Frailty & Cognition: Management of OAB in Elderly & Frail Patients

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Topics

- What are LUTS?
- Symptom definitions
- The impact of OAB on patients
- Management of OAB
- The challenge of treating OAB
- The Anticholinergic burden
- Novel treatment of OAB

Change of Terminology

- LUTS = Lower urinary tract symptoms
- LUTS instead of “prostatism”
- Storage instead of “irritative”
- Voiding instead of “obstructive”

What are LUTS

Storage symptoms	Voiding symptoms	Post-micturition symptoms
Daytime frequency	Slow stream	Post-micturition dribbling
Nocturia	Spraying	Incomplete emptying
Urgency	Intermittency	
Urinary incontinence	Hesitancy	
	Straining	
	Terminal dribbling	

Definitions

- **Urgency** - sudden compelling desire to pass urine which is difficult to defer
- **Urinary incontinence**
  - any involuntary leakage of urine (urge / stress)
  - may need to be distinguished from sweating or vaginal discharge
- **Increased daytime frequency** - the complaint by the patient who considers that he/she voids too often by day
- **Nocturia** - individual has to wake at night one or more times to void

- ICS Definitions, Abrams P et al. Neurourol Urodyn; 21:167-178 (2002)

Definition of Overactive Bladder (OAB)

Urgency, with or without urge incontinence, usually accompanied by frequency and nocturia[1]

(in the absence of local pathology and significant endocrine factors)

(International Continence Society)

1. Abrams P et al. Neurourol Urodyn 2002;21:167-178

Mrs W. E. Terrible, your classic patient?

Age:

64 year old woman

Occupation:

Recently retired from an office job

Symptoms:

- Urinary frequency (14–15 times a day)
- Urge incontinence (daily)
- Nocturia (3 times a night)

The impact of OAB on patients

How do OAB symptoms affect patients?

haven't slept

depressing

like a baby

negative

lose control

locked in

embarrassing

exhausted

terrible

no control

so tired

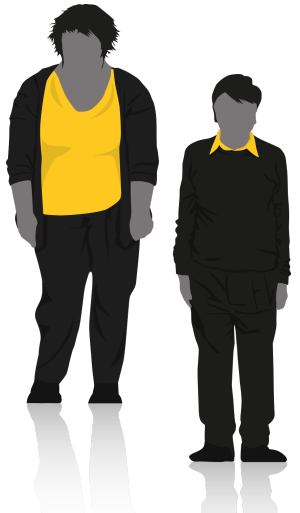
I keep it secret

Quotes from a video of real-life OAB patients talking about how OAB has affected their lives.

1. Coyne KS *et al. BJU Int* 2008; 101: 1388-95.

Overactive bladder (OAB)

- OAB is a chronic condition, affecting over 17% of the adult population (aged ≥40 years) in the UK[1,2]
- Estimated prevalence of over 5 million men and women[2]



1. Astellas, data on file NPR16031UK. February 2016.
2. Milsom I *et al. BJU Int* 2001; 87: 760-6.
3. Abrams P. *Urology* 2003; 62(Suppl 5B): 28-37.
4. Abrams P *et al. Neurourol Urodyn* 2009; 28: 287.

OAB: Diagnosis and Management

Diagnosis by History & Exclusion

Red Flags Signs:

- Recurrent UTI
- Nocturnal enuresis
- Haematuria (visible or non-visible)
- Previous or suspected urinary retention
- Renal impairment suspected to be secondary to lower urinary tract dysfunction
- Pain with voiding
- Suspected urological cancer

Treatment goals for patients

- Patients want effective relief from symptoms, with minimal side effects, so that they can get on with their lives

"sleep longer"

"go out and do normal day-to-day activities"

"being carefree"

"not having to run to the toilet every half an hour"

"not worry about going to the toilet so regularly"

"being able to control everything"

Quotes from a video of real-life OAB patients talking about what they hope for from treatment.

Treatment 1: Non-pharmacological

- Behaviour modification
- Bladder re-training
- Dietary changes/weight loss
- Pelvic floor muscle training (Kegel) exercises
- Advice on fluid management
- Reduction in caffeine intake
- Reduction of evening fluid intake

Campbell-Walsh Urology: 10th Edition. Wein et al. 2011

NICE guideline CG97

Indication	Treatment guidelines
Moderate to severe LUTS	Offer an α-blocker (alfuzosin, doxazosin, tamsulosin or terazosin)
OAB	Offer an anticholinergic
LUTS and a prostate estimated to be larger than 30g or PSA >1.4ng/ml, and high risk of progression	Offer a 5α-reductase inhibitor
Bothersome moderate to severe LUTS, and a prostate estimated to be larger than 30g or PSA >1.4ng/ml	Consider an α-blocker plus a 5α-reductase inhibitor
Storage symptoms despite treatment with an α-blocker	Consider an anticholinergic as well as an α-blocker

1. NICE clinical guidelines 2010. The management of lower urinary tract symptoms in men, CG97.

Pharmacological: Anticholinergics

- oxybutynin (Cystrin®, Kentera®Lyrinel XL®)
- tolterodine (Detrusitol®, Detrusitol XL®)
- darifenacin (Emselex®)
- solifenacin (Vesicare®)
- propiverine (Detrunorm®, Detrunorm®XL)
- trospium (Regurin®)

Key treatment issues

- Non-compliance with medication
- Long-term treatment is usually needed
- Safety & tolerability
  - Especially in frail elderly patients
  - Those with complex co-morbidities and regimens of multiple medications

Challenge of treating OAB

Anticholinergics and their challenges

- Persistence with anticholinergics remains a challenge[1,2]
- 43–83% of patients discontinue anticholinergics within the first 30 days (2011)[1]
- Patients discontinue their anticholinergics primarily due to:[3]
  - Lack of efficacy
  - Side effects (e.g. dry mouth[4])

1. Sexton CC *et al. Int J Clin Pract* 2011; 65: 567–85.
2. Wagg A *et al. BJU Int* 2012; 110: 1767–74.
3. Benner JS *et al. BJU Int* 2009; 105: 1276–82.
4. Chapple CR *et al. Eur Urol* 2008; 54: 543–62.

Identification of Key Issues

Poly-pharmacy

Many prescription and non-prescription drugs have anticholinergic activity

Age

Anticholinergic side effects are often more pronounced in those aged over 65 years [3]

Comorbidity

Adverse events caused by an antimuscarinic can exacerbate other illnesses and result in treatment discontinuation[5]

1. Anticholinergic burden scale 2012. Available at: http://www.agingbraincare.org/uploads/products/ACB_scale_-_legal_size.pdf. Last accessed: February 2016.
2. Rudolph JL *et al. Arch Intern Med* 2008; 168: 508–13.
3. Mintzer J & Burns A. *J R Soc Med* 2000; 93: 457–62.
4. NICE clinical guidance CG171. Urinary incontinence in women: management, September 2013.
5. Nitti VW *et al. Neurourol Urodyn* 2010; 29: 652–65.

Anticholinergic burden of commonly prescribed drugs

ACB SCORE 1 (MILD)			ACB SCORE 2 (MODERATE)	ACB SCORE 3 (SEVERE)		
Alimemazine	**Digoxin**	**Metoprolol**	Amantadine	**Amitriptyline**	**Hydroxyzine**	Quetiapine
Alverine	**Dipyridamole**	**Morphine**	**Carbamazepine**	Atropine	**Imipramine**	**Solifenacin**
Aripiprazole	Disopyramide	**Nifedipine**	Nefopam	**Chlorpromazine**	Methocarbamol	**Tolterodine**
Asenapine	Fentanyl	Paliperidone	Oxcarbazepine	Clemastine	Nortriptyline	Trifluoperazine
Atenolol	**Furosemide**	**Prednisone**	**Pethidine**	Clomipramine	**Olanzapine**	Trihexyphenidyl
Bupropion	Fluvoxamine	**Ranitidine**	Pimozide	**Clozapine**	Orphenadrine	Trimipramine
Captopril	**Haloperidol**	**Risperidone**		**Darifenacin**	**Oxybutynin**	**Trospium**
Cetirizine	**Hydralazine**	Theophylline		Dicycloverine	Paroxetine	
Cimetidine	**Hydrocortisone**	Trazodone		Dimenhydrinate	Perphenazine	
Codeine	**Isosorbide**	Triamterene		Doxepin	Promethazine	
Colchicine	Levocetirizine	**Venlafaxine**		**Fesoterodine**	Propantheline	
Desloratadine	**Loperamide**	**Warfarin**		Flavoxate	Propiverine	
Diazepam	Loratadine					

Adapted from the Anticholinergic burden scale 2012.[1] Drugs not listed have an ACB score of 0

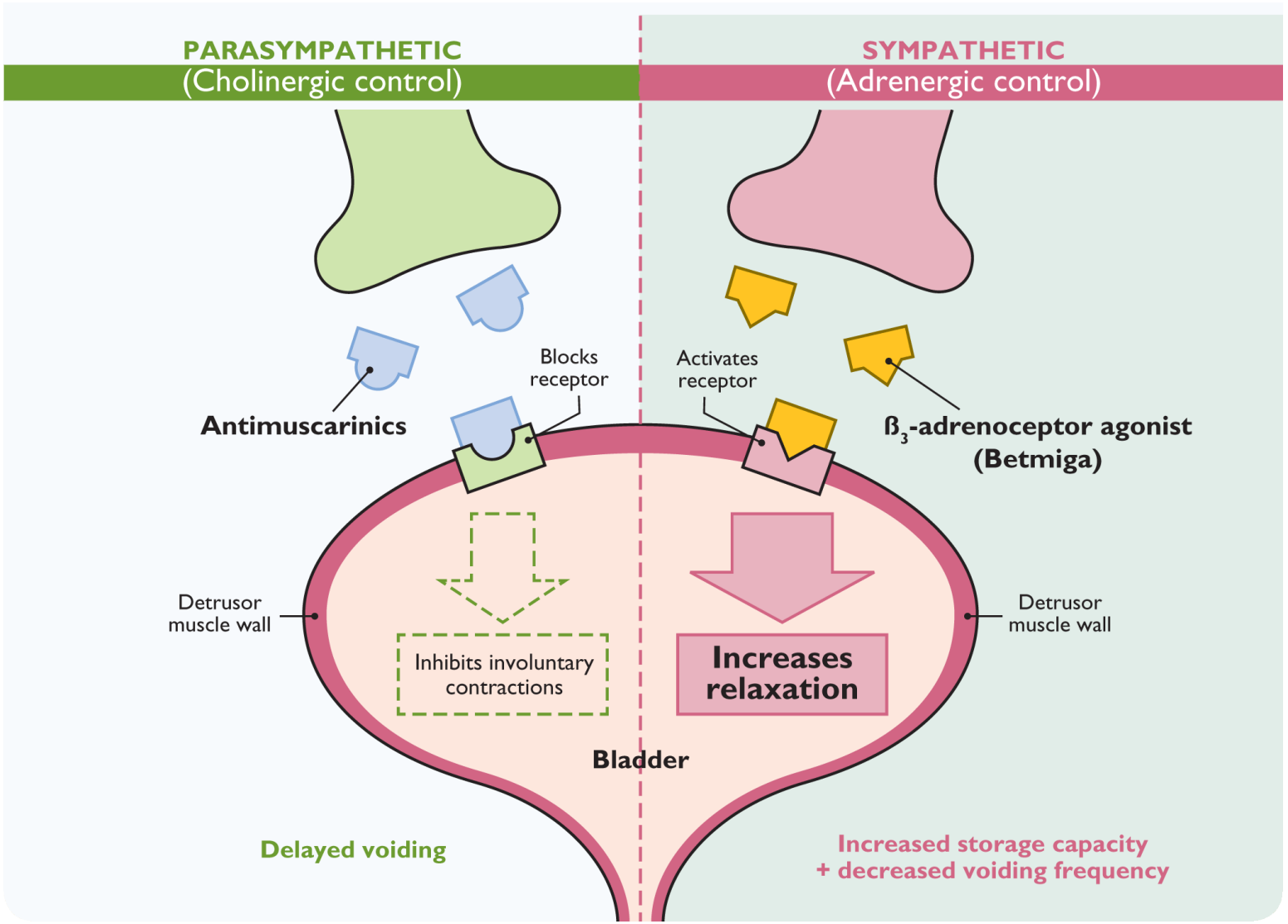
1. Anticholinergic burden scale 2012. Available at: http://www.agingbraincare.org/tools/abc-anticholinergic-cognitive-burden-scale/. Last accessed: June 2015.

Side Effects of Anticholinergic Medication

- Palpitation
- Dizziness
- Blurred vision
- Confusion
- Delirium
- Sedation
- Dry mouth / lips / eyes
- Urinary Retention
- Memory impairment
- Drowsiness
- Increased heart rate
- Hyperthermia
- Constipation
- Increased number of falls (due to hypotension)
- Decreased Sweating

Mirabegron – A novel medication

Different action to anticholinergics[1,2]



SCORPIO Results: Side Effects

- SCORPIO, a key European-Australian, randomised, double-blind, placebo- and active-controlled, 12-week Phase III trial[1]

Adverse events %	Mirabegron 50mg (n=493)	Placebo (n=494)	Tolterodine ER 4mg active control (n=495)
Dry mouth	2.8%	2.6%	10.1%
Constipation	1.6%	1.4%	2.0%
Hypertension	5.9%	7.7%	8.1%
Nasopharyngitis	2.8%	1.6%	2.8%
Headache	3.7%	2.8%	3.6%
Influenza	2.2%	1.6%	1.4%
Urinary tract infection	1.4%	1.4%	2.0%

Table adapted from Khullar *et al.*, 2013.[1] Data not shown for the unlicensed 100mg dose of mirabegron. TEAEs, treatment-emergent adverse events.

1. Khullar V *et al. Eur Urol* 2013; 63: 283–95.
2. Betmiga Summary of Product Characteristics, April 2016.

For the full list of adverse events refer to the SmPC.[2]

Tolterodine ER 4mg was included as an active control therefore direct statistical comparisons cannot be made between mirabegron and tolterodine ER 4mg.

Pharmacotherapy Failure

Refer to GP or Urologist:

- Intra-vesical injection of Botulinum Toxin A
- Neuromodulation
- Clam (augmentation) cystoplasty
- Urinary diversion

Thank you, any questions?

Mirabegron 50mg – Administration considerations[1]

Contraindications

Contraindicated in patients with:

- Any hypersensitivity to the active substance or its excipients
- Severe uncontrolled hypertension (SBP ≥180mmHg and/or DBP ≥110mmHg)

Dose adjustments

Dose adjustment to 25mg is recommended in patients with:

- Severe renal and/or moderate hepatic impairment
- Mild/moderate renal and/or mild hepatic impairment concomitantly receiving strong CYP3A inhibitors

SBP, systolic blood pressure; DBP, diastolic blood pressure.

1. Betmiga Summary of Product Characteristics, April 2016.

Mirabegron 50mg – Administration considerations[1]

Special warnings and precautions for use

Not recommended for use in patients with:[1]

- End stage renal disease (GFR <15ml/min/1.73m^2 or requiring haemodialysis)
- Severe hepatic impairment
- Severe renal impairment and/or moderate hepatic impairment concomitantly receiving strong CYP3A inhibitors

Can increase blood pressure. Blood pressure should be measured at baseline and periodically during treatment, especially in hypertensive patients.[1]

- Data are limited in patients with stage 2 hypertension (systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg

Administer with caution in patients with:[1]

- Known history of QT prolongation or who are taking medicines known to prolong the QT interval
- Clinically significant bladder outlet obstruction or who are taking antimuscarinic medications for the treatment of OAB

GFR, glomerular filtration rate.

1. Betmiga Summary of Product Characteristics, April 2016.

Mirabegron: Cardiovascular effects[1]

- Mirabegron, at therapeutic doses, has not demonstrated clinically relevant QT prolongation in clinical studies[1]
  - However, the effects of mirabegron in patients with a known **history of QT prolongation** or patients who are taking medicinal products known to **prolong the QT interval** are unknown[1]
  - **Caution** should be exercised when administering mirabegron in these patients[1]
- An increase in mean difference from placebo of approximately 1 bpm for pulse rate and approximately 1 mmHg or less in SBP/DBP was observed[1]
  - Changes in pulse rate and blood pressure are reversible upon discontinuation of treatment[1]
  - Blood pressure should be measured at baseline and periodically during treatment, especially in hypertensive patients[1]
- **Contraindicated** in patients with severe uncontrolled hypertension (SBP ≥180mmHg and/or DBP ≥110mmHg)[1]

For the full list of adverse events refer to the SmPC.[1]

DBP, diastolic blood pressure; SBP, systolic blood pressure

1.Betmiga Summary of Product Characteristics, April 2016.