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St. Joseph's Hospital

Current management of female overactive bladder and the future perspective

黃淑君醫師
Soo-Cheen Ng, M.D, Ph.D.
Department of OB/GYN,
St. Joseph's Hospital, Yunlin, Taiwan

Bladder storage symptoms

(ii) *Nocturia*: Complaint of interruption of sleep one or more times because of the need to micturate.[3 v] Each void is preceded and followed by sleep.

(iii) *Urgency*: Complaint of a sudden, compelling desire to pass urine which is difficult to defer.[vi]

(iv) *Overactive bladder (OAB, Urgency) syndrome*: Urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection (UTI) or other obvious pathology.

Neurourology and Urodynamics 29:4–20 (2010)

Overactive bladder vs. Detrusor overactivity

- Detrusor overactivity (DO) is observed in some, but not all, patients with OAB.
- In one study, among those with OAB without incontinence (OAB dry), 69% of men and 44% of women had DO; among those with OAB and incontinence (OAB wet), DO was present in 90% of men and 58% of women.
- More than 30% of patients had no OAB but had DO on cystometry.

Hashim H and Abrams P. Is the bladder a reliable witness for predicting detrusor overactivity J Urol 2006; 175: 191-95

Treatment guideline of Overactive Bladder

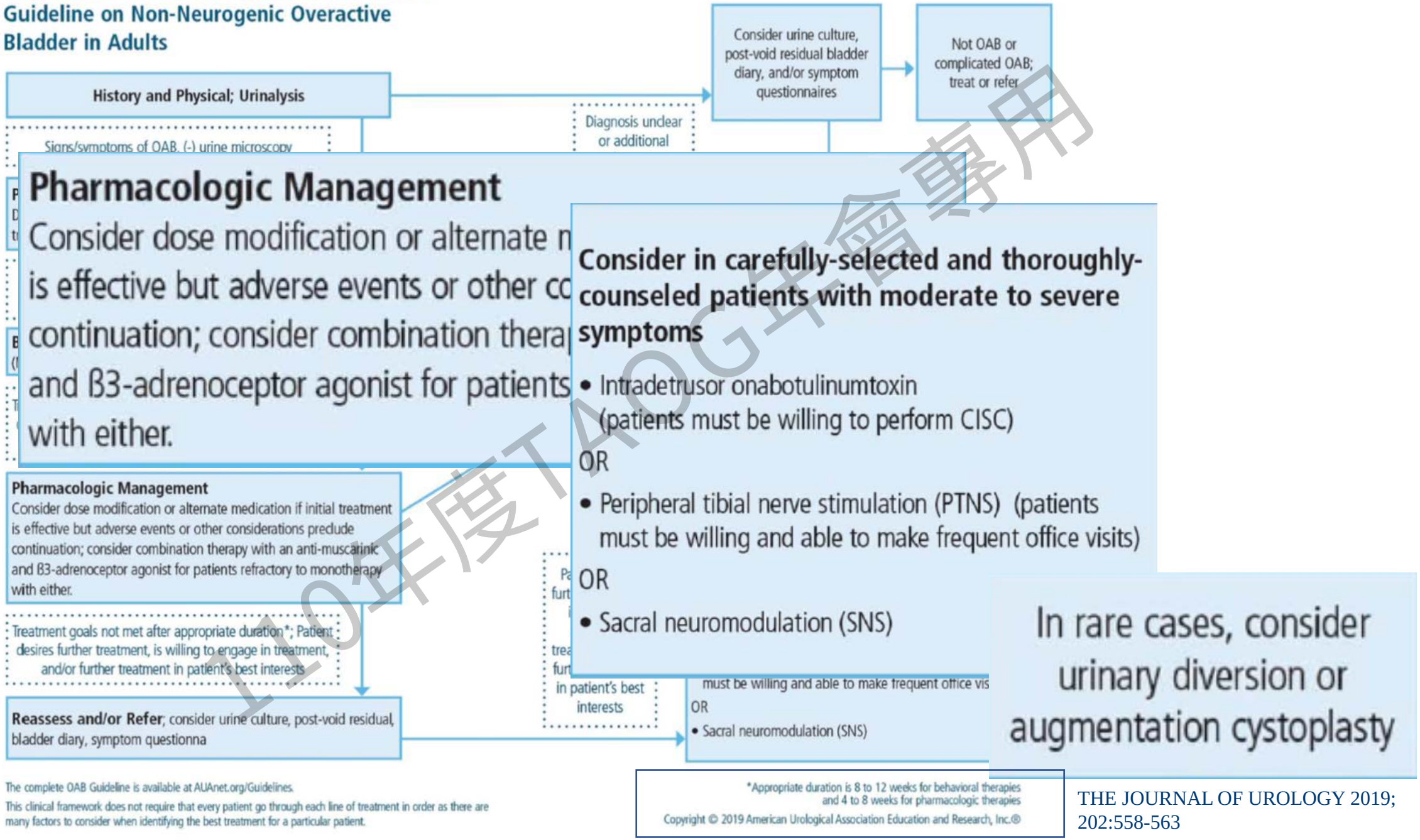
- OAB is primarily a diagnosis of exclusion
- *Current treatment aimed at relieving symptoms*

  -- not necessarily reversing pathophysiologic abnormalities
- Isolated nocturia-different evaluation and management strategies

- Treatment guideline available for OAB:

1. Lightner DJ, Gomelsky A, Souter L, Vasavada SP. Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults: AUA/SUFU Guideline Amendment 2019. J Urol. 2019;202:558-563.
2. Nambiar AK, et al. EAU Guidelines on Assessment and Nonsurgical Management of Urinary Incontinence. Eur Urol.2018;73:596-609
3. Corcos J, Przydacz M, Campeau L, Gray G, Hickling D, Honeine C et al.CUA guideline on adult overactive bladder. Can Urol Assoc J. 2017;11:E142-E173

Diagnosis & Treatment Algorithm: AUA/SUFU Guideline on Non-Neurogenic Overactive Bladder in Adults



The complete OAB Guideline is available at AUAnet.org/Guidelines.

This clinical framework does not require that every patient go through each line of treatment in order as there are many factors to consider when identifying the best treatment for a particular patient.

*Appropriate duration is 8 to 12 weeks for behavioral therapies and 4 to 8 weeks for pharmacologic therapies

THE JOURNAL OF UROLOGY 2019; 202:558-563

Table 12 – Recommendations on lifestyle interventions

Recommendations	Strength rating
Encourage obese adults with UI to lose weight and maintain weight loss.	Strong
Advise adults with UI that reducing caffeine intake may improve symptoms of urgency and frequency but not incontinence.	Strong
Review type and amount of fluid intake in patients with UI.	Weak
Provide smoking cessation strategies to patients with UI who smoke.	Strong

UI = urinary incontinence.

Behavioral treatment

- Non-active

  Scheduled toileting

  Habit training

  Prompted voiding

- Active

  Bladder training (bladder drill)

  Pelvic muscle rehabilitation

  (PFMT, stress strategies, urge strategies, biofeedback, electrical stimulation)

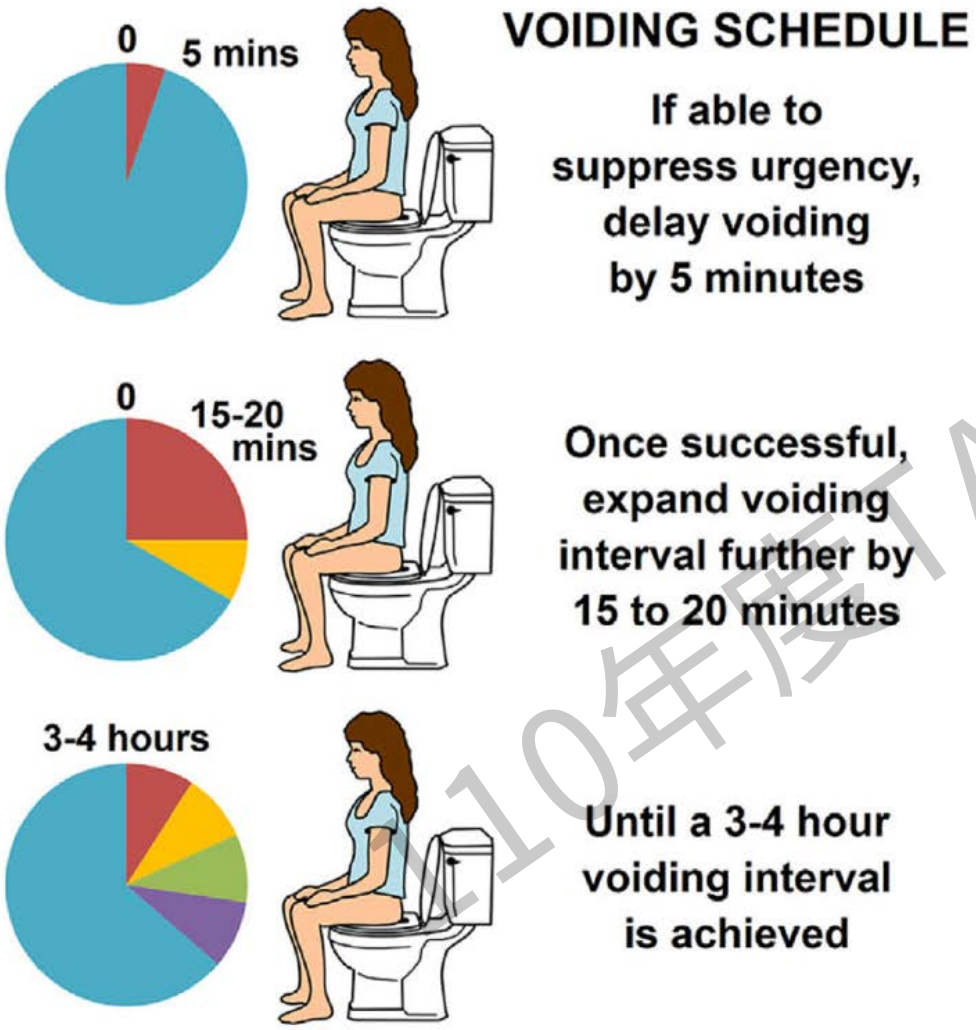
Table 13 – Recommendations on behavioural and physical therapies

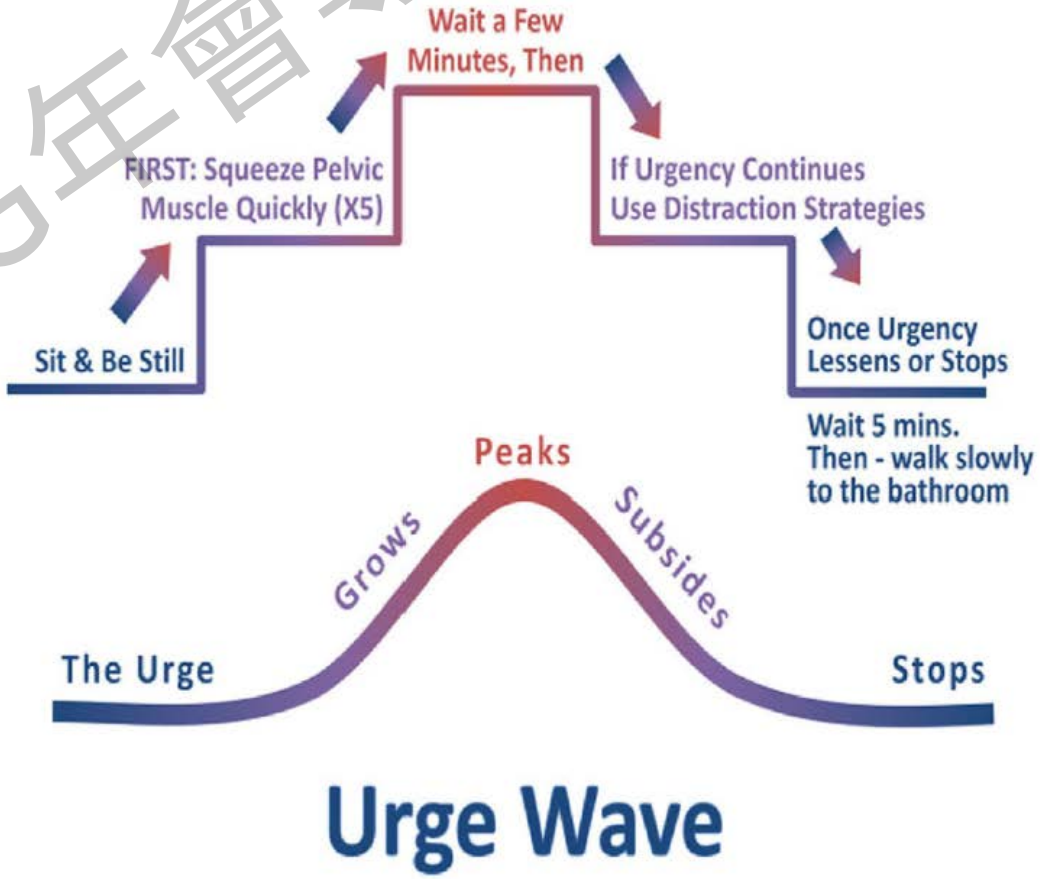
Recommendations	Strength rating
Offer prompted voiding for adults with UI who are cognitively impaired.	Strong
Offer bladder training as a first-line therapy to adults with UUI or MUI.	Strong
Offer supervised PFMT, lasting at least 3 mo, as a first-line therapy to all women with SUI or MUI (including the elderly and postnatal).	Strong
Offer instruction on PFMT to men undergoing radical prostatectomy to speed recovery from UI.	Strong
PFMT programmes should be as intensive as possible.	Strong
Do not offer electrical stimulation with surface electrodes (skin, vaginal, anal) alone for the treatment of stress UI.	Strong
Do not offer magnetic stimulation for the treatment of UI or overactive bladder in adult women.	Strong
Consider PTNS as an option for improvement of UUI in women who have not benefited from antimuscarinic medication.	Strong

MUI = mixed urinary incontinence; PFMT = pelvic floor muscle training; PTNS = percutaneous tibial nerve stimulation; SUI = stress urinary incontinence; UI = urinary incontinence; UUI = urge urinary incontinence.

EAU Guidelines EUROPEAN UROLOGY 73 (2018) 596– 609

Bladder training (bladder drill) — Education, voiding schedule, positive reinforcement





Neurourol Urodyn. 2018; 37(1): 14–26.

Table 15 – Recommendations on drugs for UUI

Recommendations	Strength rating
Offer antimuscarinic drugs or mirabegron for adults with UUI who failed conservative treatment.	Strong
Consider extended release formulations of antimuscarinic drugs whenever possible.	Strong
If an antimuscarinic treatment proves ineffective, consider dose escalation or offering an alternative antimuscarinic formulation or mirabegron or a combination.	Strong
Encourage early review (of efficacy and side effects) of patients on antimuscarinic medication for UUI.	Strong

UUI = urge urinary incontinence.

EAU Guidelines on Assessment and Nonsurgical Management of Urinary Incontinence
EUROPEAN UROLOGY 73 (2018) 596– 609

Table 2. Summary of pharmacological management of overactive bladder

Category	Drug	Brand name	Grade	Recommended doses	Considerations in medically complex elderly	Dose adjustment	Adverse events	Contraindications
Antimuscarinics	Oxybutynin	Ditropan Ditropan XL	A	IR: 5 mg BID, TID, or QID ER: 5 or 10 mg OD	Data show efficacy of 2.5mg bid.[235,272] Doses of 20 mg daily consistently associated with cognitive impairment, unreported by patients[252]	Elderly	Dry mouth, constipation, CNS AE	Pregnancy or breast-feeding; drug hypersensitivity; Uncontrolled narrow-angle glaucoma; urinary retention, paralytic ileus, GI or GU obstruction
	Oxybutynin transdermal	Oxytrol® Gelnique	A	36 mg (3.9 mg/day) patch twice weekly 10% gel: 1 sachet (100 mg/g) OD	No cognitive impairment reported in cognitively intact elderly[273]		Application site reaction, dry mouth, CNS AE	
	Tolterodine	Detrol Detrol LA	A	IR: 2 mg BID (or 1 g BID) ER: 4 mg OD (or 2 mg OD)	No cognitive impairment in cognitively intact elderly[274]	Concomitant CYP3A4 inhibitors, Renal, hepatic	Dry mouth, constipation, CNS AE, QT prolongation	
	Darifenacin	Enablex®	A	7.5 or 15 mg OD	No cognitive impairment in cognitively intact elderly [275]	Concomitant CYP3A4 inhibitors, hepatic Geriatric, Renal, hepatic	Dry mouth, constipation, dyspepsia, nausea	
	Trospium	Trosec®	A	IR: 20 mg BID	No cognitive impairment reported in cognitively intact elderly[276]	Concomitant CYP3A4 inhibitors, Renal, hepatic	Dry mouth, co nstipation, urinary retention, dry eyes, blurred vision, tachycardia, increased heart rate, and palpitation	
	Solifenacin	Vesicare®	A	5 or 10 mg OD	No cognitive impairment reported in elderly with mild cognitive impairment at 5 mg dose[277]	Concomitant CYP3A4 inhibitors, renal, hepatic	Dry mouth, constipation, blurred vision	
	Fesoterodine	Toviaz™	A	4 or 8 mg OD	No cognitive impairment in cognitively intact elderly[278]	Renal, hepatic	Dry mouth, constipation, dry eyes and dyspepsia	
	Propiverine	Mictoryl®	A	Modified release: 30 or 45 mg OD	No difference in cardiac events in elderly patients[279]	Renal, hepatic	Dry mouth, headache, accommodation disorder, visual impairment, constipation, abdominal pain, dyspepsia, and fatigue	
Beta-3 adrenoceptor agonist	Mirabegron	Myrbetriq®	A	25 or 50 mg OD		Renal, hepatic	Nausea, headache, hypertension, UTI, nasopharyngitis	Severe uncontrolled hypertension, pregnancy

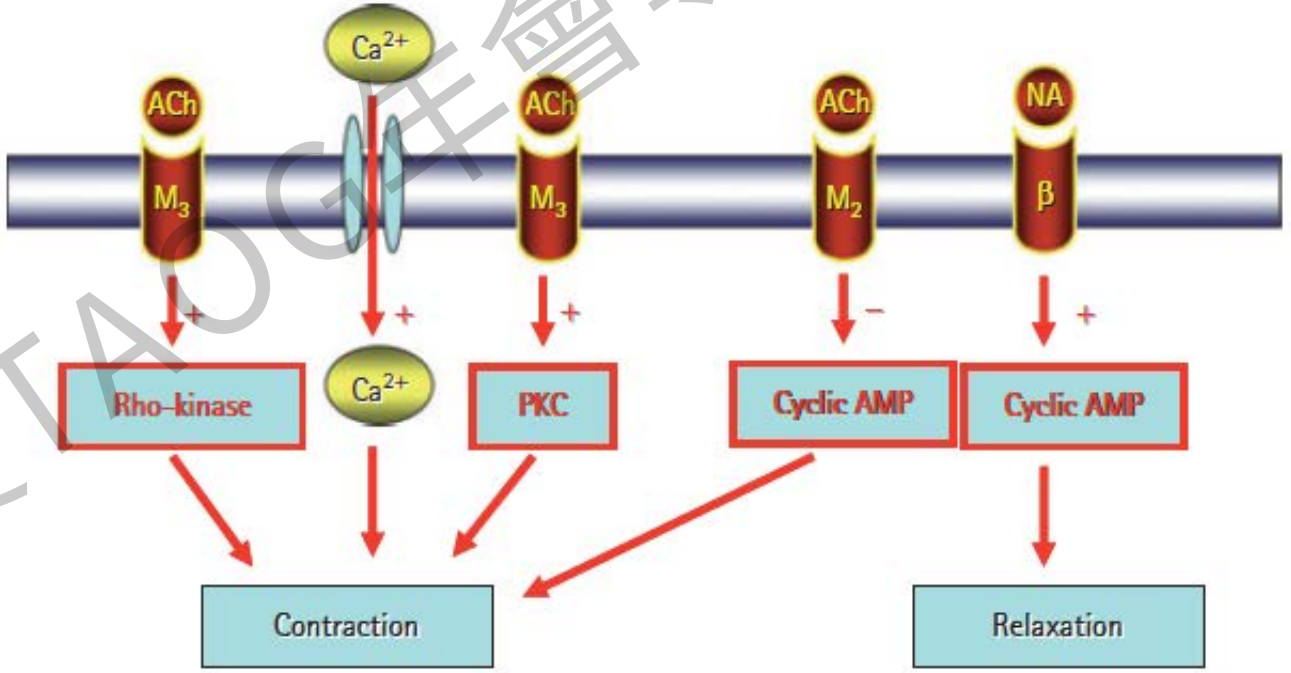
BID: twice a day; CNS AE: central nervous system adverse effects; ER: extended release; GI: gastrointestinal; GU: genitourinary; IR: immediate release; OD: once a day; QID: four times a day; TID: three times a day; UTI: urinary tract infection.

CUA guideline on adult overactive bladder
Can Urol Assoc J 2017;11(5):E142-73.

Pharmacologic management- Evidence of Combination therapy

- Drugs with different mechanisms of action.
- Co-administration appears to have no noticeable effects on pharmacokinetics.

Clin Pharmacol Drug Dev. 2013;2:255-63



Muscarinic receptor antagonists for overactive bladder
BJU international 2007

Functional Urology

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‡‡

- The study was conducted at 435 sites in 42 countries, n = 3398.
- Randomization, double-blind treatment [2:2:1:1:1:1 ratio, solifenacin 5 mg +mirabegron 25 mg (combined S5 + M25 group); solifenacin 5 mg + mirabegron 50 mg (combined S5 + M50 group); solifenacin 5 mg; mirabegron 25 mg; mirabegron 50 mg; or placebo for 12 weeks

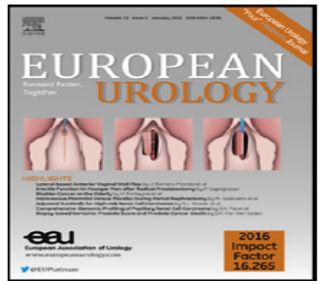
- combined therapy with solifenacin 5 mg + mirabegron 25 mg and solifenacin 5 mg+ mirabegron 50 mg provided consistent improvements in efficacy compared with the respective monotherapies across most of the outcome parameters, with effect sizes generally consistent with an additive effect.

BJU Int 2017; 120: 562–575

EUROPEAN UROLOGY 74 (2018) 501–509

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

European Association of Urology



Platinum Priority – Voiding Dysfunction

Editorial by David R. Staskin on pp. 510–511 of this issue

Long-term Safety and Efficacy of Mirabegron and Solifenacin in Combination Compared with Monotherapy in Patients with Overactive Bladder: A Randomised, Multicentre Phase 3 Study (SYNERGY II)

- The median age was 60 yr (range 19–86 yr) and 1434 patients (80%) were female.
- Treatment-emergent adverse events (TEAE) frequency was slightly higher in the combination group [M+S: 49% (n=596) vs. mirabegron: 41%(n=126) vs. solifenacin: 44%(n=134)〕.
- Overall,856 patients (47%) experienced ≧1 TEAEs.
- Serious TEAEs were reported by 67 patients (3.7%); one was considered possibly treatment-related (mirabegron group, atrial fibrillation).
- Dry mouth was the most common TEAE (M+S: 6.1% vs. solifenacin:5.9% vs. mirabegron:3.9%).

Pharmacologic management-
Evidence of Combination therapy

- BESIDE trial: 2,174 patients (83% women), OAB patients remaining incontinent after 4 weeks of solifenacin 5 mg, evaluated the efficacy, safety, and tolerability of combination therapy (solifenacin 5 mg plus mirabegron 50 mg) versus monotherapy (solifenacin 5 or 10 mg)in a 1:1:1 randomized trial

Eur Urol. 2016;70:136-145

- RCT that evaluated combination tolterodine and intravaginal estradiol cream in 58 menopausal women. Women were randomized to either oral tolterodine or estradiol cream for 12 weeks and then offered addition of the alternative therapy with follow-up at week 24 and week 52.

Female Pelvic Med Reconstr Surg 2016;22:254-60

Special considerations in frail older people

- Approximately 60% of >65 year-old people take at least one prescribed medication, 1/3 take more than 5 prescribed drug.
- Older people are at higher risk of ADEs from AMs because of age, and changes in muscarinic receptor number and distribution, blood-brain barrier transport, and drug metabolism.
- Drugs with anticholinergic effects: Antihistamines, gastrointestinal antispasmodics, antidepressants, bladder antimuscarinics, skeletal muscle relaxants, antipsychotics, antiparkinson agents etc.
- Acute impairment in specific aspects of cognition (e.g., working memory, attention, psychomotor speed) or global cognitive impairment.

Table 16 – Recommendations on treatment of UUI in elderly patients

Recommendation	Strength rating
Long-term antimuscarinic treatment should be used with caution in elderly patients especially those who are at risk of, or have, cognitive dysfunction.	Strong

UUI = urge urinary incontinence.

EUROPEAN UROLOGY 73 (2018) 596– 609

Cumulative Use of Strong Anticholinergic Medications and Incident Dementia

Association of Incident Dementia and Alzheimer's Disease with 10-year Cumulative Anticholinergic Medication Use[a]

			Unadjusted[c,d]		Adjusted[d,e]	
TSDD[b]	Follow-up time (person-years)	Number of Events	HR	95% CI	HR	95% CI
Dementia						
0	5618	136	1.00	Reference	1.00	Reference
1-90	7704	203	0.96	0.77-1.20	0.92	0.74-1.16
91-365	5051	172	1.31	1.04-1.65	1.19	0.94-1.51
366-1095	2626	102	1.39	1.07-1.82	1.23	0.94-1.62
>1095	4022	184	1.77	1.40-2.23	1.54	1.21-1.96
Alzheimer's Disease						
0	5618	112	1.00	Reference	1.00	Reference
1-90	7704	168	0.96	0.75-1.24	0.95	0.74-1.23
91-365	5051	128	1.21	0.93-1.58	1.15	0.88-1.51
366-1095	2626	83	1.38	1.03-1.85	1.30	0.96-1.76
>1095	4022	146	1.73	1.34-2.24	1.63	1.24-2.14

TSDD Total Standardized Daily Dose; HR Hazard Ratio; CI Confidence Interval; ACT Adult Changes in Thought

JAMA Intern Med. 2015 March 1; 175(3): 401–407

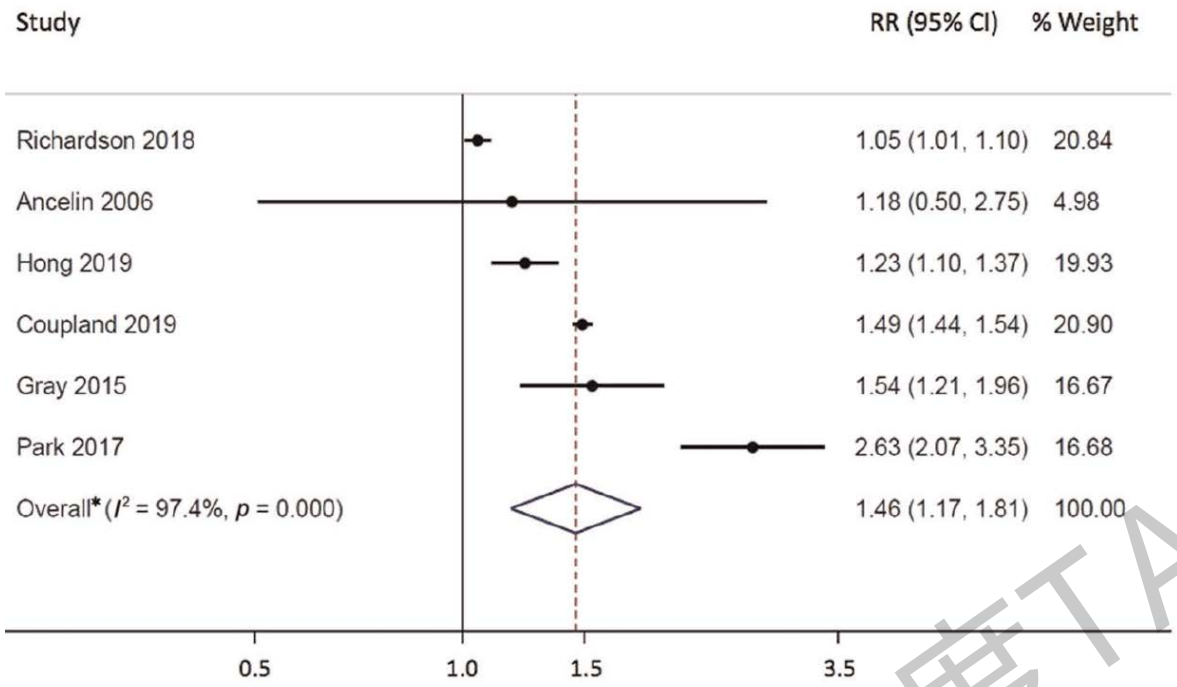
REVIEW ARTICLE

Neurourology and Urodynamics. **2021**;40:28–37

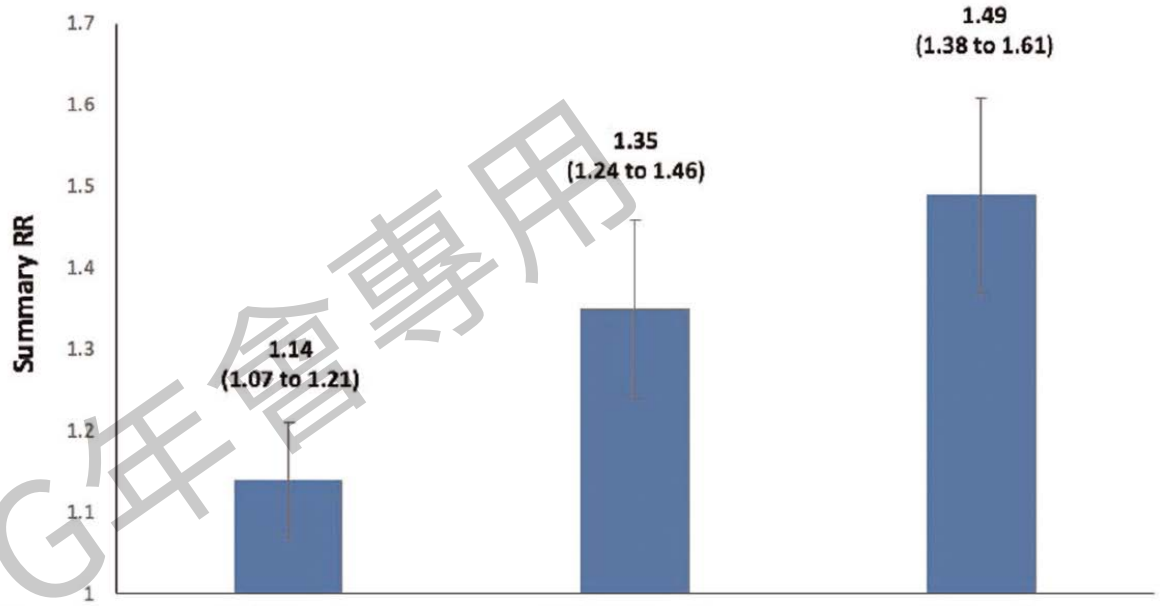
Increased risk of incident dementia following use of anticholinergic agents: A systematic literature review and meta-analysis

Roger R. Dmochowski[1] | Sydney Thai[2,3] | Kristy Iglay[3,4] | Ekene Enemchukwu[5] | Silvia Tee[6] | Susann Varano[7] | Cynthia Girman[2,3] | Larry Radican[8] | Paul N. Mudd Jr[9] | Charles Poole[10]

- Aimed to assess the impact of ≥3 months of exposure to anticholinergics as a class on the risk of dementia, mild cognitive impairment, and change in cognitive function.
- A total of 2122 records were identified. 21 studies underwent qualitative synthesis and 6 reported endpoints relevant for inclusion.



The estimate of the average RR for incident dementia was 1.46 (95% CI: 1.17–1.81; 95% PI: 0.70–3.04) and ranged from 1.05 to 2.63 across the six studies.
This relationship was consistent in studies assessing bladder antimuscarinics.



TSDD/DDD	90-365 vs. 0	365-1095 vs. 0	>1095 vs. 0
Number of Studies	3	2	2
Homogeneity *p*-value	0.070	0.474	0.790
Ratio of RRs (95% CI)	Reference	1.19 (1.07 to 1.31)	1.32 (1.20 to 1.45)

Levels of anticholinergic exposure were considered. Higher dosing comparisons producing summary RRs 1.19- and 1.32-times higher than the lowest exposure comparison.

4.2.5 *Antimuscarinic and beta3 agonist agents, the elderly and cognition*

Summary of evidence	LE
Antimuscarinic drugs are effective in elderly patients.	1b
Mirabegron has been shown to efficacious and safe in elderly patients.	1b
In older people, the cognitive impact of drugs which have anticholinergic effects is cumulative and increases with length of exposure.	2
Oxybutynin may worsen cognitive function in elderly patients.	2
Solifenacin, darifenacin, fesoterodine and trospium have been shown not to cause cognitive dysfunction in elderly people in short-term studies.	1b

4.2.5.2.13 Additional recommendations for antimuscarinic drugs in the elderly

Recommendations	GR
In older people being treated for urinary incontinence, every effort should be made to employ nonpharmacological treatments first.	C
Long-term antimuscarinic treatment should be used with caution in elderly patients especially those who are at risk of, or have, cognitive dysfunction.	B*
When prescribing antimuscarinic for urgency urinary incontinence, consider the total antimuscarinic load in older people on multiple drugs.	C
Consider the use of Mirabegron in elderly patients if additional antimuscarinic load is to be avoided.	C

**Recommendation based on expert opinion.*

Intravesical onabotulinumtoxin (BoNT-A) injection

- In patients (n=557) with OAB inadequately managed with anticholinergics, Onabotulinumtoxin A 100 U significantly decreased daily frequency of urinary incontinence episodes vs placebo (-2.65 vs -0.87, p <0.001) and 22.9% vs 6.5% of patients became completely continent, in a phase 3, placebo controlled trial.

J Urol . 2017;197(2S):S216-S223

- A systematic review and meta-analysis (6 RCTs) showed that onabotulinumtoxin A to be an effective treatment for idiopathic OAB with side effects primarily localized to urinary tract (⬆PVR, UTI, CIC).

Neurourol Urodyn 2015; 4:413-419

- A systematic review and meta-analysis(8 studies; n=419) assessed the efficacy of onabotulinumtoxin A according to injection site. Trigone-including injection has superior efficacy. The depth of injection (intradetrusor vs suburothelial) does not influence the efficacy.

World J Urol. 2018;36:305-317

Peripheral tibia nerve stimulation (PTNS)

- A multicenter, double-blind, randomized, sham controlled trial, evaluated the effectiveness of weekly PTNS (Urgent PC) vs Sham in Treatment of Overactive Bladder Symptoms (SUmiT trial, n=220). PNTS subjects achieved significant improvement (moderately or markedly) in overall bladder symptoms (54.5% vs 20.9%) from baseline ($p < 0.001$). The voiding diary parameters show significant improvement in frequency and UUI.

J Urol 2010;183:1438-43

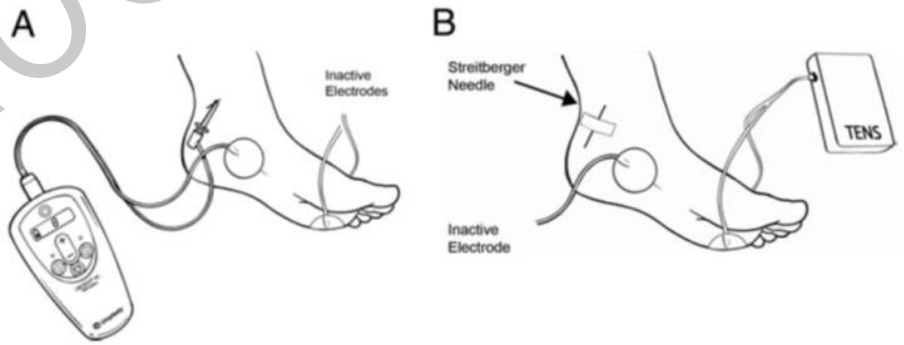
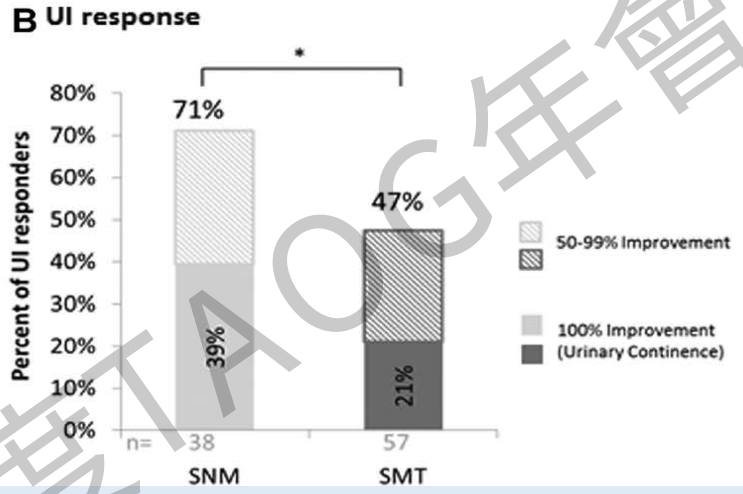


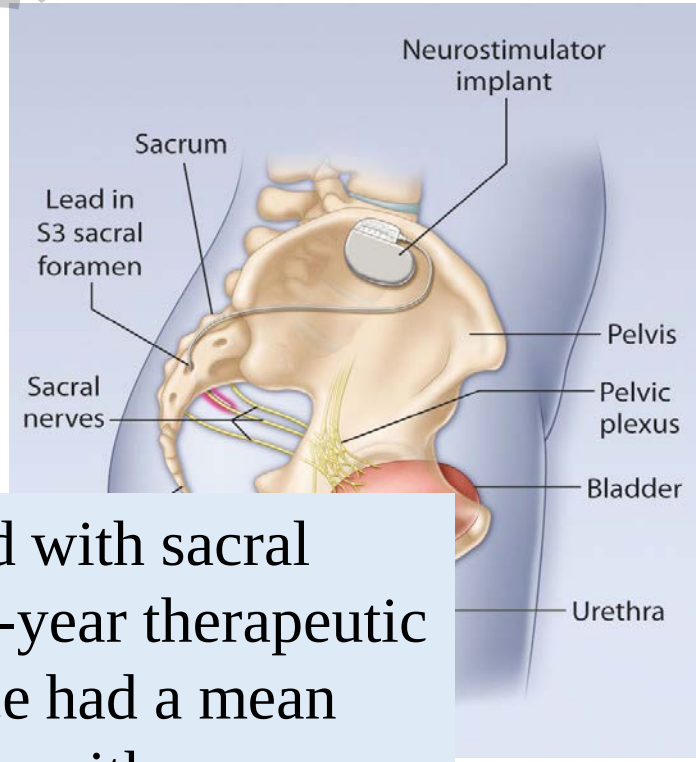
Figure 1. PTNS (*A*) and sham (*B*) setup

- Participants with an initial positive response to 12 weekly PTNS treatments, 77% sustained symptom improvement to 3 years with an average of 1 treatment per month.

J Urol. 2013;189:2194-201.

Sacral neuromodulation (SNM)





A prospective, multicenter study of patients with OAB treated with sacral neuromodulation(InterStim; Metronic, Minneapolis) : The 5-year therapeutic success rate was 82%. Subjects with urinary urge incontinence had a mean reduction from baseline of 2.0 ± 2.2 leaks per day and subjects with urgency-frequency had a mean reduction of 5.4 ± 4.3 voids per day

J Urol. 2018;199:229-236.

Future management (treatment under research)

- Transient receptor potential vanilloid 1(TRPV1) antagonist
- Liposome-encapsulated BoNT-A with intravesical instillation
- Selective bladder denervation (SBD) – radiofrequency ablation of sensory nerve
- Pudendal neuromodulation

Chen and Kuo
Lower Urinary Tract Symptom 2020;1-8

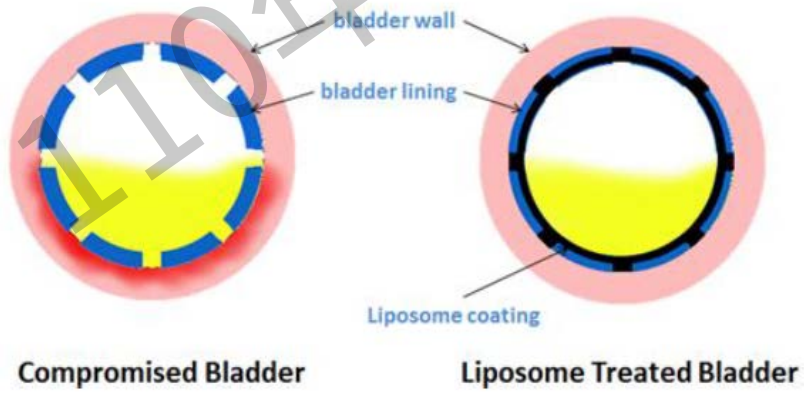
Review

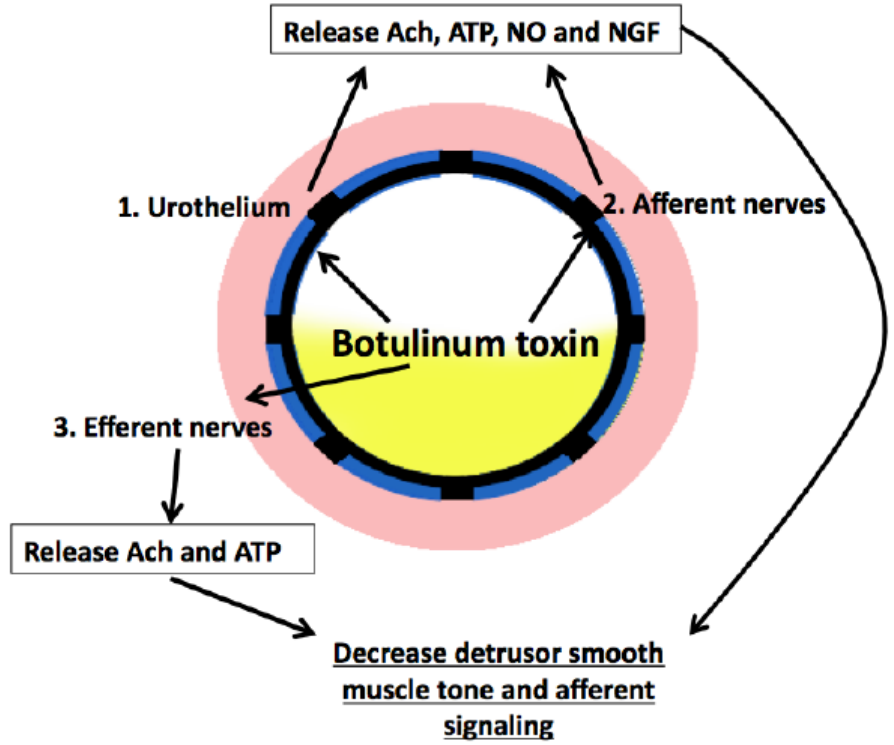
Potential Effect of Liposomes and Liposome-Encapsulated Botulinum Toxin and Tacrolimus in the Treatment of Bladder Dysfunction

Joseph J. Janicki, Michael B. Chancellor *, Jonathan Kaufman, Michele A. Gruber and David D. Chancellor

Toxin 2016

- Intravesical instillation of liposomal botulinum toxin has recently shown promise in the treatment of OAB and interstitial cystitis/bladder pain syndrome.
- Liposomes are lipid vesicles composed of phospholipid bilayers surrounding an aqueous core that can encapsulate hydrophilic and hydrophobic drug molecules to be delivered to cells via endocytosis.





Selective bladder denervation (SBD) – radiofrequency ablation of sensory nerve

Initial clinical experience with selective bladder denervation for refractory OAB

- The proportion of urgency UI treatment responders (≥50% reduction in episodes) was 79% with RF60 and 31% with RF10.

Neurourol Urodyn 2019;38:644–652

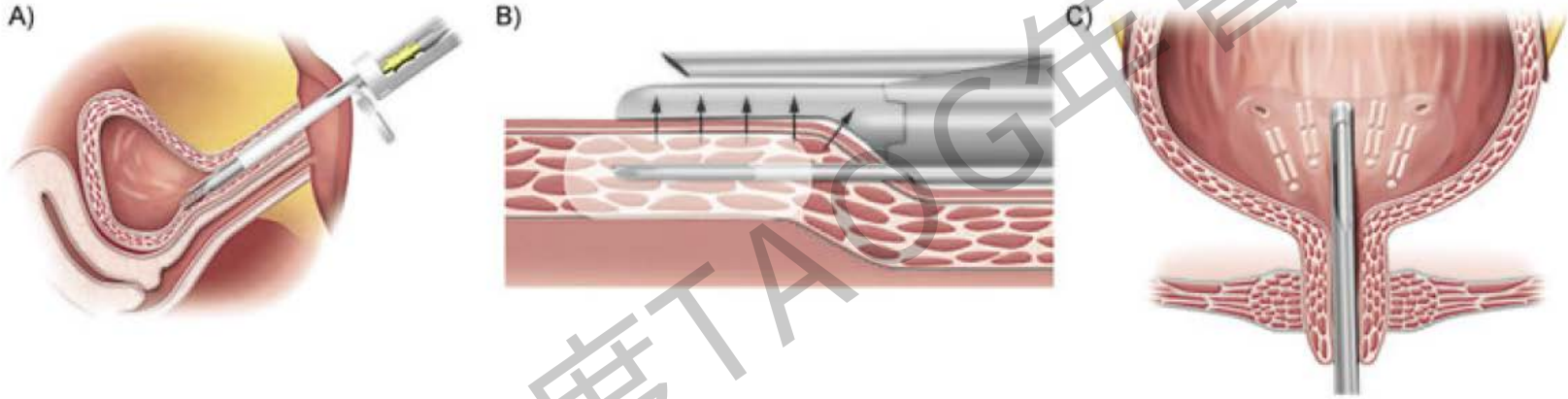


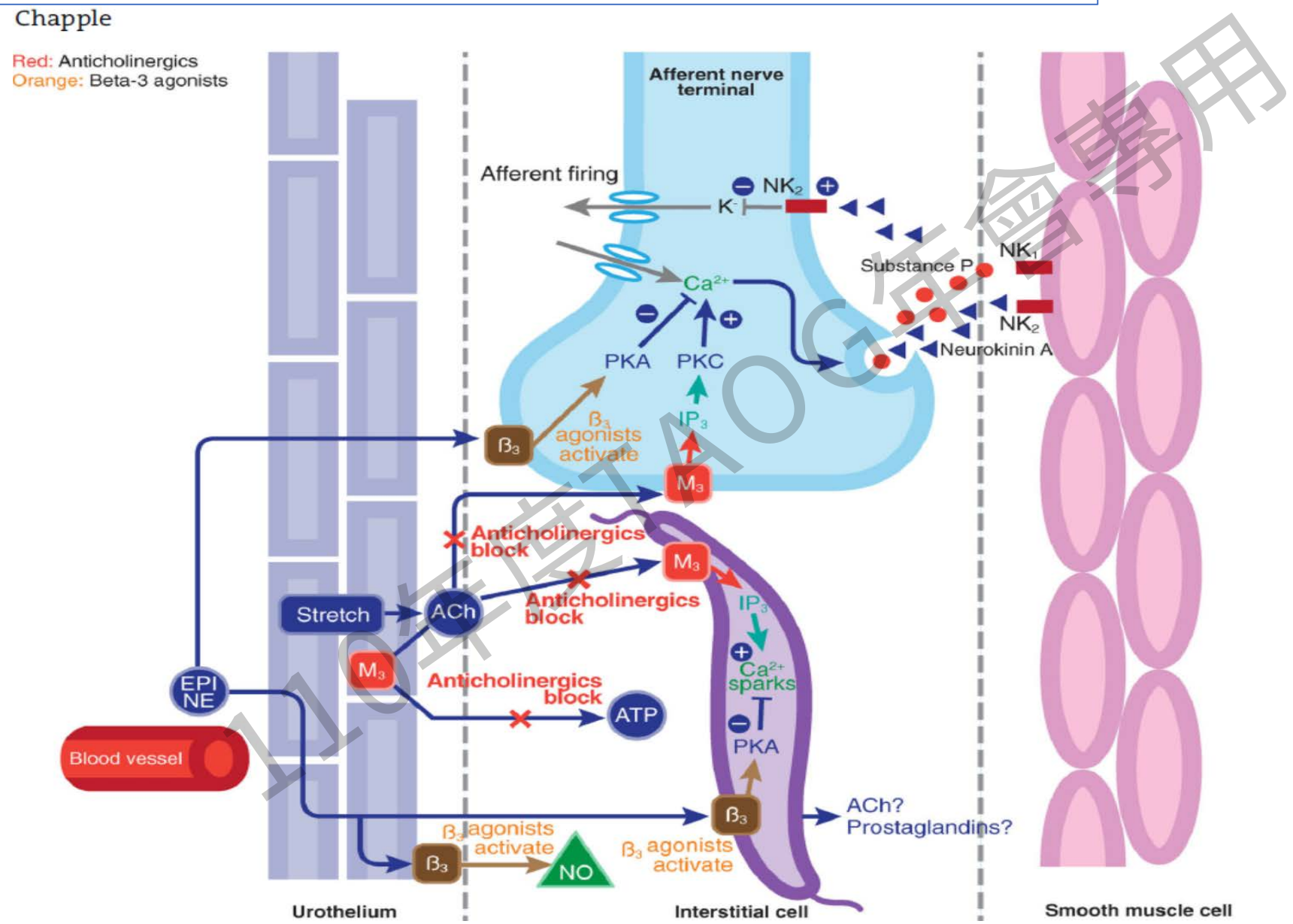
FIGURE 1 Major procedural steps with selective bladder denervation. A, The positioning of the cystoscopically directed device is shown. B, The suction on the urothelium results in immobilization of the device prior to advancement of the RF electrodes 3 mm below the urothelium. C, A schematic representation of placement of each paddle position for ablation of the entire sub-trigonal area. The markings represent areas already ablated and can be seen through the cystoscope as areas of urothelial edema as a consequence of the suction that is applied

One-year results with selective bladder denervation in women with refractory OAB

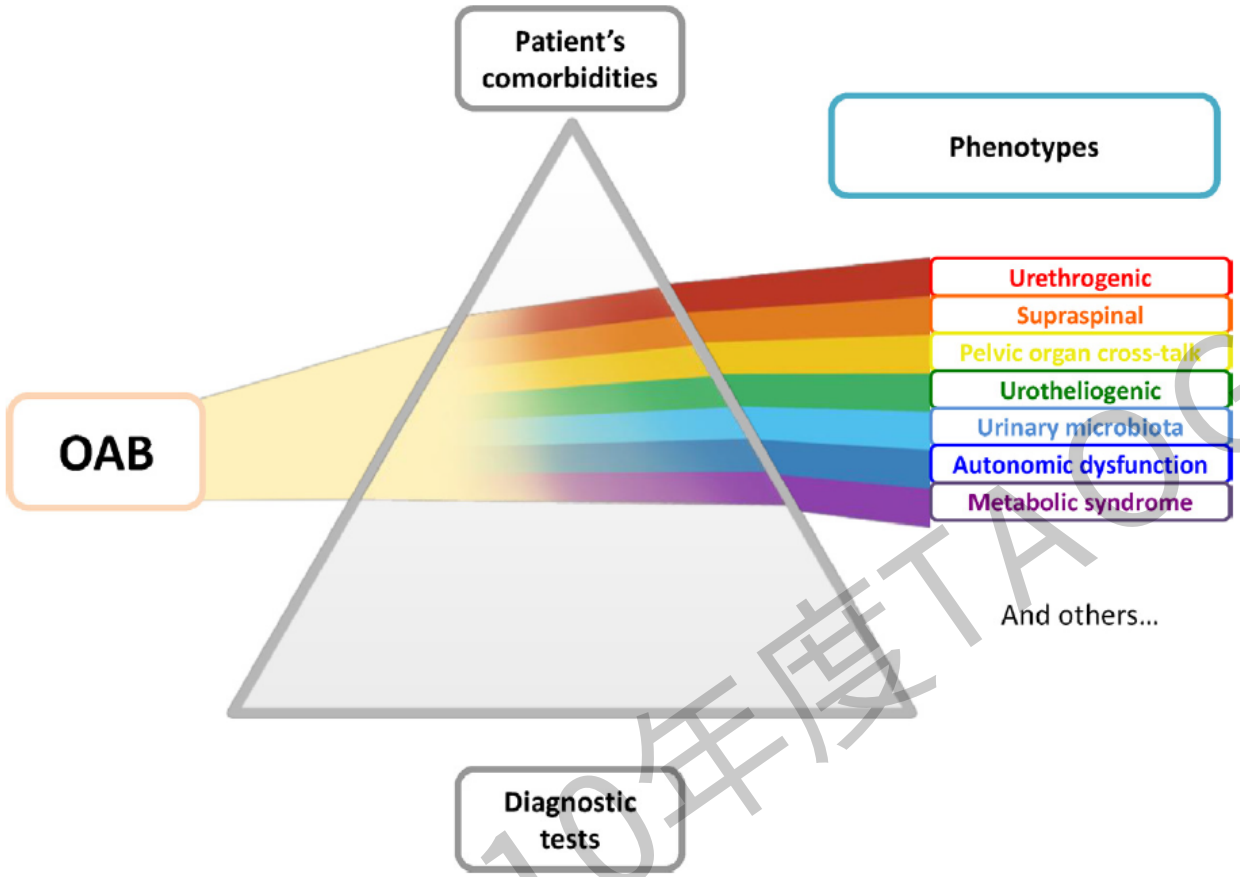
- Prospective, international, multicenter case series (n=35).
- The clinical success rate (≥50% reduction in urgency UI) was 69%, and the dry rate was 10%.

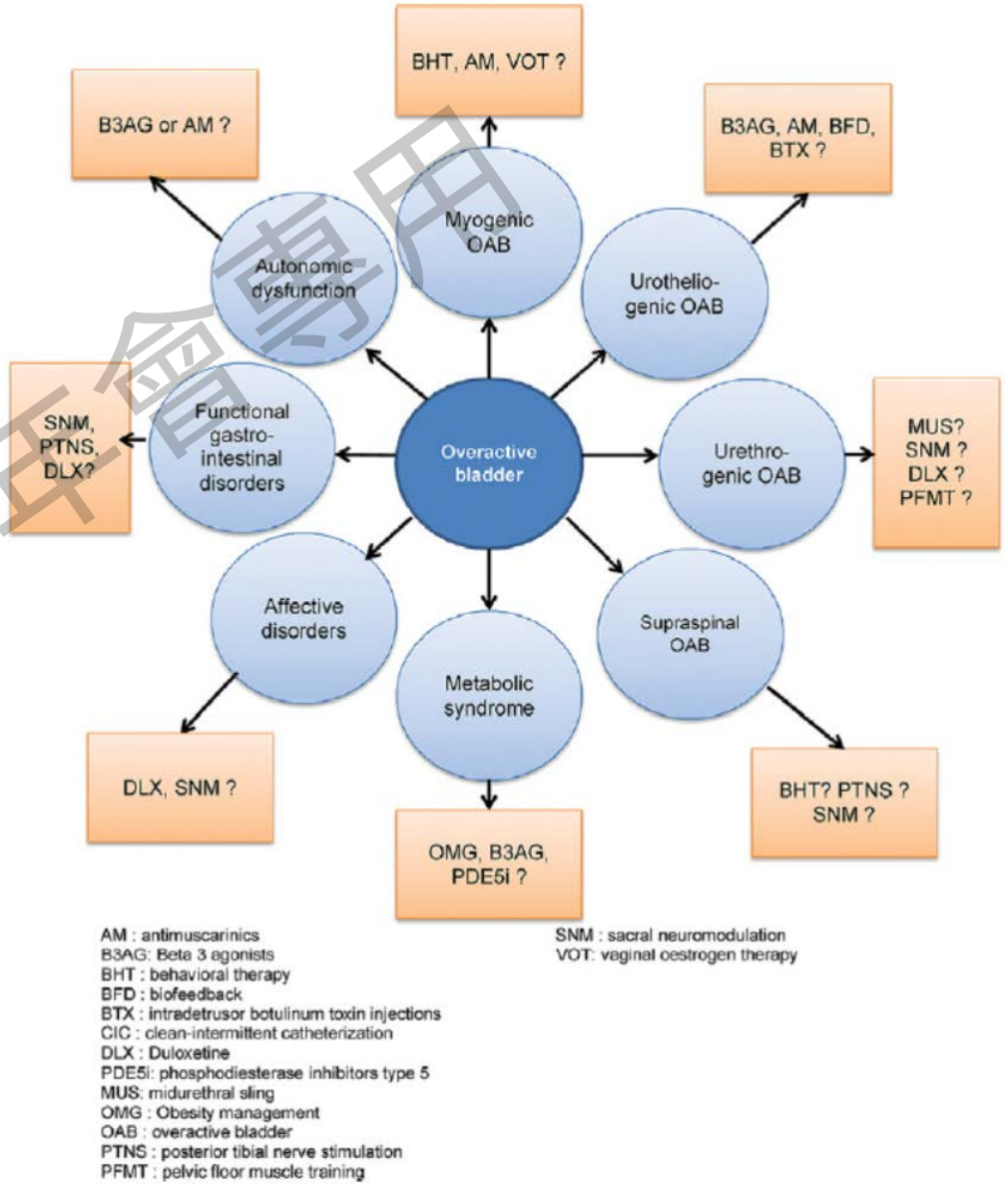
Neurourol Urodyn 2019;38:2178-2184

Better stratification of OAB



Better stratification of OAB





AM : antimuscarinics
B3AG: Beta 3 agonists
BHT : behavioral therapy
BFD : biofeedback
BTX : intradetrusor botulinum toxin injections
CIC : clean-intermittent catheterization
DLX : Duloxetine
PDE5i: phosphodiesterase inhibitors type 5
MUS: midurethral sling
OMG : Obesity management
OAB : overactive bladder
PTNS : posterior tibial nerve stimulation
PFMT : pelvic floor muscle training
SNM : sacral neuromodulation
VOT: vaginal oestrogen therapy

Seek for the underlying pathophysiological phenotypes

Tailor treatment to individual patients' characteristics.

A Comprehensive Review of Overactive Bladder Pathophysiology: On the Way to Tailored Treatment
EUROPEAN UROLOGY 7 5 (2 019) 9 8 8–10 0 0

Thank you for your attention