Chronic Bladder Discomfort

Key Point Summary:
- What is meant by chronic bladder discomfort (including Bladder Pain Syndrome)
- Incidence
- Causes
- Impact
- Investigations
- Management
- Detailed review of Bladder Pain Syndrome and Central Sensitisation.

Co-morbidities:
- Co-morbidities and other pain orientated problems are common.
- Patients will often move from one to another comorbidity or have more than one.

Chronic bladder discomfort, Bladder Pain Syndrome [I.C.] and chronic pelvic pain:
- Are very common,
- Have similar features,
- Have some important differences.
- May mimic UTI's

To be ‘Chronic’:
- They should be of more than 6 weeks duration,
- Local causes must be excluded.
- Often the original cause of the pain has resolved.

Symptoms are common in all:
- Pelvic pain / discomfort,
- Frequency urgency nocturia pain on bladder filling
- Dyspareunia,
- Mimic UTI's
Chronic Bladder Discomfort

Abstract:

Diagnosis:
- Urine output chart,
- Mssu – Micro c&s, Cytology
- Urodynamics
- Organ imaging
- Cystoscopy

Important to understand:
- Innervation / nerve pathways,
- Central sensitisation,
- Frequent similar co-morbidities.

Chronic Bladder Discomfort

Abstract:

Treatment [After exclusion and/or treatment of local pathology]:
- 1st line treatments –
  ▪ Behavioral techniques
  ▪ Oral medications intravesical medications
  ▪ Success will often be short-lived.

- 2nd line treatment –
  ▪ Sacral Neuromodulation
  ▪ ??? Botox

- 3rd line treatments -
  ▪ Ablative surgical procedures.

Chronic Bladder Discomfort

Abstract:

Chronic bladder discomfort:
Definition:
- The perception of low abdominal ‘bladder’ discomfort in response to bladder filling and/or emptying. It also includes Bladder Pain Syndrome [Interstitial Cystitis].
- > 6weeks duration.

Incidence:
- Incidence unknown
- Up to prevalence of 12,600 cases of BPS/IC per 100,000 of the population.
- Chronic bladder discomfort has a higher incidence than this.

Quality of life:
- Highlighted by the 1st International Consultation on Incontinence sponsored by the World Health Organization as a major health issue.
- Problems contributing to QoL issues include:
  - Debilitating pain
  - Frequency and urgency
  - Depressive disorders
  - Urge incontinence
  - Anxiety
  - Fear / embarrassment
  - Sleep disturbance
  - Inability to work
Once pain is chronic: [i.e. > 6 weeks]
- The processing of pain and neural pathways become important.
- The neural circuitry that controls the process of pain is complex and highly distributed.
- Involves pathways at many levels of the:
  - brain,
  - spinal cord
  - peripheral nervous system
- Is mediated by multiple neurotransmitters.
- Through these central and spinal cord connections, pain may be influenced, chronicised and catastrophised.
- The hypothalomo-pituitary axis may also be involved.

Symptoms:
The common symptoms include:
- 'Bladder' pain
- Frequency
- Nocturia
- Urgency Pain - Urge incontinence
- Pain with intercourse in women
- Mimic UTI
- Pelvic/vaginal pain/discomfort.

‘Causes’ of Chronic Bladder Discomfort:
- Situations which cause pain in any circumstance.
- the pathological sieve should be followed.

Inflammatory causes:
- Infection [incl diverticular abscess &/or fistula]
- Tumours [bladder - but remember ovarian etc.]
- Polyps
- Stones
- Reactions to medications
- Post surgical sutures/tape/mesh.
- ‘Interstitial Cystitis’

Non-inflammatory:
- Detrusor Muscle spasm.
- Overactive detrusor - over 45% of patients with Chronic Bladder Discomfort/pain will have OAD.
  - Systolic contractions
  - Reduced compliance
- Detrusor sphincter dyssinergia.
- Neurogenic bladder.
- Bladder overdistension.

Medications contributing to bladder discomfort:
- Methotrexate
- Cyclophosphamide.
- Surgam.

Diagnosis:
- A thorough history and examination are important
  - associated urinary and bowel symptoms,
  - history of sexual abuse,
  - family history,
  - co-morbidities,
  - menopause,
  - surgery – particularly pelvic surgery and medications.
- Urinalysis for blood, leukocytes, culture [and cytology] must be carried out.
- Ultrasound imaging – renal, pelvic and bladder scans.
- Urodynamic studies.
- Cystoscopy.
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**Treatment:**
- Treat any **underlying pathology** – UTI, tumours, stones, foreign bodies etc.
- Much treatment deals with the local issues – eg Anticholinergics/muscle relaxants for OAD urgency and hypersensitivity.
- Many treatments have **little evidence**: Botulinum Toxin, pentosan polysulphate sodium [Elmiron], Dimethylsulphoxide [DMSO], iAluRil.
- Psychological support.
- Physiotherapy support.

Lifestyle Changes:

- Reducing bladder stimulants such as: caffeinated beverages.
- Pelvic Floor Exercises.
- Bladder re-training.
- Tens.

**2nd Line Treatment:**
- Pharmacology
  - Antimuscarinics
  - Anticholinergics
- Beta 3 agonists

Cystoscopic findings with detrusor overactivity:
- Almost always some degree of trabeculation

**Cystoscopic findings with detrusor overactivity:**
- Severe trabeculation
Cystoscopic findings with detrusor overactivity:
- Almost always some degree of trabeculation.
- In severe causes – diverticular formation.

More severe
Trabeculation +
Early Diverticulum

Medications: [alone or in combination]
- Propantheline 15-30mg tds
- Endep 25 - 50mg nocte
- Oxybutynin 2.5-5mg bd-tds
- Trans-dermal Oxybutynin 1 patch twice a week
- Solifenacin 5-10mg daily [or divided dose]
- Darifenacin 7.5-15mg daily [or divided dose]
- Detrusitol 1-2mg bd
- Fesoterodine [not available in Australia]
- Mirabegron 25-100mg daily
- Combinations often appropriate

Dry out with drugs!

Beta 3 agonists:
- Mirabegron [Betmiga]
  - Stimulate the Beta 3 sympathetic nerves.
  - These nerves keep the detrusor muscle relaxed.
  - Generally less side effects.
  - No anticholinergic side effects.
  - ? May increase blood pressure.
  - May take a month to work.
  - Often used in combination with another medication.
  - Occasional patient with headaches.
  - Occasional patient with itching.

Beta 3 agonist [Mirabegron]
- Has transformed the medical management of OAD.
- Often used in combination with anticholinergic medication.

Bladder Pain Syndrome:
- When other pathologies have been excluded, Bladder Pain Syndrome [aka ‘interstitial cystitis’] may be the problem.
- Not uncommon
- Cause unknown
- NB. Similarities with Ulcerative colitis and Crohn’s disease.
Bladder Pain Syndrome* [Interstitial cystitis]: The Bladder Pain Syndrome (BPS) is a spectrum of urological symptoms characterised by bladder pain with typical cystoscopic features.

- Hunner’s lesions - [inflammatory areas]
- Petechial haemorrhages on emptying.

*preferred ICS terminology

Causes of BPS:

- Local causes
  - Damaged GAG layer - GAG layer
  - Thought to function as an antibacterial coating for the bladder by retarding the adhesion of pathogens.
  - Triggered by infections, toxic substances auto-immune disorders or -
  - Complex central sensitisation of pain.

So many different types of nerves.
So many different nerve pathways.
So many interactions between the nerves.

Pain theoretically originates in sensory nerve receptors:

- Nociceptors
  - Nociceptors are the specialised sensory receptors responsible for the detection of noxious (unpleasant) stimuli.
  - Transform the stimuli into electrical signals, which are then conducted to the central nervous system.
  - They are the free nerve endings of primary afferent Aδ and C fibres.
  - Inflammatory mediators [eg bradykinin, serotonin, prostaglandins, cytokines, and H+] are released from damaged tissue stimulate the Nociceptors.

These inflammatory substances:

- Act to reduce the activation threshold of nociceptors.
- Then the stimulation required to cause activation is less.
- This process is called primary sensitisation.
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**Primary afferent fibres:**
- **Aβ fibres** are highly myelinated and of large diameter.
  - respond to light touch and transmit non-noxious stimuli.
- **Aδ fibres** are lightly myelinated and smaller diameter.
  - respond to mechanical and thermal stimuli.
  - responsible for the initial reflex response to acute pain.
- **C fibres** are unmyelinated and are also the smallest type of primary afferent fibre.
  - C fibres are polymodal, responding to chemical, mechanical and thermal stimuli.
  - C fibre activation leads to slow, burning pain.

### What happens to these nerves?
- Aδ and C fibres synapse with secondary afferent neurones in the dorsal horn of the spinal cord.
- Complex interactions occur in the dorsal horn between afferent neurones, interneurones and descending modulatory pathways.
- These interactions determine activity of the secondary afferent neurones.
- There are two main pathways that carry nociceptive signals to higher centres in the brain.

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**Ascending Tracts:**
- 2 main tracts –
  - **The spinothalamic tract:**
    - Secondary afferent neurones decussate within a few segments of the level of entry into the spinal cord and ascend in the contralateral spinothalamic tract to nuclei within the thalamus.
    - These third order neurones then ascend to terminate in the somatosensory cortex. There are also projections to the periaqueductal grey matter (PAG).
    - Transmits signals that are important for pain localisation.
  - The spinoreticular tract.

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**Pain processing in the brain:**
- The experience of pain is complex and subjective,
- It is affected by factors such as cognition (e.g. distraction or catastrophising), mood, beliefs and genetics.
- The somatosensory cortex is important for the localisation of pain.
- Insular, anterior cingulate cortex and prefrontal cortex, and the thalamus also important.

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**Visceral pain:**
- Arises from the internal organs.
- The viscera are largely innervated by C fibres but also Aδ fibres.
- Visceral pain is typically diffuse and poorly localised, often described as deep, dull or dragging.
- It can be associated with autonomic changes such as nausea, vomiting, and changes in heart rate or blood pressure.
- It can also evoke strong emotional responses.
Visceral pain ctd:
- is triggered by smooth muscle distension or contraction,
- stretching of the capsule surrounding an organ,
- ischaemia and necrosis, irritation by chemicals produced during inflammatory processes.
- These are factors involved in BPS!

Central sensitisation:
- Defined operationally as ‘an amplification of neural signaling within the spinal cord & CNS that elicits pain hypersensitivity’.
- Can contribute to inflammatory, neuropathic and dysfunctional pain disorders in patients.
- The pain we experience might not necessarily reflect the presence of a peripheral noxious stimulus.
- It allows for a vicious cycle of pain escalation.

Central sensitisation introduces another dimension:
- One where the CNS can:
  ▪ change, distort or amplify pain,
  ▪ increasing its degree, duration, and spatial extent in a manner that no longer directly reflects the specific qualities of peripheral noxious stimuli,
  ▪ but affects the particular functional states of circuits in the CNS.
  ▪ ‘imprinting’ of pain.

What does this mean?
The overwhelming conclusion from these diverse epidemiological studies is:
- Chronic pain hypersensitivity in the absence of inflammation or nerve damage results in apparently phenotypically different syndromes depending on the tissue/organs affected.
- The overall similarity of the sensitivity changes may reflect a common contribution of central sensitisation, and this may account for the unexpectedly high comorbid rate of apparently different syndromes.

This comorbidity list is extensive:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>migraine</td>
<td>rheumatoid arthritis</td>
</tr>
<tr>
<td>primary headache</td>
<td>premenstrual syndrome</td>
</tr>
<tr>
<td>chronic fatigue symptom</td>
<td>chronic urticaria</td>
</tr>
<tr>
<td>systemic lupus erythematous</td>
<td>temporomandibular disorders</td>
</tr>
<tr>
<td>irritable bowel syndrome</td>
<td>fibromyalgia</td>
</tr>
<tr>
<td>cervical myofascial pain syndrome</td>
<td>chronic prostatitis and vulvodynia</td>
</tr>
<tr>
<td>chronic pelvic pain</td>
<td>U/C, Crohn’s, I/C</td>
</tr>
</tbody>
</table>

Can central sensitisation cause inflammation in organs? Probably:
Magdy Hassouna, M.D., Ph.D., senior scientist, Division of Applied and Interventional Research, Toronto Western Research Institute:
- High expression of NOS* in rats with interstitial cystitis.
- NOS has ability to send nerve impulse backwards down sensory nerves.
- This releases inflammatory substances at the origins of he sensory nerves.
- Sacral nerve stimulation reduced the expression of the NOS and the interstitial cystitis in these rats.

[*NOS – Nitric oxide synthase]
This complex central sensitisation brings into question the origins of BPS and many other conditions. While there may be some initial insult, the central sensitisation in an individual may explain the pain’s chronicity and catastrophisation. Explains why most treatments are ‘bandaids’. IC/BPS Patients are universally dissatisfied with treatment. One large-scale longitudinal investigation of actively treated IC/BPS patients (n=637, median follow-up 31 months) found no detectable improvement in symptom severity over the period of observation (Propert et al., 2000).

Treatment Options:
- Diet– Avoid:
  - Foods high in acid such as citrus fruit, cranberries, strawberries, vitamin C, some herbal or green teas or tomatoes. A plain mint/chamomile tea or just water is best.
  - Foods that stimulate nerves such as caffeine, chocolate or cola drinks.
  - Foods high in sodium or potassium such as bananas.
  - Artificial Sweeteners including aspartamine etc.
  - Fizzy drinks (including mineral water). Diet cola drinks are probably the worst as they contain acid.
  - ? Cigarettes.

Summary:
- Chronic bladder discomfort is not uncommon and may be difficult to diagnose and treat.
- There may be an initial insult/physical process to set up a pain response but the chronicity is more likely related to sensitisation in the spinal cord and other factors in the individual.
- Whether this implies some genetic susceptibility or situational cause [e.g. sexual abuse] is unclear.
- After excluding remedial causes, treatment is difficult and usually short-lived.

Remember:
- Chronic Pain is more about sensitivity than about injury.
- Treatment is about finding the appropriate stressor.
- The patient is an active participant in their own care.
- Pain is [not necessarily] a normal response to a noxious stimulus.
- Perception of pain may vary.
- Perception will depend on many other coexisting physical and emotional circumstances.
- Will also depend on the actual source/origin of the pain.
- A treatment team is usually necessary!