III Prostate day

UM DIA DEDICADO ÀS DOENÇAS DA PRÓSTATA

09 de Novembro | Hotel Meliá Paulista

LUTS/HPB: tratamento farmacológico

Quando indicar outras associações

Dr. Ricardo Vita

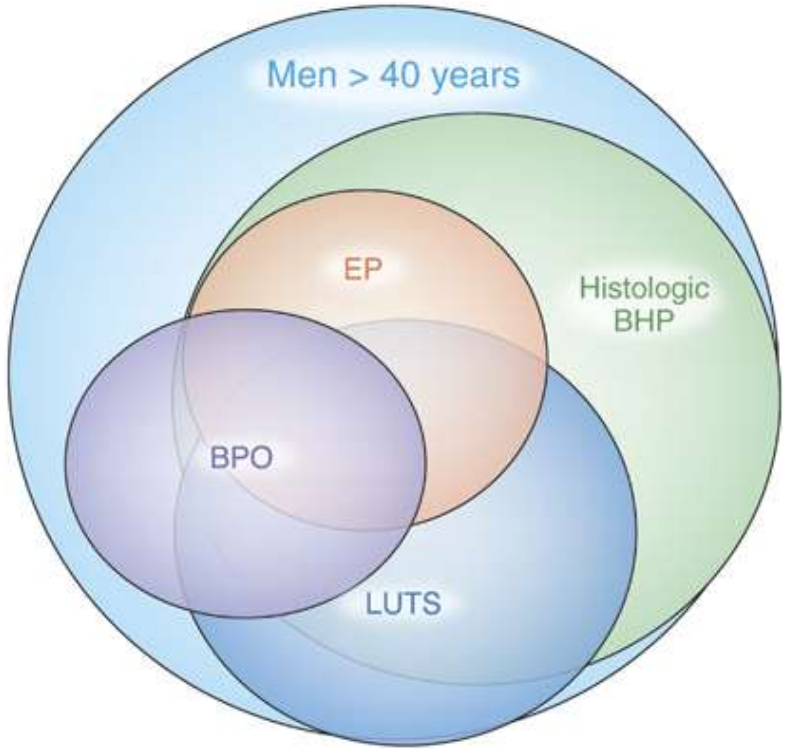
Chefe da Área de HPB da SBU
Chefe da Urologia do Hospital Militar de Área de São Paulo
Doutor em Urologia pela FMUSP

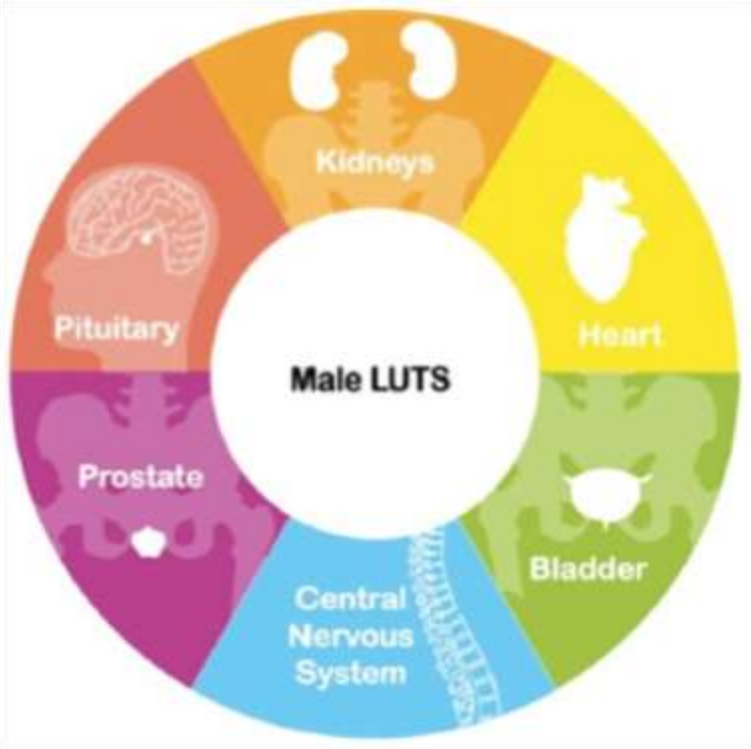
CONFLITO DE INTERESSES

De acordo com a Resolução 1595 / 2000 do Conselho Federal de Medicina e com RDC 96 / 2008 da ANVISA, declaro que:

Pesquisa Clínica como médico investigador, participo de estudos patrocinados.:
IPSEN-COVANCE, ROCHÈ
Apresentações como palestrante convidado:
ASTELLAS, ZAMBON, ACHÉ, COLOPLAST, ZODIAC
Consultoria:
ZAMBON, ASTELLAS

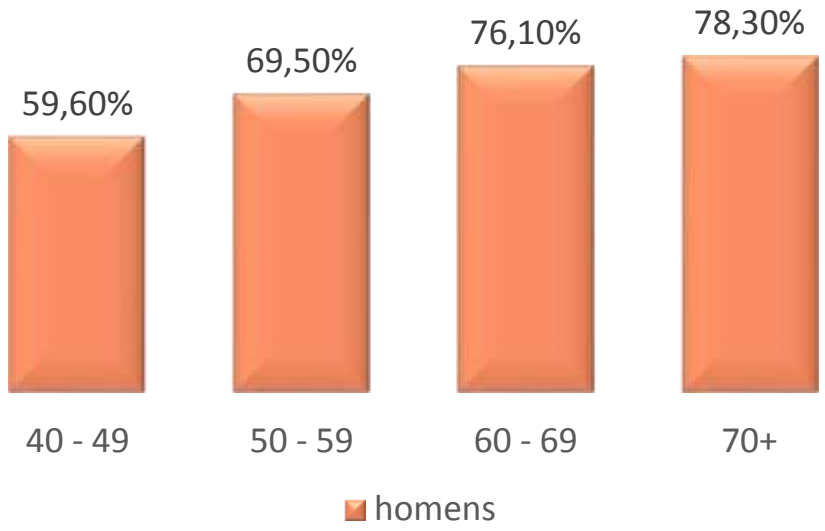
Considerando que...

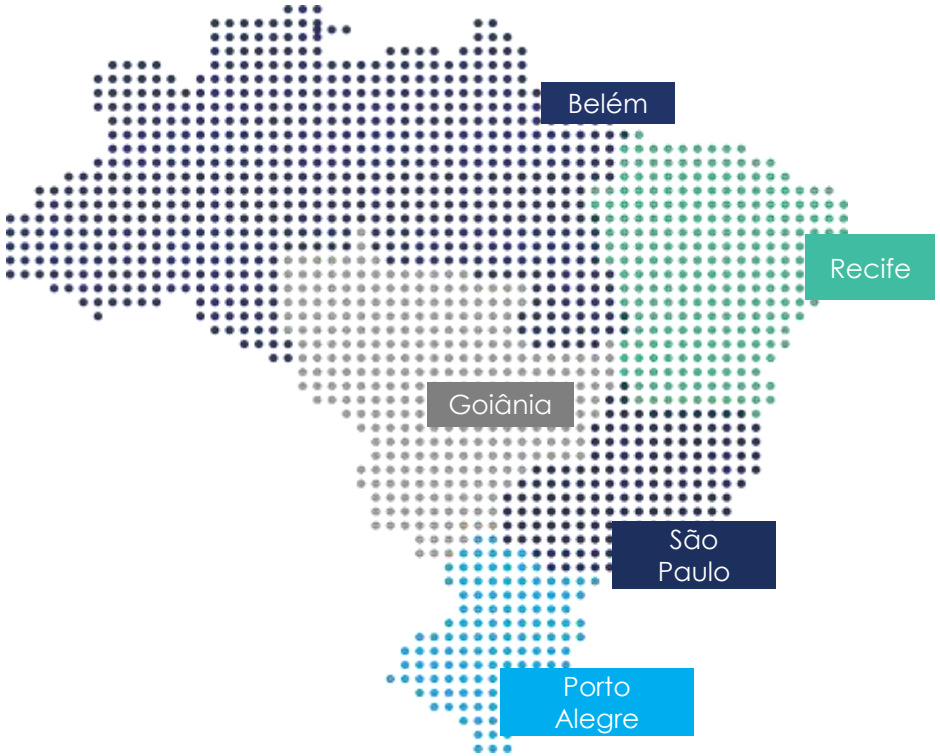




BRASIL
LUTS

- Estudo epidemiológico, transversal
- Homens e mulheres ≥ 40 anos (n = 5.184; 53% mulheres)
- 5 regiões geográficas
- Entrevistas por telefone (assistida por computador)





PREVALÊNCIA

	COM LUTS	SEM LUTS
Homens	68.7%	31.3%

Soler et al. Neurolurol Urodyn, 2017

BRASIL LUTS

SINTOMAS DE ARMAZENAMENTO		SINTOMAS DE ESVAZIAMENTO	
♂	20,6%	♂	10,4%
♀	36,4%	♀	4,4%

SINTOMAS MAIS PREVALENTES:

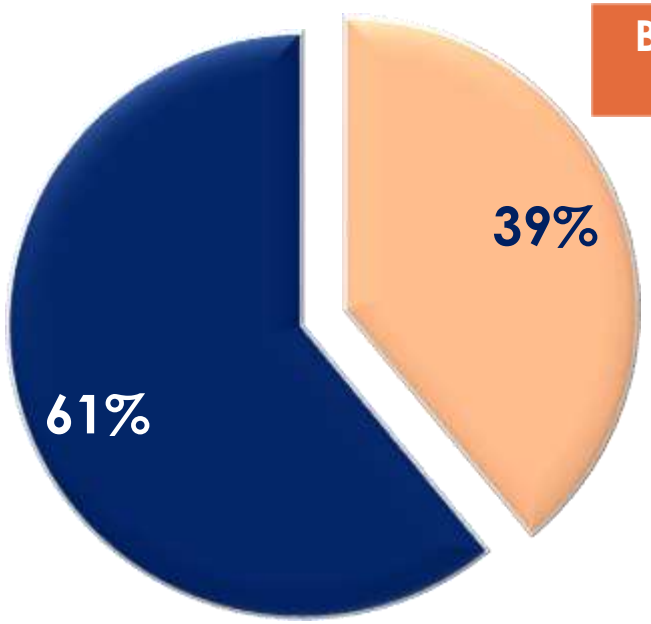
	♂	♀
Noctúria	**27,1%**	**32,4%**
Frequência urinária aumentada	**27,7%**	**32,3%**
Gotejamento terminal	**25,2%**	**17,7%**

Soler et al. Neurolurol Urodyn, 2017

BRASIL LUTS

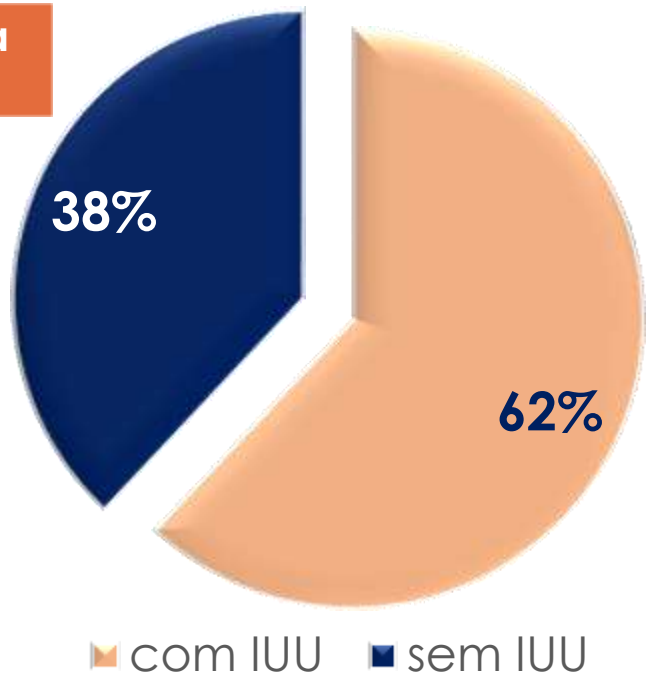
Prevalência de bexiga hiperativa

HOMENS **24,5%**



Bexiga hiperativa úmida vs seca

MULHERES **24,4%**

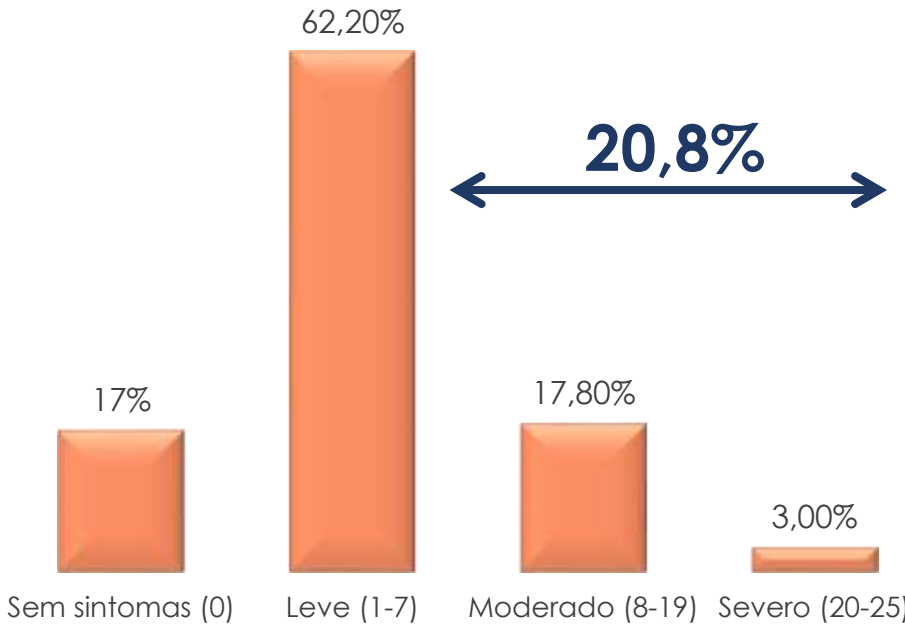


IUU = incontinência urinária de urgência

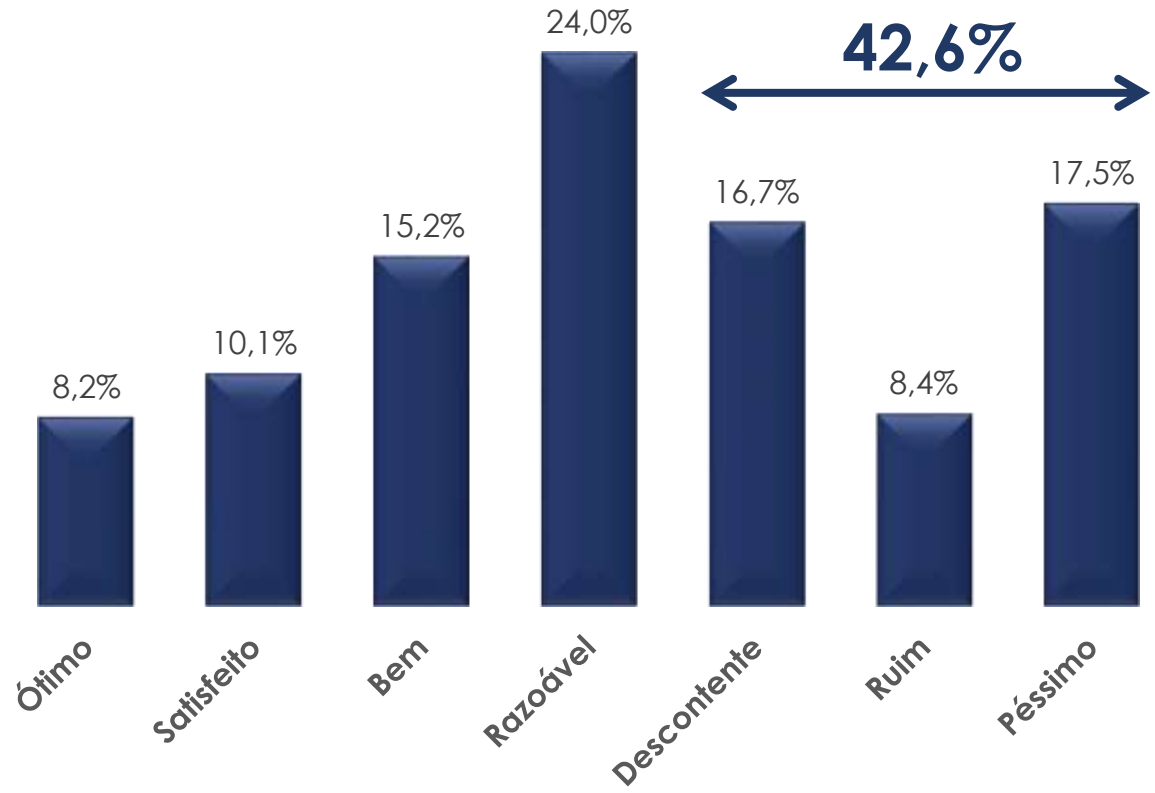
Soler et al. Neurolurol Urodyn, 2017

BRASIL
LUTS

IPSS



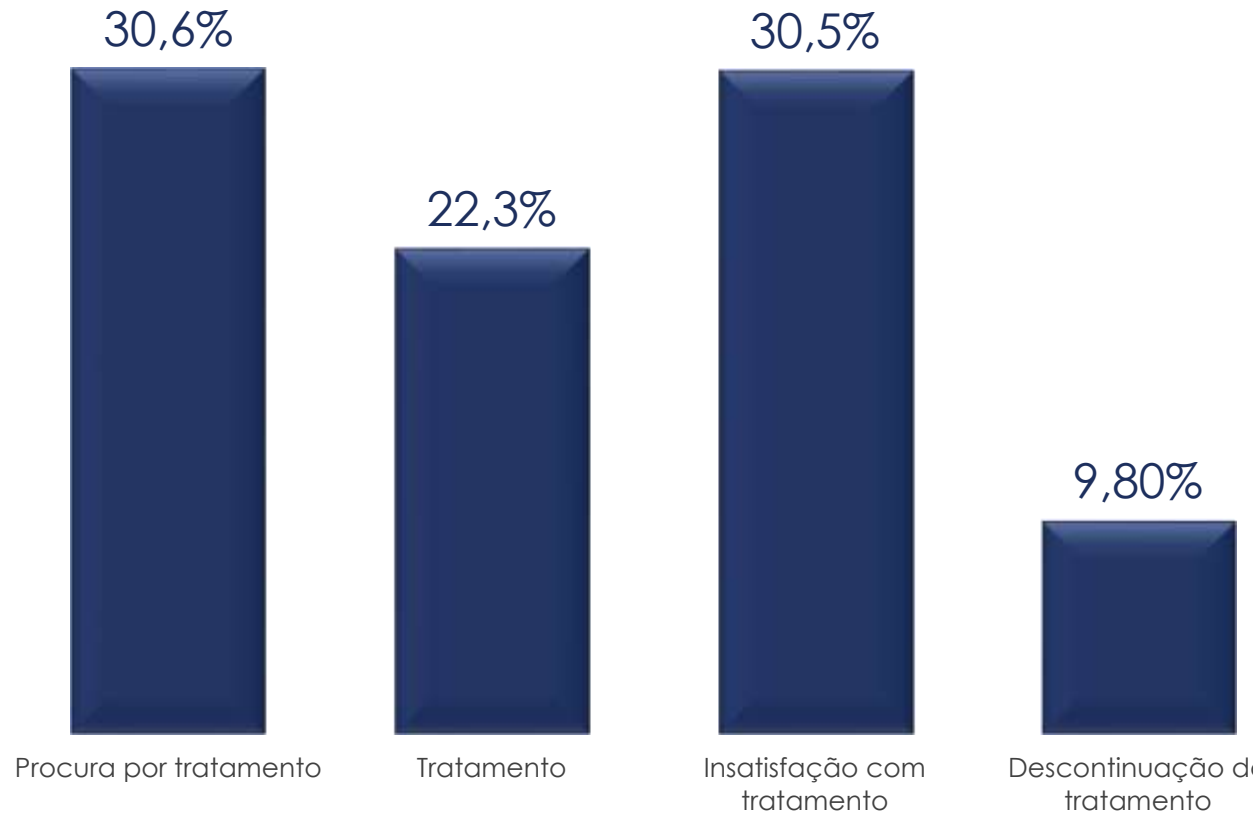
Qualidade de vida



Soler et al. Neurolurol Urodyn, 2017

BRASIL **LUTS**

Padrões de comportamento em relação a tratamento



Soler et al. Neurolurol Urodyn, 2019

Sintomas de esvaziamento

Alfa bloqueadores

I-5AR

Sintomas de armazenamento

Antimuscaríncos

Beta-3 agonistas

Disfunção erétil

I-5PDE

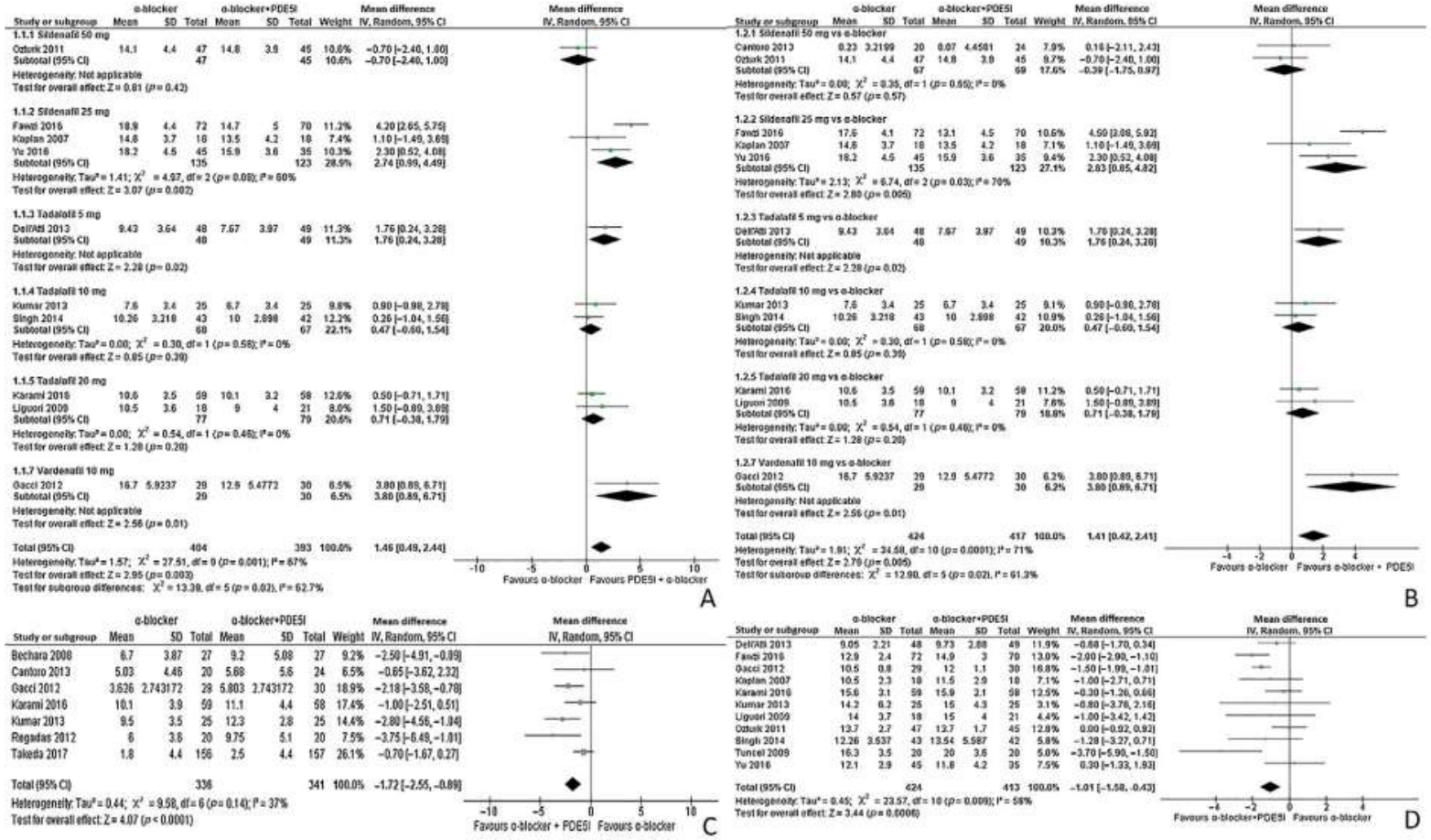
Combinações = Tratamento Personalizado

Alfa-bloqueador + I-5PDE

- LUTS importantes: melhora imediata
- Disfunção erétil

IPSS → p < 0.0001

Qmax → p = 0.0006



Kallidonis P et al. European Urology Focus, 2019

I-5PDE + I-5AR

- LUTS moderados – melhora não imediata
- Disfunção erétil
- Fatores de risco de progressão da doença
  - Idade
  - Volume prostático
  - IPSS
  - Qmax
  - RPM

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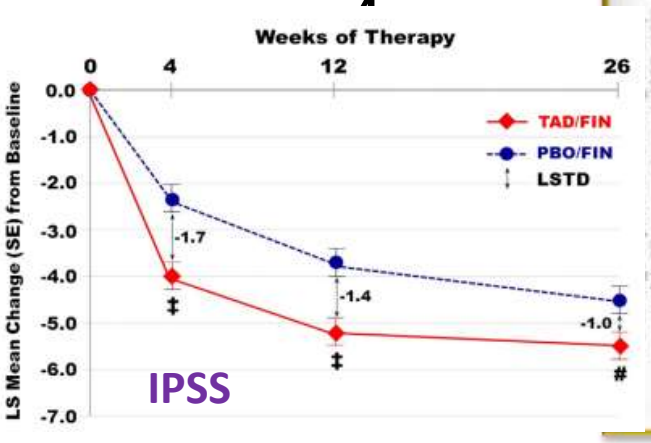
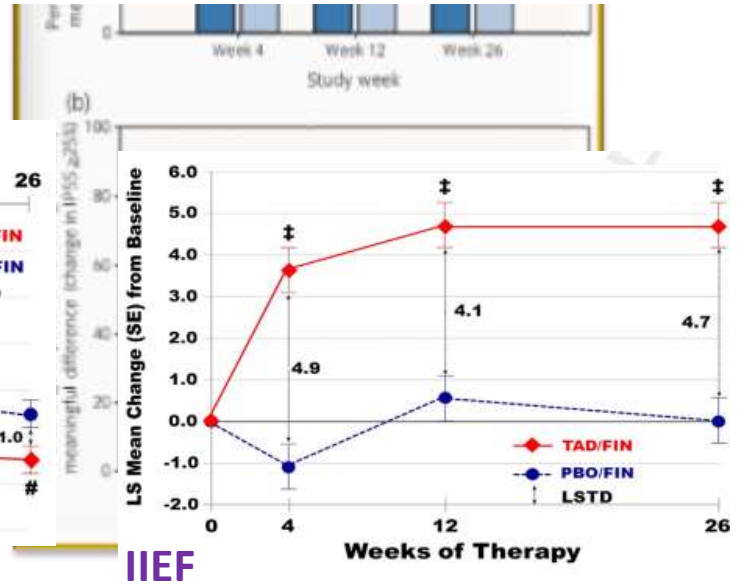
Cochrane Database of Systematic Reviews

Phosphodiesterase inhibitors for lower urinary tract symptoms consistent with benign prostatic hyperplasia

Cochrane Systematic Review - Intervention | Version published: 16 November 2018 see what's new

https://doi.org/10.1002/14651858.CD010060.pub2



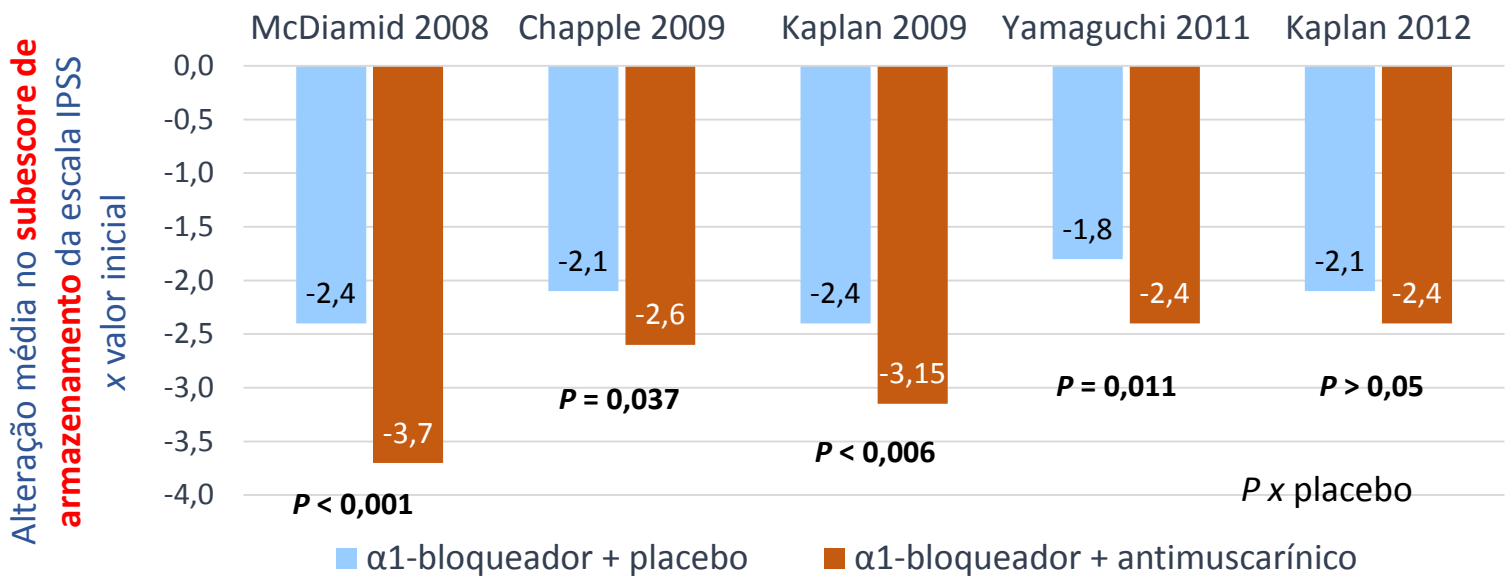


Casabé A et al. J Urol, 2014

Roehrborn CG et al. Int J Urol, 2015

Alfa-bloqueador + antimuscarínico

- LUTS mistos – componente de armazenamento importante ou refratário à monoterapia

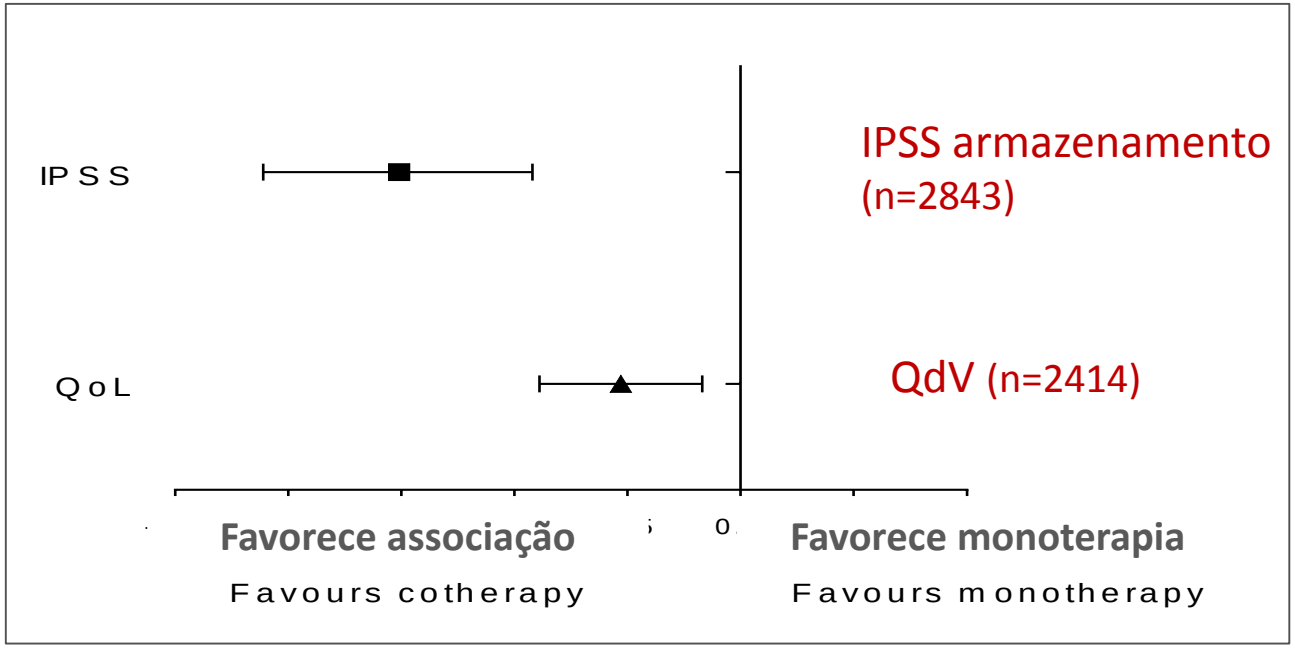


MacDiarmid SA et al. Mayo Clin Proc 2008; Chapple CR et al. Eur Urol 2009; Kaplan SA et al. J Urol 2009; Yamaguchi O et al. Urology 2011; Kaplan SA et al. BJU Int 2012

Alfa-bloqueador + antimuscarínico

- LUTS mistos – componente de armazenamento importante ou refratário à monoterapia

Meta-análise: 18 RCTs (4 semanas a 3 meses), para homens com LUTS moderados a severos



Hao N et al. Urology 2014;83:556-62

Alfa-bloqueador + antimuscarínico

- LUTS mistos – componente de armazenamento importante ou refratário à monoterapia

Patients	Soli plus TOCAS FDC (n = 1066), no. (%)
TEAEs	499 (46.8)
Mild	300 (28.1)
Moderate	159 (14.9)
Severe	40 (3.8)
Drug-related AEs	255 (23.9)
Mild	165 (15.5)
Moderate	72 (6.8)
Severe	18 (1.7)
Serious AEs	64 (6.0)
Total serious AEs, no.	86
Drug-related serious AEs	12 (1.1)
Total drug-related serious AEs, no.	12
Discontinued owing to AEs	42 (3.9)
Discontinued owing to drug-related AEs	28 (2.6)
Deaths	3 (0.3)
Drug-related deaths	0
Most frequent TEAEs (>1% patients)	
Dry mouth	132 (12.4)
Constipation	55 (5.2)
Dyspepsia	29 (2.7)
Hypertension	26 (2.4)
Urinary tract infection	24 (2.3)
Back pain	21 (2.0)
Bronchitis	12 (1.1)
Erectile dysfunction*	11 (1.0)
Nasopharyngitis	11 (1.0)

FDC = fixed-dose combination; Soli = solifenacin; TEAE = treatment-emergent adverse event; TOCAS = tamsulosin oral controlled absorption system.
Data given as number (percentage) unless otherwise indicated.
* Erectile dysfunction occurred in 11 patients (1.0%), while retrograde ejaculation and ejaculation failure, classified separately, occurred in another 7 patients (0.7%) and 2 patients (0.2%), respectively.

NEPTUNE II: Solifenacina + Tansulosina OCAS

Most frequent TEAEs (≥1% patients)	
Dry mouth	132 (12.4)
Constipation	55 (5.2)
Dyspepsia	29 (2.7)
Hypertension	26 (2.4)
Urinary tract infection	24 (2.3)
Back pain	21 (2.0)
Bronchitis	12 (1.1)
Erectile dysfunction*	11 (1.0)
Nasopharyngitis	11 (1.0)

RUA **0,7%**

Drake MJ et al. Eur Urol. 2015;67(2):262-70

TERAPIA TRIMODAL

Alfa-bloqueador + I-5AR + antimuscarínico

Yamanishi T et al. Int J Urol, 2017

RCT
32 centros
Tamsulosina 0,2mg > 8 sem

n 161

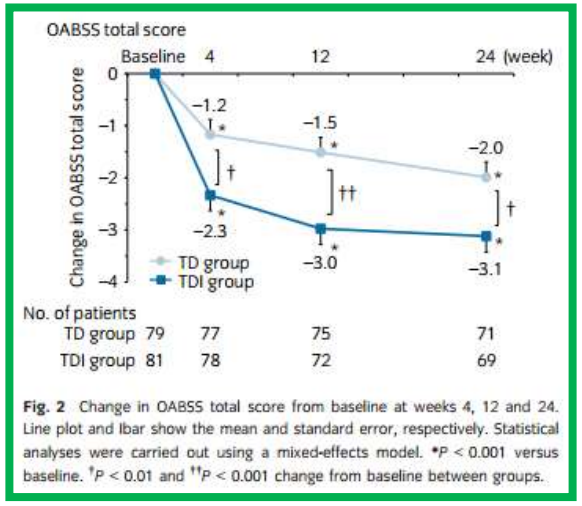
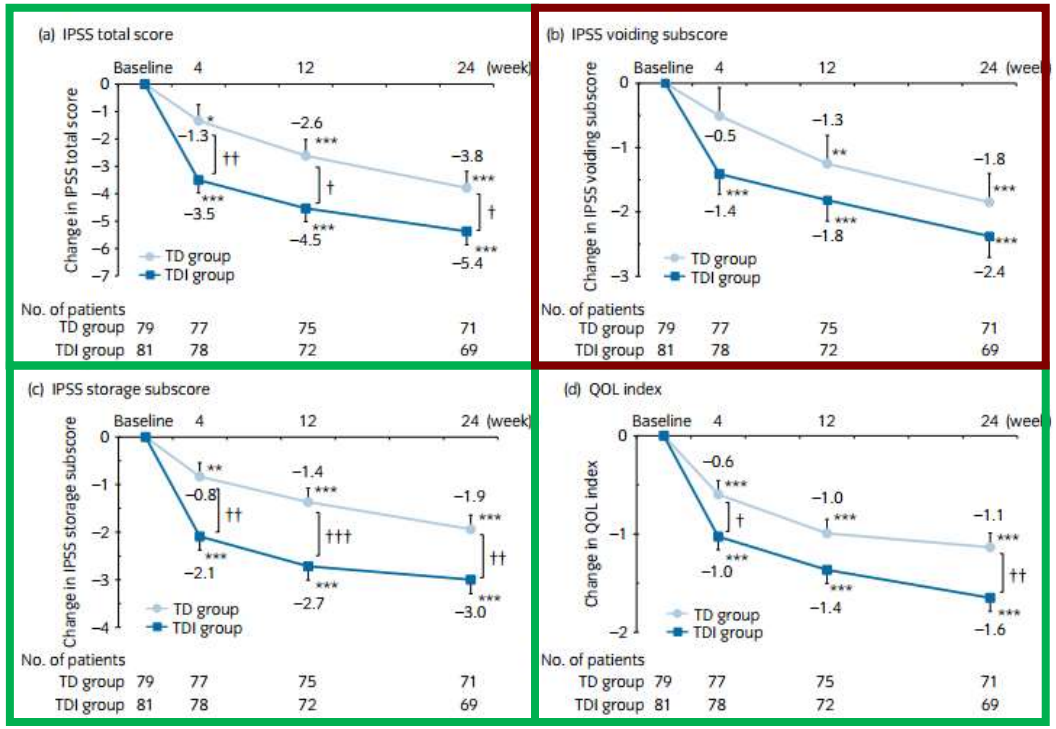


Fig. 2 Change in OABSS total score from baseline at weeks 4, 12 and 24. Line plot and Ibar show the mean and standard error, respectively. Statistical analyses were carried out using a mixed-effects model. *$P < 0.001$ versus baseline. †$P < 0.01$ and ††$P < 0.001$ change from baseline between groups.



Alfa-bloqueador + Beta-3 agonista

- LUTS mistos – componente de armazenamento importante ou refratário à monoterapia

Table 2. *Difference between groups in mean change from baseline at 8 weeks*

	Tamsulosin Monotherapy			Tamsulosin + Mirabegron			Difference in Mean Change from Baseline
	Mean ± SD Baseline	Mean ± SD 8 Wks	Mean Change from Baseline, p Value	Mean ± SD Baseline	Mean ± SD 8 Wks	Mean Change from Baseline, p Value	p Value
OABSS:							
Overall score	7.34 ± 2.67	6.47 ± 2.84	−0.87, 0.017	7.81 ± 2.48	5.60 ± 2.83	−2.21, <0.001	0.012
Q1 daytime frequency	0.68 ± 0.57	0.76 ± 0.63	0.08, 0.324	0.68 ± 0.52	0.65 ± 0.53	−0.03, 0.768	0.377
Q2 nighttime frequency	2.26 ± 0.79	2.05 ± 0.76	−0.21, 0.044	2.34 ± 0.74	2.05 ± 0.83	−0.29, 0.010	0.591
Q3 urgency	2.97 ± 0.88	2.42 ± 1.38	−0.55, 0.005	3.42 ± 1.00	2.07 ± 1.56	−1.34, <0.001	0.006
Q4 urgency incontinence	1.44 ± 1.40	1.23 ± 1.21	−0.21, 0.300	1.39 ± 1.44	0.81 ± 1.22	−0.58, 0.006	0.195
I-PSS:							
Overall score	12.94 ± 6.09	12.68 ± 8.13	−0.26, 0.770	13.97 ± 5.52	11.63 ± 5.91	−2.34, 0.011	0.099
Q1 incomplete emptying	1.39 ± 1.51	1.44 ± 1.63	0.05, 0.803	1.28 ± 1.29	1.18 ± 1.37	−0.11, 0.644	0.610
Q2 daytime frequency	2.18 ± 1.55	2.13 ± 1.69	−0.05, 0.832	2.63 ± 1.34	1.86 ± 1.33	−0.76, <0.001	0.025
Q3 intermittency	1.10 ± 1.37	1.36 ± 1.74	0.26, 0.324	1.34 ± 1.38	1.34 ± 1.54	0.00, —	0.466
Q4 urgency	2.34 ± 1.59	2.13 ± 1.49	−0.21, 0.300	2.57 ± 1.53	1.78 ± 1.49	−0.79, 0.002	0.069
Q5 weak stream	2.34 ± 1.58	2.00 ± 1.72	−0.34, 0.074	2.26 ± 1.68	2.31 ± 1.64	0.05, 0.841	0.222
Q6 straining	1.07 ± 1.26	1.28 ± 1.59	0.21, 0.440	1.13 ± 1.49	0.89 ± 1.22	−0.24, 0.404	0.254
Q7 nocturia	2.47 ± 1.10	2.31 ± 1.14	−0.16, 0.225	2.73 ± 1.13	2.26 ± 1.00	−0.47, 0.001	0.093
Voiding symptom subscore	4.52 ± 3.39	4.65 ± 4.14	0.13, 0.807	4.84 ± 3.34	4.63 ± 2.69	−0.21, 0.686	0.647
Storage symptom subscore	7.00 ± 3.30	6.57 ± 3.57	−0.42, 0.266	7.84 ± 2.73	5.81 ± 2.93	−2.03, <0.001	0.006
QOL index	3.34 ± 1.32	3.28 ± 1.39	−0.05, 0.834	3.97 ± 1.32	3.21 ± 1.33	−0.76, <0.001	0.020
Urine flow:							
Qmax	15.4 ± 7.2	14.1 ± 7.0	−1.4, 0.267	13.3 ± 7.6	13.0 ± 6.5	−0.4, 0.762	0.564
PVR	34.7 ± 28.7	38.5 ± 40.8	3.9, 0.579	37.8 ± 28.1	75.1 ± 74.1	37.3, 0.004	0.020

Alfa-bloqueador + Beta-3 agonista

Wada N et al. LUTS, 2015

TABLE 2. Clinical parameters before and after mirabegron

	Before mirabegron	8 weeks after mirabegron	*P*-value
OABSS	8.5 ± 2.3	4.7 ± 2.5	<0.001
Q1 (daytime frequency)	0.9 ± 0.4	0.5 ± 0.5	<0.001
Q2 (nocturia)	2.3 ± 0.7	1.7 ± 0.9	<0.001
Q3 (urgency)	3.6 ± 0.9	1.8 ± 1.5	<0.001
Q4 (urgency incontinence)	1.7 ± 1.4	0.7 ± 0.9	<0.001
IPSS	13.9 ± 5.0	9.1 ± 4.5	<0.001
Storage symptom score	7.9 ± 2.5	4.8 ± 1.9	<0.001
Voiding symptom score	4.7 ± 3.1	3.4 ± 2.4	0.01
QOL index	4.2 ± 0.9	2.6 ± 1.1	<0.001
Free uroflowmetry and measuring of post void residual			
Voided volume (mL)	135 ± 47	181 ± 102	0.01
Free Qmax (mL/sec)	10.7 ± 3.7	13.5 ± 6.4	<0.01
Free Qave (mL/sec)	5.5 ± 1.9	7.1 ± 3.3	<0.01
PVR (mL)	47 ± 38	63 ± 61	0.23
Voiding efficiency (%)	75 ± 15	74 ± 22	0.88
Filling cystometry			
MCC (mL)	170 ± 98	212 ± 95	0.01
Prevalence of DO *n* (%)	24 (92)	18 (69)	0.03*
Amplitude of the largest DO contraction (cmH_2O)	46 ± 27	34 ± 33	0.02
Bladder volume at the first involuntary contraction (mL)	90 ± 71	131 ± 80	0.03
Pressure-flow study			
PdetQmax (cmH_2O)	79 ± 31	68 ± 19	0.1
Qmax (mL/sec)	9.4 ± 3.4	10.5 ± 3.9	0.05
BOOI	60 ± 31	47 ± 21	0.09
BCI	126 ± 39	120 ± 27	0.45

Antimuscarínico + Beta-3 agonista

Drake MJ et al. Eur Urol, 2016

BESIDE

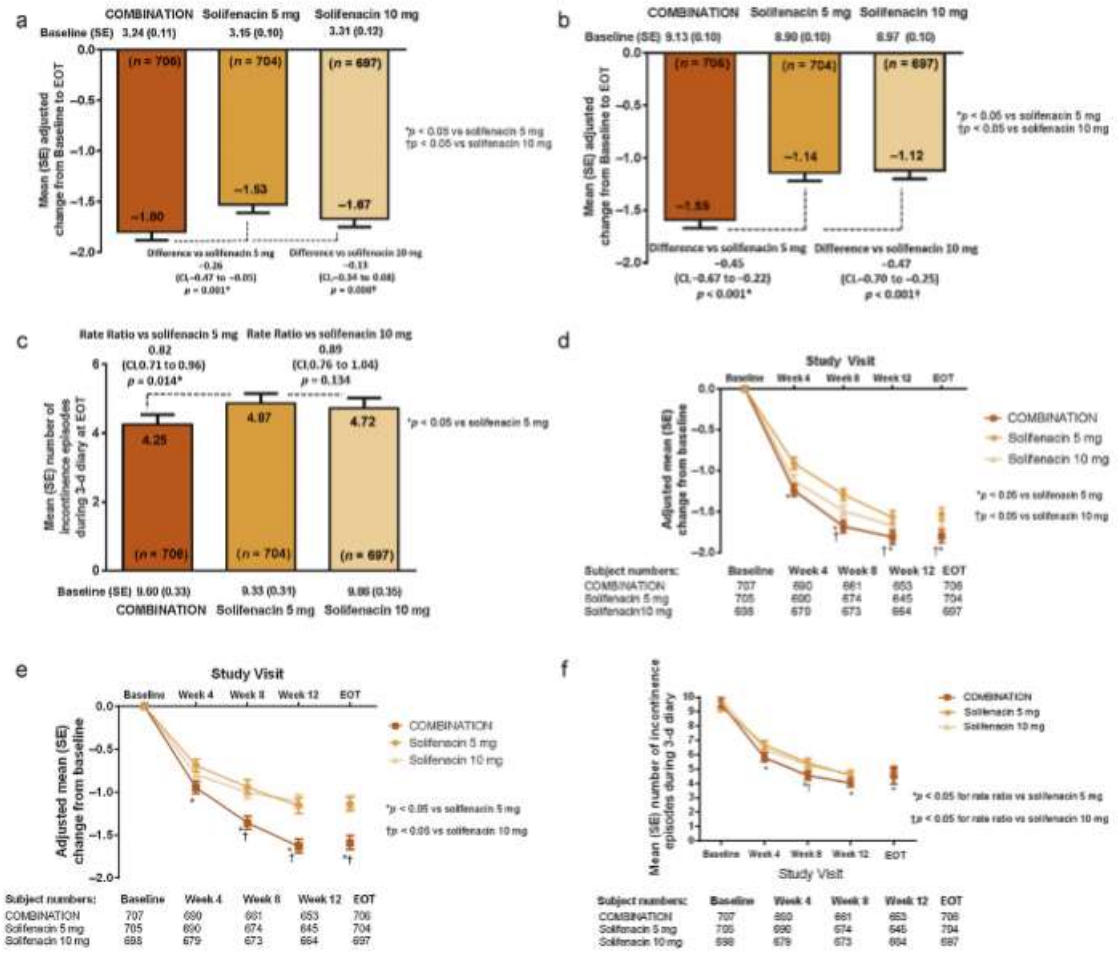
CONCLUSÃO

Combinação

Solifenacina 5 mg
+
Mirabegrona 25 / 50 mg

Mais efetiva que

Solifenacina 5mg ou Solifenacina 10mg, à exceção da NOCTÚRIA



Antimuscarínico + Beta-3 agonista

World J Urol
DOI 10.1007/s00345-016-1908-1

ORIGINAL ARTICLE

Combination treatment with mirabegron and solifenacin in patients with overactive bladder: exploratory responder analyses of efficacy and evaluation of patient-reported outcomes from a randomized, double-blind, factorial, dose-ranging, Phase II study (SYMPHONY)

P. Abrams[1] · C. Kelleher[2] · D. Staskin[3] · R. Kay[4] · A. Martan[5] · I. Mincik[6] · D. Newgreen[7] · A. Ridder[7] · A. Paireddy[7] · R. van Maanen[7]

Abrams P et al. World J Urol, 2017

- n 1306
- Duplo-cego / Randomizado
- ≥ 8micções/24h
- ≥ 1 episódio urgência/24h

SYMPHONY

CONCLUSÃO

Combinação

Solifenacina 5 / 10 mg
+
Mirabegrona 25 / 50 mg

Mais efetiva que

Solifencina 5mg ou placebo

Antimuscarínico + Beta-3 agonista

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‡‡

Herschorn S et al. BJU Int, 2017

SYNERGY

CONCLUSÃO

Combinação

Solifenacina 5 mg
+
Mirabegrona 25 / 50 mg

Mais efetiva que monoterapias

- Solifencina 5mg ou Mirabegrona

Segurança similar às monoterapias

Antimuscarínico + Beta-3 agonista

Chapple C et al. Eur Urol, 2018

EUROPEAN UROLOGY 74 (2018) 324–333

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eau
European Association of Urology

Platinum Priority – Incontinence

Editorial by Tom A.T. Marcelissen and Gommert A. Van Koeveringe on pp. 334–335 of this issue

Efficacy and Tolerability of Mirabegron Compared with Antimuscarinic Monotherapy or Combination Therapies for Overactive Bladder: A Systematic Review and Network Meta-analysis

Con Kelleher[a,], Zalmai Hakimi[b], Richard Zur[c], Emad Siddiqui[d], Khaled Maman[e], Samuel Aballéa[f], Jameel Nazir[d], Chris Chapple[g]*

- **MONOTERAPIAS X ASSOCIAÇÃO**
- Antimuscarínico + Beta-3 agonista
- **Revisão sistemática:**

CONCLUSÃO: combinação = mirabegrona 50mg

MENSAGENS

Combinação de drogas

Tratamento individualizado

Custo x benefício

Considerar “switch” terceira linha / cirurgia

Dr. Prost – Curitiba – 07/11/19