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Combination Pharmacotherapy for Treatment of Overactive Bladder

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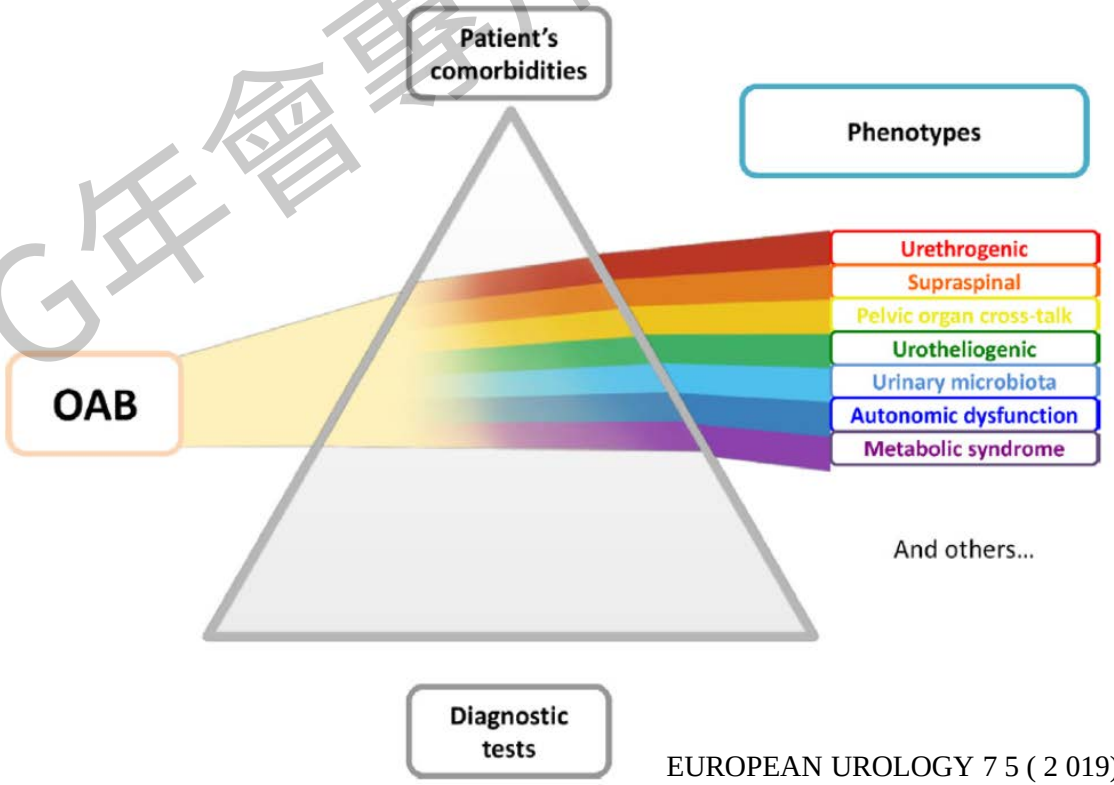
Overactive Bladder

- 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



EUROPEAN UROLOGY 7 5 (2 019) 9 8 8–10 0 0

Seek for the underlying pathophysiological phenotypes → Tailor treatment to individual patients' characteristics.

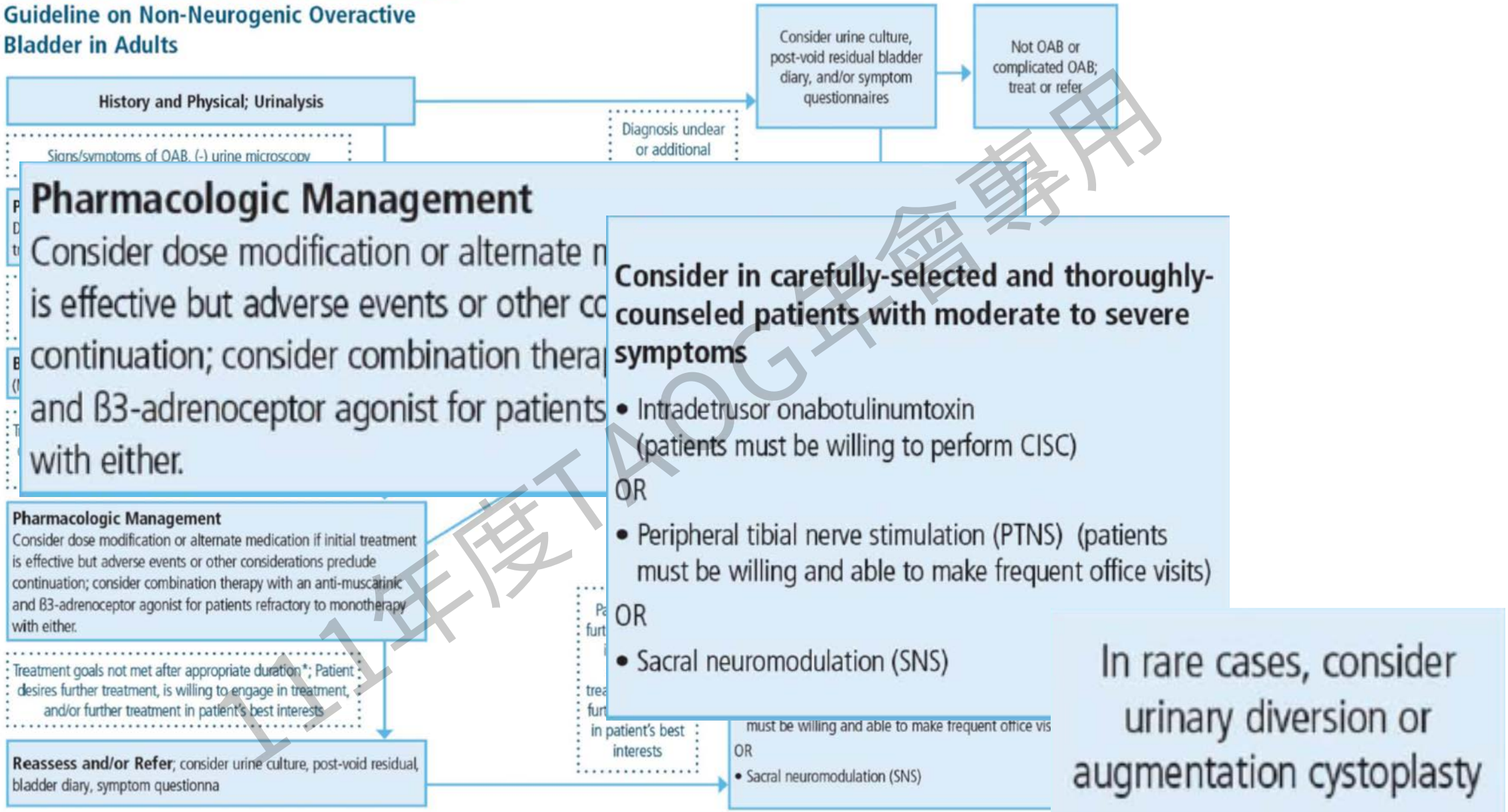
Pharmacotherapy (monotherapy or combination therapy)

- The American Urological Association, the Canadian Urological Association, and the European Association of Urology have updated their guidelines recently to include both muscarinic antagonists and beta-3 adrenergic agonists for 2nd line pharmacological treatment of OAB, along with their combination.

- 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 1 Standard treatment options for the management of overactive bladder

Therapy	Examples
First line (behavioral)	Lifestyle modifications
	Pelvic floor muscle training
	Bladder training
	Timed voiding
Second line (pharmacologic)	Anticholinergic
	Beta-3 agonists
Third line (neuromodulation/ chemodenervation)	Percutaneous tibial nerve stimulation
	Sacral neuromodulation
	Intradetrusor botulinum toxin

Kasman et al. Neurourology and Urodynamics. 2019;1–10

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

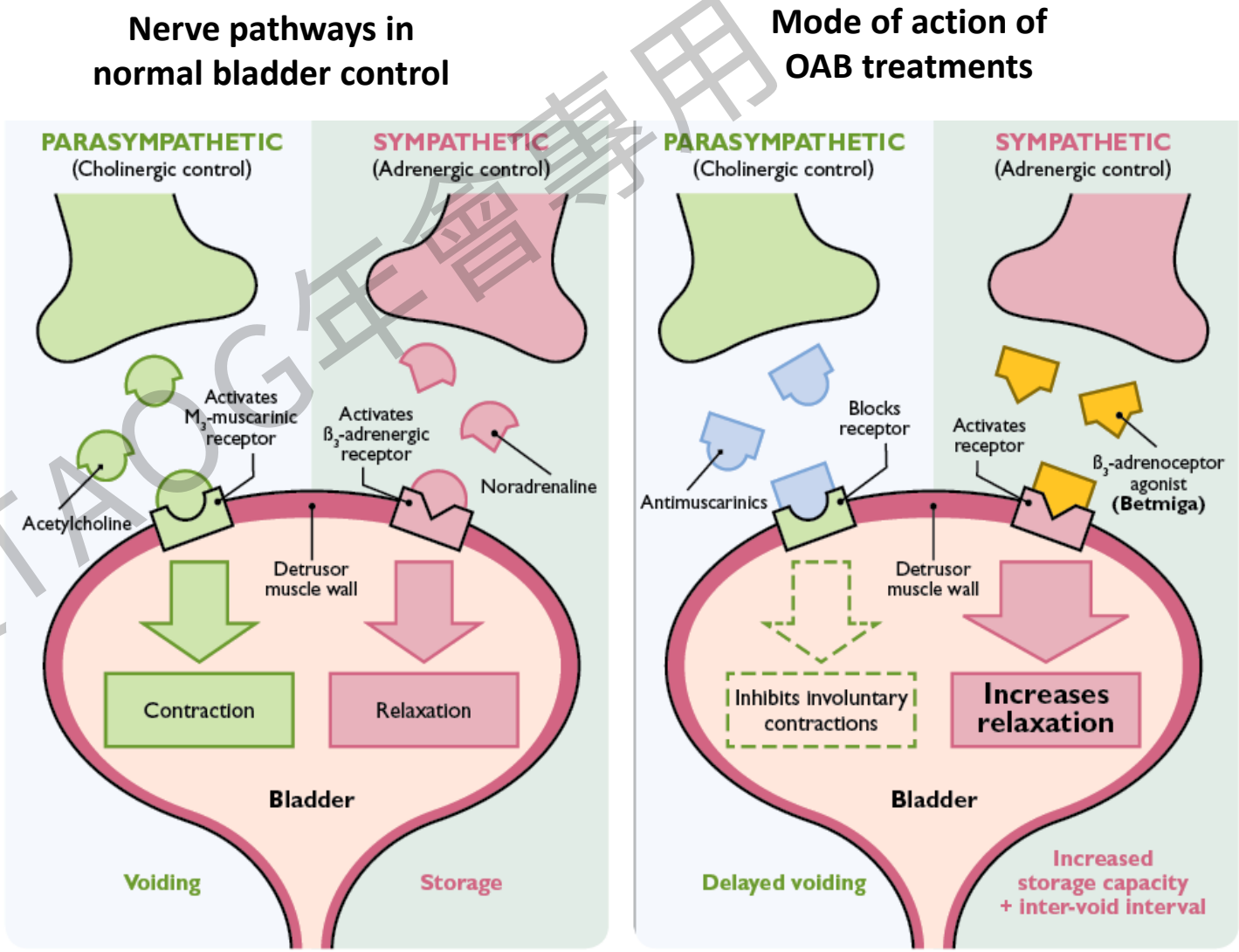
BID: twice a day; CNS AE: central nervous system adverse effects; ER: extended release; GI: gastrointestinal; GU: genitourinary; IR: immediate release; OD: once a day; QID: four times a day; TID: three times a day; UTI: urinary tract infection.

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

Mirabegron

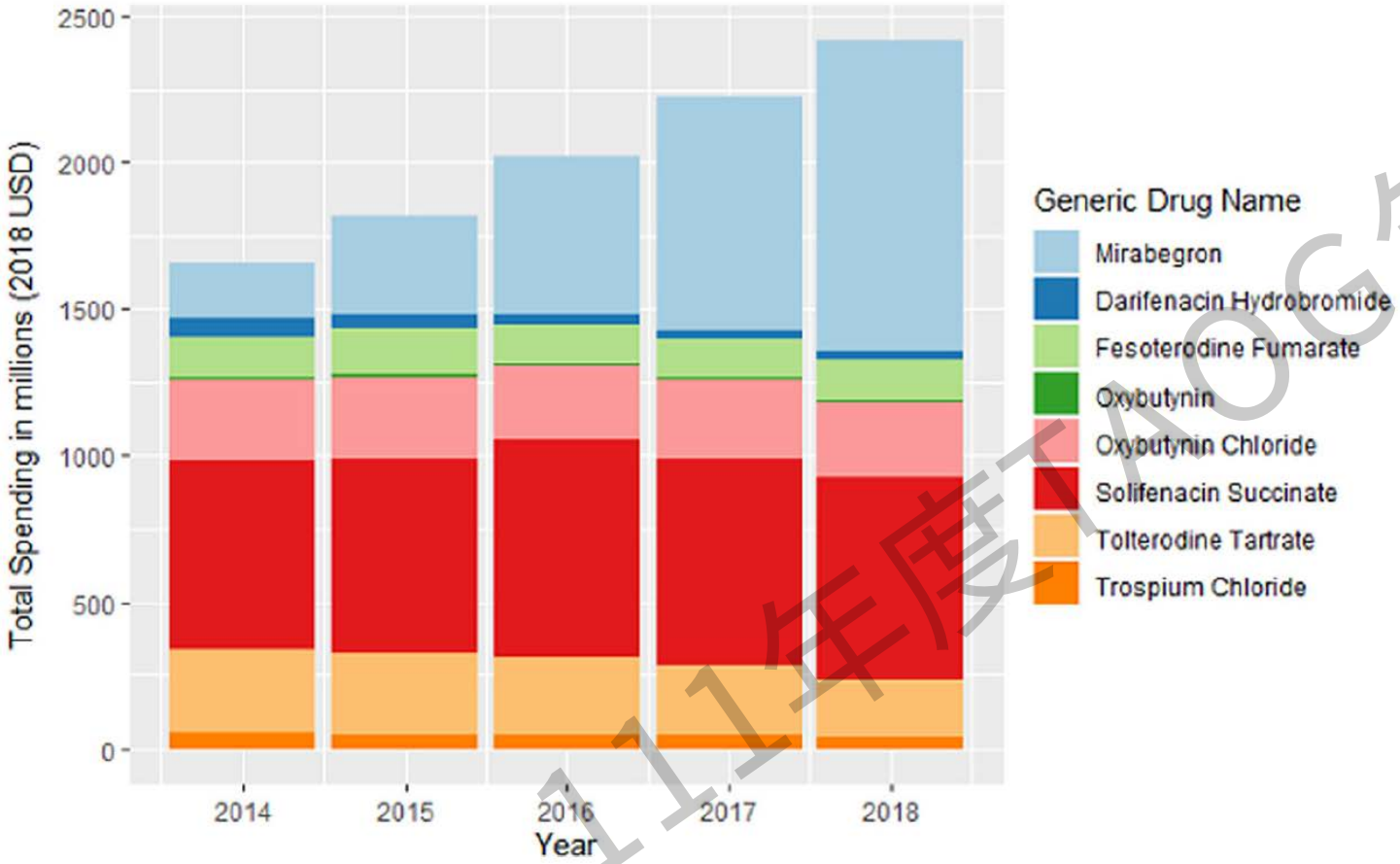
- Mirabegron -1st commercialized compound of beta-3 adrenergic agonist family.
- Developed in Japan by Astellas Pharma
- Approved for OAB treatment since 2012 (FDA;US)
- Vibegron (Beova) available in Japan since 2018

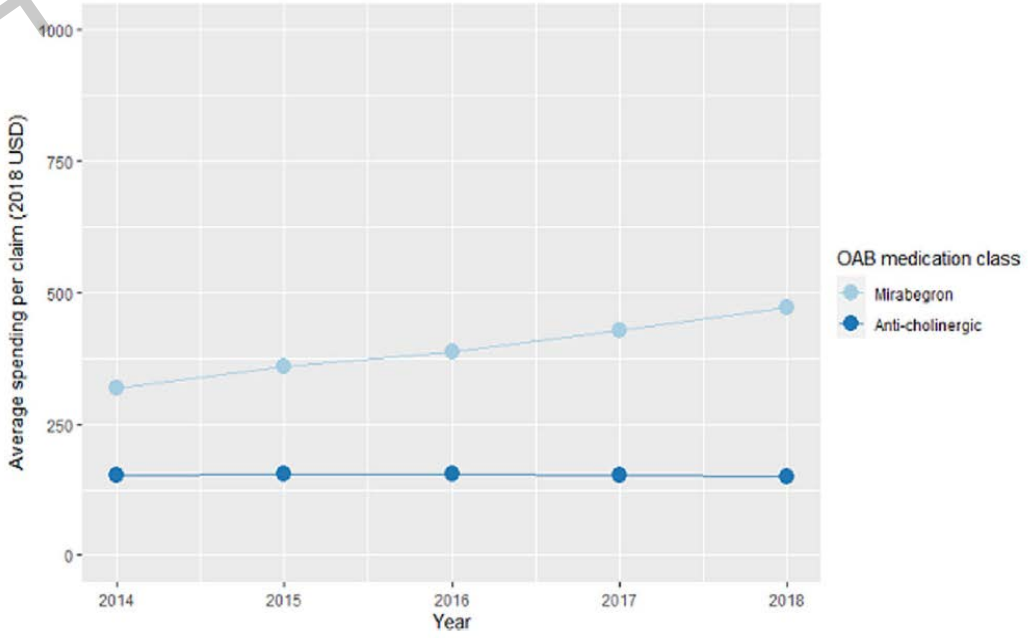
Curr Urol Rep 2020;21:49



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

Overactive bladder medication prescription trends from 2014 to 2018





Neurourol Urodyn. 2022;1–7.

TABLE 1 Total claims by year and generic drug name

Generic drug name	2014		2015		2016		2017		2018	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%
Mirabegron	585 573	5.7	944 826	9	1 399 283	12.7	1 881 553	16.8	2 261 383	20.1
Darifenacin Hydrobromide	228 575	2.2	130 710	1.2	91 474	0.8	72 441	0.6	66 568	0.6
Fesoterodine Fumarate	549 442	5.4	504 894	4.8	365 439	3.3	317 205	2.8	330 416	2.9
Oxybutynin	22 978	0.2	16 995	0.2	11 970	0.1	8131	0.1	6037	0.1
Oxybutynin Chloride	5 172 217	50.5	5 467 502	51.9	5 692 901	51.8	5 765 187	51.6	5 819 650	51.7
Solifenacin Succinate	2 183 699	21.3	1 982 808	18.8	1 876 293	17.1	1 616 754	14.5	1 376 968	12.2
Tolterodine Tartrate	1 190 691	11.6	1 190 159	11.3	1 246 480	11.3	1 189 437	10.7	1 077 789	9.6
Trospium Chloride	313 745	3.1	294 256	2.8	303 872	2.8	317 640	2.8	316 405	2.8
Total	10 246 920	100	10 532 150	100	10 987 712	100	11 168 348	100	11 255 216	100
p value	Ref.		<0.0001		<0.0001		<0.0001		<0.0001	

Note: Chi-square testing was performed. $\chi^2 = 1\,810\,584$, $df = 28$, p value <0.05.

Neurourol Urodyn. 2022;1–7.

Cost-effectiveness of Mirabegron

- Unit cost of mirabegron is higher than most antimuscarinics

Costs*		
Mirabegron	$1.46 CAD per 50 mg tablet	INESSS list of medications[39]
Tolterodine ER (generic)	$0.49 CAD per 4 mg tablet	INESSS list of medications[39]
Incontinence pads	$1.55 CAD per pad	Herschorn et al 2010[40] (adjusted to 2015 $CAD)
GP consultation	$40.05 CAD per visit	Manuel Des Médecins Omnipraticiens[41]
Specialist consultation (urology)	$62.50 CAD per visit	Manuel Des Médecins Spécialistes[42]
Loss of productivity		
Proportion of workers among OAB population	35.7%	Statistics Canada 2012[43] (≥55 years); age distribution from Nitti et al 2013[28]
Labour cost per month	$3380 CAD	Statistics Canada 2012[43] (average annual salary); age distribution from Nitti et al 2013[28]

*All prices are in Canadian dollars. CAD: Canadian dollar; EQ-5D: EuroQol five-dimensional health-related quality of life questionnaire; ER: extended release; GP: general/family practitioner; INESSS: Institute national d'excellence en santé et en services sociaux; OAB: overactive bladder; OAB-q: Overactive Bladder Questionnaire.

Can Urol Assoc J 2017;11:123-30
J Med Econ 2016;19:1135-43
PharmacoEconomics-open 2017;1:25-36
Int J Urol 2018;25: 863-70

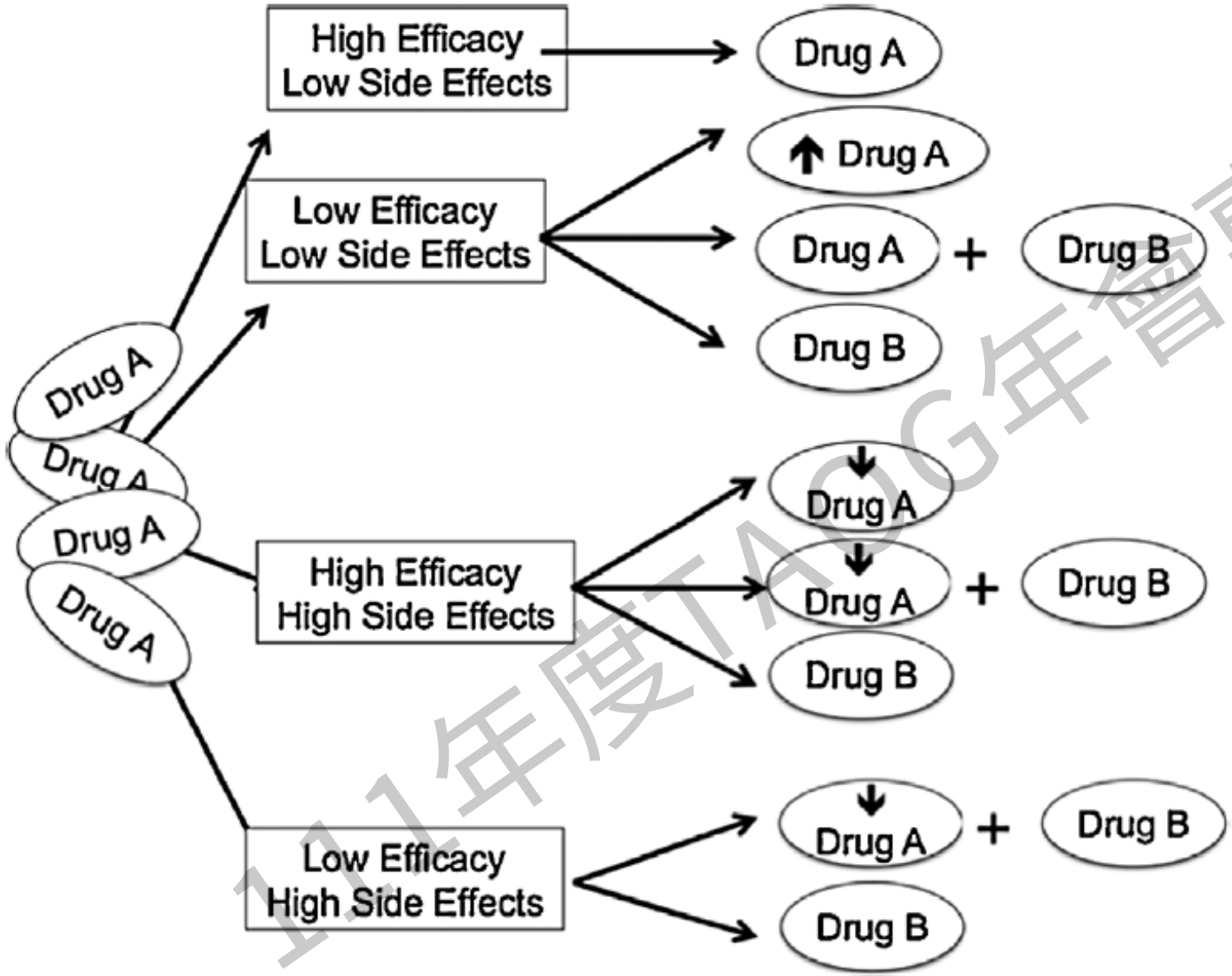


Fig. 1. Options after beginning monotherapy.

Neurourol.Urodynam. 35:288–292, 2016

TABLE II. Possible Combination for Dual Therapy

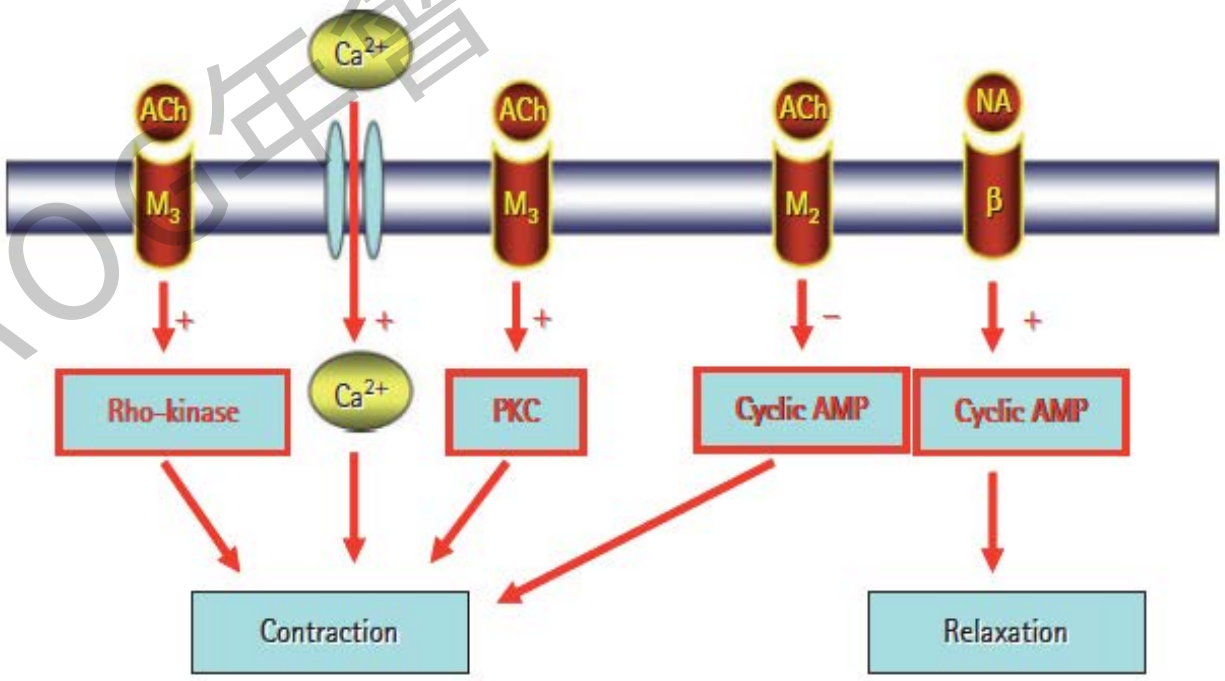
1.	antimuscarinic + β_3-agonist
2.	antimuscarinic + botulinum toxin
3.	antimuscarinic + estrogen
4.	antimuscarinic + α_1-blocker
5.	antimuscarinic + PDE5 inhibitor
6.	β_3-agonist + botulinum toxin
7.	β_3-agonist + estrogen
8.	β_3-agonist + α_1-blocker
9.	β_3-agonist + PDE5 inhibitor
10.	botulinum toxin + estrogen
11.	botulinum toxin + α_1-blockers
12.	botulinum toxin + PDE5 inhibitor
13.	estrogen + α_1-blocker
14.	estrogen + PDE5 inhibitor
15.	α_1-blocker + PDE5 inhibitor

Pharmacologic management- Evidence of Combination therapy

- Drugs with different mechanisms of action to achieve an improvement in patient quality of life, with the lowest rate of adverse events.

- 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

TABLE 3 Summarized findings of systematic review of OAB combination therapy

Combination	Author	n	Summarized finding
Anticholinergic with anticholinergic	Kosilov et al[10]	177	Combination trospium and solifenacin significantly decreased episodes of urgency, UI compared to prior monotherapy of each and placebo
	Kosilov et al[11]	341	Combination either intermittent or continuous trospium and solifenacin decreased episodes of urgency, UI compared to placebo
	Kosilov et al[12]	313	Combination intermittent or continuous trospium and solifenacin decreased episodes of urgency and UI compared to placebo
	Yi et al[13]	49	Combination propiverine and an anticholinergic, or combination tolterodine and tropsium, reduced urgency, UI compared to monotherapy of each
Anticholinergic with beta-3 agonist	Shin et al[14]	30	Combination mirabegron+propiverine decreased PPBC scores, frequency, urgency, and UI episodes compared to monotherapy
	Kosilov et al[15]	239	Mirabegron and solifenacin combination decreased OAB-q scores, frequency and UI compared to placebo or monotherapy mirabegron
	Abrams et al[16]	1306	Combination solifenacin and mirabegron improved frequency and urgency compared to monotherapy of each
	Yamaguchi et al[17]	223	Combination solifenacin with mirabegron decreased frequency, urgency, and UI compared to montherapy solifenacin
SYNERGY II	Gratzke et al[18]	1794	Combination solifenacin with mirabegron improved frequency and UI compared to monotherapy solifenacin
	Robinson et al[19]	3527	Combination solifenacin with mirabegron improved OAB-q symptom bother, HRQoL total score compared to montherapy of each and placebo
SYNERGY study	Herschorn et al[8]	3308	Combination solifenacin with mirabegron therapy improved frequency and UI compared to montherapy of each and placebo
	MacDiarmid et al[20]	2174	Combination solifenacin with mirabegron improved HRQoL and PPBC scores compared to monotherapy solifenacin
BESIDE	Drake et al[9]	2174	Combination solifenacin with mirabegron improved frequency, UI compared to monotherapy solifenacin

Neurourol Urodyn 2019;38: 2083-92

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‡‡

- To evaluate the potential of solifenacin 5 mg combined with mirabegron 25 or 50 mg to deliver superior efficacy compared with monotherapy, with acceptable tolerability, in general OAB population with UI.

- Patients aged ≥18 years with wet OAB (urgency, urinary frequency and UI) for ≥3 months who recorded on average ≥8 micturitions/24 h, ≥1 urgency episode/24 h, and ≥3 UI episodes over the 7-day micturition diary, were eligible for randomization.

BJU Int 2017; 120: 562–575

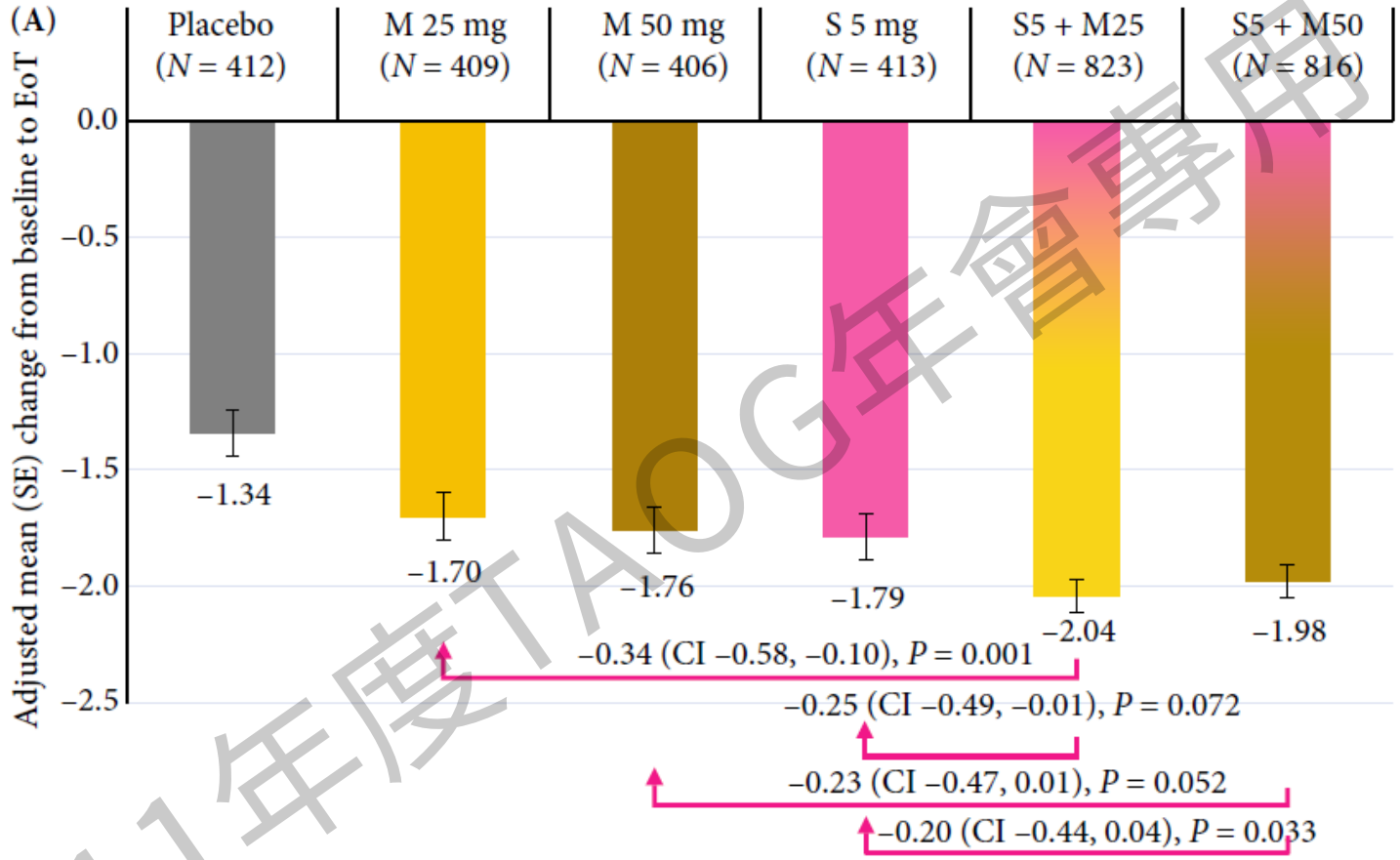
BJUI
BJU International

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

- 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.
- The study was conducted at 435 sites in 42 countries, n = 3527(randomized).
- Most patients were female (77%), 65% had UUI only, 35% had mixed UI with urgency predominant.
- The duration of wet OAB symptoms was 67months (similar across treatment groups).

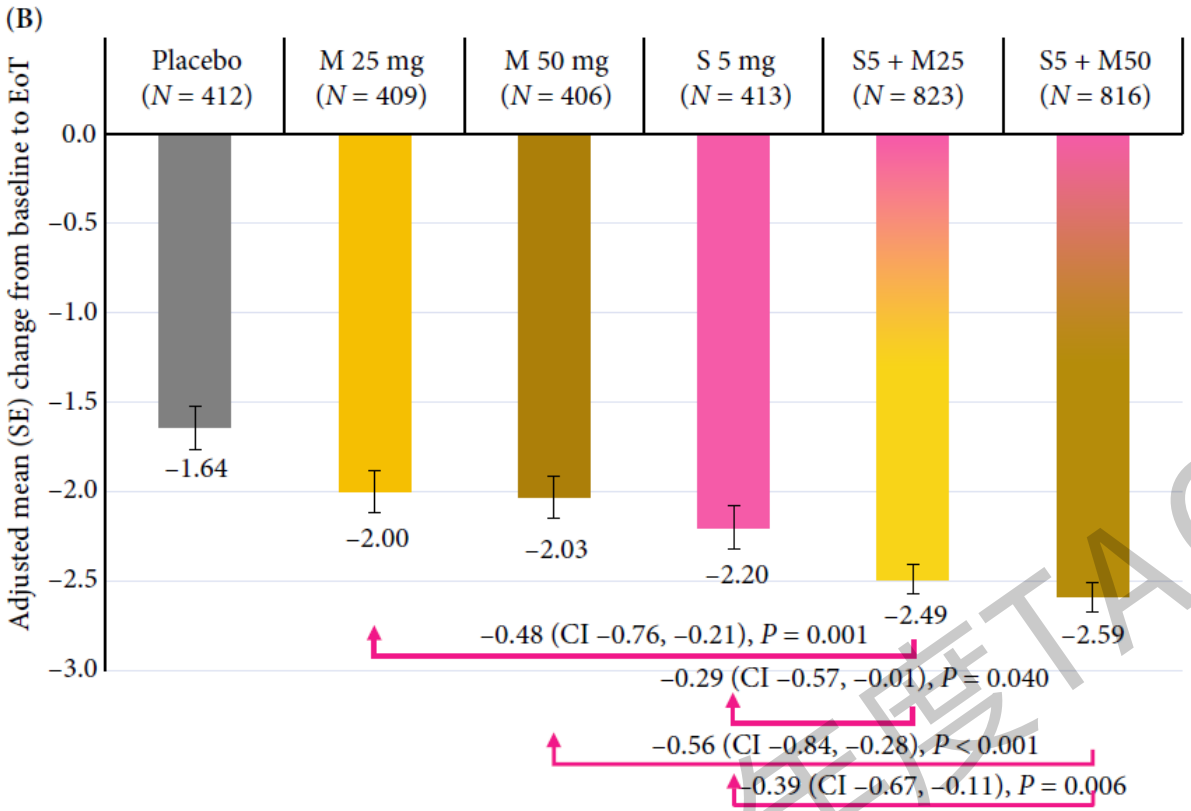
BJU Int 2017; 120: 562–575

Fig. 2 Adjusted change from baseline to EoT in (**A**) mean number of UI episodes/24 h, (**B**) mean number of micturitions/24 h, and (**C**) MVV/micturition. M, mirabegron; S, solifenacin.

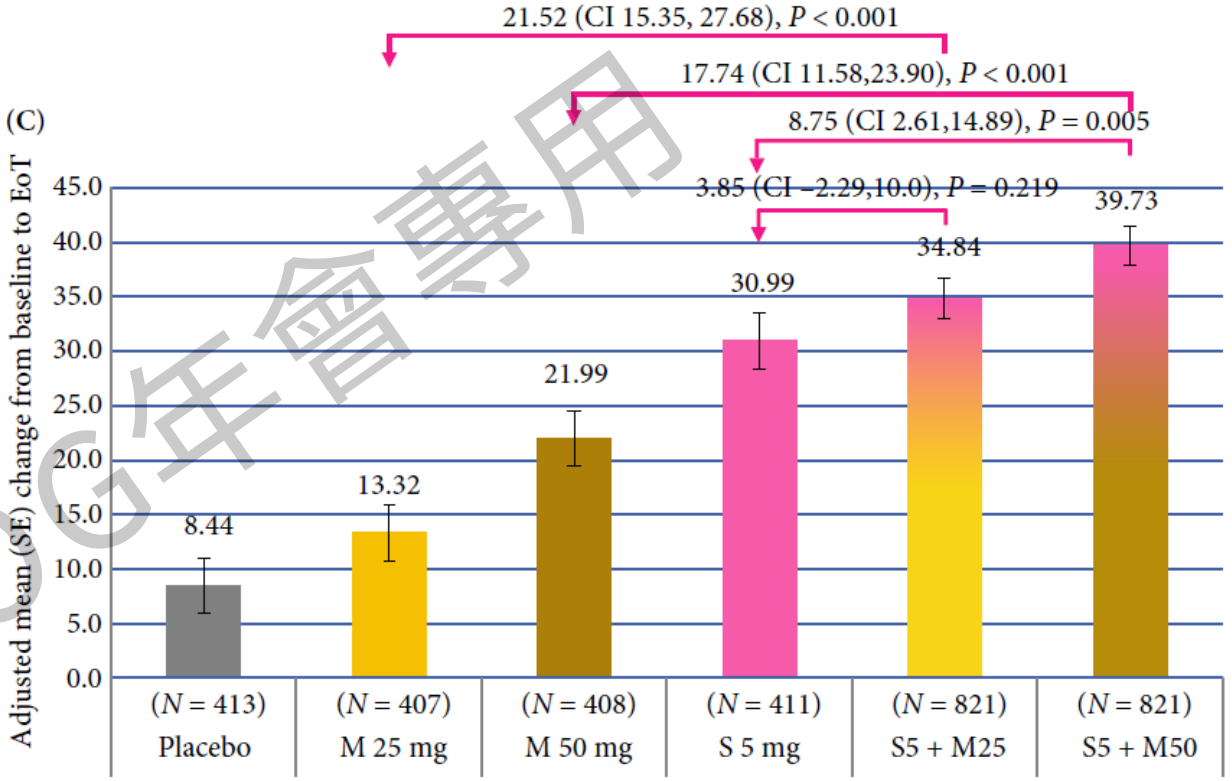


- combined therapy with solifenacin 5 mg + mirabegron 25 mg and solifenacin 5 mg+ mirabegron 50 mg provided consistent improvements in efficacy compared with the respective monotherapies across most of the outcome parameters, with effect sizes generally consistent with an additive effect.

BJU Int 2017; 120: 562–575



(B) mean number of micturitions/24 h



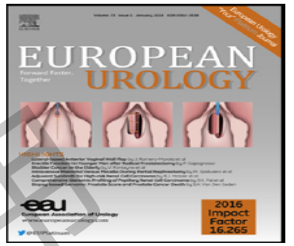
(C) MVV/micturition

Conclusions: 1) Multiple outcomes parameters (both subjective and objective) indicated improvements with combined therapy. 2) S+ M had a acceptable safety profile without new safety concern and was well tolerated, similar to monotherapies.

BJU Int 2017; 120: 562–575

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)

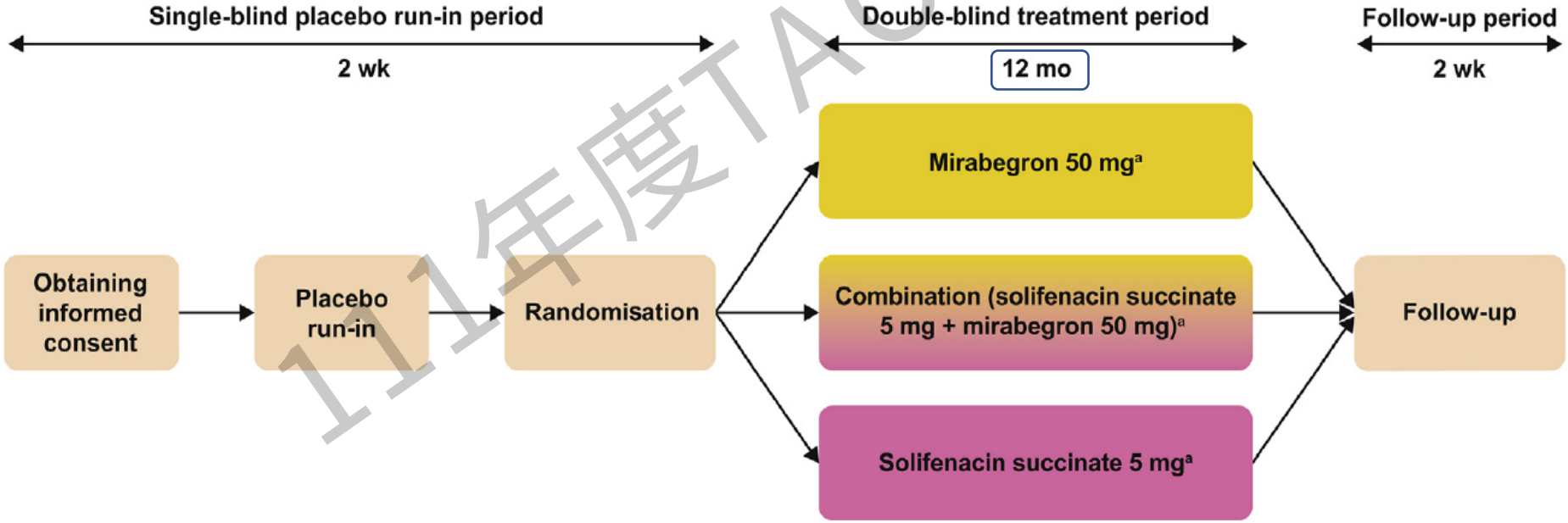


Fig. 1 – Study design. [a] Once daily.

- 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%).

TEAE	Patients, *n* (%)		
	Mirabegron (*n* = 305)	Combination (*n* = 1206)	Solifenacin (*n* = 303)
TEAEs by preferred term (≥1.0% for any group)			
Dry mouth	12 (3.9)	74 (6.1)	18 (5.9)
Nasopharyngitis	16 (5.2)	43 (3.6)	15 (5.0)
Urinary tract infection	11 (3.6)	41 (3.4)	12 (4.0)
Constipation	3 (1.0)	40 (3.3)	7 (2.3)
Headache	5 (1.6)	35 (2.9)	5 (1.7)
Escherichia urinary tract infection	6 (2.0)	35 (2.9)	3 (1.0)
TEAEs of special interest			
Hypertension [b]	4 (1.3)	23 (1.9)	4 (1.3)
Increased blood pressure [c]	6 (2.0)	30 (2.5)	7 (2.3)
QT interval prolongation [c]	3 (1.0)	3 (0.2)	0
Tachyarrhythmias (increased heart rate, tachycardia, atrial fibrillation and palpitations) [c]	8 (2.6)	36 (3.0)	3 (1.0)
Urinary tract infection [d]	19 (6.2)	101 (8.4)	18 (5.9)
Urinary retention [d]	1 (0.3)	9 (0.7)	1 (0.3)
Hypersensitivity reactions [c]	3 (1.0)	16 (1.3)	0
Glaucoma [c]	0	3 (0.2)	0
Somnolence [d]	14 (4.6)	63 (5.2)	8 (2.6)

Is Combination Better than Escalation for Overactive Bladder Therapy?

BESIDE trial:

- 2,174 patients (83% women), with 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 for 12 weeks.
- Combination therapy was significantly superior to solifenacin 5 mg with meaningful improvements in daily incontinence, daily number of micturitions noted in a 3-d diary.
- Combination therapy was noninferior to solifenacin 10mg for key secondary endpoints and superior to solifenacin 10mg in improving daily micturitions.
- The incidence of TEAEs was lowest for solifenacin 5 mg (33.1%), highest for solifenacin 10 mg (39.4%), and 35.9% for the combination. The incidence of dry mouth: combination (5.9%), solifenacin 10 mg (9.5%), solifenacin 5 mg (5.6%).

Eur Urol 2016:70:136-145

INTERNATIONAL JOURNAL OF UROLOGY

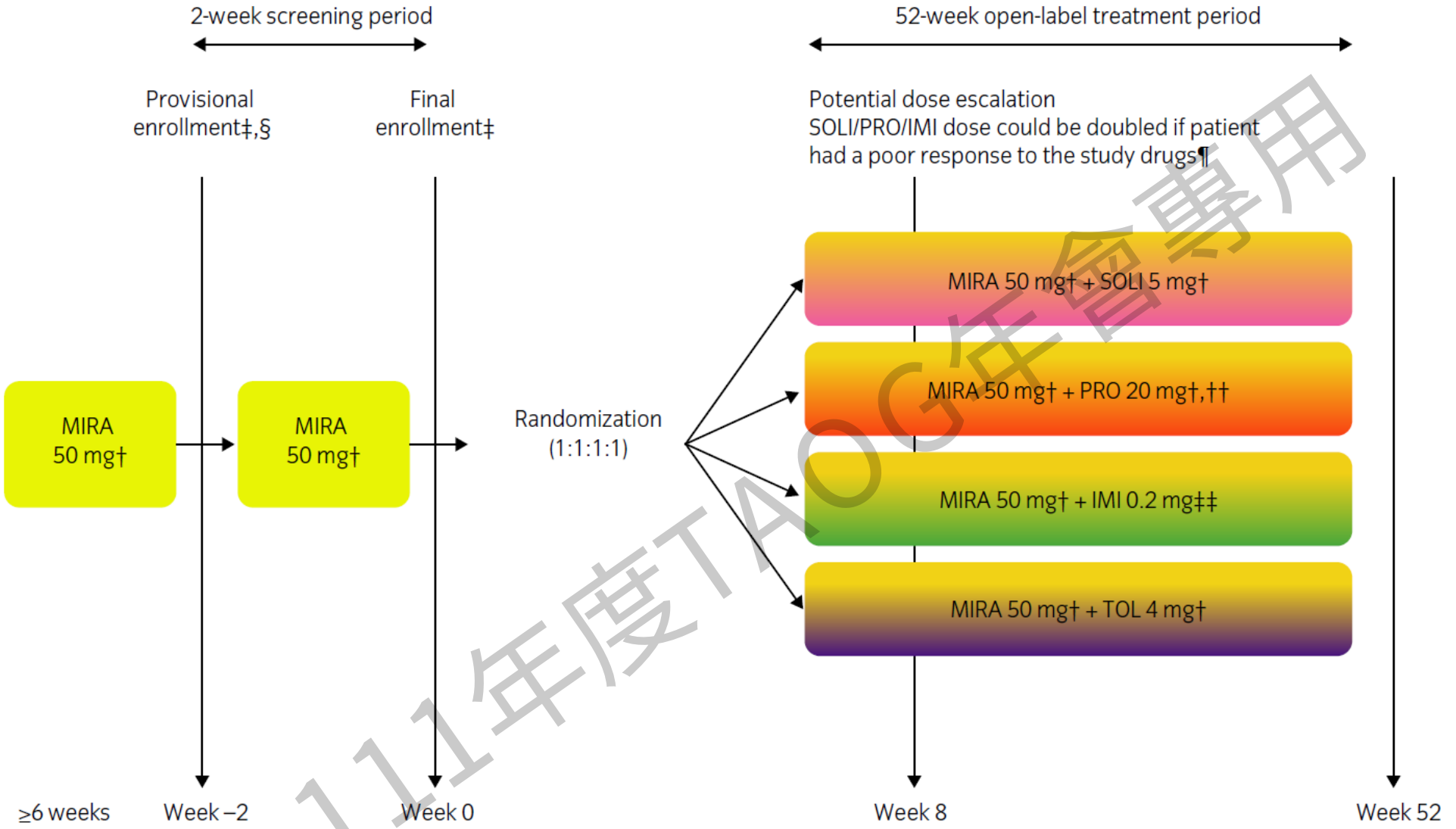
International Journal of Urology (2019) **26**, 342–352 doi: 10.1111/iju.13868

Original Article: Clinical Investigation

Long-term safety and efficacy of antimuscarinic add-on therapy in patients with overactive bladder who had a suboptimal response to mirabegron monotherapy: A multicenter, randomized study in Japan (MILAI II study)

Osamu Yamaguchi,[1] Hidehiro Kakizaki,[2] Yukio Homma,[3] Yasuhiko Igawa,[4] Masayuki Takeda,[5] Osamu Nishizawa,[6] Momokazu Gotoh,[7] Masaki Yoshida,[8] Osamu Yokoyama,[9] Narihito Seki,[10] Akira Okitsu,[11] Takuya Hamada,[11] Akiko Kobayashi[11] and Kentaro Kuroishi[11]

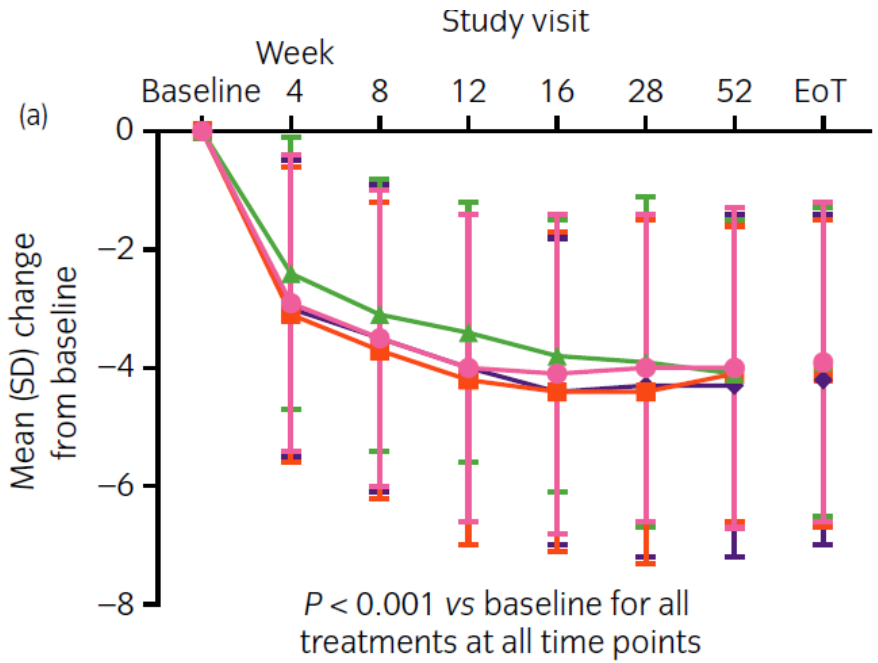
Objectives: To evaluate the long-term safety (primary objective) and efficacy (secondary objective) of antimuscarinic add-on therapy in patients receiving mirabegron.



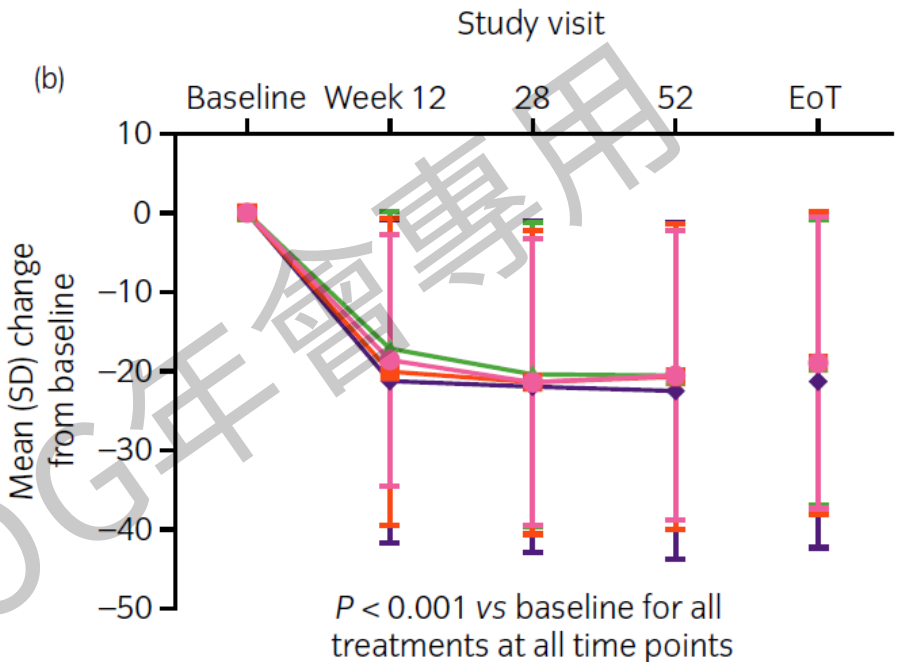
PRO = propiverine
IMI = imidafenacin

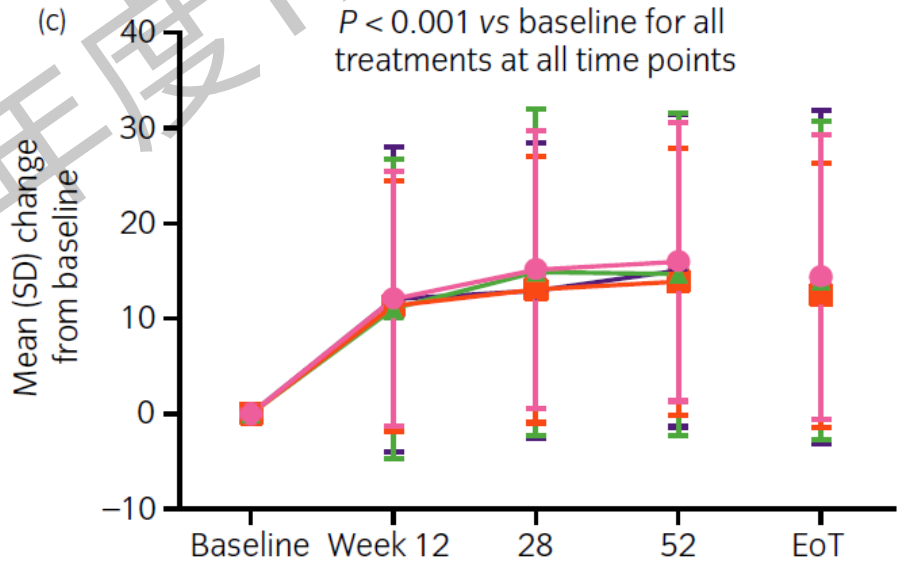
Fig. 1 Study design. †Once daily. ‡Eligibility criteria were verified. §Informed consent was obtained. ¶Furthermore, the patient was considered by the investigator to have no safety concerns and agreed to the increased dose (in the event of a TEAE, the dose could be reduced to the initial dosage). ††If the PRO dose was doubled, patients received a 20-mg dose twice daily. ‡‡Twice daily (total daily dose shown).

(a) OABSS total score



(b)OAB-q SF symptom severity score





Antimuscarinic add-on therapy is well tolerated and effective after initial treatment with mirabegron in patients with OAB.

(c) OAB-q SF total HRQoL score

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ORIGINAL CLINICAL ARTICLE

Neurourology Urodynamics ICS SUFU WILEY

Treatment patterns and costs among patients with OAB treated with combination oral therapy, sacral nerve stimulation, percutaneous tibial nerve stimulation, or onabotulinumtoxinA in the United States

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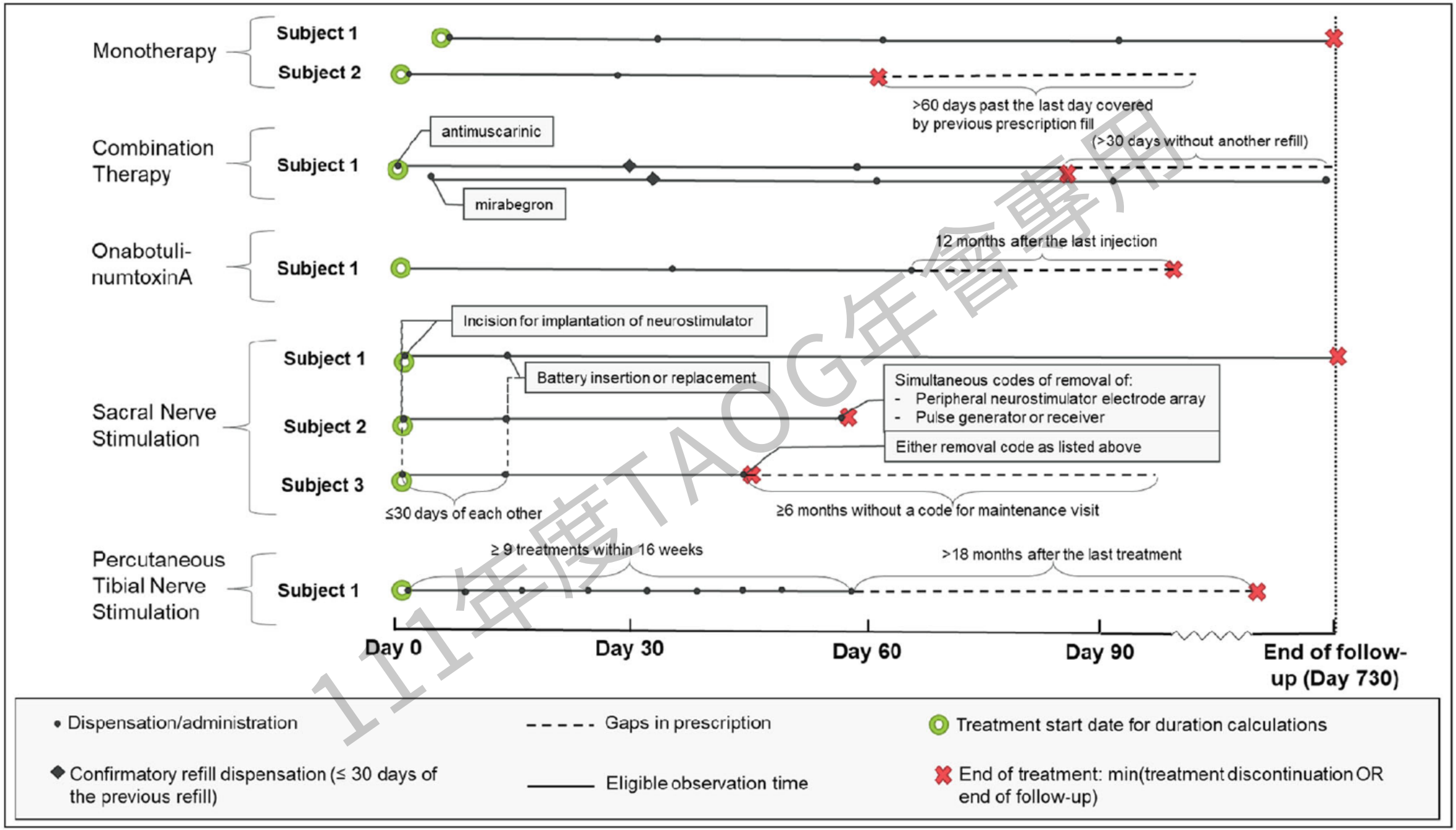
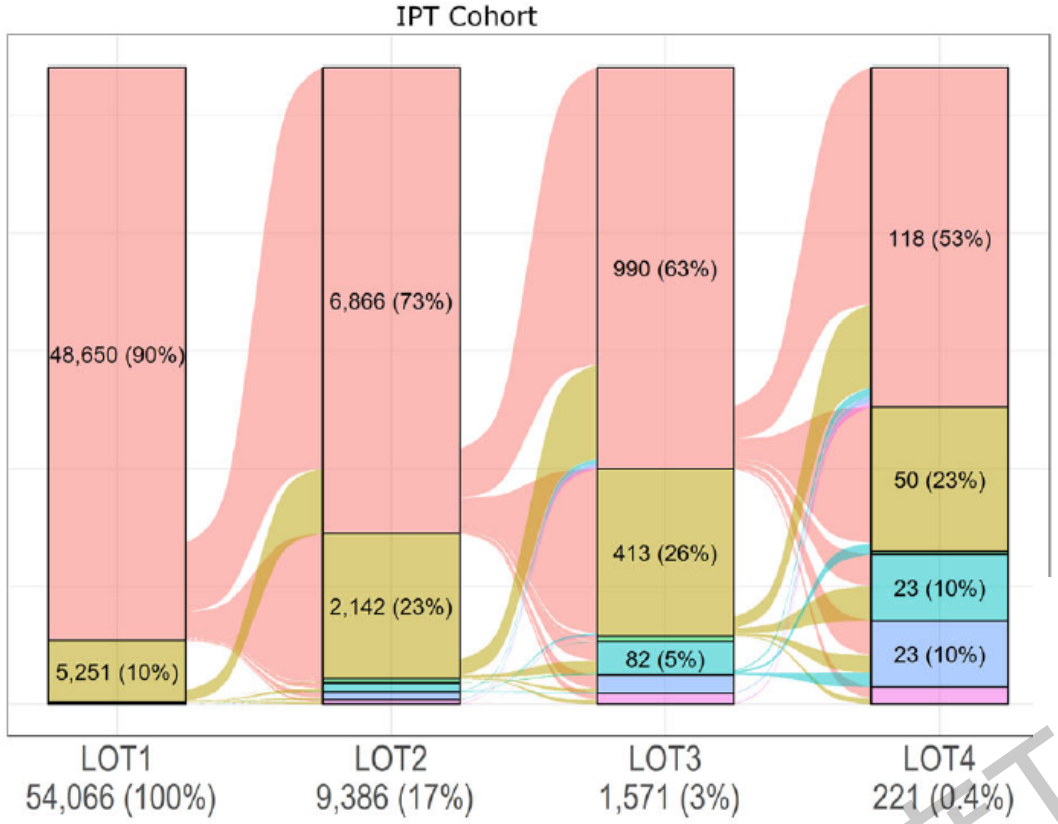
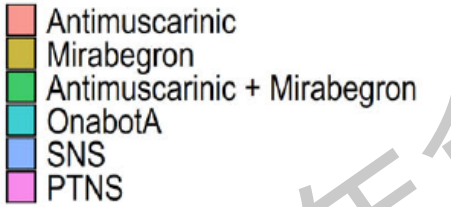
Abstract

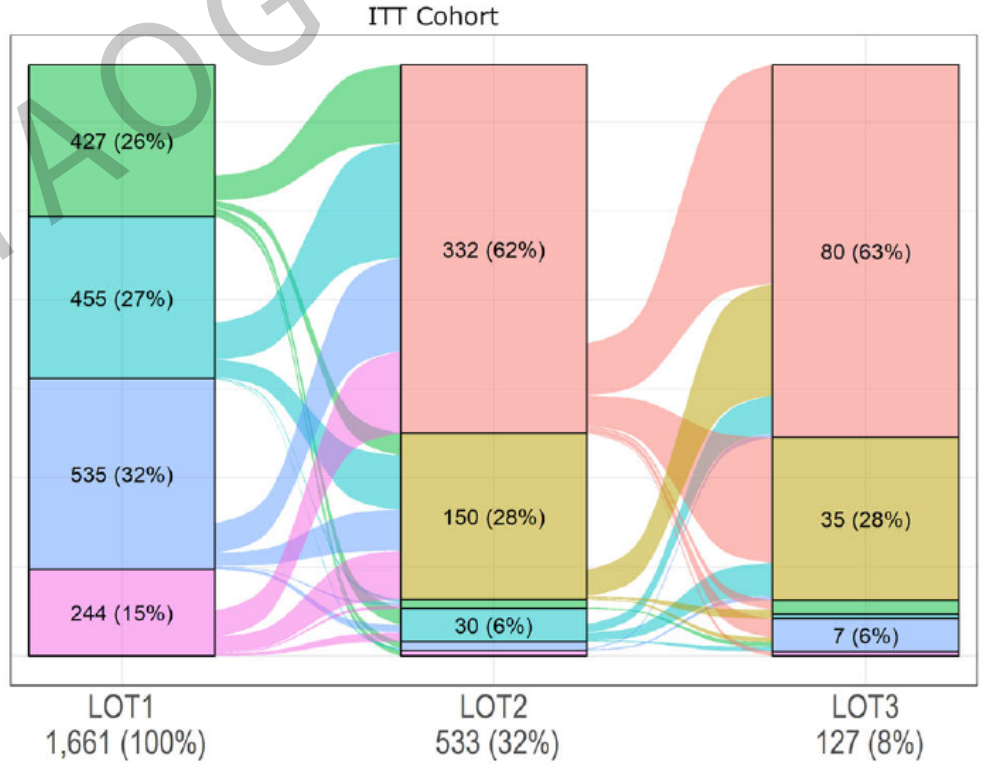
Introduction: Treatment patterns and costs were characterized among patients with overactive bladder (OAB) receiving later-line target therapies (combination mirabegron/antimuscarinic, sacral nerve stimulation [SNS], percutaneous tibial nerve stimulation [PTNS], or onabotulinumtoxinA).

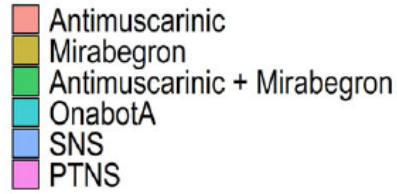
Methods: In a retrospective cohort study using 2013 to 2017 MarketScan databases, two partially overlapping cohorts of adults with OAB ("IPT cohort": patients with incident OAB pharmacotherapy use; "ITT cohort," incident target therapy) with continuous enrollment were identified; first use was index. Demographic characteristics, treatment patterns and costs over the 24-month follow-up period were summarized. Crude mean (standard deviation [SD]) OAB-specific (assessed by OAB diagnostic code or pharmaceutical dispensation record) costs were estimated according to target therapy.











Neurourology and Urodynamic 2020;39:2206-2222

IPT Cohort	All (n = 54,066)	Combimira/AM (n = 245)	onabotulinumtoxinA (n = 244)	SNS (n = 188)	PTNS (n = 98)
Medications					
Mean (SD)	1203 (1872)	5435 (3867)	1670 (1872)	1364 (1738)	1846 (1954)
Inpatient visits (hospitalizations)					
Mean (SD)	45 (1298)	0 (0)	214 (2515)	61 (812)	0 (0)
ER visits (inpatient and outpatient)					
Mean (SD)	7 (225)	0 (0)	14 (142)	10 (142)	0 (0)
Outpatient visits					
Mean (SD)	538 (3312)	1597 (5086)	8299 (12 564)	38 528 (27 895)	4780 (4466)
Physician visits, mean (SD)					
GP	45 (327)	81 (233)	502 (3315)	637 (2597)	173 (1030)
Specialist	206 (688)	646 (1619)	2415 (2490)	4123 (4246)	3547 (2953)
Other	287 (2962)	870 (3743)	5382 (11 202)	33 768 (26 803)	1060 (2777)
Procedures					
Mean (SD)	71 (1625)	804 (4022)	2883 (6838)	13 867 (20 469)	2844 (2116)
Total, mean (SD)	1787 (4105)	7032 (5854)	10 183 (13 725)	39 954 (28 113)	6626 (5173)

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Take home messages

- Beta-3 adrenoceptor agonist, offer an alternative option for OAB patients who do not respond to or tolerate antimuscarinic drugs.
- Combination therapy (solifenacin 5 mg plus mirabegron 25 or 50 mg) appears to provide an efficacy benefit compared with monotherapy, with the expected side effects of individual antimuscarinics.
- Combination therapy provide optimizing efficacy and acceptable tolerability profile in comparison to a higher antimuscarinic dose.

Thank you for your attention

Pharmacologic management-
Evidence of Combination therapy

- RCT that evaluated combination tolterodine and intravaginal estradiol cream in 58 menopausal women with OAB. Women were randomized to either oral tolterodine or estradiol cream(nightly for 6 weeks then twice per week) 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

- RCT compared 3 months combination of oral desmopressin 25 μg plus 4 mg tolterodine (n=49) with 4 mg tolterodine/placebo monotherapy (n=57) in women with OAB and nocturia.

Low Urin Tract Symptoms. 2018;10:221-230