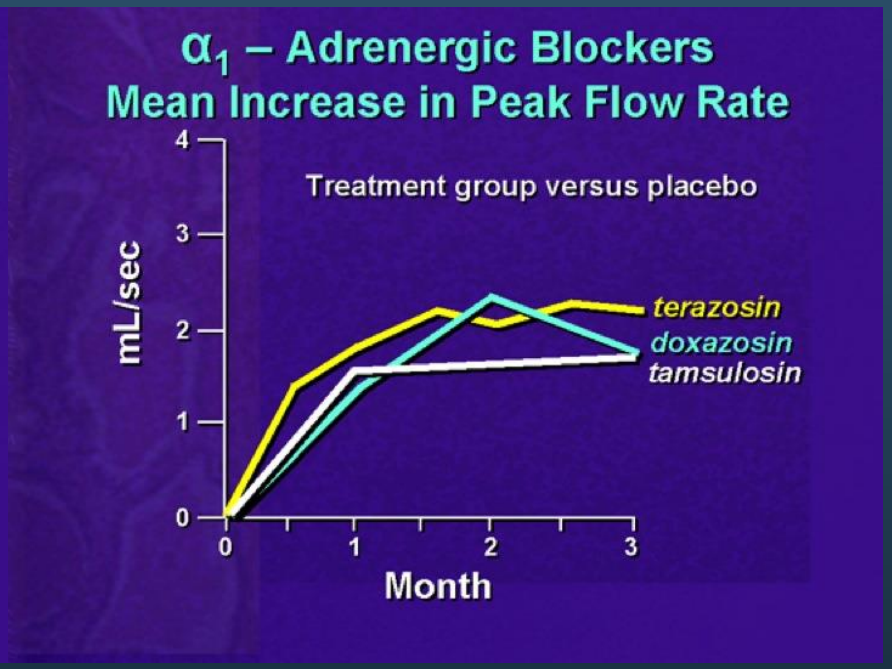
RAPAFLO® 8mg (silodosin) capsules

Alpha-blocker Competitive Efficacy Review



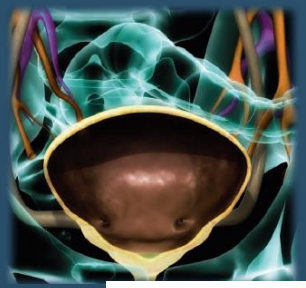
Doxazosin,Terazosin and Tamsulosin improvement in symptoms and Qmax



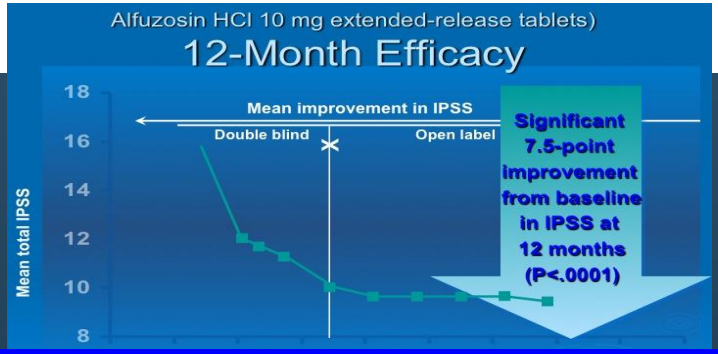


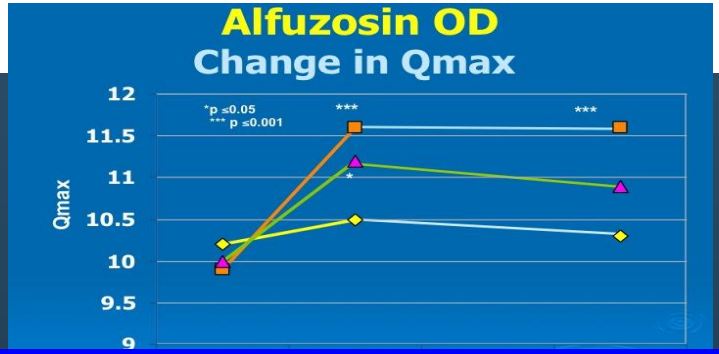
About a 3 point improvement in IPSS symptom score
About a 2-3 ml/sec improvement in Qmax

Data from prescribing product insert information

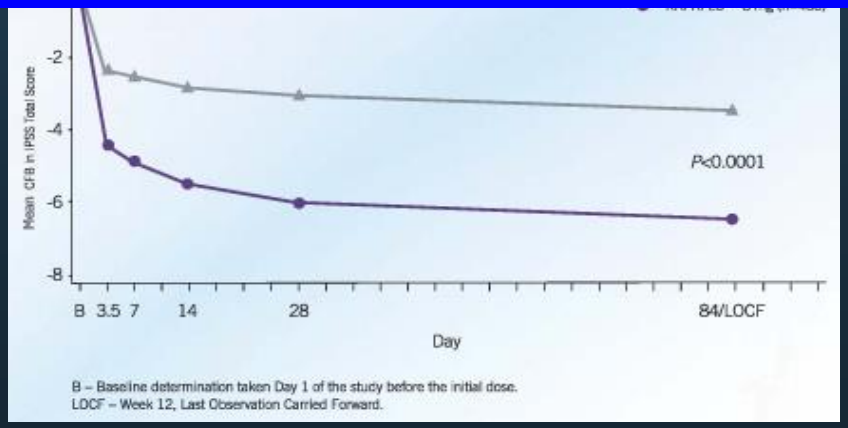


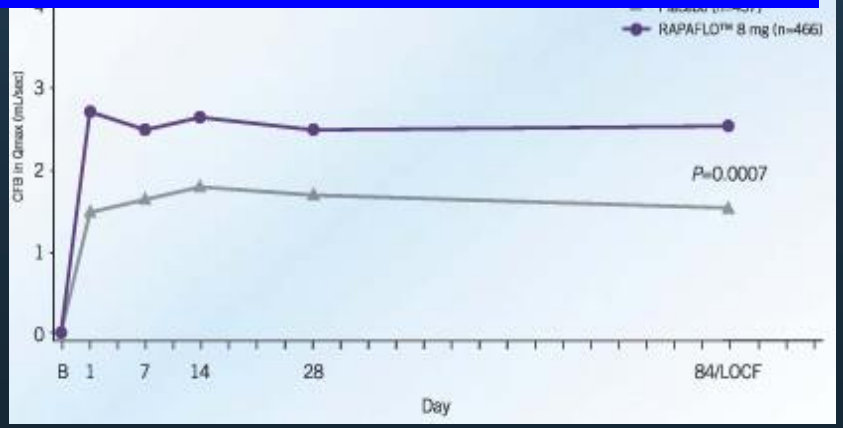
Alfuzosin and Silodosin Improvement in Symptoms and Qmax





About a 3 point improvement in IPSS
About a 1-2 ml/sec improvement in Qmax





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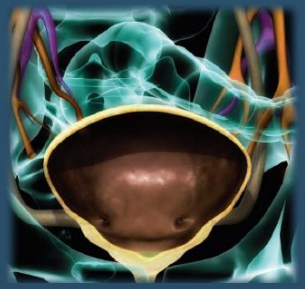

Why Do Patients Fail Medical Therapy

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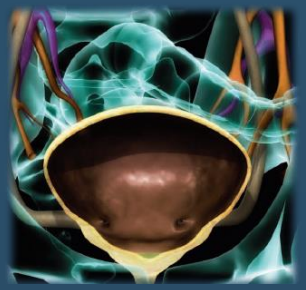
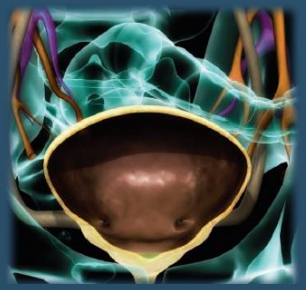
  - **Are alpha blockers the same?**
  - **Differences among 5 ARI's?**
  - **Combination with PDE – 5 may not be effective**
  - **Antimuscarinics / β3 - agonists target the bladder**
- **Intolerable side effects**



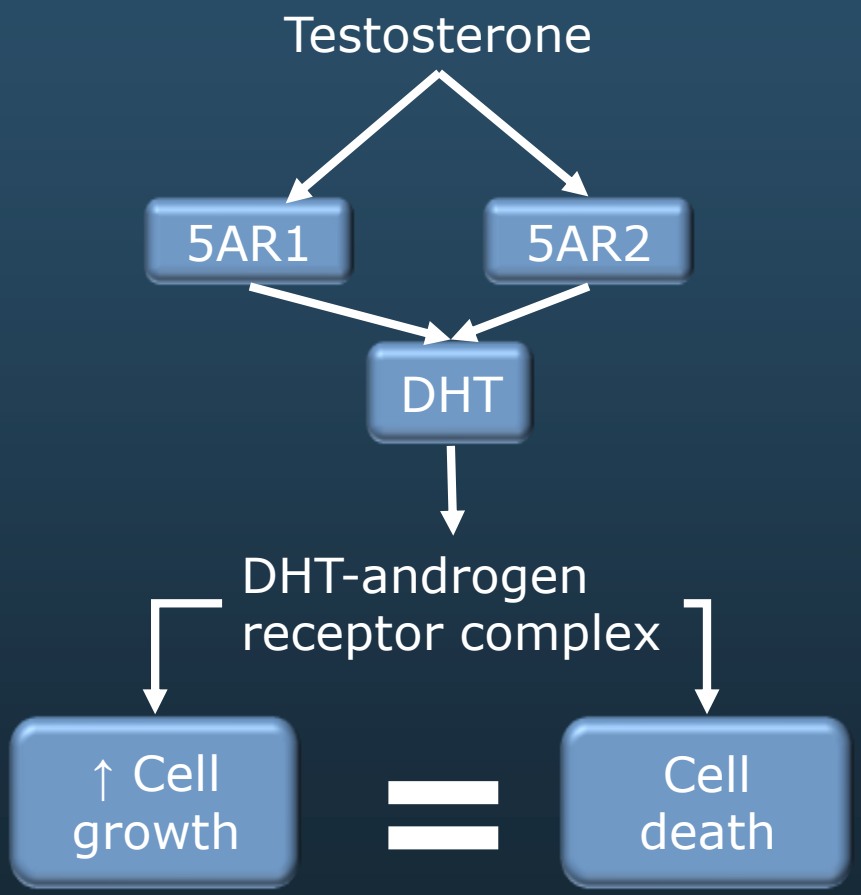
ALPHA ADRENERGIC BLOCKERS
Adverse Effects

Drug	Asthenia	Head Ache	Syncope	↓ BP	↓ Libido	EjD	ED
Uroxatral (alfusozin ER)	2.7	3.0	5.7	0.4	nr	nr	1-2
Cardura (doxazosin IR)	8	9.9	15.6	1.7	0.8	≤ 1	1.1
Cardura XL (doxazosin XL)	3.9	6	5.3	1.7	nr	nr	< 1
Rapaflo (silodosin)	1-2	2-4	3.2	2.6	nr	28.1	nr
Flomax 0.4 mg 0.8 mg	7.8 8.5	19.3 21.1	14.9 17.1	0.2 0.4	1 2	8.4 18.1	r
Hytrin (terazosin)	7.4	4.9	9.1	≤5.5	nr	nr	1.6-2



5α-reductase inhibitors (5ARIs)

- For long-term use in men with enlarged prostates
- Exert an androgen effect on the prostate:
  - Finasteride: inhibits 5α-reductase type 2 only
  - Dutasteride: inhibits 5α-reductase types 1 and 2
- Act to reduce serum DHT concentrations
- Long half-life for dutasteride:
  - Finasteride: 6-8 hours
  - Dutasteride: 3-5 weeks

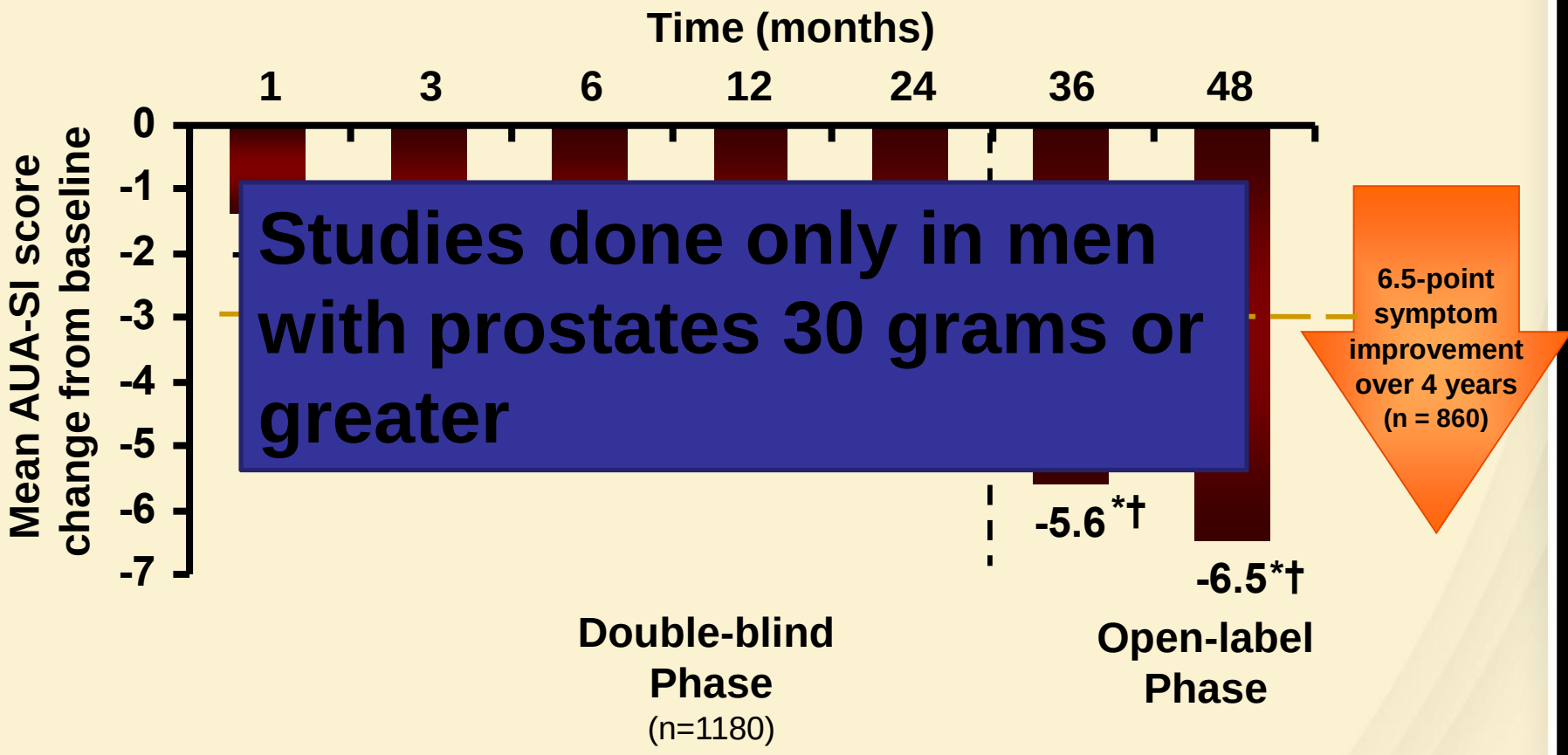


5AR1: 5α-reductase receptor 1;
5AR2: 5α-reductase receptor 2; DHT: dihydrotestosterone

Oelke M et al. Management of Male LUTS. European Association of Urology. 2012 [www.uroweb.org/gls/pdf/12_Male_LUTS_LR%20May%209th%202012.pdf]

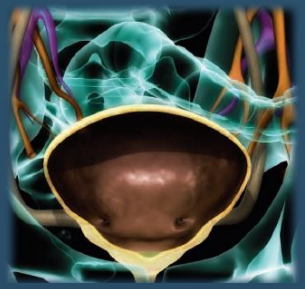
Dutasteride Reduces Symptoms

Pooled Results from Three Randomized, Placebo-controlled, 2-year Clinical Studies with 2-year Open-label Extension Phase with AVODART 0.5 mg daily



*$P < 0.001$ between treatment groups
†$P < 0.001$ vs month 24

Debruyne F, et al. *Eur Urol*. 2004;46:488-94.

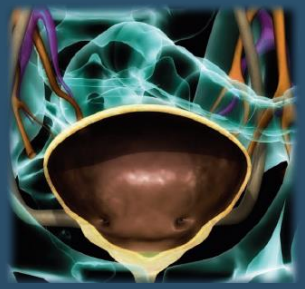


Efficacy 5ARIs

- **Clinical effects are observed after a minimum treatment period of 6–12 months; therefore, long-term treatment necessary**
- **After 2–4 years of treatment, IPSS is reduced by ~15–30% and prostate size ↓by 20-30%**
- **Symptom reduction (IPSS) is dependent on prostate size at treatment initiation**
- **In men with prostate sizes <30-40 ml efficacy is comparable with** placebo

IPSS: International Prostate Symptom Score

OelkeM et al. Management of Male LUTS. European Association of Urology. 2012 [www.uroweb.org/gls/pdf/12_Male_LUTS_LR%20May%209th%202012.pdf]

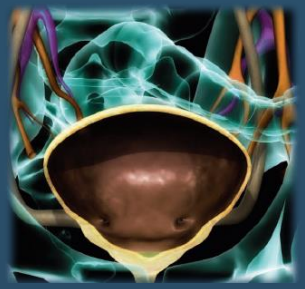


Efficacy 5ARIs

- Symptom (IPSS) reduction with 5-ARIs depends on:
  - Baseline PSA values >4.4 µg/l → fastest symptom relief
  - Prostate volume >58 ml significant ↓ IPSS compared with smaller prostate volumes
- Reduce the risk of urinary retention or need-for-surgery

IPSS: International Prostate Symptom Score

OelkeM et al. Management of Male LUTS. European Association of Urology. 2012 [www.uroweb.org/gls/pdf/12_Male_LUTS_LR%20May%209th%202012.pdf]



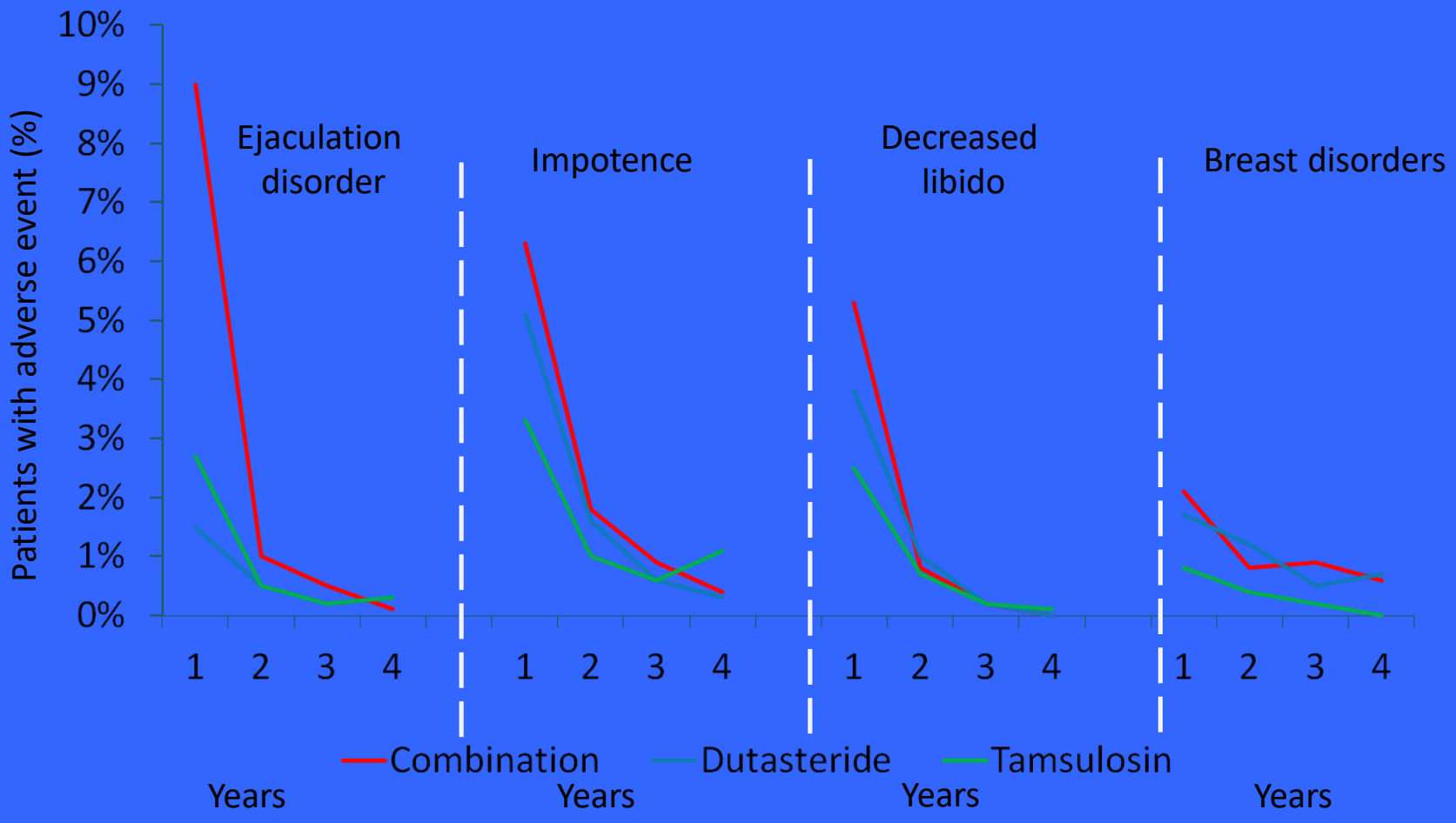
Adverse Events of 5α-Reductase Inhibitors are Comparable

Adverse Events	Dutasteride[1]		Finasteride[2]	
	Dut	Placebo	Fin	Placebo
Erectile dysfunction	7	4	8	4
Altered libido	4	2	6	3
Altered Ejaculation	2	<1	4	1
Gynecomastia	2	<1	1	0.2

[1]24 mo study; [2]48 mo study.

Sexual AEs associated with 5ARIs occur early in therapy & decrease after the first year

CombAT study

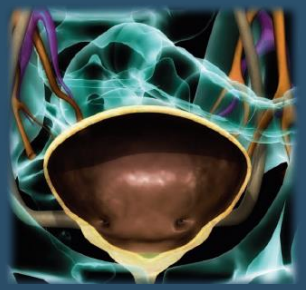


Graphs adapted from Duodart European Summary of Product Characteristics Dec 2014;

A 5 Year Study Of 5 – Alpha Reductase Inhibitors In Men With Benign Prostatic Hyperplasia: Finasteride Has Equal Efficacy And Prostate Volume Reduction But Has Less Sexual Side Effects And Breast Enlargement Than Dutasteride

Steven A. Kaplan, Doreen E. Chung, Richard K. Lee, Scott Melamed, Alexis E. Te

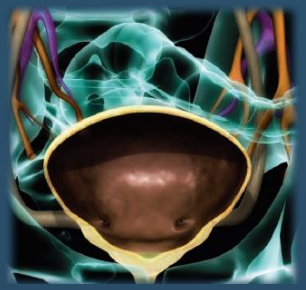
Weill Cornell Medical College
Cornell University



Finasteride Versus Dutasteride Results

Parameter	Finasteride (817)	Dutasteride (813)
Prostate Volume Reduction % at 12M	-26.7	-26.3
AUA SI @ 3M	-3.8	-3.6
AUA SI @ 12M	**-5.5**	**-5.8**
Qmax @ 12M	1.7 ml/sec	2.0 ml/sec

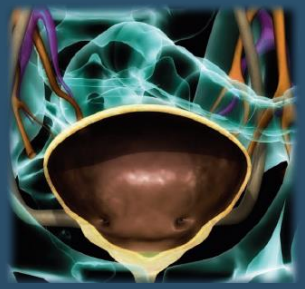
NO DIFFERENCE BETWEEN THE TWO GROUPS



Sexual Adverse Events

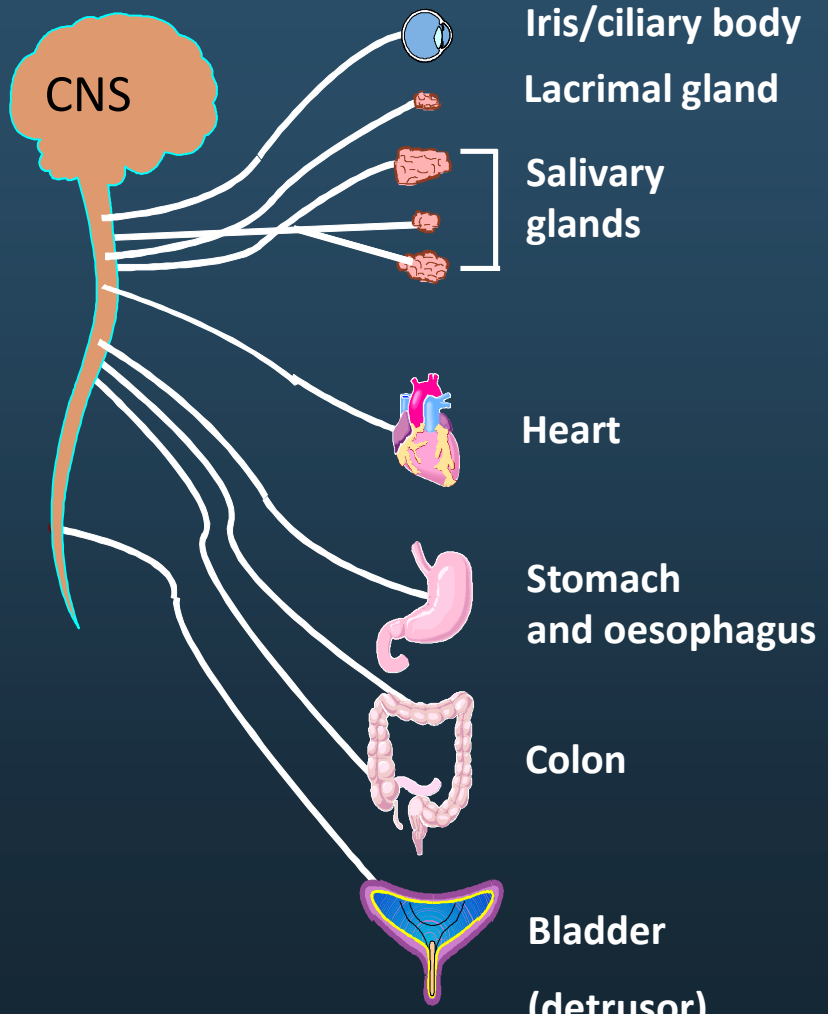
Parameter	Finasteride	Dutasteride
Change in IIEF	-2.4	-3.5
W		
Ejaculatory dysfunction		
Decreased libido	1.4%	2.7%
Breast tenderness / enlargement	1.2%	3.5%

Significantly higher in dutasteride group ($p < 0.01$)



Muscarinic Receptor Antagonists

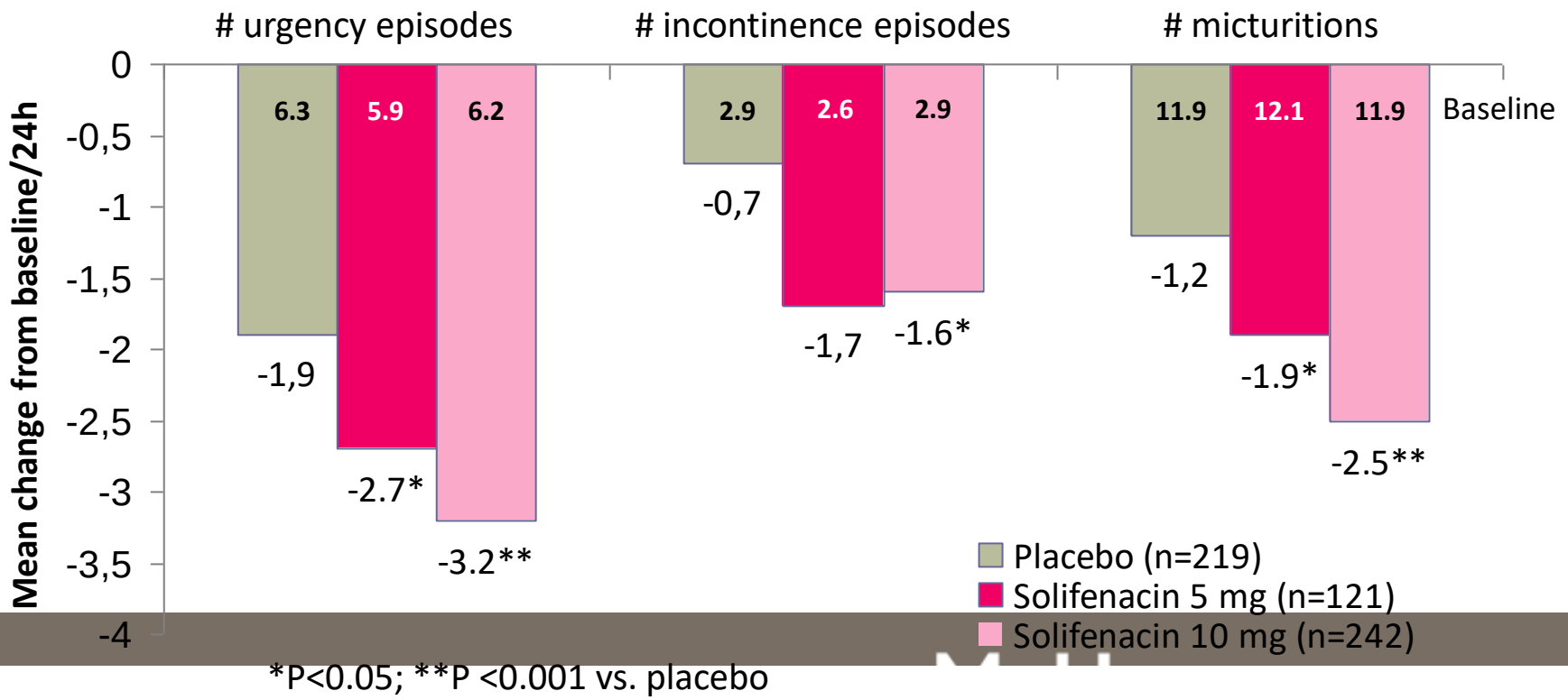
- Five muscarinic receptors have been described (M_1-M_5)
- Expressed in the bladder, salivary glands, and synapses in the CNS
- M_2 and M_3 are most predominant in the bladder
- Only M_3 is involved in bladder contractility
- Inhibition of muscarinic receptors reduce smooth cell conctractions of the bladder



Oelke M et al. Management of Male LUTS. European Association of Urology. 2012 [www.uroweb.org/gls/pdf/12_Male_LUTS_LR%20May%209th%202012.pdf]

Efficacy Antimuscarinics in Male LUTS

Meta-analysis: subgroup analysis of 582 men from 4 RCTs (phase III) evaluating the efficacy and safety of solifenacin (12 weeks) in male OAB patients (n=2,848)



*P<0.05; **P <0.001 vs. placebo

RCT: randomised controlled trial; OAB: overactive bladder

van Kerrebroeck P et al. Eur Urol Suppl 2005; 4: 61 (abstract 233)
Chapple CR et al. Int J Clin Pract 2006; 60: 959 - 966

Antimuscarinics ONLY in Male LUTS

Trials	Duration (weeks)	Treatment	Patients [N]	Voiding frequency [%]	Nocturia [%]	Urgency Incontinence [%]	IPSS [%]	LE
Kaplan et al. (2005)	25	Tolterodine 1 x 4mg/d (after α-blocker failure)	43	-35.7 [a]	-29.3 [a]	-	-35.5 [a]	**2b**
Roehrborn et al. (2006)	12	Placebo	86	-4	-	-40	-	**1b**
		Tolterodine 1 x 4mg/d	77	-12	-	-71 *	-	
Kaplan et al. (2006)	12	Placebo	374	-7.9	-17.6	-	-	**1b**
		Tolterodine 1 x 4mg/d	371	-10.8 *	-18.8	-	-	
Kaplan et al. (2006)	12	Placebo	215	-13.5	-23.9	-13	-44.9	**1b**
		Tolterodine 1 x 4mg/d	210	-16.5	-20.1	-85 *	-54	
Dmochowski et al. (2007)	12	Placebo	374	-5.6	-17.6	-	-	**1b**
		Tolterodine 1 x 4mg/d	371	-8.7	-18.8	-	-	
Höfner et al. (2007)	12	Tolterodine 1 x 4mg/d	741	-20 [a]	-42.9 [a]	-100	-37.9 [a]	**2b**
Herschorn et al. (2009)	12	Placebo	124	-10.2	-	59.3	-	**1b**
		Fesoterodine 1 x 4mg/d	111	-13.2 *	-	-84.5 *	-	
		Fesoterodine 1 x 8mg/d	109	-15.9 *	-	-100 *	-	

IPSS: International Prostate Symptom Score

Oelke M et al. Management of Male LUTS. European Association of Urology. 2012 [www.uroweb.org/gls/pdf/12_Male_LUTS_LR%20May%209th%202012.pdf]

PVR and Urinary Retention

-Monotherapy Antimuscarinics-

TRIAL	Duration [weeks]	Treatment	Patients [N]	PVR [ml]	Rentention N	Rentention %
Kaplan et al. 2005	25	Tolterodine 1x4 mg/d	43	- 22*	0	0
Roehrborn et al. 2006	12	Placebo	86		0	0
		Tolterodine 1x4 mg/d	77		1	1.3
Kaplan et al. 2006	12	Placebo	374		2	0.5
		Tolterodine 1x4 mg/d	371		3	0.8
Kaplan et al. 2006	12	Placebo	215	- 3.6	3	1.4
		Tolterodine 1x4 mg/d	210	+ 5.3	2	0.9
Dmochowski et al. 2007	12	Placebo	374		2	0.5
		Tolterodine 4 mg/d	371		4	1.1
Höfner et al. 2007	12	Tolterodine 1x4 mg/d	741	0	8	0.7
Chapple et al. 2009	12	Placebo	323	+ 1,1	6	1.9
		Tolterodine 1x4 mg/d	329	+ 14.3 *	6	1.8
Herschorn et al. 2010	12	Placebo	124		1	0.8
		Fesoterodine 1x4 mg/d	120	+ 9.6**	1	0.8
		Fesoterodine 1x8 mg/d	114	+ 20.2**	6	5.3

* P=0.023

**P=0.035

Adapted from Oelke M. UniMed Science. Hampel (Ed) 2009 pp84 - 97

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

PVR: post-void residual

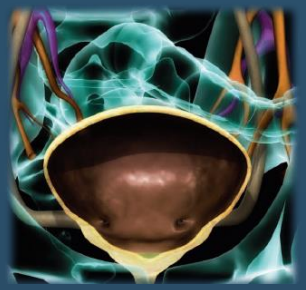
The Health Improvement Network (THIN) Database: Focused Safety Study of Acute Urinary Retention (AUR) in Men

Luis Alberto García-Rodríguez, Elisa Martín-Merino, Elvira Luján Massó-González, Claus G. Roehrborn

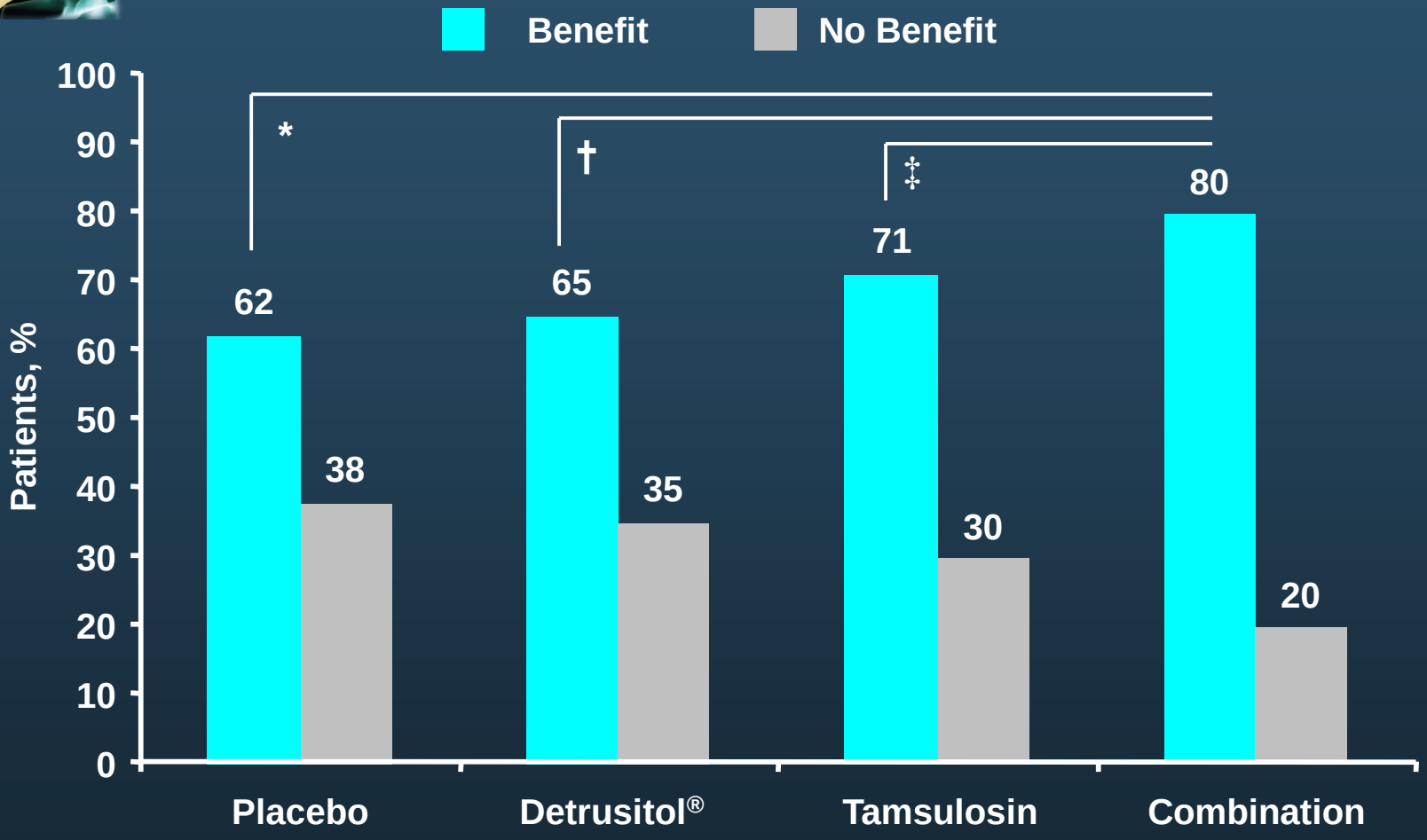
This study was funded by Pfizer Inc

	Number (%) of Patients			
	Cases (n=1844)	Controls (n=10,000)	RR†	95% CI
Use				
Non-use	1706 (93)	9727 (97)	1	
Timing of use				
Current use	94 (5)	154 (2)	2.9	2.2–3.7
Recent use	15 (<1)	39 (<1)	1.7	0.9–3.1
Past use	29 (2)	80 (<1)	1.6	1.0–2.5
Duration: Current use				
≤30 days	38 (40)	22 (14)	8.3	4.8–14.2
31 days-1 year	28 (30)	60 (39)	2.0	1.2–3.1
>1 year	28 (30)	72 (47)	2.0	1.3–3.1
Daily dose/indication: Current use				
Low/medium dose	84 (89)	138 (90)	2.8	2.1–3.8
High dose urogenital	10 (11)	16 (10)	3.0	1.3–6.8

*Percentages for timing of use are based on overall study cohort (1844 cases; 10,000 controls); percentages for duration and daily dose are based on the number of patients currently using antimuscarinics (94 cases, 154 controls).
†Relative risk estimates were adjusted for age, calendar year, general practitioner visits, and oral antimuscarinic use.

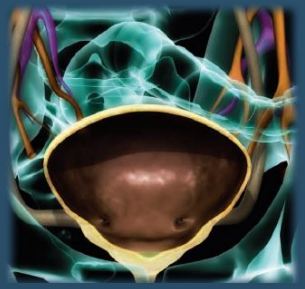


Treatment with Tolterodine plus Tamsulosin Resulted in Significant Treatment Benefit at Week 12



*P < .001 between-group comparisons.
†P = .001 between-group comparisons.
‡P < .05 between-group comparisons.

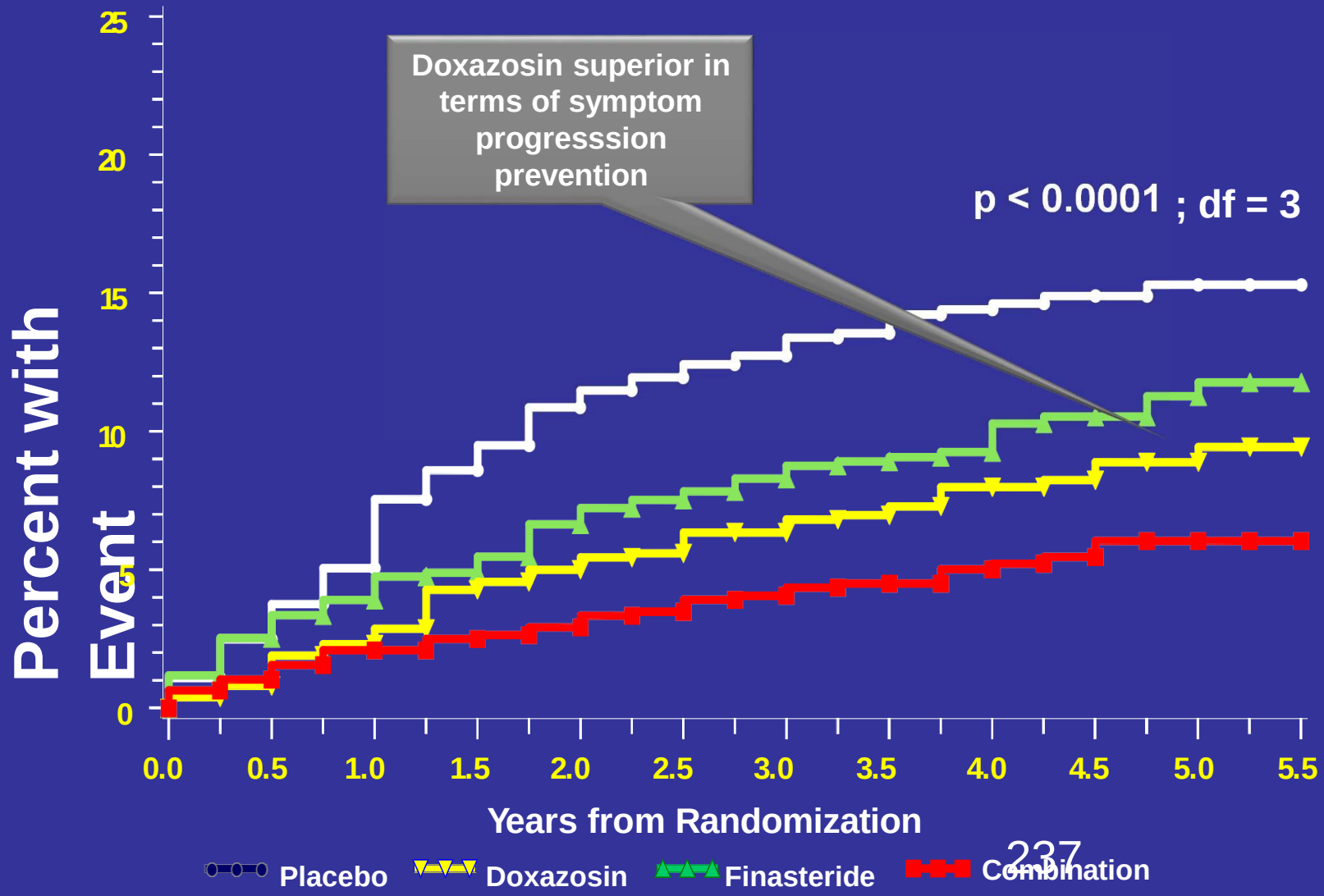
Kaplan SA et al. *JAMA*. 2006;296:2319-2328.



Why Do Patients Fail Medical Therapy

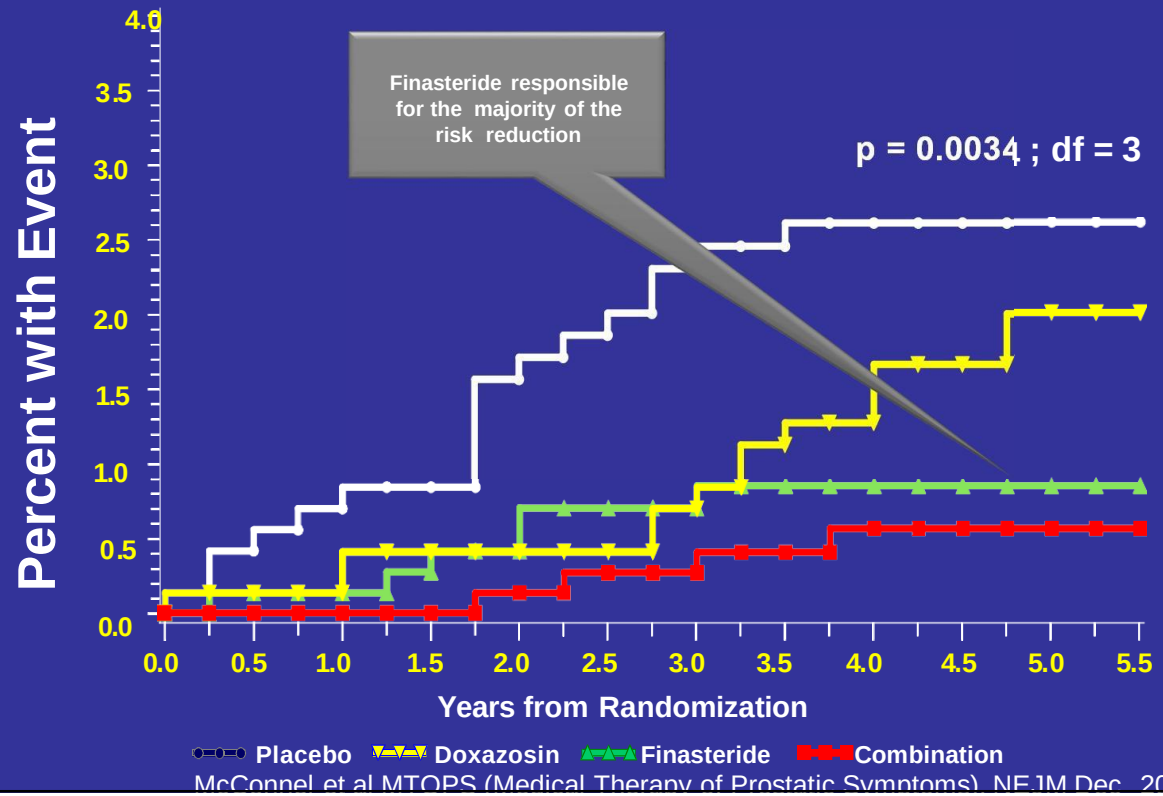
- **Symptoms not relieved**
  - Are alpha blockers the same?
  - Differences among 5 ARI's?
- **Intolerable side effects**
- **BPH progression**
  - Symptom progression
  - Need for surgery
  - Urinary retention

Cumulative Incidence of >4-Pt AUA Rise



McConnel et al MTOPS (Medical Therapy of Prostatic Symptoms) NEJM Dec 2003

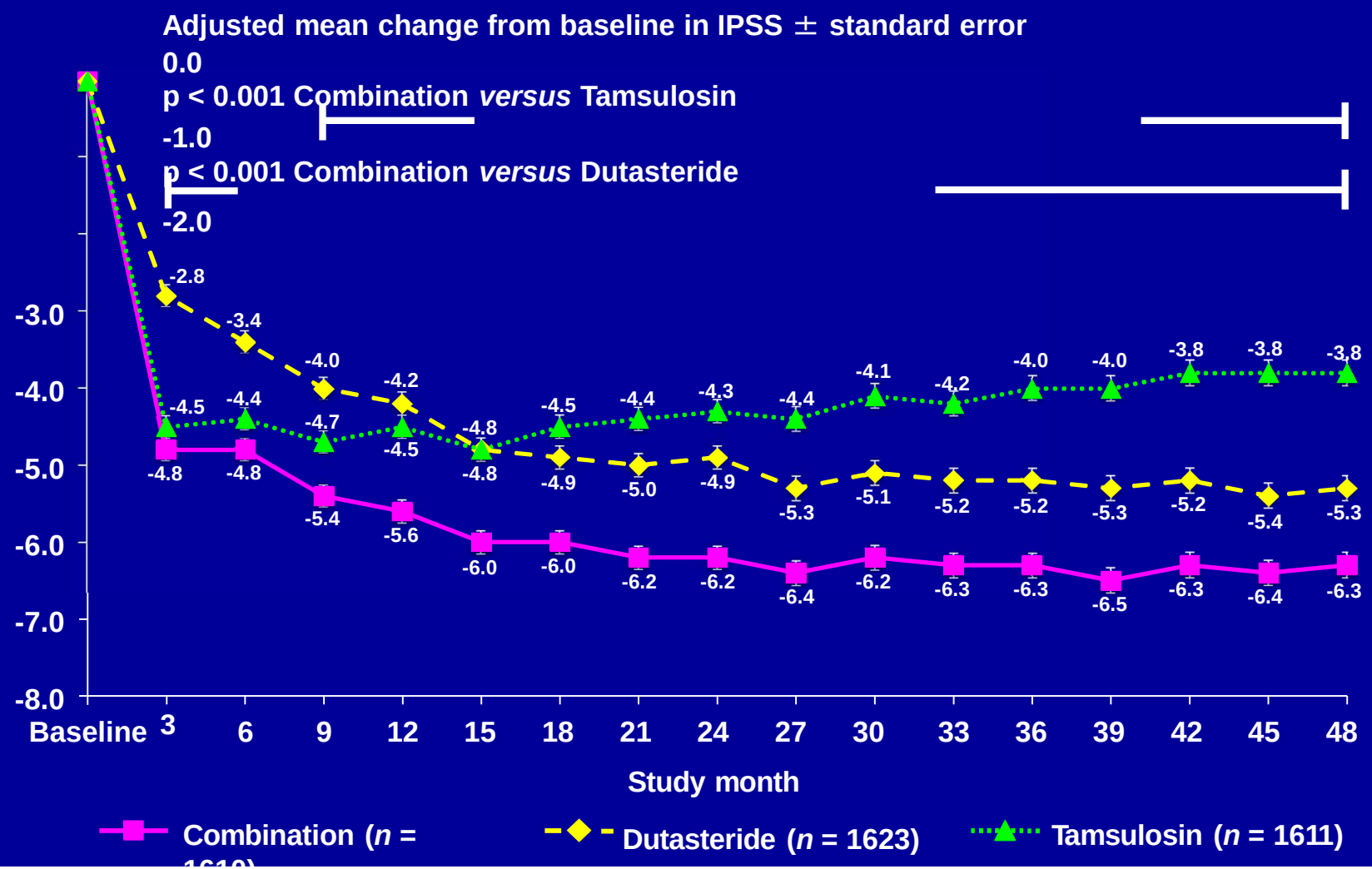
Cumulative Incidence of AUR



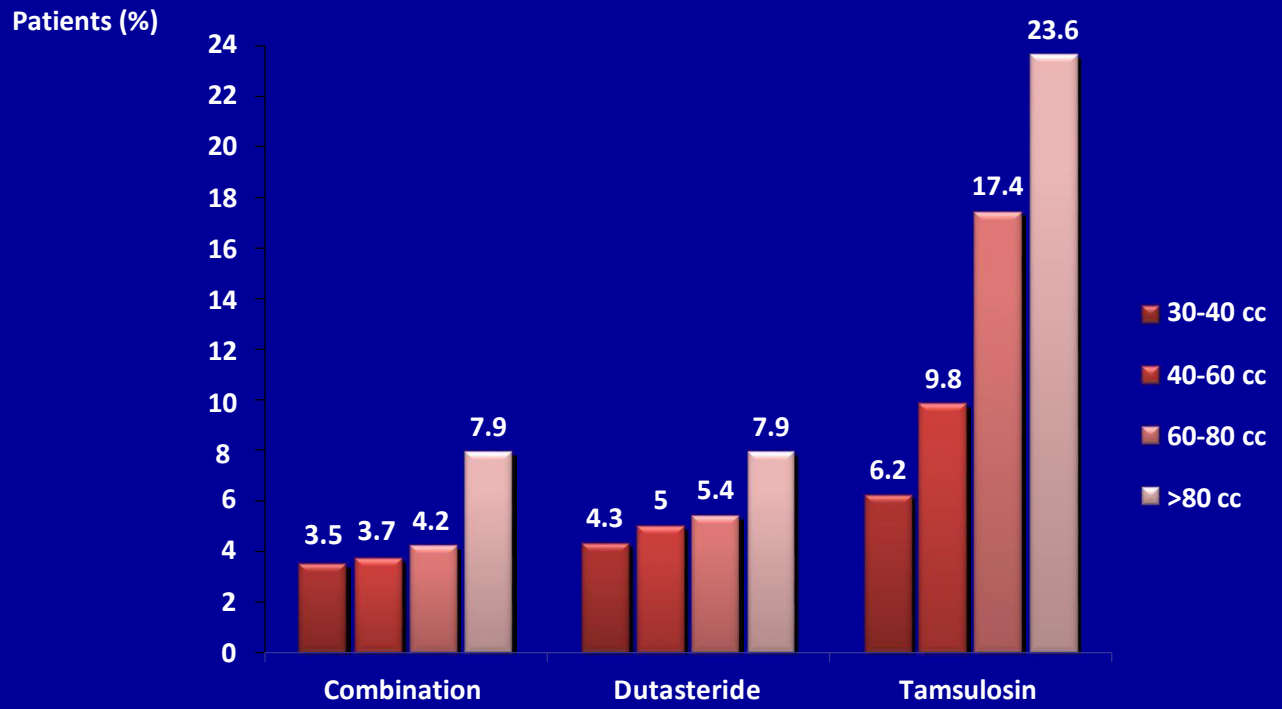
McConnel et al MTOPS (Medical Therapy of Prostatic Symptoms), NEJM Dec. 2003

CombAT IPSS

Adjusted mean change from baseline (LOCF)



Stratification by baseline total prostate volume (mL) for AUR or surgery risk



250

MTOPS: Adverse Events

	Combination N = 786	Finasteride N = 768	Doxazosin n = 756
Erectile Dysfunction	5.11%	4.53%	3.56%
Dizziness	5.35%	2.33%	4.41%
Postural Hypotension	4.33%	2.56%	4.03%
Asthenia	4.20%	1.56%	4.08%
Decreased libido	2.51%	2.36%	1.56%
Abnormal Ejac	3.05%	1.78%	1.10%

MTOPS (Medical Therapy of Prostatic Symptoms), NEJM Dec 2003
Other reported AEs <2%: peripheral edema, dyspnea, allergic reaction, somnolence
*AEs reported above are the rates per 100 person-years of follow up (incidence density). Mean follow up – 4.5 yrs

251

CombAT Trial: Adverse Events

reported over 24 months

	Combination N = 1,610	Dutasteride N = 1,623	Tamsulosin n = 1,611
Ejaculation disorders (RE, ejaculation failure, semen volume decreased)	8.4%	1.4%	2.7%
Erectile Dysfunction	7.4%	6.0%	3.8%
Decreased libido	5.1%	4.1%	2.6%
Dizziness	1.6%	0.7%	1.7%
Breast disorders (enlargement, tenderness, nipple pain)	3.6%	3.4%	1.4%

Journal of Urology, Feb 2008
Other reported AEs <2%: peripheral edema, dyspnea, allergic reaction, somnolence

Long-Term Effects of Doxazosin, Finasteride and Combination Therapy on Quality of Life in Men with Benign Prostatic Hyperplasia

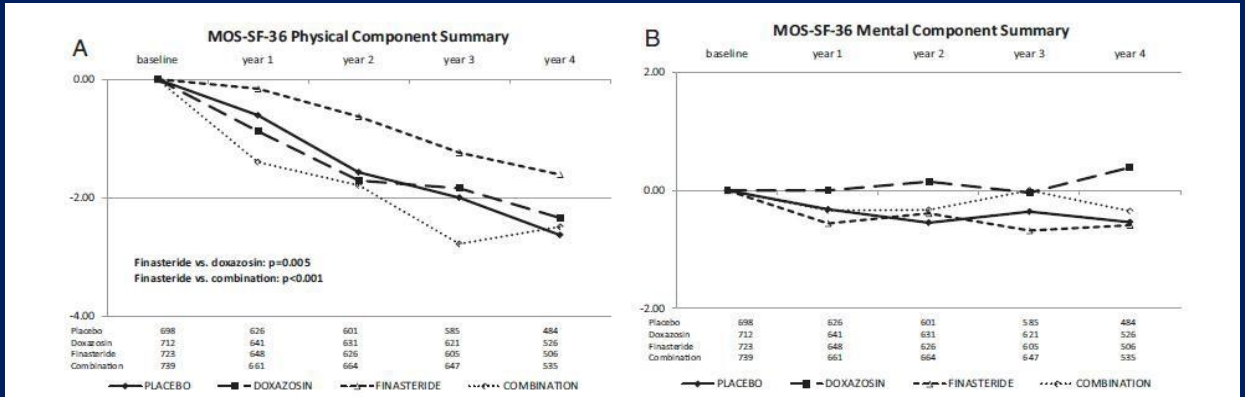
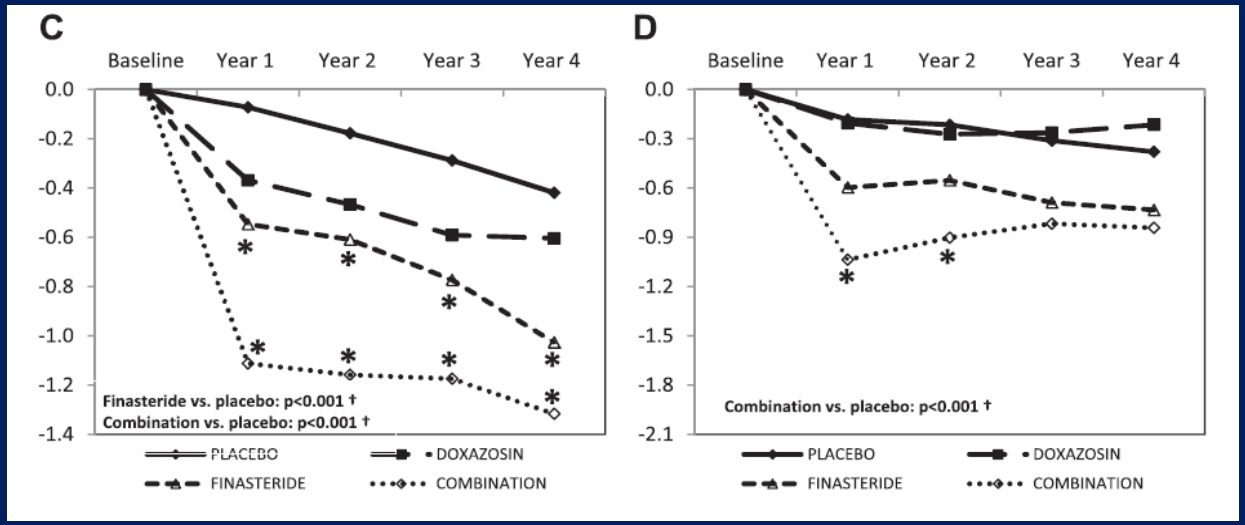


Figure 1. Mean change from baseline in quality of life measures over time in MOS-SF-36 Physical Component Summary and MOS-SF-36 Mental Component Summary. Wei-Lachin test of stochastic ordering was used to determine p values for all followup visit measurements.

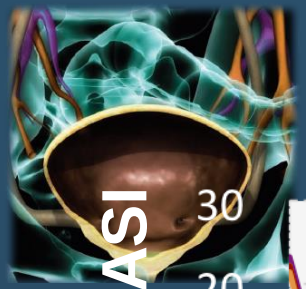
Fwu et al J Urol 190:187, 2013

Change in Sexual Function in Men with Lower Urinary Tract Symptoms/Benign Prostatic Hyperplasia Associated with Long-Term Treatment with Doxazosin, Finasteride and Combined Therapy

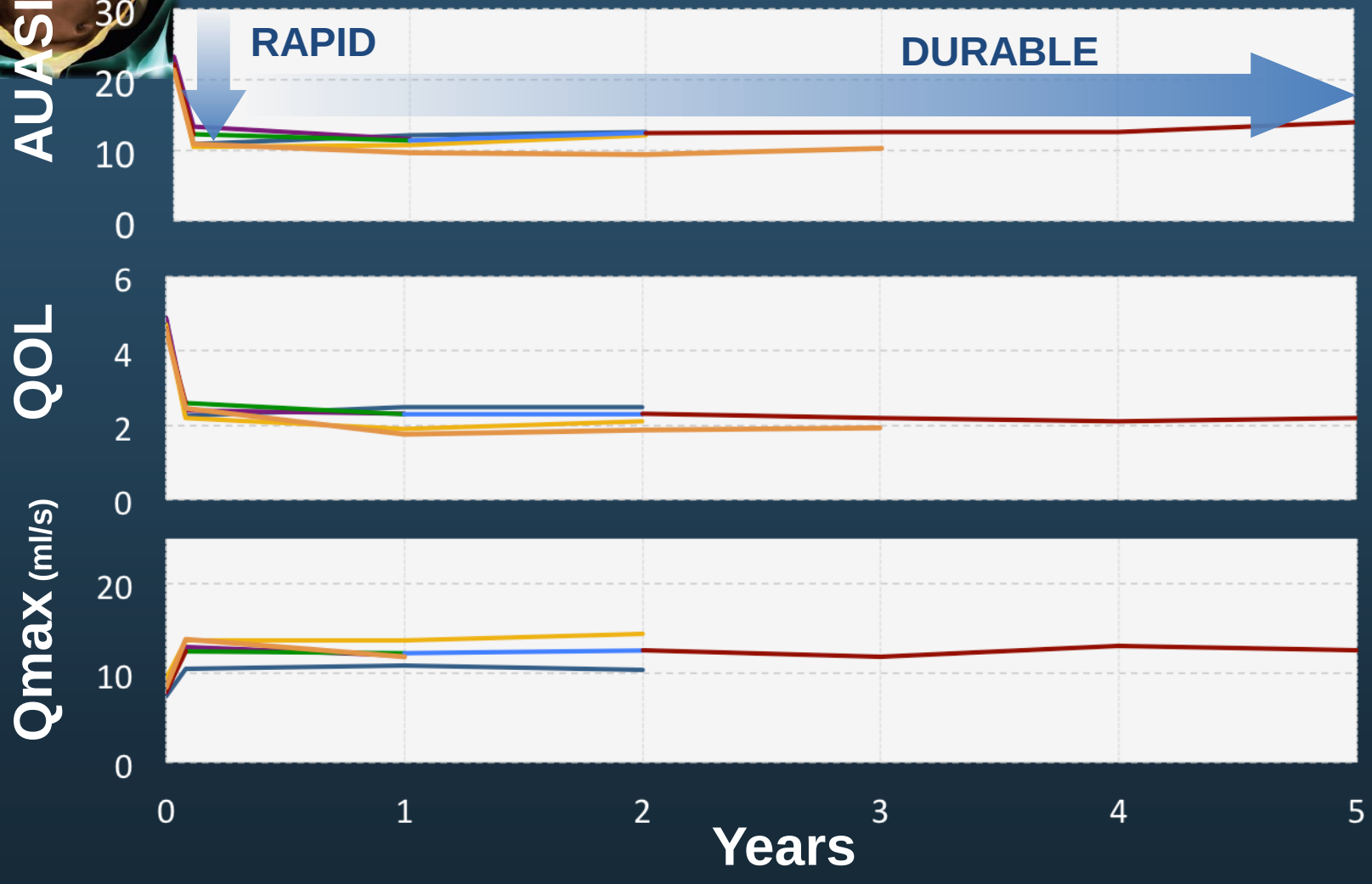


Δ C, ejaculatory function.D, sexual problem assessment

Fwu et al J Urol 191:1828, 2014

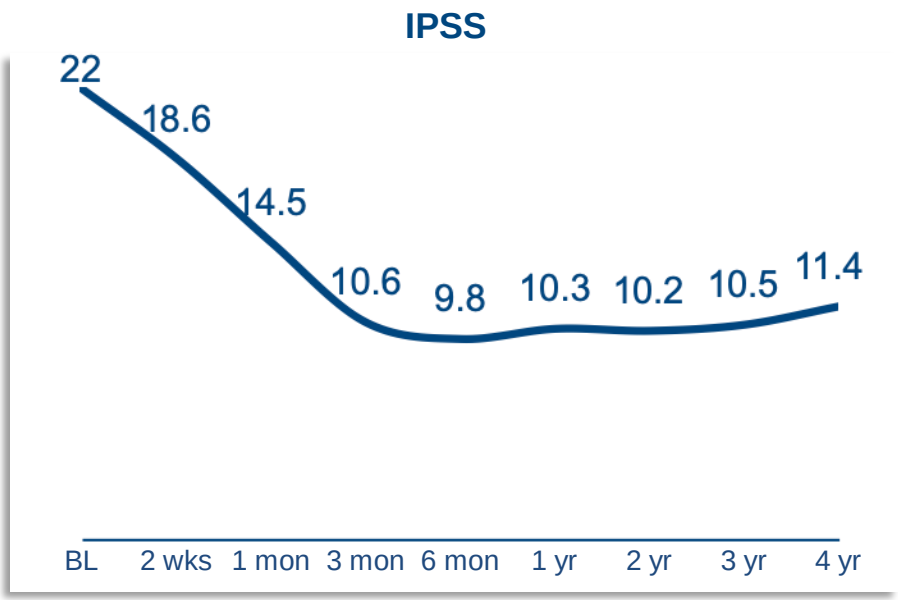


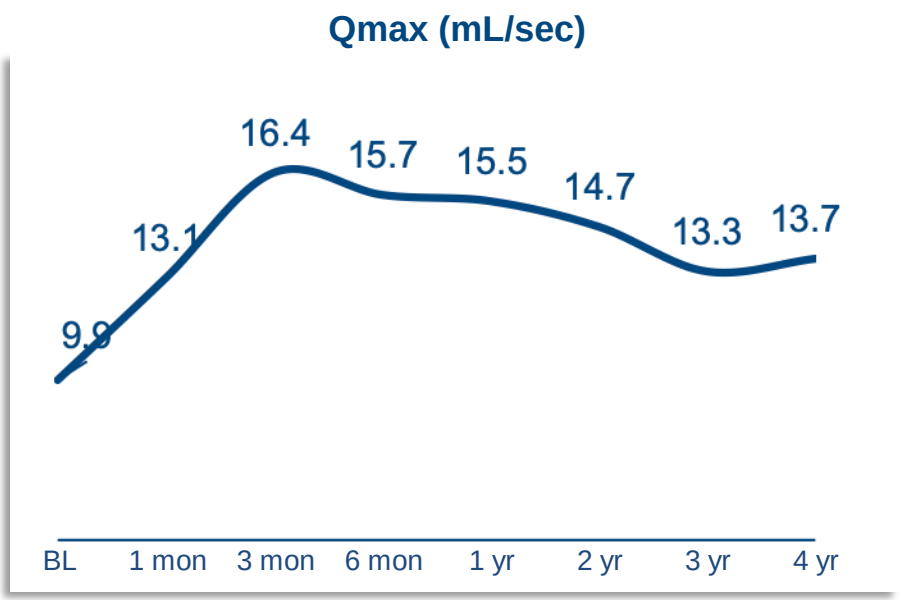
Reproducible Results: Rapid & Durable



Roehrborn AUA2017; Gratzke BJUI 2017; Gange AUA2017;
McNicholas Eur Urol 2013; Chin Urology 2012

IPSS and Qmax were significantly improved from baseline[1-3]

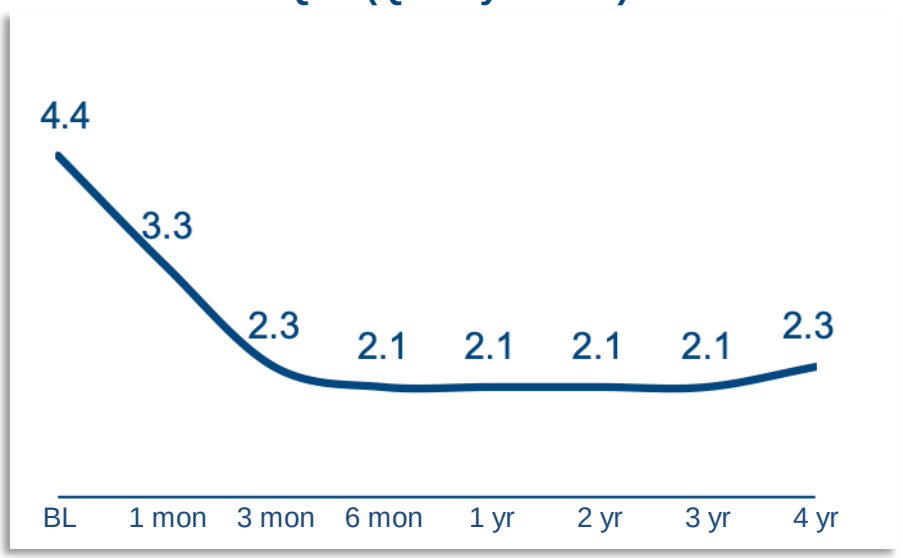


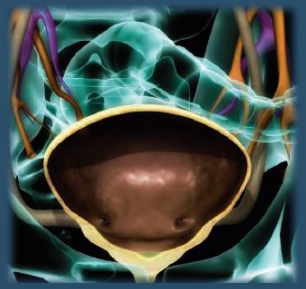


Quality of life and BPH II remained significantly improved[1-3]

BPH II (Impact Index)

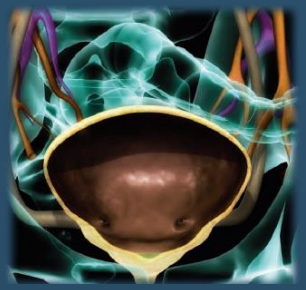
QoL (Quality of Life)





Medical Treatment Failure

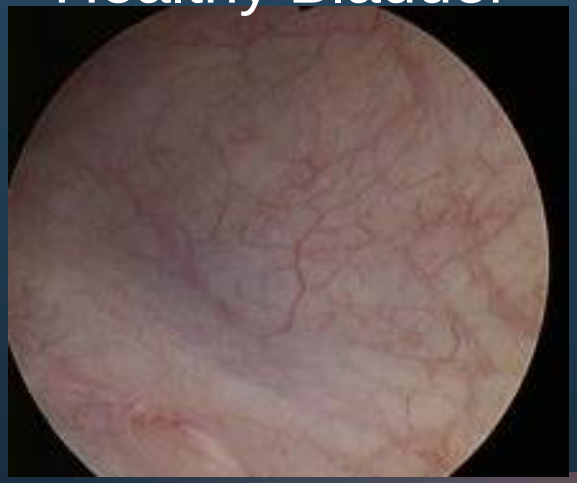
- **Focus has been on BPH / Bladder issues**
  - **Bladder failure**
  - **Delaying MIST / surgery**



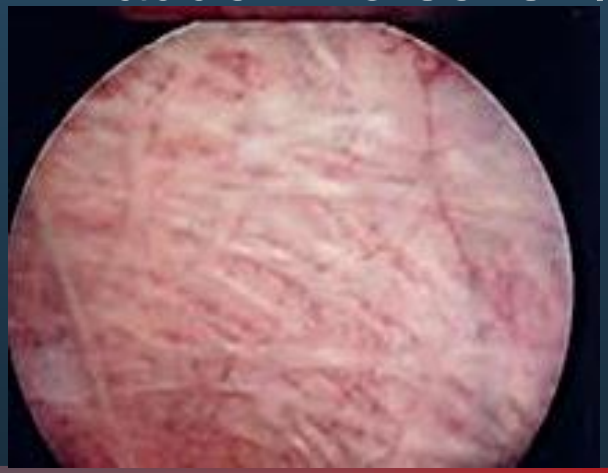
Sooner Than Later?

BPH Starts → Drugs Can Be Insufficient → Surgery Can Be Too Late

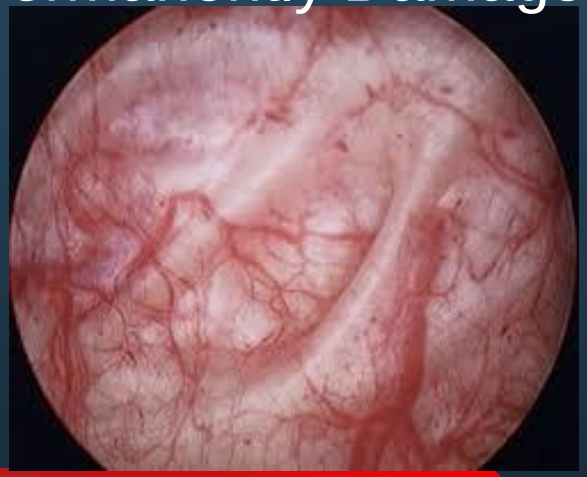
Healthy Bladder



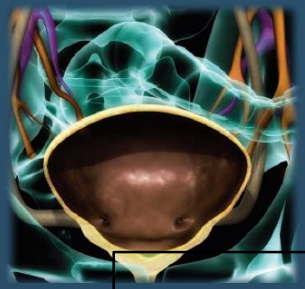
Bladder Worsens



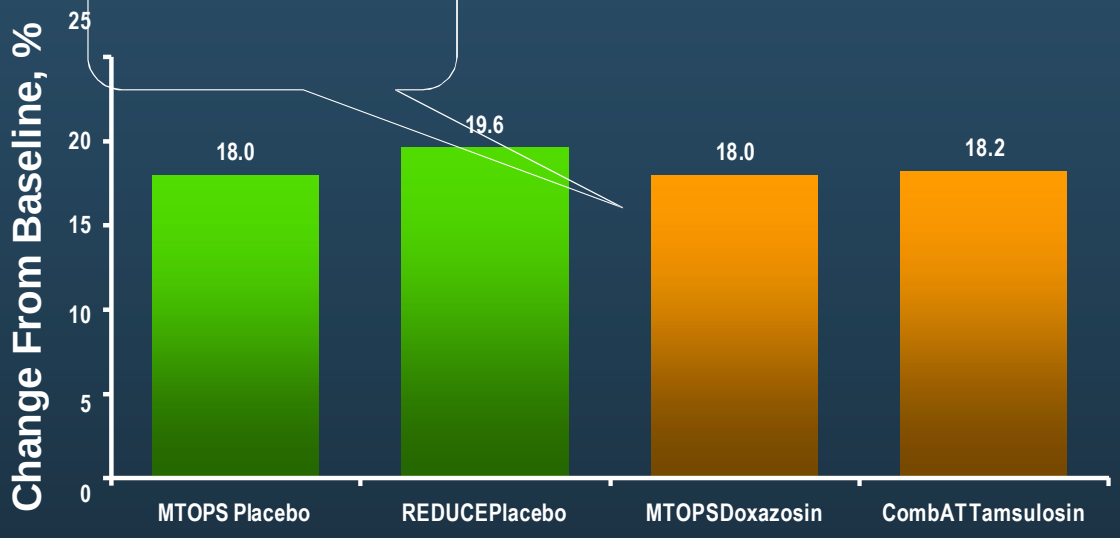
Permanently Damaged



Disease Progression



Prostate Volume Change Over 4 Years in Placebo and α-Blocker Treatment Arms



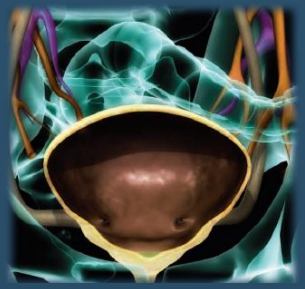
CombAT, Combination of Avodart and Tamsulosin; MTOPS, Medical Therapy of Prostate Symptoms; REDUCE, REduction by DUtasteride of prostate Cancer Events.

McConnell JD, et al. *N Engl J Med*. 2003;349(25):2387-2398; Roehrborn CG, et al. *Eur Urol*. 2010;57(1):123-131; Roehrborn CG, et al. *Urology*. 2011;78(3):641-646.

Medical Treatment Failure

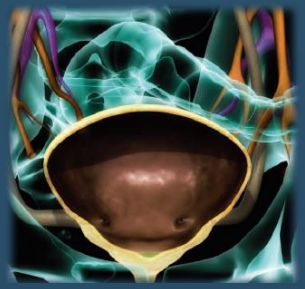
- **What % stay on medical therapy?**
  - 77.1% @ 54 months [1]
  - 56.9% @ 42 months [2] (terazosin)
  - 58.4% @ 48 months [3] (doxazosin)

1. Hong et al (Eur Urol, 2003) 2. Lepor H et al (Urology, 1995) 3. Lepor H et al (J Urol, 1997)

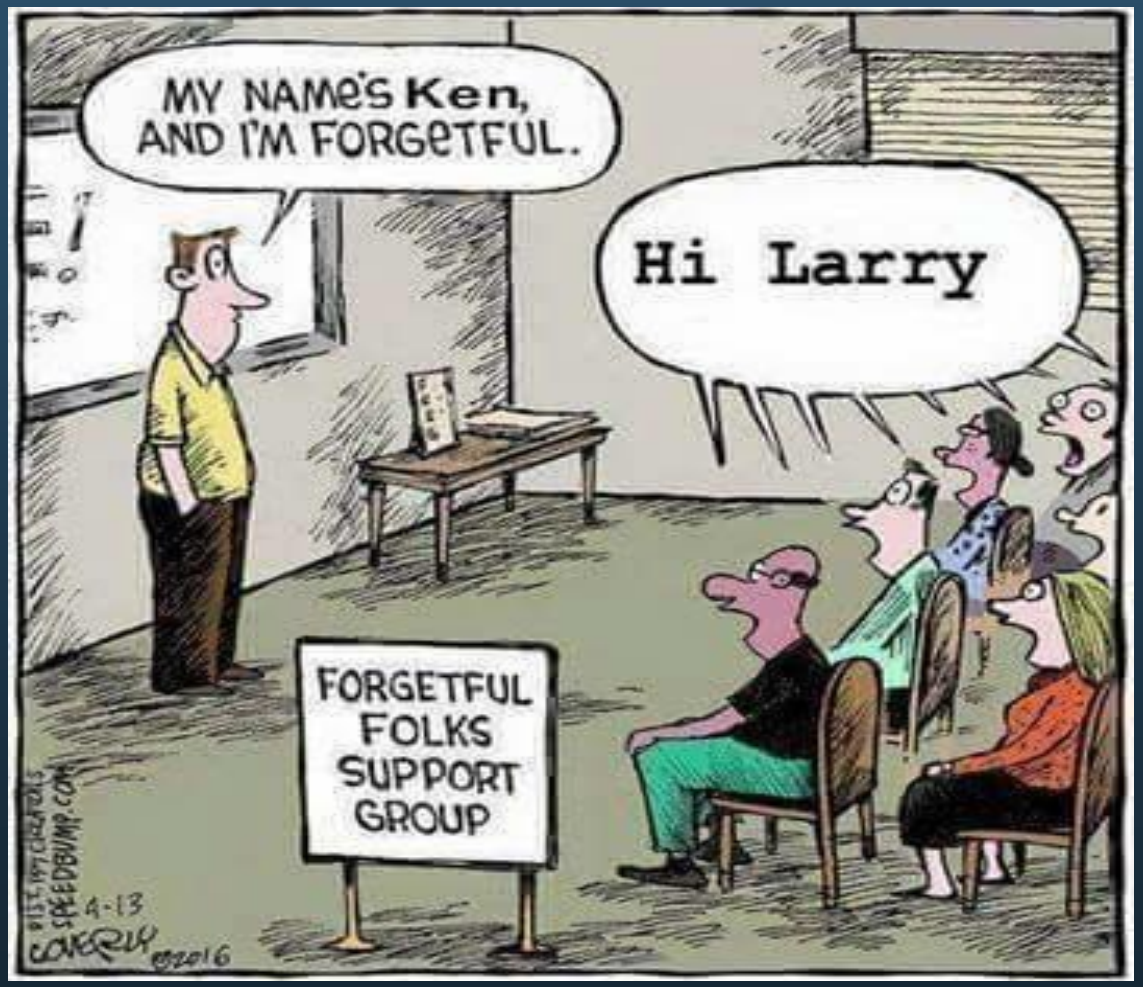


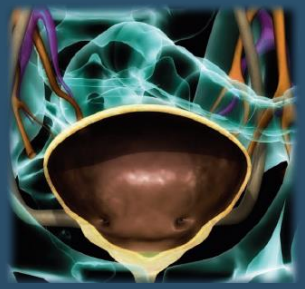
Medical Treatment Failure

- Emerging data on long term consequences
  - Dementia
  - Depression
  - Suicide risk



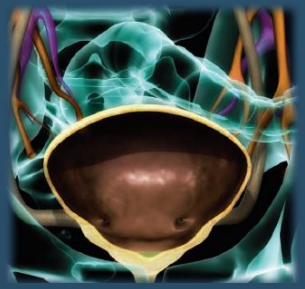
Medical Treatment Failure
Cognitive Issues are Real!





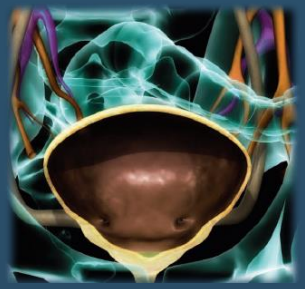
Medical Treatment Failure There Are No Rules!

- No widespread accepted criteria
- Urology focused



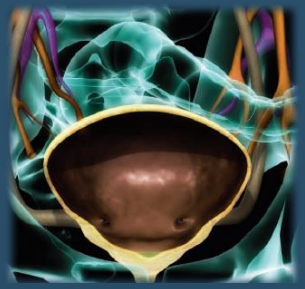
Long Term Use of Statins

- **Statin – associated muscle symptoms (SAMS)**
  - **? Nocebo effect**
  - **Negative expectations about effects of treatment arising from information provided by clinicians / media about possible side effects**
  - **Leads to higher than expected rates**
- **We sometimes over atttribute an adverse event rather than examine other possible causes**



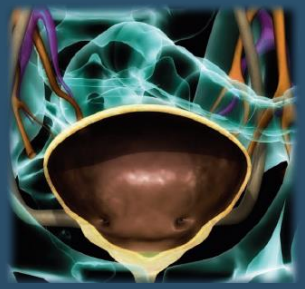
Long Term Use of Statins

- **Cognitive function**
  - **Pandemic of dyslipidemia and insulin resistance**
  - **Evolving demographic patterns affecting prevalence of dementia**
- **Associated risk between high cholesterol and Alzheimer's Disease**
  - **Conflicting hypotheses if statins help or are a detriment**



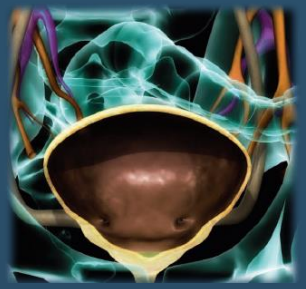
Long Term Use of Statins

- FDA concluded that there was no direct effect
  - Labeling for statins amended to include cognitive side effects such as memory loss and confusion



Long Term Use of 5 – α Reductase Inhibitors

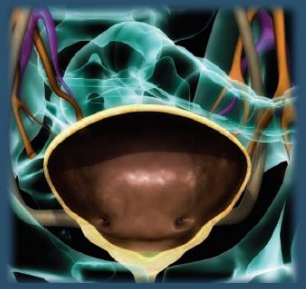
- **Hypothetical link between 5 – ARI and depression**
  - **Role of 5 – ARI in synthesis of endogenous regulating neuroactive steroids and modulation of neuroendocrine stress response**
  - **Dysregulation can lead to depression**
  - **Positive association between cognitive function and androgens**



Long Term Use of 5 – α Reductase Inhibitors

- **Linkage date between Medicare claims and PCPT (focused on finasteride)**
  - **10% higher rate of depression claims**

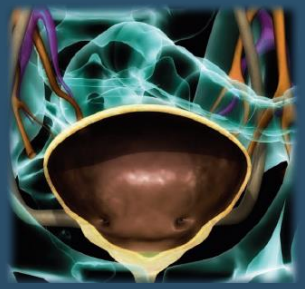
Unger JM, et al JNCI 108 (12):djw 168, 2016



Long Term Use of 5 – α Reductase Inhibitors

- **Population – based retrospective matched cohort study > 93,000 Canadian men using either finasteride / dutasteride**
  - **Medication duration: 1.57 years**
  - **Mean age 75**
  - **Suicide attempts significantly elevated until 18 months of follow up and not thereafter**
  - **Depression and self harm WERE increased**

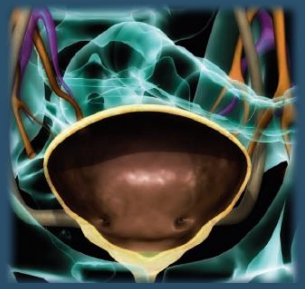
Welk B, et al JAMA Int Med 177(5): 683 – 691, 2017



Long Term Use of 5 – α Reductase Inhibitors

- **Cross sectional survey of 4035 Polish men with BPH**
  - **1.5 fold increased rate of depression**
  - **? How many were alopecia use**

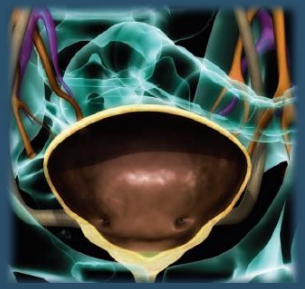
Pietrzyk, 2015



Long Term Use of 5 – α Reductase Inhibitors

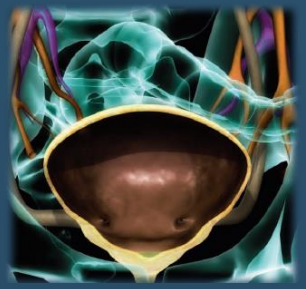
- **In former users of finasteride with persistent sexual side affects (post finasteride syndrome)**
  - **Mean age 31.7 (controls 26.2)**
  - **Higher rates of depression and suicide**

Irwig MS, J Clin Psych 73:1220, 2012



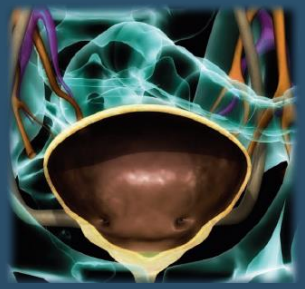
Long Term Use of 5 – α Reductase Inhibitors

- **Challenge in analyzing date**
  - **Assessment of depression (Beck Depression Inventory versus ICD – 9,10)**
  - **Medication duration (< 1 year to > 7 years)**
  - **Controls (placebo, control, alpha blocker)**



Long Term Use of 5 – α Reductase Inhibitors

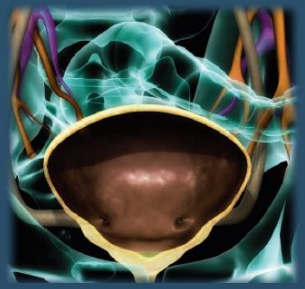
- **Overall summary suggests a real possibility of 5 – ARI use and decreased cognitive function**
  - **Should be part of the shared decision making discussion**



Long Term Use of Tamsulosin

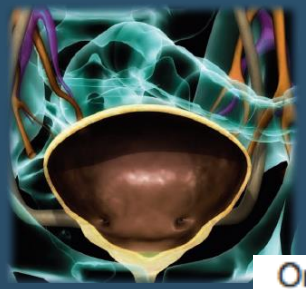
- **Medicare data (2006–2012) in men aged ≥65 years and diagnosed with BPH.**
  - **Men taking tamsulosin (n = 253 136) were matched at a 1:1 ratio using propensity-scores to patients who used no BPH-medication (n = 180 926), dutasteride (n = 34 027), and finasteride (n = 38 767).**

Pharmacoepidemiol Drug Saf. 2018;27:340–348.



Long Term Use of Tamsulosin

- **The median follow-up period for all cohorts was 19.8 months.**
- **After propensity-score matching, the tamsulosin cohort had an incidence of dementia of 31.3/1000 person-years compared with only 25.9/1000 person-years in the no-BPH-medication cohort.**



Anticholinergic and Dementia

Original Investigation | January 26, 2015

Cumulative Use of Strong Anticholinergics and Incident Dementia

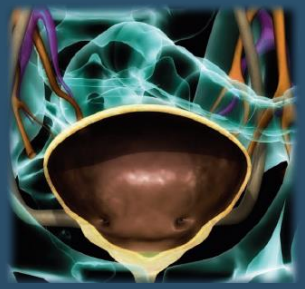
A Prospective Cohort Study

ONLINE FIRST

Shelly L. Gray, PharmD, MS[1]; Melissa L. Anderson, MS[2]; Sascha Dublin, MD, PhD[2,3]; Joseph T. Hanlon, PharmD, MS[4]; Rebecca Hubbard, PhD[2,5,6]; Rod Walker, MS[2]; Onchee Yu, MS[2]; Paul K. Crane, MD, MPH[7]; Eric B. Larson, MD, MPH[2,7]

- Mean follow-up of 7.3 years, N=3434
- 23.2% developed dementia of which 79.9% developed Alzheimer disease.
- 10-year cumulative dose-response relationship observed for dementia and Alzheimer Dz (test for trend, P < .001).
-Results were robust in secondary, sensitivity, and post hoc analyses.

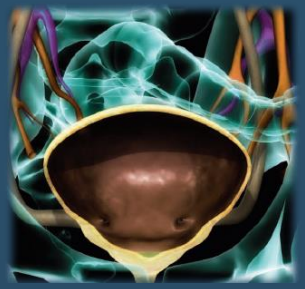
Conclusions and Relevance Higher cumulative anticholinergic use is associated with an increased risk for dementia. Efforts to increase awareness among health care professionals and older adults about this potential medication-related risk are important to minimize anticholinergic use over time.



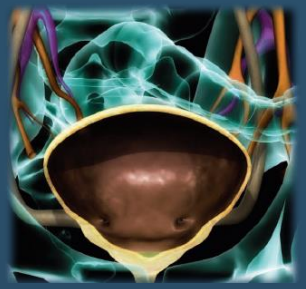
Anticholinergics and Dementia

- Assess associations between anticholinergics and risk of dementia in persons 55 years or older
- 284,343 cases (63.1% women)
  - 1 – 11 years prior to Dx of dementia
  - OR 1.06 – 1.49 (TSDD > 1095)
  - 10.3% attributable rate.

JAMA Int Med 10.1001/jamainternmed.2019.0677



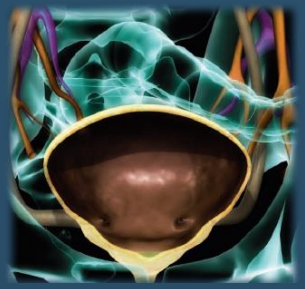
Medical Treatment Failure Depends on Definition



Key Points

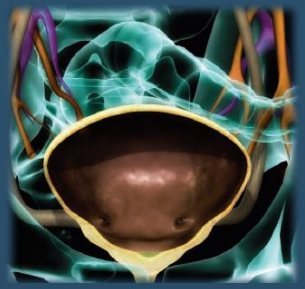
- Criteria arbitrary and not well defined
  - Is it enough if the patient is happy
- Does medical therapy make sense for a QOL condition?
- In a BPH world where MIST / surgery are improving does medical therapy make sense?

WE NEED TO DEFINE MEDICAL FAILURE



No one has a monopoly on truth, and science continues to advance. Yesterday's heresies may be tomorrow's conventional wisdom.

Dean Ornish



I Reject Most Conventional Wisdom

Steven A. Kaplan