

# Pharmacotherapy in Pain Management

---



**Mr Keng Jin Ng**

Consultant Urological Surgeon

The Princess Grace Hospital, London

# Disclosures

---

Consultant / speaker for:

Astellas, BMI Hospitals, GSK, Lilly, Menarini,  
Pfizer, Speciality European Pharma, Syner-Med

# Urological pain syndrome

## Interstitial cystitis

Hypersensitive bladder syndrome

Bladder pain syndrome / chronic pelvic pain

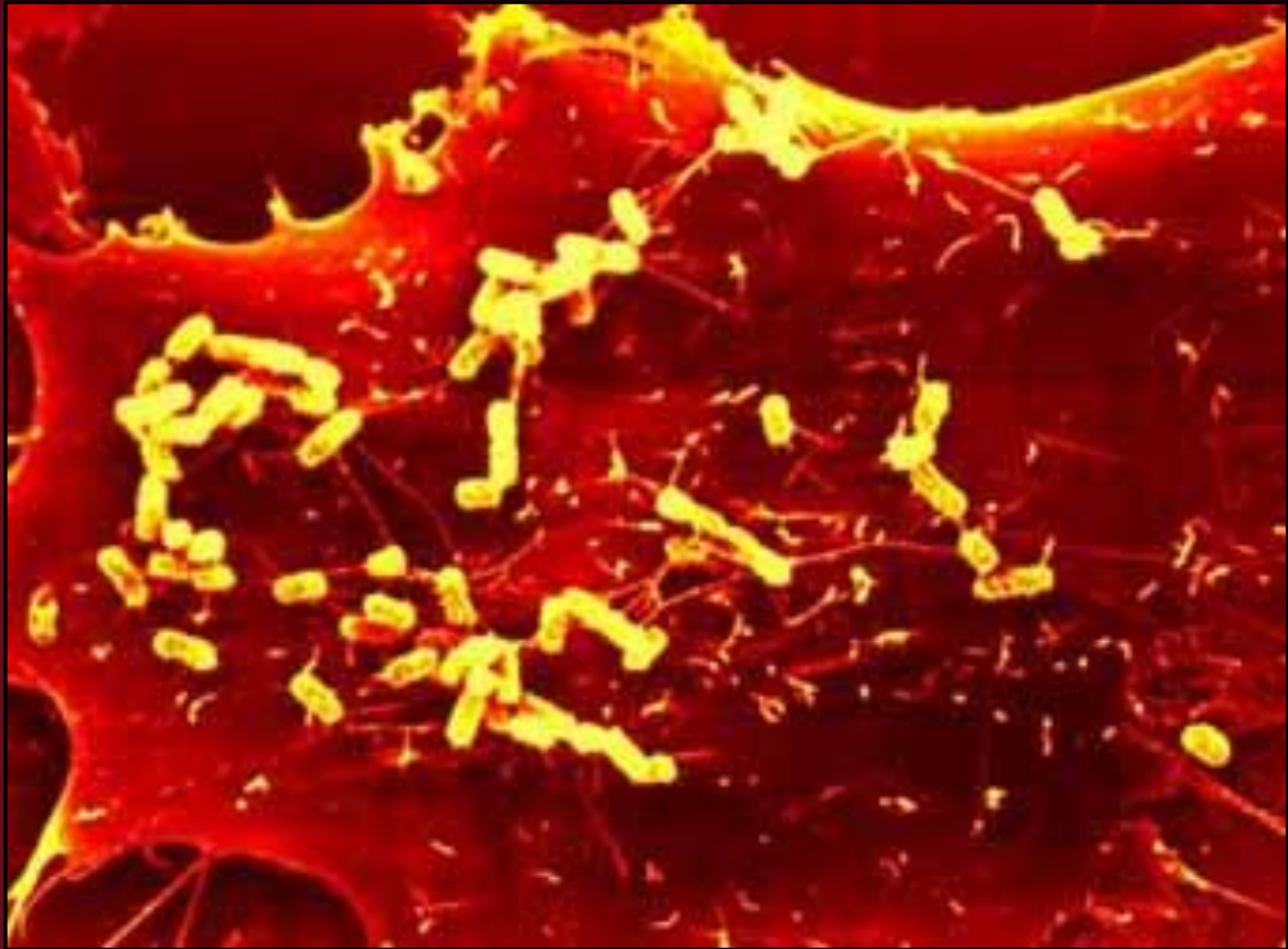
**Prostatitis** – bacterial, abacterial, prostadynia

? International consensus – definition

# Key points: PBS – interstitial cystitis (wide spectrum)<sup>1</sup>

- Cracks in bladder
- Neurogenic inflammation
- Pudendal neuropathy (in severe cases)

# *E. coli* adhering to urothelium



# Genotypic trait<sup>1</sup>

- Susceptible:<sup>1</sup>
  - Lewis a+b-, Lewis a-b-
  - Receptor binding by pathogenic bacteria
- Identified by recurrent ‘UTI’ >2x per year<sup>2</sup>
- Childhood presentation<sup>1</sup>

1. Sheinfeld J, et al. *N Engl J Med.* 1989; 320(12):773–7.

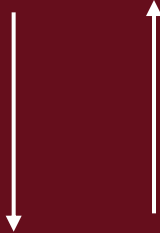
2. Dason S, et al. *Can Urol Assoc J.* 2011;5(5):316-22.

# Interlinked

- Bacterial cystitis



(Cracked urothelium)



- Interstitial cystitis  
(neurogenic inflammation)

Antibiotic regimens

Pentosan polysulfate  
Hyaluronic acid  
Chondroitin sulphate  
Lidocaine 4%

Nerve stabilisation

# Interstitial cystitis: glomerulation





# IC-Smart Diet<sup>1</sup>

## The truth about the foods you eat

Did you know that certain foods can cause additional distress when you're suffering with interstitial cystitis (IC)? Typically, foods high in acid and potassium, as well as beverages containing caffeine and alcohol, should be avoided. Here are some helpful guidelines for an IC-smart diet:

### Fruits

#### Allowable:

Blueberries, melons (other than cantaloupe), and pears

**Avoid:** Other fruits and juices



### Meats/Fish

#### Allowable:

Poultry, fish, and some meats (not including those listed below)

**Avoid:** Aged, canned, cured, processed, or smoked meats/fish; anchovies; caviar; chicken livers; corned beef; or meats that contain nitrates or nitrites



### Vegetables

**Allowable:** Potatoes, homegrown tomatoes, and some vegetables (not including those listed below)

**Avoid:** Fava beans, lima beans, onions, rhubarb, tofu, and store-bought tomatoes



### Nuts

**Allowable:** Almonds, cashews, and pine nuts

**Avoid:** Most other nuts



### Milk/Dairy

**Allowable:** White chocolate, cottage cheese, American cheese, and milk

**Avoid:** Aged cheeses, sour cream, eggs, yogurt, and chocolate



### Beverages

**Allowable:** Bottled or spring water; decaffeinated, acid-free coffee or tea; some herbal teas

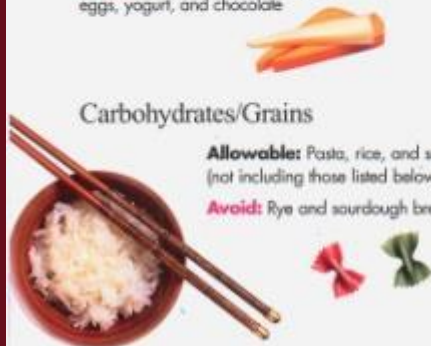
**Avoid:** Alcoholic beverages, including beer and wine; carbonated drinks; coffee; tea; and cranberry juice



### Carbohydrates/Grains

**Allowable:** Pasta, rice, and some breads (not including those listed below)

**Avoid:** Rye and sourdough breads



### Seasonings

**Allowable:** Garlic and some other seasonings (not including those listed below)

**Avoid:** Mayonnaise, miso, spicy foods (especially Chinese, Mexican, Indian, and Thai foods)



### Don't forget about preservatives

**Avoid:** Benzal alcohol; citric acid; monosodium glutamate; aspartame; saccharin; and foods containing preservatives, artificial ingredients/colors

# PBS / IC: Direct treatment of underlying pathology

- Oral medication:
  - Elmiron (pentosan polysulphate) – FDA approved
- Bladder instillation

When considering chronic pelvic pain associated with IC...

## ELMIRON is the only FDA-approved oral medication

Fundamental for lasting relief from the pain or discomfort of interstitial cystitis (IC)



- **ELMIRON is fundamental therapy for IC**  
Whatever else you may use for short-term relief of IC pain, ELMIRON should be your choice for long-term therapy.
- **GAGs may be essential for bladder protection**  
Studies suggest that glycosaminoglycans (GAGs) may maintain a physical barrier between the bladder wall and the urine, so irritating urinary solutes cannot reach underlying cell membranes.
- **ELMIRON appears to reinforce the protective layer**  
Although its mechanism of action is not fully understood, ELMIRON resembles the GAG layer that protects the bladder lining.
- **ELMIRON treats an underlying pathology**<sup>1,2,3</sup>  
ELMIRON may act as a buffer to control cell permeability, preventing irritating solutes from reaching epithelial cells.
- **ELMIRON reduces painful symptoms long term**<sup>4</sup>  
Significant improvement in 5 months in a majority of patients. With sustained relief for up to 3 years in patients who remain on therapy.

In an 8-year retrospective study, adverse events tended to be infrequent, mild, and transient. Dizziness, nausea, diarrhea (reversible upon discontinuation), headache, rash, dyspepsia, abdominal pain, liver function abnormalities, and diarrhea occurred at a frequency of 1% to 4%.

ELMIRON is contraindicated in patients with known hypersensitivity to the drug, structurally related compounds, or excipients.

The mechanism of action of ELMIRON in interstitial cystitis is unknown.

References: 1. Parsons CL, Parsons JK. Interstitial cystitis. In: Raz S, ed. Female Urology, 2nd ed. Philadelphia, PA: WB Saunders Co; 1996:147-182. 2. Parsons CL. Evaluation and Managing Interstitial Cystitis. Englewood Cliffs, NJ: Lippincott Williams & Wilkins; 1997. 3. Parsons CL. The therapeutic role of sulfated polysaccharides in the urinary bladder. *Urol Clin North Am* 1994;21(5):919-933. 4. Hertz RC, Roy JL, Mee PA, et al. A cohort of chondroitin sulfate proteoglycans on the bladder uroepithelium in interstitial cystitis. *Urology* 1998;48:517-521. 5. Hanno PM. Analysis of long-term Elmiron therapy for interstitial cystitis. *Urology* 1991;37(suppl): 64J-69-66. 6. Parsons CL, Danzoo S, Chiles SJ, Hanno P, Sant SA, Webster G. A quantitatively controlled method to study prospectively interstitial cystitis and demonstrate the efficacy of pentosan polysulfate. *J Urol* 1993;150:848-848.

**ELMIRON**  
(pentosan polysulfate sodium) ELMIP  
ELMIP Capsules

Forms a foundation for IC management

ORTHOMCNEIL

Visit us at [www.elmiron100.com](http://www.elmiron100.com)

ELMIRON is a registered trademark of NRI Research, Inc. under license to Ortho-McNeil Pharmaceutical, Inc.

Please see the full summary of prescribing information on the adjacent page.

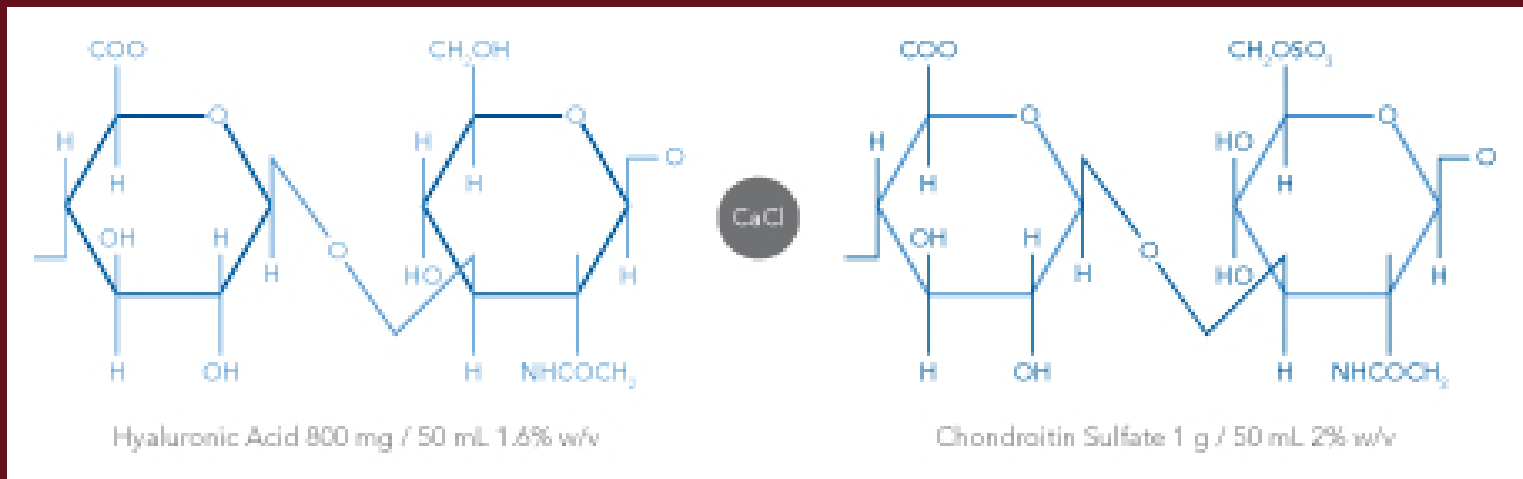
© OMP 2003, 1548 028509

This product is not licensed in the UK

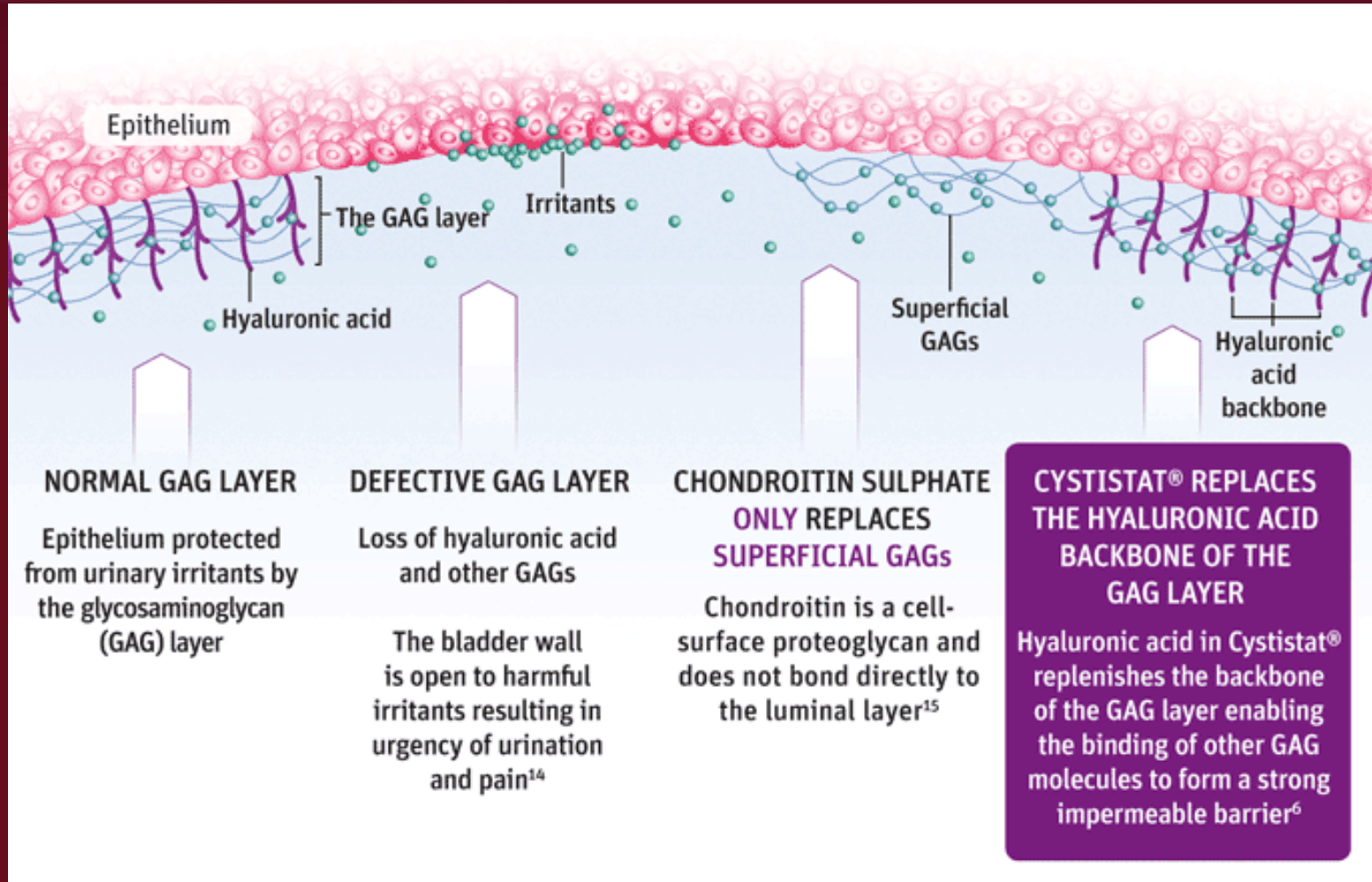
# PBS / IC: Direct treatment of underlying pathology

- Oral medication:
  - Elmiron (**pentosan polysulphate**) – FDA approved
- Bladder instillation
  - **Hyaluronic acid** ( Cystistat, Hyacyst )
  - **Chondroitin sulphate** ( Uracyst )
    - NB. iAluRil (hyaluronic acid plus hyaluronic acid)
  - **4% lidocaine** ( Cystilieve )

# Patching the cracks – with GAGs



# Patching the cracks – with GAGs



# PBS / IC: other supportive treatment

- Multimodal approach:
  - **Inflammation**: mast cell “stabilisers” – hydroxyzine, montelukast
  - **Neurogenic pain**:

# Montelukast treatment

- Mast cell “stabiliser”:
  - Reduce neurogenic inflammation (leukotriene antagonist) – prevent further escalation in release of mediators
  - (? Mast Cell Activation Syndrome)
  - consider in combination with **mirabegron** (  $\beta$ -3 agonist) to reduce bladder spasm



# PBS / IC: other supportive treatment

- Multimodal approach:
  - **Inflammation**: mast cell “stabilisers” – hydroxyzine, montelukast
  - **Neurogenic pain**: neuralgia – pregabalin  
Central sensitisation – opioids, tapentadol

# Pregabalin treatment

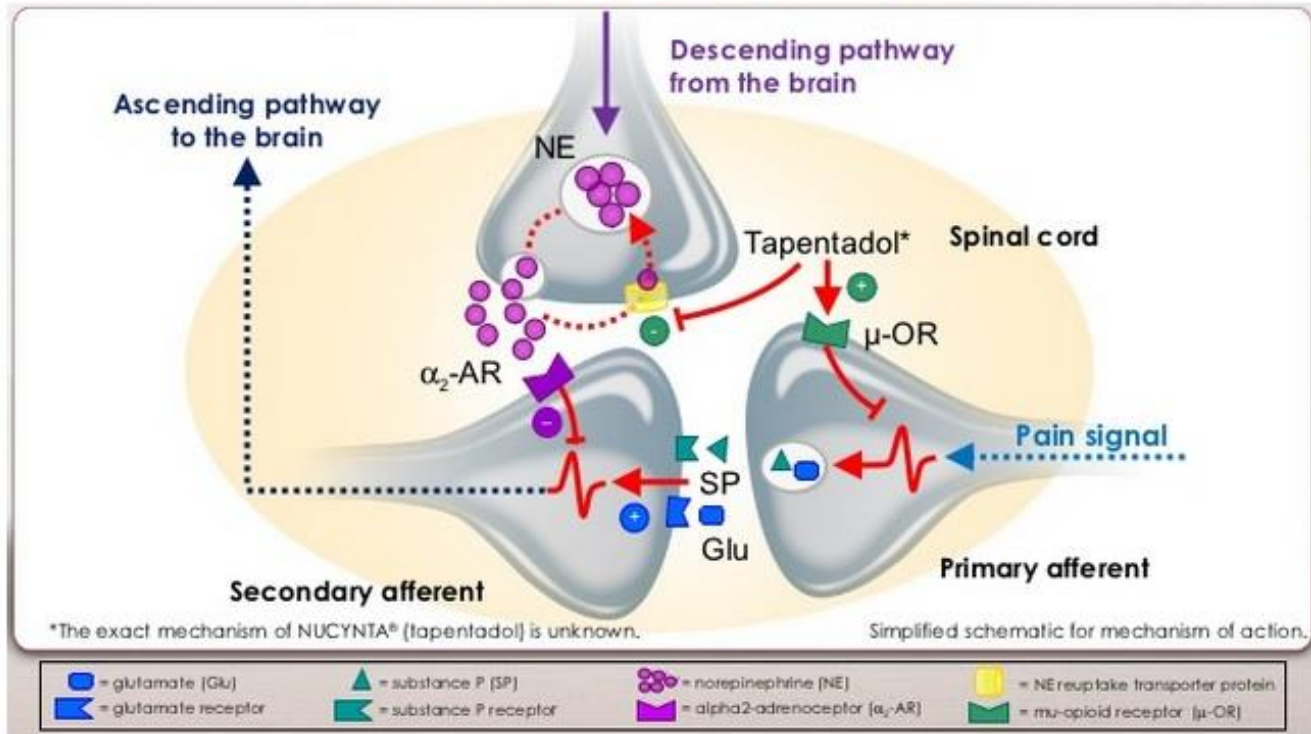
- Nerve stabiliser:
  - Reduce neuralgia / **neuropathic** pain ( burning, tingling, sharp shooting ) in urethra
  - gradual titration, starting with 75 mg nocte

# Tapentadol treatment

- Dual mechanism:
  - $\mu$  receptor agonist (opiod)
  - Noradrenaline reuptake inhibitor : boost effects of opiod
  - no obvious addiction
  - ideal for **Central Sensitisation**

# Tapentadol treatment

## DUAL MECHANISM OF ACTION: NOREPINEPHRINE REUPTAKE INHIBITOR AND $\mu$ -OPIOID RECEPTOR AGONIST



Sources: Tzschentke et al, 2007; Vanderah, 2007; Pertovaara, 2006; Janssen Pharmaceuticals, Inc.

# PBS / IC: other supportive treatment

- Multimodal approach:
  - Inflammation: mast cell stabilisers – hydroxyzine, montelukast
  - Neurogenic pain: neuralgia – pregabalin  
Central sensitisation – opioids, tapentadol
  - Myofascial pain: **physiotherapy – muscle relaxation exercise**
  - **Psychological**: relaxation techniques / meditation
  - Neuromodulation: **SNS / PTNS**

# PBS / IC – treatment: what next?

---

IC: interstitial cystitis;  
PBS: painful bladder syndrome

# Botox



# Botox: submucosal injection

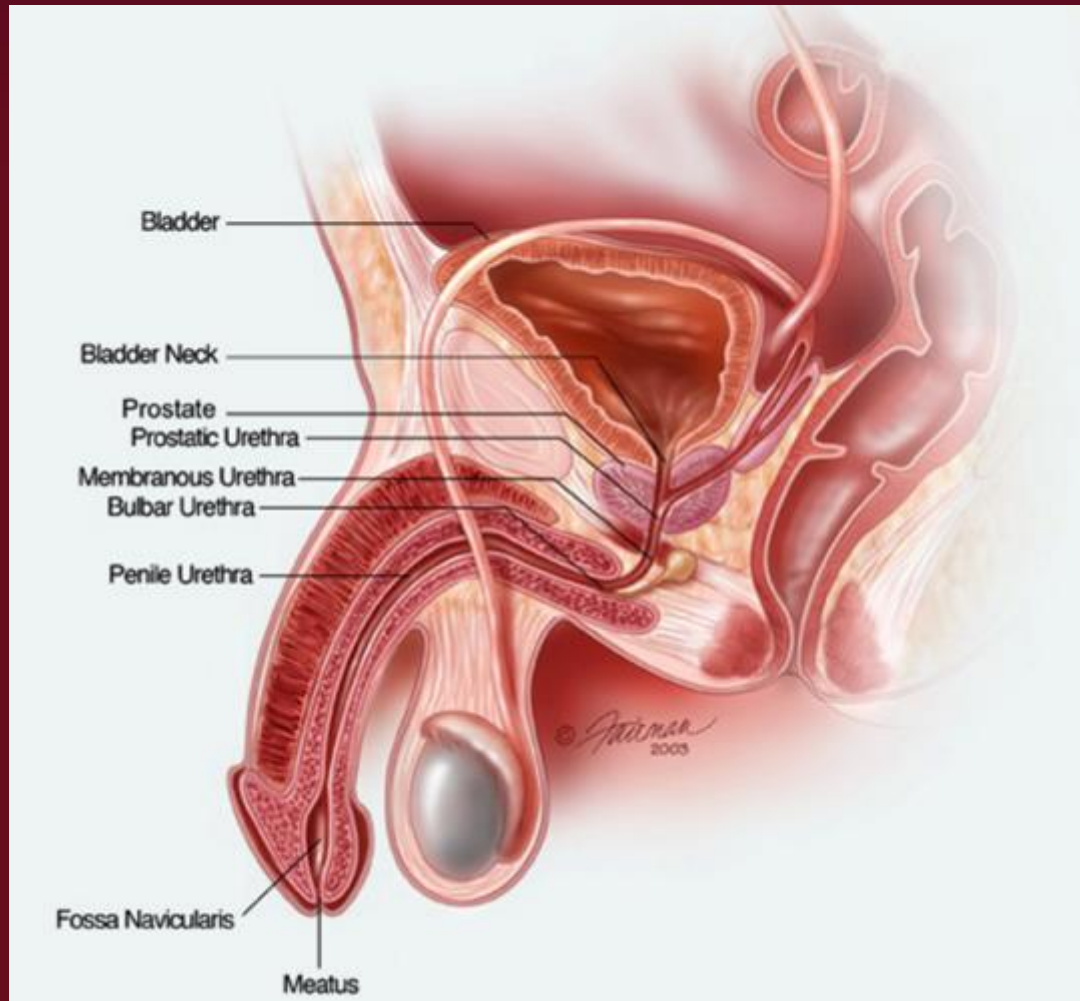




# Botox: submucosal injection



# Prostatitis



# Prostatitis: Direct treatment of underlying pathology

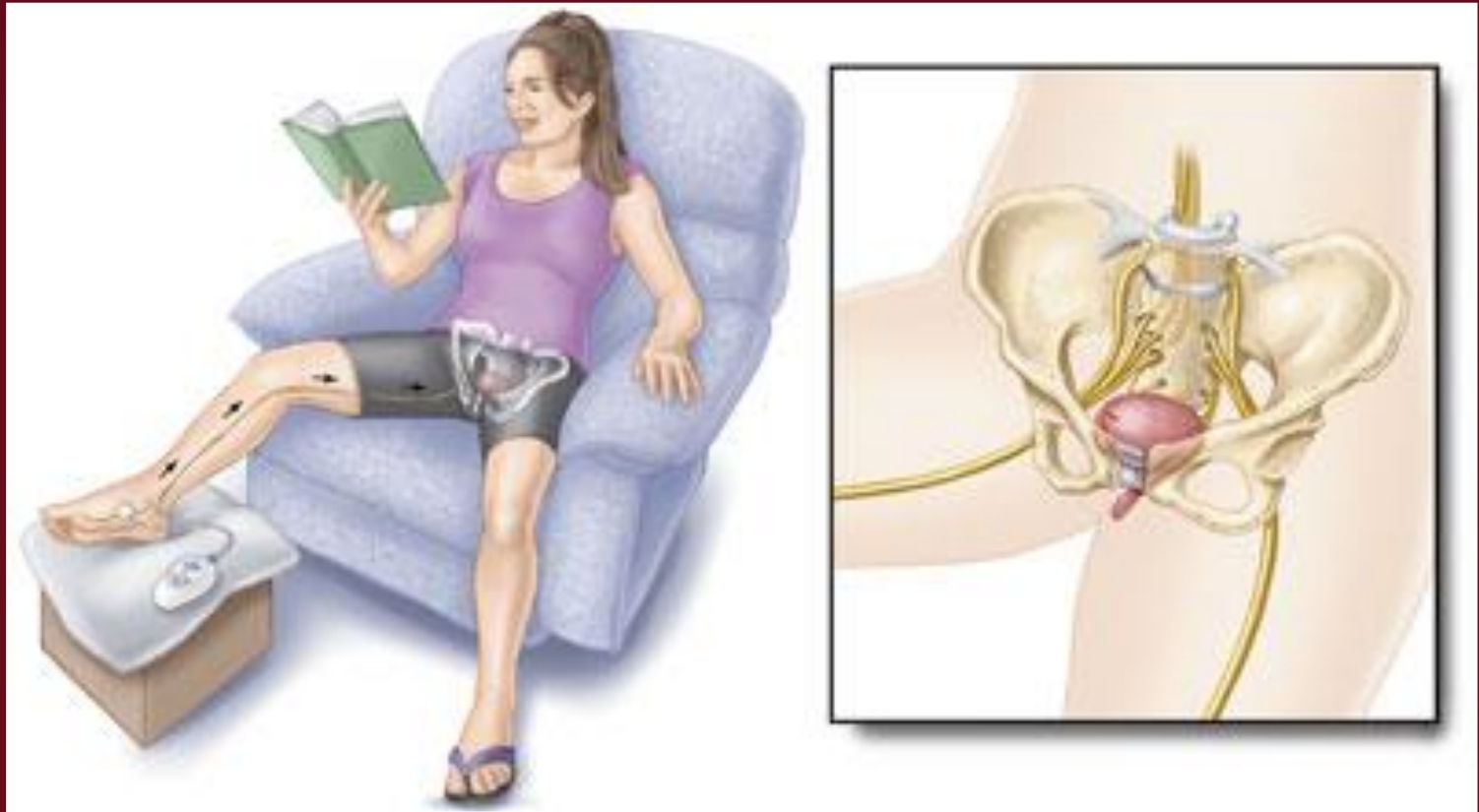
- Oral medication:
  - $\alpha$  – blockers : **Tamsulosin, Alfuzosin**
    - Treating dynamic obstruction
  - **Tadalafil** (Cialis) 5mg od
    - Treating background ischaemia/inflammation/smooth muscle tension

# A few exciting things

---

- 3 treatments to help optimise management
- 1 new concept

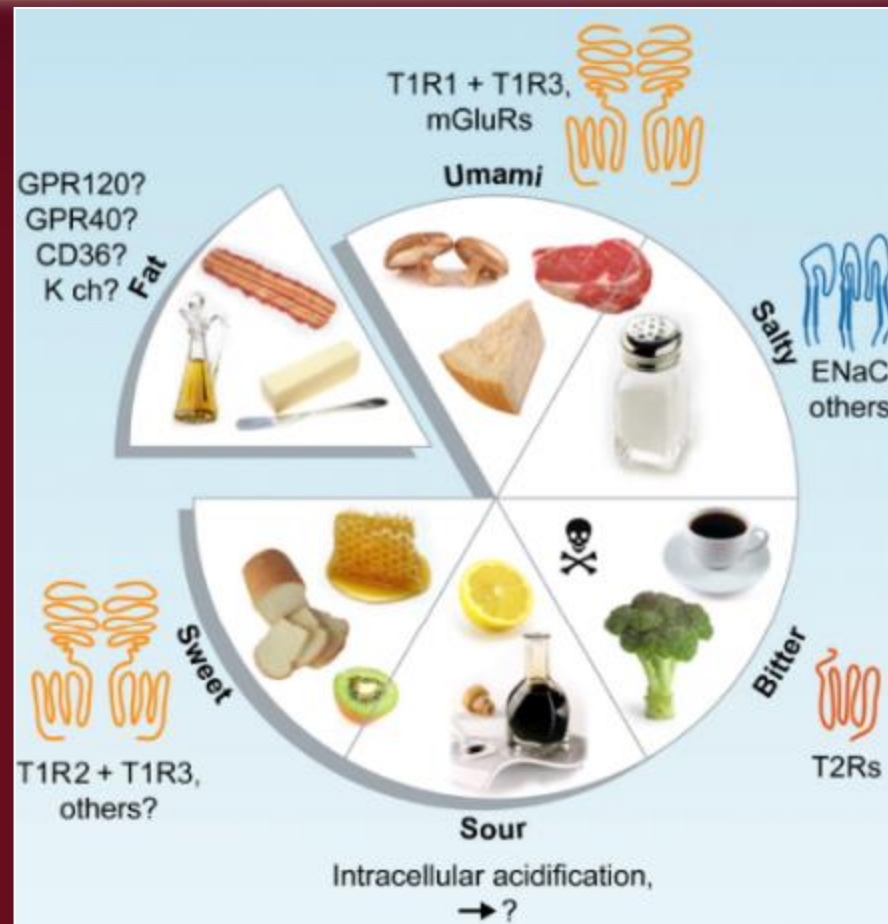
# Posterior tibial nerve stimulation



# Percutaneous tibial nerve stimulation (PTNS)

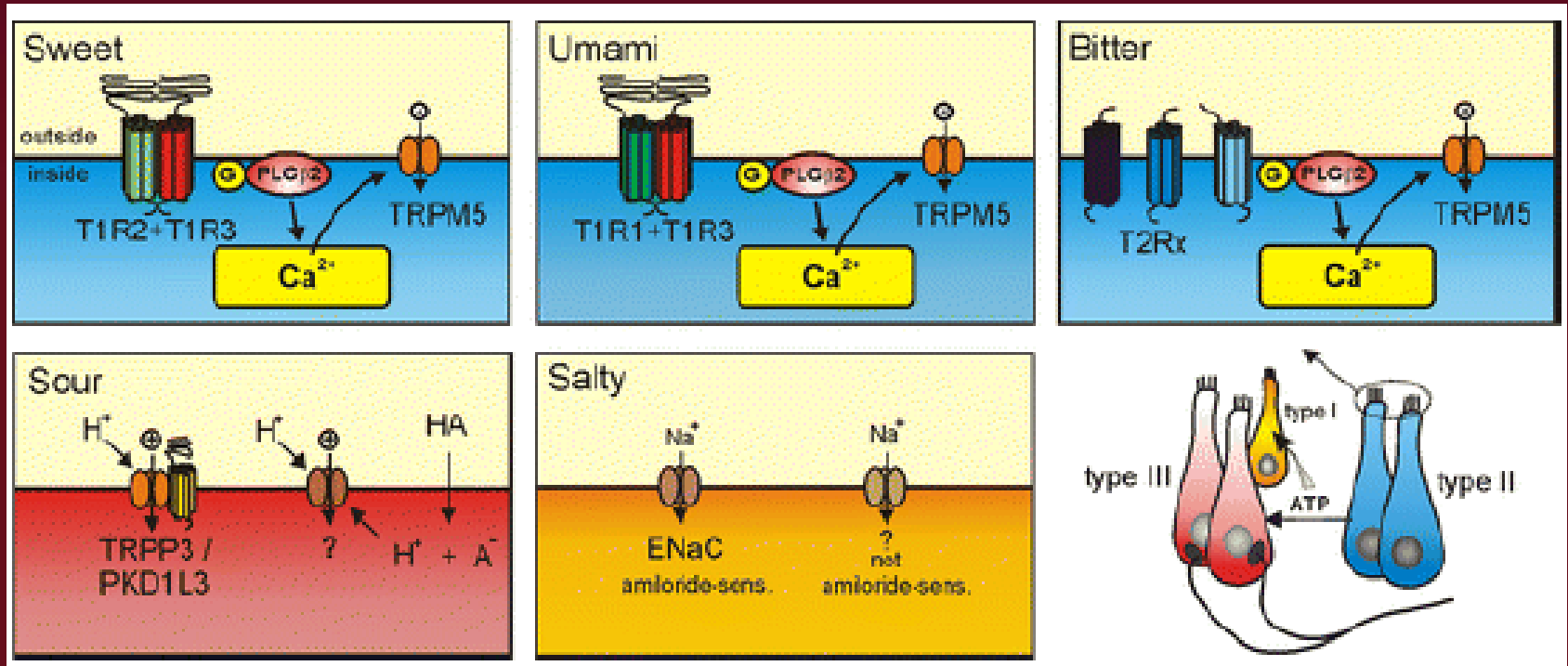
- Helps optimise overall treatment
  - Relaxes bladder muscle spasm
  - Increase bladder capacity rapidly to accommodate instillation treatment
- May abolish pudendal neuropathy
  - ‘Rebooting’ the pelvic nerve plexus
  - ? Blocking / abolishing neuronal cross talk

# Taste buds



CD36: cluster of differentiation 36; ENaC: epithelial sodium channel; GPR: G-protein coupled receptor; K ch: potassium channel; mGluR: metabotropic glutamate receptor; T1R1/2/3: taste receptor type 1 member 1/2/3; T2R: taste receptor type 2

# Taste bud receptors



ATP: adenosine triphosphate; ENaC: epithelial sodium channel; PCL: phospholipase C; PKD1L3: polycystin 1 like 3, transient receptor potential channel interacting; T1R1/3: taste receptor type 1 member 1/3; T2Rx: taste receptor type 2 member x; TRPM5: Transient receptor potential cation channel subfamily M member 5; TRPP3: transient receptor potential polycystic 3



# Taste buds (urethral) – cholinergic

- Urethral ‘taste buds’ receptors<sup>1</sup>
  - Transmits via **cholinergic** nerves
  - Looks like detector for sweetness but transmits ‘**unpleasant**’ signals centrally – like bitterness
  - **Sweets**, cakes → urethral throbbing, tingling

# Taste buds (urethral) – cholinergic

---

- Urethral ‘taste buds’ receptors
- Treatment – **anti-cholinergics**
  - Solifenacin (Vesicare), Fesoterodine (Toviaz)

# Urethral colonisation – new concept

- MSU – RBCs; WBCs; positive for bacteria  $>10^5$  cfu<sup>1</sup>
  - Classic UTI
- MSU – RBCs; WBCs; negative for bacteria<sup>2</sup>
  - Classic interstitial cystitis
- MSU – no RBCs; no WBCs; positive for bacteria  $>10^5$  cfu
  - Classic **urethral colonisation?**

1. Schmiemann G et al. *Dtsch Arztebl Int.* 2010;107(21):361-7.

2. Scott VCS et al. *Urology* 2015; 86(3): 425-431.

cfu: colony-forming units; MSU: midstream specimen of urine; RBC: red blood cell; UTI: urinary tract infection; WBC: white blood cell

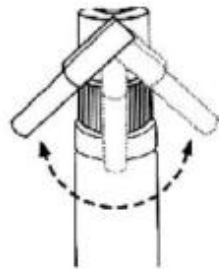
# Urethral colonisation – treatment

- Antibiotics – **tissue type**:
  - Trimethoprim, ciprofloxacin
- Vaginal **oestrogenisation** (promotes lactobacilli):
  - Vagifem, Ovestin
- Vaccine – **Uromune?**<sup>1</sup> This product is not licensed in the UK
  - Against 4 typical bacteria:
    - *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus vulgaris*, and *Enterococcus faecalis*

# Uromune<sup>1</sup>

## PROCEDURE:

Rotate the nozzle sideways to unblock the push button



Direct the nozzle under your tongue and spray



**UROMUNE**<sup>®</sup>  
Perlingual **SPRAY**

TREATMENT
2 per day
 2 puffs in one dose <b>SHAKE BEFORE USING</b>
DURATION 3 MONTHS

Syner-Med

**Syner-Medica Ltd**

Syner-Med House

120 High Street

Purley

Surrey

CR8 2AD

Telephone No: +44 (0) 208 655 6380

Fax No: +44 (0) 208 655 6398

# Future – vaccine

- Eradicate **bacteria reservoir**
  - Deep layers of bladder urothelium
  - Urethral glandular ducts
- Prevents repeat invasion long term
  - **Genetically vulnerable** (Lewis a+b-, a-b-)

# PBS / IC – summary

- Importance of identifying patient Symptom complex
- Multimodality approach  
Individualised treatment (phenotyping)  
Exciting new modalities
- Great research opportunities

# Thank you

---

