Urinary Incontinence and Overactive Bladder Update NICE Guidelines on UI for women - GP Perspectives

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KING'S HEALTH PARTNERS

Pioneering better health for all

Guy's and St Thomas' NHS

NHS Foundation Trust

COI

- Allergan – unrestricted educational grant, advisor
- Astellas, Pfizer - Honoraria for lectures, advisory boards

Objectives

- NICE Update on UI
- Important aspects related to primary care
- Mirabegron data
- Cases
- Discussion / Question Time

NICE Guideline Development Group

Urinary incontinence in women: management

Clinical guideline
Published: 11 September 2013
nice.org.uk/guidance/cg171

- 2 Uro-gynaecologists
- 1 Urologist
- 1 GP
- 1 Geriatrician
- 1 nurse specialist
- 1 physiotherapist
- 1 continence advisor
- 2 patients

What it covers

- Stress Urinary incontinence (UI)
- Urgency Urinary Incontinence
- Mixed Urinary incontinence
- Overactive Bladder (OAB)

Primary Care Assessment

- Decide which is the predominant type of UI
- If SUI predominant symptom in MUI, discuss OAB drugs before offering surgery [new 2013]

- Screen for predisposing Conditions

- Identify possible lifestyle modifications

Primary care Assessment 2

- Questionnaires - ICIQ, BFLUTS, I-QOL, SUIQQ, UISS, SEAPI-QMM, ISI and KHQ
- 3 day voiding diary
- Per vaginal examination
  - Masses
  - Prolapse
  - Finger squeeze - to assess whether PFE will be of benefit [amended 2013]
- PVR measurements (scan better than catheter)
  - Voiding dysfunction
  - Recurrent UTI

No longer recommended

- Pad tests
- Q tip test / Bonney / Marshall tests
- Imaging except bladder scan

To Culture or not to culture?

	UTI Symptoms	No UTI Symptoms
+ve urine dip	MSU Empirical antibiotics	MSU Antibiotics only if positive culture
-ve Urine dip	MSU Empirical antibiotics if clinical concern	No MSU

Red Flags – urgent referral

- Non-visible haematuria 50yrs+
- Visible haematuria
- Recurrent/persisting UTI with haematuria 40yrs+
- Suspected malignancy

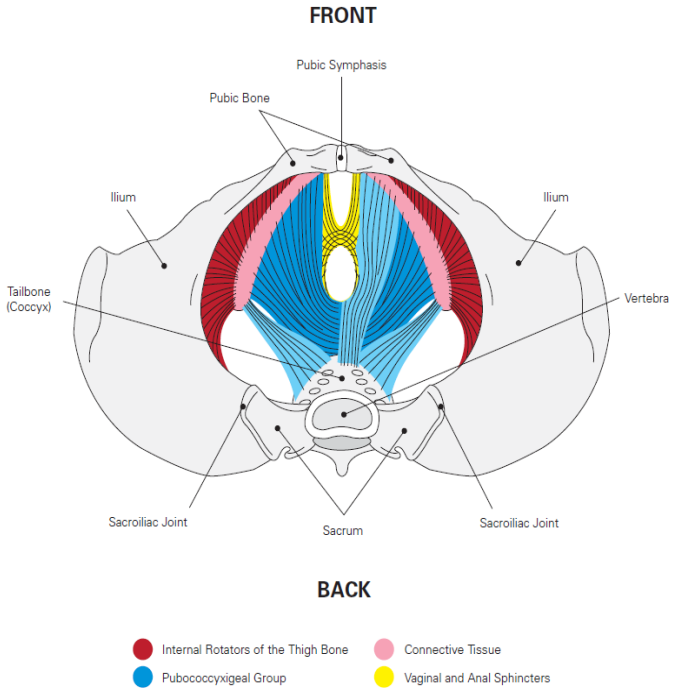
Immediate specialist referral

- Persisting bladder/urethral pain
- Benign pelvic masses
- Associated faecal incontinence
- Neurological disease
- Voiding dysfunction
- Suspected Fistulae
- Previous pelvic surgery/radiation
- Palpable bladder on bimanual or abdo examination

Stress UI treatment

- Pelvic floor exercises
  - Supervised tuition
  - 3 months duration
  - At least 8 repetitions three times per day
  - No routine use of biofeedback

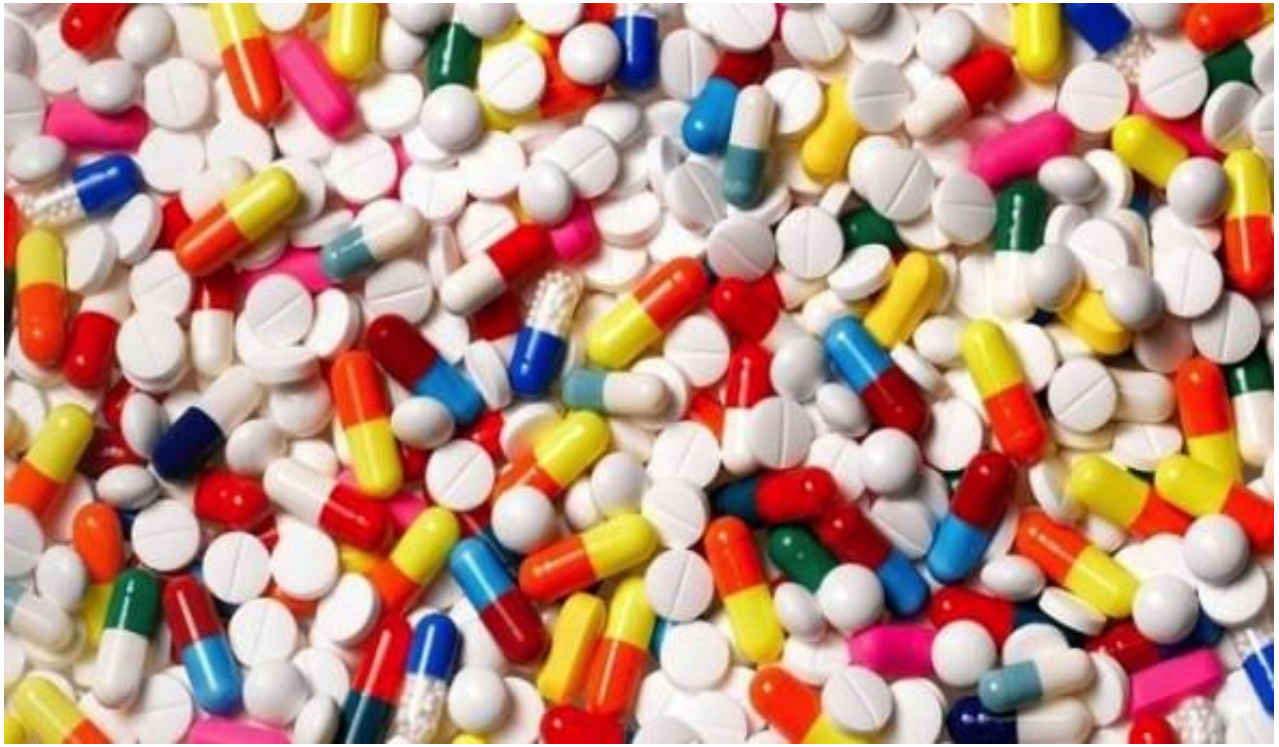
- Mixed UI also do Bladder training



Urge UI & OAB initial treatment

- Lifestyle modifications
- Lose weight
- Offer intravaginal oestrogens in postmenopausal women with vaginal atrophy
- Bladder training
    - 6 weeks
    - If no improvement at 6 weeks move to medication

Medical management of OAB & UUI



- Consider voiding dysfunction, anticholinergic load, AEs

Medical Management OAB & UUI

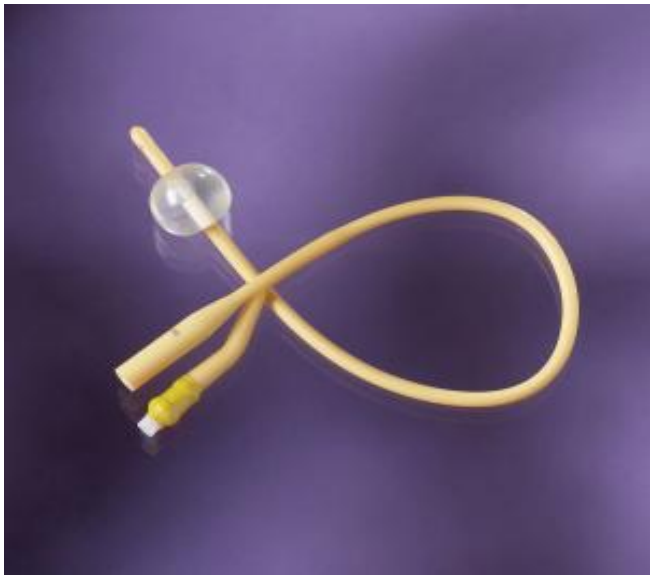
- First line anti-cholinergics
    - Immediate release oxybutinin (not in frail or elderly)
    - Immediate release tolterodine
    - Darifenacin
- Face to face or telephone review at 4 weeks
    - Starting a medication
    - Changing medication
    - Changing dose of a medication

Medical Management OAB & UUI 2

- Second line treatments
  - Transdermal oxybutinin if can't tolerate tablets
  - Another drug with the lowest acquisition cost
- Third line treatment
  - Mirabegron
- Can refer to secondary care if patient wants an alternative treatment to medication at any point

Follow up of patients on medical management

- Annual review if younger than 75 years
- Six monthly review if older than 75 years



Nocturia – avoid in > 65 in those with CV disease or HT, caution in cystisc fibrosis

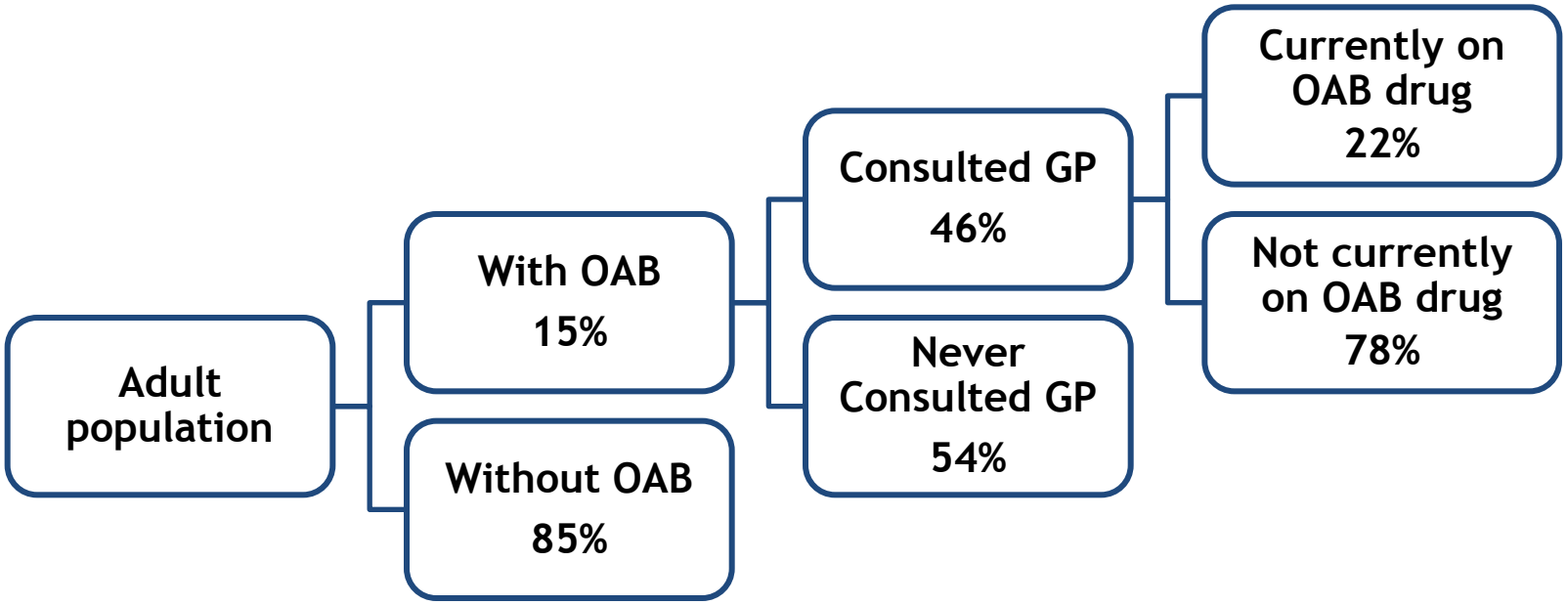
In women who prefer drugs vs surgery for SUI

Catheters

- **Indications for Indwelling urethral catheters**
- chronic urinary retention in women who are unable to manage intermittent self- catheterisation
- skin wounds, pressure ulcers or irritations that are being contaminated by urine distress or disruption caused by bed and clothing changes
- Pt preference

- **Indwelling suprapubic catheters**
- may be associated with lower rates of symptomatic UTI, 'bypassing', and urethral complications than indwelling urethral catheters.

OAB patient demographics (UK)[1]



Data presented is from 2010/2011.

Astellas, Data on File VES12228UK. July 2012. Data is sourced from Lightspeed Consumer Panels (with Millward Brown, survey conducted by Millward Brown and CSD Patient Data).

Antimuscarinics

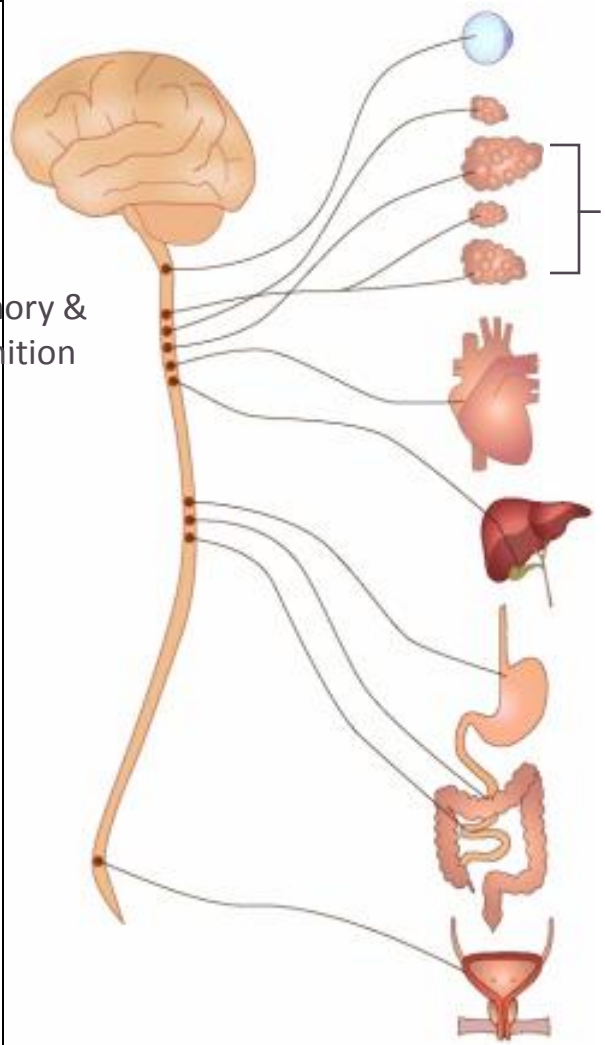
- Currently the most widely used therapy for OAB[1] with a long history of use
- Evidence to date suggests they are an efficacious therapeutic option for OAB, which also improves quality of life[2]
- Around 70-90% of patients stop their treatment within 1 year,[3,4] this may be due to:[5-7]
  - Adverse effects of medication
  - Low sensitivity to beneficial effects (poor efficacy)
  - Inadequate follow-up after instigating therapy
  - Drug–drug interactions
  - Lack of efficacy

1.Chapple CR, et al. *Urology*. 2002;60(Suppl 5A):82–9.
2.Chapple CR, et al. *Eur Urol*. 2008;54:543–62.
3.Basra RK, et al. *BJU Int* 2008;102:774–9.
4.D'Souza AO, et al. *J Manag Care Pharm* 2008;14:291–301
5.Thüroff JW, et al. *Eur Urol* 2011;59:387–400.
6.Kelleher CJ, et al. *Br J Obstet Gynaecol* 1997;104:988–93.
7.Andersson KE, et al. Pharmacological treatment of urinary incontinence. 3rd International Consultation on Incontinence. Monaco, June 26–29, 2004.

Muscarinic Receptors in Organs of the Parasympathetic Nervous System & CNS

M1: CNS

Dizziness
Somnolence
Impaired memory &
Impaired cognition



M2, M3, M5: Iris / Ciliary Body = Blurred Vision

M2, M3: Lacrimal Gland = Dry Eyes

M2, M3: Salivary Glands = Dry Mouth
(parotid, sublingual, submaxillary)

M2: Heart = Tachycardia

M2: Gall Bladder

M3: Stomach = Dyspepsia

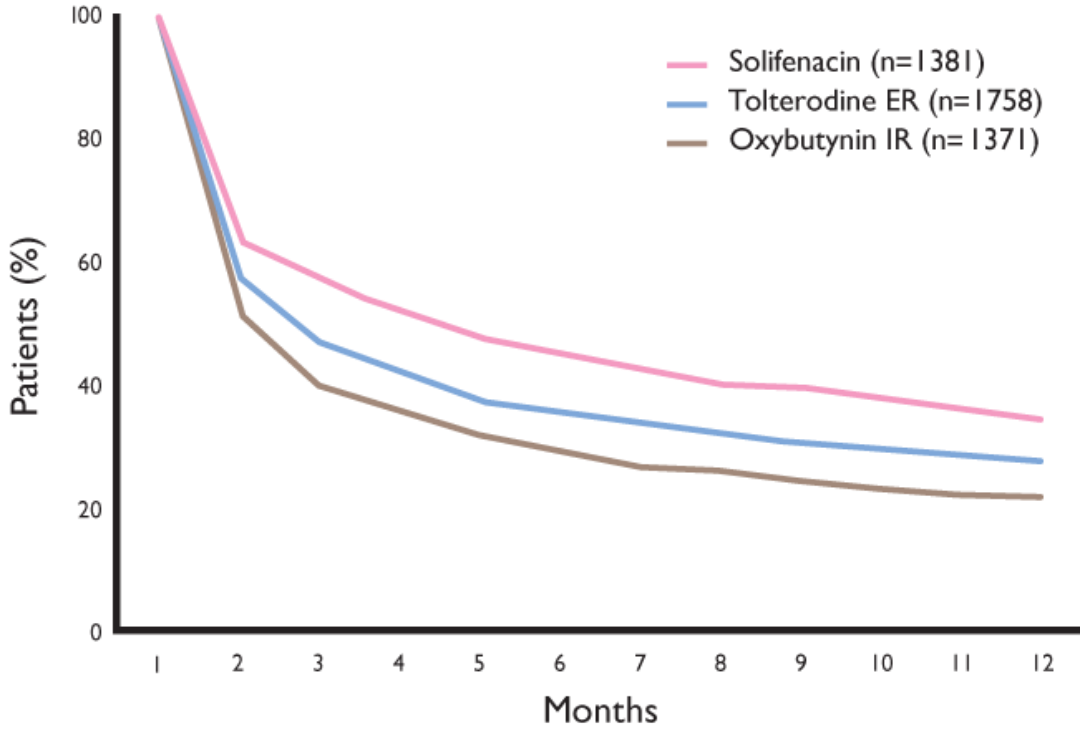
M2, M3: Colon/ Small Intestine = Constipation

M3, M2: Bladder (detrusor muscle)
M2 : M3 receptors = 80% : 20%, but M3 is more involved in detrusor contraction

The challenge of persistence with antimuscarinics

Patients remaining on antimuscarinic treatments over one year[1]

A 12-month retrospective analysis of prescription data from 4833 OAB patients, prescribed antimuscarinic treatment between January–December 2007[1]



ER, extended release; IR, immediate release
Adapted from Wagg *et al.*, 2012.[1]

1.Wagg A *et al*. *BJU Int* 2012;**110**(11):1767–1774.

Mirabegron is a first in class, selective β_3-adrenoceptor (AR) agonist[1]

- Both efficacy and side effects (including dry mouth) of antimuscarinic therapy are related to their specific interaction at the muscarinic receptor[2,3]

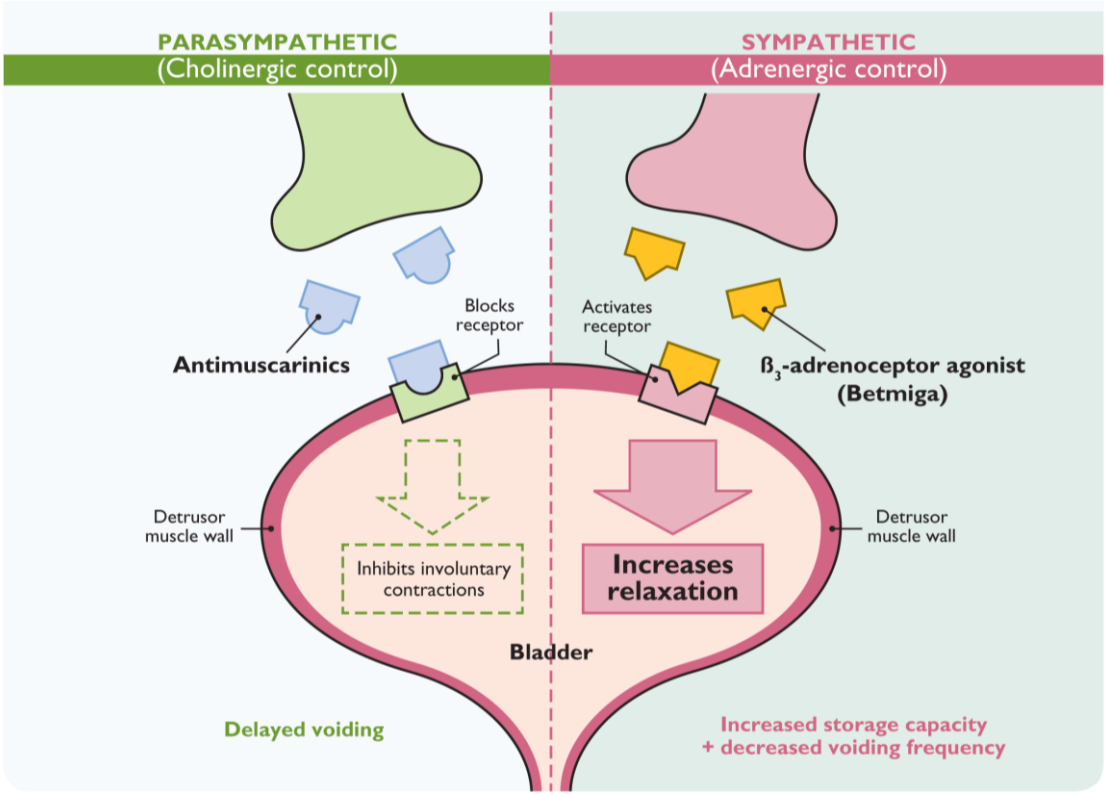
- 97% of bladder ß-ARs are of the $ß_3$-AR subtype[4]

1. Gras J. *Drugs of Today* 2012;**48**(1):25-32.
2. Hegde SS. *Br J Pharmacol* 2006;**147**(Suppl 2):S80–S87.
3. Staskin DR, Zoltan E. *Rev Urol* 2007;**9**(4):191–196.
4. Yamaguchi O. *Urology* 2002;**59**:(Suppl: 5A)25–29.

Date of preparation: February 2013. BET13018UK

Mirabegron is a novel treatment for OAB that works differently to antimuscarinics[1,2]

Mode of action of OAB treatments[1,3]



Adapted from Betmiga Summary of Product Characteristics, December 2012[1] and Chu *et al.*, 2006.[3]

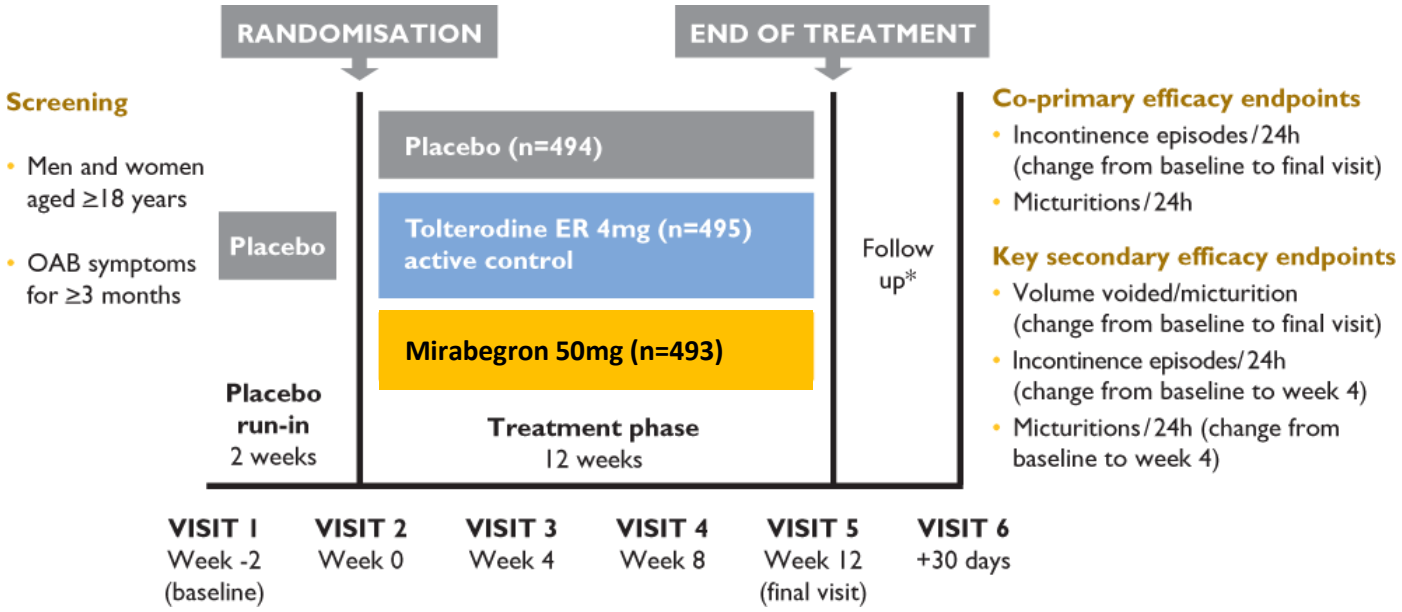
1.Betmiga Summary of Product Characteristics, December 2012.
2.Gras J. *Drugs of Today* 2012;**48**(1):25-32.
3.Chu F, Dmochowski R. *Am J Med* 2006;**119**(3A):3S–8S.

Date of preparation: February 2013. BET13018UK

SCORPIO: A key European-Australian, 12-week, Phase III trial in patients with OAB[1]

SCORPIO trial design[1]

A randomised, double-blind, placebo- and active-controlled, 12-week Phase III trial of 1978 patients with OAB[1]



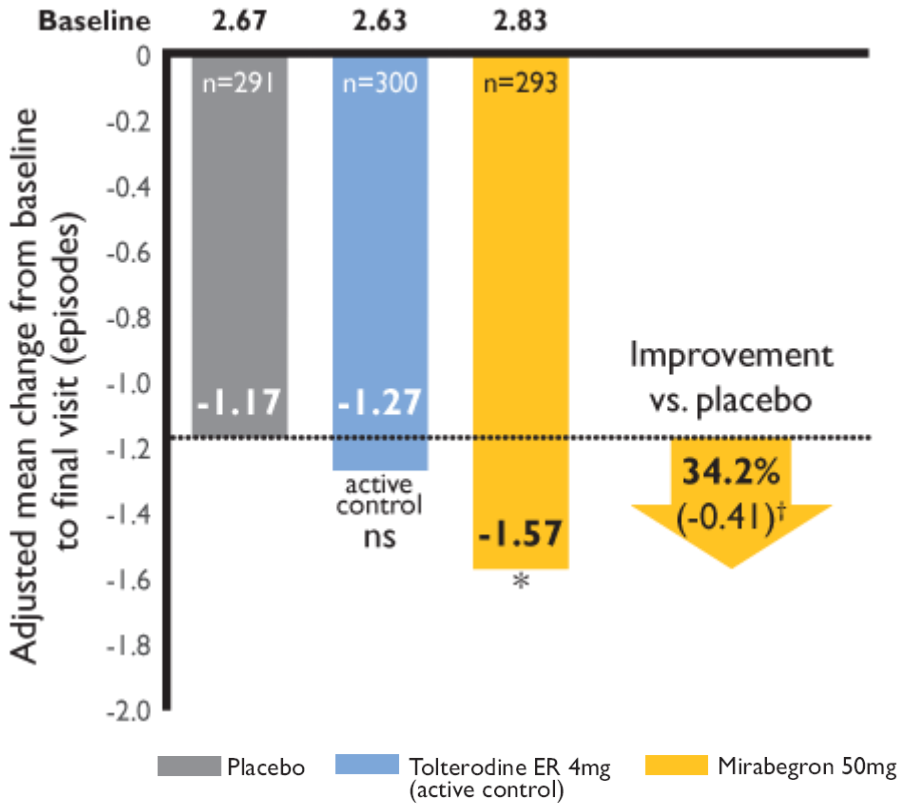
Adapted from Khullar *et al.*, 2013.[1]
*Evaluation of adverse events and concomitant medication by telephone or visit for a period of 30 days.
Tolterodine ER (extended-release) 4mg was included as an active control in this study.

1.Khullar V *et al. Eur Urol* 2013;**63**(2):283–295.

Date of preparation: February 2013. BET13018UK

SCORPIO: Improvements in incontinence episodes/24h (co-primary endpoint)[1]

Incontinence episodes/24h (FAS-I)



Adapted from Khullar *et al.,* 2013.[1]

Tolterodine ER (extended-release) 4mg was included as an active control in this study.

FAS-I = all full analysis set patients who had ≥1 incontinence episode at baseline.

ns = no statistically significant difference vs. placebo.

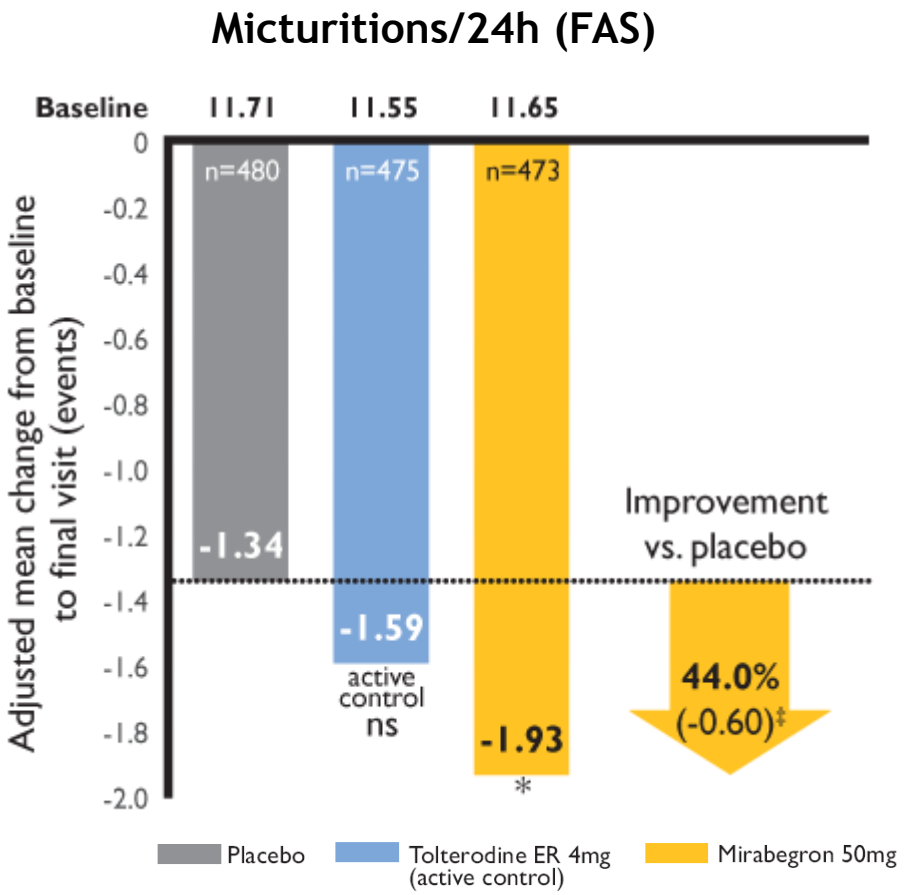
*Statistically significant improvement vs. placebo ($p<0.05$).

†Mean difference vs. placebo (95% two-sided CI: -0.72, -0.09).

1. Khullar V *et al. Eur Urol* 2013;**63**(2):283–295.

Date of preparation: February 2013. BET13018UK

SCORPIO: Improvements in micturitions/24h (co-primary endpoint)[1]



Adapted from Khullar *et al.,* 2013.[1]

Tolterodine ER (extended-release) 4mg was included as an active control in this study.

FAS = full analysis set

ns = no statistically significant difference vs. placebo.

*Statistically significant improvement vs. placebo (p<0.05).

‡Mean difference vs. placebo (95% two-sided CI: -0.90, -0.29).

1. Khullar V *et al. Eur Urol* 2013;**63**(2):283–295.

Date of preparation: February 2013. BET13018UK

SCORPIO: Additional secondary endpoints and other measures[1,2]

- Statistically significant improvements were seen with mirabegron 50mg vs. placebo ($p<0.05$) in secondary endpoints:[1,2]
  - Urgency episodes/24h (grade 3 or 4 using the PPIUS*)[1]
  - Nocturia episodes/24h[2]

Other measures:

- Additionally, in a responder analysis, nearly half of patients who were incontinent at baseline were dry (based on a 3-day micturition diary) at the end of the study with mirabegron 50mg (45% of patients; n=132/293). The improvements over placebo were not statistically significant[1]

*PPIUS = Patient Perception of Intensity of Urgency Scale.

1.Khullar V *et al. Eur Urol* 2013;**63**(2):283–295;
2.Astellas, data on file MIR/12/001/EU, 2012.

Date of preparation: February 2013. BET13018UK

SCORPIO: Most common AEs (≥2% in any treatment group)[1]

- In the three, 12-week Phase III studies, the most common adverse reactions reported for mirabegron 50mg were tachycardia and urinary tract infections (1.2% and 2.9% respectively). Serious adverse reactions included atrial fibrillation (0.2%)[2]
- In SCORPIO, rates of drug discontinuation due to AEs were low and comparable in the active groups (<5%)[1]

Incidence of most common (≥2%) AEs[1]

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

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.
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**(2):283–295.
2.Betmiga Summary of Product Characteristics, December 2012.

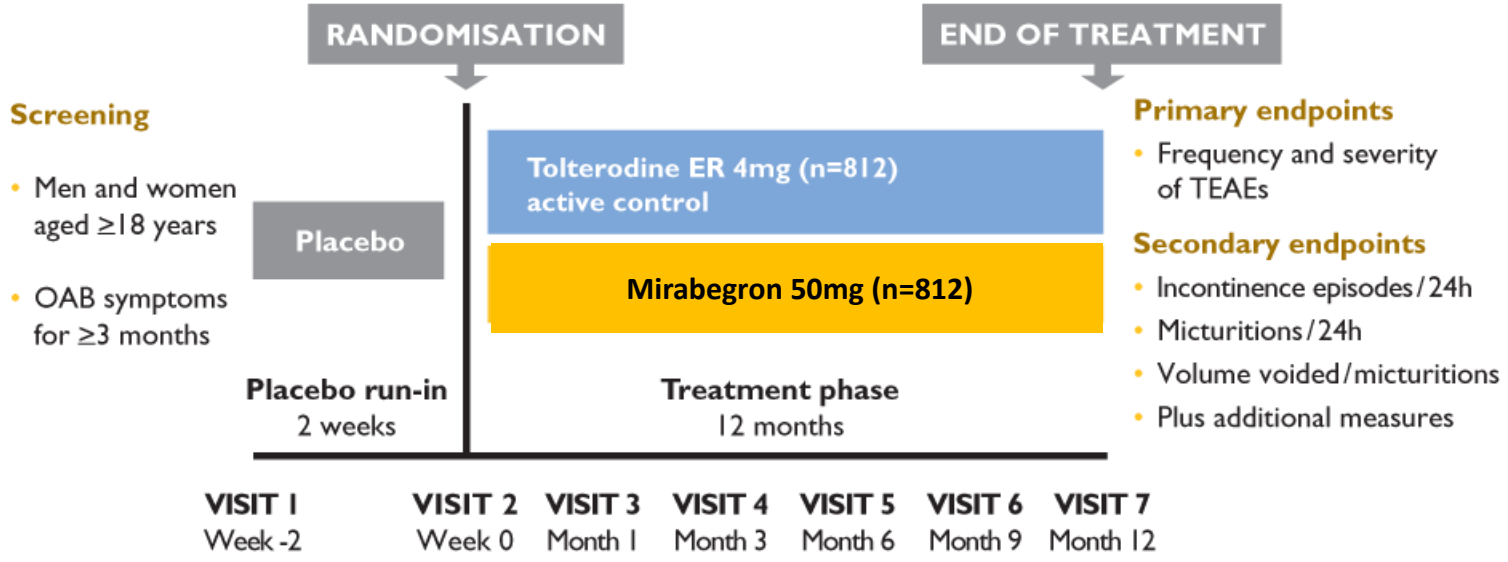
Date of preparation: February 2013. BET13018UK

TAURUS: 12-month extension study looking at the safety and efficacy of mirabegron[1]

TAURUS trial design: long-term safety and efficacy of mirabegron

A multi-centre, 12-month, double-blind study of 2444 patients with OAB[1]

Tolterodine ER 4mg was an active control



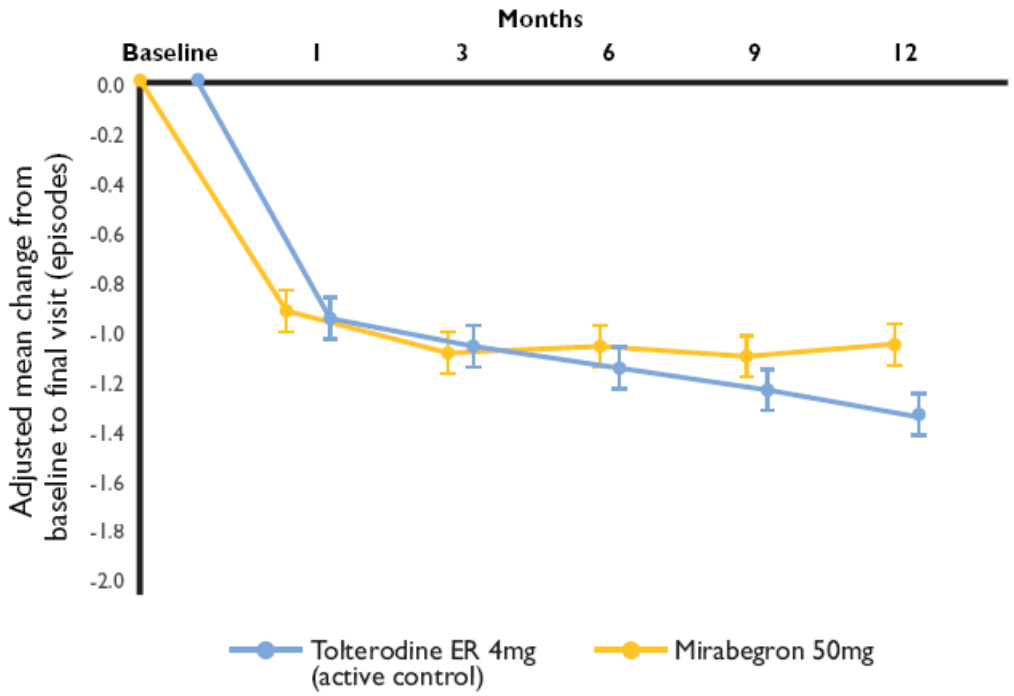
Adapted from Chapple *et al.*, 2013.[1] Eligible patients who completed Phase III, 12-week mirabegron studies could be enrolled, but required a minimum 30-day drug washout. The study was not designed to demonstrate a statistically significant difference in efficacy between treatment groups. Tolterodine ER 4mg was an active control. No direct statistical comparisons can be made between tolterodine ER 4mg and mirabegron 50mg.

1.Chapple CR *et al. Eur Urol* 2013;**63**(2):296–305.

Date of preparation: February 2013. BET13018UK

TAURUS: Efficacy variables over 52 weeks (secondary endpoint)

Mean number of incontinence episodes/24h (FAS-I)[1]



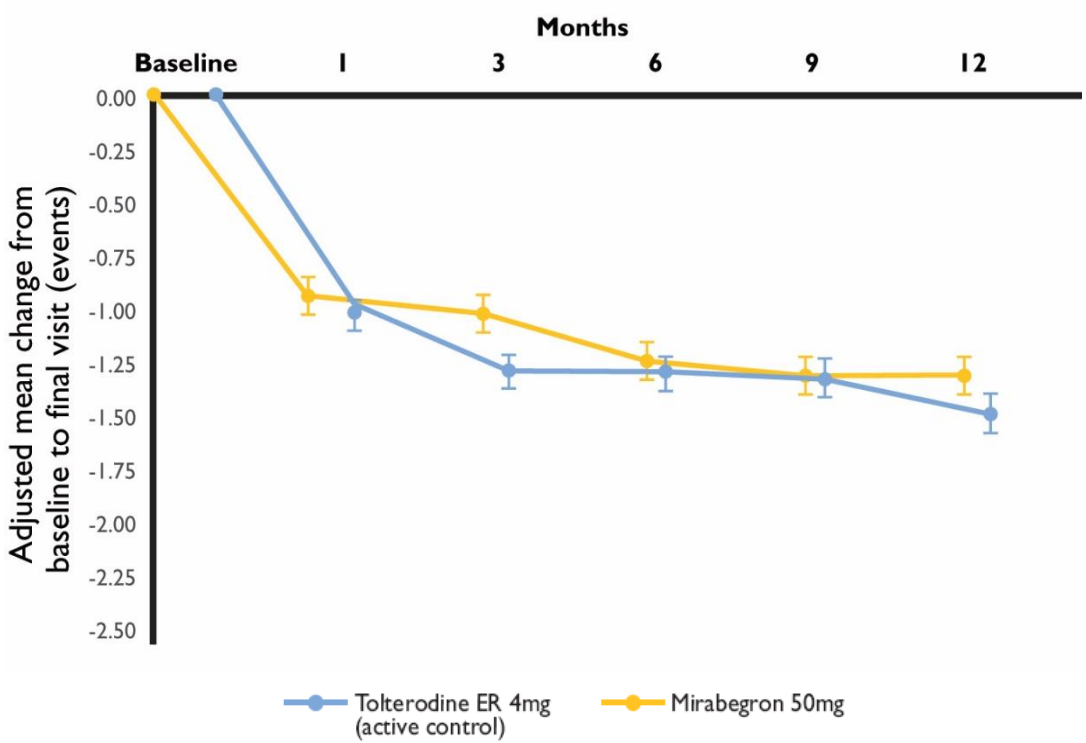
Adapted from Chapple CR *et al.*, 2013.[1]
Tolterodine ER (extended-release) 4mg was included as an active control in this study.
FAS-I = all full analysis set patients who had ≥1 incontinence episode at baseline.

1.Chapple CR *et al. Eur Urol* 2013;**63**(2):296–305.

Date of preparation: February 2013. BET13018UK

TAURUS: Efficacy variables over 52 weeks (secondary endpoint)

Mean number of micturitions/24h (FAS)[1]



Adapted from Chapple CR *et al.*, 2013.[1]
Tolterodine ER (extended-release) 4mg was included as an active control in this study.
FAS = full analysis set.

1.Chapple CR *et al. Eur Urol* 2013;**63**(2):296–305.

Date of preparation: February 2013. BET13018UK

Mirabegron 50mg – Administration considerations[1]

Contraindications

Patients with any hypersensitivity to the active substance or its excipients.

Dose adjustments

Dose adjustment to 25mg is recommended in patients with; mild/moderate renal and/or mild hepatic impairment receiving strong CYP3A inhibitor concomitantly and in patients with severe renal and/or moderate hepatic impairment.

Special populations

Should not be used in patients with:

- ◆End stage renal disease or requiring haemodialysis
- ◆Severe hepatic impairment
- ◆Severe uncontrolled hypertension (SBP ≥180mmHg and/or DBP ≥110mmHg)
- ◆Not recommended in patients with severe renal impairment and/or moderate hepatic impairment concomitantly receiving strong CYP3A inhibitors

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

1.Betmiga Summary of Product Characteristics, December 2012.

Date of preparation: February 2013. BET13018UK

NICE Technology Appraisal 290 (June 13)

NICE National Institute for Health and Care Excellence

Mirabegron for treating symptoms of overactive bladder

NICE technology appraisal guidance 290

1 Guidance

1.1 Mirabegron is recommended as an option for treating the symptoms of overactive bladder only for people in whom antimuscarinic drugs are contraindicated or clinically ineffective, or have unacceptable side effects.

1.2 People currently receiving mirabegron that is not recommended for them in 1.1 should be able to continue treatment until they and their clinician consider it appropriate to stop.

Mirabegron: Summary of key clinical data

- In clinical trials, mirabegron (50 mg) significantly reduced the number of daily micturitions and incontinence episodes compared with placebo[1–3]
  - –The efficacy of mirabegron was similar to tolterodine[4]

- Overall, mirabegron was well-tolerated, with a lower incidence of the well-known side effects of anticholinergics, such as dry mouth[1-4]

1. NCT00912964 http://clinicaltrials.gov/ct2/show/results/NCT00912964?sect=X430125#othr. Last accessed July 2013.
2. Nitti VW, et al. *J Urol* 2013;189:1388–95. 3. Khullar V, et al. *Eur Urol* 2013;63:283–95. 4. Chapple C, et al. *Eur Urol* 2013;63:296–305.

Dr Julian Spinks

Case Studies

Declaration of interests

I have received honoraria for speaking/writing from the following:

I currently advise or do work for:

I am chairman of :

Penny

Penny

- Age 85
- Widow 13 years, Lives alone
- Put on Oxybutynin 2.5mg X3 4 years ago during an admission to hospital for a hip replacement.
- Now increased
  - Frequency
  - Urgency
  - Some urgency incontinence
- Exam and urinalysis unremarkable

Complicating factors

- Recent admission for heart failure secondary to atrial fibrillation
- Early cognitive decline
- Other Medications
  - Metoprolol
  - Furosemide
  - Ramipril
  - Prochlorperazine
  - Co-codamol 15/500
  - Ranitidine

Initial thoughts?

Dilemmas

- Poorly controlled OAB
- Diuretics may worsen the situation
- Cognitive decline means caution when using anticholinergics
- Other drugs have anticholinergic properties
  - Ranitidine
  - Metoprolol
  - Prochlorperazine
- Co-codamol may be causing constipation

What would you do?

Pharmacological Options

- Increase oxybutynin
  - But likely to cause cognitive decline
- Use another Anticholinergic
  - E.g. Trospium or Fesoterodine
- Use Mirabegron
  - But ? Link to atrial fibrillation

Other measures

- Look at medication changes
  - Minimise diuretic dose
- Look for less cholinergic load from other drugs
  - Why on prochlorperazine?
  - Swap ranitidine to Proton Pump Inhibitor
  - Swap metoprolol for bisoprolol
- Ensure home is continence-friendly
- Candidate for botulinum toxin?
  - Probably not as unlikely to be able to self catheterise

Outcome

- Furosemide dose halved as heart rate controlled
- Prochlorperazine stopped
- PPI started
- Commode provided
- Put on Fesoterodine

- Good result with frequency and urgency controlled. Rarely incontinent.

Rose

Case Study: Rose


*

- Rose (96) is in a residential home due to failure to cope at home.
- The home wants her catheterised as she is incontinent several times a day and this predates her admission by several months

*Not a real Patient

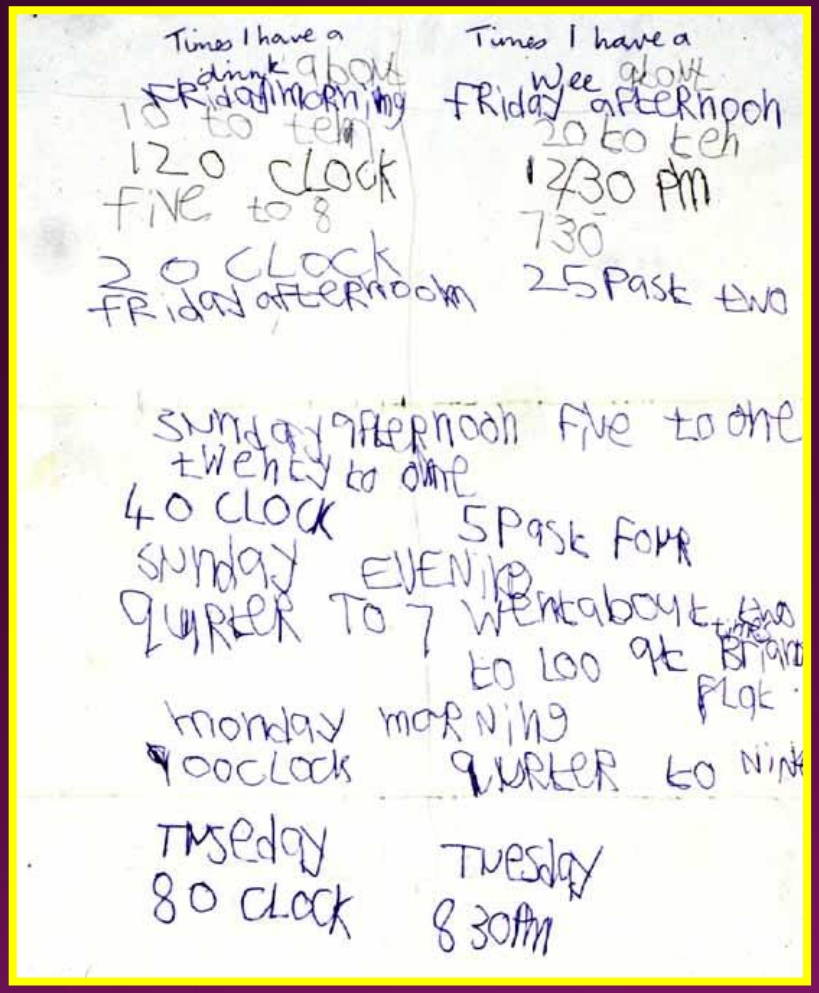
Would you catheterise?

Rose History

- PMH hypertension treated with Indapamide.
- Ankle oedema on furosemide
- No ops
- Non-smoker
- 2 children via normal delivery age 26
- Frequently wets the chair and her bed. Sometimes says she needs the toilet/commode but leaks before she gets there

Rose Exam/investigations

- Abdominal/pelvic exam
  - Slight uterine prolapse. Atrophic. Excoriation on buttocks
- Urinalysis Nitrite pos but afebrile
- Bladder diary
  - Staff asked patient to complete
- Bloods
  - eGFR 64
  - BNP 26



Times I have a drink about
FRIday morning
10 to ten
12 O CLOCK
FIVE to 8
2 O CLOCK
FRIday afternoon

Times I have a wee about
FRIday afternoon
20 to ten
12.30 PM
7.30
25 Past two

SUNday afternoon FIve to one
twenty to one
4 O CLOCK
5 Past FOUR
SUNday EVENing
QUARTER TO 7 went about two
to 100 at Bryan
FLat.
Monday morning
9 OO CLOCK
QUARTER TO NINE

TUSeday
8 O CLOCK

TUesday
8.30AM

Rose

- Second bladder diary
  - Fluid intake 1litre, mostly tea
  - Daytime frequency X12 (mostly incontinence)
  - Commonly wet in chair/bed or halfway down corridor to toilet

What would you do?

Continence Advisor

- Found
  - Rose sat at far end of day room away from the toilet
  - Her room had no en-suite toilet
  - Staff waited until called to assist toileting
- Action
  - Moved to chair near toilet
  - Commode placed in room
  - Fluids changed and increased
  - Staff to ensure out regular prompted voiding

Other action and outcome

- Antihypertensive reviewed and stopped.
- Furosemide stopped
- Prescribing delayed until effect of conservative measures known
- NO catheterisation

- Rose continues to have occasional incontinence
- Excoriation gone
- Staff and relatives happy

Samantha

Samantha

- 42 year-old mother of two
- Normal deliveries
- No previous presentations for incontinence
- Cholecystectomy 4 years previously
- Otherwise uneventful previous medical history

Samantha History

- "I was so fed up that I went to Harley Street"
- 8 year history of
  - Frequency
  - Urgency
  - Urgency incontinence
- No
  - Incontinence on movement, coughing, sneezing etc
  - Other urogenital symptoms
- She had been recommended she see a Urogynaecology Specialist in Harley street by a friend. This did not ned a GP referral.
- She has a letter

Specialist letter

- "Many thanks for referring Samantha"
- "She gives a history of incontinence so I felt it prudent to proceed to urodynamics"
- "The urodynamics showed some detrusor overactivity and urodynamic stress incontinence"
- "I have recommended a mid-urethral tape procedure"
- As she has no insurance, I would be grateful if you would refer her to my NHS clinic at St Famous Hospital

What would you do?

Outcome

- Difficult consultation
- Agreed to be referred to a different professor at St Elsewhere's
- Copy of original letter plus my concerns sent

- New specialist

- "I agree with you that the primary problem is OAB. I have passed the patient on to my urogynae nurse for bladder retraining and PFMT and started her on Solifenacin"