PHARMACOLOGIC MANAGEMENT OF URINARY INCONTINENCE IN WOMEN

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POTENTIAL COI

- Advisor/Consultant to
- Avadel
- Axonics
- Allergan
- Medtronic
- Roivant
- Serenity
- Valencia

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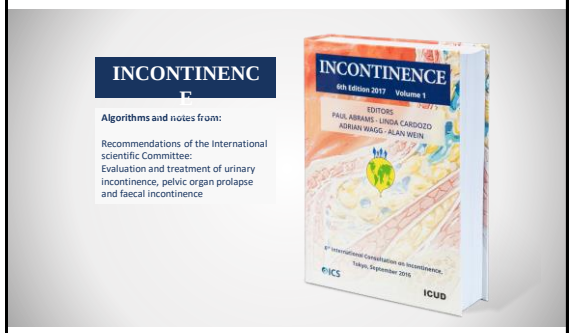
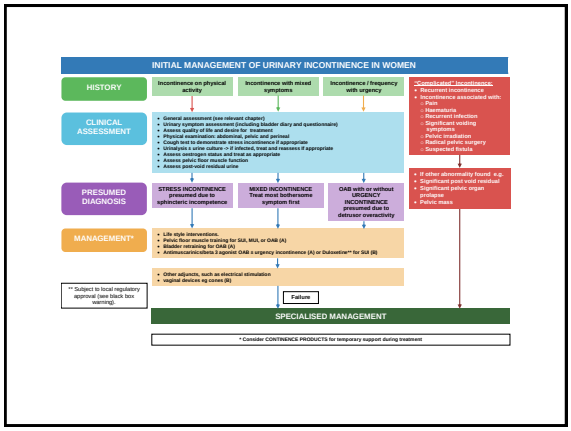
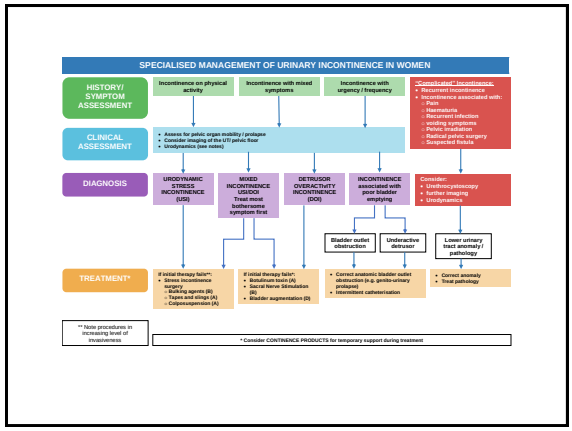






Potential Management Strategies : SUI

1. Increase intraurethral closure pressure during filling/storage, not during emptying

Duloxetine was withdrawn from the approval process in the US for SUI in women and will not be discussed

Potential Management Strategies: OAB/DO

1. Decrease activation on motor (efferent) or/and sensory (afferent) side of micturition cycle
2. Decrease residual urine and thereby increase FBC (functional bladder capacity)
3. Decrease urine volume and thereby increase time to activation
4. Treatment of associated/causative factors, e.g. bladder outlet obstruction, prolapse, SUI

OAB: Ideal Drug

- Block Urgency
- Block DO
- No effect on Voluntary Voiding
- Minimal AEs
- No safety issues

OAB Treatment Goals

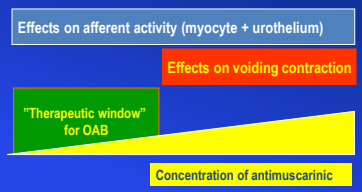
- Symptom relief
- Ultimate goal is symptom resolution

BUT

- Realistic goal is symptom improvement, not cure
- Patient expectations must be realistic

Antimuscarinics

Rationale for Use of Antimuscarinics in OAB



Karl Erik Andersson

ICI-2013, 2016(Committee 8)

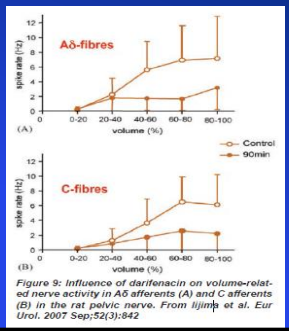


Figure 9: Influence of darifenacin on volume-related nerve activity in Aδ afferents (A) and C afferents (B) in the rat pelvic nerve. From Iijima et al. Eur Urol. 2007 Sep;52(3):842

Metrics for OAB Efficacy

- Frequency
- Volume Voided
- Urgency(episodes or severity)
- Urgency Incontinence Episodes
- Nocturia
- Quality of life(various metrics)

Reported Efficacy of Antimuscarinic Therapy (M+F)(Medians)

- UUI reduction: 55-80%; Placebo 35-40%
  - Drug/placebo=1.4-2
- Urgency reduction: 30-50%; Placebo 15-25%
  - Drug/placebo=2
- Frequency reduction: 15-20%
  - Placebo: 10-12%
- QOL increases – any metric

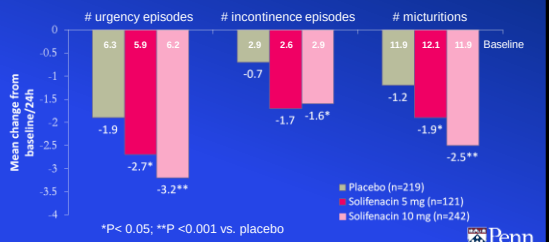
- Wein and Chapple. Overactive Bladder in Clinical Practice , 2012

Reported Adverse Events of Antimuscarinics

- Dry mouth: 9.6-35%
  - Placebo: 6-10%
- Constipation: <2-21.3%
- Cardiac: not in clinical doses
- Cognitive: ?oxybutynin IR
  - Inconsistent (LOE 2-EAU)

Antimuscarinic Monotherapy Improves Storage Symptoms

Meta-analysis: subgroup analysis of 582 men from 4 RCTs (phase III) evaluating the efficacy and safety of solifenacin (12 weeks) in male OAB patients (n=2,848)



*P< 0.05; **P <0.001 vs. placebo

Van Kerrebroeck P et al. Eur Urol Suppl 2005; 4: 61 (abstract 233)
Chapple CR et al. Int J Clin Pract 2006; 60: 959 - 966

Antimuscarinics: Efficacy

- To level the playing field, take measures from FDA approved labelling/product information
- FDA allows frequency, UUI episodes, volume voided, not urgency episodes. They generally use means, not medians
- Use solifenacin(revised 2016), fesoterodine (revised 2011)

Efficacy: Incontinence Episodes (Decrease) (%)

Solifenacin (5 mg)	2.6 (1.4) (54)	2.6 (1.6) (61)	-
Placebo	2.7 (0.8) (30)	3.2 (1.3) (41)	-
Solifenacin (10 mg)	2.6 (1.5) (55)	2.8 (1.6) (57)	2.9 (2.0) (69)
Placebo	2.7 (0.8) (30)	3.2 (1.3) (41)	2.9 (1.2) (41)
Fesoterodine (4 mg)	3.8 (2.06) (54)	3.9 (1.77) (45)	
Placebo	3.7 (1.2) (32)	3.7 (1.0) (27)	
Fesoterodine (8 mg)	3.7 (2.27) (61)	3.9 (2.42) (62)	
Placebo	3.7 (1.2) (32)	3.7 (1.0) (27)	

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Efficacy : Urinary Frequency (Decrease)

Solifenacin (5 mg)	12.1(2.2)(18%)	12.1 (2.4)	-
Placebo	12.2(1.2)(10%)	12.3 (1.7)	-
Solifenacin (10 mg)	12.3(2.3)(19%)	12.1 (2.9)	11.5 (2.4)
Placebo	12.2 (1.2)	12.3 (1.7)	11.8 (1.3)
Fesoterodine (4 mg)	11.6 (1.74)	12.9 (1.86)	
Placebo	12 (1.02)	12.2 (1.02)	
Fesoterodine (8 mg)	11.9 (1.94)	12.0 (1.94)	
Placebo	12.0 (1.02)	12.2 (1.02)	

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Efficacy: Volume voided (Increase)

Solifenacin (5mg)	150 (33)	148 (32)	-
Placebo	144 (7.4)	147 (11)	176 (13)
Solifenacin (10 mg)	147 (39)	146 (37)	174 (46)
Fesoterodine (4 mg)	160 (27)	152 (17)	
Placebo	150 (10)	159 (18)	
Fesoterodine (8 mg)	154 (33)	156 (33)	

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Efficacy of Antimuscarinic Agents vs Placebo from Published Trials

	Frequency Drug %	Frequency Placebo %	Ratio	UUI Drug %	UUI Placebo %	Ratio
Tolterodine ER (4 mg)* [1]	-22	-15	1.47	-71	-33	2.15
Oxybutynin ER (10 mg)**	NA	NA	NA	NA	NA	NA
Oxybutynin TDS (3.9 mg)* [2]	-18	-8.7	2.07	-75	-50	1.5
Trospium (20 mg BID)** [3]	-18.1	-8.4	2.15	-59	-44	1.34
Trospium (20 mg BID)** [4]	-20.5	-13.5	1.52	-63	-43	1.47
Solifenacin (5 mg)** [5]	-19.6	-12.8	1.53	-62.7	-42.5	1.48
Solifenacin (5 mg)** [6]	-17	-8	2.12	-65	-40	1.63
Solifenacin (10 mg)** [5]	-21.9	-12.8	1.71	-57.1	-42.5	1.34
Solifenacin (10 mg)** [6]	-20	-8	2.5	-63	-40	1.58
Darifenacin (7.5 mg)* [7]	-16.6	-9.1	1.82	-68.4	-53.8	1.27
Darifenacin (15 mg)* [7]	-17.4	-9.9	1.76	-76.8	-58.3	1.31

*Median % change for baseline **Mean % change from baseline. From V.Nitti

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Does Treatment Affect Urgency?

- Since URGENCY is the primary symptom of OAB and since virtually all studies on all drugs have mentioned data on reduction, it seems reasonable to use this as a "marker" of efficacy
- Answer is YES

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CONCLUSIONS AND RELEVANCE The use of AC medication was associated with increased brain atrophy and dysfunction and clinical decline. Thus, use of AC medication among older adults should likely be discouraged if alternative therapies are available.

JAMA Neurol. doi:10.1001/jamaneurol.2016.0580
Published online April 18, 2016.

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Antimuscarinics and Cognitive Dysfunction

- This concern seems to have ebbed among urologists since AUA 2016 but remains a matter of concern, especially in the elderly

ICI Assessments(International Consultation on Incontinence)

Table 1. ICI assessments 2008: Oxford guidelines (modified)

Levels of evidence

Level 1: Systematic reviews, meta-analyses, good quality randomized controlled clinical trials (RCTs)
Level 2: RCTs, good quality prospective cohort studies
Level 3: Case-control studies, case series
Level 4: Expert opinion

Grades of recommendation

Grade A: Based on level 1 evidence (highly recommended)
Grade B: Consistent level 2 or 3 evidence (recommended)
Grade C: Level 4 studies or "majority evidence"(optional)
Grade D: Evidence inconsistent/inconclusive (no recommendation possible) or the evidence indicates that the drug should not be recommended

ICI 2016, INCONTINENCE 2017

	Level of Evidence	Grade of Recommendation
Antimuscarinic drugs		
Atropine, hyoscyamine	3	C
Darifenacin	1	A
Fesoterodine	1	A
Imidafenacin	1	A
Propantheline	2	B
Solifenacin	1	A
Tolterodine	1	A
Trospium	1	A
Drugs with mixed actions		
Oxybutynin	1	A
Propiverine	1	A
Flavoxate	2	D

All 1-A Antimuscarinics, and Combined Action(OAB/DO)(ICI 2016

Documented beneficial effect

Acceptable side effect profile

Antimuscarinics (EAU 2017)

- "Mainstay of treatment for UUI"
- Problem: Lack of standard definition of improvement
- Problem: Lack of use of "cure" as primary outcome
- "In general, systematic reviews note that the overall treatment effect…is usually small but larger than placebo"

Antimuscarinics (EAU 2017)

"…ER and IR formulations…offer clinically significant short term cure and improvement rates for UUI compared with placebo"

"…IR formulations tend to be associated with more side effects…"

"…every drug where cure of UI was available showed superiority to placebo…but the absolute effect of the size is small"

Antimuscarinics: EAU(2017)

Summary of evidence	LE
There is limited evidence that one antimuscarinic drug is superior to an alternative antimuscarinic drug for cure or improvement of urgency urinary incontinence.	1b
Higher doses of antimuscarinic drugs are more effective to cure or improve urgency urinary incontinence, but with a higher risk of side effects.	1b
Once daily (extended release) formulations are associated with lower rates of adverse events compared to immediate release ones, although similar discontinuation rates are reported in clinical trials.	1b
Dose escalation of antimuscarinic drugs may be appropriate in selected patients to improve treatment effect although higher rates of adverse events can be expected.	1b
Transdermal oxybutynin (patch) is associated with lower rates of dry mouth than oral antimuscarinic drugs, but has a high rate of withdrawal due to skin reaction.	1b

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Recommendations for Antimuscarinics (EAU 2017)

Recommendations	GR
Offer antimuscarinic drugs for adults with urgency urinary incontinence who failed conservative treatment.	A
Consider extended release formulations in patients who do not tolerate immediate release antimuscarinics.	A
If antimuscarinic treatment proves ineffective, consider dose escalation or offering an alternative treatment.	B
Consider using transdermal oxybutynin if oral antimuscarinic agents cannot be tolerated due to dry mouth.	B
Offer and encourage early review (of efficacy and side effects) of patients on antimuscarinic medication for urgency urinary incontinence.	C

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Antimuscarinic Agents EAU Guidelines(2017)

No consistent evidence that one is superior to another for cure or improvement of UUI or QOL (LOE 1a)

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Antimuscarinics

- Efficacy similar
- Differing characteristics exist and have given rise to various marketing strategies and comparisons (our best vs your worst), mostly having to do with theoretical rather than real edges
- Decisions revolve around perceived tolerability, safety, and efficacy (latter based on personal experience)

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Combined Behavioral and Drug Therapy for Urge Incontinence

" Whether drug and behavioral therapy are combined from the onset or used sequentially in a stepped program, the evidence from the present study is that two interventions combined have a greater potential to enhance outcome than could be achieved by either intervention alone."

Burgio K et al. JAGS. 2000;48:370-374.

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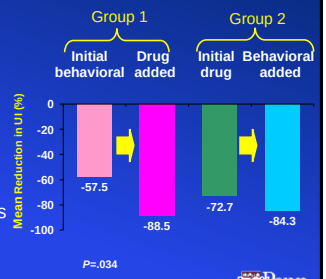
Behavioral Modification Is Effective, But Combination With Drug Therapy Works Better

- Behavioral modification
  - Education
  - Diet
  - Timed voiding
  - Delayed voiding
  - Pelvic floor exercises



Burgio KL et al. J Am Geriatr Soc. 2000;48:370-374.

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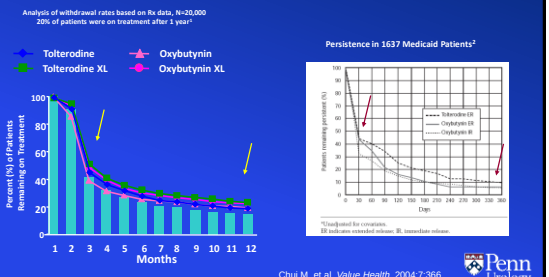
Antimuscarinics for OAB: Poor Persistence



Chui M, et al. *Value Health.* 2004;7:366.

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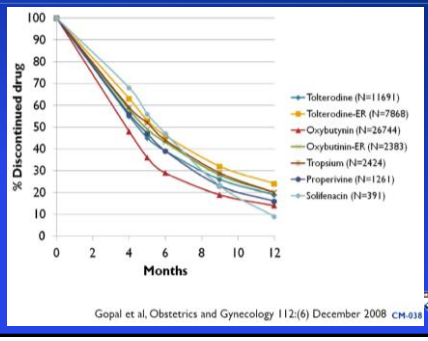
Antimuscarinic therapy of OAB Time to discontinuation - US



Gopal et al, Obstetrics and Gynecology 112:(6) December 2008 CM-038

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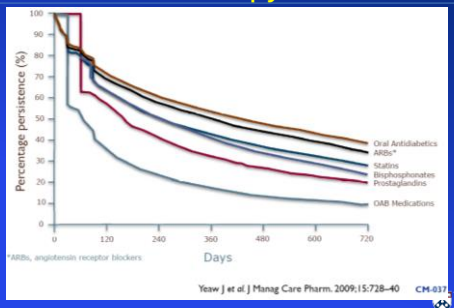
Time to drug discontinuation in six chronic therapy classes



Yeaw J et al J Manag Care Pharm. 2009;15:728–40 CM-037

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Poor Adherence (EAU 2017)

Low efficacy 41.3%
Adverse events 22.4%
Cost 18.7%
+
IR vs ER preparations
Lower persistence among young adults
Unrealistic expectations of treatment
Higher in women
Minorities more apt to d/c or switch

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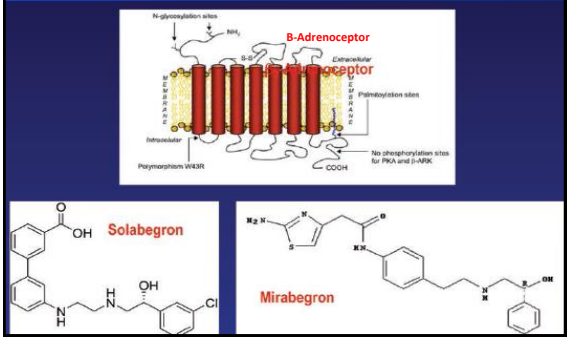
Beta-3 Agonists (ICI-2016)



Mirabegron: MOA in OAB

Direct relaxing effect on Detrusor SM

1. Activation of adenylyl cyclase → cyclic AMP
2. Opening bladder K+ channels may be important; activation causes hyperpolarization

Suggestion of activation of pre-junctional receptors to down-regulate Ach release from cholinergic terminals

Afferent inhibition suggested as well

Rougel et al, Pharmacol Res, 2014; 80; 14-20
D'Agostino et al, Eur J Pharmacol, 2015; 758: 115-122
Sammaringed by Andersson et al, 2017 INCONTINENCE, in press

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Mirabegron

NITTI et al, EAU 2011, North America (885)
1328 Patients, Placebo Run In (047)

		Placebo	50 mg M	100 mg M
INCONTINENCE EPISODES	Baseline	3.03	2.77	2.69
	↓4 weeks	0.72	1.20*	1.18*
	↓12 weeks	1.13	1.47	1.63*
	↓%	37.3	53.1	61.7
	D/P Ratio		1.42	1.65
FREQUENCY	Baseline	11.51	11.8	11.66
	↓4 weeks	0.77	1.19*	1.37*
	↓12 weeks	1.05	1.66*	1.75*
	↓%	9.1	14.1	15.0
	D/P Ratio		1.55	1.65
VOLUME VOIDED	Baseline	157.5	156.3	157.6
	↓4 weeks			
	↓12 weeks	7.0	18.2	18.0
	↓%	4.44	11.6	11.4
	D/P Ratio		2.6	2.6

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Mirabegron

KHULLAR et al, EAU 2011 Europe/Australia (886)
1978 Patients, Placebo Run In (046)

		Placebo	50 mg M	100 mg M	T 4 mg
INCONTINENCE EPISODES	Baseline	2.63	2.83	2.89	2.63
	↓4 weeks	0.65	1.04*	1.03	
	↓12 weeks	1.17	1.57*	1.46*	1.27
	↓%	43.8	55.5	50.5	48.3
	D/P Ratio		1.27	1.13	1.10
FREQUENCY	Baseline	11.71	11.65	11.51	11.54
	↓4 weeks	0.77	1.16*	1.29*	
	↓12 weeks	1.34	1.93*	1.77*	1.59
	↓%	11.4	16.6	15.4	13.8
	D/P Ratio		1.46	1.35	1.21
VOLUME VOIDED	Baseline	156.7	161.1	158.3	158.8
	↓4 weeks				
	↓12 weeks	12.30	24.20	25.60	25.0
	↓%	7.8	15.0	16.2	15.7
	D/P Ratio		1.92	2.08	1.97

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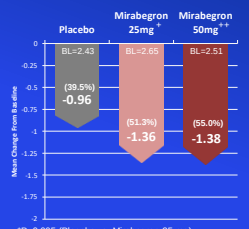
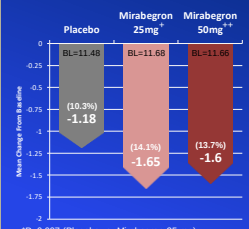
Primary Outcomes

Reduced episodes of Incontinence per 24 hours



*P=0.005 (Placebo vs. Mirabegron 25 mg)
**P=0.001 (Placebo vs. Mirabegron 50 mg)

Reduced micturition (urinary) frequency per 24 hours



*P=0.007 (Placebo vs. Mirabegron 25 mg)
**P=0.015 (Placebo vs. Mirabegron 50 mg)

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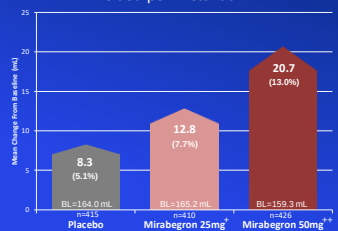
Herschorn S, Barkin J, Castro-Diaz D, et al. *Urology*. 2013;82(2):313–20.

Secondary Outcome

Increase in urine volume voided per micturition



+P=0.15; ***not significant*** (Placebo vs. Mirabegron 25 mg)
++P<0.001 (Placebo vs. Mirabegron 50 mg)

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Herschorn S, Barkin J, Castro-Diaz D, et al. *Urology*. 2013;82(2):313–20.
ClinicalTrials.gov identifier: NCT00912964 [cited 12/19/13].

Adverse Events: Mirabegron

Table 1: Percentages of Patients with Adverse Reactions, Derived from All Adverse Events, Exceeding Placebo Rate and Reported by 1% or More Patients Treated With Myrbetriq 25 mg or 50 mg Once Daily in Studies 1, 2, and 3

	Placebo (%)	Myrbetriq 25 mg (%)	Myrbetriq 50 mg (%)
Number of Patients	**1380**	**432**	**1375**
Hypertension*	7.6	11.3	7.5
Nasopharyngitis	2.5	3.5	3.9
Urinary Tract Infection	1.8	4.2	2.9
Headache	3.0	2.1	3.2
Constipation	1.4	1.6	1.6
Upper Respiratory Tract Infection	1.7	2.1	1.5
Arthralgia	1.1	1.6	1.3
Diarrhea	1.3	1.2	1.5
Tachycardia	0.6	1.6	1.2
Abdominal Pain	0.7	1.4	0.6
Fatigue	1.0	1.4	1.2

*Includes reports of blood pressure above the normal range, and BP increased from baseline, occurring predominantly in subjects with baseline hypertension.

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Safety Assessments

Most frequent (≥ 2% in any treatment group) treatment emergent adverse events

	Placebo N=433	Mirabegron 25 mg N=432	Mirabegron 50 mg N=440
Hypertension	8.5%	11.3%	10.7%
Nasopharyngitis	3.2%	3.5%	5.7%
Urinary Tract Infection (UTI)	2.3%	4.2%	4.8%
Headache	4.4%	2.1%	2.7%
Upper Respiratory Tract Infection	1.8%	2.1%	1.6%
Dry Mouth	2.1%	1.9%	1.6%
Dizziness	0.5%	2.3%	0.9%
Nausea	2.3%	1.2%	1.4%
Back Pain	2.1%	1.4%	0.9%

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Herschorn S, Barkin J, Castro-Diaz D, et al. *Urology*. 2013;82(2):313–20.

Beta-3 agonist (Mirabegron)

- 1A (ICI-2016) for efficacy-LUTS/OAB/DO
- LOE 1a from EAU for cure/improvement of UUI

LUTS/OAB/DO (ICI-2016)

	Level of Evidence	Grade of Recommendation
Beta-AR antagonists		
Terbutaline (beta 2)	3	C
Salbutamol (beta 2)	3	C
Mirabegron (beta 3)	1	A
PDE-5 Inhibitors+		
(Sildenafil, Taladafil, Vardenafil)	1	B

B3AR Agonists (EAU Guidelines 2017)

Summary of evidence	LE
Mirabegron is better than placebo and as efficacious as antimuscarinics for improvement of urgency urinary incontinence symptoms.	1a
Adverse event rates with mirabegron are similar to placebo.	1a
Patients inadequately treated with solifenacin 5 mg may benefit more from the addition of mirabegron than dose escalation of solifenacin.	1b

Recommendation	GR
In patients with UUI and an inadequate response to conservative treatments offer mirabegron, unless they have uncontrolled hypertension.	A

Mirabegron: Summary (EAU 2016)

Summary of evidence	LE
Mirabegron is better than placebo for improvement of UUI symptoms.	1a
There is no evidence that mirabegron is better than placebo for curing incontinence.	1b
Mirabegron is no more effective than tolterodine.	1b
Adrenergic-mediated side effects of mirabegron appear mild and not clinically significant in a trial setting.	1a
Discontinuation rates from mirabegron are similar to tolterodine in a trial setting.	1b

Mirabegron: Recommendation (EAU 2016)

Recommendation	GR
Offer mirabegron to people with urgency urinary incontinence, but inform patients receiving mirabegron that the possible long-term side effects remain uncertain.	B

Questions to be Answered

- How is the efficacy compared to current "Gold Standard" titratable antimuscarinics?
- Is there an additive effect (or Not) with antimuscarinics?
  - (Symphony Study) To improve treatment of overactive bladder, mirabegron/solifenacin in combination was compared with each drug alone and placebo. Combination therapy improved OAB symptoms and had similar safety and acceptability.

Abrams P, et al. Combination Treatment with Mirabegron and Solifenacin in Patients with Overactive Bladder: Efficacy and Safety Results from a Randomised, Double-Blind, Dose-ranging, Phase 2 Study (Symphony). Eur Urol (2014). In Press

Platinum Priority – Voiding Dysfunction
Editorial by XXX on pp. x–y of this issue

Combination Treatment with Mirabegron and Solifenacin in Patients with Overactive Bladder: Efficacy and Safety Results from a Randomised, Double-blind, Dose-ranging, Phase 2 Study (Symphony)

Paul Abrams [a,], Con Kelleher [b], David Staskin [c], Tomasz Rechberger [d], Richard Kay [e], Reynaldo Martina [f], Donald Newgreen [f], Asha Paireddy [f], Rob van Maanen [f], Arwin Ridder [f]*

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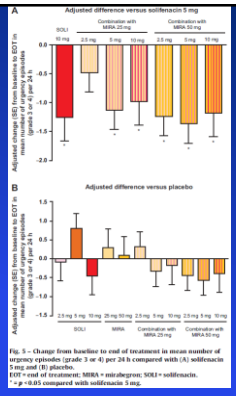

Fig. 1 – Change from baseline to end of treatment in mean number of urgency episodes (grade 3 or 4) per 24 h compared with (A) solifenacin 5 mg and (B) placebo.
EOT = end of treatment; MIRA = mirabegron; SOLI = solifenacin.
* = $p < 0.05$ compared with solifenacin 5 mg.

Abrams *et al.*

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Mixed Urinary Incontinence (EUA 2017)

Summary of evidence	LE
Limited evidence suggests that antimuscarinic drugs are effective for improvement of the urgency urinary incontinence component in patients with mixed urinary incontinence.	2
Duloxetine is effective for improvement of both stress urinary incontinence and urgency urinary incontinence in patients with mixed urinary incontinence.	1b

Recommendations	GR
Treat the most bothersome symptom first in patients with mixed urinary incontinence.	C
Offer antimuscarinic drugs or beta3 agonists to patients with urgency-predominant mixed urinary incontinence.	A*
Consider duloxetine for patients with mixed urinary incontinence unresponsive to other conservative treatments and who are not seeking cure.	B

Elderly (EUA 2017)

Summary of evidence	LE
Antimuscarinic drugs are effective in elderly patients.	1b
Mirabegron has been shown to be 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

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

ESTROGEN(ICI, 2016)

- For LUTS/OAB/DO:

  2 C
- For SUI in Women:

  2 D

ESTROGEN

- Cochrane Meta Analysis (2012):

The combined results of 6 trials of systemic administration(oral oestrogen) resulted in worse incontinence than placebo. However there was some evidence that oestrogen used locally as vaginal creams or pessaries improved incontinence. Overall there was less frequency and urgency in those women treated with local oestrogen"

Cody et al, 2012, Cochrane Database Syst Rev Oct 17; 10:CD001405

INTERESTING IDEA

- SARMS and SERMS

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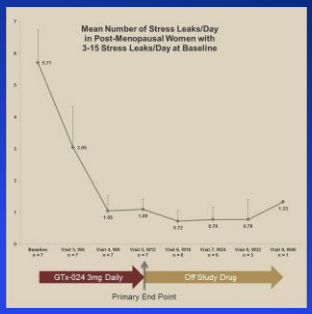

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THANK YOU

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