Pharmacological treatment of UI in older people

“Good” drugs for older persons are:

- effective
- reliably metabolized with no drug- drug interactions
- Tolerable, with few associated treatment emergent adverse events
- required only for the short term or, “as needed” for symptom control

The evidence – practice paradigm

Evidence

- Trials in applicable population
- Relevant results
- Critical analysis

Practice

- Underlying beliefs
- Empiric observation
- Experience of harms

Older persons views on what they'd undertake for treatment of UI

	Yes (n)	%	No (n)	%
Pelvic floor exercises for 6 months	75	67.0	37	33
Pelvic floor exercises for the rest of your life	41	38.7	65	61.3
Regular medication (pills) for the rest of your life	58	**50.4**	57	**49.6**
Medications (pills) to take just when you need them	94	**85.5**	16	**14.5**
Major surgical operation	14	12.6	97	87.4
Minor surgical operation	23	20.9	87	79.1
Long term catheter in your bladder	7	6.2	106	93.8
Learning to catheterize yourself	15	13.3	98	86.7
Wearing a pessary and removing it / cleaning it yourself*	18	22.5	51	64.6

* Women only

Wagg, A. 2015 unpublished data

Changes in Pharmacokinetics/Pharmacodynamics

Change in older adults	Clinical significance
Changes in gastric acidity affecting absorption	Potential reduction in absorption of weakly basic drugs Potential enhanced absorption of weakly acidic drugs*
Reduced carrier-mediated permeability	Reduced absorption of certain nutrients
Reduced first –pass metabolism	May or may not be relevant depending on the extent of first-pass metabolism and therapeutic indices
Reduced hepatic blood flow by 20-50%	Reduced clearance of drugs with high extraction ratios
Reduced phase I metabolising capacity	Reduction in metabolism of some drugs that undergo Phase I metabolism
Reduced renal function	Reduced elimination of drugs, depending on the renal function of the individual

* Where increased pH is present
PK = pharmacokinetics;
PD = pharmacodynamics

Reeve E, et al. *Expert Opin Drug Metab Toxicol*. 2015;11(4):491-508.

Pharmacological interventions from ICI - 6

- Short-term treatment with oxybutynin-IR has small to moderate efficacy in reducing urinary frequency and urgency UI when added to behavioural therapy in long term care residents. **(Level 2)**
- Low dose oxybutynin-ER does not cause delirium in cognitively impaired nursing home residents **(Level 1)**
- Oxybutynin IR has been associated with cognitive adverse effects in persons with dementia and/or Parkinson's disease **(Level 3)**, although the incidence and prevalence are unknown **(Level 4)**
- Oxybutynin has been associated with tachycardia **(Level 3)**, but not associated with QTc prolongation **(Level 3)** or ventricular arrhythmia **(Level 2)**
- Oxybutynin is less effective in persons with impaired orientation, cerebral cortical under-perfusion, and reduced bladder sensation **(Level 2)**
- Oxybutynin is less well tolerated, versus solifenacin, in older people **(level 2)**

Wagg, A. et al. "Incontinence in frail older persons" in Incontinence, Report of the 6th ICI 2017. ICS. Bristol

Pharmacological interventions from ICI - 6

- Tolterodine and solifenacin have been associated with cognitive impairment (**Level 3)**, although the incidence and prevalence are unknown. **(Level 4)**
- Solifenacin (5mg/day) is associated with no impairment of cognition in older persons with mild cognitive impairment versus placebo **(level 2)**
- Excessive anticholinergic load is associated with cognitive impairment in frail older adults **(level 3)**
- Anticholinerigc agents should be prescribed with due regard to underlying anticholinergic burden in older persons **(level 3)**
- The effect of cholinergic load on persons with mild dementia is uncertain **(level 3)**

Wagg, A. et al. “Incontinence in frail older persons” in Incontinence, Report of the 6th ICI 2017. ICS. Bristol

Pharmacological interventions from ICI - 6

- Fesoterodine is effective in ameliorating the symptoms of OAB in robust community dwelling and medically complex older people, identified by VES-13 **(level 1).**
- There is insufficient evidence to determine the efficacy, tolerability, and safety of the following agents in the frail elderly **(Level 4)**:
- **a)** Intravesical oxybutynin
- **b)** Transdermal oxybutynin
- **c)** Trospium
- **d)** Tolterodine
- **e)** Darifenacin
- **f)** Solifenacin
- **g)** Mirabegron
- **h)** Duloxetine
- **i)** Oral and topical oestrogen

NEW EVIDENCE AVAILABLE

Wagg, A. et al. "Incontinence in frail older persons" in Incontinence, Report of the 6th ICI 2017. ICS. Bristol

Prospectively gathered data on old (65+) and oldest old (75+)

Darifenacin

STUDY:

n = 400, mean age 72 years randomized (2:1) to receive 12 weeks of double-blind treatment with darifenacin (7.5 mg once daily for 2 weeks, then optional titration to 15 mg daily) or placebo

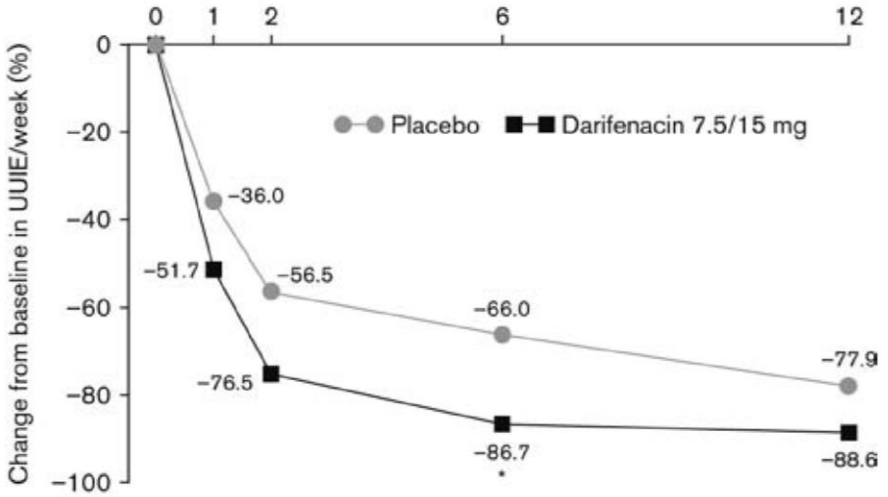
AE:

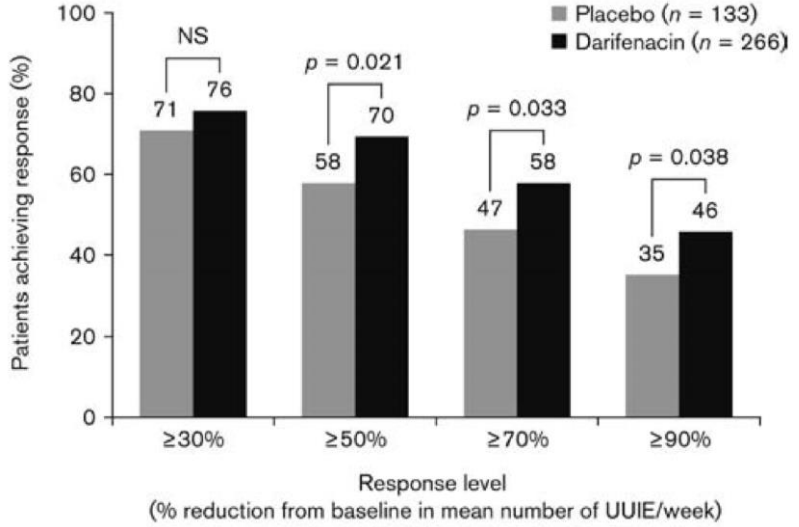
149 patients (56.0%) receiving darifenacin and 60 patients (45.1%) receiving placebo, of which 99 (37.2%) and 24 (18.0%) were considered to be related to the study drug, respectively

dry mouth – darifenacin 59 (22.2%), placebo 5 (3.8%) and constipation, darifenacin, 41 (15.4%) placebo, 11 (8.3%)

PROM:

Total OAB-q score treatment differences of 7.6 and 8.1 at Weeks 6 and 12, respectively in favour of darifenacin, $p < 0.001$ at both time points





Curr Med Res Opin. 2007 Oct;23(10):2347-58

Prospectively gathered data on old (65+) and oldest old (75+)

Fesoterodine

STUDY:

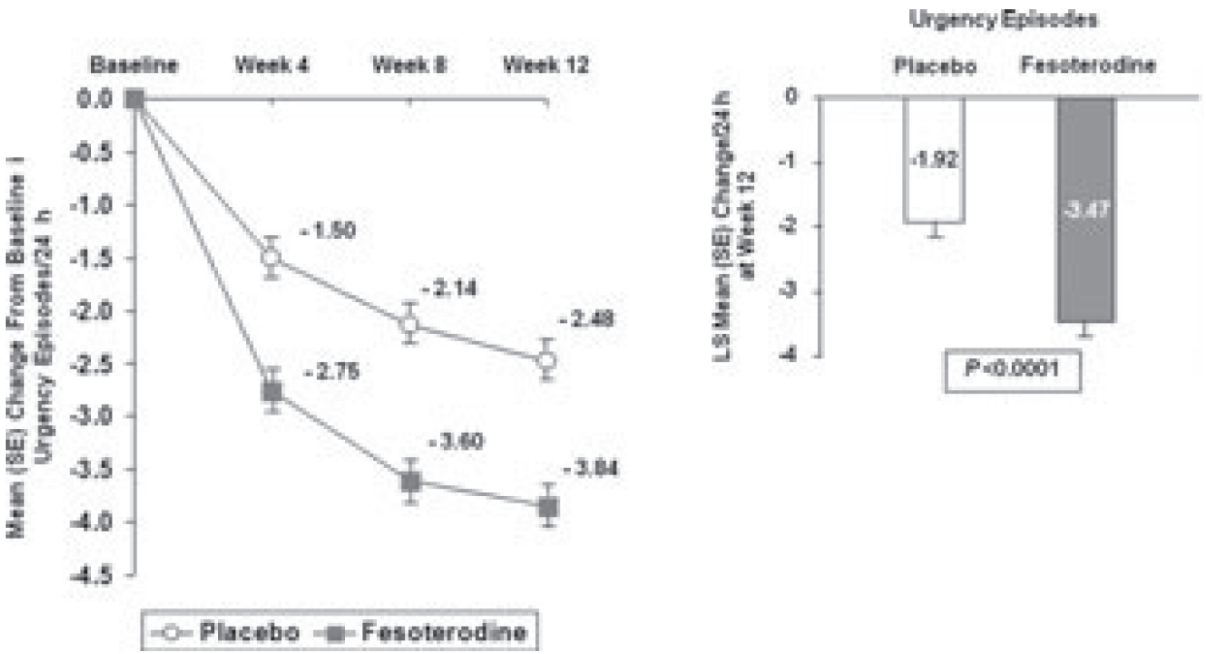
Fesoterodine or placebo for 12 weeks, with stratification according to age (>75 vs ≤75) and dosing time. Participants started on 4 mg and could increase to 8 mg at week 4 or 8 and de-escalate to 4 mg at week 8

AE:

Any AE – 36.1% placebo, 62.2% fesoterodine. Dry mouth fesoterodine 33.9%, placebo 5.3% (76% mild-moderate). No change in MMSE scores.

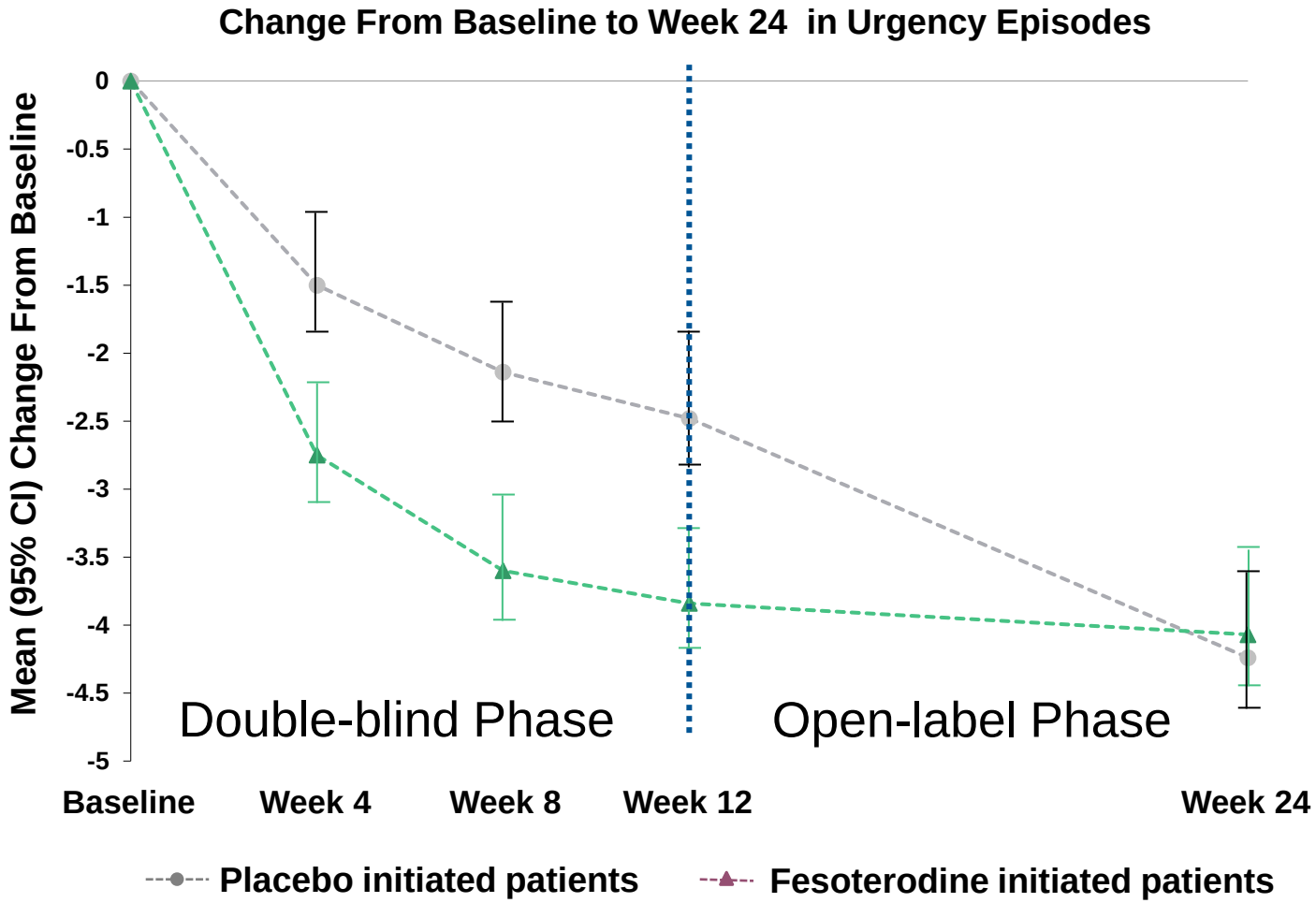
PROM:

The odds of response on the TBS, OAB-S, PPBC, and UPS were significantly greater in the fesoterodine group than placebo (P < .001 for TBS, OAB-S, and PPBC



J Am Geriatr Soc. 2013 Feb;61(2):185-93

SOFIA: Fesoterodine
Urgency Episodes *(Primary endpoint)*



- **By week 8, 64% of fesoterodine-treated participants opted for dose escalation.**
- **At week 12, all patients received fesoterodine**

Wagg et al. Neurourol Urodynam 2014;33:106–114.

Prospectively gathered data on old (65+) and oldest old (75+)

Fesoterodine in the vulnerable elderly

STUDY:

566 patients, mean age 75 (65-91) randomized 1:1 fesoterodine: placebo. All pts VES-13 >3. 50% of subjects in each group demonstrated significant levels of exhaustion and fatigue on the CES-D, 42% demonstrated impaired mobility on the TUG.

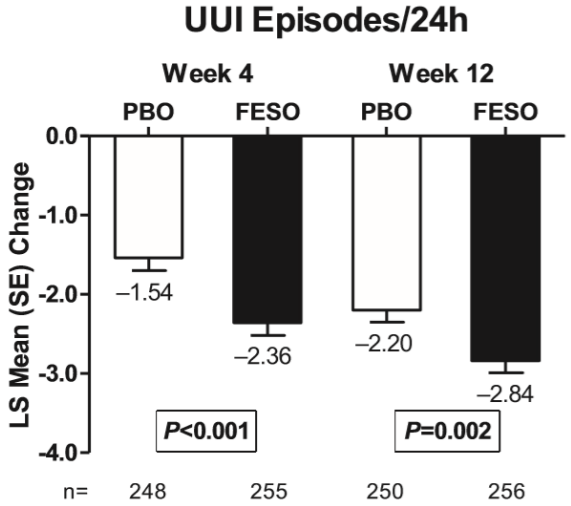
AE:

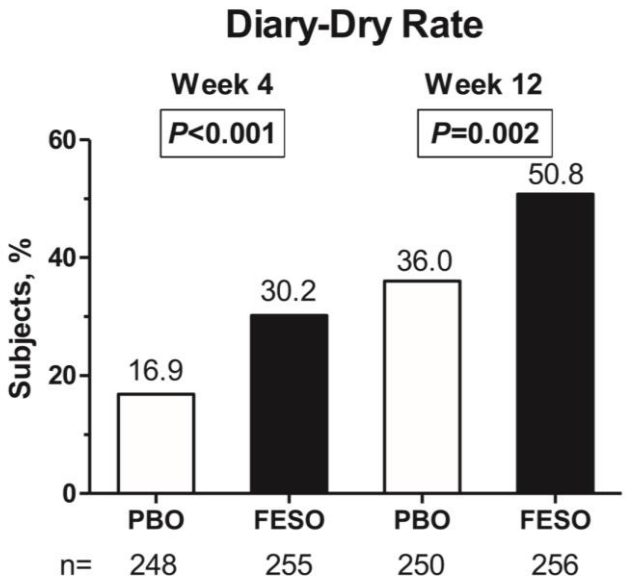
TEAE: placebo 42.7% fesoterodine 56.2%. Dry mouth, p:6.0% fesoterodine 23.5%, constipation, p: 4.3%, fesoterodine 11.1% urinary retention p: 0 fesoterodine 3.2% - 1/3 required catherization

No change in MMSE.

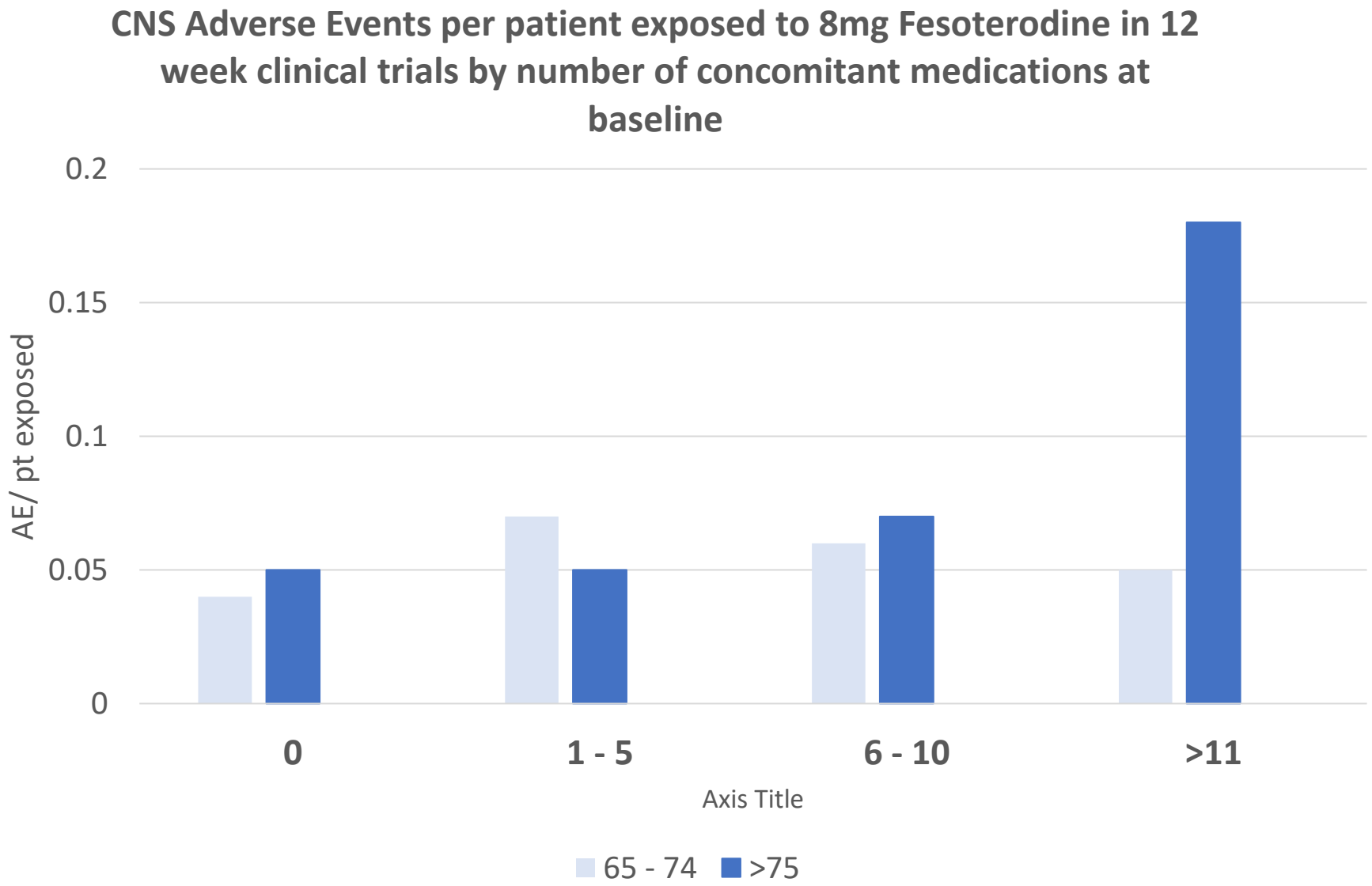
PROM:

12 week change in OAB symptom bother: placebo: -20.1(1.6), fesoterodine: -28.1 (1.6), p<0.005





J Urol 2014;191(2):395-404



Age Ageing. 2017 Jul 1;46(4):620-626.

Prospectively gathered data on old (65+) and oldest old (75+)

MIRABEGRON

STUDY:

12 week phase 4, double-blind, randomized, placebo-controlled study. Randomized 1:1 to mirabegron/placebo, stratified by age <75/≥75 years, 442 placebo, 445 mirabegron. Co-primary endpoints of micturition frequency and incontinence episodes/24h. Population “equivalent” to community dwelling elderly

Wagg et al. Presented at ICS 2018

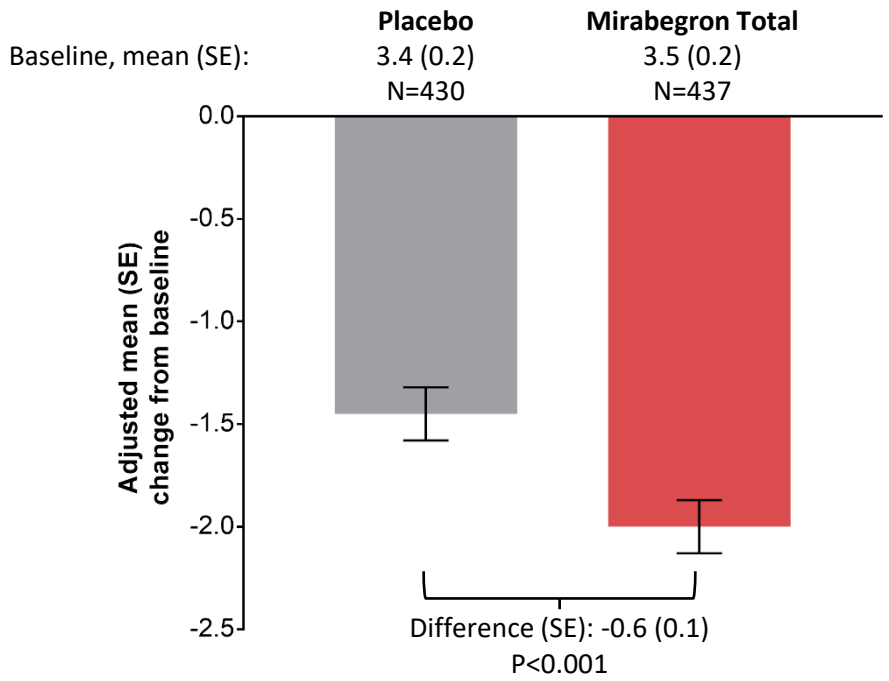
Baseline characteristics

	Placebo	Mirabegron 25 mg	Mirabegron 50 mg	Mirabegron Total
Demographic characteristics, SAF	N=442	N=226	N=219	N=445
Female sex, n (%)	324 (73.3)	168 (74.3)	149 (68.0)	317 (71.2)
Age group ≥75 years, n (%)	124 (28.1)	66 (29.2)	59 (26.9)	125 (28.1)
BMI (kg/m^2), n (%)				
<25	91 (20.6)	60 (26.5)	48 (21.9)	108 (24.3)
≥25–<30	150 (33.9)	84 (37.2)	73 (33.3)	157 (35.3)
≥30	201 (45.5)	82 (36.3)	98 (44.7)	180 (40.4)
Asian race, n (%)	54 (12.2)	58 (25.7)	1 (0.5)	59 (13.3)
Hispanic or Latino ethnicity, n (%)	43 (9.7)	27 (11.9)	14 (6.4)	41 (9.2)
OAB characteristics, FAS-I	N=431	N=220	N=217	N=437
Duration of symptoms (months), mean ± SD	119.9 ± 112.4	118.8 ± 119.2	123.4 ± 112.5	121.1 ± 115.8
Micturitions/24 h, n (%)[a]				
<8	20 (4.6)	1 (0.5)	11 (5.1)	12 (2.7)
≥8–<10	165 (38.3)	66 (30.0)	81 (37.3)	147 (33.6)
≥10–≤15	221 (51.3)	143 (65.0)	117 (53.9)	260 (59.5)
>15	24 (5.6)	10 (4.5)	8 (3.7)	18 (4.1)
Incontinence episodes/24 h, n (%)[b]				
>0–≤2	183 (42.5)	114 (51.8)	81 (37.3)	195 (44.6)
>2–<4	98 (22.7)	40 (18.2)	59 (27.2)	99 (22.7)
≥4	146 (33.9)	66 (30.0)	76 (35.0)	142 (32.5)

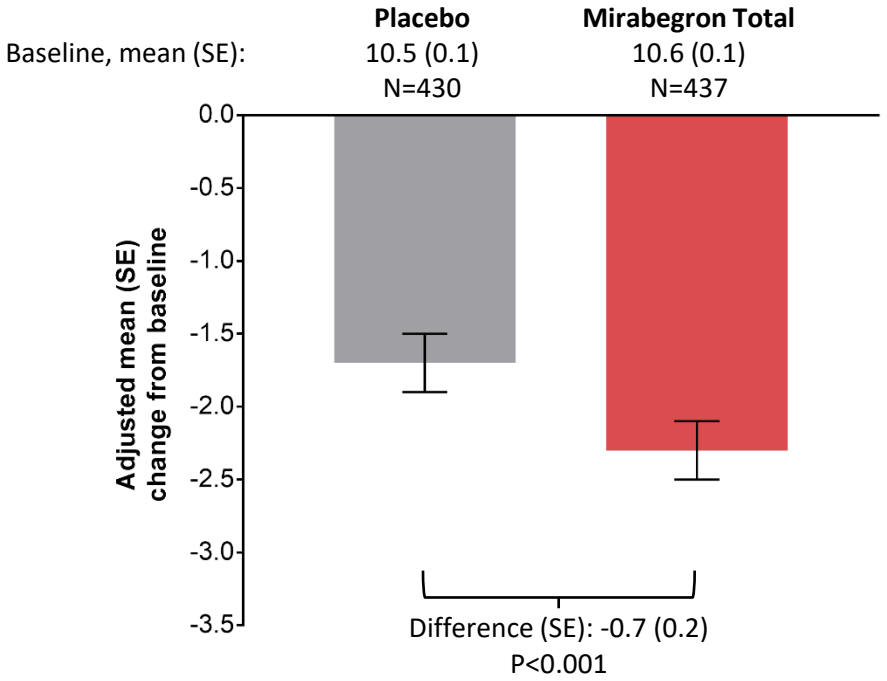
Safety analysis set (SAF): all randomized subjects who received ≥1 dose of study medication.
Full analysis set - incontinence (FAS-I): all patients who received ≥1 dose of study medication after randomization, reported ≥1 micturition at baseline and post-baseline, and ≥1 incontinence episode at baseline.
Treatment groups are according to the last treatment the patient received.
a. Data missing for 1 patient in the placebo group.
b. Data missing for 4 patients in the placebo group and 1 patient in the mirabegron 50 mg group.
BMI, body mass index; SD, standard deviation.

Co-primary endpoints: change in mean number of incontinence episodes and micturitions/24 h (FAS-I)

Change in mean number of incontinence episodes/24 h from baseline to EOT



Change in mean number of micturitions/24 h from baseline to EOT



Number of patients with zero incontinence episodes at EOT:

Placebo: 30.4% Mirabegron Total: 38.4%

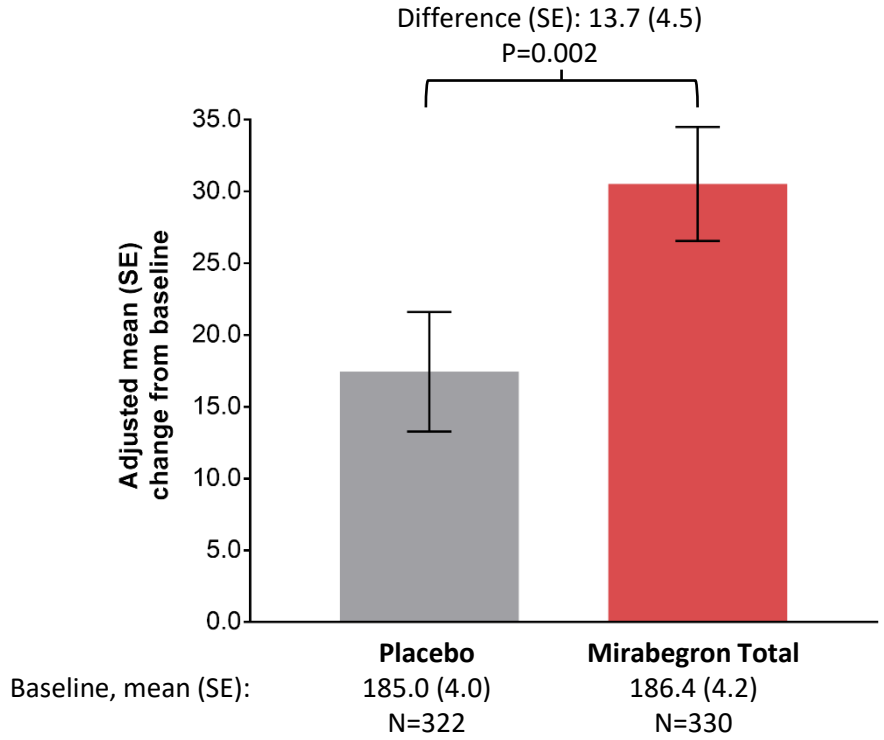
OR (95% CI): 1.50 (1.09–2.06); P=0.012

Adjusted mean changes generated from ANCOVA models with treatment group, sex, age group (<75 or ≥75 years), and country as fixed factors and baseline value as a covariate.

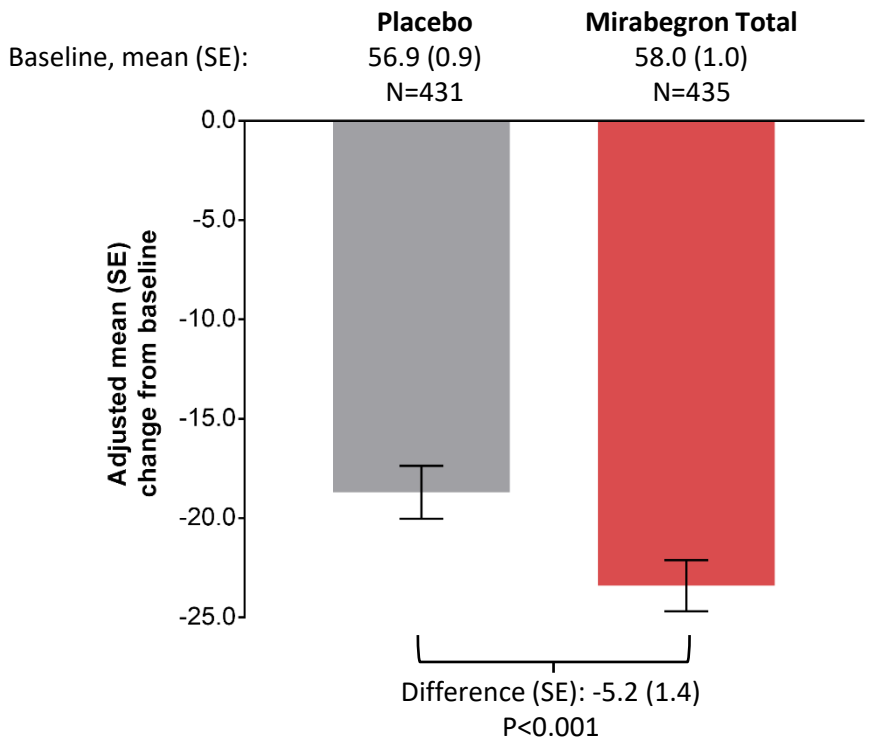
ANCOVA, analysis of covariance; SE, standard error.

Change in mean volume voided per micturition and OAB-q symptom bother (FAS-I)

Change in mean volume voided/ micturition (mL) from baseline to EOT

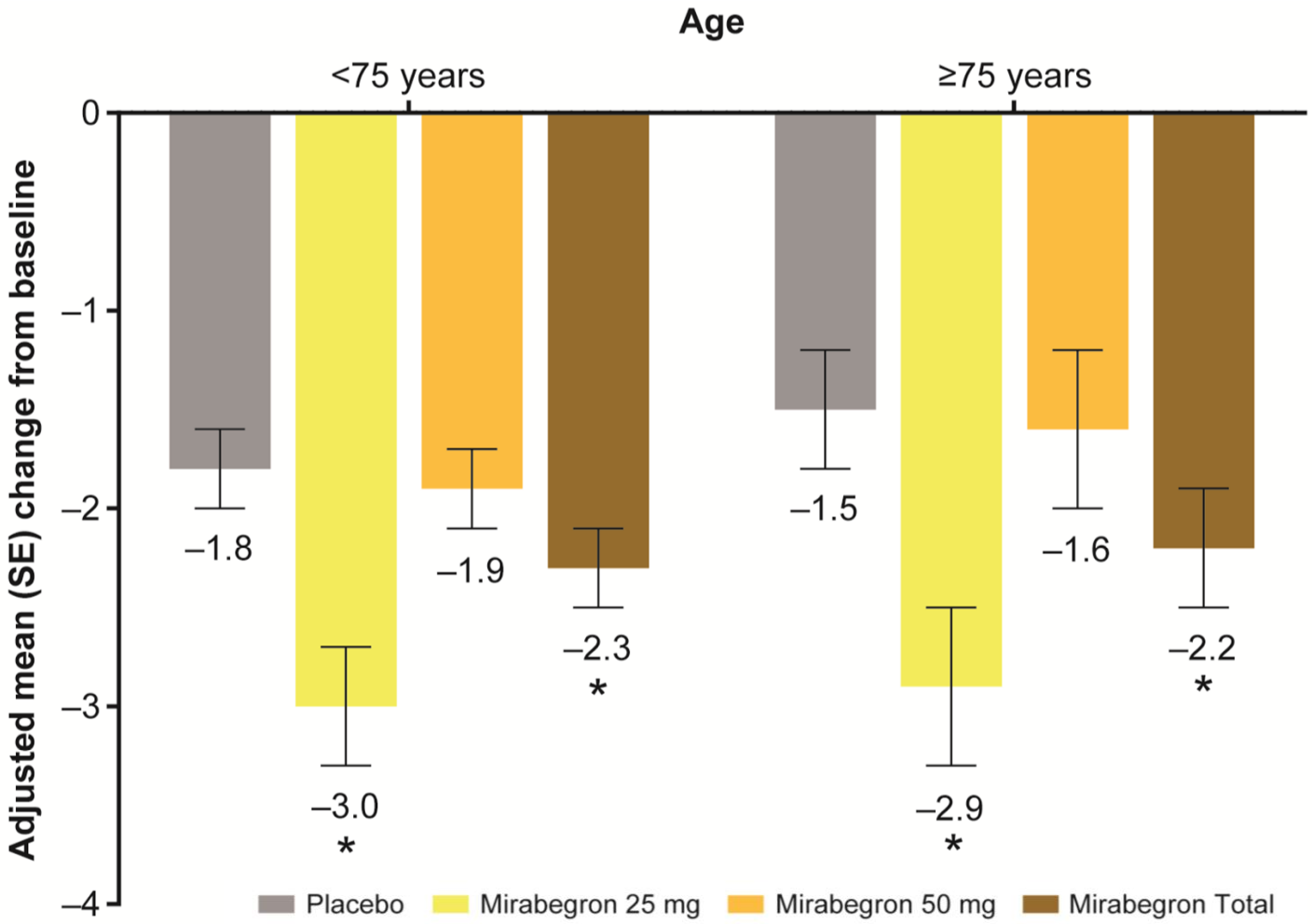


Change in OAB-q symptom bother score from baseline to EOT

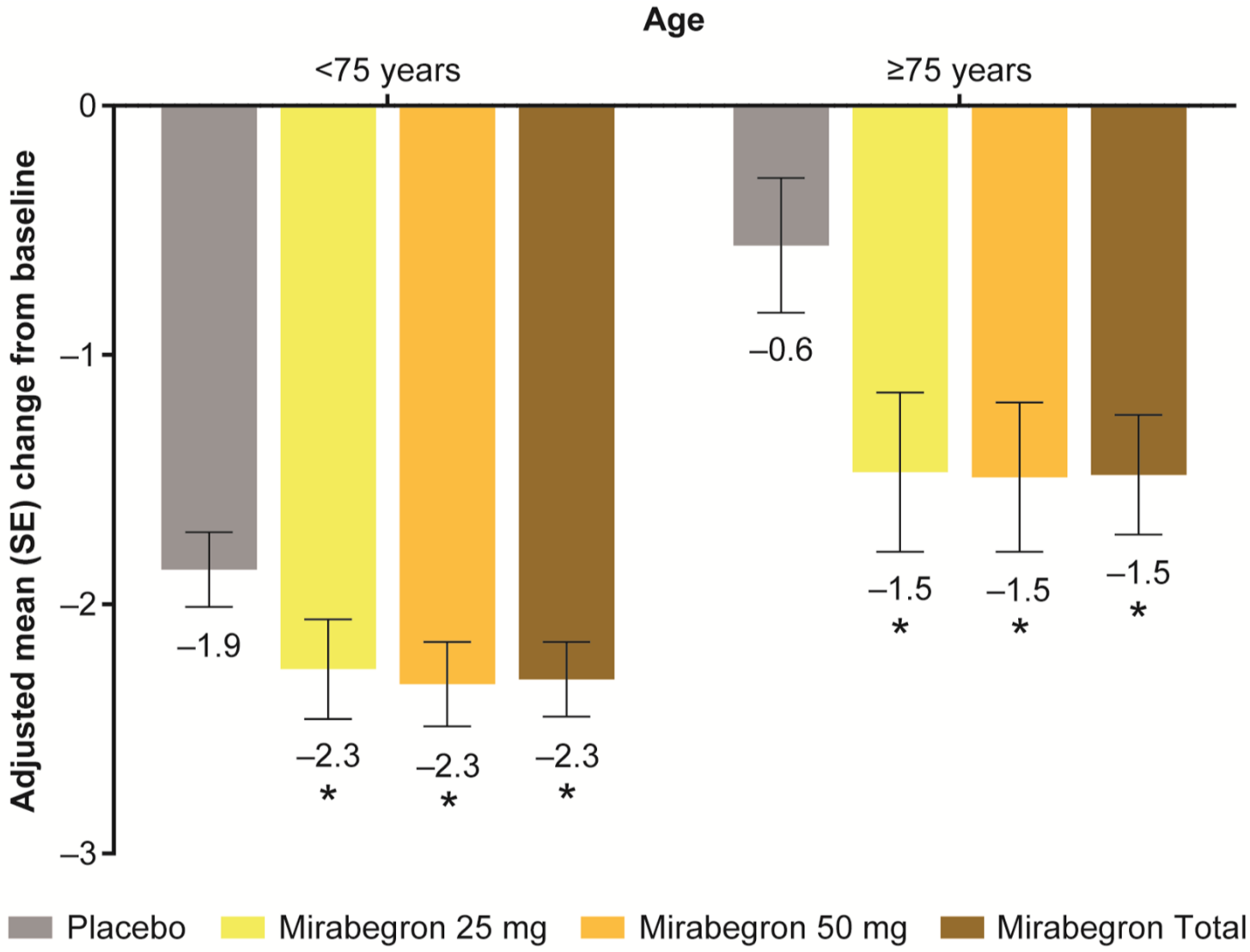


Adjusted mean changes generated from ANCOVA models with treatment group, sex, age group (<75 or ≥75 years), and country as fixed factors and baseline value as a covariate.
OAB-q, overactive bladder questionnaire.

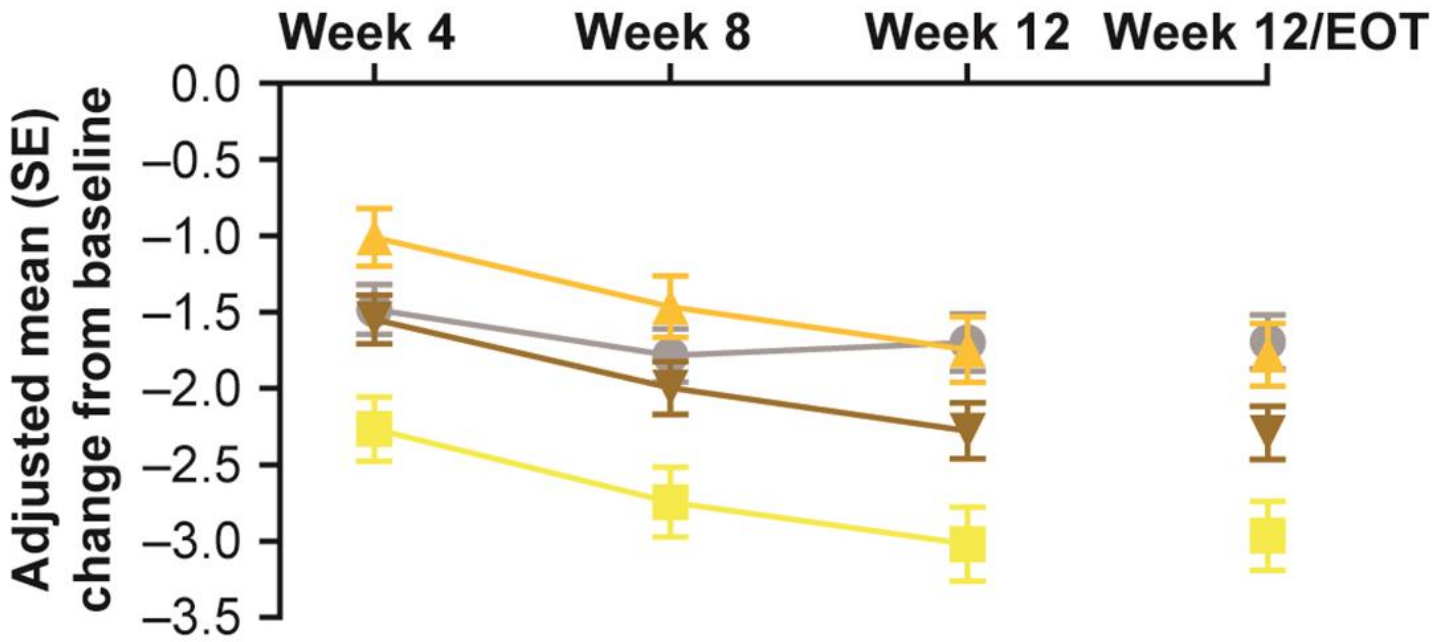
Micturitions/24h by age



Incontinence episodes/24h by age



Micturitions/24h

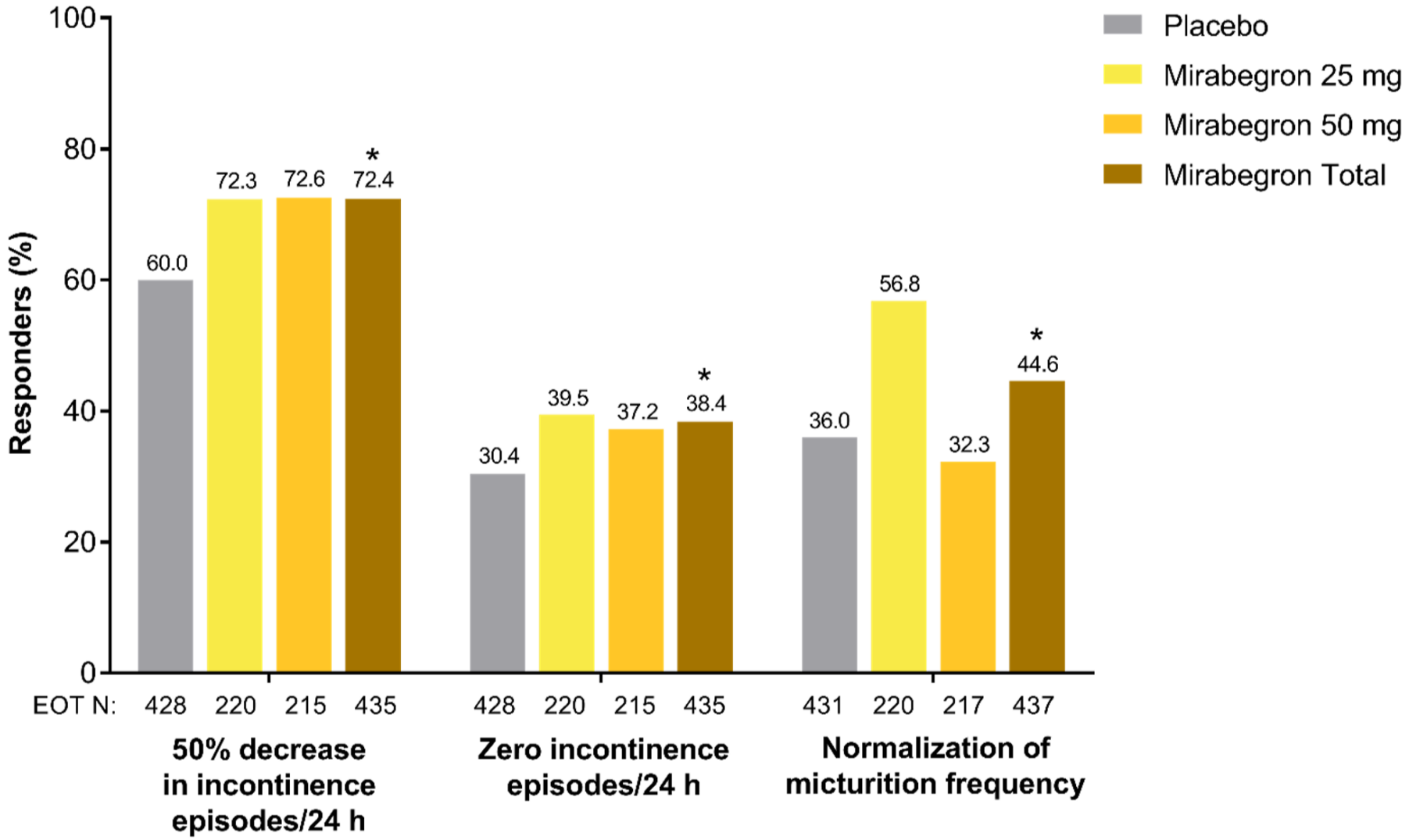


Difference (SE) vs placebo at EOT[a]

Mirabegron total	−0.7 (0.2)	$p < 0.001$
Mirabegron 25 mg	−1.3 (0.2)	$p < 0.001$
Mirabegron 50 mg	−0.1 (0.2)	$p = 0.705$

Placebo Mirabegron 25 mg Mirabegron 50 mg Mirabegron Total

Responder analysis at end of treatment – all wet patients



Treatment-emergent adverse events (SAF)

	Placebo, N=442	Mirabegron 25 mg, N=226	Mirabegron 50 mg, N=219	Mirabegron Total, N=445
≥1 TEAE[a]	174 (39.4)	100 (44.2)	109 (49.8)	209 (47.0)
Drug-related TEAEs	57 (12.9)	47 (20.8)	37 (16.9)	84 (18.9)
Serious TEAEs	12 (2.7)	7 (3.1)	8 (3.7)	15 (3.4)
Serious drug-related TEAEs	2 (0.5)	0	0	0
TEAEs leading to discontinuation	14 (3.2)	8 (3.5)	6 (2.7)	14 (3.1)
Most frequent TEAEs[b]				
Urinary tract infection[c]	31 (7.0)	16 (7.1)	9 (4.1)	25 (5.6)
Headache	12 (2.7)	15 (6.6)	8 (3.7)	23 (5.2)
Diarrhea	6 (1.4)	11 (4.9)	2 (0.9)	13 (2.9)
Fatigue	14 (3.2)	6 (2.7)	4 (1.8)	10 (2.2)
Upper respiratory tract infection	10 (2.3)	3 (1.3)	7 (3.2)	10 (2.2)
Nausea	6 (1.4)	7 (3.1)	1 (0.5)	8 (1.8)
Dizziness	7 (1.6)	1 (0.4)	5 (2.3)	6 (1.3)
Nasopharyngitis	10 (2.3)	3 (1.3)	2 (0.9)	5 (1.1)

No significant change in Montreal Cognitive Assessment score during the study

Mean (SD) score change from baseline to EOT: Placebo: 0.2 (2.3) Mirabegron Total: 0.1 (2.4)

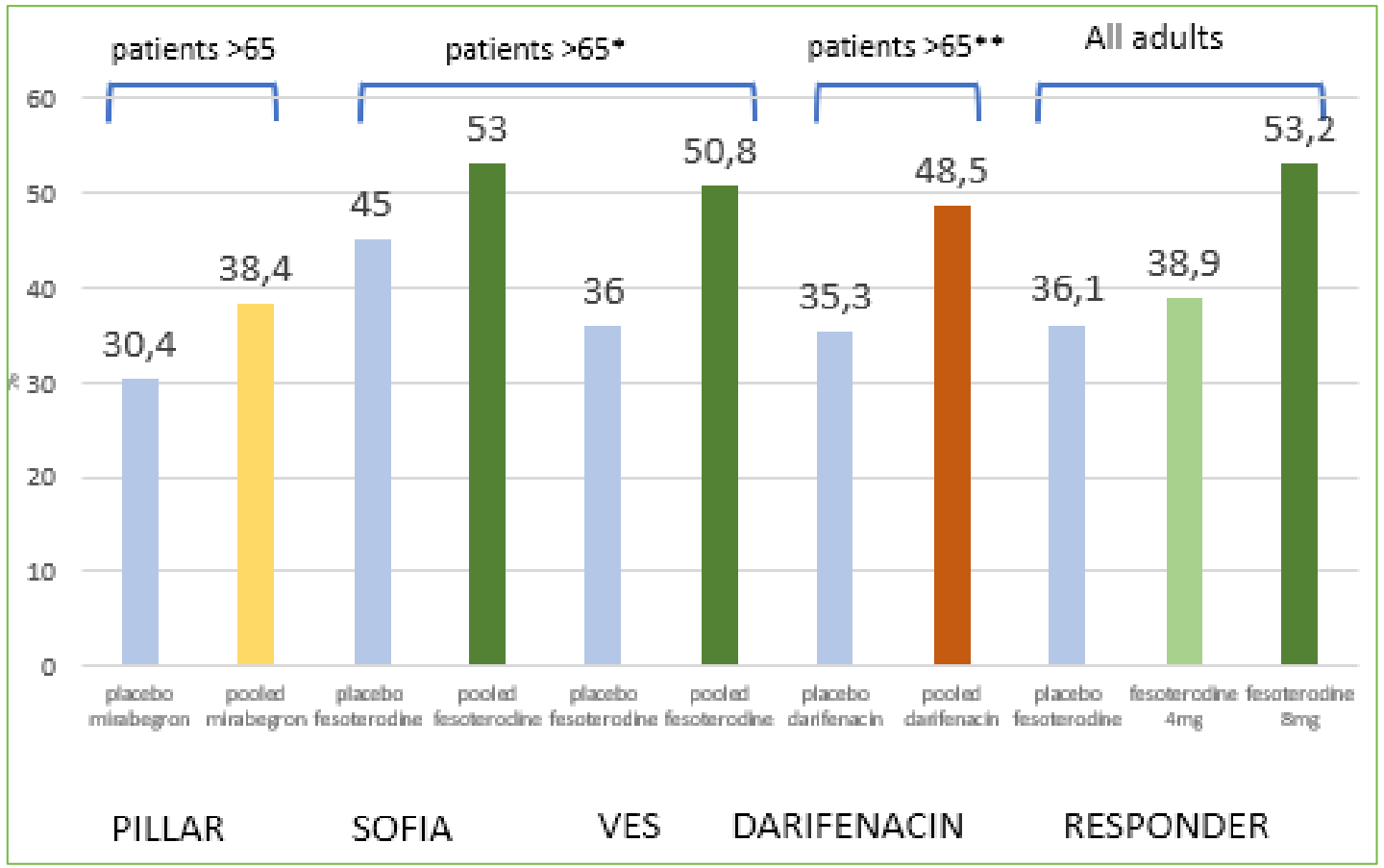
MedDRA version 20.1

a. Treatment-emergent adverse event (TEAE), an adverse event that started or worsened during the study period after first study medication dose.

b. Affecting ≥2% of any treatment group.

c. Escherichia urinary tract infection, streptococcal urinary tract infection, urinary tract infection, or urinary tract infection bacterial.

No incontinence at 12 weeks



* In SOFIA, patients had to be “dry” at both week 8 & 12 to be included

** in the darifenacin study, patients had to be dry for 3/7 to be included

Wagg A, ICS 2018 Abstr 268 (https://www.ics.org/2018/abstract/268) Wagg A et al. J Am Geriatr Soc. 2013 Feb;61(2):185-93 Dubeau CE et al. J Urol 2014;191(2):395-404
Chapple C et al. Curr Med Res Opin. 2007 Oct;23(10):2347-58 Wagg A, ICS 2018 Abstr 151 (https://www.ics.org/2018/abstract/151)

Age and Ageing Advance Access published June 23, 2015

Age and Ageing 2015; **0:** 1–11
doi: 10.1093/ageing/afv077

SYSTEMATIC REVIEW

Appropriateness of oral drugs for long-term treatment of lower urinary tract symptoms in older persons: results of a systematic literature review and international consensus validation process (LUTS-FORTA 2014)

Matthias Oelke[1], Klaus Becher[2], David Castro-Diaz[3], Emmanuel Chartier-Kastler[4], Mike Kirby[5,6], Adrian Wagg[7], Martin Wehling[8]

Rationale for Developing the Consensus on LUTS treatments

- Several drug classes with proven efficacy are available for treatment of LUTS[1,2,3]
  - i.e. α-blockers, antimuscarinics, 5α-reductase inhibitors, phosphodiesterase type 5 (PDE5) inhibitors, and β_3-agonists
- No systematic comparative study on the published evidence base for their appropriateness or inappropriateness for older (≥65 years) men and women[4]

1. Gormley EA, et al. American Urological Association guideline 2014
2. O'Leary MP. Am J Manag Care. 2006;12(Suppl 5):S129-40
3. McVary KT, et al. AUA guideline: management of benign prostatic hyperplasia (BPH) 2010
4. Oelke M, et al. Submitted 2015.

FORTA-LUTS

Selected drugs for the long-term treatment of lower urinary tract symptoms in older people

Drug class (drugs in alphabetical order)	Agent	FORTA class[a]	Number of raters[b]	Consensus coefficient, Round 1 (cut-off 0.800)	Expert ratings on a numerical scale: A = 1, B = 2, C = 3, D = 4 Round 1 (R1) Round 2 (R2) Mean (Mode)
5α-reductase inhibitors	Dutasteride	B	5	1.000	2.0; 2
	Finasteride	B	5	0.900	2.2; 2
α_1-blockers	Alfuzosin	D	5	0.900	3.8; 4
	Doxazosin	D	5	0.900	3.8; 4
	Silodosin	C	5	1.000	3.0; 3
	Tamsulosin	C	5	1.000	3.0; 3
	Terazosin	D	5	0.800	R1: 3.6; 4 R2: 3.8; 4
Antimuscarinics	Darifenacin	C	5	1.000	3.0; 3
	Fesoterodine	B	5	0.900	2.2; 2
	Oxybutynin standard dose/ immediate release	D	5	0.900	3.8; 4
	Oxybutynin low dose/extended release	C	4	1.000	3.0; 3
	Propiverine	D	5	0.700	R1: 3.4; 3 R2: 3.8; 4
	Solifenacin	C	5	1.000	3.0; 3
	Tolterodine	C	5	1.000	3.0; 3
	Trospium	C (B)	5	0.800	R 1: 2.4; 2 R 2: 2.6; 3
β_3-agonist	Mirabegron	C	5	1.000	3.0; 3
PDE5 inhibitor	Tadalafil	C	5	0.900	2.8; 3

LUTS, lower urinary tract symptoms.
[a]Original FORTA class in parentheses if different from consensus results.
[b]No changes between Rounds 1 and 2.

Oelke M et al. Age Aging 2015: 1-11

LUTS - FORTA

FORTA A (Absolutely) **Indispensable drug, clear-cut benefit in terms of efficacy/ safety ratio proven in elderly patients for a given indication**	
FORTA B (Beneficial) Drugs with proven or obvious efficacy in the elderly, but limited extent of effect or safety concerns	Dutasteride Fesoterodine Finasteride
FORTA C (Caution) Drugs with questionable efficacy/safety profiles in the elderly, to be avoided or omitted in the presence of too many drugs, lack of benefits or emerging side effects; review/find alternatives	Silodosin Tamsulosin Darifenacin Mirabegron Oxybutynin ER Solifenacin Tolterodine Trospium Tadalafil
FORTA D (Don't) Avoid in the elderly, omit first, review/find alternatives	Alfuzosin Doxazosin Terazosin Oxybutynin IR Propiverine

Caveat: limitations of evidence, evidence – practice gaps

Oelke M et al. Age Aging 2015; 44: 745 - 755.

Summary

- 2/3 of patients with OAB are >65
- Frailty and medical complexity are common
- Older people are more likely to need pharmacological management
- Older people are more likely to need higher doses of drug (cf mirabegron?)
- In some trials the treatment effect is slightly smaller in older than younger people
- The rate of CNS AE reported in clinical trials is low