

The Interstitial Cystitis/ Bladder Pain Syndrome (IC/BPS) Oral Therapies

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Disclosures

- Abbvie Pharmaceuticals, Consultant
- Alivio Pharmaceuticals, Consultant
- Spero Therapeutics, Consultant
- Ironwood Pharmaceuticals, Consultant

Interstitial Cystitis Treatment

Self Help



- Bladder retraining
- Behavior modification
- Physical therapy / Yoga
- Herbal therapy
- Biofeedback/electrical stimulation
- Acupuncture
- Warm Baths / Heating pads
- **Dietary modification**





Dietary Changes



- Not everyone is sensitive to every food
- **Elimination Diet/Don't Stop Drinking!!!**
- Use of Dietary Supplements: Ca-glycerophosphate (Preliel®), Polycitra-K®, baking soda)



Intensive Systematic Dietary Manipulation (ISDM) for IC/BPS

- Controlled one-year trial
30 IC/BPS patients received ISDM
10 IC/BPS patient received non-intensive DM

Development of dietary guidance		
Low-Risk Foods	Food Category	Foods That Should Be Avoided
Rice, wheat, oatmeal	Grain	Rye, sourdough bread
Beef, pork, chicken, mutton	Meat	Meat products containing spices (wiener, bacon, etc.)
Cod, flatfish, salmon, shellfish, crab, shrimp	Seafood	Canned food, seafood products containing spices
Chicken egg	Egg	
Milk, cheese (mozzarella, cheddar)	Dairy products	Yogurt, cheese containing spices, aged cheese

Results:

Clinical effects of ISDM and NIDM					
ISDM/NIDM	OSSI	OSPI	Urinary Urgency	Pelvic/Bladder Pain	QOL
(a) Before: ISDM/NIDM	11.8 ± 0.1/11.2 ± 0.4	10.8 ± 0.1/10.3 ± 0.4	6.4 ± 0.1/6.0 ± 0.1	6.2 ± 0.1/6.0 ± 0.2	5.1 ± 0.0/5.3 ± 0.1
(b) After 3M: ISDM/NIDM	9.8 ± 0.1/10.6 ± 0.4	8.8 ± 0.1/10.0 ± 0.4	5.1 ± 0.1/5.7 ± 0.2	4.8 ± 0.1/6.1 ± 0.1	3.9 ± 0.0/5.2 ± 0.1
(c) After 1 year: ISDM/NIDM	8.7 ± 0.1/9.6 ± 0.4	7.7 ± 0.1/9.5 ± 0.3	4.6 ± 0.1/5.9 ± 0.1	4.0 ± 0.1/6.1 ± 0.1	3.1 ± 0.0/4.8 ± 0.1
P value*: ISDM/NIDM	<.0001/NS	<.0001/NS	<.0001/NS	<.0001/NS	<.0001/NS

NS, not significant.
Data, mean ± standard error.
* P value: (a) vs (b), (b) vs (c).

All assessment parameters improved beyond controls at all time points up to one year

Comestible Sensitivity



IC/BPS

- Grapefruit Juice
- Spicy Foods
- Caffeinated Coffee

CP/CPPS

- Caffeinated Coffee
- Spicy foods
- Hot Peppers
- Grapefruit

- *****
- Spirulina

- TUMS

- Alginic acid
- Calcium glycerophosphate

- Calcium polycarbophil (Fibercon®)
- Psyllium Fiber (Metamucil®)
- Docusate (Colace®)
- Ca glycerophosphate (Prelief®)

GI - GU CROSSTALK

Shorter B, Lesser M, Moldwin RM, Kushner L. Effect of comestibles on symptoms of interstitial cystitis. J Urol, 2007,178:145-52.

Herati A, Shorter B, Tai J, Lesser M, Moldwin R. Differences in food sensitivities between female interstitial cystitis/painful bladder syndrome and chronic prostatitis/chronic pelvic pain syndrome patients. J Urol, 181:22 (Abs 60).

Urinary Anesthetics

Used frequently but rarely discussed ...

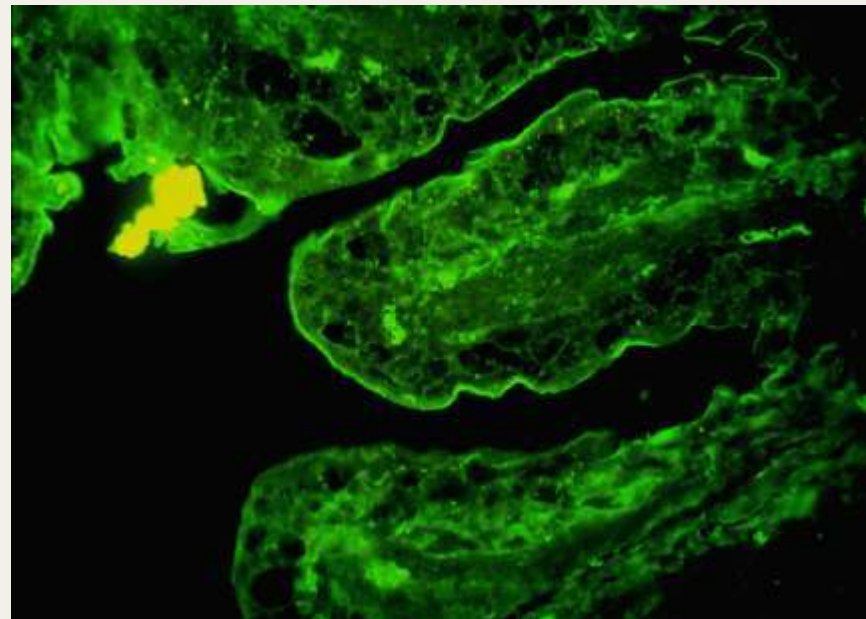
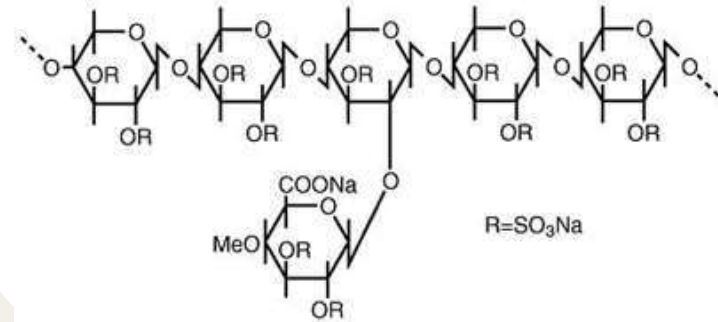
- Phenazopyridine (Pyridium)
- Combo meds (Urised, Prosed DS, Uribel)
 - Antispasmodic
 - Hyocyamine
 - Atropine
 - Anti-infective
 - Methenamine
 - Methylene blue
 - Benzoic acid
 - Analgesic
 - Phenyl salicylate



Pentosan Polysulfate Sodium (Elmiron®)

- “Heparinoid”
- FDA approved for IC/BPS symptoms
- 30-47% efficacy (12 weeks)
- Relief may require 3 to 6 months of continuous therapy

Dosage = 100 mg t.i.d.



Pentosan Polysulfate Sodium

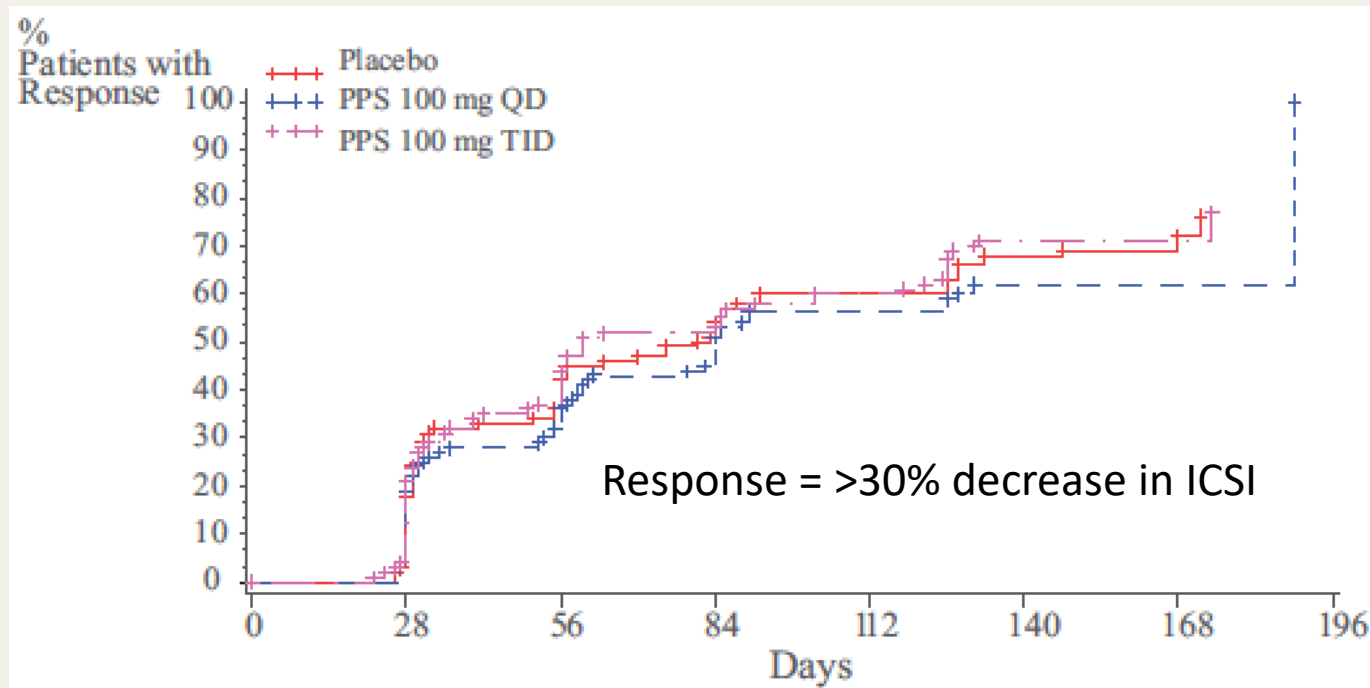
Side Effects (1% to 4%)

- Alopecia, reversible upon discontinuation
- GI — diarrhea, nausea
- Headache
- Rash
- Dyspepsia
- Abdominal pain
- Liver function abnormalities
- Dizziness



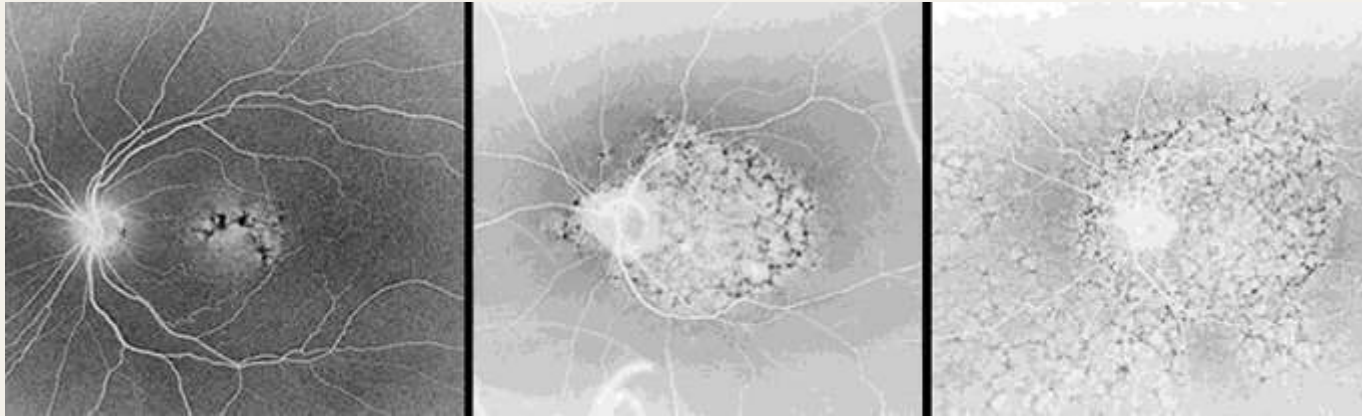
Pentosanpolysulfate Sodium

- 368 IC/BPS patients
- Received pentosan polysulfate sodium 100 mg once daily or 3 times daily, or matching placebo for 24 weeks



Nickel JC, Herschorn S, Whitmore KE, et al: Pentosan Polysulfate Sodium for Treatment of Interstitial Cystitis/Bladder Pain Syndrome: Insights from a Randomized, Double-Blind, Placebo Controlled Study. J. Urol. 2015: 1-6.

PPS and Pigmentary Maculopathy?



Representative fundus autofluorescence imaging demonstrating a variety of disease presentations. Retinal pathology was subjectively more apparent on fundus autofluorescence imaging.

Long term use/High dose 📌 Pigmented Maculopathy?

Symptoms: Blurred vision, subjectively prolonged dark adaptation, metamorphopsia

Pearce WA, Chen R and Jain N: Pigmentary Maculopathy Associated with Chronic Exposure to Pentosan Polysulfate Sodium. *Ophthalmology* 2018; **125**: 1793–1802.

Hanif AM, Armenti ST, Taylor SC, et al: Phenotypic Spectrum of Pentosan Polysulfate Sodium–Associated Maculopathy. *JAMA Ophthalmol* 2019: 1–8.

Tricyclic Antidepressants

Amitriptyline (Elavil®) 10 to 75 mg qhs

- Central + peripheral anticholinergic action
- Block reuptake of serotonin + **NE**
- Sodium channel blocker
- Antihistaminic properties (H2 blocker)

Amitriptyline

- Prospective, randomized, placebo-controlled study
Improvement in urgency and pain ($p < 0.001$)¹
- Long-term efficacy after mean of 19 months
64% response rate
31% drop out
Mean dose = 55 mg²
- RCT (Interstitial Cystitis Collaborative Research Network)
No difference from Placebo until 50 mg³



1. Van Ophoven A, et al. A prospective, randomized, placebo controlled, double blind study of amitriptyline for the treatment of interstitial cystitis. J Urol, 172: 533-536, 2004

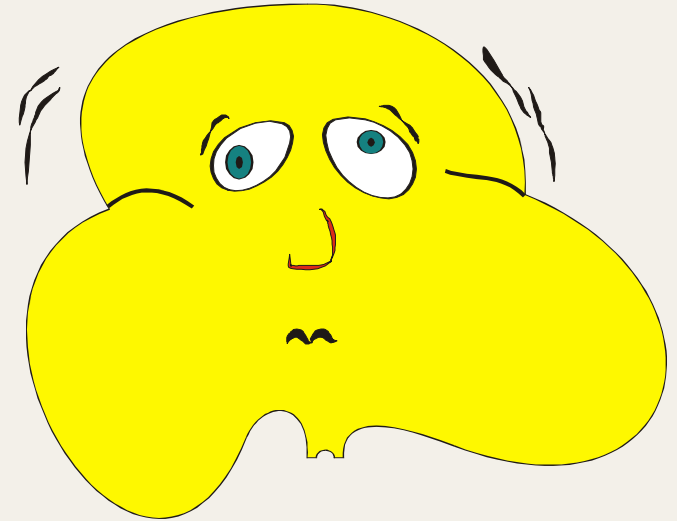
2. Van Ophoven A, et al. Long-term results of amitriptyline treatment for interstitial cystitis. J Urol, 174: 1837-1840, 2005

3. Foster et al. Effect of Amitriptyline on Symptoms in Treatment Naïve Patients With Interstitial Cystitis/Painful Bladder Syndrome. J Urol, (2010) vol. 183, 1853-1858.

Tricyclic Antidepressants

Adverse Reactions

- **Constipation**
- Morning Lethargy
- Dry Mouth
- Urinary Retention
- Weight Gain
- Decrease in Sex Drive / Orgasm
- Palpitations
- Liver function abnormalities



How to Use Amitriptyline Most Effectively

- Start with the lowest dosage (10-25 mg)
- Increase dose as per patient tolerance and symptom improvement
- Take dose with dinner (not just before bedtime)
- Never start before constipation is treated

Alternatives within this group:

Nortriptyline (Pamelor[®]), Doxepin (Sinequan[®])

Antihistamines

- Hydroxyzine (*Vistaril[®], Atarax[®])
 - ✓ Inhibits mast cell release of histamine
 - ✓ Sedative
 - ✓ 10 to 25mg qhs x1 wk; up to 75mg/day
 - ✓ Requires up to 3 months for effect



Cimetidine and IC/BPS

- Seshadri study
 - 9 patients, uncontrolled
 - 300mg bid x 1 month
 - 44% with complete/sustained response
- Thilagarajah study
 - 34 patients, RCT
 - 400mg bid x 3 month**
 - median symptom scores decreasing from 19 to 11 (P<0.001). (19.4 to 18.7 in the placebo group)

Seshadri P, Emerson L, Morales A. Cimetidine in the treatment of interstitial cystitis. *Urology*. 1994;44(4):614-616.

Thilagarajah R, Witherow RO, Walker MM. Oral cimetidine gives effective symptom relief in painful bladder disease: a prospective, randomized, double-blind placebo-controlled trial. *BJU Int* 2001;87:207–12.

Other Useful Medications

- Antiseizure agents
 - Gabapentin(Neurontin[®])
Up to 3,600 mg per day
 - Pregabalin (Lyrica[®])
Up to 300 mg per day



Mixed reviews for chronic pelvic pain

Agarwal MM and Sy ME: Gabapentenoids in pain management in urological chronic pelvic pain syndrome: Gabapentin or pregabalin? *Neurourol Urodynam* 2017; **36**: 2028–2033.

Horne, A. W. *et al.* Gabapentin for chronic pelvic pain in women (GaPP2): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet* **396**, 909–917 (2020).

Cyclosporine A

- Potent immunosuppressant
- Only retrospective studies available
- Dosing 2-3 mg/kg/day
- ~85% "favorable response" in HL patients.
- Dropout from adverse effects, i.e., renal dysfunction, HTN
- Only 3 of 10 patients without HL responded
- Success rate of 68% (23 of 34) for HL patients

- Forrest JB, Payne CK and Erickson DR: Cyclosporine A for Refractory Interstitial Cystitis/Bladder Pain Syndrome: Experience of 3 Tertiary Centers. JURO 2012; **188**: 1186–1191.
- Crescenze IM, Tucky B, Li J, et al: Efficacy, Side Effects, and Monitoring of Oral Cyclosporine in Interstitial Cystitis-Bladder Pain Syndrome. URL 2017; 107: 49–54.
- Vollstedt A, Tennyson L, Turner K, et al: Evidence for Early Cyclosporine Treatment for Hunner Lesion Interstitial Cystitis. Female Pelvic Medicine Reconstr Surg 2022; **28**: e1–e5.

Know Your Customer..

Bladder Centric Pain	Centralized /Widespread Pain
Tricyclic antidepressants (TCA)	TCA's
Neuroleptics	Neuroleptics
selective 5-HT and noradrenaline re-uptake inhibitors (SNRI)	SNRIs
Antihistamines	Neuromodulation
Pentosan polysulfate	Cannabis?
Urinary anesthetics	
Intravesical agents	
Hydrodistention/ fulguration	
Neuromodulation	
Intratrigenal Botulinum toxin A	
Cyclosporine	
Urinary diversion	

For best results...Mix and Match...

- Typical patient medical regime:
 - Dietary changes
 - Amitriptyline 25 mg qhs (at 7– 8 PM)
 - Hydroxyzine 25 mg
 - Intravesical therapy q 2weeks or prn (self-therapy)

In Conclusion...

- Only one FDA-approved IC/BPS oral therapy...Unmet medical need!
- All oral therapies based upon identified pathologies
- A good therapy is a bad therapy if used incorrectly
- Know your customer!