Canadian Urological Association

Men's Health Educational Forum

Presenter Disclosures

Presenter: Dean Elterman

- **Relationships with financial sponsors:**

  Membership on advisory boards/speakers' bureaus

  --Astellas, Boston Scientific, Duchesnay, Pfizer, Procept, MediTate, Medtronic, Urotronic

Presenter: Ryan Flannigan

- **Relationships with financial sponsors:**

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  --Paladin (speaking honoriaria), Boston Scientific (speaking honoraria & Educational Grant)

  Membership on advisory boards/speakers' bureaus

  --Acerus (Advisory board)

  Funded Grants, research, or clinical trials

  --CUASF, VCHRI, ASRM, CIHR, NFRF (competitive research grants)

Disclosure of Financial Support

- **This program has received financial support from Astellas and Paladin in the form of an educational grant.**

- **<u>Potential for conflict(s) of interest</u>:**
  - **Dean Elterman** has received honorarium from the CFPC
  - **Ryan Flannigan** has received honorarium from the CFPC
  - **Astellas** developed/licenses/distributes/benefits from the sale of, etc. a product that will be discussed in this program
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Mitigating Potential Bias

The scientific planning committee of this program have complete control over the content of this program.

There has been no influence from the sponsors on the content.

The scientific content of this program was developed by the **Canadian Urological Association**.

Learning Objectives

By the end of this session, participants will:

- apply the latest treatments in Overactive Bladder as they relate to the CUA guidelines
- review the mechanisms of action of all agents in Overactive Bladder
- integrate in their practice new treatment options in the management of Peyronie's Disease

Overactive Bladder

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Assistant Professor, University of Toronto

Overactive Bladder: Definition

ICS Standardization Committee Definition:

"Urgency, with or without urge incontinence, usually with frequency and nocturia *can be described as the overactive bladder syndrome..."*

Abrams et al. Neurourology and Urodynamics 2002; 21:167-178

Overactive Bladder

- Symptom complex
  - **Urgency**
  - Frequency (>8/day)
  - Nocturia (>2)
  - +/- Urgency incontinence
- Associated with other conditions

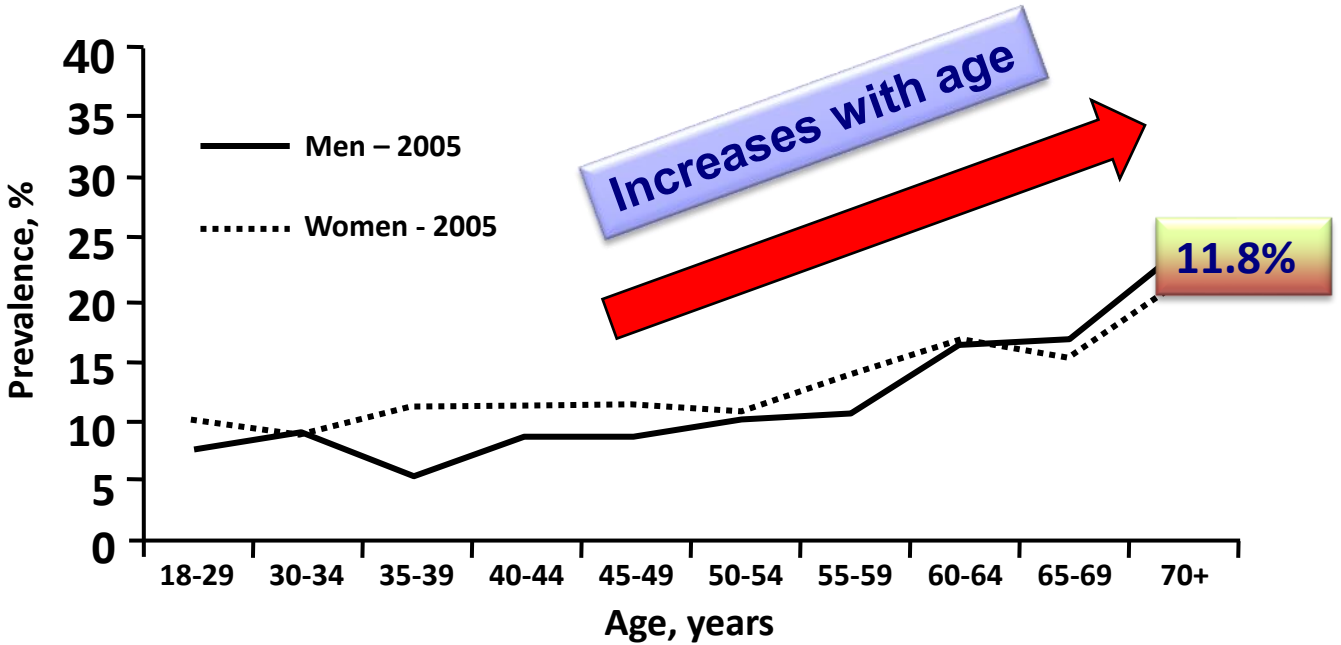
Abrams et al. Neurourology and Urodynamics 2002; 21:167-178

Rovner and Wein. *Clinical Geriatrics*, 2002

Prevalence of OAB by Age

EPIC study 2005

19,165 participants in Canada, Germany, Italy, Sweden and UK



Irwin et al. Eur Urol 2006; 50:1906-1915.

LUTS Are Similar for Men and Women

Storage	Voiding	Postvoiding
Urgency	Hesitancy	Dribbling
Frequency	Poor flow	Incomplete emptying
Urgency incontinence	Intermittency	
Nocturia	Straining	
Other incontinence		

Abrams P et al. *Urology*. 2003;61:37-49.

LUTS Are Similar for Men and Women

Storage	Voiding	Postvoiding
Urgency	Hesitancy	Dribbling
Frequency		
Urgency incontinence	Intermittency	
Nocturia	Straining	
Other incontinence		

OAB symptoms

Abrams P et al. *Urology.* 2003;61:37-49.

DIFFERENTIATING OAB FROM MALE LOWER URINARY TRACT SYMPTOMS (LUTS)

WISE symptoms
Presence of one or more could indicate a prostate-related condition

Presenting Symptom	OAB	Male LUTS
Frequency	Yes	Yes
Urgency	Yes	Yes
Nocturia	Often	Yes
Weak stream	No	Yes
Incomplete emptying	No	Yes
Straining/hesitancy	No	Yes
Elevated PSA	No	Occasionally
Pain	No	No
Dysuria	No	No
Pyuria	No	No
Gross hematuria	No	Rare

BPH = benign prostatic hyperplasia.

Male LUTS often overlap with symptoms of OAB.
But OAB can also exist on its own.

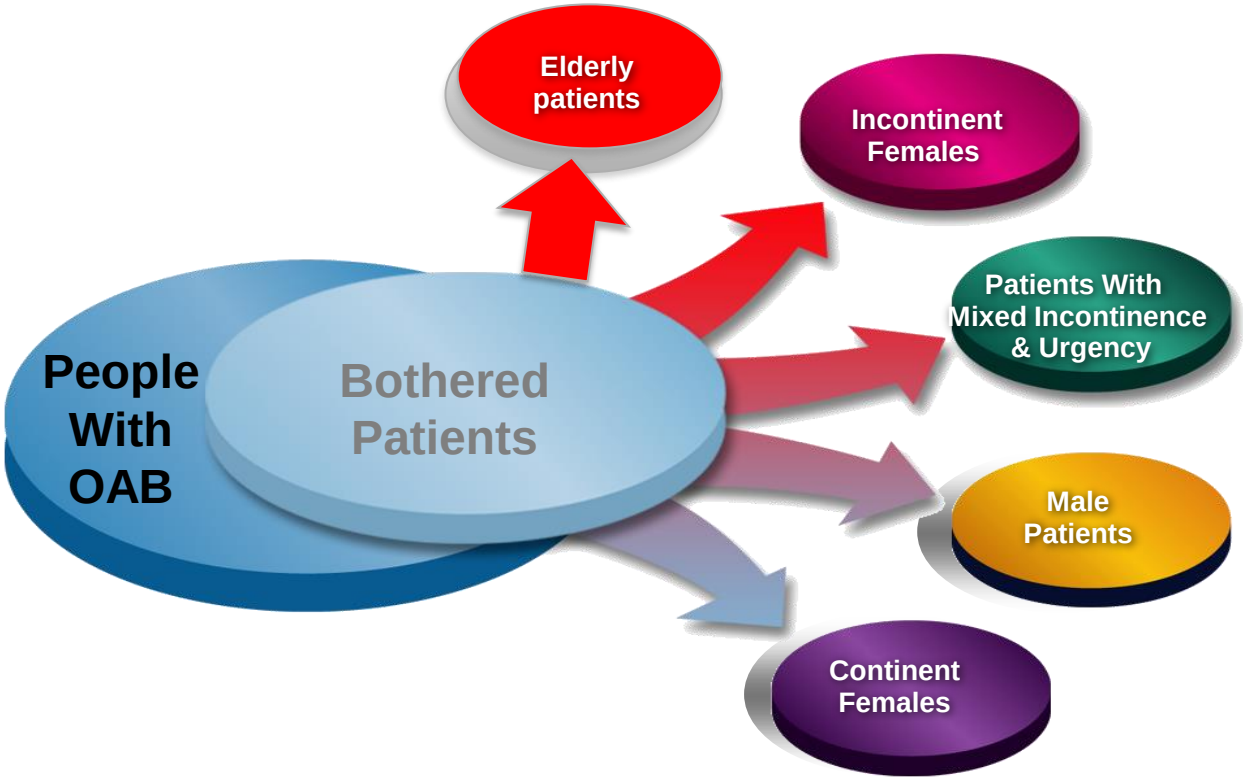
Nitti V, Taneja S. *Int J Clin Pract.* 2005;59:825-830; Prostate Cancer Canada Network: Prostate Cancer Symptoms; Prostate Cancer Canada Network, Non-Cancerous Conditions: Benign Prostatic Hyperplasia; Nickel et al. *Can Urol Assoc J* 2010;4(5):310-316.

Possible co-existing conditions with OAB

- BPH, BPO, BOO, LUTS
- Prolapse
- Atrophic vaginitis
- Pelvic floor dysfunction
- Neuropathic process
- Painful bladder syndrome
- Diabetes
- GU malignancy
- Urinary tract infection
- Nocturnal polyuria

Corcos et al. CUAJ, 2017; 11(5):E142-73

All Patient Types Have Bothersome OAB Symptoms



Diagnosis of OAB

Importance of history

- ***Clinical principle (AUA):*** The clinician should engage in a diagnostic process to document symptoms and signs that characterize OAB and exclude other disorders that could be the cause of the patient's symptoms; the minimum requirements for this process are a careful history, physical exam, and urinalysis.
- There is a universal agreement that taking a history should be the first step in the assessment of OAB patients ***(Level of evidence 2b, Grade B) (CUA)***

Gormley EA, et al. J Urol. 2015;193:1572-80
Corcos et al. CUAJ, 2017; 11(5):E142-73

Initial assessment

- **Urinalysis**
  - To R/O UTI and hematuria
    - Dipstick
    - Microscopy
    - Culture
- **Asymptomatic bacteriuria ($>10^5$ CFU/ml)**
  - Frequent in elderly, diabetic and catheterized patients, or in those with neurogenic lower urinary tract dysfunction
  - Not to be routinely treated
    - Except in pregnant women **(Level of evidence 1a, Grade B)**
    - Before urological procedures **(Level of evidence 3b, Grade B)**

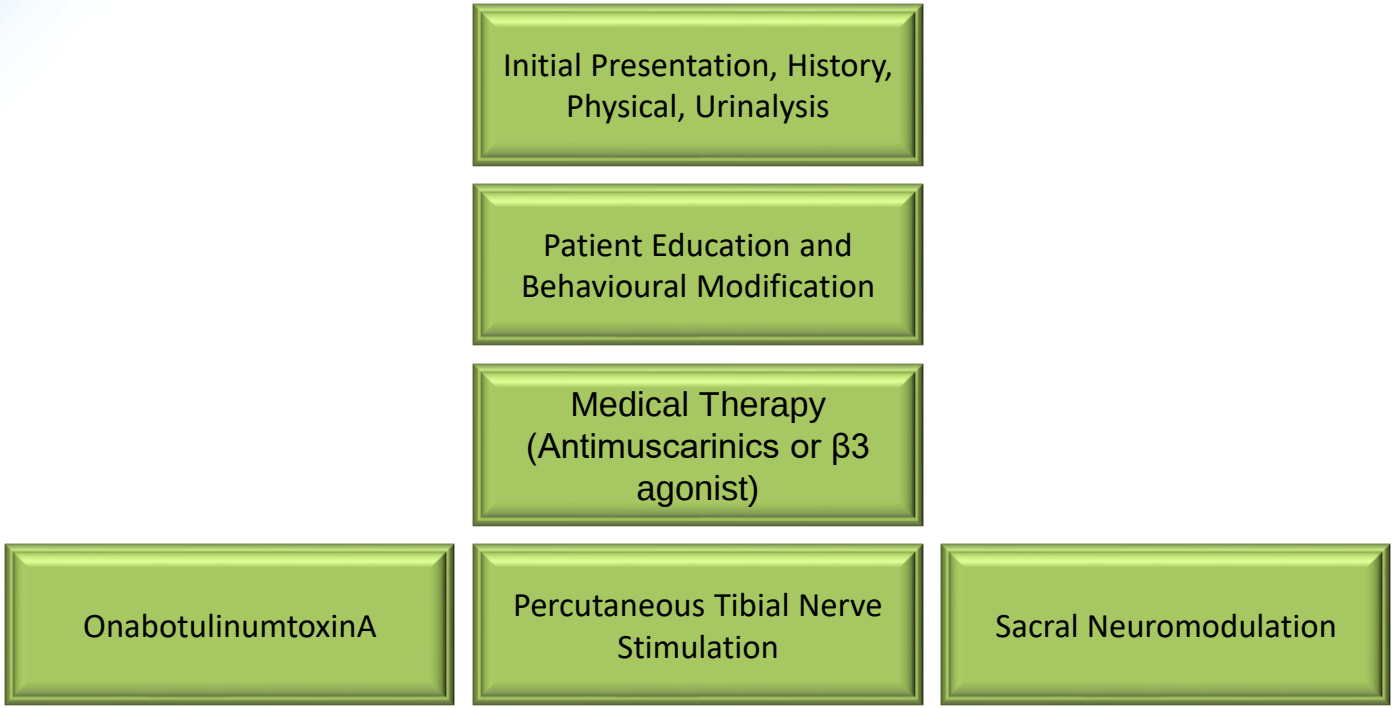
Abrams et al. 6th ICI 2017, Recommendations
Gormley EA, et al. J Urol. 2015;193:1572-80
Corcos et al. CUAJ, 2017; 11(5):E142-73

Additional tests

- ***Clinical Principle (AUA):*** a urine culture and/or post-void residual assessment may be performed and information from bladder diaries and/or symptom questionnaires may be obtained.
- **PVR (CUA)**
  - Voiding symptoms
  - Incontinence or prostatic surgery
  - Neurologic diagnoses
  - To minimize risks
  - >250-300mL may be of concern
  - Bladder scan preferable to catheterization

Gormley EA, et al. J Urol. 2015;193:1572-80
Corcos et al. CUAJ, 2017; 11(5):E142-73

Management of OAB



Bartley et al. Curr Urol Rep, 2013; 14:541-8

OAB therapy

- ***Expert Opinion***

  OAB is not a disease; it is a symptom complex that generally is not a life-threatening condition. After assessment has been performed to exclude conditions requiring treatment and counseling, **no treatment is an acceptable choice made by some patients and caregivers.**

- ***Clinical Principle***

  Clinicians should provide education to patients regarding normal lower urinary tract function, what is known about OAB, the benefits vs. risks/burdens of the available treatment alternatives and the fact that acceptable symptom control may require trials of multiple therapeutic options before it is achieved.

Gormley EA, et al. J Urol. 2015;193:1572-80

First-line therapy

- ***Standard (AUA)***: Behavioral therapies (e.g., bladder training, bladder control strategies, pelvic floor muscle training, fluid management) should be offered as first line therapy to all patients with OAB.
- **CUA Guidelines similar**
  - BT and PFMT effective methods of treatment in certain cases ***(Evidence strength Grade B)(CUA)***.
  - Lifestyle changes - fluids/caffeine intake, weight control, dietary modifications, management of bowel regularity, and optimization of other comorbidities (i.e., diabetes, CHF, OSA) can be effective ***(Evidence strength Grade B/C).(CUA)***

Gormley EA, et al. J Urol. 2015;193:1572-80
Corcos et al. CUAJ, 2017; 11(5):E142-73

Behavioural + pharmacologic

- ***Recommendation (AUA):*** Behavioral therapies may be combined with pharmacologic management. (Grade C)

Gormley EA, et al. J Urol. 2015;193:1572-80

Second-line treatments (CUA)

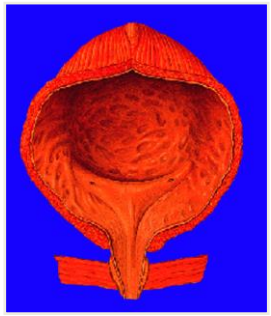
- Oral AMs, transdermal oxybutynin or oral beta-3 agonist *(Evidence strength Grade A)*.
- Start with lowest dose *(Evidence strength Grade B).*
- If the initial drug is not tolerated or inadequate, give an alternative drug with different mechanism *(Expert opinion)*.
- Watch for adverse events and contraindications *(Expert opinion).*
- Avoid Immediate release formulations of AMs if other formulations are available *(Evidence strength Grade A).*
- Persistent incontinence after initial treatment with an AM could be treated with combination of solifenacin and mirabegron *(Evidence strength Grade C).*

Corcos et al. CUAJ, 2017; 11(5):E142-73

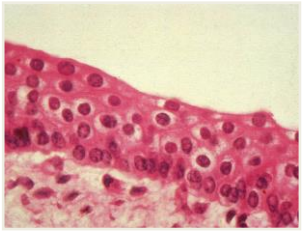
Pharmacologic Management of Overactive Bladder

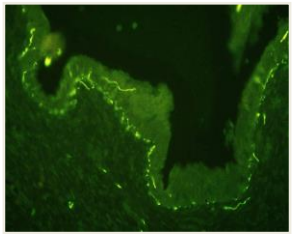
Antimuscarinics for OAB

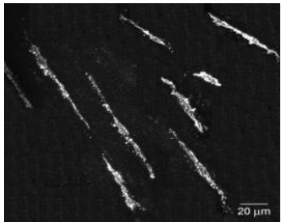
Rationale for Treatment

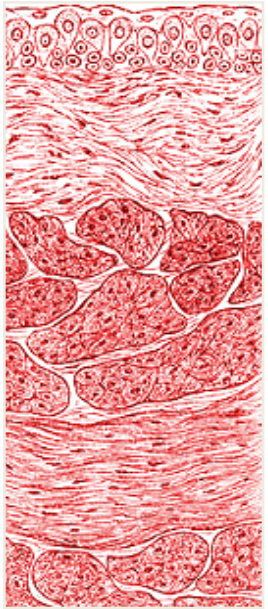


Blockade of muscarinic receptors at both detrusor and non-detrusor sites may prevent OAB symptoms and detrusor overactivity [without depressing the contraction during voiding]









Antimuscarinic Medication – Level of evidence

Drug	Level of Evidence	Grade of Recommendation
Darifenacin	1	A
Fesoterodine	1	A
Solifenacin	1	A
Toterodine	1	A
Trospium	1	A
Oxybutynin	1	A
Propiverine	1	A
Flavoxate	2	D

Andersson et al. 6th ICI, 2017

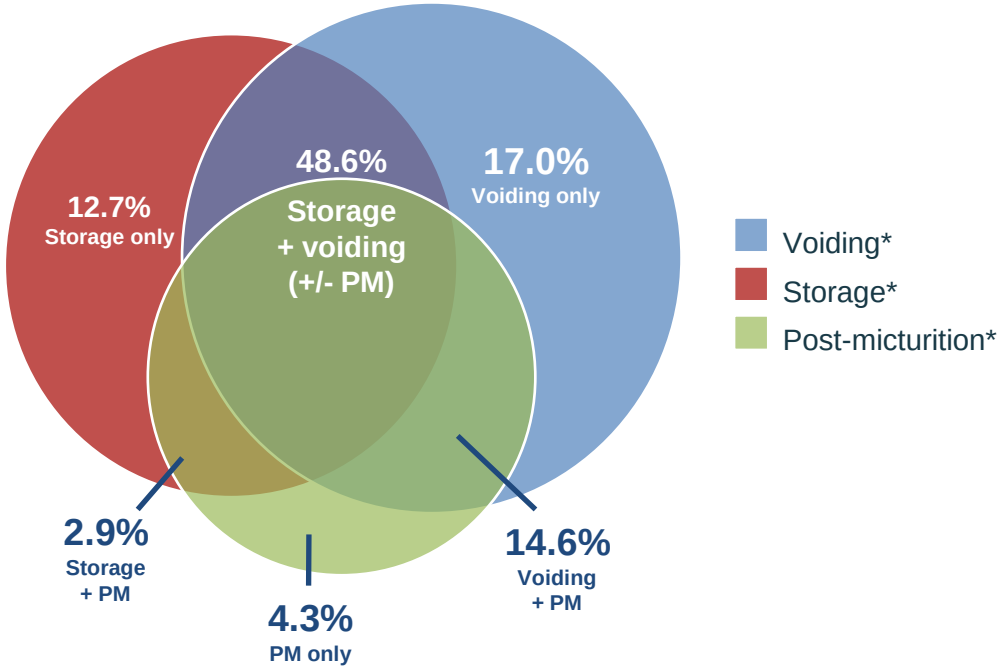
OAB and BOO

- Men with LUTS also have OAB symptoms
- Benefit of adding an anticholinergic to an alpha blocker in the treatment of patients with symptomatic BOO from BPH

Men with OAB often present with an overlap of LUTS

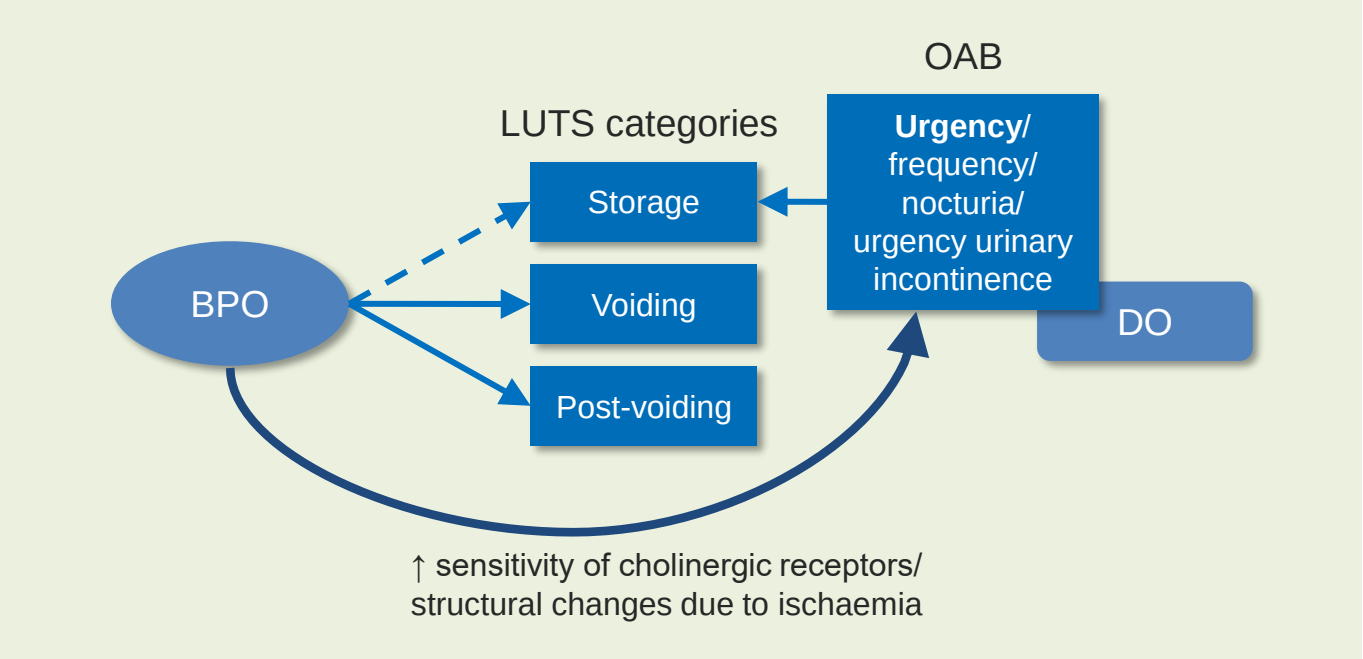
~50% of all male patients with LUTS report a **combination of storage and voiding symptoms**

EpiLUTS survey (N=14,139)



*Adapted from Sexton CC, *et al*. 2009 to exclude patients who reported no LUTS.
EpiLUTS, Epidemiology of LUTS study; LUTS, lower urinary tract symptoms; PM, post-micturition.
Sexton CC, *et al. BJU Int*. 2009;103(Suppl 3):12–23.

The relationships between BPO, OAB and male LUTS



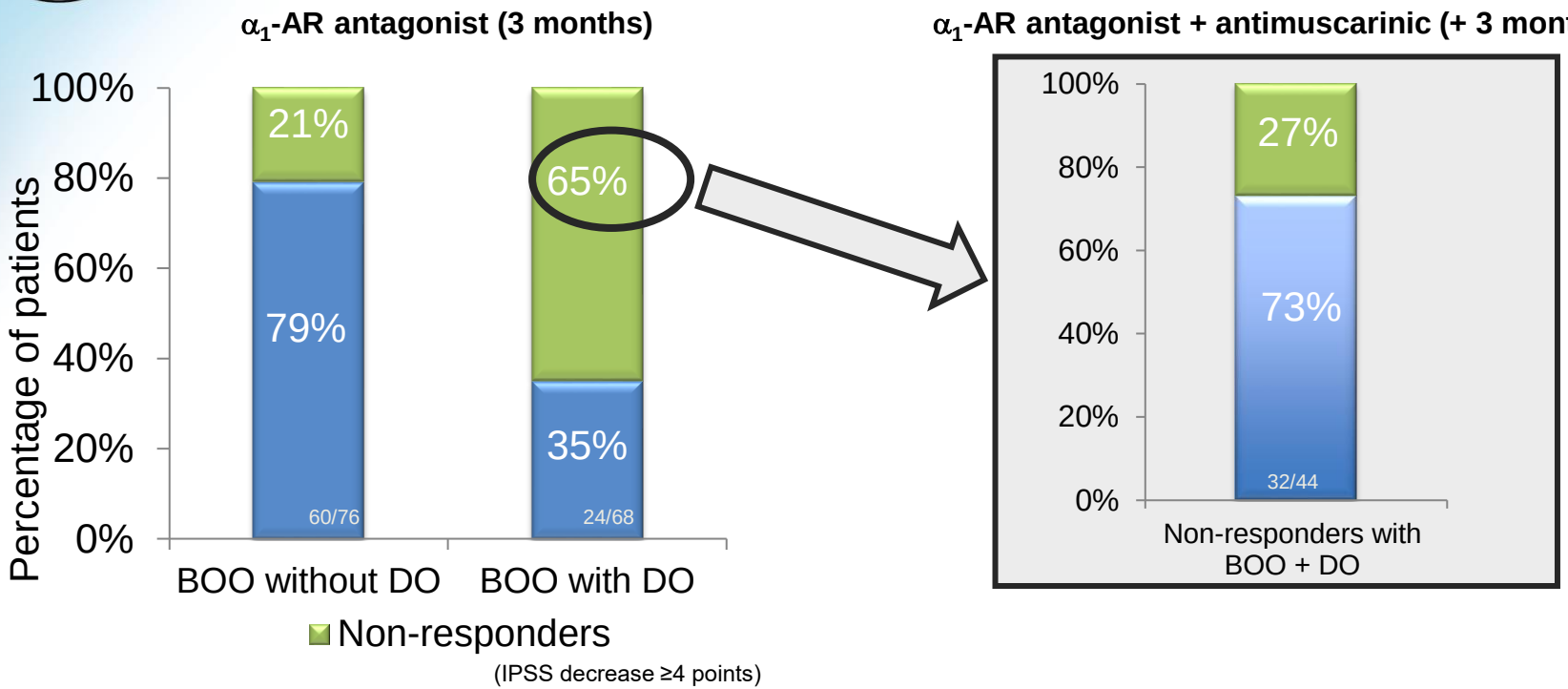
BPH, benign prostatic hyperplasia; BPO, benign prostatic obstruction; DO, detrusor overactivity; LUTS, lower urinary tract symptoms.
Adapted from Athanasopoulos A, *et al. Eur Urol.* 2011;60:94–105.

Antimuscarinics in males

- Tolterodine
- Oxybutynin ER
- Propiverine
- Solifenacin
- Fesoterodine

- **Mainly 12-week trials with alpha-blockers**
- **Significant improvement in storage symptoms**
- **Non-significant improvement in many outcome measures**
- **Low risk of retention**

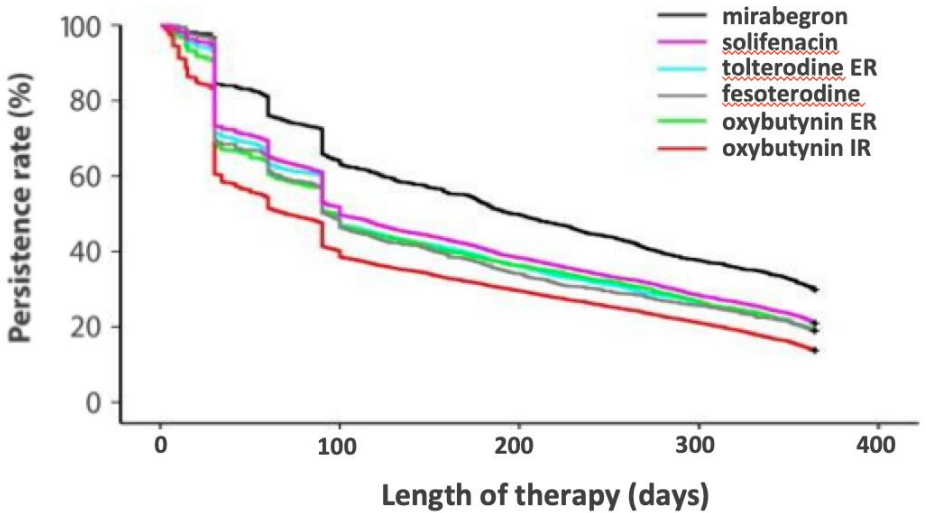
a1-adrenergic receptor antagonist monotherapy is not sufficient in all men with LUTS



AR, adrenergic receptor; BOO, bladder outlet obstruction; DO, detrusor overactivity; IPSS, International Prostate Symptom Score.

Lee JY, *et al*. *BJU Int.* 2004;94:817–820.

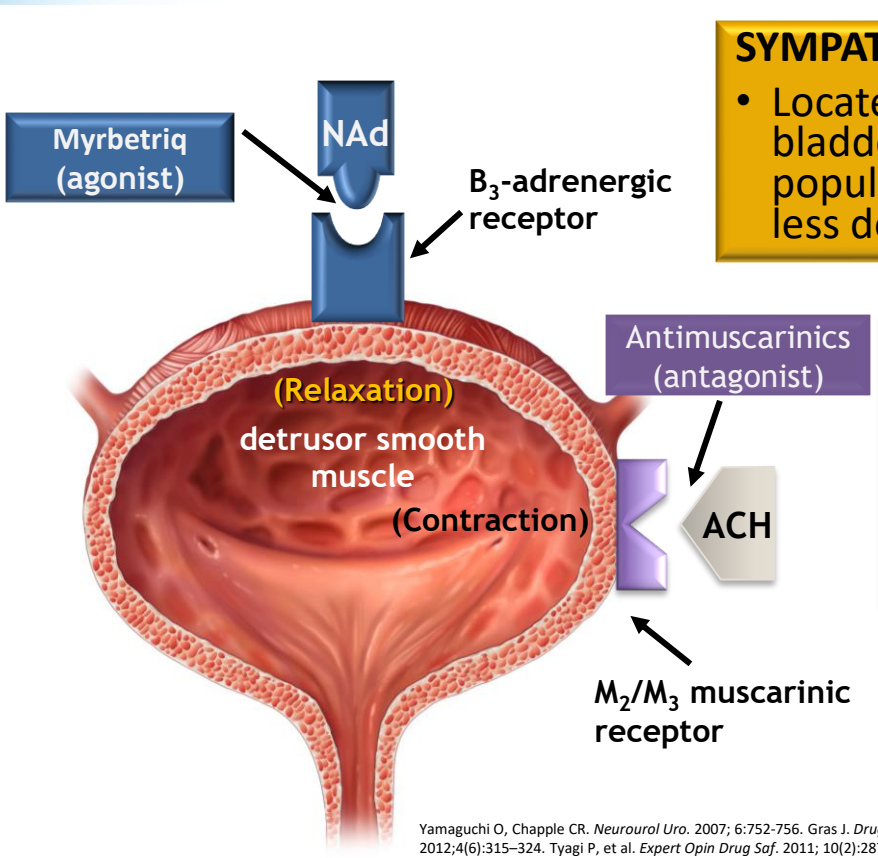
Levels of Treatment Persistence Over 12 Month With Antimuscarinic Treatment



- Data were extracted from the medical records of >1,200,000 registered patients via general practice software, and anonymized prescription data were collated for all eligible patients with documented OAB (n = 4833).
- **After 12 months <35% of patients were still on antimuscarinic treatment**

Wagg A et al. BJU Int. 2012;110(11):1767-1774.

Mirabegron B_3-agonist



SYMPATHETIC (Beta)

- Located throughout the bladder, more densely populating the dome and less dense in the trigone

PARASYMPATHETIC (Cholinergic)

- Located throughout the "body" of the bladder, trigone and bladder neck

Yamaguchi O, Chapple CR. *Neurourol Uro.* 2007; 6:752-756. Gras J. *Drugs of Today*. 2012;48(1):25-32. Sacco E ,Bientinesi R. *Ther Adv Urol*. 2012;4(6):315–324. Tyagi P, et al. *Expert Opin Drug Saf*. 2011; 10(2):287-294. Hicks A, et al. *J Pharmacol Exp Ther.* 2007;323:202-209 ; Takeda M, et al. *J Pharmacol Sci* 2010; 112: 121-127; Fowler CJ et al. *Nat Rev Neurosci* 2008; 9: 453-466.

Mixed treatment comparison (MCT): Mirabegron vs. Antimuscarinics

- 50 mg Mirabegron compared with 44 RCTs involving 27,309 patients
- As efficacious as AMs in reducing frequency, incontinence, and UUI episodes, with exception of solifenacin 10 mg
- Lower dry mouth than AMs

Maman et al. Eur Urol, 2014; 65:755-65

Persistence and adherence of mirabegron vs. antimucarinics in Canada

- 19,485 pts. (74% female, 92% naïve, 20% ≥65y)

Median number of days on drug	***Experienced***	***Naïve***
Mirabegron	299	196
AMs	96-242	70-100
Persistence at 12 months		
Mirabegron	39%	30%
AMs	14-35%	14-21%

- Patients remained on mirabegron longer and had greater persistence and adherence rates

Wagg et al. CUAJ 2015; 9:343-50

Systematic review adherence and persistence: AMs vs. mirabegron

- 30 studies with electronic claims databases
- Overall persistence 5% to 47% and 1-year adherence 15% to 44%

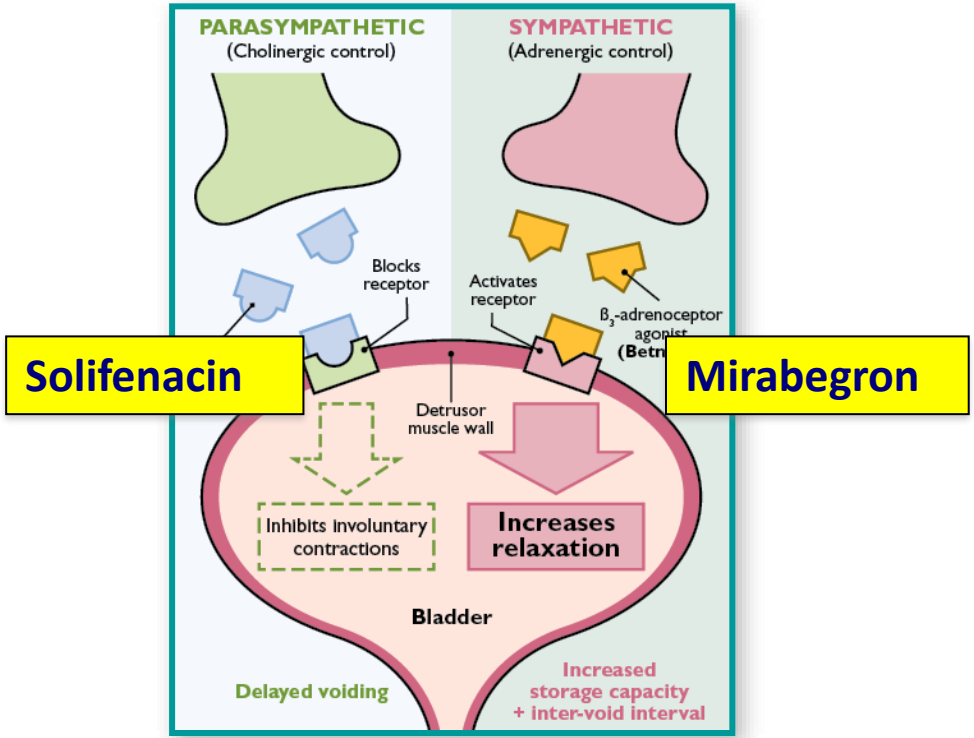
	AMs	Mirabegron
1-year persistence	12-25%	32-38%
Median time to discontinuation	<5 months (1 study 6.5 months)	5.6-7.4 months
Medication possession ratio mean (median)	0.41-0.53 (0.19-0.49)	0.59 (0.65)
Mean proportion of days covered	0.55	0.66

- Mirabegron had better characteristics

Yeowell et al. BMJ Open 2018;8:e021889.

Antimuscarnics and beta-3 agonists in OAB - Mode of Action

Mode of action of OAB treatments



Adapted from Chu FM, Dmochowski R. Am J Med 2006;119(3 Suppl 1):3–8.

Combination

EUROPEAN UROLOGY 70 (2016) 136–145

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Voiding Dysfunction

Editorial by Barbara Padilla-Fernández and David Castro-Díaz on pp. 146–147 of this issue

Efficacy and Safety of Mirabegron Add-on Therapy to Solifenacin in Incontinent Overactive Bladder Patients with an Inadequate Response to Initial 4-Week Solifenacin Monotherapy: A Randomised Double-blind Multicentre Phase 3B Study (BESIDE)

Marcus J. Drake [a,], Christopher Chapple [b], Ahmet A. Esen [c], Stavros Athanasiou [d], Javier Cambronero [e], David Mitcheson [f], Sender Herschorn [g], Tahir Saleem [h], Moses Huang [h], Emad Siddiqui [h], Matthias Stölzel [i], Claire Herholdt [h], Scott MacDiarmid [j], on behalf of the BESIDE study investigators*

Combination

BJUI
BJU International

BJUI
BJU International

Efficacy and safety of combinations of mirabegron and solifenacin compared with monotherapy and placebo in patients with overactive bladder (SYNERGY study)

Sender Herschorn*, Christopher R. Chapple†, Paul Abrams‡, Salvador Arlandis§, David Mitcheson¶, Kyu-Sung Lee**, Arwin Ridder††, Matthias Stoelzel††, Asha Paireddy††, Rob van Maanen†† and Dudley Robinson‡‡

*Department of Surgery/Urology, University of Toronto, Sunnybrook Health Sciences Centre, Toronto, ON, Canada, †Department of Urology, Royal Hallamshire Hospital, Sheffield, UK, ‡Bristol Urological Institute, Southmead Hospital, Bristol, UK, §Hospital Universitario La Fe, Valencia, Spain, ¶St. Elizabeth's Medical Center, Brighton, MA, USA, **Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, ††Astellas Pharma Global Development, Leiden, The Netherlands, and ‡‡Kings College Hospital, London, UK

Long-term combination treatment with solifenacin and mirabegron in patients with overactive bladder (SYNERGY II)

- All treatments were generally well tolerated over the 12-month study period
  - Slightly increased frequency of overall TEAEs in the combination group
  - Most common TEAEs were dry mouth (combination and solifenacin) and nasopharyngitis (mirabegron)
- Clear and clinically relevant improvements in efficacy with combination compared with each monotherapy, both in terms of
  - Primary variables: mean number of incontinence episodes/24 h and micturitions/24 h
  - Secondary variables: MVV per micturition, OAB-q Symptom Bother scores, TS-VAS score

Gratzke et al, Eur Urol 2018; 74:501– 9

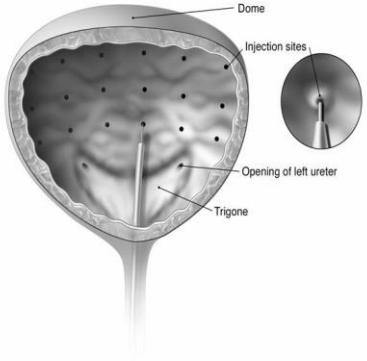
Refractory OAB

- Patients who are refractory to behavioral and pharmacologic therapy should be evaluated by an appropriate specialist if they desire additional therapy. ***Expert Opinion***

Gormley EA, et al. J Urol. 2015;193:1572-80

Third-line treatments (AUA)

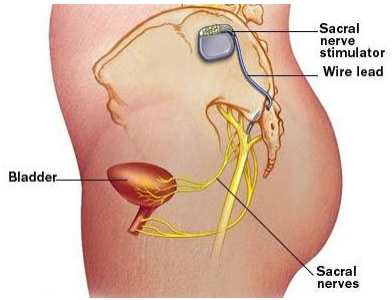
- Intradetrusor onabotulinumtoxinA (100U) in the carefully-selected and thoroughly-counseled patient who has been refractory to first- and second-line OAB treatments.
- The patient must be able and willing to return for frequent post-void residual evaluation and able and willing to perform self-catheterization if necessary. ***Standard Option (Evidence Strength Grade B C)***



Gormley EA, et al. J Urol. 2015;193:1572-80

Other third-line treatments

- Peripheral tibial nerve stimulation ***(C)***
- Sacral neuromodulation ***(C)***
- CUA assigned ***level B*** evidence.



Gormley EA, et al. J Urol. 2015;193:1572-80
Corcos et al. CUAJ, 2017; 11(5):E142-73

Additional treatments

- Indwelling catheterization, augmentation cystoplasty, or other urinary diversions are rare long-term management strategies for OAB and should only be considered after all other medical and surgical options have been exhausted and only after careful consideration of the likely benefits and risks. ***(Evidence strength Grade D)***

Gormley EA, et al. J Urol. 2015;193:1572-80
Corcos et al. CUAJ, 2017; 11(5):E142-73

OAB treatment in the elderly

Elderly concerns

- Anticholinergic burden - polypharmacy
  - Xerostomia (dry mouth)
  - Constipation
  - Cognition

Drugs with strong ACh properties

- Antihistamines
- Antidepressants
- Antimuscarinics
- Antiparkinsonian
- Antipsychotics
- Skeletal muscle relaxants
- Antiarrhythmics
- Antiemetics

>50 drugs

AGS Beers Criteria. JAGS, 2015; 63:2227–46.

ACh drugs and dementia – Case-control study

- 40,770 patients with a new diagnosis of dementia (2006-2015) and 283,933 controls without dementia
- Daily ACh drugs 4-20 years before diagnosis
- 14,553 (35%) cases and 86,403 (30%) controls given ≥1 drug with ACB of 3 (definite ACh activity)
  - Dementia was associated with increasing ACB score.
  - GI drugs with ACB 3 and Cardiovascular drugs with ACB of 1 NOT linked to dementia.
  - Risk increased with greater exposure to anti-depressant, urological (oxybutynin/tolterodine), and anti-Parkinsonian drugs with ACB of 3

Richardson et al. BMJ, 2018 epub

OAB treatment in elderly

- **Trospium**[1]
  - Hydrophilicity and quaternary amine structure may limit BBB penetration
- **Transdermal oxybutynin**[1]
  - Avoids first pass metabolism through liver and decrease AM AEs
- **Fesoterodine**
  - RCTs in aged and vulnerable elderly[2]; pooled analysis[3]
- **Darifenacin**[1]
  - M3 specific and weak affinity for brain M1 receptors
- **Solifenacin**
  - Observational study[4]
- **Mirabegron**[5]

1. McFerren and Gomelsky, Drugs Aging 2015; 32:809-19
2. Dubeau et al. J Urol 2014; 191:395-404
3. Wagg, Arumi, Herschorn et al. Age Ageing, 2017; 46:620-6
4. Hampel et al. Urol Int; 2017; 98:350-7
5. Wagg, et al. ICS, 2018

Adherence and its impact on costs and absenteeism

- 2001-2011 claims database of 27 large US employers
- 1.5 million employees; 2960 prescribed OAB drugs
- 380 (12.8%) ≥80% adherent; 2580 (87.2%) <80% adherent
- Lower adherence – increased copay and copay as a percentage of salary
- High adherence – lower medical, sick leave, and short-term disability costs, and higher drug costs

Kleinman et al. J Managed Care Spec Phar m 2014; 20:1047-56

Drug persistence affects PROs

- 952 OAB pts. who started antimuscarinics in prospective observational study
- All pts. paid drug and prescription costs
- Drug persistence and compliance at 4, 12, 24 weeks
- At 24 weeks 56.8% on drug
- Persistent pts. had sig. higher OABSS and OABq short form than non-persistent.
  - Older age and OAB dry

Kim et al. Qual Life Res, 2016; 25:2021-9

Follow-up

- The clinician should offer follow up with the patient to assess compliance, efficacy, side effects and possible alternative treatments.
- 12 weeks
- ***Expert Opinion***

Gormley EA, et al. J Urol. 2015;193:1572-80
Corcos et al. CUAJ, 2017; 11(5):E142-73

Conclusions

- Bothersome OAB is common in men and women and increases with age.
- Diagnosis is straightforward
- Treatment approach involves patient education, behavioural therapy and medications.
- More than one therapeutic trial may be necessary and may involve different medications.
- Third-line therapy available for refractory patients
- Long-term follow-up required.
- Successful treatment is beneficial

Managing Peyronie's Disease in 2020

Ryan Flannigan MD FRCSC
Assistant Professor, Department of Urologic Sciences, UBC
Director of Male Reproduction & Sexual Medicine Research Program
Clinical Lead Prostate Cancer Supportive Care Program, Sexual Medicine, BC
Adjunct Assistant Professor, Weill Cornell Medicine, NY

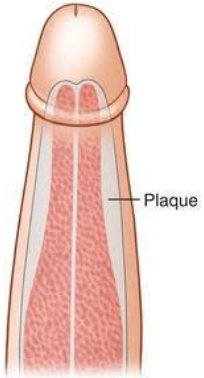
Objectives

- Review of Peyronie's Disease
- Review of medical and surgical management options for Peyronie's Disease

What Is Peyronie's Disease (PD)?

- Disorder of abnormal scar formation characterized by development of a plaque within the tunica albuginea

- Plaque may be palpable and can lead to penile deformity and bother[1]
  - Curvature
  - Indentation
  - Hour Glass deformity
  - Distal Tapering
  - Penile shortening
  - ED

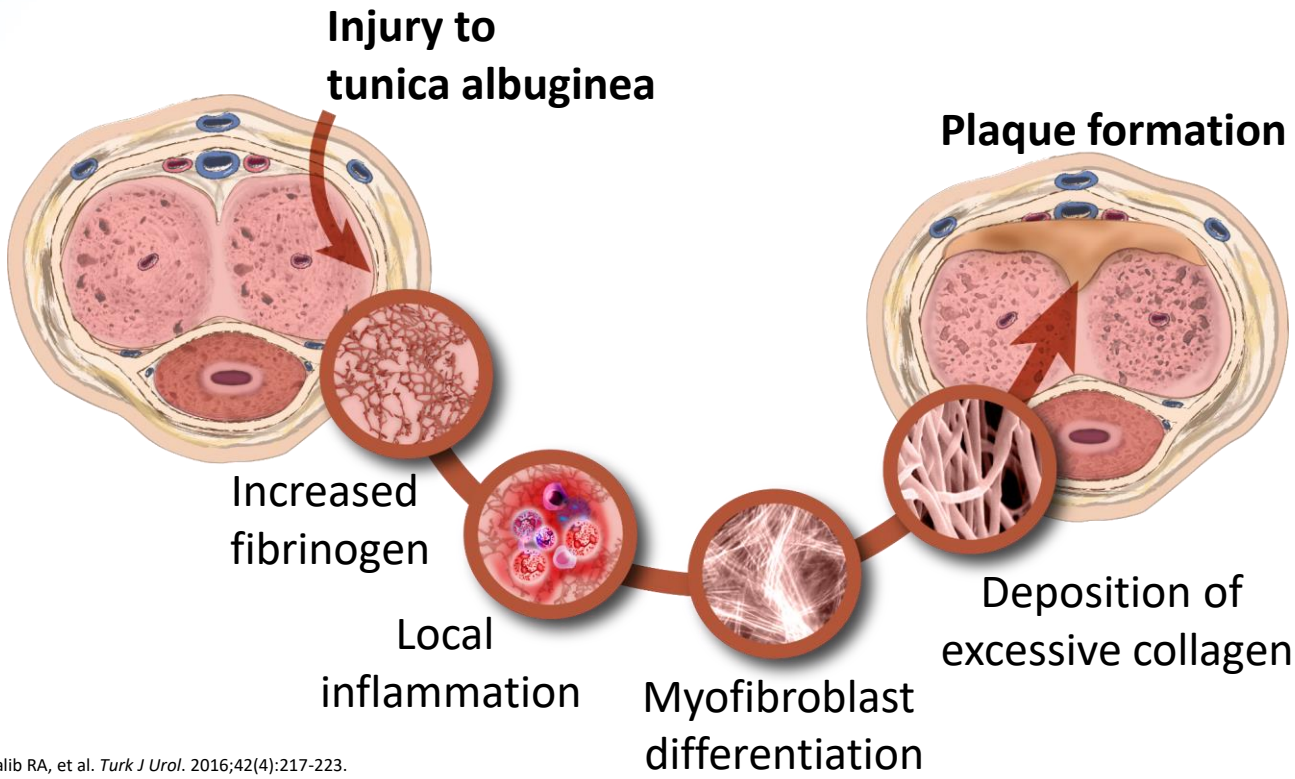


- Penile curvature deformity is usually first symptom noticed and the most common presenting symptom[1]

ED=erectile dysfunction.

1. Nehra A, et al. *J Urol.* 2015;194(3):745-753; 2. Al-Thakafi S, Al-Hathal N. *Transl Androl Urol.* 2016;5(3):280-289.

Pathophysiology of the Fibrotic Process Leading to PD



1. Talib RA, et al. *Turk J Urol*. 2016;42(4):217-223.

Natural History/Progression of PD

Acute (active)[1-3]

- Progression in plaque size and curvature deformity
- Painful erections*

Chronic (stable)[1-4]

- Stable plaque size
- Stable curvature deformity
- Decreased (if any) pain

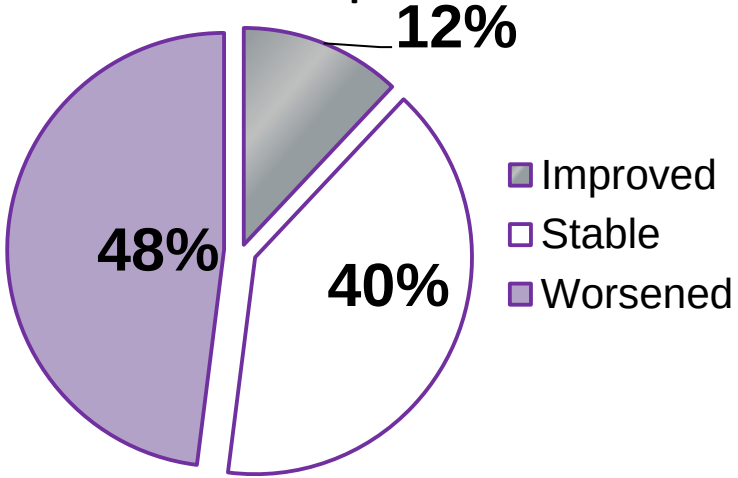
collagenase clostridium histolyticum has only been studied in the chronic (stable) phase in patients with a baseline curvature deformity of at least 30 degrees

*Not universally present.

1. Ralph D, et al. *J Sex Med*. 2010;7(7):2359-2374; 2. Jalkut M, et al. *Rev Urol*. 2003;5(3):142-148;
3. Kadioglu A, et al. *Nat Rev Urol*. 2011;8(2):95-106; 4. Devine CJ Jr, et al. *J Urol*. 1997;157(1):285-290.

The majority of Peyronie's Cases do not Improve Spontaneously

Change in Curvature in Patients (n=217) With PD After Mean 14.5-Months Follow-up[1*]



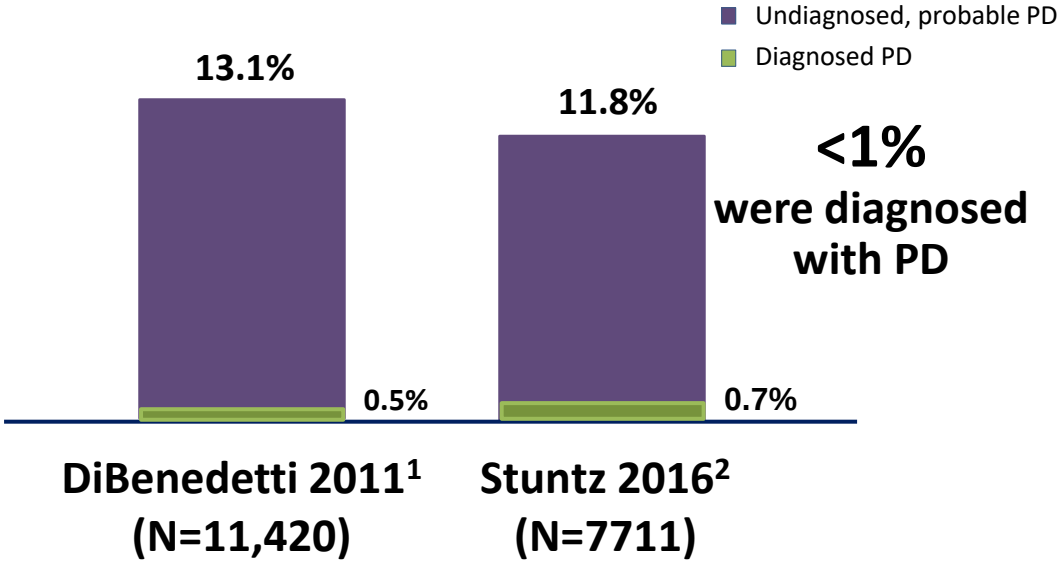
Patients were included if they had PD, as defined by a palpable plaque, presented within 6 months of PD onset (by self-diagnosis of penile nodule or abnormality), elected not to pursue medical treatment, were followed at least 12 months after baseline assessment, and were able to achieve erectile rigidity sufficient for penetration after intracavernous injection.

*Data from 217 patients with Peyronie's disease and curvature followed for at least 12 months after initial assessment (mean follow-up,14.5 months). Initial assessment occurred within 6 months of onset of PD (defined as self-diagnosis of penile nodule or abnormality). A 5-degree or greater change in curvature was deemed an alteration (improvement or worsening).

1. Mulhall JP, et al. *J Urol*. 2006;175(6):2115-2118.

Peyronie's May Be Underdiagnosed

- Most common among men in their 50's & 60's
- Increased incidence among men with Celtic & Scandinavian descent.
- Associated with Dupytren's contractures
- Prevalence of ED in patients with PD has been reported to be 37% to 58%[1-5]
- Underdiagnosed.



A Cross-sectional, Population-based Survey Among a Convenience Sample Broadly Representative of the US Population in Terms of Age, Gender and Region

1. DiBenedetti DB, et al. *Adv Urol.* 2011;2011:282503; 2. Stuntz M, et al. *PLoS One*. 2016;11(2):1-10.

Evaluation and Diagnosis of PD

- **History and clinical exam[1,2]**
  - Penile pain
  - Curvature during erection
  - Palpable plaque
  - Penile shortening
  - Erectile function
  - Psychological bother
  - Functional impairment
- Degree of curvature and volume of plaque are highly variable[1,2]
  - Dorsal curve most common
  - Degree of curvature can range up to 180°

Photo courtesy of Laurence Levine, MD.

1. Bilgutay AN, Pastuszak AW. *Curr Sex Health Rep.* 2015;7(2):117-131; 2. Al-Thakafi S, Al-Hathal N. *Transl Androl Urol.* 2016;5(3):280-289.

Interventions Lacking Evidence[1-3]

Oral and Topical Treatments

- Vitamin E
- Tamoxifen
- Procarbazine
- Omega-3 fatty acids
- Combination of vitamin E with L-carnitine
- Acetyl esters of carnitine
- Pentoxifylline
- Potassium para-aminobenzoate (Potaba)
- Colchicine

Intralesional Injections

- Corticosteroids

Other

- Electromotive therapy with verapamil
- Extracorporeal shock wave therapy (ESWT) (*only for pain reduction)

Although used in clinical practice, none of the above modalities are indicated for PD

1. Ralph D, et al. *J Sex Med*. 2010;7(7):2359-2374; 2. Hatzimouratidis K, et al. *Eur Urol*. 2012;62(3):543-552; 3. Peyronie's Disease: AUA Guideline. American Urological Association website. https://www.auanet.org/education/guidelines/peyronies-disease.cfm. Accessed July 25, 2016.

Peyronie's Management

Intralesional Injections

- Collagenase Clostridium Histolyticum
- Verapamil
- Interferon

- +/- Penile Traction Therapy

Surgical

- Penile Plication
- Penile Plaque Incision Grafting
- Penile Implant

Other Considerations

- Treating Pain?
  - NSAIDs
  - Extracorporeal shock wave therapy (ESWT)

Although used in clinical practice, none of the above modalities are indicated for PD

1. CUA Peyronie's Disease Guideline. 2. Peyronie's Disease: AUA Guideline. On Peyronie's Disease

Verapamil Injections

Verapamil Injection Therapy

- Clinical studies date back to 1990s
- MOA: Inhibits calcium-dependent extracellular collagen transport and upregulates collagenase activity in plaques
- Many reports showing benefit, however variable in terms of response to treatment given heterogeneity of the disease
  - Variables in treatment response:
    - Technical: Volume injected, frequency, concentration, duration of therapy
    - Patient considerations: Duration of disease, extent of disease, calcifications?
- Predictors of efficacy were younger patient, higher dilutions of verapamil and greater baseline curvature (Chung et al. J Urol 2013, Moskovic et al. BJU Int 2011)

Verapamil Injection Therapy

- Arena *et al.* 1995
- 39 patients received verapamil injections
  - Those with PD <1 yr 50% had reduction in curvature
  - Those with PD >1 yr 10% had reduction in curvature

- Indicated that treatment in the **active phase** may be beneficial
- MOA of verapamil fits with efficacy in acute phase

Interferon alpha-2b Injections

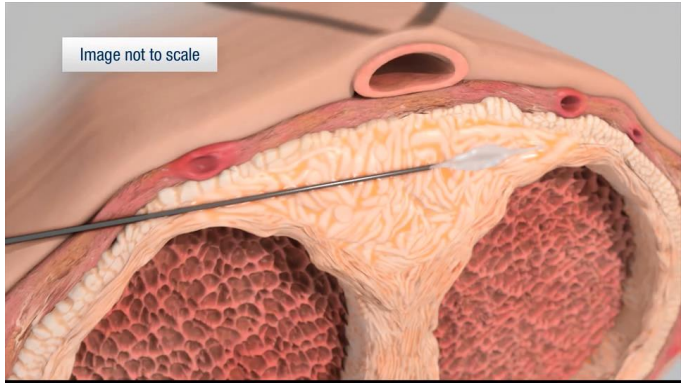
Interferon alpha-2B Injections

- Single-blinded multi-centre controlled study
  - 117 patients: 50 received INF & 53 controls
    - 103 completed study
  - Mean history of disease 1.7 years
  - INF arm: 10cc 500,000U each week for 6 weeks
  - Evaluated 4 weeks post treatment
- Improved penile curvature 27% vs 8.9%
- Greater improvement in painful erections 68% vs. 28%
- Reduced plaque size 54% vs 20%
- Side-effects included sinusitis, flu-like symptoms, swelling ecchymosis
- Several retrospective studies have shown benefit as well

Collagenase Clostridium Histolyticum Injections

Collagenase Injection Therapy

- Collagenase therapy involves an office-based injection that enzymatically breaks down the penile plaque that causes deformity.
- Involves 4-8 injections over 4-6 months
- Well tolerated
- Most effective non-surgical therapy
- ***Temporarily available** in Canada until medication stock lasts (~1-1.5 years)



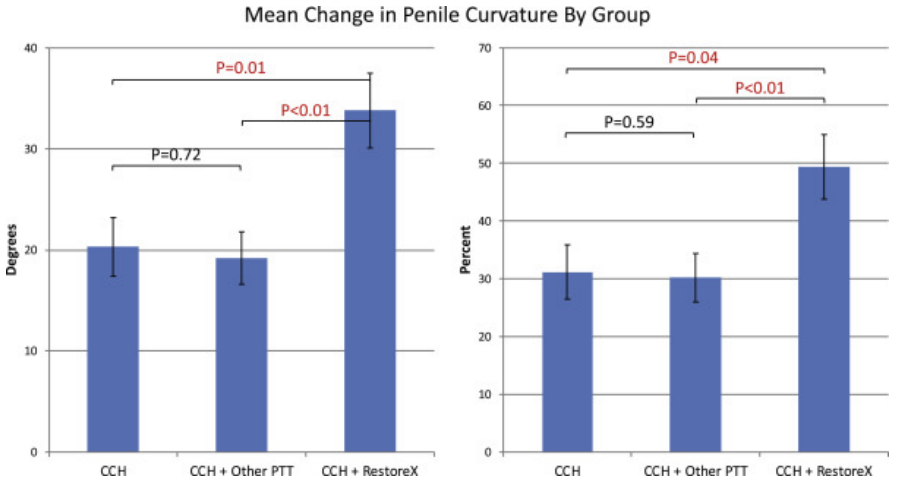
Collagenase Injection Therapy

- **IMPRESS 1& 2 trials** (Gelbard *et al.* 2013)
  - N=832 men with Peyronie's disease across 54 sites.
  - Design: RCT 2:1 Collagenase to Placebo enrollment
  - Therapy: 4 sets of 2 injections, with penile modeling
  - 17º vs 9.3º improvement favoring collagenase therapy.
  - Significant reduction in patient bother (PDQ questionnaire) p<0.01
  - Minimal severe side effects

- **Follow up studies** (Raheem *et al.* 2017)
  - Established fewer injections with increased dose demonstrates similar efficacy.
  - 1 injection per month x 3 months

Collagenase + Traction

- **Angulated Penile Traction** (Alom *et al.* JSM 2019)
  - N = 287, 113 with complete data included.
- CCH injections at point of maximal curvature, original protocol w/ 0.9mg per dose.
- NON-randomized 3 Arms:
  - CCH with modeling, n=52
  - CCH with generic traction device, n=45
  - CCH with RestoreX device (0.9 hours/day), n=16
- Results:
  - 20.3º degree with CCH (44%); -0.7cm
  - 19.2º degrees with traction (32%); -0.4cm
  - **33.8º with RestoreX (63%); +1.9cm length**

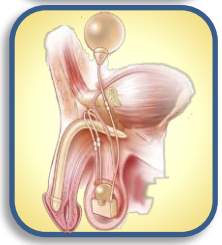


Peyronie's Surgery

Surgical Treatment of PD

Tunica plication[1,3]

Incision or partial excision of the plaque and grafting[1,3]



Implantation of penile prosthesis with straightening maneuvers[1]

Indications (per 2010 ISSM Guidelines)[1]

- Stable disease
- Compromised ability or inability to engage in coitus
- Extensive plaque calcification
- Failed conservative treatment
- Patient wants the most rapid and reliable result

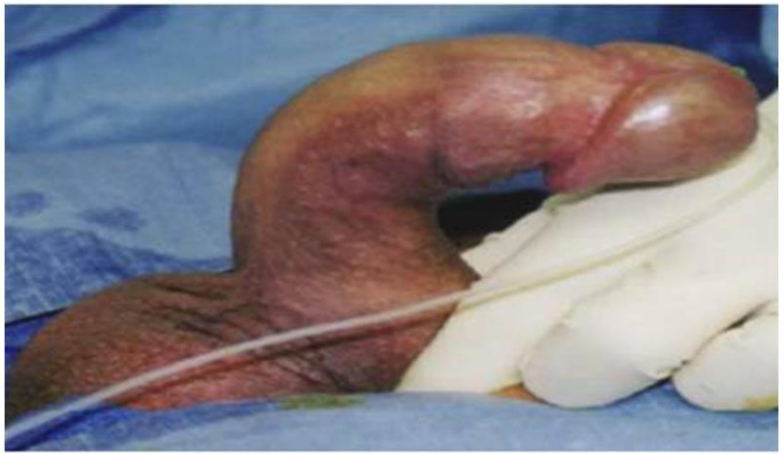
Potential Complications[2]

- Penile shortening
- Erectile dysfunction
- Penile numbness

ISSM=International Society for Sexual Medicine.

1. Ralph D, et al. *J Sex Med*. 2010;7(7):2359-2374; 2. Hatzimouratidis K, et al. *Eur Urol*. 2012;62(3):543-552; 3. Peyronie's Disease: AUA Guideline. American Urological Association website. https://www.auanet.org/education/guidelines/peyronies-disease.cfm. Accessed July 25, 2016.

Summary



- Peyronie's Disease may effect up to 13% of men and is largely undiagnosed.
- Enquire about penile shape changes associated with ED.
- Injection based therapy and surgical therapy may be effective treatments for many of these men.
- Locate a Urologist specializing in Peyronie's to perform a full evaluation and management for these individuals.

Thank you!

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