



Overactive Bladder Epidemiology and Management

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Definitions

- **Overactive bladder (OAB)** ¹
 - detrusor overactivity suspected to be the cause of urgency with or without urge incontinence usually with frequency and nocturia
- **Frequency** ¹
 - voids too often by day
- **Urgency** ¹
 - sudden, strong desire to pass urine, which is difficult to defer

Refs

1. Abrams P, Cardozo L, Fall M, *et al.* The standardization of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the ICS. *Neurol Urodynamics*. 2002;21:167-178

Definitions

- **Urinary incontinence** ¹
 - any involuntary leakage of urine
- **Urge incontinence** ¹
 - involuntary leakage of urine accompanied by or immediately preceded by urgency
- **Nocturia** ¹
 - individual has to wake at night one or more times to void

Refs

1. Abrams P, Cardozo L, Fall M, *et al.* The standardization of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the ICS. *Neurol Urodynamics*. 2002;21:167-178

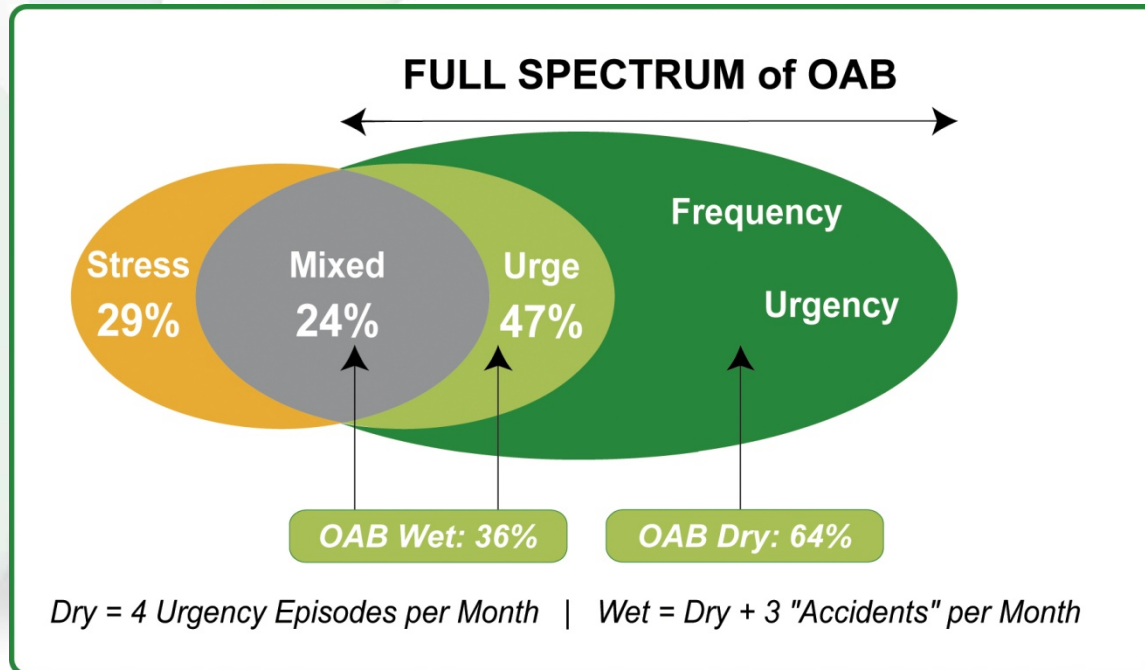
Definitions

- **Stress incontinence** ¹
 - involuntary leakage on effort or exertion, or on sneezing or coughing
- **Mixed incontinence** ¹
 - involuntary leakage associated with urgency and also with exertion, effort, sneezing or coughing

Refs

1. Abrams P, Cardozo L, Fall M, *et al.* The standardization of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the ICS. *Neurolog Urodynamics*. 2002;21:167-178

Prevalence



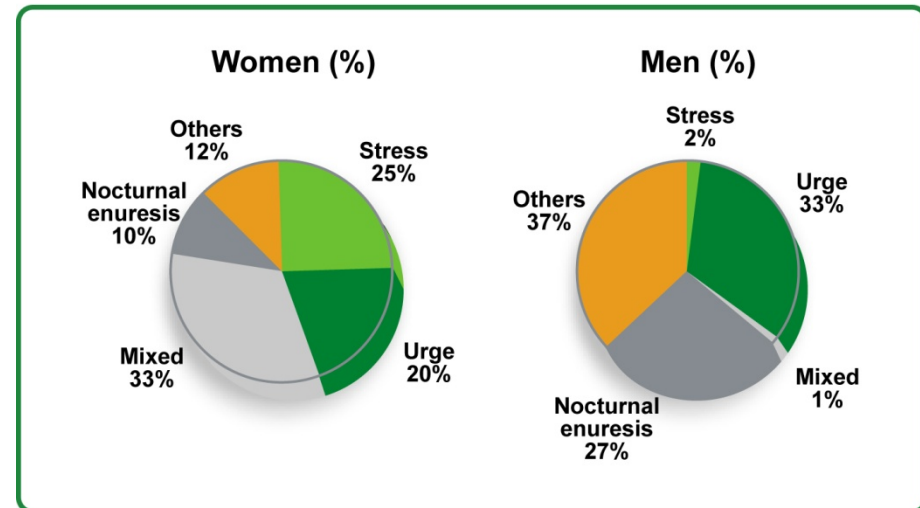
Refs

1. Abrams P, Cardozo L, Fall M, *et al.* The standardization of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the ICS. *Neurolog Urodynamics*. 2002;21:167-178
2. Stewart K, *et al.* Overactive bladder patients and the role of the pharmacist. *J Am Pharm Assoc*. 2002;42:469-478
3. Hampel *et al.* *Urology* 1997 Vol. 50 Suppl. 6A pp4-14

Prevalence of Urinary Incontinence

- Urinary incontinence (UI) has been estimated to affect 2-3 million individuals in the UK ⁴
- the incidence of urinary incontinence is higher in women than in men ⁴

Distribution of different types of urinary incontinence in men and women ^{4,5}



Refs

4. Cardozo L, Staskin D, Kirby M. *Urinary Incontinence in Primary Care*. Oxford, UK: Isis Medical Media Ltd; 2000:19-37

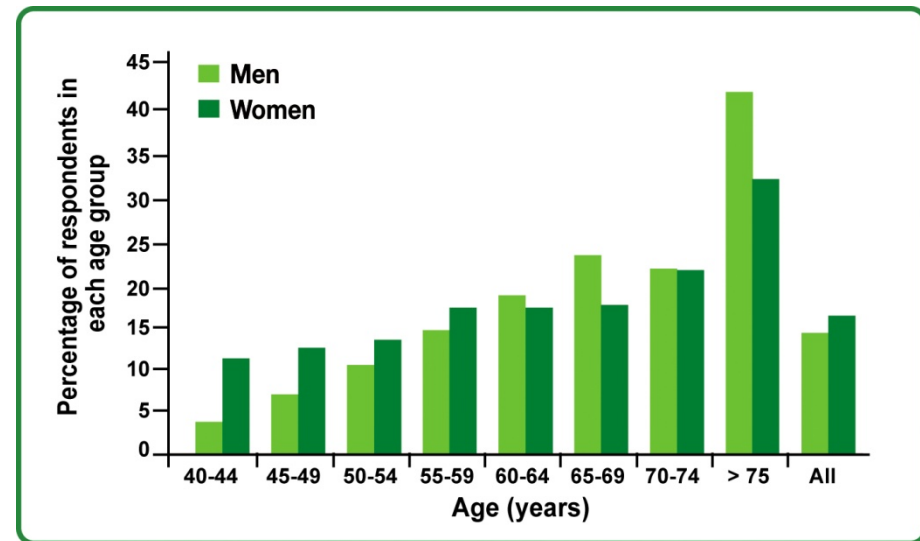
5. Feneley *et al*. *British Journal of Urology* 1979; 51,493-496

Prevalence of overactive bladder

Population-based survey carried out in six European countries including the UK

- estimated prevalence in the UK of > 5 million
- increased with advancing age
- equally apparent in men and women

Prevalence (%) of OAB symptoms, grouped according to age and gender

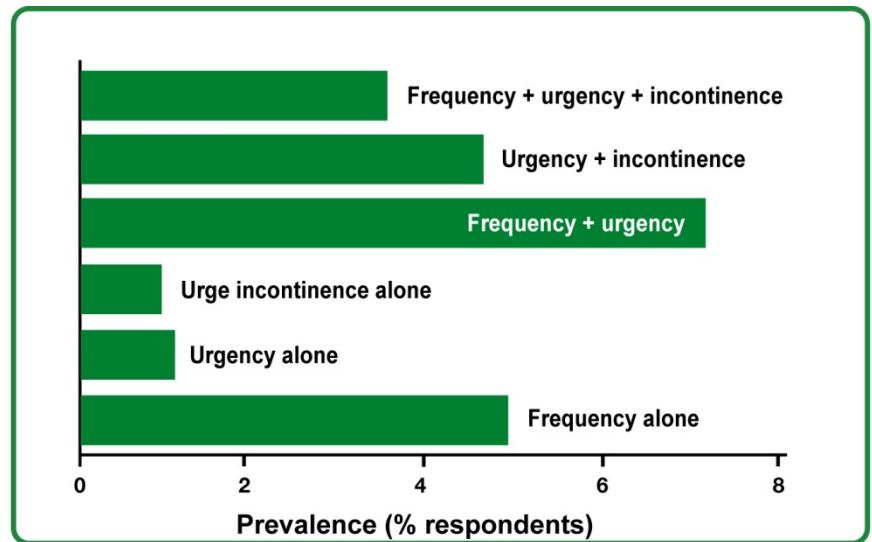


Prevalence of overactive bladder

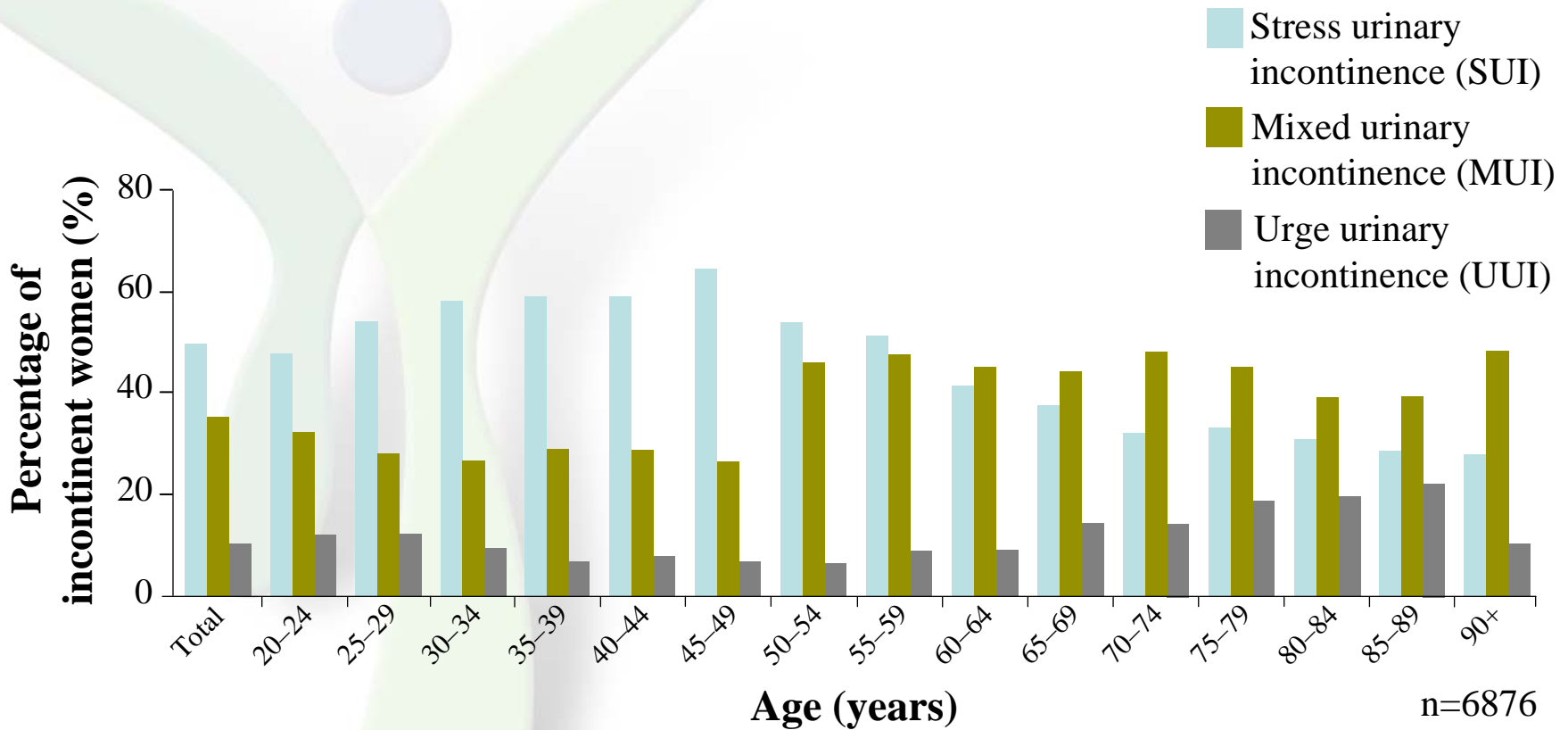
Most commonly reported symptoms

- frequency - 85%
- urgency - 54%
- urge incontinence - 36%

Prevalence of the different OAB symptoms

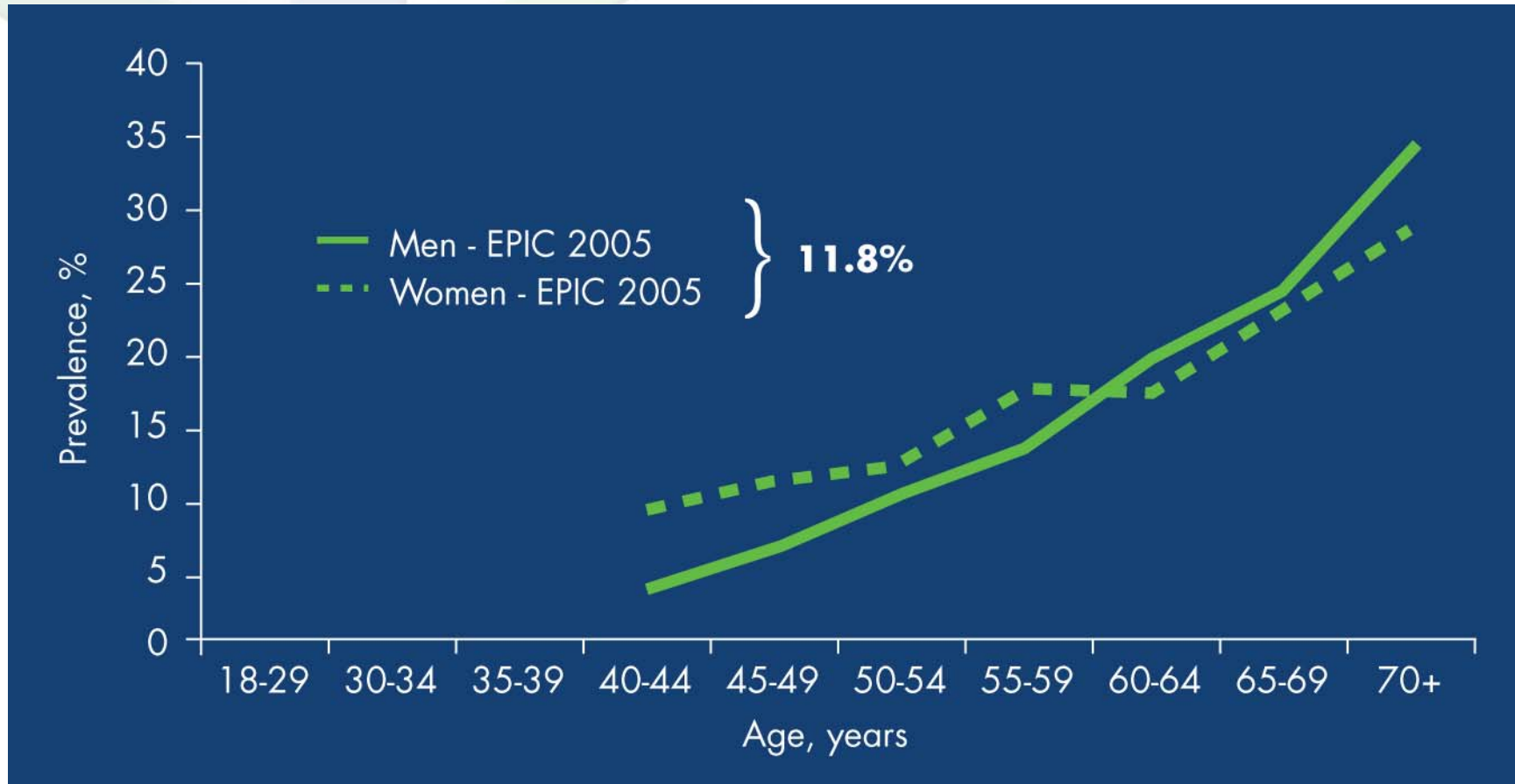


Relative proportions of UI by age¹



1. Hannestad YS et al. *J Clin Epidemiol* 2000; **53**: 1150–1157.
Reproduced with permission from Professor David Castro-Diaz.

OAB Symptoms are Prevalent in Both Men and Women and Increase With Age



Prevalence of overactive bladder

EPIC study *

- European population-based study
- Overall prevalence of OAB was 11.8%
- Similar in men and women
- Increased with age

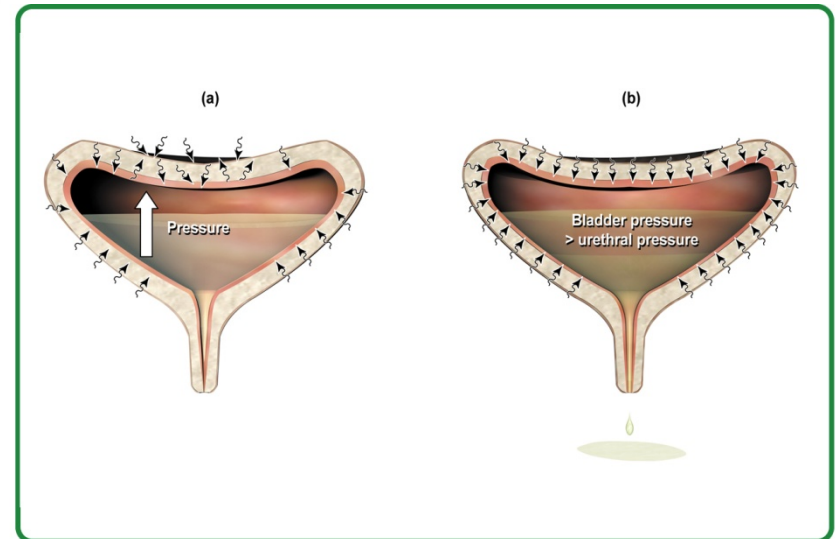
* used 2002 ICS definitions

Refs

7. Irwin DE, Milsom I, Hunskaar S, et al. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. EUR UROL 2006;50:1306-1315.

Classification - Overactive bladder

- inappropriate contractions of the detrusor muscle during the storage phase of the micturition cycle
- frequency
- urgency
- urge incontinence
- nocturia
- motor urgency
 - idiopathic
 - neurogenic
- sensory urgency



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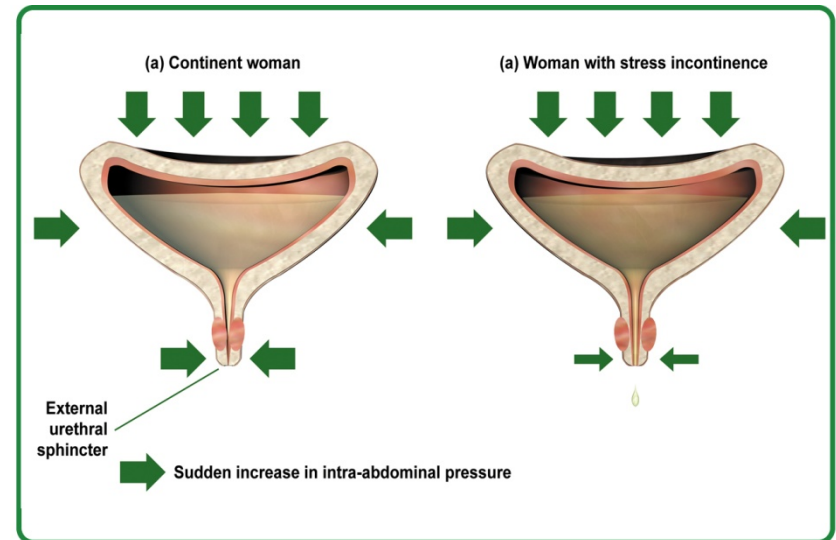
Refs

1. Abrams P, Cardozo L, Fall M, *et al.* The standardization of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the ICS. *Neurol Urodynamics*. 2002;21:167-178



Stress incontinence

- the involuntary leakage of urine on effort or exertion, or on sneezing or coughing
- sudden increase in abdominal pressure causes the pressure within the bladder to exceed the maximum closure pressure of the urethra in the absence of activity of the detrusor muscle
- prevalence of stress incontinence in women increases with advancing age, reaching a peak around the menopause (45-54 yrs of age)



Refs

4. Cardozo L, Staskin D, Kirby M. *Urinary Incontinence in Primary Care*. Oxford, UK: Isis Medical Media Ltd; 2000:19-37

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Mixed incontinence and other types of bladder problems

- mixed incontinence describes a combination of urge incontinence and stress incontinence
- overflow incontinence
- post-micturition dribble
- daytime incontinence in children (polysymptomatic enuresis)
- night-time incontinence in children (monosymptomatic nocturnal enuresis)

Refs

4. Cardozo L, Staskin D, Kirby M. *Urinary Incontinence in Primary Care*. Oxford, UK: Isis Medical Media Ltd; 2000:19-37

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Aetiology

NEUROGENIC DETRUSOR OVERACTIVITY

- Stroke
- Parkinson's disease
- Hydrocephalus
- Brain cancer
- Multiple sclerosis
- Spinal cord injury
- Spina bifida

IDIOPATHIC DETRUSOR OVERACTIVITY

- Idiopathic urethral obstruction
- Benign prostatic hyperplasia
- Bladder stones
- Bladder cancer
- Bladder infection
- Poor functioning of the urethral sphincter

Refs

4. Cardozo L, Staskin D, Kirby M. *Urinary Incontinence in Primary Care*. Oxford, UK: Isis Medical Media Ltd; 2000:19-37

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Aetiological factors

- Age
- Childbirth
- Gynaecological surgery
- Oestrogen status
- Connective tissue changes
- Lifestyle , such as obesity, chronic constipation, and smoking.

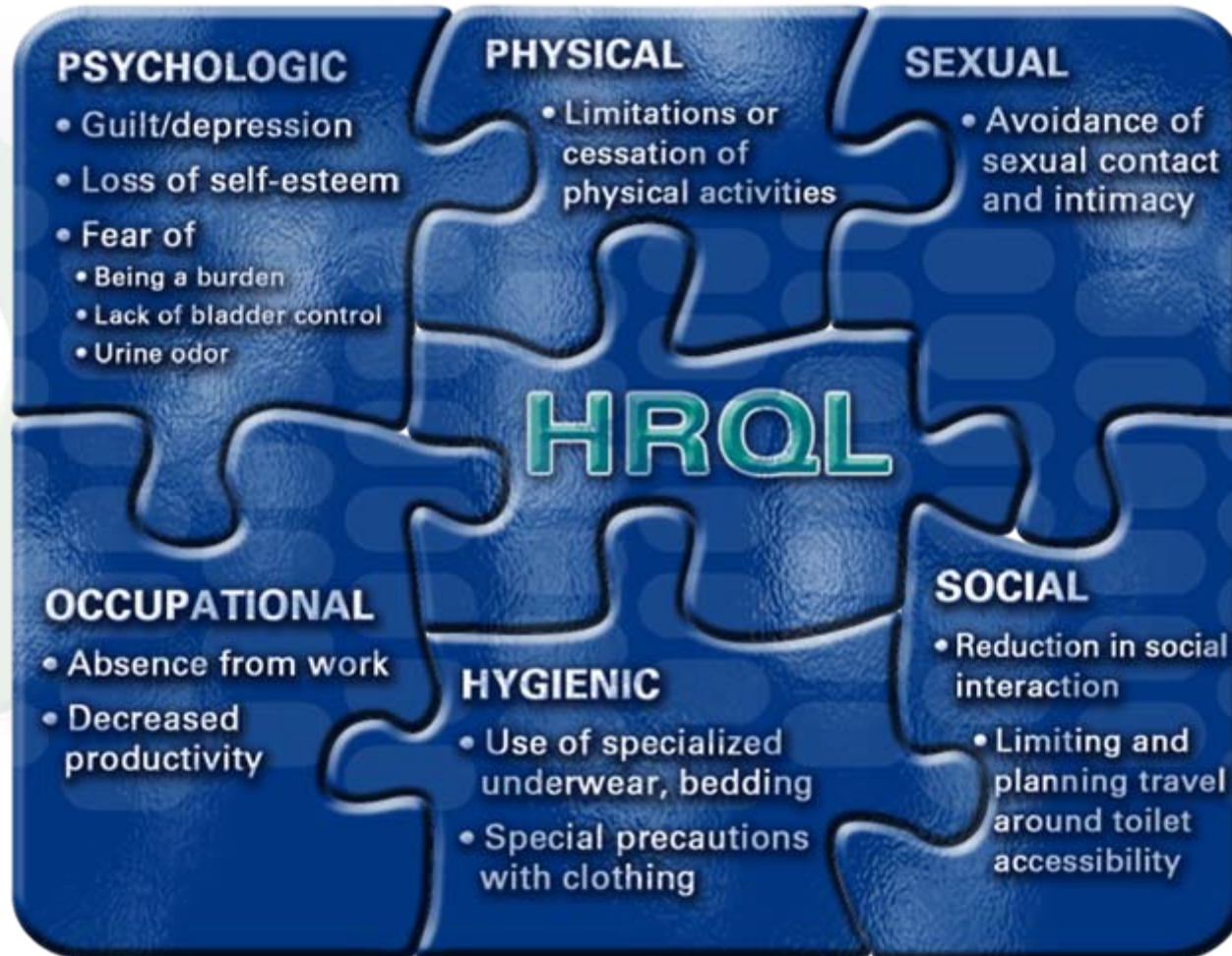
Refs

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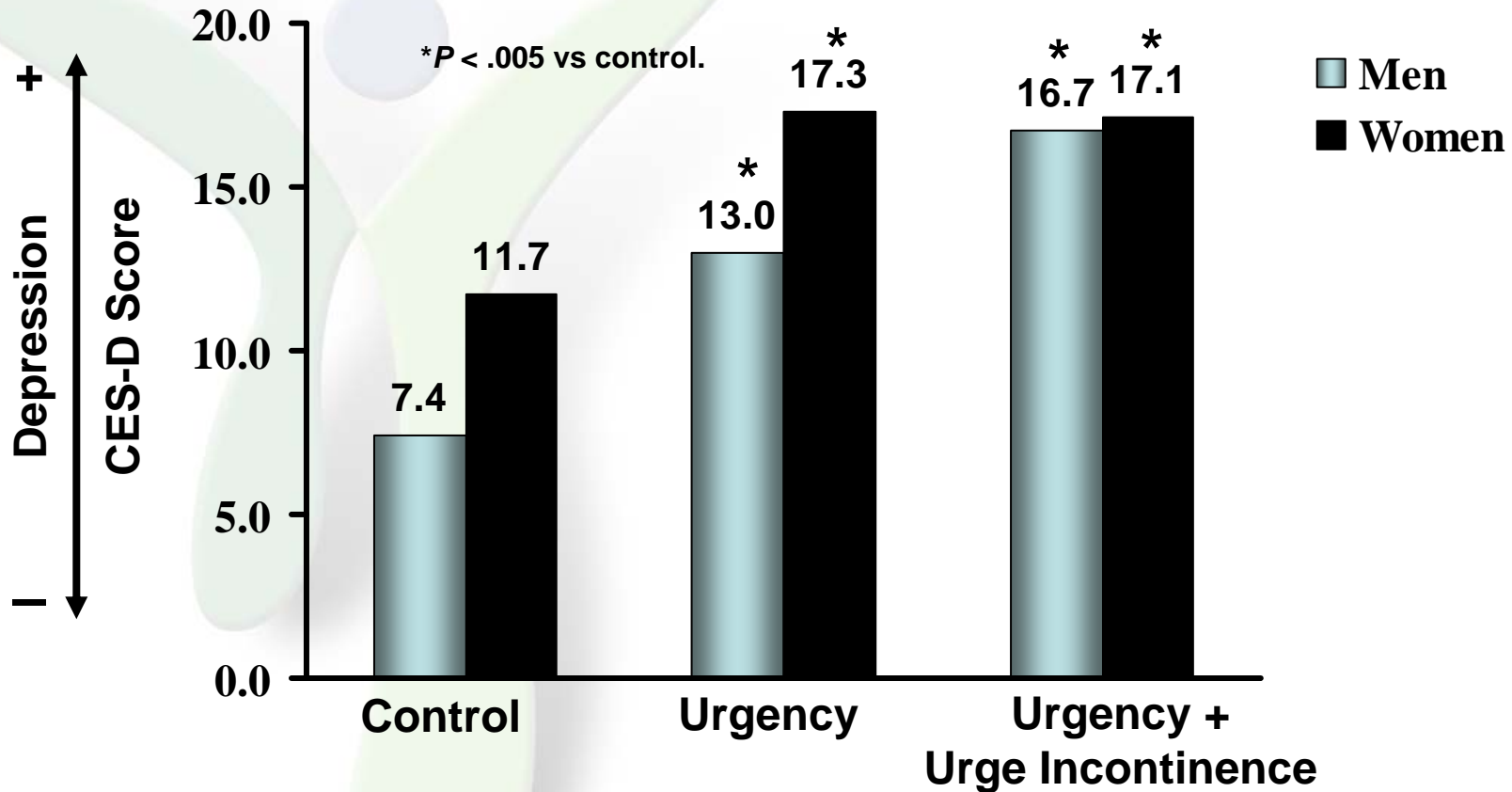
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OAB Symptoms Have a Significant Negative Impact on Health-Related Quality of Life

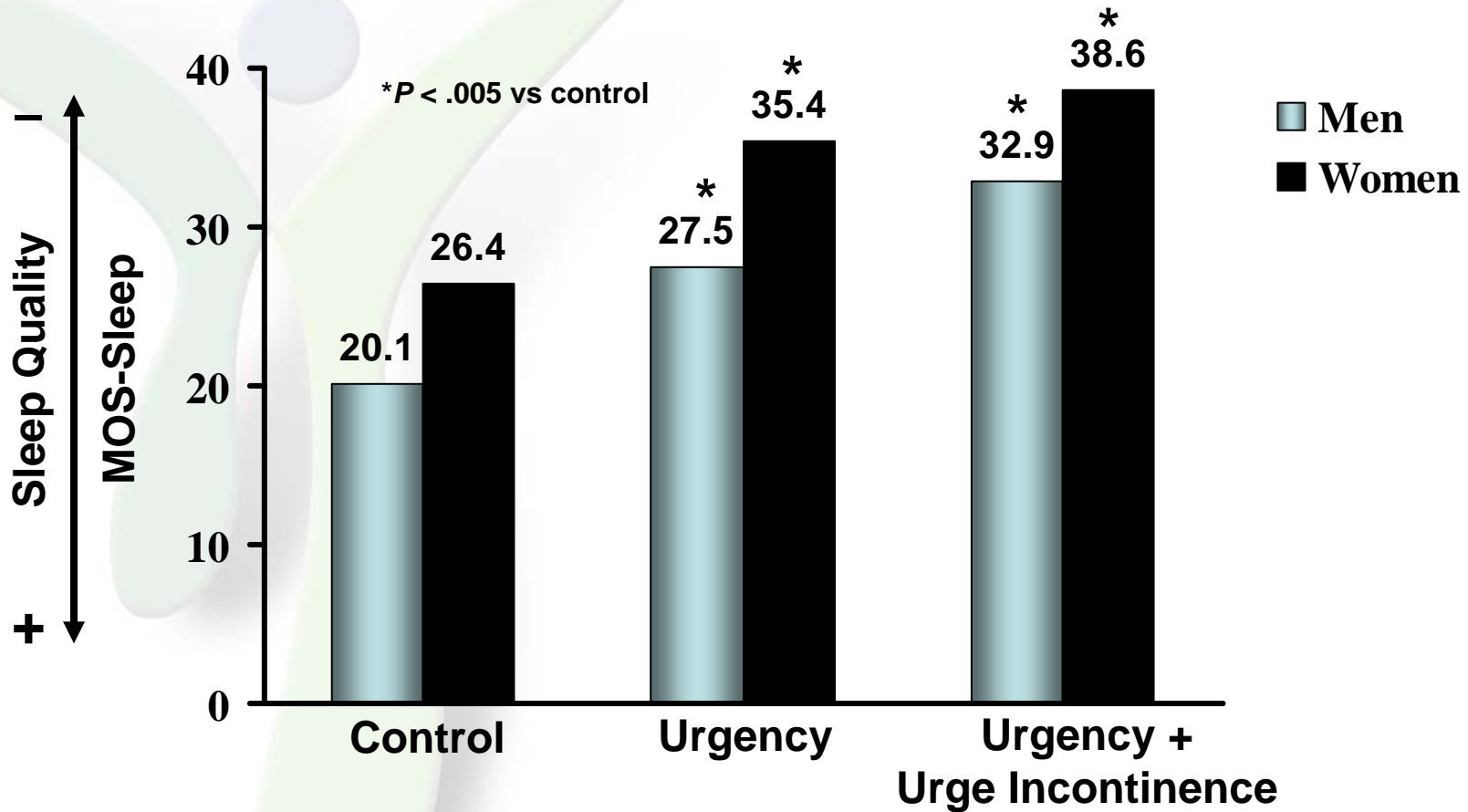


Effect of Urgency With and Without Urge Incontinence on Depression



CES-D = Centre for Epidemiologic Studies Depression Scale.

Effect of Urgency With and Without Urge Incontinence on Sleep Quality



MOS-Sleep = Medical Outcomes Sleep Scale.

Impact of OAB Symptoms on Sexual Functioning

Postal (SQoL-F) Questionnaire Survey of 127 Women with OAB and Urinary Incontinence at Five Urology/Urogynaecology Centres

Women with Sexual
Dysfunction
(59.0)

Healthy Women
(90.1)

SQoL-F Score

18
(Minimum
Score)

Women with
OAB (61.0)

108
(Maximum
Score)

Constipation Can Negatively Impact a Patient's Urinary Symptoms



- **Lower urinary tract symptoms**

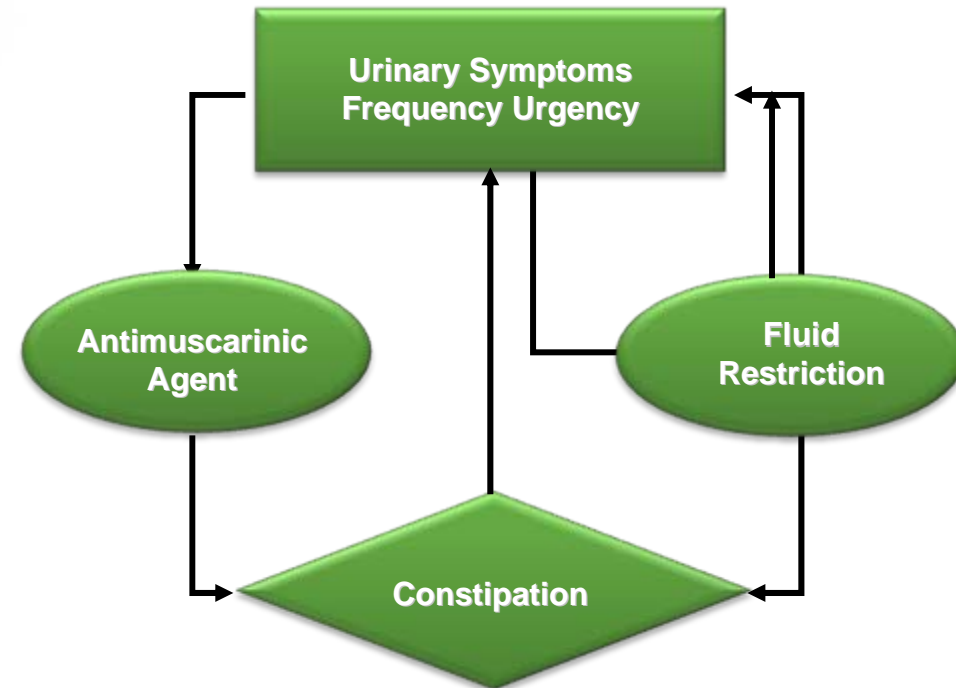
may worsen because of anatomic obstruction from constipated stool in the lower colon or rectum

- Patients with urologic disorders such as OAB are at **increased risk of constipation** due to

- Voluntary fluid intake restriction
- Medication that can exacerbate constipation

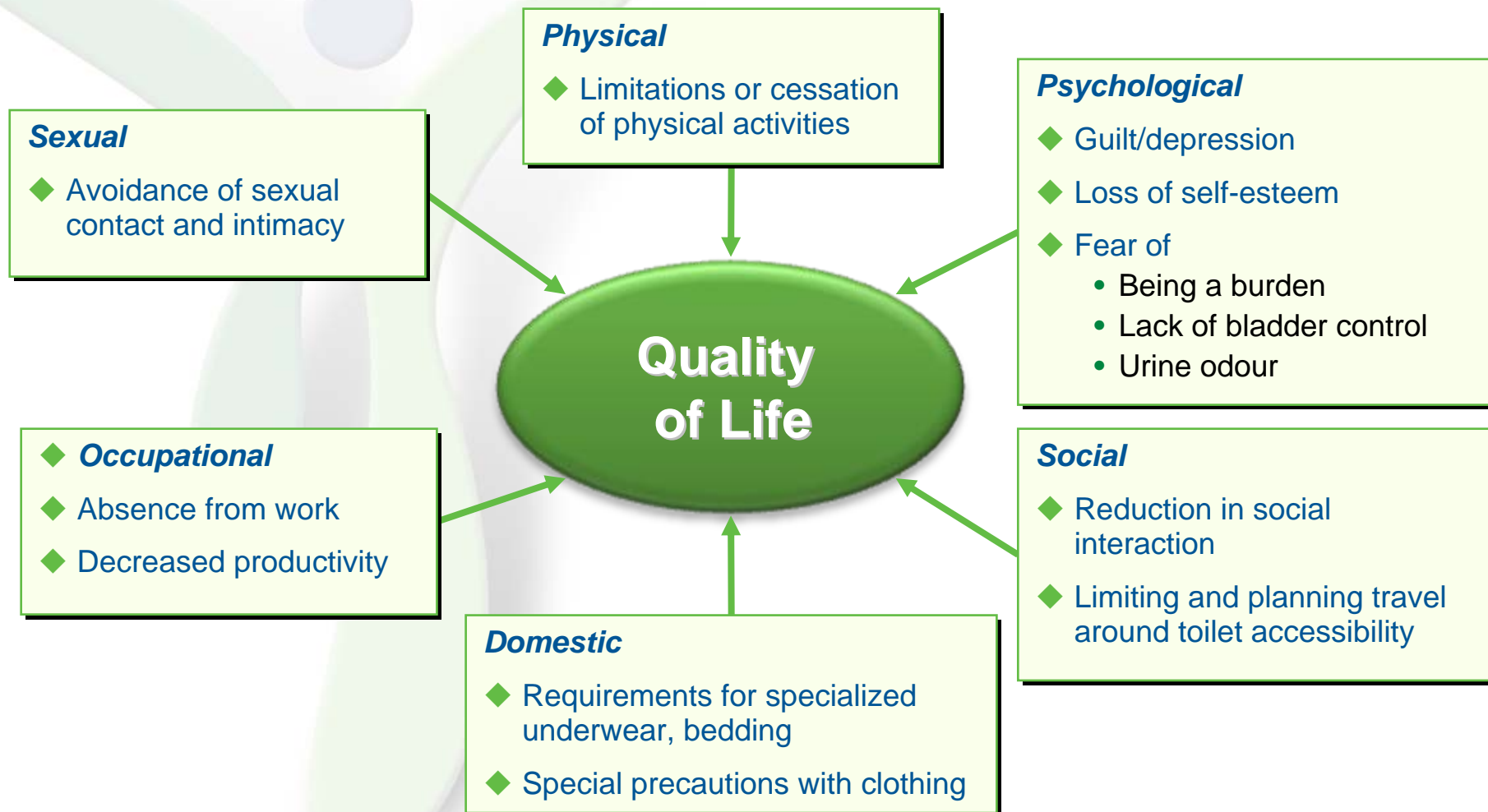
- Treating constipation has been shown to improve lower urinary tract symptoms in a clinical trial setting

Constipation can aggravate OAB symptoms

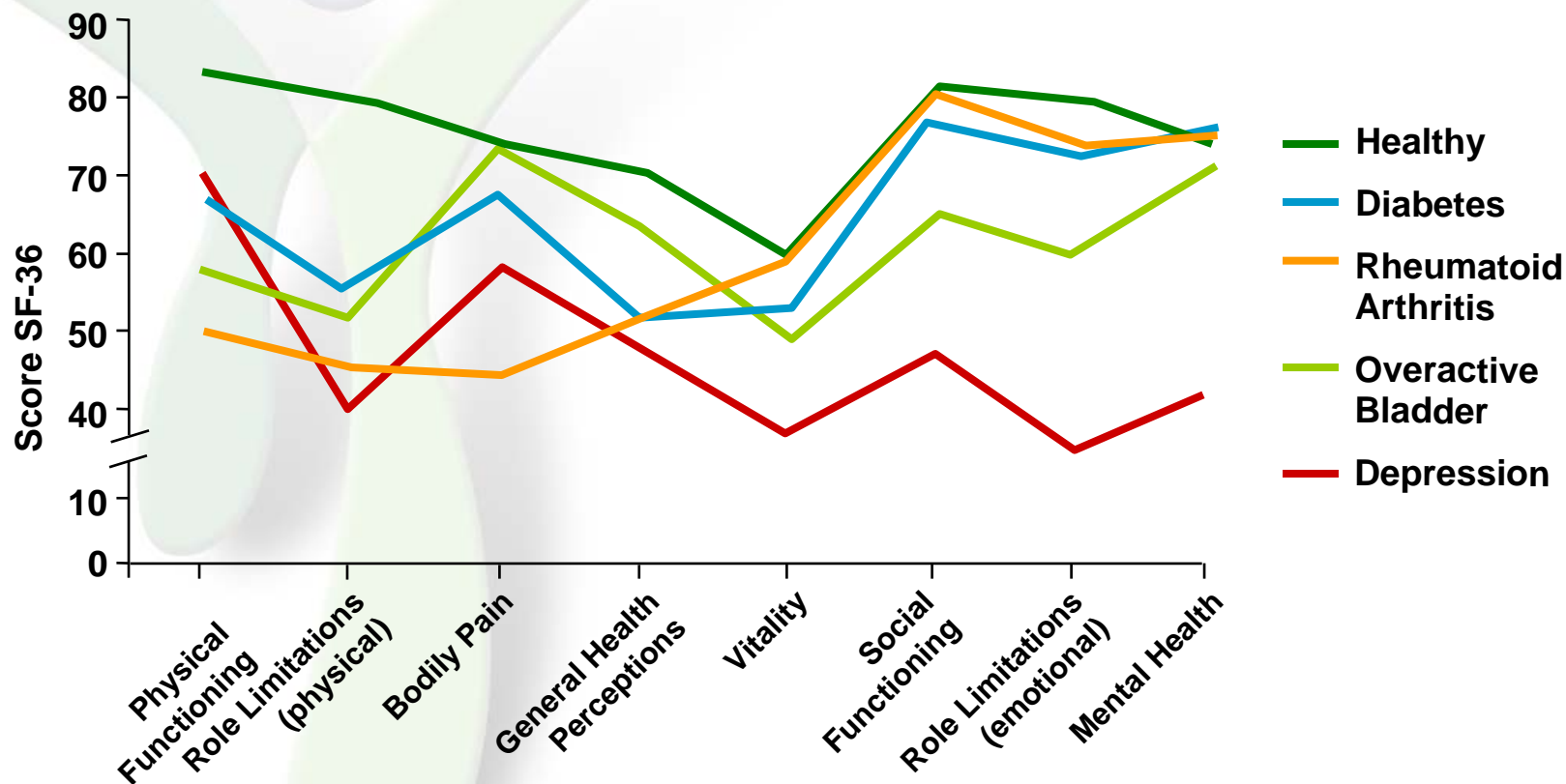


Incidence of Constipation Needs to Be Taken Into Account When Selecting an Antimuscarinic Drug, Especially in the Elderly

Impact of Overactive Bladder on Quality of Life



Impact on HRQL Compared with Other Conditions

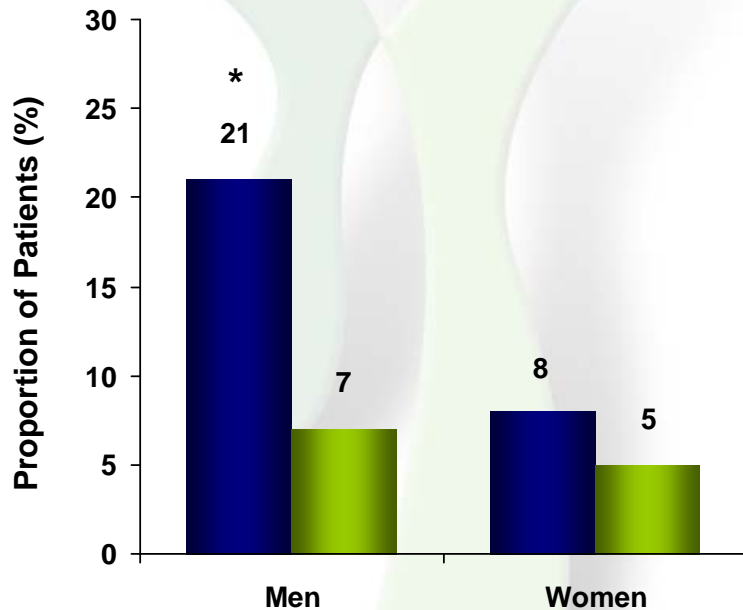


SF-36 self administered questionnaire measuring health perception. Low score means decrease in HRQL.

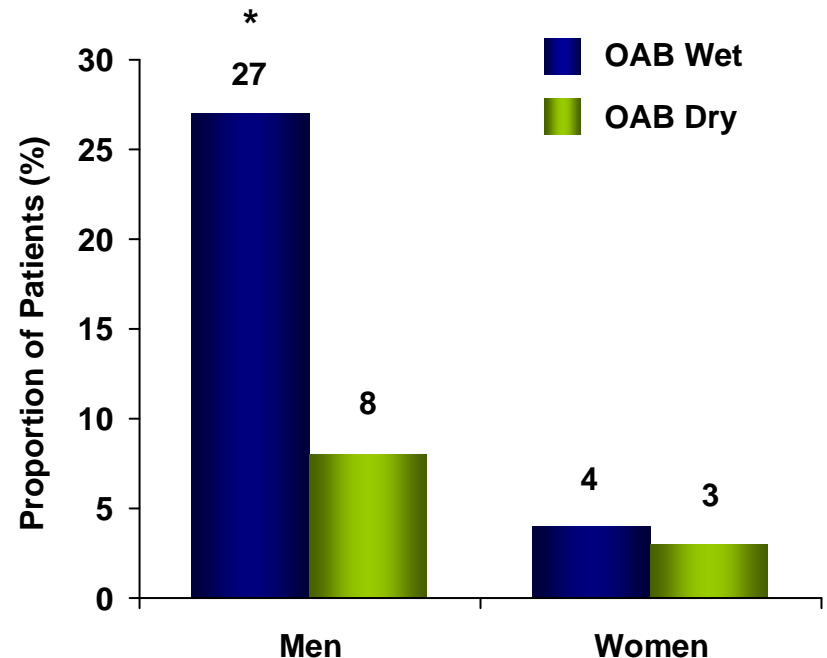
Impact of OAB Symptoms on Employment and Daily Life




OAB Symptoms Affect Decisions About Work Location and Hours



OAB Symptoms May Influence Voluntary Termination or Early Retirement



A stylized human figure with a light grey head and torso, and large, light green, teardrop-shaped limbs. The figure is positioned on the left side of the slide, with its arms raised and legs spread, suggesting a sense of movement or health.

Management and Treatment of OAB

Management of OAB

- Given the significant medical, social, and economic impact of OAB, it is crucial to optimize management
- The NICE guidelines in the UK state that behavioral therapy and bladder retraining is first line and then pharmacotherapy can be initialised.
- At present, antimuscarinic agents are first-line pharmacotherapy for OAB

Management of OAB

- Treat the cause.
- Lifestyle changes/education.
 - Behavioural.
 - Fluid intake, constipation, anxiety etc.
 - Bladder training (70% improvement).
- Drugs.
- Surgery.
 - Usually last resort. Augmentation 'Clam' Cystoplasty

Drugs for OAB

- Darifenacin
- Flavoxate
- Imipramine (Tricyclics)
- Oxybutynine ,
 - Immediate release
 - Transdermal (Kentera)
 - Intravesical
- Propantheline
- Propiverine
- Solifenacin (Vesicare)
- Tolterodine (Detrusitol), tabs, Extended release
- Fesoteridine (Toviaz)
- Trospium

Evidence statements for antimuscarinic drugs

- Treatment with darifenacin, oxybutynin, solifenacin, tolterodine and trospium in women with OAB is associated with improvements in frequency, leakage episodes and quality of life.
- There is ***no evidence of a clinically important difference in efficacy between antimuscarinic drugs***
- immediate release oxybutynin is the most cost effective antimuscarinic drug.

Evidence statements for antimuscarinic drugs

- Propiverine may be associated with an improvement in frequency.
- There is limited evidence that doxepin reduces night-time leakage episodes and nocturia.
- There is no evidence of efficacy for the use of flavoxate, propantheline or imipramine for the treatment of UI or OAB.

Evidence statements for antimuscarinic drugs

- Antimuscarinic adverse effects are common with all antimuscarinic drugs, and ***dry mouth*** is more likely with oral IR oxybutynin than tolterodine, trospium, ER or transdermal oxybutynin, but skin reactions are very common with the latter.

Obesity and Urinary Incontinence

Five cross-sectional studies found that the prevalence or risk of UI or OAB was higher with increased BMI, specifically:

- increased risk of UI with BMI > 25.
- women with regular UI had the highest mean BMI.
- increased risk of two or more nocturia episodes versus one episode for women with BMI of 30 or more versus less than 20

NICE Guideline Recommendation.

Women with UI or OAB who have a BMI > 30 should be advised to lose weight.

Recommendations for behavioural therapies

Bladder training lasting for a minimum of 6 weeks should be offered as first-line treatment to women with urge or mixed UI. [A]

If women do not achieve satisfactory benefit from bladder training programmes, the combination of an antimuscarinic agent with bladder training should be considered if frequency is a troublesome symptom. [A]

In women with UI who also have cognitive impairment, prompted and timed voiding toileting programmes are recommended as strategies for reducing leakage episodes. [A]

Recommendations for antimuscarinic drugs

Immediate release non-proprietary oxybutynin should be offered to women with OAB or mixed UI as first-line antimuscarinic drug treatment, if bladder training has been ineffective.

If immediate release oxybutynin is not well tolerated, darifenacin, solifenacin, tolterodine, trospium or an extended release or transdermal formulation of oxybutynin should be considered as alternatives.

Women should be counselled about the adverse effects of antimuscarinic drugs. [A]

Propiverine should be considered as an option to treat frequency of urination in women with OAB, but is not recommended for the treatment of UI. [A]

Flavoxate, propantheline and imipramine should not be used for the treatment of UI or OAB in women. [A]

Desmopressin

Desmopressin (DDAVP) is a synthetic analogue of vasopressin or antidiuretic hormone,

Acts by inhibiting diuresis while avoiding vasopressive effects.

Used at night, it decreases nocturnal urine production.

There is insufficient evidence that desmopressin reduces incontinence in adult women.

BEWARE: A reduction in serum sodium is very common (more than 10%). Commonest in elderly and soon after initiating treatment.

Recommendation

The use of desmopressin may be considered specifically to reduce nocturia in women with UI or OAB who find it a troublesome symptom. [A

Diuretics

- There is insufficient evidence to support the use of diuretics for the treatment of nocturia in women with UI.

Evidence statements for Duloxetine

- Duloxetine is a serotonin and noradrenaline reuptake inhibitor (SNRI) that acts chiefly in the sacral spinal cord. It is thought that the resultant increase in pudendal nerve activity increases urethral sphincter contraction and closure pressure.
- It is licensed for use in ***moderate to severe stress UI***.
- Short-term studies (up to 12 weeks) suggest that the use of duloxetine is associated with a reduction in leakage episodes, an increased voiding interval and improved quality of life in women with stress UI or mixed UI where stress-related leakage is the predominant symptom
- The combination of duloxetine and PFMT is more effective than no treatment. It remains unclear whether the combination is better than either treatment alone.

Recommendation for duloxetine

- Duloxetine is ***not*** recommended as a first-line treatment for women with predominant stress UI.
- Duloxetine should ***not*** routinely be used as a second-line treatment for women with stress UI, although it may be offered as second-line therapy if women prefer pharmacological to surgical treatment or are not suitable for surgical treatment.
- If duloxetine is prescribed, women should be counselled about its adverse effects.

Recommendations for oestrogens

- Systemic hormone replacement therapy is not recommended for the treatment of UI. [A]
- Intravaginal oestrogens are recommended for the treatment of OAB symptoms in postmenopausal women with vaginal atrophy. [A]

Recommendation for Complementary Therapies

- Hypnotherapy, Acupuncture, Herbal medicines.
- Poor-quality evidence shows that acupuncture may reduce nocturia and both stress and urge incontinence in the short term (up to 4 weeks) but it is unclear whether any particular acupuncture treatment is more effective than others
- Despite poor evidence some women may still chose to explore this area for treatment of UI or OAB
- ***Complementary therapies are not recommended for the treatment of UI or OAB.*** [D]

Botox

- Botulinum toxin is a potent neurotoxin derived from the bacterium *Clostridium botulinum*.
- Two strains are available for clinical use, types A and B.
- Botulinum toxin is known to block the release of acetylcholine and it will temporarily paralyse any muscle into which it is injected.
- However, the precise mechanism of action when injected into the detrusor muscle is unknown.
- It can be injected directly into the bladder wall and performed as a day case procedure using a flexible cystoscope.

Recommendations for Botulinum Toxin

Bladder wall injection with botulinum toxin A should be used in the treatment of idiopathic detrusor overactivity only in women who have not responded to conservative treatments and who are willing and able to self-catheterise.

Women should be informed about the lack of long-term data.

The use of botulinum toxin A for this indication is outside the UK marketing authorisation for the product. Informed consent to treatment should be obtained and documented.

Botulinum toxin B is not recommended for the treatment of women with idiopathic OAB. [D]

Vanilloid receptor agonists

- Resiniferatoxin is a derivative of capsaicin (chilli pepper). Intravesical installation.
- In a study by Palma (2004) in women refractory to antimuscarinic treatment, urgency and urge UI were significantly reduced 1 month after resiniferatoxin treatment.
- No relevant studies of sufficient quality regarding the use of capsaicin are identified.

Overactive bladder syndrome (OAB) with or without urge UI

Do an MSU

- Recommend caffeine reduction.
- First-line treatment for urge or mixed UI should be bladder training lasting at least 6 weeks. If frequency remains troublesome, consider adding an antimuscarinic drug.
- If bladder training is ineffective, prescribe non-proprietary oxybutynin.
 - Counsel the woman about adverse effects of antimuscarinic drugs.
 - If oxybutynin is not tolerated, alternatives are darifenacin, solifenacin, tolterodine, trospium, or different oxybutynin formulations.
 - Carry out an early treatment review after any change in drug.
- In postmenopausal women with vaginal atrophy, offer intravaginal oestrogens for OAB symptoms.
- In women with UI who also have cognitive impairment, prompted and timed toileting programmes may help reduce leakage episodes.
- Do not routinely use electrical stimulation in OAB.

OAB with or without urge UI

- Discuss the risks and benefits of surgical and non-surgical options.
- Consider the woman's child-bearing wishes during the discussion.

If conservative treatments have failed, consider:

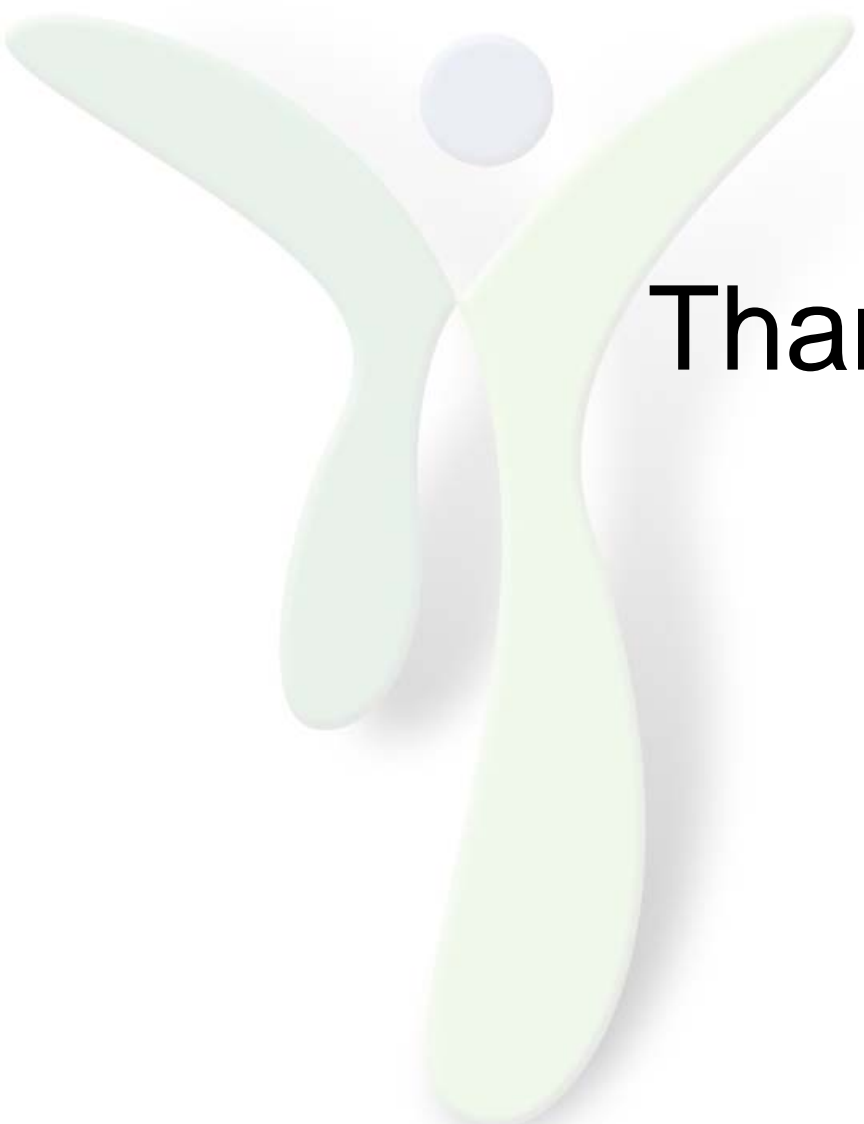
- botulinum toxin A to treat idiopathic detrusor overactivity in those willing and able to self-catheterise; explain the lack of long-term data;
- sacral nerve stimulation for UI due to detrusor overactivity;
- augmentation cystoplasty in those willing and able to self-catheterise; explain common and serious complications and the small risk of malignancy in the augmented bladder*
- urinary diversion if sacral nerve stimulation and augmentation cystoplasty are not appropriate or unacceptable.

Other treatments for UI or OAB

- Consider desmopressin to reduce troublesome nocturia.
- Consider propiverine to treat frequency of urination in OAB.

The following are not recommended:

- propiverine for the treatment of UI
- flavoxate, imipramine and propantheline
- systemic hormone-replacement therapy
- complementary therapies.



Thank You





Quality of life

- **Social**
 - Reduction in social interaction/increased social isolation
 - Alteration of travel plans (e.g. plan trips around availability of toilets)
 - Cessation of some hobbies
- **Psychological**
 - Depression
 - Loss of self-respect/dignity/low self-esteem
 - Apathy
 - Guilt
 - Denial
 - Feeling of lack of control over bladder function
 - Feeling of being a burden
 - Fear of smelling of urine
- **Occupational**
 - Absence from work
- **Domestic**
 - Neglect of household chores
 - Marital/family problems
 - Requirement for specialist bedding, underwear
 - Special precautions on clothing (e.g. wear dark clothes to hide signs of OAB)
- **Physical**
 - Limitation or cessation of physical activities
 - Elderly people may be placed in nursing homes as a result of their incontinence
- **Sexual**
 - Avoidance of sexual contact

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Refs

8. AFUD American Foundation for Urological Disease 2003 Background Information:1-4
9. Khullar V *et al*, Abstract No. 241



Measuring quality of life

- self assessment questionnaires
- individuals with OAB have an impaired quality of life compared with the normal population
- women suffering from OAB have a poorer quality of life than those suffering from stress incontinence.¹⁰

Refs

10. Wyman *et al* (abstract) *Obstet. Gynecol.* 1987;70:378-381

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Economic costs

- costs associated with OAB have shown a significant increase in recent years and are anticipated to continue to rise - as elderly population increases
- likely to be much higher than currently estimated
 - only direct costs considered
 - indirect costs ignored

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Care costs

- **National Service Framework for Older People** ¹¹
 - person-centred care
 - identifying patients at risk
 - medicines and older people
- **Department of Health Good Practice in Continence Services** ¹¹
 - review of continence services initiated in 1998
 - concluded that continence services should
 - be integrated,
 - focus on identifying patients
 - assess their condition
 - put appropriate treatment in place
- **Continence Advisors** ¹²

Refs

11. DOH web site www.dh.gov.uk Publications and Statistics, 2001:1-194

12. RCN publication 001 952 *Improving continence care for patients - The role of the nurse: 1-8*

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References

1. Abrams P, Cardozo L, Fall M, *et al.* The standardization of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the ICS. *Neurol Urodynamics*. 2002;21:167-178
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6. Milsom *et al.* *BJU International* 2001: 87,760-766
7. Irwin DE, Milsom I, Hunskaar S, *et al.* Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. *EUR UROL* 2006;50:1306-1315.
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9. Khullar V *et al*, Abstract No. 241
10. Wyman *et al* (abstract) *Obstet. Gynecol.*1987;70:378-381
11. DOH web site www.dh.gov.uk Publications and Statistics, 2001:1-194
12. RCN publication 001 952 *Improving continence care for patients - The role of the nurse: 1-8*

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Background to overactive bladder



Ref: TOV080
Date of Preparation: April 2008
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Drugs Used to Treat OAB

Drug	Dose	Side Effects
Oxybutynine(Ditropan)	2.5mgsbd-5mgs qds	Dry Mouth(78%), Blurred vision(11%) GI Symptoms(40%)
Tolterodine(Detrusitol)	1-2mgsqds(XL 4mgs)	Dry Mouth (40%)
Propantheline	15-30mgs qds	Prominent anticholinergic side effects.
Propiverine (Detrunorm)	15mgs tds	Dry mouth (12%) Drowsiness(10%)
Trospium (Regurin)	20mgs bd	Quarternary ammonium compound

Drugs Used to Treat OAB

Drugs	Dose	Side Effects
Imipramine	10-25mgs tds	Postural hypotension Tricyclic antidepressant
Desmopressin (DDAVP)	20-40mgs intranasally at night	Hyponatraemia. Antidiuretic. headache. nausea.
Dicyclomine	10-40mgs qds	Smooth muscle relaxant. dry mouth
Solafenicin	5-10mgs daily	M3-receptor antagonist Dry mouth
Vaginal Oestrogen creams	0.5gms pv daily for 2ks then twice weekly	

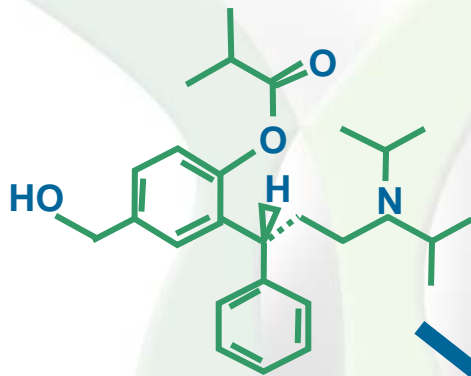
Background to overactive bladder

- 
- **Definitions**
 - **Prevalence**
 - **Classification**
 - **Aetiological factors**
 - **Quality of life**
 - **Economic costs**

What Links Fesoterodine to Tolterodine?

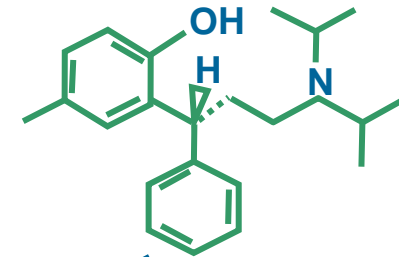


Fesoterodine



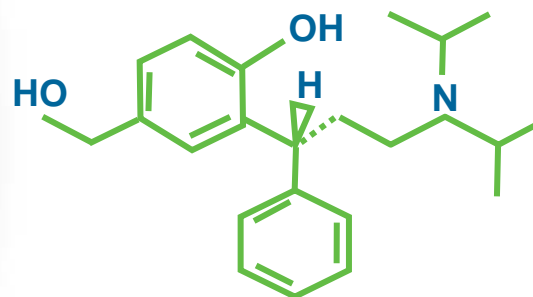
Rapid conversion
by ubiquitous
esterases

Tolterodine



Liver
metabolism
(CYP2D6)

Both fesoterodine and
tolterodine form 5-HMT
(the active metabolite)
via *different* pathways

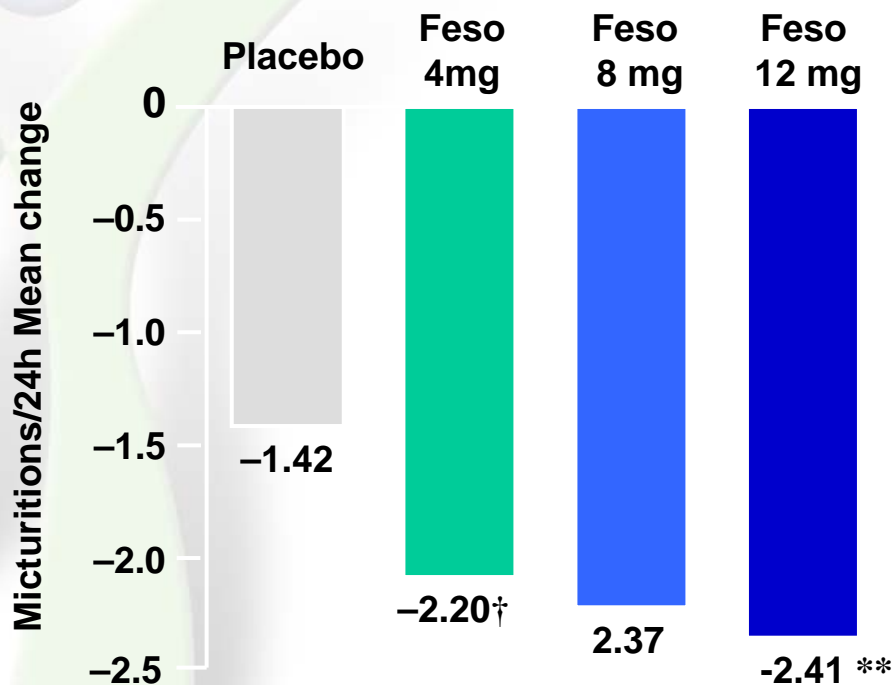


5-Hydroxymethyl Tolterodine (5-HMT)*

*Also known as SPM 7605 and DD01.

SP582: Treatment with 4mg, 8mg and 12mg Fesoterodine Produced Significant Reductions in Number of Micturitions per 24 hours compared with Placebo by Week 12

Mean Change from Baseline in Micturitions per 24 Hours



All vs. placebo

†p = 0.003 *p = 0.0012 **p = 0.0002

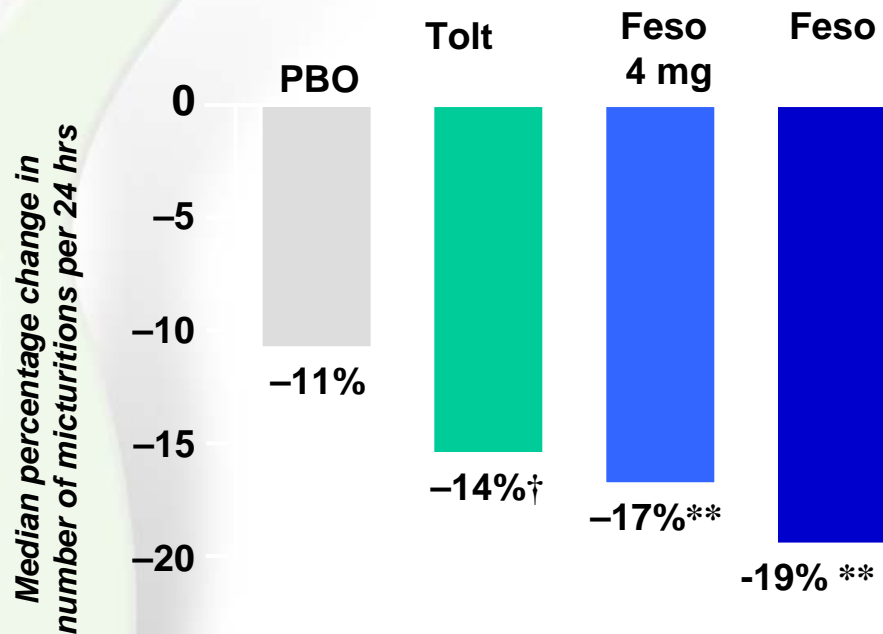
Trial SP 582: Adverse Events

• AEs Reported by $\geq 1\%$ in any Treatment Group

Event	Placebo (n = 183)	4 mg (n = 186)	8 mg (n = 173)	12 mg (n = 186)
Dry mouth %	9	25	26	34
Headache %	16	17	16	15
Influenza-like symptoms %	8	9	4	4
Abdominal pain %	4	3	8	8
Nausea %	7	5	2	6
Constipation %	3	2	3	6
Back pain %	3	3	4	2
Coughing %	4	3	<1	3
Dizziness %	3	4	1	2
Abnormal vision%	1	0	0	1

SP583: Treatment with Fesoterodine Produced Significant Reductions in Number of Micturitions per 24hrs Compared to Placebo at Week 12

Median Percentage Change from Baseline in number of micturitions per 24 hours*



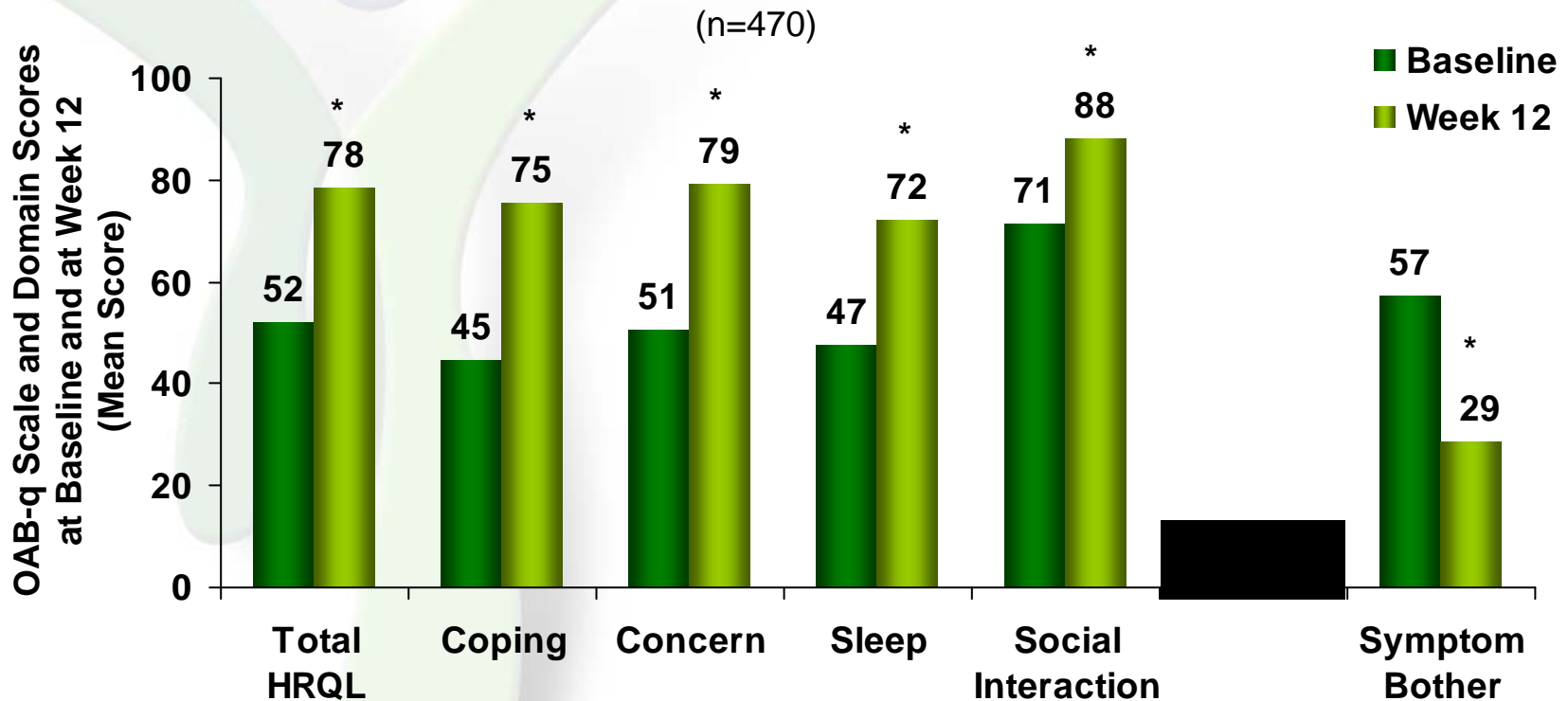
Average baseline values = 12, 11.5, 11.6, 11.9
Change from baseline^s = -0.95, -1.73, -1.76, -1.88

not
0.001 vs. placebo

Treatment with Fesoterodine Resulted in Improved OAB-q Scores Compared with Baseline



Overactive Bladder Questionnaire Scores



Minimally important difference (MID) = 10 points for all OAB-q scales and domains.

HRQL = health-related quality of life.

Higher HRQL and domain scores indicate improvement; lower Symptom Bother score indicates improvement.

* $p < 0.0001$ vs baseline.

Wyndaele JJ et al. Presented at IUGA 2008.

Tolerability

In a phase III pivotal study¹

- Low discontinuation rate¹
 - **Less than 1%** incidence of treatment discontinuation due to dry mouth or constipation² in a clinical trial involving **1,120 patients**
- Low incidence of CNS and Cardiovascular Adverse Events
 - Similar to **placebo** in **all groups**¹

	Placebo (n = 283)	Fesoterodine 4 mg (n = 272)	Fesoterodine 8 mg (n = 287)
Alanine aminotransferase (ALT)	<1%	<1%	2.1%
Constipation	1.4%	3.3%	4.5%
Dry eye	0%	2.2%	4.2%
Dry mouth	7.1%	21.7%	33.8%
Severe dry mouth	0%	0%	3%
Dry throat	0%	<1%	2.8%
Influenza	2.1%	3.3%	<1%
Nasopharyngitis	2.5%	2.9%	1.7%
Nausea	<1%	<1%	1.4%

Please refer to the full Toviaz SPC for further detailed information on adverse events

Summary of Toviaz® Characteristics

- Proven Efficacy¹
- Demonstrated Tolerability^{1,2}
- Improved Quality of Life compared with placebo³
- Flexible dosage: 4 mg and 8 mg²
 - Starting dose: **4 mg** titrated up to **8 mg** based on individual response
- Once-daily dosing
- No food effect⁴
- Same active metabolite as tolterodine (5-HMT)

¹Chapple C, et al. *Eur Urol*. 2007. Oct; 52(4):1204-12.

²Khullar V, et al. *Urology* 2008 May;71(5)839-43

³Kelleher C, et al. *BJU Int* 2008 Jul;102(1):56-61

⁴Toviaz® EMEA Scientific discussion