TIBIAL NERVE STIMULATION: ONE OF SEVERAL NEW OPTIONS FOR THE MANAGEMENT OF OVERACTIVE BLADDER IN WOMEN

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Declaration of Conflict of Interest

No relationship with pharmaceutical industry

Invented a pessary for SUI

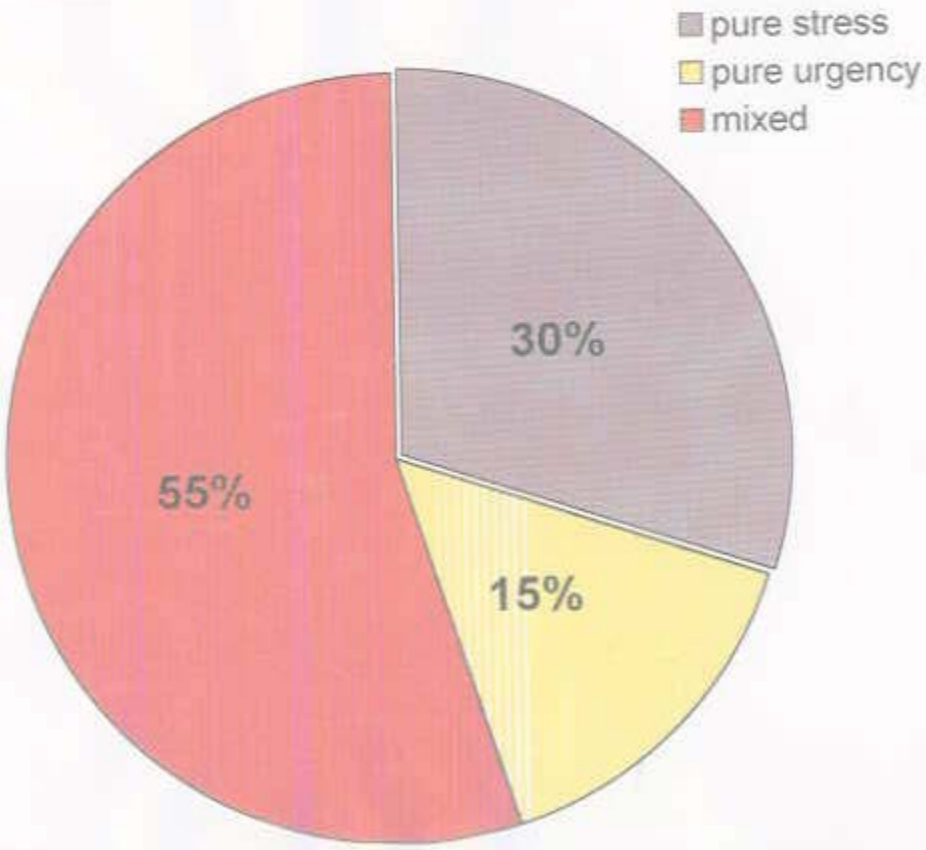
Objectives

Tibial nerve stimulation- the procedure and evidence

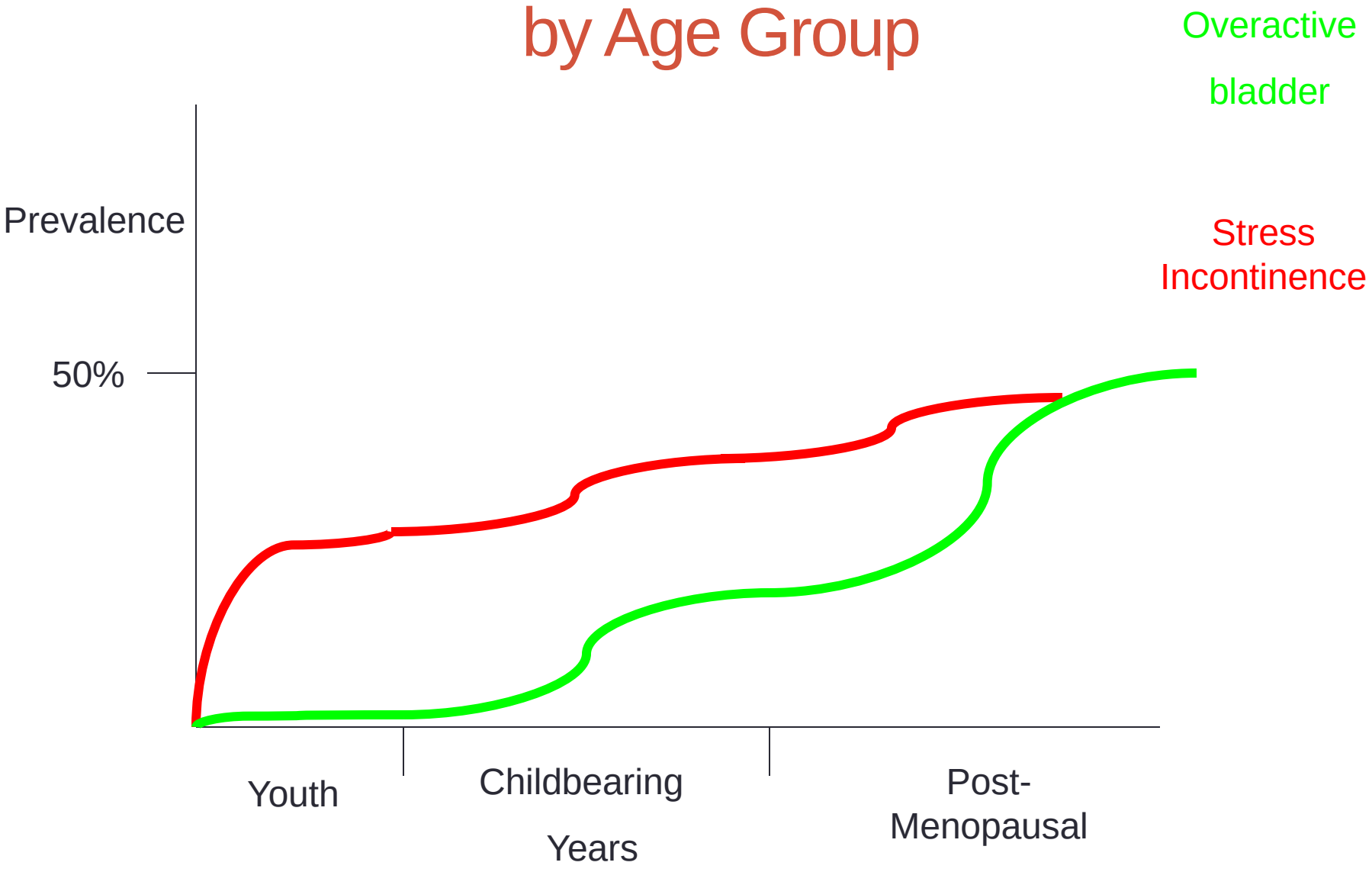
- Mirabegron new β3 agonist – evidence

Impact on management of Overactive bladder

Prevalence of Urinary Incontinence Symptoms



Prevalence of Stress Incontinence by Age Group

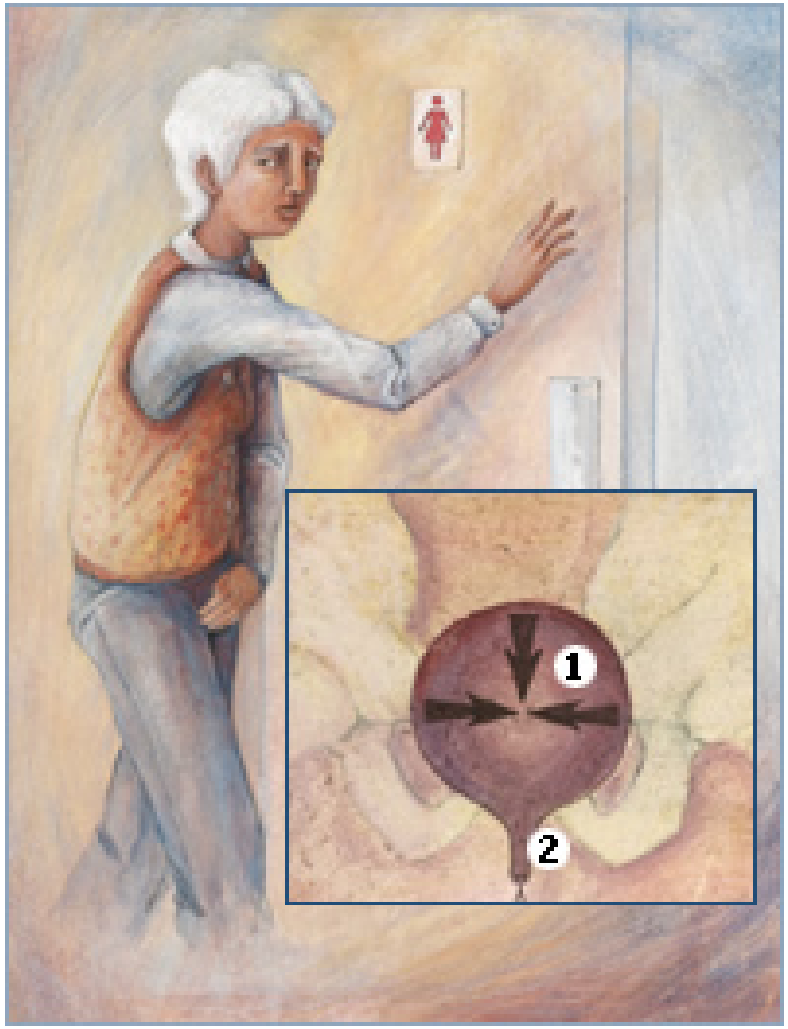


Urgency Incontinence

A loss of urine that is associated with a strong desire to urinate and an inability to delay long enough to get to a toilet.

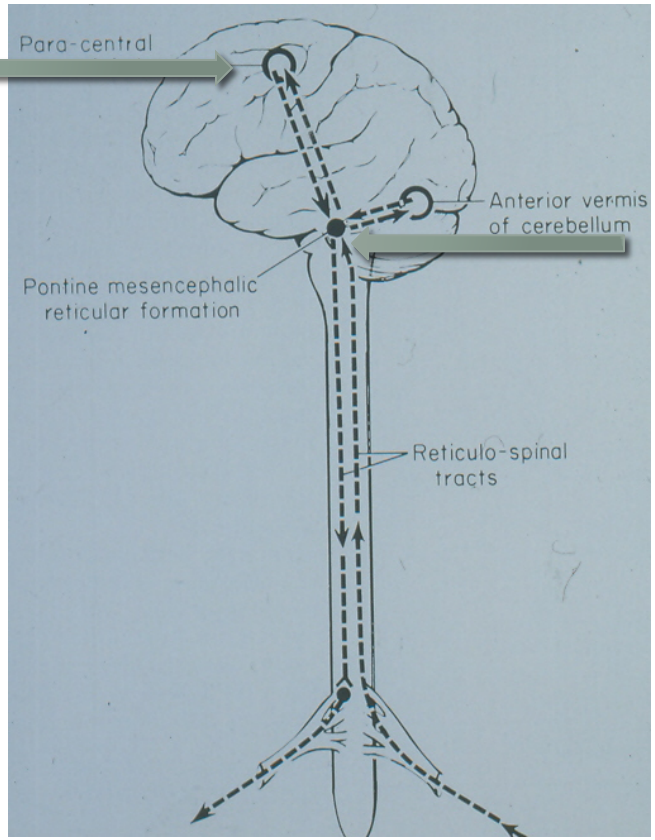
It usually involves a large amount of urine loss at one time (soaked clothing, running down legs).

It may include urine loss on the way to the bathroom or the "key in the lock" / "hand on the doorknob" syndrome (no urge to urinate until the key is in the doorlock or the hand is on the knob and then it is impossible to wait).



Neurologic control of the bladder

Cerebral cortex micturition center

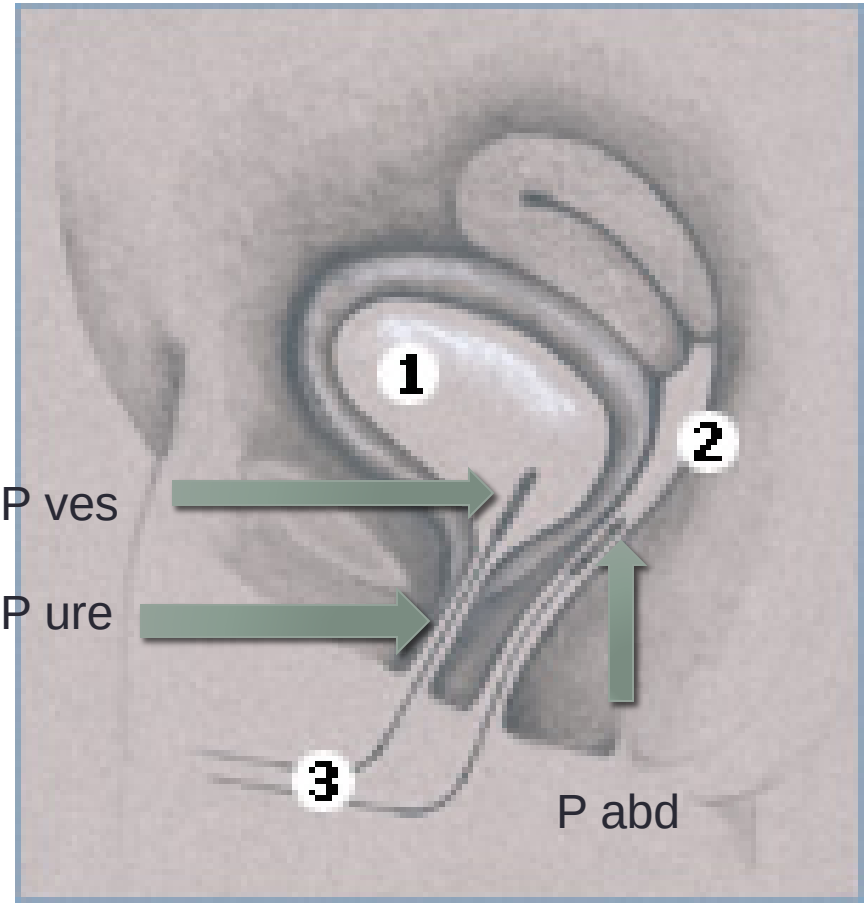


Pontine micturition center

Causes of Overactive Bladder

- Increased local irritation
  - UTI
  - Lifestyle
  - Stones
- Neurogenic
- Idiopathic

Cystometry



- Simulate bladder storage
- Standardized filling rate
- Looking for bladder instability
- Ist, full, max cyst cap
- Stimulate at regular intervals

Unstable bladder on CMG

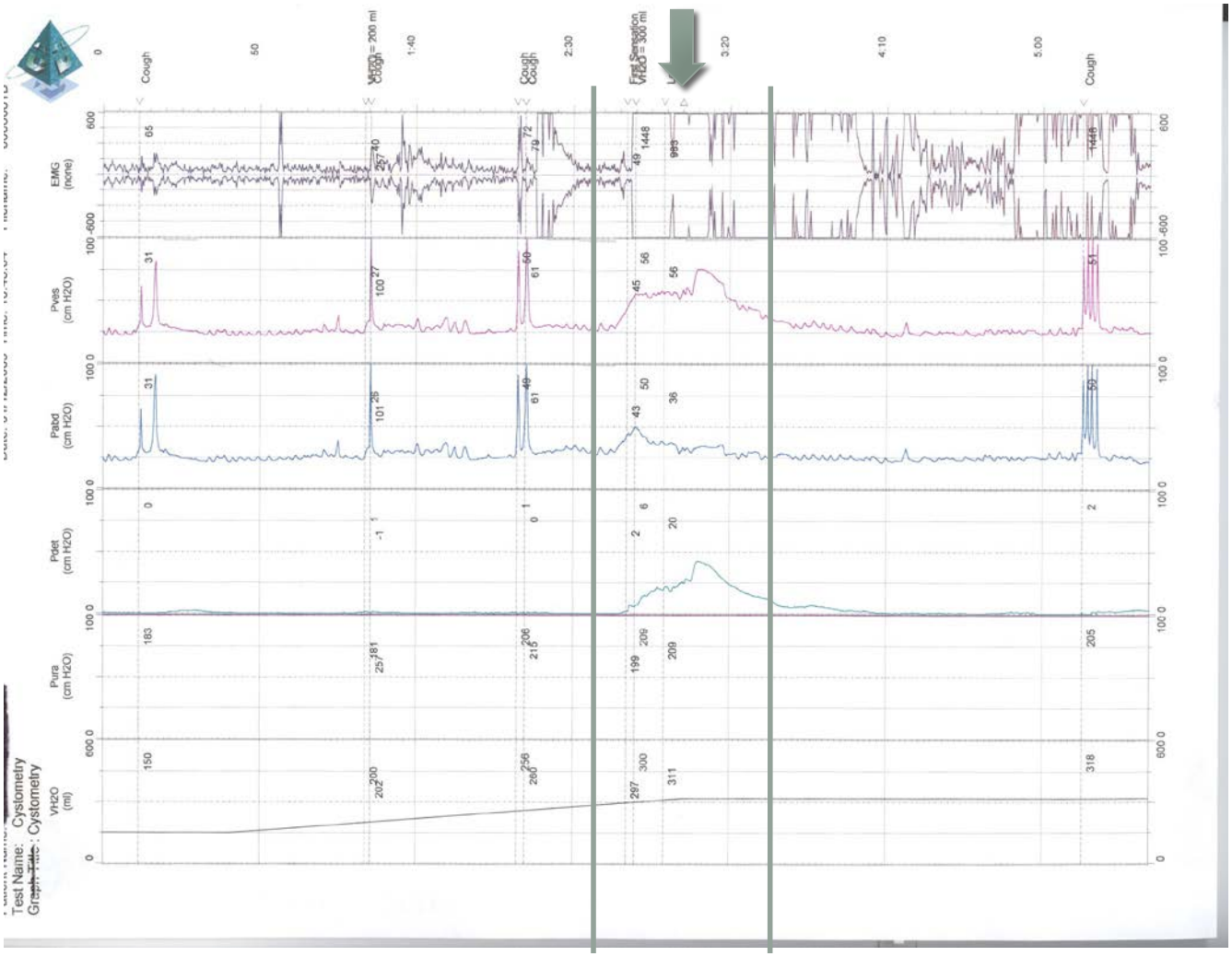
EMG

PVES

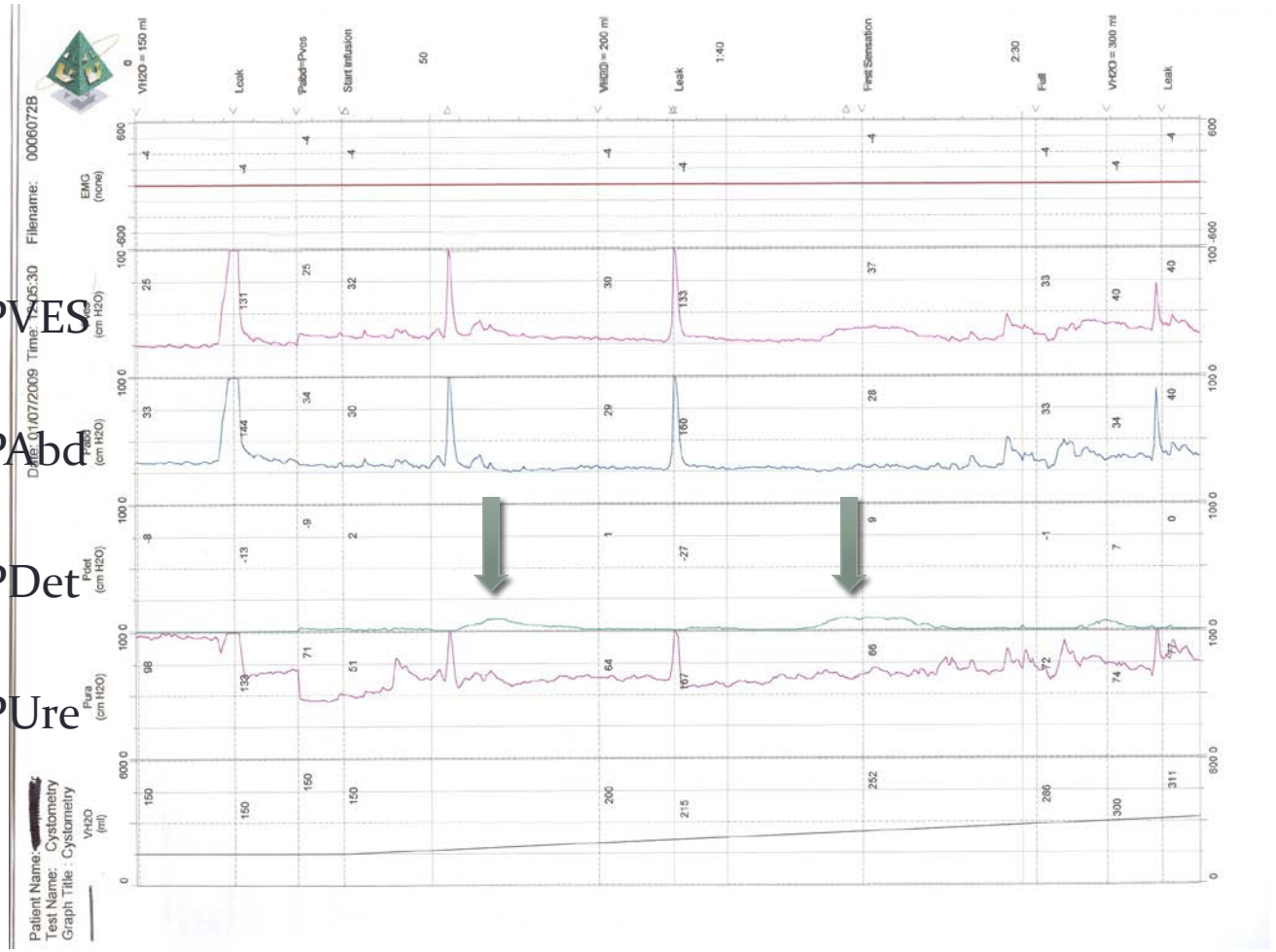
PAbd

PDet

PUre



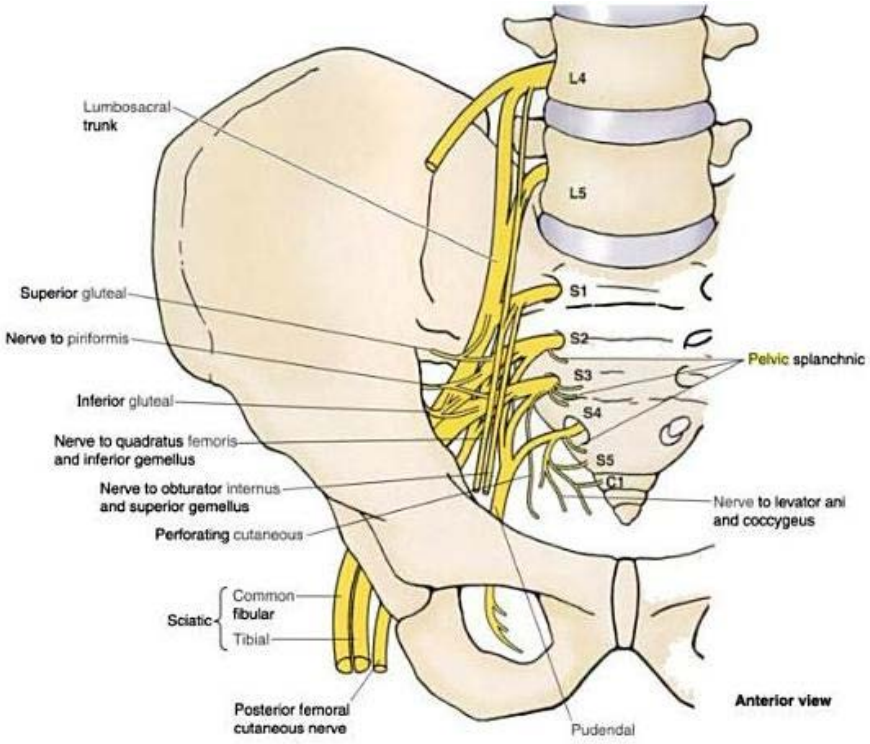
Unstable Bladder

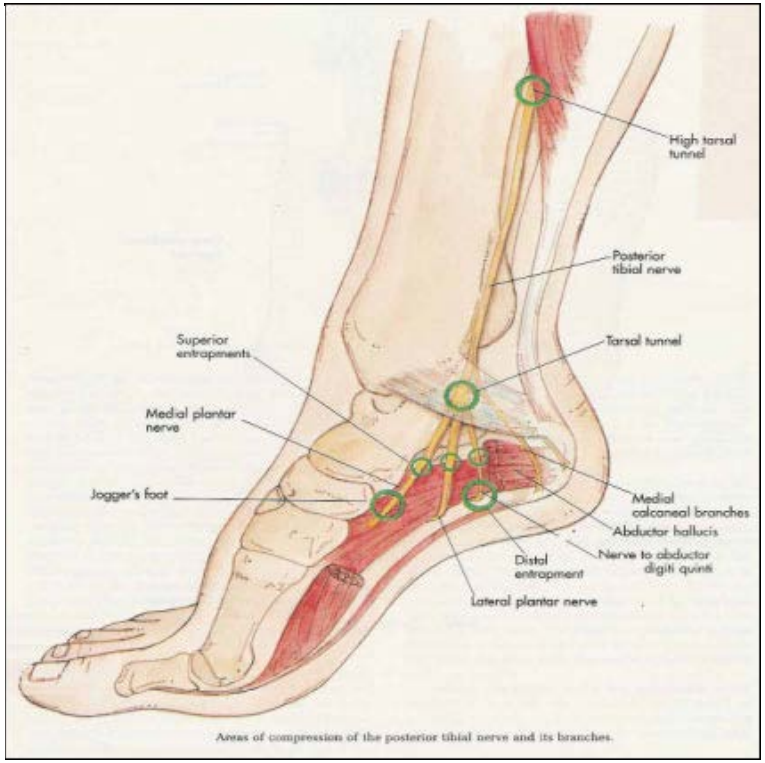


Treatment options for Overactive Bladder

- Identify and treat source of local irritation (UTI)
- Lifestyle modification
- Bladder retraining
- Medications
- Neuromodulation
- Botox

Origin and Anatomy of Tibial nerve





Neuromodulation : Tibial Nerve Stimulation

Neuromodulation : Tibial Nerve Stimulation

- Once per week for 12 weeks
- Session lasts 30 minutes
- Placement of needle is painless
- Stimulation is mild

Efficacy of Tibial Nerve Stimulation

- Introduced in 2000 at UCSF Medical center
- Multicenter Randomized trial **(OrBIT Trial)**
  - Compared TNS to Detrol LA 4 mg
  - Both groups had significant improvement
  - Subjective improvement –
    - TNS – 80%
    - Detrol – 55%
  - 73% of TNS group who responded continued for 12 months and were able to sustain benefits with treatment every 3 weeks

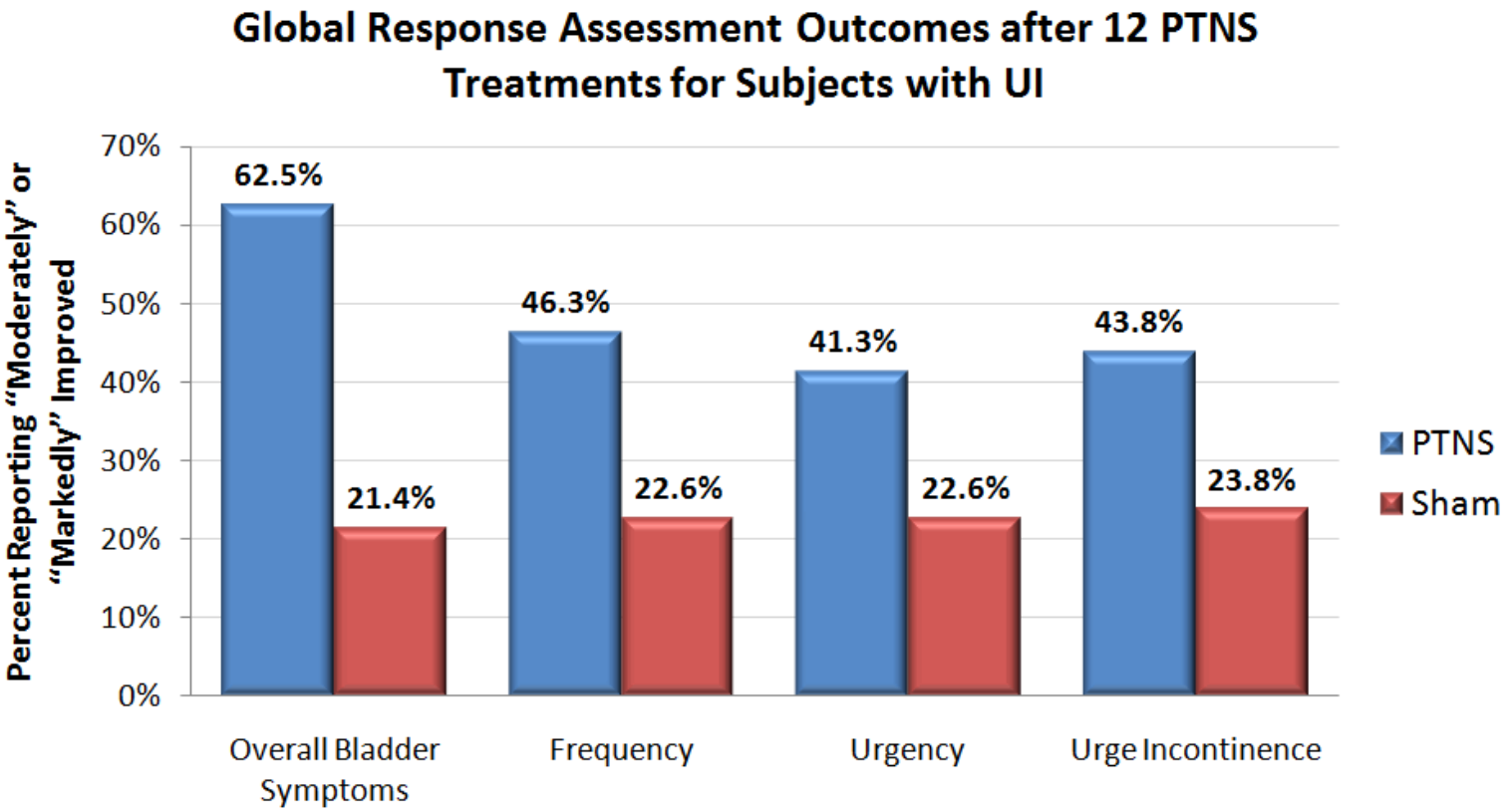
Efficacy of Tibial Nerve Stimulation

- Multicenter randomized trial **(SUmiT Trial)**

- Compared TNS to sham
  - 55% of TNS group responded
  - 21% of the sham group
- Effective in women who failed meds

- Cost is significant
  - $800 for 12 weeks
  - $66 / session

Neuromodulation : Tibial Nerve Stimulation



PTNS statistically significant compared to sham for all GRA parameters

TNS vs Oxybutinin vs combined therapy

- Randomized prospective study – 12 weeks
- 3 groups
  - Gr I – TNS 30 minutes x2 / week
  - Gr II – Oxybutynin 10mg slow release OD
  - Gr III- combination of above
- Outcomes

Group	OAB score	P value
Group I	5.9	
Group II	4.6	
Group III	2.9	P= 0.01

  - At 24 months Gr I and Gr III maintained scores, Gr II went up
  - Souto SC World J Urol 2013 Jun 8.

STEP study of Tibial Nerve Stimulation

- 50 participants of the SUmiT trial who were successfully treated
- 14 week tapering protocol followed by personal treatment plan
  - 2 week intervals – for 2 treatments
  - 3 week intervals- for 2 treatments
  - 4 week interval – for 1 treatment
- Duration 36 months
- Median Treatments 1.1 / month
- 77% maintained moderate or marked improvement

- Peters KM J Urol 2013:189:2194-201.

Cochrane Review
Effectiveness of TNS for overactive bladder
Neuro Urodyn 2012;31;1206-1216

- 4 randomized trials compared TNS to sham – significant difference favoured TNS RR 7.02 CI 1.69-29.17
- 2 randomized trials compared TNS to anticholinergics – no difference between therapies
- 10 prospective non-randomized studies
  - Pooled subjective success - 61.4%
  - Pooled objective success – 60.9%

Cochrane reviews of TNS

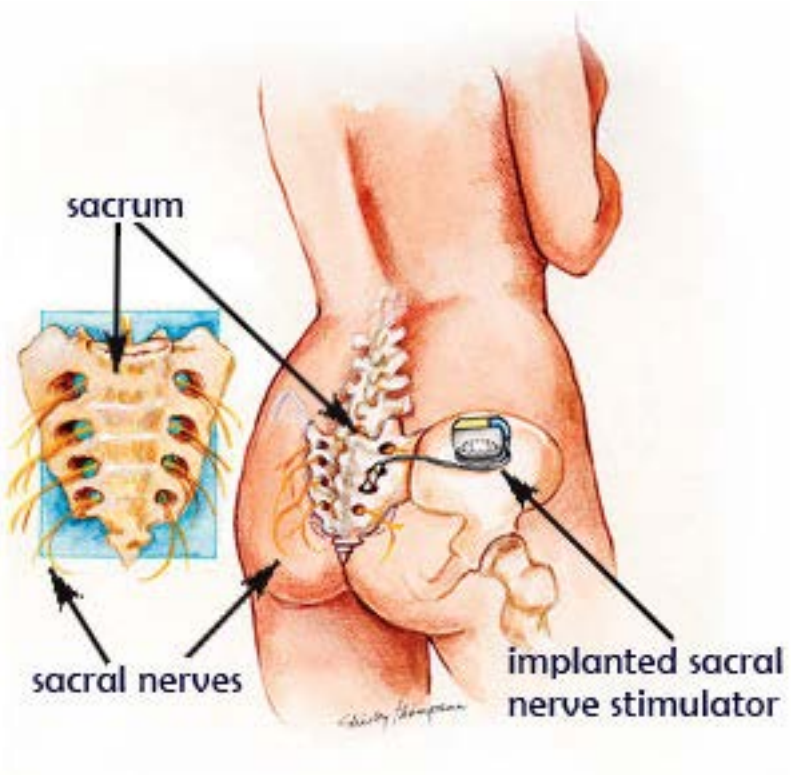
- Tirlapur SA - Nerve stimulation for chronic Pelvic pain and bladder pain syndrome
- Acta Obstet Gynecol Scand 2013;92:881-7
  - Controlled studies
  - 169 patients in three studies TNS
  - Improvements in pain, urinary and quality of life scores
- Rai BP -Anticholinergic drugs vs non-drug therapies for non-neurogenic overactive bladder syndrome in adults
- Cochrane Database Syst Rev 2012 Dec 12
  - 23 trials
  - 7 trials compared electrical stim to anticholinergics
  - Only TNS showed significant subjective improvement rates vs anticholinergics

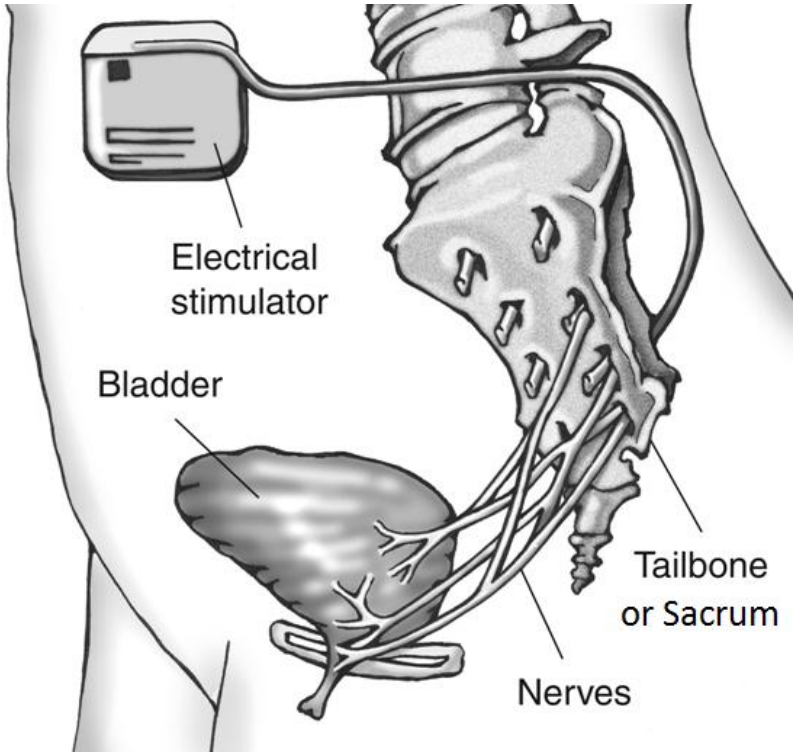
IWK Experience

- Using TNS for ~ 2 years

- Criteria
  - Pure overactive bladder or minimal stress in mixed incontinence picture
  - Failed trial of at least three anticholinergics
  - Other medical reason to avoid pharmacologic Rx
- Approximately 2/3s respond to treatment
- Clinical trial looking at duration of initial treatment and follow-up protocols

Neuromodulation: Sacral Nerve Stimulation





Neuromodulation: Sacral Nerve Stimulation

- $14,000 per patient
- Invasive procedure
- 30% not eligible
- 30% gain no benefit
- 33% of patients need further operations

Cost of Neuromodulation Therapies

- Tibial nerve vs sacral nerve stimulation

- Patients who successfully completed initial therapy
  - TNS - $4,867 — 71% remained on therapy
  - SNS – $24,342 — 90% remained on therapy

Martinson M. J Urol 2013; 189:210-16.

Mirabegron β3 agonist

- B receptors in detrussor muscle
  - **Detrussor relaxation** during filling
  - **Extends the storage phase** of micturition
  - Doesn't affect bladder contraction

- Bioavailability
  - Dependent upon absorption- food intake reduces it
  - Metabolism – genetic influence- CYP2D6

- Anticholinergics
  - **Block detrussor contraction** that initiates voiding
  - **They can interfer** with bladder emptying

Mirabegron – Blossom trial

- 100 mg and 150 mg BID
- Tolterodine 4mg OD
- Placebo OD
- Inclusion criteria
  - ≥ 3 episodes of severe urgency / day
  - > 8 voids in 24 hours
- Primary outcome – change in mean number of micturitions in 24 hrs
- Mean decrease 1 mic / 24 hrs
- Mean reduction – 17%,18%, 11% and 9%

Mirabegron – Dragon trial

- 1110 patients randomized 12 weeks (919 analyzed)
- Dosages – 25,50,100 and 200 OD
- Tolterodine 4mg OD
- Placebo OD
- Outcome
  - Significant dose dependent reduction of mean number of micturitions/ 24hrs
    - Mirabegron – 1.9 -2.2
    - Placebo – 1.4
  - Increase in mean voided volume
    - Mirebegron - 15.7 – 33.3 ml
    - Placebo – 7.3 ml

Mirabegron – Subsequent Clinical trials

- 2 randomized placebo controlled trials
- Inclusion - ≥ 8 voids in 24 hrs , ≥ 3 urgency episodes / day
- Study 1 – mirabegron – 50mg, 100mg vs placebo
  - Reduction in mean # of incontinence episodes -1.5, -1.6 , -1.1
  - Reduction in # of micturitions /24hrs -1.7,-1.8, -1.1
  - Number of patients with no incontinence was not reported
- Study 2 – mirabegron 50mg, 100mg, Tolter 4mg, placebo
  - Reduction in mean # of incontinence episodes -1.5, -1.6 , -1.2, -1.1
  - Reduction in # of micturitions/24hrs -1.8,-1.9, -1.6 -1.3
  - The difference in responders (dry after Rxment)
    - Mirabegron – 45%
    - Placebo – 41% (p= 0.26)
  - Improvements in quality of life in all active treatment groups

Mirabegron – 12 month Safety Study

- Mirabegron 50mg, 100mg
- Tolteridine – 4 mg

- Incidence and severity of treatment related side-effects

- Results
  - No difference in patients D/C because of side effects 5.9-6.4%
  - More dry mouth in the tolteridine group

Assessment of clinical trial data

- Follow-up very short
- No study done to compare mirabegron to anti-muscarinic
- Urgency – key symptom of OAB was secondary end-point
- High placebo response calls into question efficacy of mirabegron vs nothing, in clinical practice – absolute improvement small:
  - One less incontinence episode and micturition every 2 days with mirabegron
- Exclusions
  - End stage renal disease
  - Severe hepatic impairment
  - Uncontrolled hypertension

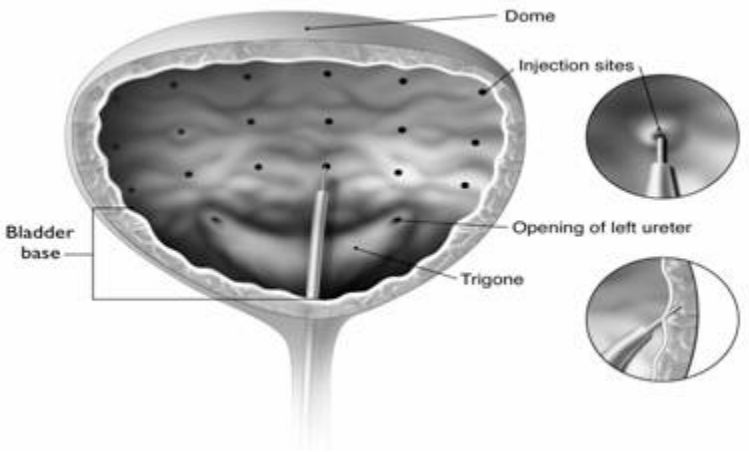
Side –effects of Mirabegron

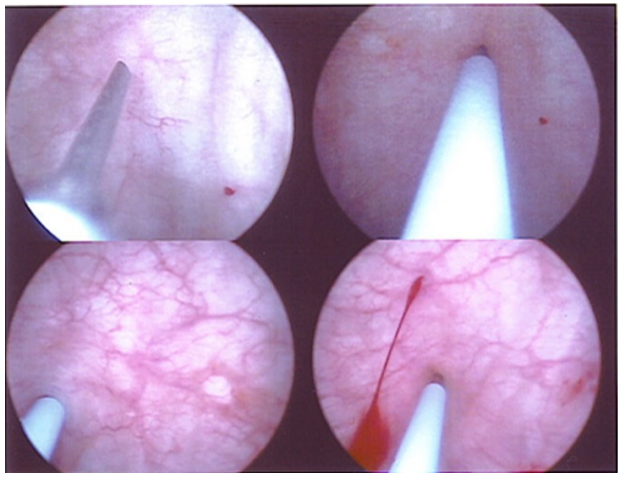
- Appears to be well tolerated
- Commonest side-effects
  - Tachycardia – 1.2%
  - UTI's – 2.9%
  - Serious adverse events – atrial fibrillation – 0.2%
- Important identified risks
  - Increased heart rate
  - Tachycardia
- Important potential risks
  - QT prolongation
  - Hypertension
  - UTI
- Drug interactions – some anti-arrhythmics, tricyclic ad

Mirabegron

- Conclusions
  - Clinical effectiveness similar to antimuscarinics
  - Different side-effect profile – less dry mouth
  - Differences in costs and effectiveness small
- Recommendations (NICE)
  - Anti-muscarinic drugs should be first choice
  - Use Mirabegron when Anti-muscarinics
    - are contraindicated (glaucoma)
    - Clinically ineffective
    - Have unacceptable side-effects
  - May be preferable in elderly patients because of
    - Greater aversion to dry mouth
    - Less likely to cause cognitive dysfunction

Botox Injections





Botox Injections

- General or local anaesthetic – 10-30 minutes
- 10-30 injection sites
- May need to self-cath after procedure
- Lasts 3-6 months

How does this information affect our management of OAB ?

- Effective treatment options
  - Lifestyle modification
  - Anticholinergics
  - B3 agonist
  - Tibial nerve stimulation
  - Sacral nerve stimulation
  - Botox injections
- How do we choose and in what order?
- Factors to consider
  - Efficacy
  - Safety
  - Cost
  - Convenience
  - Patient preference

Convenience

- Lifestyle modification can be done in your own home
- Drugs, once purchased last for a month
- Tibial nerve stim requires frequent visits to hospital or other facility
- Sacral nerve stim and botox are surgical procedures and most likely will require frequent follow-up

Efficacy

- Lifestyle modification can be very effective
- Pharmacologic options – no clearly superior option
- Neuromodulation is as effective as pharmacologic treatment
- Botox – effective but no comparison trials

Safety

- Lifestyle modification- safest option, no contraindications
- Tibial nerve stimulation – no complications, no side-effects, no contraindications
- Pharmacotherapy – low rate of significant complications, significant side-effects result in low long-term compliance rate, all have contraindications
- Sacral neuromodulation – invasive, low rate of severe complications
- Botox – invasive, low rate of severe complications

Cost

- Lifestyle modification usually saves money
- Pharmacotherapy is expensive $85- $100/month (Usually covered by insurance)
- Tibial nerve stimulation – initial therapy expensive ~$800 for 12 treatments but maintenance could be as low as $66/month(not covered by insurance)
- Sacral nerve stimulation very expensive up front cost ~$14,000 and high rate of malfunction with on-going costs
- Botox - $2-3000 with repeat treatment every 3-4 months

Patient Preference

- Lifestyle modification – nobody likes it
- Pharmacotherapy – high none compliance
- Tibial nerve – well tolerated but inconvenient
- Sacral nerve stim – invasive and inconvenient
- Botox – invasive but well tolerated

Conclusions

- Options for treating overactive bladder are expanding
- Choice of therapy will be influenced by a number of patient factors
- Algorithm
  - Lifestyle
  - Bladder drill
  - Tibial nerve stim
  - Pharmacotherapy
    - Anticholinergics followed by β3 agonist
  - Sacral nerve stim and botox for resistant cases

QUESTIONS AND COMMENTS

Investigations of Urinary Incontinence

- Urine C&S
- QUID questionnaire
- Urolog

URINE C&S

QUID Questionnaire

Please complete all questions. Do not leave any questions blank. For each question, mark the box that most accurately describes how often you experience your symptoms.

Do you leak urine (even small drops), wet yourself, or wet your pads or undergarments...						
	None of the time	Rarely	Once in a while	Often	Most of the time	All of the time
1. When you cough, laugh or sneeze?						
2. When you bend down or lift something up?						
3. When you walk quickly, jog, or exercise?						
Do you leak urine (even small drops), wet yourself, or wet your pads or undergarments...						
4. While you are undressing to use the toilet?						
5. Do you get such a strong and uncomfortable need to urinate that you leak urine (even small drops) or wet yourself before reaching the toilet?						
6. Do you have to rush to the bathroom because you get a sudden, strong need to urinate?						

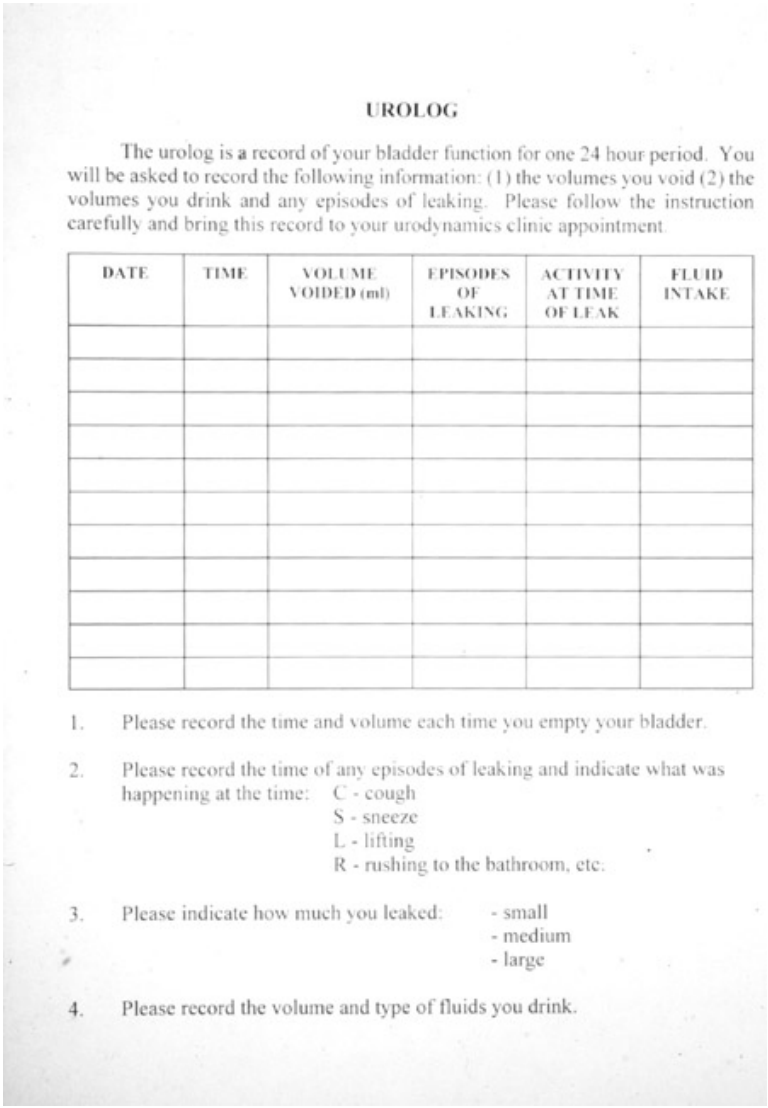
Assessment of Incontinence Type

A score on the first three questions (#1, 2, 3) of ≥ 4 correlates with **stress incontinence.**
A score on the last three questions (#4, 5, 6) of ≥ 6 correlates with **urge incontinence or urgency incontinence.**

Urolog

Information you get

- Urinary frequency
- Volumes voided
- Incontinence episodes
- Precipitating factors
- Fluid intake



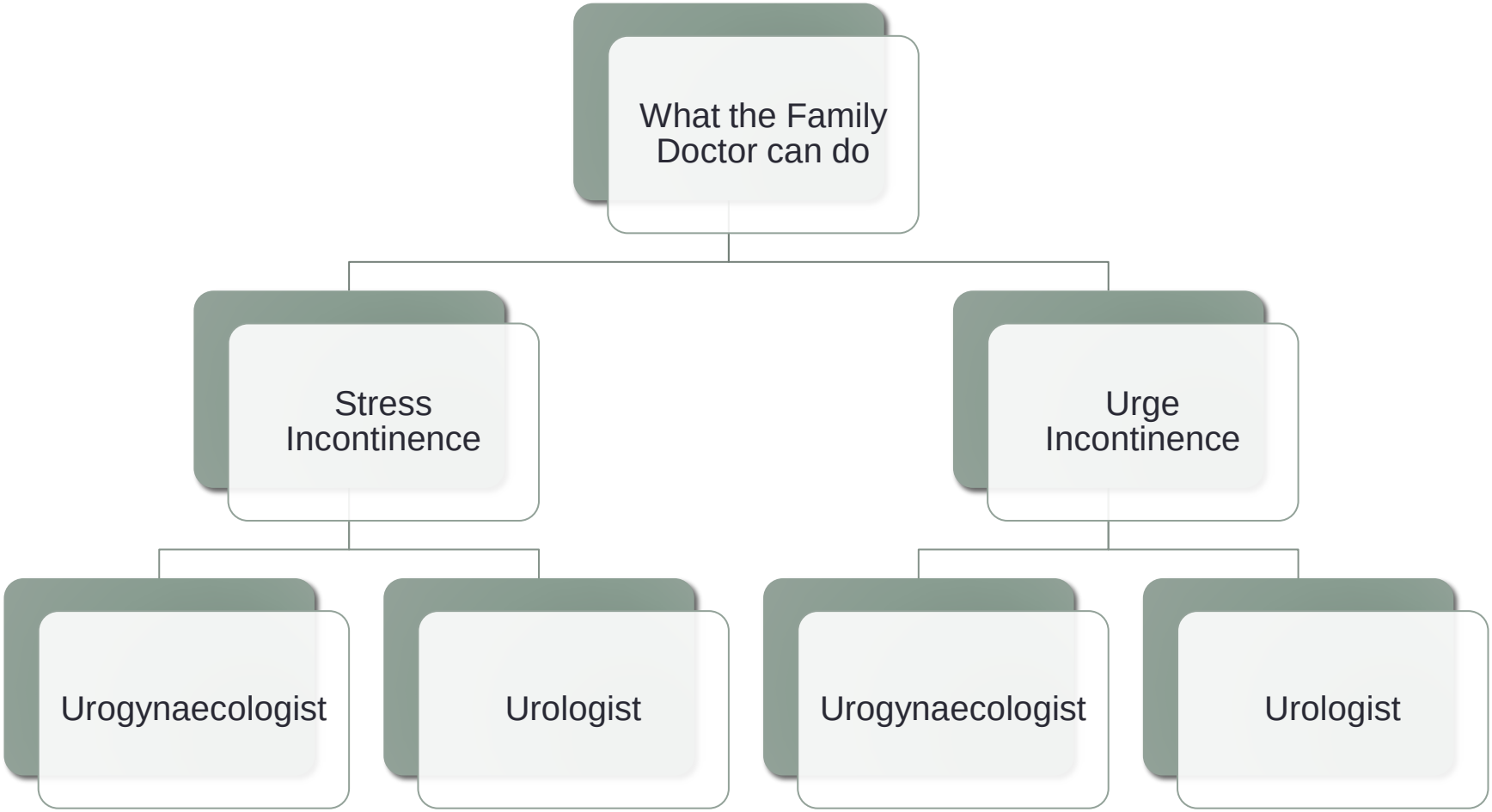
UROLOG

The urolog is a record of your bladder function for one 24 hour period. You will be asked to record the following information: (1) the volumes you void (2) the volumes you drink and any episodes of leaking. Please follow the instruction carefully and bring this record to your urodynamics clinic appointment.

DATE	TIME	VOLUME VOIDED (ml)	EPISODES OF LEAKING	ACTIVITY AT TIME OF LEAK	FLUID INTAKE

1. Please record the time and volume each time you empty your bladder.
2. Please record the time of any episodes of leaking and indicate what was happening at the time: C - cough
   S - sneeze
   L - lifting
   R - rushing to the bathroom, etc.
3. Please indicate how much you leaked: - small
   - medium
   - large
4. Please record the volume and type of fluids you drink.

How to triage and Direct Your Patient



What the Family Doctor Can do

- Identify and treat UTI
- Direct patient to reliable information

  www.womensbladderhealth.com
  - Advise patient on lifestyle changes
  - Advise on Kegels exercises – refer to physio

Stress incontinence

Urogynaecologist

- Pessaries
- Midurethral slings
- Retropubic slings
- Burch procedure
- Periurethral bulking

Urologist

- Midurethral slings
- Retropubic slings

Urge Incontinence

Urogynaecologist

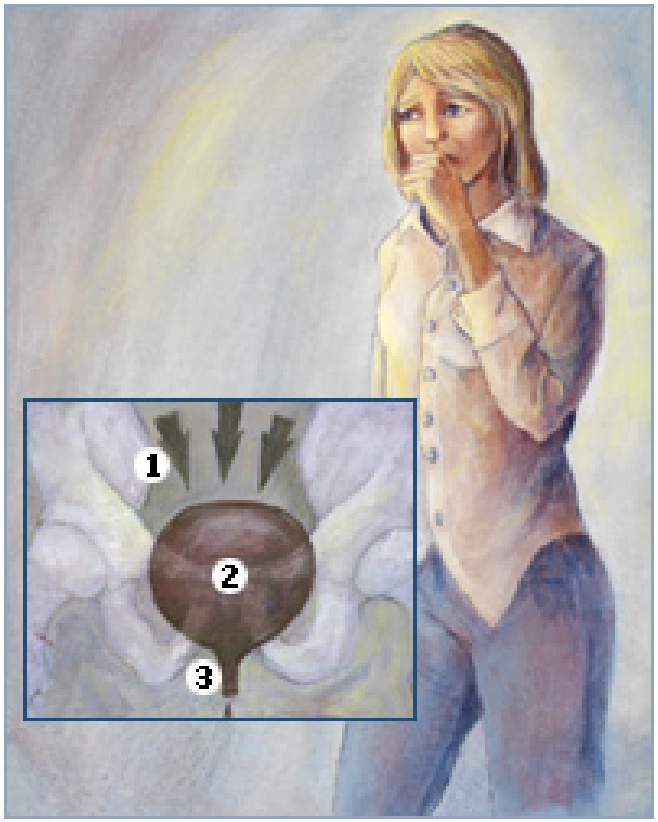
- Full evaluation using urodynamics
- Anticholinergics
- Tibial nerve stimulation

Urologist

- Full evaluation using urodynamics
- Anticholinergics
- Sacral nerve stimulation
- Botox?
- Bladder augmentation

Stress Incontinence - failure of the urethra, the "valve" which closes the bladder.

The involuntary loss of small amounts of urine in response to increased pressure on the bladder (for example, when a person coughs, sneezes, laughs, or lifts heavy objects urine leaks out).



Indications for Cystometry

- Assess bladder capacity
  - Ist sensation – 100 -200 ml
  - Volume at normal desire to void – 150 – 350 ml
  - Maximum cystometric capacity - 300 -600 ml
- Bladder compliance
  - Increase of no more than 15 cm of H_2O
- Detrusor stability

QUESTIONS AND COMMENTS?