# Guidelines on
# Chronic Pelvic Pain

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# 1. INTRODUCTION

## 1.1 The guideline

The European Association of Urology (EAU) Guidelines Group for Chronic Pelvic Pain have prepared this guidelines document to help medical professionals assess the evidence-based management of chronic pelvic pain. The multidisciplinary panel of experts includes urologists, a neuro-urologist, anaesthesiologists, a gynaecologist and a psychologist.

### *1.1.1 Publication history*

The Chronic Pelvic Pain Guidelines were first published in 2003, with partial updates in 2007 and 2008. This 2011 publication presents an unrevised version of the full text. A full text update is foreseen in 2012.

A quick reference document presenting the main findings of the Chronic Pelvic Pain guidelines is also available alongside scientific publications in the society journal European Urology (1,2). All texts can be viewed and downloaded for personal use at the EAU website: http://www.uroweb.org/guidelines/online-guidelines/.

## 1.2 Level of evidence and grade of guideline recommendations*

References used in the text have been assessed according to their level of scientific evidence (Table 1), and guideline recommendations have been graded (Table 2) according to the Oxford Centre for Evidence-based Medicine Levels of Evidence (3). The aim of grading recommendations is to provide transparency between the underlying evidence and the recommendation given.

**Table 1: Level of evidence (LE)***

| Level | Type of evidence |
|---|---|
| 1a | Evidence obtained from meta-analysis of randomised trials |
| 1b | Evidence obtained from at least one randomised trial |
| 2a | Evidence obtained from one well-designed controlled study without randomisation |
| 2b | Evidence obtained from at least one other type of well-designed quasi-experimental study |
| 3 | Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports |
| 4 | Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities |

*Modified from Sackett et al. (3).*

It should be noted that when recommendations are graded, the link between the level of evidence and grade of recommendation is not directly linear. Availability of randomised controlled trials (RCTs) may not necessarily translate into a grade A recommendation where there are methodological limitations or disparity in published results.

Alternatively, absence of high level evidence does not necessarily preclude a grade A recommendation, if there is overwhelming clinical experience and consensus. In addition, there may be exceptional situations where corroborating studies cannot be performed, perhaps for ethical or other reasons and in this case unequivocal recommendations are considered helpful for the reader. The quality of the underlying scientific evidence – although a very important factor – has to be balanced against benefits and burdens, values and preferences and cost when a grade is assigned (4-6).

The EAU Guidelines Office, do not perform cost assessments, nor can they address local/national preferences in a systematic fashion. But whenever this data is available, the expert panels will include the information.

**Table 2: Grade of recommendation (GR)***

| Grade | Nature of recommendations |
|---|---|
| A | Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial |
| B | Based on well-conducted clinical studies, but without randomised clinical trials |
| C | Made despite the absence of directly applicable clinical studies of good quality |

**Modified from Sackett et al. (3).*

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## 1.4 Definition of pain (WHO)

'Pain management is a necessity in the work of each physician.' F. Sauerbruch, 1936

Pain can be defined as an unpleasant sensory and emotional experience associated with either real or potential tissue damage, or it can be described in terms of such damage (1). Pain is the most common symptom of any illness. In its management, firstly, the physician needs to discover and treat the cause of the pain; secondly, to treat the pain itself, whether or not the underlying cause is treatable; and thirdly to relieve the suffering caused by the pain.

One function of the nervous system is to provide information about the occurrence of or the threat of injury. The sensation of pain, by its inherent aversive nature, contributes to this function. The response of the peripheral neural apparatus via primary sensory neurones (known as nociceptors), to noxious (injurious or potentially injurious) stimuli alerts the organism to injury (potential injury). Acute pain is an important and adaptive element of the normal nervous system. In chronic or persistent pain, the purpose of the pain is lost. Such pain often represents an aberration of neural processing.

Nociceptive or neuropathic pain. 'Pain' is used to describe all sensations that are perceived as hurting; it requires the higher centres. The causes of pain may be many. For example, pain can be nociceptive or neuropathic, with many pains having both a neuropathic and nociceptive component:

- Nociceptive pain is caused by direct stimulation of nociceptors in the periphery; peripheral inflammation may or may not be present. An example of physiological nociceptive pain is when an individual perceives pain due to hot water running over their skin resulting in the individual withdrawing from the stimulus and there is no injury. Pathological nociceptive pain, however, is often associated with tissue damage and inflammation, with inflammation having the effect of increasing the perception of pain associated with peripheral stimulation.
- Neuropathic pain is caused by a lesion to the peripheral or central nervous system.

Acute or chronic pain. Pain may also be described as either acute or chronic pain:

- Acute pathological pain has an acute onset and is short-lived, usually less than a week or so, and is associated with tissue trauma, e.g. following surgery. Transient acute pain may also be caused by acute nerve injury, e.g. local injury to the ulnar nerve from hitting the elbow. Although the mechanisms of acute and chronic pain may overlap, the mechanisms of acute pain resolve quickly in contrast to chronic pain.
- Chronic (also known as persistent) pain occurs for at least 3 months. However, the mechanisms involved are more important than the duration of the pain. Chronic pain is associated with changes in the central nervous system (CNS), which may maintain the perception of pain in the absence of acute injury. These changes may also magnify perception so that non-painful stimuli are perceived as painful (allodynia), while painful stimuli are perceived as more painful than expected (hyperalgesia).

The bladder provides a good example of how changes in the CNS affect sensory perception. An

acute pain insult to the bladder can produce functional changes within the CNS, so that pain persists even after removal of the stimulus. These central functional changes may also be associated with a dysaesthetic (unpleasant sensation) response; for instance, mild distension or stimulation of the bladder by urine not normally perceived, may produce the urge to urinate. Furthermore, core muscles, including pelvic muscles, may become hyperalgesic with multiple trigger points, while other organs may also become sensitive, e.g. the uterus with dyspareunia and dysmenorrhoea, the bowel with irritable bowel symptoms. The spread of abnormal sensory responses between the organs and musculoskeletal system is a well-described consequence of the CNS changes and a crucial cause of complex chronic pelvic pains. Functional abnormalities such as urinary retention may also occur.

Chronic pain is associated with various psychological responses, partly due to the long duration of the pain and partly due to neuroplasticity of the CNS. Chronic pain inhibits feelings, emotions, thinking and reactions, while reduced mobility and inhibited physiological functions restrict social interactions and work. Although there are established management strategies, pain is often undertreated because many clinicians have a poor understanding of the principles of pain therapy. Efforts are needed to improve this situation. When appropriate, management should be both holistic and multidisciplinary.

Deep visceral pain. There are important differences between cutaneous and deep visceral pain. Unlike cutaneous pain, deep visceral pain is diffuse and poorly localised. It may be accompanied by strong autonomic responses, such as sweating and changes in heart rate, blood pressure and respiration. Deep visceral pain may also be produced by stimuli that are not tissue-damaging, e.g. bowel and bladder distension (2,3), and may be associated with referred pain and cutaneous and deep tissue hyperalgesia.

Modulation of pain. Pain transmission from the periphery to the higher brain centres via the spinal cord is not a simple, passive process involving exclusive pathways. The relationship between a stimulus causing pain and the way it is perceived by an individual is dramatically affected by circuitry within the spinal cord and the brain. The sensation of pain is modulated as it is transmitted upwards from the periphery to the cortex. It is modulated at a segmental level and by descending control from higher centres, with the main neurotransmitters involved being serotonin, noradrenaline and the endogenous opioids.

### *1.4.1 **Innervation of the urogenital system***

Studies on the response properties of visceral afferents from the urinary tract have highlighted the differences between nociception in the skin and viscera. Most visceral primary afferents from the bladder, urethra, reproductive and other pelvic organs are encoded for both noxious and non-noxious stimuli (4-6). Increasing afferent traffic results in a change from non-noxious sensation to noxious.

Ureter. Ureteric afferents are thinly myelinated or unmyelinated and respond to direct probing of a limited area of tissue. They can be differentiated into two groups (7):

- The first group responds to ureteral contractions and is excited by low levels of distension (average threshold 8 mmHg). They appear to encode levels of distension throughout and beyond the physiological range.
- The second group does not respond to peristaltic contractions of the ureter, but can be excited by distension with a wide range of thresholds.

Urinary bladder. Two groups of afferent fibres signal noxious stimuli in the urinary bladder, mostly nonmyelinated fibres, with some myelinated fibres (4).

Graded distension of the healthy urinary bladder in humans initially gives rise to a sensation of fullness and eventually pain, as the volume of urine increases and the intravesical pressure exceeds about 25-35 mmHg (8-11). In the inflamed bladder, the sensations during bladder emptying become unpleasant and painful. Nearly all visceral primary afferents from the bladder are small myelinated or unmyelinated fibres.
Some afferents exhibit a low level of ongoing discharge when the bladder is empty. Distension excites mainly thin myelinated afferents, with pressure thresholds corresponding to levels at which humans report the first sensation of fullness. Nearly all afferents are activated by the intraluminal pressures reached during normal, non-painful micturition. The activation of a large number of initially unresponsive afferents indicates that peripheral afferent mechanisms encoding pain from pelvic viscera are highly malleable and are strongly affected by tissue state. These changes are important for signalling pain and discomfort in inflammatory conditions where there is a group of afferents that become activated by the inflammation.

Male reproductive organs. More than 95% of fibres of the superior spermatic nerve are unmyelinated, with most showing polymodal properties (i.e. responses to mechanical, chemical and thermal stimuli) (12). Myelinated and unmyelinated afferent fibres form a homogeneous group with polymodal receptors in the testis and/or epididymis. Prostaglandins sensitise the afferents to other stimuli (13).

### *1.4.2* ***References***


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## 1.5 Pain evaluation and measurement

### *1.5.1* ***Pain evaluation***

The symptom of pain must be fully evaluated. As pain is subjective, the history provides the main evaluation. Examination and investigations provide further understanding of the pain syndrome and exclude other conditions. Pain rating(s) are essential in patient and treatment evaluation.

Pain evaluation includes:

- baseline and ongoing regular evaluation of severity;
- an initial detailed history to include: chronology of onset and progression, character, site pain perceived and radiation, aggravating and relieving factors, associated symptoms;
- questions about thoughts, emotions and behaviour associated with the pain;
- detailed examination, not only of the painful area but of the whole patient, particularly the musculoskeletal and nervous systems;
- investigations to identify well-defined/confusable/non-pain syndromes;
- regular review of the condition as appropriate and its response to interventions.

### *1.5.2* ***Pain measurement***

Pain can only be measured subjectively. The most reliable and well-understood method is a numerical rating scale, from 0 (no pain) to 10 (extreme pain), with half-points marked. This is superior to the widely used visual analogue scale (VAS), which is a 10-cm line with the same labels at the ends. Alternatively, a simple verbal rating scale can be used, e.g. ‘none’, ‘mild’, ‘moderate’, ‘severe’. Both numerical and verbal scales can be used by patients without the need for paper and pen, unlike the visual analogue scale.

0 1 2 3 4 5 6 7 8 9 10

No pain Extreme pain

Since pain is multidimensional, a single rating scale combines these dimensions in unknown quantities. Depending on the clinical question, treatment, patient and setting, it can be helpful to assess separately pain intensity, pain distress, and interference of pain with activities of daily life. It can also be helpful to ask about average pain, worst pain (as even if this only occurs rarely, it can still reveal what patients should avoid) and pain on, for example, bladder voiding. Pain reduction or relief is measured directly using a percentage, from 0% = no relief up to 100% = total relief.
See www.britishpainsociety.org/members_pain_scales.htm for pain scales in English and other languages.
The Brief Pain Inventory (1) consists of four 0 to 10 numerical scales for pain (current, average, worst, and least) and seven scales for interference with aspects of daily life: general activity, mood, walking ability, normal work, relationships with other people, sleep, and enjoyment of life. The EuroQoL is a quality-of-life scale (2) available in several European languages and free for non-commercial use. It asks about mobility, self-care, pain, usual activities, and psychological status (www.euroqol.org).

#### *1.5.3 **References***


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# 2. CHRONIC PELVIC PAIN

## 2.1 Background

#### *2.1.1 **Introduction to chronic urogenital pain syndromes***

Pain perceived within the pelvis may arise from a range of different mechanisms, many of which remain poorly understood. Some conditions have become ‘well-defined’ over the years and it is very important that these are identified and treated by an evidence-based approach, e.g. pudendal neuralgia.

Basic investigations must therefore be undertaken to rule out ‘well-defined’ pathologies. If the results are negative, a ‘well-defined’ pathology is unlikely. Any further investigations should be done only for specific indications, e.g. for subdivision of a pain syndrome.

In many cases, the mechanisms involved are the neural-axial central sensitisation described above and that are so familiar in other fields of chronic pain. There is now no doubt that these central changes can produce states of visceral and/or muscle hypersensitivity with long-term pain, sensory dysaesthesia, and functional abnormalities. These need to be addressed, as well as the cognitive, behavioural, emotional, and sexual consequences of the underlying disease process and long-term pain. This is why the assessment and management of these areas are also expanded in these guidelines with the aim to emphasise a multidisciplinary approach.

Earlier EAU guidelines on chronic pelvic pain (CPP) introduced a classification system aimed at replacing old-fashioned terminology based on spurious assumptions of cause. The main emphasis was to make clear that it should not be presumed that pathology would be found where the pain is perceived. The EAU guidelines moved away from using ‘prostatitis’ and ‘interstitial cystitis’ in the absence of proven inflammation or infection, while the suffixes ‘algia’ and ‘dynia’ have often been used to provide a tangible diagnosis, which in itself may have a therapeutic benefit. In this edition of the guidelines, however, we have decided to avoid such terms completely. Instead, our definitions are based on the recommendation for terminology laid down by the International Continence Society (ICS) (1) and follow the axial structure of the International Association for the Study of Pain (IASP) classification (Table 3) (2).

Pain syndrome terms were introduced to indicate the multiple mechanisms involved, both physical and psychological. This approach has been reviewed on many occasions over the past few years and has been found to be robust. The EAU guidelines expand this approach, so avoiding spurious diagnostic terms, which are associated with inappropriate investigations, inappropriate treatments, inappropriate patient expectations and, ultimately, a worse prognostic outlook.

**Table 3: EAU classification of chronic urogenital pain syndromes. This classification represents the efforts of many groups, as indicated in the main text. The work is in progress and further changes in this classification system are likely***

| Axis I Region | | Axis II System | End organ pain syndrome as identified from Hx, Ex and Ix | | Axis III | Axis IV Referral characteristics | Axis V Temporal characteristics | Axis VI Character | Axis VII Associated symptoms | Axis VIII Psychological symptoms |
|---|---|---|---|---|---|---|---|---|---|---|
| Chronic pelvic pain | Pelvic pain syndrome | Urological | Bladder pain syndrome | | (See Table 3 on ESSIC classification) | Suprapubic<br>Inguinal<br>Urethral<br>Penile/clitoral<br>Perineal<br>Rectal<br>Back<br>Buttocks | ONSET<br>Acute<br>Chronic<br><br>ONGOING<br>Sporadic<br>Cyclical<br>Continuous<br><br>TIME<br>Filling<br>Emptying<br>Immediate post<br>Late post<br><br>PROVOKED | Aching<br>Burning<br>Stabbing<br>Electric<br><br>Other | URINARY<br>Frequency<br>Nocturia<br>Hesitance<br>Poor flow<br>Pis en deux<br>Urge<br>Urgency<br>Incontinence<br>Other<br><br>GYNAECOLOGICAL<br>e.g Menstrual<br><br>SEXUAL<br>e.g. Female dyspareunia<br>impotence<br><br>Gastrointestinal<br><br>MUSCULAR<br>Hyperalgesia<br><br>CUTANEOUS<br>Allodynia | ANXIETY<br>About pain<br>or putative<br>cause of pain<br>Other<br><br>DEPRESSION<br>Attributed to<br>pain/impact<br>of pain<br><br>Attributed to<br>other causes<br>or unattributed<br><br>SHAME,<br>GUILT related<br>to disclosed<br>or undisclosed<br>sexual<br>experience/s<br><br>PTSD<br>SYMPTOMS<br>Reexperiencing<br>Avoidance<br>Hyperarousal |
| | | | Urethral pain syndrome | | | | | | | |
| | | | Prostate pain syndrome | Type A inflammatory | | | | | | |
| | | | | Type B non-inflammatory | | | | | | |
| | | | Scrotal pain syndrome | Testicular pain syndrome | | | | | | |
| | | | | Epididymal pain syndrome | | | | | | |
| | | | | Post-vasectomy pain syndrome | | | | | | |
| | | | Penile pain syndrome | | | | | | | |
| | | Gynaecological | Endometriosis associated pain syndrome | | | | | | | |
| | | | Vaginal pain syndrome | | | | | | | |
| | | | Vulvar pain syndrome | Generalised vulvar pain syndrome | | | | | | |
| | | | | | Localised vulvar pain syndrome | Vestibular pain syndrome | | | | |
| | | | | | | Clitoral pain syndrome | | | | |
| | | Anorectal | | | | | | | | |
| | | Neurological | e.g. Pudendal pain syndrome | | | | | | | |
| | | Muscular | | | | | | | | |
| | Non pelvic pain syndrome | e.g. Neurological | e.g. Pudendal neuralgia | | | | | | | |
| | | e.g. Urological | | | | | | | | |

*Hx = History; Ex = Examination; Ix = Investigation; ESSIC = European Society for the study of IC/BPS; PTSD = post-traumatic stress disorder.*

**The table presented is not comprehensive; for the purpose of this document the main emphasis has been on the urological pain syndromes.*

## 2.2 Definitions of chronic pelvic pain terminology

Although this latest EAU CPP guideline retains the basic terminology used in previous EAU CPP guidelines, older terminology has been removed (Table 4).

**Table 4: Definitions of chronic pelvic pain terminology**

| Terminology | Description |
|---|---|
| *Chronic pelvic pain* | Non-malignant pain perceived in structures related to the pelvis of either men or women. In the case of documented nociceptive pain that becomes chronic, pain must have been continuous or recurrent for at least 6 months. If non-acute and central sensitisation pain mechanisms are well documented, then the pain may be regarded as chronic, irrespective of the time period. In all cases, there often are associated negative cognitive, behavioural, sexual, and emotional consequences (5,6). |
| *Pelvic pain syndrome* | Persistent or recurrent episodic pelvic pain associated with symptoms suggesting lower urinary tract, sexual, bowel or gynaecological dysfunction. No proven infection or other obvious pathology (adopted from ICS 2002 report) (1). |
| *Bladder pain syndrome* | Suprapubic pain is related to bladder filling, accompanied by other symptoms such as increased daytime and night-time frequency. There is an absence of proven urinary infection or other obvious pathology. This term has been adopted from the ICS 2002 report (1), where the term painful bladder syndrome was used; the name has been changed to bladder pain syndrome to be consistent with other pain syndrome terminology (5,6). The European Society for the Study of BPS/IC (ESSIC) publication places greater emphasis on the pain being perceived in the bladder (4). |
| *Urethral pain syndrome* | Recurrent episodic urethral pain, usually on voiding, with daytime frequency and nocturia. Absence of proven infection or other obvious pathology (1). |
| *Penile pain syndrome* | Pain within the penis that is not primarily in the urethra. Absence of proven infection or other obvious pathology (5,6). |
| *Prostate pain syndrome* | Persistent or recurrent episodic prostate pain, associated with symptoms suggestive of urinary tract and/or sexual dysfunction. No proven infection or other obvious pathology (5,6).<br>Definition adapted from the National Institutes of Health (NIH) consensus definition and classification of prostatitis (7) and includes conditions described as 'chronic pelvic pain syndrome'. Using the NIH classification system, prostate pain syndrome may be subdivided into type A (inflammatory) and type B (non-inflammatory). |
| *Scrotal pain syndrome* | Persistent or recurrent episodic scrotal pain associated with symptoms suggestive of urinary tract or sexual dysfunction. No proven epididymo-orchitis or other obvious pathology (1). |
| *Testicular pain syndrome* | Persistent or recurrent episodic pain localised to the testis on examination, which is associated with symptoms suggestive of urinary tract or sexual dysfunction.<br>No proven epididymo-orchitis or other obvious pathology. This is a more specific definition than scrotal pain syndrome (1). |
| *Post-vasectomy pain syndrome* | Scrotal pain syndrome that follows vasectomy (1). |
| *Epididymal pain syndrome* | Persistent or recurrent episodic pain localised to the epididymis on examination. Associated with symptoms suggestive of urinary tract or sexual dysfunction. No proven epididymo-orchitis or other obvious pathology (a more specific definition than scrotal pain syndrome (5,6). |
| *Endometriosis-associated pain syndrome* | Chronic or recurrent pelvic pain where endometriosis is present but does not fully explain all the symptoms (5,6). |
| *Vaginal pain syndrome* | Persistent or recurrent episodic vaginal pain associated with symptoms suggestive of urinary tract or sexual dysfunction. No proven vaginal infection or other obvious pathology (1). |
| *Vulvar pain syndrome* | Persistent or recurrent episodic vulvar pain either related to the micturition cycle or associated with symptoms suggestive of urinary tract or sexual dysfunction. There is no proven infection or other obvious pathology (1). |

| | |
|---|---|
| *Generalised vulvar pain syndrome* (formally dysaesthetic vulvodynia) | Vulval burning or pain that cannot be consistently and tightly localised by point-pressure 'mapping' by probing with a cotton-tipped applicator or similar instrument. The vulvar vestibule may be involved but the discomfort is not limited to the vestibule. Clinically, the pain may occur with or without provocation (touch, pressure or friction) (8). |
| *Localised vulvar pain syndrome* | Pain consistently and tightly localised by point-pressure mapping to one or more portions of the vulva. Clinically, pain usually occurs as a result of provocation (touch, pressure or friction) (8). |
| *Vestibular pain syndrome* (formerly vulval vestibulitis) | Pain localised by point-pressure mapping to one or more portions of the vulval vestibule (8). |
| *Clitoral pain syndrome* | Pain localised by point-pressure mapping to the clitoris (8). |
| *Anorectal pain syndrome* | Persistent or recurrent, episodic rectal pain with associated rectal trigger points/ tenderness related to symptoms of bowel dysfunction. No proven infection or other obvious pathology (5,6). |
| *Pudendal pain syndrome* | Neuropathic-type pain arising in the distribution of the pudendal nerve with symptoms and signs of rectal, urinary tract or sexual dysfunction. No proven obvious pathology (5,6). (This is not the same as the well-defined pudendal neuralgia). |
| *Perineal pain syndrome* | Persistent or recurrent, episodic, perineal pain either related to the micturition cycle or associated with symptoms suggestive of urinary tract or sexual dysfunction. No proven infection or other obvious pathology (1). |
| *Pelvic floor muscle pain syndrome* | Persistent or recurrent, episodic, pelvic floor pain with associated trigger points, which is either related to the micturition cycle or associated with symptoms suggestive of urinary tract, bowel or sexual dysfunction. No proven infection or other obvious pathology (5,6). |

### 2.3 Classification of chronic pelvic pain syndromes

The EAU classification of 2004 has been updated to provide a classification related to investigation and further management of the pain syndromes. This allows for a possible overlap of mechanisms between different conditions. It also encourages recognition of overlapping symptoms and their treatment by a multidisciplinary approach (Table 3) (3). Axes VII and VIII are very important, because they emphasise the importance of interdisciplinary, multidisciplinary assessment, and management. This includes assessment and management of psychological symptoms and early involvement of the pain management centre.

Currently, there is no ideal classification for conditions considered to be chronic pain syndromes. The axes used in Table 3 are based on the IASP classification (2). Much of the terminology comes from the ICS classification of chronic pain (1) with input from the International Society for the Study of Vulvovaginal Disease (ISSVD), the IASP special interest group, Pain of Urogenital Origin (PUGO) group, and Specialists in Pain International Network (SPIN). The major controversy in classifying chronic pain is that a pain may involve multiple sites, aetiologies, and mechanisms. At a consensus meeting led by A.P. Baranowski and a PUGO working group in November 2006, it was suggested that a patient should be described as having one or two pain syndromes in the case of pain perceived at one or two sites, respectively. If the patient's pain was poorly localised or perceived in three or more sites, the patient would be diagnosed with chronic pelvic pain syndrome (CPPS), with no need for further system or end-organ subdivision. This decision recognised that poor localisation in pain suggests overlapping mechanisms. This approach continues to be discussed and publications from a further consensus meeting are planned.

A physician using the classification in Table 3 should start on the left of Table 3 and proceed to the right only if they can truly and confidently confirm the pain to be perceived in the appropriate system and organ. In many cases, it may not be possible to go further than labelling a condition as a pelvic pain syndrome. For example, in many cases previously described as 'prostadynia', it may not be possible to state categorically that the pain stems from the prostate and not other sites, e.g. pelvic floor muscles. Such cases are therefore labelled pelvic pain syndrome.

Although BPS/IC is well defined (see ESSIC reference [4]), many patients, who have been previously labelled as suffering from IC, would not meet the research criteria. These patients would therefore be labelled using Table 3 at some point to the left of IC, possibly as bladder pain syndrome (previously known as the painful bladder syndrome [1]). The term 'pain syndrome' is used when the primary pathology, which may be well defined and at one site to start with, progresses to produce a more complicated picture of pain, involving multiple sites and mechanisms. The condition has therefore become a complex of symptoms and signs, i.e. a syndrome.

The axial classification includes referral, temporal, and character axes. These descriptors should also be collected for audit and research purposes. It should also be noted whether or not the pain is provoked, e.g.

by pressure.

This EAU classification system aims to draw together the expertise of specialist groups and continues to undergo revision. The European Society for the Study of IC/PBS have recently shown a way forward by defining the bladder pain syndrome/IC syndrome, supported by an international consensus editorial (3,4). As with the EAU system, ESSIC excluded well-defined (confusable) conditions. ESSIC has further divided the bladder pain syndrome/IC syndrome according to the results of cystoscopy and biopsy (Table 5) (4).

**Table 5: ESSIC classification of types of bladder pain syndrome according to the results of cystoscopy with hydrodistension and of biopsies (4)**

| | | Cystoscopy with hydrodistension | | |
|---|---|---|---|---|
| | **Not done** | **Normal** | **Glomerulations[a]** | **Hunner's lesion[b]** |
| Biopsy | | | | |
| Not done | XX | 1X | 2X | 3X |
| Normal | XA | 1A | 2A | 3A |
| Inconclusive | XB | 1B | 2B | 3B |
| Positive[c] | XC | 1C | 2C | 3C |

*[a] Cystoscopy: glomerulations grade 2-3; [b] With or without glomerulations; [c] Histology showing inflammatory infiltrates and/or detrusor mastocytosis and/or granulation tissue and/or intrafascicular fibrosis.*

## 2.4 References


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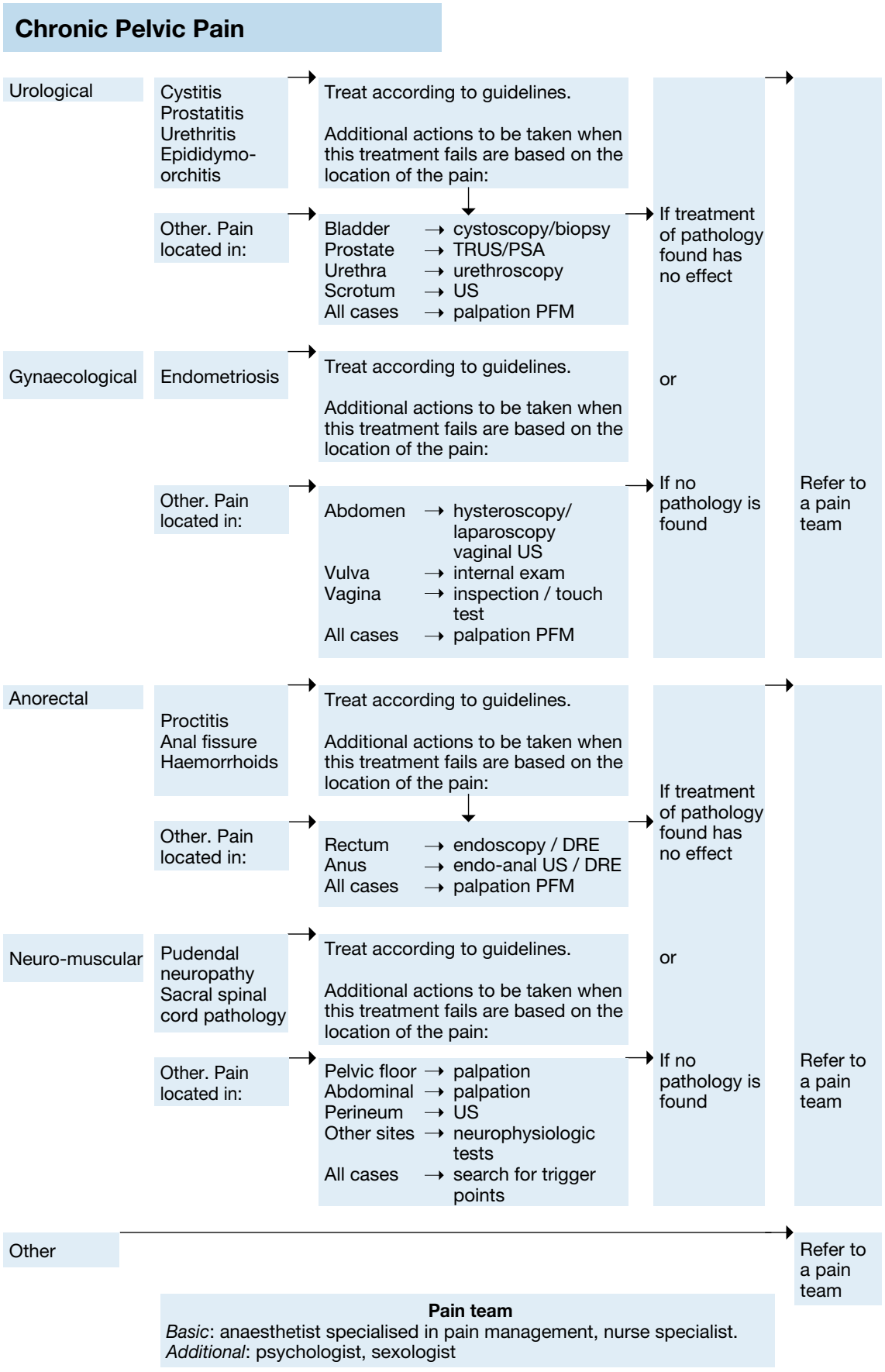
## 2.5 An algorithm for chronic pelvic pain diagnosis and treatment

### *2.5.1 How to use the algorithm*

The algorithm for diagnosing and treating CPP (Figure 1) has been written to guide a physician through the process from diagnosis to management. A physician should follow steps 1 to 6 (Table 6), while referring to the correct column in the algorithm. Further guidance on which diagnostic tools should be used in specific pain locations is provided in different chapters of this guideline.

**Figure 1: An algorithm for diagnosing and managing CPP**




*DRE = digital rectal examination; US = ultrasound; PFM = pelvic floor muscles; TRUS = transrectal ultrasonography; PSA = prostate specific antigen.*

**Table 6: Step-by-step guidance on using the algorithm for diagnosis and treatment of CPP**

| Step | Action | Algorithm |
|---|---|---|
| 1 | Start by considering the organ system where the symptoms appear to be primarily perceived | First column |
| 2 | 'Well-defined' conditions, such as cystitis, should be diagnosed and treated according to national or international guidelines | Second column and upper part third column |
| 3 | When treatment has no effect on the pain, additional tests (e.g. cystoscopy or ultrasound) should be performed | Lower part third column |
| 4 | When these tests reveal any pathology, this should be treated appropriately | Fourth column |
| 5 | If treatment has no effect, the patient should be referred to a pain team | Fifth column |
| 6 | If no well-defined condition is present or when no pathology is found by additional tests, the patient should also be referred to a pain team | Fifth column |

The only aspect of diagnosis that is specific for CPP is where the pain is localised. However, because pain is perceived in structures related to the pelvis, this has led to many organ-specific, but often not well-defined, local disease syndromes.

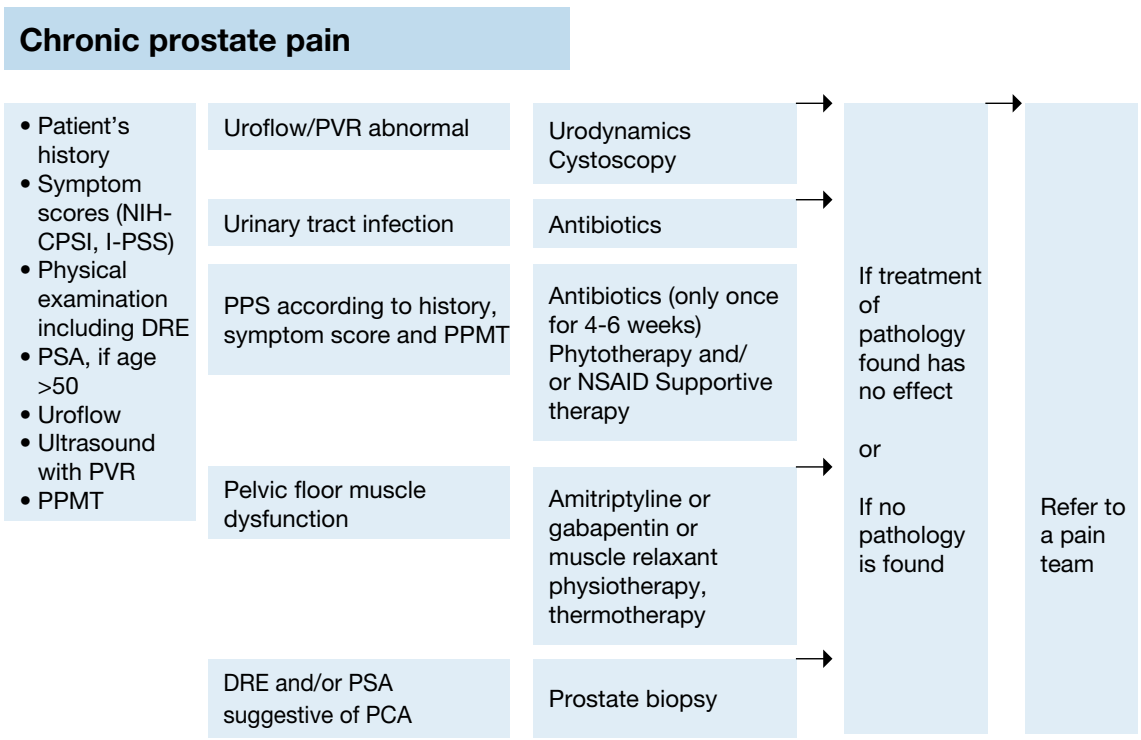
Because CPP is pain perceived in structures related to the pelvis, it is necessary to approach diagnosis of a patient with CPP as a chronic pain patient. Confining the diagnosis to a specific organ may overlook multisystem functional abnormalities requiring individual treatment and general aspects of pain in planning investigation and treatment.

For the above reasons, we advocate early involvement of a multidisciplinary pain team. In practice, this should mean that well-known diseases, e.g. 'true' cystitis and endometriosis, will be diagnosed and treated early. If treating such conditions does not reduce symptoms, or such well-defined conditions are not found, then further investigation may be necessary, depending on where the pain is localised.

It should be noted, however, that over-investigation may be as harmful as not performing appropriate investigations. The EAU algorithms introduce the concept of the 'minimum investigations' required to exclude a well-defined condition.

## 2.6 Prostate pain syndrome (PPS)

**Figure 2: General diagnostic and treatment algorithm for chronic prostate pain**




*NIH-CPSI = National Institute of Health chronic prostatitis symptom index; I-PSS = international prostate*

*symptom score; DRE = digital rectal examination; PSA = prostate-specific antigen; PVR = post-void residual urine; PPMT = pre-post-massage test; PPS = prostate pain syndrome; PCA = prostate cancer; NSAID = non-steroidal anti-inflammatory drug.*

### *2.6.1* ***Introduction***

Chronic prostatitis is an obscure and poorly understood disease. Restricted physical access has made it difficult to study the prostate gland, resulting in a lack of certainty about the aetiology, a lack of distinguishing clinical features, non-uniform diagnostic criteria, and a protracted treatment course.

In about 5-10% of cases, clinical prostatitis has a proven bacterial aetiology. The remaining 90% of cases, in which laboratory methods have not found a bacterial cause, are classified as 'chronic non-bacterial prostatitis' or 'prostatodynia' (1-3). An appreciation of the fact that symptoms do not necessarily indicate isolated prostatic disease has led to a renaming of the condition: 'Chronic prostatitis associated with chronic pelvic pain syndrome' (CP/CPPS). This is now the term used by the NIH for patients with symptomatic prostatitis of non-bacterial origin (4).

### *2.6.2* ***Definition***

Chronic prostatitis associated with chronic pelvic pain syndrome is discomfort or pain in the pelvic region over a minimum of 3 months, with sterile specimen cultures and either significant, or insignificant, white blood cell counts in prostate-specific specimens (i.e. semen, expressed prostatic secretions, and urine collected after prostate massage) (4). According to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) classification, CP/CPPS is prostatitis category III (5) (Table 7). At present, there are no clinically relevant diagnostic or therapeutic results arising from differentiating inflammatory (NIH Cat. IIIA) from non-inflammatory (NIH Cat. IIIB) CP/CPPS. CP/CPPS Cat. III is therefore considered as one entity. According to the more general definition described in Section 2.2 (see Table 4), the disease is referred to as 'prostate pain syndrome (PPS)' throughout the rest of this chapter.

**Table 7: Classification of prostatitis according to NIDDK/NIH**

| | | |
|---|---|---|
| I | Acute bacterial prostatitis (ABP) | |
| II | Chronic bacterial prostatitis (CBP) | |
| III | Chronic pelvic pain syndrome (CPPS) | |
| | A | Inflammatory CPPS: WBC in semen/EPS/VB3 |
| | B | Non-inflammatory CPPS: no WBC semen/EPS/VB3 |
| IV | Asymptomatic inflammatory prostatitis (histological prostatitis) | |

*WBC = white blood cells; EPS = expressed prostatic secretions; VB3 = voided bladder urine-3.*

### *2.6.3* ***Pathogenesis***

The aetiology and pathophysiology of PPS remains a mystery. Acute bacterial prostatitis is a different disease to chronic prostatitis syndromes. Patients with PPS show no evidence of inflammation; they do not have urethritis, urogenital cancer, urethral stricture, or neurological disease involving the bladder nor exhibit any overt renal tract disease (4).

As often occurs with pelvic pain syndromes, there are several, poorly evidenced, hypotheses to explain the aetiology of PPS:

- Pain and subsequent irritative and obstructive voiding symptoms may be caused by lower urinary tract obstruction (LUTS), due to bladder neck problems, detrusor sphincter dysfunction, urethral stricture or dysfunctional voiding, resulting in high-pressure voiding (6-11).
- Intraprostatic ductal reflux caused by high-pressure turbulent voiding due to an anatomical abnormality (12-15).
- Microbiological cause, due to apparently harmless lower urinary tract commensals which require more sensitive isolation methods to be identified (4).
- Immunological processes precipitated by an unrecognised antigen or an autoimmune process (16-18). Urinary reflux into the prostatic ducts and acini might stimulate a sterile inflammatory response (13).
- A neuromuscular aetiology (19-21), in which symptoms represent a type of reflex sympathetic dystrophy of the perineum and pelvic floor.
- An interstitial cystitis-like pathogenic mechanism based on a significant overlap of symptomatology (pain, voiding symptoms) and cystoscopic or urodynamic findings. In patients diagnosed with PPS, a bladder-oriented interstitial cystitis mechanism accounts for the symptoms and the prostate is involved only indirectly (22).

### 2.6.4 ***Diagnosis***

PPS is a symptomatic diagnosis, which is diagnosed from a 3-month history of genitourinary pain and an absence of other lower urinary tract pathologies (see above). Determination of the severity of disease, its progression and treatment response can be assessed only by means of a validated symptom-scoring instrument (23,24). Quality of life (QoL) should also be measured because it can be as poor as in acute myocardial infarction, unstable angina pectoris or Crohn's disease (25,26). Reliable, valid indexes of symptoms and QoL are the NIH Prostatitis Symptom Index (NIH-CPSI) (27) and the International Prostate Symptom Score (I-PSS) (28). These subjective outcome measures are recommended for the basic evaluation and therapeutic monitoring of patients in urological practice and have been translated and validated for many European languages.

In PPS urodynamic studies demonstrate decreased urinary flow rates, incomplete relaxation of the bladder neck and prostatic urethra, as well as abnormally high urethral closure pressure at rest. The external urethral sphincter is normal during urination (6,29).

Laboratory diagnosis has been classically based on the four-glass test for bacterial localisation ('gold standard') (30). Besides a sterile pre-massage urine (voided bladder urine-2 [VB2]), PPS shows less than 10,000 colony-forming units of uropathogenic bacteria in expressed prostatic secretions (EPS) and insignificant numbers of leucocytes or bacterial growth in ejaculate. However, this test is too complex for use by practising urologists (4). Diagnostic efficiency may be enhanced cost-effectively by a simple screening procedure, i.e. the two-glass test or pre-post-massage test (PPMT) (31). In an extensive analysis of both tests, PPMT was able to indicate the correct diagnosis in more than 96% of patients (32).

A general algorithm for diagnosis and treatment of chronic prostatic pain is shown in Figure 2.

### 2.6.5 ***Treatment***

Because of the unknown cause of PPS, many therapies used are based on anecdote. Most patients require multimodal treatment aimed at the main symptoms and taking comorbidities into account. In the past few years, results from RCTs have led to advances in standard and novel treatment options. Graded recommendations are given in Table 8.

*2.6.5.1 Alpha-blockers.* Positive results from RCTs of alpha-blockers, e.g. terazosin (33), alfuzosin (34), doxazosin (35), and tamsulosin (36), have led to a widespread use of alpha-antagonists in the treatment of PPS during the last years. The effects of alpha-antagonists may include improved outflow performance by blocking the alpha-receptors of the bladder neck and prostate and by direct action on alpha1A/1D-receptors in the CNS (36). In contrast, a meta-analysis of nine trials (n = 734) could not show a beneficial effect on pain (37). Moreover, a recent adequately powered large placebo-controlled randomised trial of 12-week treatment with alfuzosin failed to show any significant difference in the outcome measures with the exception of the Male Sexual Health Questionnaire scores (38). Overall, the use of alpha-blockers for the treatment of PPS can no more be recommended and it should probably be restricted to patients with proven bladder outlet obstruction.

*2.6.5.2 Antibiotic therapy*. Empirical antibiotic therapy is widely used because some patients have improved with antimicrobial therapy. Patients responding to antibiotics should be maintained on medication for 4-6 weeks or even longer. Unfortunately, culture, leucocyte, and antibody status of prostate-specific specimens do not predict antibiotic response in patients with PPS (39), and prostate biopsy culture findings do not differ from those of healthy controls (40). Long-term results with trimethoprim-sulphamethoxazole have remained poor (41-43). More encouraging results have been obtained with quinolones, including ciprofloxacin (44) and ofloxacin (39,45), but overall, antibiotic treatment of the PPS is based only on weak evidence. After one unsuccessful course of a quinolone antibiotic over 4–6 weeks, other therapeutic options should be offered.

*2.6.5.3 Non-steroidal anti-inflammatory drugs*. Non-steroidal anti-inflammatory drugs may have favourable results in some patients. Immunomodulation using cytokine inhibitors or other approaches may be helpful, but proper trials are needed before this type of therapy can be recommended (46,47). Only one RCT has been published. This was for rofecoxib, which is no longer on the market; statistical significance was achieved in some of the outcome measures (48).

*2.6.5.4 Corticosteroids are not recommended*. A few anecdotal case reports have shown some improvement. However, no significant benefits were shown in a low-power, placebo-controlled, randomised pilot study of a short course of oral prednisolone (49).

*2.6.5.5 Opioids* produce modest pain relief in some patients with refractory PPS, though there is limited data on the long-term efficacy of opioids in non-cancer pain. Opioid treatment carries the risks of side effects,

reduced QoL, addiction, opioid tolerance, and opioid-induced hyperalgesia (50). Urologists should use opioids for PPS in collaboration with pain clinics and with other treatments.

*2.6.5.6 5-alpha-reductase inhibitors*. A few small pilot studies with 5-alpha-reductase inhibitors supported the view that finasteride may improve voiding and pain (51-54). In a randomised trial, finasteride provided better amelioration of symptoms compared to saw palmetto over a 1-year period, but lacked a placebo-control arm (55). A 6-month placebo-controlled study showed a tendency towards better outcome in favour of finasteride without statistical significance, possibly because of a lack of power (56).

*2.6.5.7 Allopurinol*. An RCT of allopurinol was conducted based on the hypothesis that urine reflux into prostatic ducts causes prostatic inflammation via high concentrations of purine and pyrimidine base-containing metabolites in prostatic secretions (57). However, positive results were not considered to be sufficient for recommendation by reviewers of the Cochrane Database (58). In addition, a recent randomised placebo-controlled trial of allopurinol as an adjunct to ofloxacin has not shown any benefit (59).

*2.6.5.8 Phytotherapy*. Positive effects of phytotherapy have been documented. Although a validated symptom score was not used, an RCT of a pollen extract (Prostat/Poltit) showed significant symptom improvement in the pollen-treated group (60). Another pollen extract, Cernilton N, provided only weak improvement. For 'uncomplicated' cases, a 36% cure rate could be shown over a 6-month period in a prospective study (61). Quercetin, a polyphenolic bioflavonoid with documented antioxidant and anti-inflammatory properties, improved NIH-CPSI scores significantly in a small RCT (62). In addition, high-dose oral PPS, as for interstitial cystitis, is able to ameliorate symptoms and improve QoL significantly in men with PPS, suggesting a possible common aetiology (63). In contrast, treatment with saw palmetto, most commonly used for benign prostatic hyperplasia, did not improve symptoms over a 1-year period (55).

*2.6.5.9 Muscle relaxants* (diazepam, baclofen) are claimed to be helpful in sphincter dysfunction or pelvic floor/perineal muscle spasm, but there have been only few prospective clinical trials to support these claims (21). In a recent RCT, a triple combination of a muscle relaxant (tiocolchicoside), an anti-inflammatory drug (ibuprofen) and an alpha-blocker (doxazosin) was effective in treatment-naïve patients, but not superior to an alpha-blocker alone (64).

*2.6.5.10 Supportive therapies*, such as biofeedback, relaxation exercises, lifestyle changes (i.e. diet, discontinuing bike riding), acupuncture, massage therapy, chiropractic therapy, or meditation, have all been claimed to improve symptoms (4,65). In a small, sham-controlled, double-blind study, 4-week electromagnetic therapy showed a significant, sustained effect over a 1-year period (66). Some patients have reported favourable effects from heat therapy, e.g. transrectal hyperthermia (67-70), and transurethral thermotherapy (71-75).

*2.6.5.11 Surgical management*, including transurethral incision of the bladder neck (9), radical transurethral resection of the prostate (76,77) or in particular radical prostatectomy, has a very limited role and requires an additional, specific indication (65). In addition, the treatment effect of transurethral needle ablation of the prostate (TUNA) was only comparable to sham treatment (78).

**Table 8: Treatment of PPS**

| | LE | GR | Comment |
|---|---|---|---|
| Alpha-blockers | | Not recommended | Not effective according to recent large randomised trial |
| Muscle relaxants | 3 | C | Only very limited data |
| Antimicrobial therapy | 3 | B | Quinolones<br>If previously untreated (naïve) only, reassess after 2-3 weeks.<br>Duration 4-6 weeks |
| Opioids | 3 | C | As part of multimodal therapy for treatment-refractory pain in collaboration with pain clinics |
| Non-steroidal anti-inflammatory drugs | 1b | B | Long-term side effects have to be considered |
| Steroids<br>Immunosuppressive agents | 3 | Not recommended | Not outside clinical trials |

| | | | |
|---|---|---|---|
| 5-alpha-reductase inhibitors | 1b | B | If benign prostatic hyperplasia is present |
| Phytotherapy | 1b-3 | B | |
| Biofeedback,<br>relaxation exercise<br>Lifestyle changes<br>Massage therapy<br>Chiropractor therapy<br>Acupuncture<br>Meditation | 2a-3 | B | As supportive, second- line therapies |
| Electromagnetic therapy | 1b | C | Not outside clinical trials |
| Transrectal hyperthermia<br>Transurethral thermotherapy | 3 | C | |
| Transurethral incision of the bladder neck<br>Transurethral resection of the prostate<br>Radical prostatectomy | 3 | Not recommended in general | Specific additional indication required |

*2.6.6* ***References***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## 2.7 Bladder pain syndrome/interstitial cystitis (BPS/IC)

### *2.7.1* ***Introduction***

Interstitial cystitis describes a chronic, distressing bladder condition (1). The so-called 'ulcer', which is a typical cystoscopic finding in 10-50% of IC patients, was first described by Guy L Hunner at the beginning of the last century (2,3). Subsequent research (4-6) showed that IC was not a single entity, but had different endoscopic and histopathological presentations.

It is very important to realise that IC is a heterogeneous spectrum of disorders, which are still poorly defined, and that inflammation is an important feature in only a subset of patients. To embrace all patients suffering from bladder pain, the terms painful bladder syndrome (PBS) or bladder pain syndrome (BPS) have been suggested as more accurate terminology (7,8). This terminology assumes that IC represents a special type of chronic inflammation of the bladder, while PBS or BPS refers to pain in the bladder region. The term bladder pain syndrome or BPS will be used in these guidelines.

### *2.7.2* ***Definition***

An extremely wide variety of diagnostic criteria have been used because of the difficulty in defining IC. In the late 1980s, NIDDK consensus criteria were established to ensure that scientific studies would be relatively comparable (Table 9) (9). The NIDDK criteria produce a diagnosis of IC by exclusion. Bladder pain, urgency and the finding of submucosal haemorrhages, called glomerulations, are the only positive elements. Identification of circumscribed Hunner-type lesions is an automatic inclusion criterion. Although generally accepted, the NIDDK criteria provide only a minimum framework to establish the diagnosis and some have felt them to be too restrictive for clinical use (10). Whatever the method used, heterogeneity seems currently unavoidable (6,11,12).

**Table 9: NIDDK workshop research definition of IC (9)***

**Automatic inclusions**

- Hunner's ulcer

**Positive factors**

- Pain on bladder filling relieved by emptying
- Pain (suprapubic, pelvic, urethral, vaginal or perineal)
- Glomerulations on endoscopy
- Decreased compliance on cystometrogram.

**Automatic exclusions**

- < 18 years old
- Benign or malignant bladder tumours
- Radiation cystitis
- Tuberculous cystitis
- Bacterial cystitis
- Vaginitis
- Cyclophosphamide cystitis
- Symptomatic urethral diverticulum
- Uterine, cervical, vaginal or urethral cancer
- Active herpes
- Bladder or lower ureteral calculi
- Waking frequency < five times in 12 hours
- Nocturia < two times
- Symptoms relieved by antibiotics, urinary antiseptics, urinary analgesics, e.g. phenazopyridine hydrochloride
- Duration < 12 months
- Involuntary bladder contractions (urodynamics)
- Capacity > 400 mL, absence of sensory urgency.

** Bladder distension was defined arbitrarily as 80 cm water pressure for 1 minute (sic). Two positive factors were necessary for inclusion in the study population. Under anaesthesia, patients were sub-stratified at the end of the study into two groups according to bladder capacity < 350 mL and > 350 mL.*

Recently, ESSIC has suggested a standardised scheme of diagnostic criteria (13) to make it easier to compare different studies. In a consensus statement, the diagnosis of BPS was preferred as the general term to match the current taxonomy of chronic pain syndromes.

Bladder pain syndrome should be diagnosed on the basis of symptoms of pain associated with the urinary bladder, accompanied by at least one other symptom, such as day-time and/or night-time urinary frequency, the exclusion of confusable diseases as the cause of symptoms, and if indicated, cystoscopy with hydrodistension and biopsy (Table 10) (8).

**Table 10: ESSIC classification of types of bladder pain syndrome according to the results of cystoscopy with hydrodistension and of biopsies (8)**

| | | **Cystoscopy with hydrodistension** | | |
|---|---|---|---|---|
| | **Not done** | **Normal** | **Glomerulations[a]** | **Hunner's lesion[b]** |
| Biopsy | | | | |
| Not done | XX | 1X | 2X | 3X |
| Normal | XA | 1A | 2A | 3A |
| Inconclusive | XB | 1B | 2B | 3B |
| Positive[c] | XC | 1C | 2C | 3C |

*[a] Cystoscopy: glomerulations grade 2-3; [b] With or without glomerulations; [c] Histology showing inflammatory infiltrates and/or detrusor mastocytosis and/or granulation tissue and/or intrafascicular fibrosis.*

### *2.7.3* ***Pathogenesis***

There are many different hypotheses about the causes of BPS/IC.

*Infection*. No micro-organism has been found to be the cause despite the extensive use of sophisticated microbiological detection methods. Although it has been suggested that fastidious bacteria may be responsible (14), no immunological evidence of recent or remote bacterial infection has been found (15). The results of viral culture (16,17) and polymerase chain reaction methods (18,19) have been just as disappointing. Although urine culture from a few IC patients has contained bacteria, antibiotic treatment has been ineffective. Nevertheless, the possibility of a microbiological contribution has not been looked upon as a 'closed book', including *Helicobacter pylori*, though no *H. pylori* DNA has been detected in bladder biopsies (20).

*Inflammation* is an essential part of classic IC, with pancystitis and perineural inflammatory infiltrates of lymphocytes and plasma cells (17). Inflammation is scant in non-ulcer IC (6).

*Mast cell activation*. Mast cells are multifunctional immune cells that contain highly potent inflammatory mediators, such as histamine, leukotrienes, serotonin, and cytokines (21). Many of the symptoms and findings in classic IC, such as pain, frequency, oedema, fibrosis, and neovascularisation in the lamina propria, may be due to the release of mast cell-derived factors. There is a ten-fold increase in the mast cell count in bladder tissue from patients with classic IC compared with controls. In non-ulcer IC, however, the mast cell count is normal or only slightly increased (6,21,22).

*Urothelial dysfunction/glycosaminoglycan (GAG)-layer defects*. All patients with IC present with fragility of the bladder mucosa, expressed as fissures or rupture of the bladder urothelium on distension (mucosal cracking). In classic IC, the presence of granulation tissue indicates a reparative process (23). In patients with classic IC, urothelial detachment and gross defects of the urothelial lining are characteristic findings. However, in some non-ulcer IC patients, multiple superficial defects are seen after bladder distension (23), including widened tight junctions and increased permeability (24,25). These changes could be consistent with defects in the GAG-layer that expose the submucosal nerve filaments to noxious chemicals in urine (26,27). Urinary uronate and sulphated GAG levels are increased in patients with severe BPS/IC, suggesting that such substances may become useful markers for monitoring (28).

*Autoimmune mechanisms*. Numerous studies of autoantibodies have been performed since the 1970s in patients with IC (29), but the findings have been far from specific. Some of the clinical and histopathological characteristics are similar to other autoimmune phenomena. Antinuclear antibodies have been described (30,31), which has led to the hypothesis of a lupus-like reaction (32,33). In fact, only some BPS patients demonstrate autoantibodies and the proposal that autoantibody titres could reflect disease severity is untested (34).

Immune deposits in bladder wall vasculature were found by Mattila (35), while other studies by the same group have implicated complement activation (36). Immunohistochemical and cytoflourometric analyses of the bladder mucosa have highlighted differences between classic and non-ulcer IC patients. In classic IC, intense T-cell infiltrates and B-cell nodules were seen, whereas only some T-cell infiltration was observed in non-ulcer IC (37). The inadequate description of patients in many studies, particularly when it comes to subtyping IC patients, has made it difficult to interpret data. Systemic aspects, especially the potential association with Sjögren's syndrome, are interesting features of BPS/IC (38).

*Nitric oxide metabolism*. Inevitably, nitric oxide synthetase activity has been scrutinised (39). Oral administration of L-arginine (40) has been shown to increase nitric oxide-related enzymes and metabolites in the urine of patients with BPS/IC (41). However, the relevance of this finding is not clear. An intriguing fact is that evaporation of nitric oxide from the urine is dramatically increased in patients with classic disease, as well as during periods of symptoms decreased by treatment; however, patients with non-ulcer IC, have similar nitric oxide levels to controls (42). To further illustrate the complexity involved, it has been suggested that inducible nitric oxide synthetase-dependent nitric oxide production may have a role in epithelial barrier dysfunction in cats with feline interstitial cystitis (43).

*Neurobiology*. An increase in the sympathetic innervation and activation of purinergic neurotransmission has been reported in BPS patients. The S-100 family of proteins appears in Schwann cells of the peripheral nervous system (44). Decreased levels of S-100 protein were found in non-ulcer BPS patients compared with controls (45). However, this finding conflicts with that of Hohenfellner et al. (46), who used 'polyclonal antihuman protein gene product 9.5 antibody' and found that the overall nerve content increased in IC patients compared with controls. They did not subtype their patients into classic and non-ulcer forms.

Tyrosine hydroxylase is the rate-limiting enzyme for all catecholamine synthesis. An increase in

tyrosine hydroxylase immunoreactivity has been described in bladder tissue from IC patients but not in controls (47); this could be interpreted as a sign of increased sympathetic outflow. Recent reports have suggested that autonomic responses and CNS processing of afferent stimuli are altered in patients with CPP/BPS/IC (47,48). The distinctive ultrastructural appearance of specimens from patients with non-ulcer IC prompted Elbadawi and Light to hypothesise neurogenic inflammation as a trigger to a cascade of events (49).

*Toxic agents*. Toxic constituents in the urine may cause injury to the bladder in BPS. One hypothesis is that heat labile, cationic urine components of low molecular weight may exert a cytotoxic effect (50). Defective constitutive cytokine production may decrease mucosal defences to toxic agents (51). Tamm-Horsefall protein is a factor whose protective function may be due to its sialic acid content, which is compromised in BPS/IC individuals (52).

*Hypoxia*. A decrease in the microvascular density in the suburothelium has been observed (53). A recent study, found that bladder perfusion decreased with bladder filling in IC patients, but that the opposite occurred in controls (54). Hyperbaric oxygen therapy has been on trial in an RCT; a total of 30 treatment sessions of hyperbaric oxygenation appeared to be safe, effective and feasible (55).

*Complex pathogenic interactions*. In recent years, more complex, multifaceted mechanisms have been proposed. Theoharides et al. have shown that activation of mast cells in close proximity to nerve terminals can be influenced by oestradiol as well as corticotrophin-releasing hormone (56). Okragly et al. found elevated levels of tryptase, nerve growth factor, neurotrophin-3, and glial cell line-derived neurotrophic factor in IC compared with controls (57). These findings prompted suggestions that IC may result from interactions between the nervous, immune and endocrine systems. Recently, it was proposed that the epithelial distribution of mast cells in classic IC could be explained by the epithelial co-expression of stem cell factor and interleukin-6 (IL-6). According to Abdel-Mageed et al., IC patients showed an increased expression of p65, a nuclear factor kappa B subunit (58). Subsequent data has shown a five-fold increase in the expression of the gene for IL-6 after activation of nuclear factor-kappa B (59), although IL-6 is a ubiquitous cytokine.

### *2.7.4* ***Epidemiology***

Reports of the prevalence of BPS/IC have varied tremendously. However, it should be remembered when comparing studies that most of them have used only symptomatic diagnostic criteria and/or have different study populations. The first systematic study by Oravisto et al. in 1975 found that IC affected approximately 10/100,000 (18/100,000 in women) of the population in Finland (60), with rather similar findings reported 15 years later in the USA (although figures were demonstrated to be dependent on the method of evaluation) (61), as well as in 1995 in the Netherlands with a prevalence of 8-16/100,000 (62). However, other reports claim that the prevalence of IC is underestimated and may exceed 0.5% among adults in the USA (63), with recent US reports suggesting that 50-60/100,000 may be affected (64). Thirty years after the Oravisto study, Leppilahti et al. (65) reported higher figures in Finland of 239/100,000 clinically confirmed probable IC and 530/100,000 possible/probable IC. These figures suggested that BPS/IC was much more common than previously thought.

Recent reports generally claim higher figures than earlier ones. A recent Austrian study reported the overall prevalence of IC as 306/100,000 women, with the highest value (464/100,000) in middle-aged women (aged 40-59 years) (66). A review has claimed that 20% of women may be affected (67). In contrast, the incidence of physician-diagnosed incidence in Olmsted County (MN, USA) was extremely low at 1.1/100,000 (68).

There is a female predominance of about 10:1 (4,60,69,70) and it seems that the disease is more common among Caucasians (70).

The relative proportions of classic and non-ulcer disease are unclear. Messing and Stamey reported that classic IC accounted for about half of all patients with IC (5). The same rate has been reported from Sweden (12). Centres in the USA with large patient databases have found that the classic Hunner-type accounts for 5-10% of cases of BPS (71). Koziol et al. recently presented a very large study from the USA, in which classic IC accounted for approximately 20% of cases (72).

Evidence that BPS may have a genetic component is increasing. According to Parsons (73), 35% of 466 patients with BPS and 33% of 166 patients with urethral syndrome reported urgency/frequency problems in female relatives. Warren et al. (74) surveyed 2,058 patients of the Interstitial Cystitis Association (ICA) for first-degree relatives with IC and found a higher prevalence than in the general population. The authors also determined the concordance of IC among ICA twins (75); among the co-twins of eight monozygotic twin respondents, five had probable or confirmed IC, while none of 26 dizygotic co-twins were affected.

BPS/IC has significant economic costs. Excluding indirect costs, the incremental medical cost attributable to this symptom complex in the USA has been estimated to more than $100 million/year (61).

### *2.7.5* ***Association with other diseases***

An association between BPS and inflammatory bowel disease, systemic lupus erythematosus, irritable bowel syndrome, fibromyalgia, and panic disorders has been reported (76-79). An excellent review has explored co-morbidities of BPS/IC with other unexplained clinical conditions presented in the literature (80). The review found a significant overlap of symptoms, suggesting a common stress response pattern, including an increased sympathetic nervous system activity in a subset of patients with many associated conditions. In this context it is interesting to note that feline interstitial cystitis leads to increased corticotrophin-releasing factor activity and decreased adrenocortical reserve.

### *2.7.6* ***Diagnosis***

The diagnosis of BPS is made using symptoms, examination, urine analysis, cystoscopy with hydrodistension and biopsy (see Figure 3). Patients present with characteristic pain and urinary frequency, which is sometimes extreme and always includes nocturia.

The character of the pain is the key symptom of the disease:

- Pain is related to the degree of bladder filling, typically increasing with increasing bladder content;
- It is located suprapubically, sometimes radiating to the groins, vagina, rectum or sacrum;
- Pain is relieved by voiding but soon returns (6,81-83).

The differences between the two IC subtypes include clinical presentation and age distribution (12), and they may be discriminated non-invasively (72). The two subtypes respond differently to treatment (84-87) and express different histopathological, immunological, and neurobiological features (22,23,37,45,47,88,89).

Classic IC is a destructive inflammation with some patients eventually developing a small-capacity fibrotic bladder or upper urinary tract outflow obstruction. There is no such progression in non-ulcer disease (6,90). Endoscopically, classic IC displays reddened mucosal areas often associated with small vessels radiating towards a central scar, sometimes covered by a small clot or fibrin deposit (6). The scar ruptures with increasing bladder distension, producing a characteristic waterfall-type of bleeding. There is a strong association between classic IC and reduced bladder capacity under anaesthesia (6,12,91).

*Cystoscopy*. Non-ulcer IC displays a normal bladder mucosa at initial cystoscopy. The development of glomerulations after hydrodistension is considered to be a positive diagnostic sign. A recent report showed that there was no difference in cystoscopic appearance between patients with non-ulcer IC and women without bladder symptoms about to undergo tubal ligation (92). It has also been noted that glomerulations are not always constant when observed over time (93).

Some maintain that cystoscopy with hydrodistension provide little useful information above the history and physical examination findings (94,95). On the other hand, others have found a strong correlation between pain and cystoscopic findings in patients with untreated IC, with the difference in results compared to other studies possibly due to treatment effects (96). Glomerulations may be involved in the disease mechanism, as such findings are highly associated with overexpression of angiogenetic growth factors in the bladder and neovascularisation (97).

The European Society for the Study of IC/PBS believes objective findings are important and that a standardised scheme of diagnostic criteria would help improve the uniformity and comparability of different studies (13).

*Biopsies* are helpful in establishing or supporting the clinical diagnosis of both classic and non-ulcer types of disease (13,23,98). Important differential diagnoses to exclude by histological examination are carcinoma in situ and tuberculous cystitis.

*Potassium chloride bladder permeability test* has been used in the diagnosis of IC (99), but recent reports have suggested that it lacks discriminating power (100,101). A modified test using less concentrated solution has been suggested. This test, though painless in contrast to the original procedure, decreased the maximum cystometric volume in 90% of patients with BPS/IC, but not in controls (102). Furthermore, it has been suggested that the potassium sensitivity test can help to predict the response to GAG treatment (103).

*Symptom scores* may help to describe symptoms in an individual patient and as outcome measures. The O'Leary-Sant Symptom Index, also known as the Interstitial Cystitis Symptom Index (ICSI) has recently been validated successfully in a large study (104).

### *2.7.7* ***Biological markers***

It is an attractive idea to support or even better to confirm the clinical diagnosis using a biological marker. Finding a universally helpful one is hampered by heterogeneity within the diagnostic group of BPS and by usually making a diagnosis merely on symptoms. Many candidate markers have been suggested. One of the

most interesting is antiproliferative factor, which is present in BPS/IC and is associated with downregulation of heparin-binding epidermal growth factor-like growth factor (105). Nitric oxide is interesting because of its ability to discriminate classic from non-ulcer disease with minimal invasiveness (42).

### *2.7.8* ***IC in children and males***

According to NIDDK criteria, children aged under 18 years is an exclusion criterion. However, occasional cases of BPS of both subtypes have been identified in younger patients (106). There is increasing evidence that very young individuals and children may also be affected, though prevalence figures are low (107). Thus, BPS/IC cannot be excluded on the basis of age.

There is a marked female predominance with a female to male ratio of 10:1. However, the diagnosis must also be considered in men presenting with relevant symptoms (108). It has been argued that many men diagnosed with chronic prostatitis may present with signs consistent with NIDDK criteria of BPS/IC and that these diagnoses are inter-related (109,110). However, differences in urinary markers suggest that BPS/IC and CPP/CP may be different disorders with distinct pathophysiologies (111).

### *2.7.9* ***Medical treatment***

*Analgesics*. Since pain is often a dominant symptom, many patients will try commonly used analgesics at some stage of disease. However, pain relief is disappointing because the visceral pain experienced in BPS/IC responds poorly to analgesic drugs. No systematic studies have been presented on conventional analgesics. Short-term opioids may be indicated for breakthrough or exacerbated pain and periodic flare-ups.

Long-term opioids may be considered after all other available therapeutic options have been exhausted, Urologists should obtain informed consent, arrange for regular follow-up, and be prepared to recognise opioid-induced side effects (112). Because BPS/IC is a chronic disease, long-term opioids should be used only exceptionally and under close surveillance.

*Corticosteroids*. Reports on outcome with corticosteroid therapy have been both promising (113) and discouraging (114). Soucy et al. (115) suggest a trial of prednisone (25 mg daily for 1 to 2 months, afterwards reduced to the minimum required for symptom relief) in patients with severe ulcerative IC, which is otherwise unresponsive to conventional treatment. The side effects of steroids can be very serious, making it very difficult to justify their use.

*Antiallergics*. Mast cells may play a role in IC. Among the substances released by mast cells is histamine. Histamine receptor antagonists have been used to block the $H_1$ receptor subtype (116) as well as the $H_2$ receptor (117), with variable results.

*Hydroxyzine* is a histamine H1-receptor antagonist, which blocks neuronal activation of mast cells by inhibiting serotonin secretion from thalamic mast cells and neurons (118). Hydroxyzine hydrochloride (Atarax) is usually given, starting with 25 mg at bedtime, increasing to 50 mg/day or if tolerated 75 mg. The most common side effects are sedation and generalised weakness that usually resolve after a period of treatment. In the first series using hydroxyzine, > 90% of patients showed an improvement across the whole range of symptoms. Interestingly, an improvement was noted in associated symptoms including migraine, irritable bowel syndrome and allergies (116).

Although these initial results were supported by a further uncontrolled study (116,119), a prospective RCT of hydroxine or sodium pentosanpolysulphate compared to placebo failed to show a statistically significant effect (120). However, the study was underpowered, which may be why it failed to demonstrate a statistically significant outcome for either drug compared to placebo. Combination therapy showed the highest response rate of 40%, with a placebo response rate of 13%.

*Amitriptyline*. The tricyclic antidepressant, amitriptyline, has alleviated symptoms in BPS/IC, probably via mechanisms such as blockade of acetylcholine receptors, inhibition of reuptake of released serotonin and norepinephrine, and blockade of the histamine H1 receptor. It is also an anxiolytic (121). Several reports have indicated amelioration after oral amitriptyline (4,122,123).

In a prospective RCT study, 48 patients (124) were treated for 4 months with amitriptyline. Drug dosages were escalated in 25 mg increments at 1-week intervals up to a maximum dosage of 100 mg. Amitriptyline significantly improved the mean symptom score, pain and urgency intensity, while frequency and functional bladder capacity improved but were not statistically significant.

In a subsequent, prospective, open-label study (125), a response rate of 64% with an overall mean dose of 55 mg was seen with long-term amitriptyline for 20 months. Patient overall satisfaction was good to excellent in 46%, with significant improvement in symptoms. A therapeutic response was observed in all

patients fulfilling NIDDK criteria and those with a clinical diagnosis of IC. Anticholinergic side effects (mouth dryness, weight gain) were common and considered to be a drawback of amitriptyline.

*Pentosanpolysulphate sodium* (Elmiron) has been evaluated in double-blind, placebo-controlled studies. Pentosanpolysulphate sodium is thought to substitute for a defect in the GAG layer. Subjective improvement of pain, urgency, frequency, but not nocturia, was reported in patients taking the drug compared to placebo (126,127). In an open multicentre study, Pentosanpolysulphate sodium had a more favourable effect in classic IC than in non-ulcer disease (87).

The normal dose is 150-200 mg twice daily between meals. However, absorption is incomplete. An RCT compares 300 mg of Pentosanpolysulphate sodium with evaluated dosages of 600 and 900 mg in 380 IC patients. Mean ICSI scores improved significantly for all dosages (128). However, treatment response was not dose-dependent but related more to treatment duration. At 32 weeks, about half of all patients were responders. Most adverse events were mild and resolved without intervention.

In contrast, a prospective RCT comparing Pentosanpolysulphate sodium and hydroxine against placebo failed to demonstrate a statistically significant outcome for either drug, though Pentosanpolysulphate sodium approached statistical significance ($p = 0.064$) (120). Combination therapy showed the highest response rate of 40% compared to 13% with placebo. For patients with an initial minor response to Pentosanpolysulphate sodium, additional subcutaneous administration of heparin appeared helpful (129).

*Antibiotics* have a limited role in the treatment of BPS/IC. A prospective RCT pilot study of sequential oral antibiotics in 50 patients found that overall improvement occurred in 12/25 patients in the antibiotic group and 6/25 in the placebo group, while 10 and 5 patients reported an improvement in pain and urgency, respectively. Antibiotics alone or in combination may be associated with decreased symptoms in some patients, but do not represent a major advance in therapy for BPS/IC (130).

*Immunosuppressants*. Azathioprine, 50-100 mg daily, was given to 38 patients, resulting in disappearance of pain in 22 and urinary frequency in 20 (131). Cyclosporin A (CyA) (132) and methotrexate (133) were initially evaluated in open studies, with a good effect on pain, but a limited effect on urgency-frequency.
More recent studies of CyA have reported promising results (134,135). In 23 patients, daily voidings, maximal bladder capacity, and voided volume improved significantly after 1 year of treatment. The effect was maintained throughout 5 years' follow-up, with 20/23 patients reporting no bladder pain. However, symptoms recurred within months of discontinuing CyA.

In a subsequent randomised study (135), 64 patients fulfilling the NIH-criteria were randomised to 1.5 mg/kg CyA twice daily or low-dose (3 x 100 mg) pentosanpolysulphate sodium for 6 months. CyA was superior to pentosanpolysulphate sodium in all clinical outcome parameters, with the frequency of micturition significantly reduced in CyA-treated patients, and clinical global response rates of 75% (CyA) and 19% (pentosanpolysulphate sodium) ($p < 0.001$). However, there were more adverse events in the CyA arm (including induced hair growth, gingival pain and hyperplasia, paresthesias in extremities, abdominal pain, flushing, muscle pain and shaking) and only 29 patients completed the 6-month follow-up in both groups. During CyA therapy, careful follow-up is mandatory, including regular blood pressure measurement and serum creatinine.

*Gabapentin* is an antiepileptic drug, which is used as adjunctive treatment in painful disorders. Gabapentin may reduce the use of co-therapeutics, such as opioids. Two patients with IC showed improved functional capacity and received adequate pain control when gabapentin was added to their medication regimen (136). In an uncontrolled dose-escalation protocol with 21 chronic genitourinary pain patients (137), 10 had improved with gabapentin at 6 months. The study included eight IC patients, of whom five responded to gabapentin.

*Pregabalin* is an alpha(2)-delta ligand that binds to and modulates voltage-gated calcium channels, exerting its intended effect to reduce neuropathic pain (138). Pregabalin is the second of only two medications that are US FDA-approved for the treatment of neuropathic pain associated with diabetic peripheral neuropathy; it is used for the treatment of post-herpetic neuralgia. Studies on IC are still lacking.

*Suplatast tosilate* (IPD-1151T) is an oral immunoregulator that suppresses helper T-cell mediated allergic processes. Fourteen women with IC treated with suplatast tosilate reported significantly increased bladder capacity and decreased symptoms after 1 year of treatment. No major side effects occurred and therapeutic effects correlated with a reduction in blood eosinophils, immunoglobulin E and urinary T-cells (139). Comparative controlled data are unavailable.

*Quercetin* is a bioflavinoid that may be effective in male pelvic pain syndrome. It was first tested in a limited,

open-label study with hopeful results (140). Theoharides et al. (141) reported on the dietary supplement CystoProtek formulated from quercetin and the natural GAG components, chondroitin sulphate and sodium hyaluronate. In an uncontrolled study, symptoms were significantly improved in 37 IC patients (NIH-criteria), who had failed all forms of therapy and who took six capsules per day for 6 months. Larger controlled studies are warranted by this result.

*Recombinant human nerve growth factor*. A small randomised study (142) was performed on 30 patients (NIH-criteria), who received either placebo or one of two dosages (0.1 or 0.3 mg/kg) of recombinant human nerve growth factor weekly for 3 months. Significant improvement was seen after 3 months as measured by subjective improvement and ICSI score, while mast cells were significantly reduced and nerve cells elevated ($p < 0.05$) in a dose-dependent manner. Side effects were arthralgias (5%), myalgias (4%), and myasthenia and asthenia (2%).

The results suggest that recombinant human nerve growth factor is safe and shows preliminary evidence of efficacy in patients with BPS/IC, but further studies are needed to define its role.

### *2.7.10* ***Intravesical treatment***

Intravesical application of medications establishes high concentrations at the target with few systemic side effects. Disadvantages include the need for intermittent catheterisation, which can be painful in IC patients, the cost, and the risk of infection.

*Local anaesthetics*. There are sporadic reports of successful treatment of IC with intravesical lidocaine (143,144). Alkalization of lidocaine prior to intravesical application improved pharmacokinetics (145). In an uncontrolled study, significant immediate symptom relief was reported in 94% of patients and sustained relief after 2 weeks in 80%, using instillations of combined heparin and alkalinized lidocaine (40,000 U heparin, 2% lidocaine (160 mg), and 3 mL 8.4% sodium bicarbonate) (146).

*Pentosanpolysulphate sodium* is a glycoprotein aimed at replenishing the GAG layer, which is applied intravesically due to poor bioavailability following oral administration. A double-blind placebo-controlled study (147) was performed in 20 patients, of whom 10 received intravesical pentosanpolysulphate sodium (300 mg in 50 mL of 0.9% saline) twice a week for 3 months and 10 received placebo. At 3 months, four patients in the pentosanpolysulphate sodium group and two patients in the placebo group gained significant symptomatic relief. Bladder capacities showed a statistically significant increase only in patients treated with pentosanpolysulphate sodium. At 18 months, symptoms were relieved in eight patients, who were still receiving pentosanpolysulphate sodium instillations, and in four patients not receiving pentosanpolysulphate sodium.

*Intravesical heparin* was proposed as a coating agent. In an open, prospective, uncontrolled trial (148), 48 IC patients received instillations of 10,000 units in 10 mL sterile water three times per week for 3 months. In over half of the patients studied, intravesical heparin controlled the symptoms, with continued improvement after 1 year of therapy. Kuo et al. (149) reported another uncontrolled trial of intravesical heparin (25,000 units twice a week for 3 months) in women with frequency-urgency syndrome and a positive potassium test. The study included 10 patients with IC, of whom eight reported symptomatic improvement. Baykal et al. (150) evaluated intravesical heparin plus dorsal tibial nerve stimulation in 10 refractory IC patients. Voiding frequency, pain scores and maximum cystometric capacity were significantly better after 2 and 12 months compared to pretreatment values.

*Hyaluronic acid (hyaluronan)* is a natural proteoglycan aimed at repairing defects in the GAG layer. A response rate of 56% at week 4 and 71% at week 7 was reported in 25 patients treated with hyaluronic acid (151). After week 24, effectiveness decreased, but there was no significant toxicity. Nordling et al. (152) and Kallestrup (153) reported a 3-year follow-up of a 3-month, prospective, non-randomised study evaluating the effect of intravesical hyaluronic acid on BPS/IC symptoms. Of the 20 patients, 11 chose to continue treatment beyond the initial trial, and modest beneficial long-term effects were noted in about two-thirds of patients. Reduction in urinary frequency was less effective and mostly due to an improvement in night-time voids.

Another study (154) demonstrated a similar favourable effect of hyaluronic acid on pain reduction. Forty-eight patients were treated with typical symptoms and a positive potassium (0.4 M) sensitivity test with weekly instillations of 40 mg hyaluronic acid for 10 weeks. Visual analogue scale scores showed symptom relief due to hyaluronic acid therapy, irrespective of bladder capacity. The improvement was particularly evident in patients with a reduction in C(max) $\leq$ 30% compared to patients with a reduction of < 30% with 0.2 M KCl solution ($p = 0.003$).

*Chondroitin sulphate*. Intravesical chondroitin sulphate (155) demonstrated beneficial effects in patients, who

had given a positive potassium stimulation test, in two non-randomised, uncontrolled, open-label pilot studies. Steinhoff (156) treated 18 patients with 40 mL instilled intravesically once a week for 4 weeks and then once a month for 12 months. Thirteen of 18 patients were followed for the entire 13-month study. Twelve of these patients responded to treatment within 3-12 weeks. A total of 6/13 (46.2%) showed a good response, 2/13 (15.4%) had a fair response, 4/13 (30.8%) had a partial response, and 1/13 (7.7%) showed no response.

In a second trial (157), 24 refractory patients with BPS/IC were treated with high-dose (2.0%) chondroitin sulphate instillations twice weekly for 2 weeks, then weekly with 0.2% solution for 4 weeks, and monthly thereafter for 1 year. The average symptom improvement reported in 20 patients completing the trial was 73.1% (range 50–95%). The time to optimum response was 4-6 months. More concentrated 2.0% solution was needed in eight patients to maintain results. A Canadian phase II/III non-randomised, uncontrolled, community-based, open-label efficacy and safety study is underway.

*Dimethyl sulphoxide (DMSO)* is a chemical solvent and water-soluble liquid that penetrates cell membranes. It is claimed to have analgesic, anti-inflammatory, collagenolytic, and muscle relaxant effects. It is also a scavenger of the intracellular OH radical believed to be an important trigger of the inflammatory process. It has been tested empirically and found to alleviate symptoms in IC. DMSO is now a standard treatment.

In a controlled, crossover trial (158), 33 patients received instillations of 50% DMSO solution and placebo (saline). All patients received both regimens, which were administered intravesically every 2 weeks for two sessions of four treatments each. Subjective improvement was noted in 53% of patients receiving DMSO versus 18% receiving placebo, and objective improvement in 93% and 35%, respectively. Other uncontrolled trials with DMSO have reported response rates of 50-70% for a period of between 1 and 2 months (159). Rossberger et al. (160) evaluated the discomfort and long-term of DMSO instillations in a total of 28 patients. Side effects were not more common or pronounced in patients with classic compared to non-ulcer disease. After DMSO instillations, a residual treatment effect lasting 16-72 months could be seen.

DMSO is contraindicated during urinary tract infections or shortly after bladder biopsy. It temporarily causes a garlic-like odour. Because there has been a case report in which DMSO treatment may have caused pigmented eye lens deposits (161), ophthalmic review should be considered during treatment.

*Bacillus Calmette Guérin*. The tuberculosis vaccine, Bacillus Calmette-Guérin (BCG), is used for its immunomodulatory properties in the intravesical treatment of superficial bladder carcinoma. In 1997, a small prospective, double-blind pilot study on intravesical BCG demonstrated a 60% BCG versus 27% placebo response rate in 30 patients who received six weekly instillations of Tice strain BCG or placebo (162). In a subsequent 24-33 months' follow-up report, eight of the nine responders reported favourably. BCG did not worsen symptoms in non-responders (163). However, these results are at variance with two controlled trials.

In a prospective, double-blind crossover trial of BCG and DMSO (86), BCG treatment failed to demonstrate any benefit. Another randomised, placebo-controlled, double-blind trial on 260 refractory IC patients (164) reported global response rates of 12% for placebo and 21% for BCG ($p = 0.062$). Small improvements were observed for all secondary outcomes (voiding diary, pain, urgency, symptom indexes, and adverse events), some of which were greater with BCG, but with only borderline statistical significance. In a subsequent study (165), 156 non-responders from both groups were offered treatment with open-label BCG. The low response rate (18%) for BCG in this series is a further argument against the routine use of BCG as treatment for BPS/IC.

*Vanilloids* disrupt sensory neurones (166). Resiniferatoxin (RTX) is an ultrapotent analogue of the chilli pepper extract capsaicin, causing less pain on instillation and therefore no anaesthesia. Chen et al. (167) investigated RTX tolerability (0.05 µM or 0.10 µM) in 22 BPS/IC patients versus placebo. The most commonly reported adverse event was pain during instillation (RTX > 80.0%, placebo 25.0%) but no serious adverse events were reported.

In a small RCT on 18 patients with hypersensitive bladder disorder and pain (168), RTX significantly reduced mean frequency, nocturia, and pain scores by about 50%. In another study of seven patients with detrusor hyperreflexia, RTX improved urinary frequency, incontinence and bladder capacity (169). In a small open-label study with single-dose RTX in patients with frequency and urgency (170), RTX significantly improved lower urinary tract symptoms, urodynamic parameters, and QoL for up to 6 months.

These results are in contrast with an RCT in 163 BPS/IC patients randomly assigned to receive a single intravesical dose of 50 mL of either placebo or RTX (in the dosages 0.01, 0.05, or 0.10 µM) (171). RTX resulted in a dose-dependent increase in instillation pain, but otherwise was well tolerated. It did not improve overall symptoms, pain, urgency, frequency, nocturia, or average void volume during 12 weeks' follow-up.

More favourable results were reported from a prospective study on multiple intravesical instillations of RTX (172) (0.01 µM once weekly for 4 weeks). Among 12 patients (one drop-out for severe pain), the overall satisfactory rate was 58.3%, with several scales of symptom and QoL significantly improved after

RTX treatment. There was no significant increase in functional bladder capacity or change in urodynamic parameters.

Modification of urine pH. A prospective, randomised, double-blind cross-over study was performed in 26 women, who received instillations of various pH values. There was no evidence that changes in urinary pH affected the pain associated with IC (173).

### *2.7.11* ***Interventional treatments***

*Bladder distension*. A frequently cited report by Bumpus et al. (174) claims that hydrodistension achieved symptom improvement in 100 patients over several months. However, the study did not define either patient population or symptoms and the methods used were inadequately described. Reports by Ormond (175) and Longacre (176) were just as vague during the 1930s. In 1957, an uncontrolled retrospective study was presented by Franksson (177), who treated 33 patients with repeated, up to 10-fold, distensions. Twelve patients had improved symptoms for up to 4 weeks, in 14 patients for up to 6 months, and in seven patients for up to 1 year. British studies from the 1970s reported contradictory results. Dunn et al. (178) claimed to have achieved complete absence of symptoms in 16/25 patients during a mean follow-up of 14 months using the Helmstein method (179), where an intravesical balloon is distended at the level of systolic blood pressure for 3 hours. Bladder rupture occurred in two cases. These results disagree with those of Badenoch (113), who failed to note any improvement in 44/56 patients after hydrodistension. Twenty years later, McCahy (180) rejected balloon hydrodistension because of inefficacy and a complication rate of 20%. In the recent literature, bladder necrosis following hydrodistension is extremely rare (181).

In 2002, Glemain et al. (182) reported an uncontrolled study on 65 IC patients treated by 3-hour balloon hydrodistension. Treatment efficacy in the 33 retrospectively and 32 prospectively studied patients was 38% and 60% at 6 months, and 22% and 43% at 1 year, respectively. Results were superior for bladder capacities above 150 mL.

Ottem and Teichmann (2006) reported a retrospective study of 84 BPS/IC patients (94), among which 56% reported short-lived improvement from hydrodistension. Rose et al. investigated bladder distension using electromotive drug administration (EMDA) (183,184), as an alternative to general anaesthesia. Among 11 patients, the distension capacity achieved by EMDA was nearly identical to that in the operating room and cystoscopic findings were similar. Yamada et al. (185) reported on repeated hydrodistension in 52 IC patients (NIH-criteria). Under epidural anaesthesia, the bladder was repeatedly distended to maximal capacity and distension was repeated on the following day for 30 minutes. Five patients were classified as good responders, 30 as moderate responders and 17 as poor responders. Overall, hydrodistension was effective for about 70% of patients for more than 3 months without serious complications.

According to a study by Erickson et al. (186), the median symptom score for newly diagnosed patients decreased after distension, but only a few patients had at least 30% symptom improvement. Bladder distension altered levels of urine antiproliferative factor and heparin-binding epidermal growth factor-like growth factor towards normal. However, the mechanism of symptom relief after distension remains unknown.

In a retrospective review of 185 patients who underwent hydrodistension (187), results failed to identify any statistically significant differences in objective findings (anaesthetic capacity, glomerulations) following distension, or any therapeutic benefits, when patients were categorised according to presenting symptoms.

Although bladder hydrodistension is a common treatment for BPS/IC, scientific justification is scarce. It represents a diagnostic tool, but has a limited therapeutic role.

*Electromotive drug administration (EMDA)* enhances tissue penetration of ionised drugs by iontophoresis. Adapted for the bladder, it uses a transurethral anode and a suprapubic skin cathode. EMDA is expensive and the subject of uncontrolled studies only.

Six IC patients were treated with EMDA using lidocaine (1.5%) and 1:100,000 epinephrine in aqueous solution, while the bladder was dilated to maximum tolerance (188). Significant bladder enlargement was achieved and voiding symptoms and pain decreased. In four patients, the results were reported as ‘durable’. Rosamilia et al. (189) treated 21 women using EMDA with lidocaine and dexamethasone, followed by cystodistension. A good response was seen in 85% of patients at 2 weeks, with 63% still responding at 2 months. Complete resolution of pain was achieved in 25% of patients reviewed at 6 months. Using a similar technique, Riedl et al. (190) noted complete resolution of bladder symptoms in 8/13 patients lasting 1-17 months. Partial or short-term improvement was observed in three patients. Two patients experienced aggravated pain for several days after therapy. A 66% increase in bladder capacity was observed. Upon symptom recurrence, treatments were repeated with equal efficacy in 11 patients.

*Transurethral resection (TUR) coagulation and LASER.* Endourological ablation of bladder tissue aims to eliminate urothelial, mostly Hunner, lesions. In a case report, Kerr (191) described a transurethral resection of a 1-cm ulcer in a woman who experienced symptom resolution for 1 year. Subsequently, Greenberg et al. (69)

reported on 77 patients with Hunner ulcers treated over a 40-year period: 42 were managed conservatively, seven underwent fulguration and 28 were treated by TUR in a non-randomised fashion. Fulguration improved symptoms in 5/7 patients. All patients experienced symptom recurrence in less than 1 year and efficacy was not superior to non-surgical treatment.

In another series of 30 classic IC patients (192), complete TUR of visible lesions resulted in an initial disappearance of pain in all patients and a decrease in frequency in 21 patients. A relapse was noted in one-third of patients after 2-20 months, while the remaining two-thirds were still pain-free after 2-42 months. The same group recently reported the largest series of patients with classic IC treated by complete TUR of all visible ulcers (193). A total of 259 TURs were performed on 103 patients. Ninety-two patients experienced amelioration, with symptom relief lasting longer than 3 years in 40%, while most of the remaining patients responded well to subsequent TUR.

Transurethral application of the neodymium-yttrium-aluminium-garnet (Nd-YAG) laser is suggested as an alternative to TUR for endoscopic treatment in IC. Shanberg et al. (194) treated five refractory IC patients, four of whom demonstrated cessation of pain and frequency within several days. Follow-up at 3-15 months revealed no relapse except mild recurrent voiding symptoms. This series was extended to 76 patients treated at two institutions (195). Although 21 of 27 patients with Hunner ulcers noted symptom improvement, 12 experienced relapse within 18 months. In the group without ulcers, only 20 of 49 patients improved, of whom 10 required further therapy within 1 year.

In a later study, 24 patients with refractory classic IC underwent ablative Nd-YAG laser ablation of Hunner's ulcers (196). All patients showed symptom improvement within days without complications. At 23 months, mean pain and urgency scores, nocturia and voiding intervals had improved significantly. However, relapse in 11 patients required up to four additional treatments. Endourological resections are not applicable to non-ulcer IC. These techniques may provide long-term alleviation of symptoms, but none are a cure for the disease. Controlled studies are still lacking. Endourological resections are not applicable to non-ulcer BPS/IC. These techniques may provide long-term alleviation of symptoms, but none of them cure the disease. Controlled studies are still lacking.

*Botulinum toxin A (BTX-A)* may have an anti-nociceptive effect on bladder afferent pathways, producing both symptomatic and urodynamic improvements (197). Thirteen BPS/IC patients were injected with 100-200 IU of Dysport or BTX into 20 to 30 sites submucosally in the trigone and floor of the bladder. Overall, 9 (69%) patients noted an subjective improvement and ICSI scores improved by 70% ($p < 0.05$). There were significant decreases in daytime frequency, nocturia, and pain, and a significant increase in first desire to void and maximal cystometric capacity. However, these results are in contrast with another study of BTX in 10 patients with BPS/IC (198). One hundred units were injected suburothelially into 20 sites in five patients, while 100 units were injected into the trigone in the remaining five patients. None of the patients became symptom-free; two patients showed only limited improvement in bladder capacity and pain score.

*Hyperbaric oxygen (HBO).* In a prospective pilot study, six patients underwent 30 sessions of 100% hyperbaric oxygen inhalation and were followed up over 15 months. Four patients rated the therapeutic result as excellent or good, while two showed only short-term amelioration (199).

In a subsequent double-blind, sham-controlled study (200), 3/14 patients on HBO and no control patients were identified as responders ($p < 0.05$). At 12 months, three patients (21.4%) still reported a treatment response. Hyperbaric oxygenation resulted in a decrease of baseline urgency and pain ($p < 0.05$). ICSI scores decreased from 26 to 20 points in patients on HBO, while sham treatment did not result in any improvement.

These results suggest that HBO is a safe and feasible therapeutic approach, with moderate effects on a small subgroup of BPS/IC patients. Disadvantages include high costs, limited availability of treatment sites and time-consuming treatment.

#### *2.7.12* ***Treatments of limited efficacy and absence of recent publications***

*Cimetidine*. The H2-blocker cimetidine has been reported to improve symptoms in bladder pain syndrome (201). Thirty-six patients were enrolled in a double-blind clinical study with oral cimetidine versus placebo for 3 months. Patients receiving cimetidine showed a significant improvement in symptom scores, pain and nocturia, although histologically the bladder mucosa showed no qualitative changes in either group (202).

*Prostaglandins*. Misoprostol is a prostaglandin that regulates various immunological cascades. Twenty-five IC patients received 600 µg of misoprostol daily for 3 months, with responders treated for a further 6 months. At 3 months, 14 had significantly improved, with 12 showing a sustained response after a further 6 months. However, the incidence of adverse drug effects was 64% (203).

*L-arginine*. Oral treatment with L-arginine, the substrate for nitric oxide synthase, has been reported to

decrease BPS/IC-related symptoms (204-206). Nitric oxide has been shown to be elevated in patients with IC (207). However, others could not demonstrate either symptomatic relief or change in nitric oxide production after treatment (208,209).

*Anticholinergics*. Oxybutynin is an anticholinergic drug used in overactive detrusor dysfunction. Intravesically administered oxybutynin was combined with bladder training in one study, with improvement of functional bladder capacity, volume at first sensation and cystometric bladder capacity (210). However, the effect on pain was not reported.

*Duloxetine* inhibits both serotonin and noradrenaline reuptake. In an observational study, 48 women were prospectively treated with duloxetine for 2 months following an up-titration protocol to the target dose of 2 x 40 mg duloxetine per day over 8 weeks (211). Duloxetine did not result in significant improvement of symptoms. Administration was safe, but tolerability was poor due to nausea. Based on these preliminary data, duloxetine cannot be recommended as a therapeutic approach for BPS/IC.

*Clorpactin* is a detergent of hypocloric acid previously used to treat IC (212-216). Due to high complication rates (214-217), clorpactin instillations can no longer be recommended.

### *2.7.13* ***Nonpharmalogical treatments***

Behavioural bladder training techniques are attractive for BPS/IC patients with predominant symptoms of frequency/urgency but hardly any pain. Parsons et al. (218) included 21 selected BPS/IC patients on a protocol, which focused on progressively increasing micturition intervals. Fifteen patients reported a 50% decrease in urgency, frequency and nocturia, and there was a moderate increase in bladder capacity. Chaiken et al. (219) retrospectively analysed 42 patients, who had been instructed in diary keeping, timed voiding, controlled fluid intake and pelvic floor muscle training. After 12 weeks, voiding intervals increased by a mean of 93 minutes and daily micturitions were reduced by an average of nine voids. Overall, 88% of the patients reported markedly improved or improved symptoms.

*Diet*. Dietary restrictions are among the many physical self-care strategies found among BPS/IC patients (220). In an analysis of the Interstitial Cystitis Data Base (ICDB) cohort study, special diets were among the five most commonly used therapies (221). Bade et al. (222) found that IC patients consumed significantly less calories, fat and coffee, but more fibre. Scientific data on a rationale for such diets are unavailable.

The concentration of some metabolites and amino acids appears to be changed in IC (223). A study of the metabolism of the arylalkylamines (tryptophan, tyrosine, tyramine, phenylalanine) in 250 patients revealed an inability to synthesise normal amounts of serotonin and a noradrenaline metabolite. In this study, dietary restriction of acid foods and arylalkylamines lessened the symptoms, but did not alter specific abnormalities in dopamine metabolism.

In another, non-randomised, prospective study of BPS/IC patients with nutrition-related exacerbations, calcium glycerophosphate was reported to ease food-related flares (224). The observed efficacy seems little better than would be expected with placebo.

Overall, dietary management is a common self-care strategy in BPS/IC and offers a cost-effective therapeutic approach. Comprehensive instructions on how to identify individual trigger foods are given in the IC-Network Patient Handbook (225). However, scientific data are limited and dietary restriction alone does not produce complete symptomatic relief.

*Acupuncture*. In non-curable and agonising diseases like BPS/IC, desperate patients often try complementary medicines, such as acupuncture. However, scientific evidence for such treatments is often poor, with contradictory results from a few low-evidence reports on acupuncture, with any effects appearing to be limited and temporary.

A significant increase in capacity occurred after acupuncture in 52 women with 85% reporting an improvement in frequency, urgency and dysuria and symptoms (226). However, at follow-up at 1 and 3 years, these effects were no longer detectable and the authors concluded that repeated acupuncture was necessary to maintain beneficial effects (227).

In a non-randomised comparison in females with urethral syndrome, 128 patients treated by acupuncture and traditional Chinese medicine were compared to 52 patients treated by Western medicine as controls. Efficacy rates and urodynamic parameters were significantly better in the acupuncture group (228). In contrast, in a prospective study on the effect of acupuncture in IC (229), no differences in frequency, voided volumes or symptom scores were noted and only one patient improved for a short period of time.

*Hypnosis* is a therapeutic adjunct in the management of cancer, surgical disease and chronic pain. Although

used in urological patients (230,231), there is no scientific data on its effect on IC symptoms.

*Physiotherapy*. General body exercise may be beneficial in some BPS/IC patients (232). An uncontrolled trial of transvaginal manual therapy of the pelvic floor musculature (Thiele massage) in 21 BPS/IC patients with high-tone dysfunction of the pelvic floor resulted in statistically significant improvement on several assessment scales (233). Langford (234) prospectively examined the role of specific levator ani trigger point injections in 18 females with CPP. Each trigger point was identified by intravaginal palpation and injected with 5 mL of a mixture of 10 mL of 0.25% bupivacaine, 10 mL of 2% lidocaine and 1 mL (40 mg) of triamcinolone. A total of 13 out of 18 (72%) women improved with the first trigger point injection, with 6 out of 18 (33%) women completely pain-free.

*Intravaginal electrical stimulation* was applied to 24 women with CPP in the form of ten 30-minute applications, two or three times per week. Stimulation was effective in alleviating pain, as evaluated at the end of treatment and 2 weeks, 4 weeks and 7 months after completion of treatment ($p < 0.05$). There were significantly fewer complaints of dyspareunia following treatment ($p = 0.0005$) (235).

### *2.7.14* ***Surgical treatment***

When all efforts fail to relieve disabling symptoms, surgical removal of the diseased bladder is the ultimate option (236-239). Three major techniques of bladder resection are common:

- supratrigonal (i.e. trigone-sparing) cystectomy;
- subtrigonal cystectomy;
- radical cystectomy including excision of the urethra.

All techniques require substitution of the excised bladder tissue, mostly performed with bowel segments.

*Techniques without bladder removal*. As early as 1967, Turner-Warwick reported that mere bladder augmentation without removal of the diseased tissue was not appropriate (240). Sporadic reports that unresected IC bladders cease to cause symptoms when excluded from the flow or urine are scarce (5,241).

*Supratrigonal cystectomy* with subsequent bladder augmentation represents the most favoured continence-preserving surgical technique. Various intestinal segments have been used for trigonal augmentation, including ileum (113,242-249), ileocecum (248-255), right colon (113,249,256), and sigma (243,245,246,251,255). Substituting gastric segments (257,258) seems to be less helpful because the production of gastric acids may maintain dysuria and persistent pain.

The therapeutic success of supratrigonal cystectomy has been reported in many studies. In 1966, von Garrelts reported excellent results in 8/13 patients with a follow-up of 12-72 months (245). In 1977, Bruce et al. achieved satisfactory relief of IC symptoms by ileocystoplasty and colocystoplasty in eight patients (243). Dounis and Gow reported seven IC patients whose pain and frequency were considerably improved after supratrigonal cystectomy with ileocecal augmentation (259).

In 1991, Kontturi et al. employed segments of colon and sigmoid colon in 12 cases (255). All five patients augmented with sigmoid colon remained symptom-free over 4.7 years of follow-up. Two of seven cases augmented with colon required secondary cystectomy with formation of an ileal conduit. Nielsen et al. reported a series of eight patients undergoing supratrigonal cystectomy with ileocaecocystoplasty. While symptoms resolved in two patients, treatment failure in another six patients necessitated secondary cystectomy and ileal conduit formation (250).

Linn et al. (260) followed six BPS/IC patients after supratrigonal cystectomy with an ileocaecal augmentation for a period of 30 months and reported that all patients were symptom-free and voided spontaneously.

In 2002, Van Ophoven et al. (236) reported the long-term results of trigone-preserving cystectomy and consecutive orthotopic substitution enteroplasty in 18 women with IC, using ileocaecal (n = 10) or ileal (n = 8) segments. At a mean follow-up of nearly 5 years, 14 patients were completely pain-free, 12 voided spontaneously and 15 had complete resolution of dysuria. Ileocaecal bowel segments showed superior functional results, since in the group augmented with ileum, three patients required self-catheterisation and one a suprapubic catheter. Overall, surgery achieved a significant improvement in diurnal and nocturnal frequencies, functional bladder capacity and symptom scores, with only two treatment failures.

In more recent reports with longer follow-ups, the debate on the outcome of BPS/IC patients undergoing cystectomy continues and results vary greatly between different surgeons and patient populations.

Chakravarti (261) presented a retrospective review of 11 patients, who had undergone a trigone-preserving orthotopic substitution caecocystoplasty for intractable classical IC and were followed up for a mean period of 9 years. All had symptomatic relief and an increase in bladder capacity to normal. There was no mortality and minimal post-operative morbidity, with two patients requiring intermittent self-catheterisation

due to high residual volumes. No significant urinary reflux or metabolic complications were noted. However, two patients required a cystectomy after 4 and 6 years, respectively, due to recurrent trigonal disease in one patient and urethrotrigonal hypersensitivity following intermittent self-catheterisation in the other. One patient developed an advanced adenocarcinoma in the caecal segment 7 years after the primary operation.

Blaivas et al. (262) reported less favourable results. Long-term outcomes of augmentation enterocystoplasty or continent urinary diversion were analysed in 76 patients with benign urological disorders, including seven patients with a clinical diagnosis of IC. The BPS/IC patients all failed surgical treatment because of persistent pelvic pain and failure to achieve adequate bladder capacity rather than because of incontinence. The authors currently consider BPS/IC to be a contraindication for enterocystoplasty.

In contrast, Navalon et al. (263) reported a 32-month follow-up of four women suffering refractory IC who underwent supratrigonal cystectomy with orthotopic substitution iliocystoplasty. Suprapubic pain disappeared in all cases, as well as lower urinary tract symptoms, with good control of urinary frequency day and night in the immediate post-operative period. All patients reported high satisfaction with the outcome.

*Subtrigonal cystectomy.* Although less popular, subtrigonal cystectomy has also been reported (260,264-267). Subtrigonal resection has the potential of removing the trigone as a possible disease site, but at the cost of requiring ureteral reimplantation with associated risks of leakage, stricture, and reflux. Nurse et al. reported trigonal disease in 50% within their cohort (13/25) and blamed surgical failures on the trigone left in place (268). In contrast, Linn et al. indicated that the level of resection was not solely responsible for treatment success. While completely curing six patients by supratrigonal resection, there were three failures among 17 subtrigonal resections and half of the successful subtrigonal resections required self-catherisation to support voiding of the ileocaecal augmentate (260). A recent report on female sexuality after cystectomy and orthotopic ileal neobladder (269) included eight patients. Pain was relieved in all eight patients, but only one patient regained a normal sexual life post-operatively.

*Selecting patients and technique*. Bladder pain syndrome/interstitial cystitis is benign and does not shorten life, so that operative procedures rank last in the therapeutic algorithm. However, severely refractory patients should not have to tolerate unsuccessful conservative treatments for years when surgical options are available.

Detailed counselling and informed consent must precede any irreversible type of major surgery, which should only be undertaken by experienced surgeons. The choice of technique will be influenced by the experience of the surgeon. The appropriate extent of tissue resection should be based on the endoscopic and histopathological findings. Some surgeons recommend pre-operative cystoscopy and bladder capacity as a prognostic parameter for operative success (241). Responders and failures following orthotopic substitution differed in mean pre-operative bladder capacity (200 mL vs 525 mL, respectively) (250). These findings were supported by Peeker et al. (270), who found that patients with end-stage classic IC had excellent results following ileocystoplasty while patients with non-ulcer disease were not helped. These results have recently been confirmed by another report from the same institution. A retrospective analysis of 47 patients fulfilling the NIH criteria, who underwent reconstructive surgery using various techniques during 1978-2003 (271), resulted in complete symptom resolution in 32/34 patients with classic Hunner-type disease, but only 3/13 patients with non-ulcer disease.

Cystectomy with formation of an ileal conduit stills ranks first in current US practice trends in surgical IC therapy (272). For cosmetic reasons, however, techniques of continent diversion are preferred, particularly in younger patients. After orthotopic bladder augmentation, particularly when removing the trigone, voiding may be incomplete and require intermittent self-catheterisation. Patients considering these procedures should be advised and must be considered capable of performing, accepting and tolerating self-catheterisation.

For patients with BPS/IC who develop recurrent pain in the augmented bladder or continent pouch after enterocystoplasty or continent urinary diversion, Elzawahri (273) recommends retubularization of a previously used bowel segment to form a urinary conduit. For younger patients, it may be important to know that pregnancies with subsequent lower-segment Caesarean section after ileocystoplasty have been reported (274).

Reconstructive surgery for refractory BPS/IC is an appropriate last resort only for well-selected patients with refractory end-stage disease. The decision to embark on major reconstructive surgery should be preceded by a thorough pre-operative evaluation, with an emphasis on assessment to determine the relevant disease location and subtype.

A summary of the treatment options for BPS/IC, including a rating of the level of evidence and grade of recommendation, is given in Tables 11 and 12. Figure 3 provides an algorithm for the diagnosis and therapy of BPS/IC based on the information discussed above.

**Table 11: Medical treatment of BPS/IC**

| | LE | GR | Comment |
|---|---|---|---|
| Analgesics | 2b | C | Indications limited to cases awaiting further treatment |
| Corticosteroids | 3 | C | Corticosteroids not recommended as long-term treatment |
| Hydroxyzine | 1b | A | Standard treatment, even though limited efficacy shown in RCT |
| Cimetidine | 1b | B | Insufficient data |
| Amitriptyline | 1b | A | Standard treatment |
| Sodium pentosanpolysulphate | 1a | A | Standard treatment |
| Data contradictory | | | |
| Antibiotics | 1b | A | Limited role in the treatment of IC |
| Prostaglandins | 3 | C | Insufficient data on IC, adverse effects |
| L-arginine | 1b | C | Effect in IC uncertain |
| Cyclosporin A | 1b | A | RCT: superior to PPS but more adverse effects |
| Duloxetin | 2b | C | No effect, tolerability poor |
| Oxybutynin/tolterodine | 3 | C | Limited indication in IC |
| Gabapentin | 3 | C | Preliminary data so far |
| Suplatast tosilate | 3 | C | Preliminary data so far |
| Quercetin | 3 | C | Preliminary data so far |

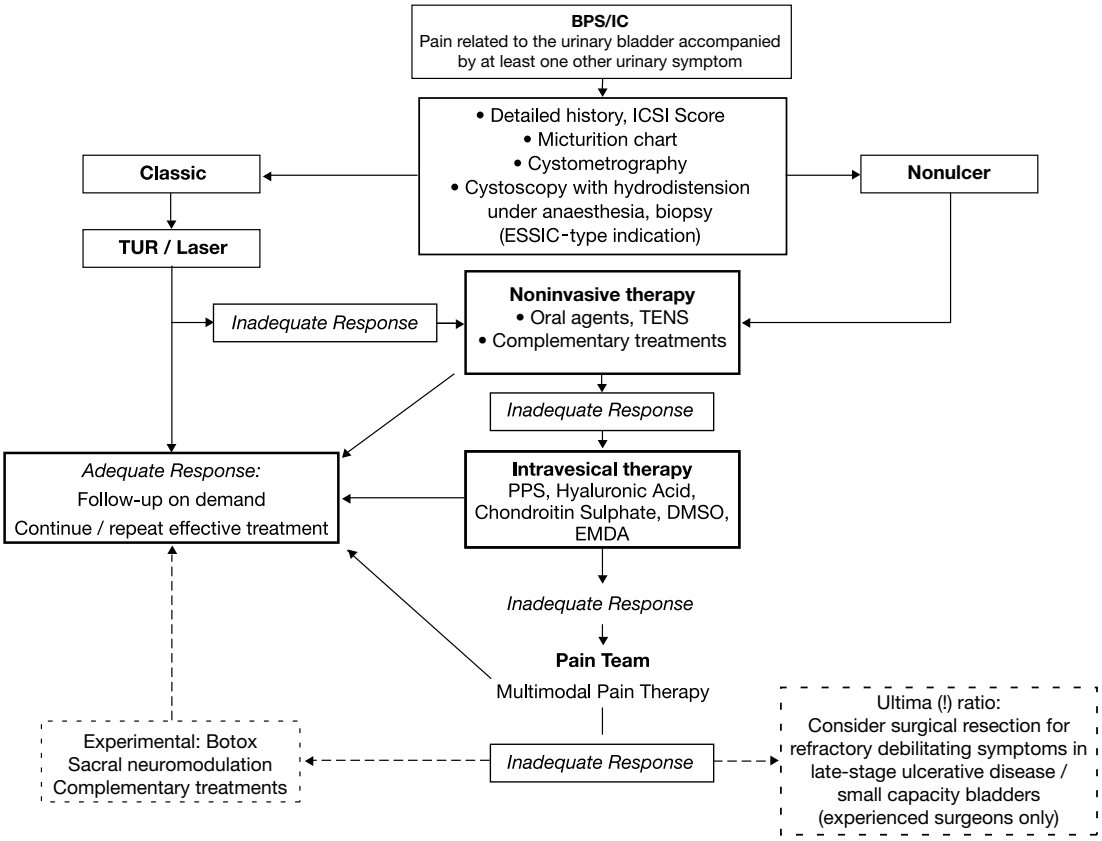
*RCT = randomised controlled trial; IC = interstitial cystitis; PPS = pentosanpolysulphate sodium.*

**Table 12: Intravesical, interventional, alternative and surgical treatment of BPS/IC**

| | LE | GR | Comment |
|---|---|---|---|
| Intravesical anaesthesia | 3 | C | |
| Intravesical PPS | 1b | A | |
| Intravesical heparin | 3 | C | |
| Intravesical hyaluronic acid | 2b | B | |
| Intravesical chondroitin sulphate | 2b | B | |
| Intravesical DMSO | 1b | A | |
| Intravesical Bacillus Calmette Guérin | 1b | Not recommended | |
| Intravesical clorpactin | 3 | Not recommended | Obsolete |
| Intravesical vanilloids | 1b | C | Data contradictory |
| Bladder distension | 3 | C | |
| Electromotive drug administration | 3 | B | |
| Transurethral resection (coagulation and laser) | NA | NA | Hunner's lesions only |
| Nerve blockade/epidural pain pumps | 3 | C | For crisis intervention; affects pain only |
| Sacral neuromodulation trials | 3 | B | Not recommended beyond clinical |
| Bladder training | 3 | B | Patients with little pain |
| Manual and physical therapy | 3 | B | |
| Diet | 3 | C | |
| Acupuncture | 3 | C | Data contradictory |
| Hypnosis | | No data | |
| Psychological therapy | 3 | B | |
| Surgical treatment | NA | NA | Largely variable data ultima ratio, experienced surgeons only |

*PPS = pentosanpolysulphate sodium; DMSO = dimethyl sulphoxide; NA = type of evidence not applicable, since RCTs are unethical in such surgical procedures.*

**Figure 3: Flowchart for the diagnosis and therapy of bladder pain syndrome/interstitial cystitis**




*2.7.15* ***References***


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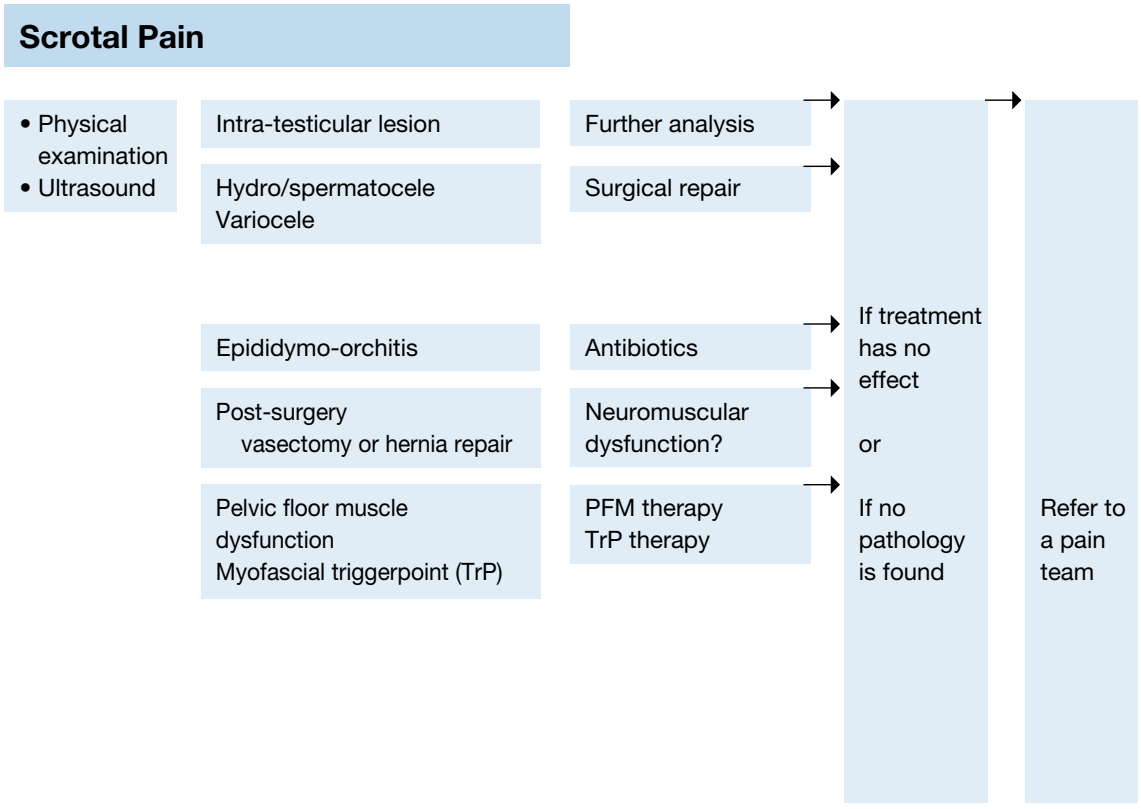
**Figure 4: An algorithm for diagnosing and managing scrotal pain**



## 2.8 Scrotal pain

Acute scrotal pain is a well-known urological emergency, while chronic scrotal pain is a common reason for men to contact their general practitioners. However, although chronic scrotal pain is not life-threatening and does not require immediate action, it has a considerable effect on a patient's QoL. The prevalence of chronic scrotal pain is unknown.

A physical examination should always be done in patients with scrotal pain. Gentle palpation of each component of the scrotum is performed to search for masses and for painful spots. A DRE is done to look for prostate abnormalities and examine the pelvic floor muscles. Scrotal ultrasound has limited value in finding the cause of the pain (1).

If physical examination is normal, ultrasound is sometimes performed to reassure the patient that there is no tumour in the testis. Ultrasound can be used to diagnose hydroceles, spermatoceles, cysts and varicoceles. The urine should be analysed. Magnetic resonance imaging (MRI) and computed tomography (CT) scans may be used to help with assessment (2).

The ilioinguinal and genitofemoral nerves are the most prominent afferent nerves for the scrotum (3). The pudendal nerve supplies the skin of the perineum.

### *2.8.1 **Management of different conditions***

*Intra-testicular lesion*. Proceed with further analysis. If tumour is suspected, orchiectomy should be performed.
*Hydro/spermatocele*. Painful fluid-filled spaces in the scrotum can be removed surgically.

*Varicocele*. When localisation of the pain and the pattern of aggravation in standing position are clear, correction can be performed.

*Epididymo-orchitis*. An infection of the testis or epididymis is usually an acute problem. Chronic epididymitis has been discussed as an entity in literature. The nature of such a chronic inflammation can be infective or based on an obstruction of the vas deferens. For treatment, antibiotics should be tried first for a longer period, up to 3 months, and when needed combined with anti-inflammatory drugs (4).

*Post-surgical procedures*. Procedures, such as vasectomy and hernia repair, may be complicated by scrotal pain. Scrotal pain after vasectomy occurs in about 15-19% (5,6) and is caused by congestion of the vas deferens and testis. Although antibiotics can be used, the results remain unclear. A spermatic cord blockade is also an option (7).

Surgical options for both vasectomy and hernia repair include removal of the epididymis, with recent results varying from 43-62% (6,8). Results for denervation of the spermatic cord are reported to be as high as 96% for complete pain relief (9). In post-vasectomy pain, a vasovasostomy might help to overcome the obstruction and thereby improve the pain (10).

*Pelvic floor muscle dysfunction*. At rectal examination, the pelvic floor muscles may be overactive, which means they contract when relaxation is needed, sometimes painfully. An overactive pelvic floor should be treated by physiotherapy (11-13) (See Chapter 6 on Pelvic floor function and dysfunction).

*Myofascial trigger points* is a type of end-stage surmenage of muscles. Pain in the scrotum can be the result of trigger points in the pelvic floor, but also in the lower abdominal musculature. Treatment consists of applying pressure to the trigger point and stretching the muscle (14,15) (See Chapter 6 on Pelvic floor function and dysfunction).

If no pathology is found, or when specific therapy has no effect, the patient should be referred to a multidisciplinary pain team or pain centre (16).

Recommendations for the treatment of scrotal pain syndrome are listed in Table 13.

**Table 13: Treatment of scrotal pain syndrome**

| | LE | GR | Comment |
|---|---|---|---|
| Orchiectomy | 1a | A | In case of intratesticular tumour |
| Excision | 3 | B | Hydrocele or varicocele |
| Antibiotics | 3 | C | For up to 3 months |
| Surgical intervention | 3 | C | Epididymectomy, denervation spermatic cord. Vaso-vasostomy |
| Pelvic floor muscle therapy | 1b | A | Including trigger point treatment |

*2.8.2* ***References***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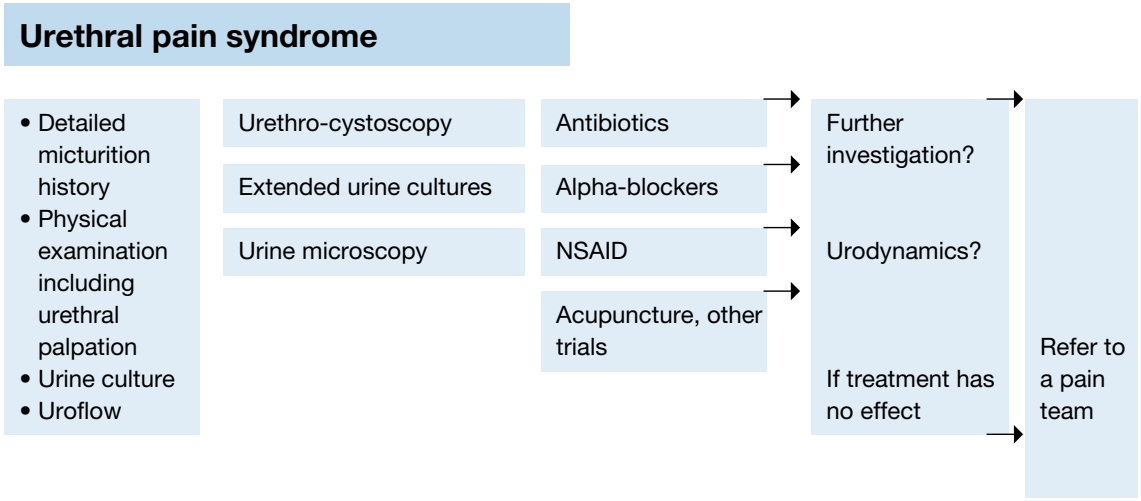
## 2.9 Urethral pain syndrome

**Figure 5: An algorithm for diagnosing and managing urethral pain syndrome**




Urethral pain syndrome is a less well-defined entity and scientific studies are scant. Positive diagnostic signs are urethral tenderness or pain on palpation and a slightly inflamed urethral mucosa found during endoscopy. Hypotheses about the aetiology include concealed infections of the periurethral glands or ducts, according to the anatomical description by Huffman (1), and oestrogen deficiency. Others consider urethral syndrome to be a less severe form of 'early' BPS/IC (2).

In clinical practice, the diagnosis of urethral pain syndrome is commonly given to patients who present with the symptoms of dysuria (with or without frequency, nocturia, urgency and urge incontinence) in the absence of evidence of urinary infection. The 'absence of urinary infection' cause diagnostic problems as the methods typically used to identify urinary infection are extremely insensitive. Dysuria is pain or discomfort experienced in association with micturition. The classical symptom of a burning sensation in the urethra during voiding caused by infection is well known. The external dysuria experienced by women with vaginitis when urine passes over the labia is less appreciated.

Biochemical testing and microbiological culture of urine is important in assessing lower urinary tract symptoms and has been reviewed in some detail in the elderly (3).

There is confusion about the concept of significant bacteriuria. This may be accepted as $10^5$ colony-forming units (CFU) of a single species in asymptomatic women. However, it may be as low as $10^2$ CFU of a single species of a known urinary pathogen in symptomatic women. Many automated culture systems have a sensitivity of $10^4$ CFU, while urinary leucocyte esterase and nitrite tests are correlated only with cultures as high as $10^5$ CFU (4). In addition, many laboratory culture systems detect only just over 50% of infections in midstream urine specimens from genuinely infected patients (4).

A narrow spectrum of aetiological agents causes 85-90% of cases of acute, uncomplicated cystitis in women. Nearly one-third of acutely dysuric women with urinary tract infections caused by *Escherichia coli, Staphylococcus saprophyticus* or *Proteus spp*. have midstream colony counts in the range of $10^2$-$10^4$ bacteria/mL. Investigators have also identified causative organisms by more invasive techniques, such as culturing specimens obtained by catheterisation or suprapubic aspiration. Failing to identify an organism does not mean that it is not present.

Although rarely included, proper manual urine microscopy using a haemocytometer should be part of a definitive work-up. Nowadays, most laboratories screen urine in wells using inverted microscopes or rely on robotic detection of pyuria, which are both insensitive methods. This is regrettable because studies have shown that significant pyuria is a nearly universal indicator of urinary tract infection, although it is not specific for differentiating cystitis from urethritis, particularly urethritis due to *Chlamydia trachomatis*. In relation to the latter, dysuria also merits the microscopic examination of a urethral smear after it has been Gram stained. If present, a purulent urethral exudate will be obvious, although a causative micro-organism will be identified in less than 50% of cases. The expression 'non-specific urethritis' is apposite and honestly states our current ignorance.

Urethral trauma arising from intercourse may cause pain and dysuria. This condition used to be called 'honeymoon cystitis', and friction and trauma to the urethra may be the cause in the absence of infection. Women with pelvic floor dysfunction sometimes describe similar symptoms, as do post-menopausal women, in whom trauma is associated with oestrogen deficiency, loss of lubrication, and vaginal dryness.

Unless a thorough assessment is carried out, bearing in mind the comments described above,

the diagnosis of urethral pain syndrome does not seem credible. There are no data available to answer the inevitable question, 'how common is dysuria in the presence of negative rigorous investigation of the bladder and urethra?'

#### *2.9.1 **Treatment***

There is no consensus on treatment. Management may require a multidisciplinary approach. Various modalities including antibiotics, alpha-blockers, acupuncture, and laser therapy have been proved successful. Psychological support is important (5). An algorithm for diagnosing and managing urethral pain syndrome is given in Figure 5.

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# 3. PELVIC PAIN IN GYNAECOLOGICAL PRACTICE

## 3.1 Introduction

The approach to pelvic pain presenting to the gynaecologist relies upon the same principles, namely to discover remediable causes and treat them using the most effective available therapies. However, the greatest therapeutic challenge will be provided by the 30% of patients in whom no cause can be found (1).

## 3.2 Clinical history

It is essential to start by taking a detailed medical history. The nature, frequency and site of the pain, and its relationship to precipitating factors and the menstrual cycle, may provide vital clues to the aetiology. A detailed menstrual and sexual history, including any history of sexually transmitted diseases and vaginal discharge is mandatory. Discrete inquiry about previous sexual trauma may be appropriate.

## 3.3 Clinical examination

Abdominal and pelvic examination will exclude any gross pelvic pathology (tumours, scarring and reduced uterine mobility), as well as demonstrating the site of tenderness if present. Abnormalities in muscle function should also be sought.

#### *3.3.1 **Investigations***

Vaginal and endocervical swabs to exclude infection are mandatory and cervical cytology screening is advisable. Pelvic ultrasound scanning provides further information about pelvic anatomy and pathology. Laparoscopy is the most useful invasive investigation to exclude gynaecological pathology (2) and to assist in the differential diagnosis (3).

## 3.4 Dysmenorrhoea

Pain in association with menstruation may be primary or secondary.

Primary dysmenorrhoea classically begins at the onset of ovulatory menstrual cycles and tends to decrease following childbirth (4). Explanation and reassurance may be helpful, together with the use of simple analgesics progressing to the use of (NSAIDs, which are particularly helpful if they are started before the onset of menstruation. NSAIDs are effective in dysmenorrhoea probably because of their effects on prostaglandin

synthetase. Suppression of ovulation using the oral contraceptive pill reduces dysmenorrhoea dramatically in most cases and may be used as a therapeutic test. Because of the chronic nature of the condition, potentially addictive analgesics should be avoided.

Secondary dysmenorrhoea suggests the development of a pathological process and it is essential to exclude endometriosis (5) and pelvic infection.

## 3.5 Infection

A history of possible exposure to infection should be sought and it is mandatory in all cases to obtain swabs to exclude chlamydia and gonorrhoea, as well as vaginal and genital tract pathogens (6). Patient's sexual contacts need to be traced in all cases with a positive culture. If there is any doubt about the diagnosis, laparoscopy may be very helpful.

Primary herpes simplex infection may present with severe pain (7), associated with an ulcerating lesion and inflammation, which may lead to urinary retention (8). Hospitalisation and opiates may be needed to achieve adequate analgesia.

### *3.5.1* ***Treatment***

Treatment of infection depends on the causative organisms. Subclinical chlamydial infection may lead to tubal pathology. Screening for this organism in sexually active young women may reduce the incidence of subsequent subfertility.

Chronic pelvic inflammatory disease is no longer common in developed countries, but still poses a significant problem with chronic pain in the Third World.

## 3.6 Endometriosis

The incidence of endometriosis is rising in the developed world. The precise aetiology is still a source of debate, but an association with nulliparity is well accepted.

The condition may be suspected from a history of secondary dysmenorrhoea and often dyspareunia, as well as the finding of scarring in the vaginal fornices on vaginal examination, with reduced uterine mobility and adnexal masses. Laparoscopy is the most useful diagnostic tool (9,10).

Endometriotic lesions affecting the urinary bladder or causing ureteric obstructions can occur, as well as lesions affecting the bowel, which may lead to rectal bleeding in association with menstruation.

### *3.6.1* ***Treatment***

As in primary dysmenorrhoea, analgesics and NSAIDs are helpful in easing pain at the time of menstruation. Hormone treatment with progestogens or the oral contraceptive pill may halt progress of endometriosis, but is not curative. A temporary respite may be obtained by using luteinising hormone releasing hormone (LHRH) analogues to create an artificial menopause, though the resulting oestrogen deficiency may have marked long-term side effects, such as reduced bone density and osteoporosis in those taking more than six months worth of treatment. These drugs are used prior to surgery to improve surgical outcome and reduce surgical complications.

Surgery for endometriosis is challenging and the extensive removal of all endometriotic lesions is essential. The best results are achieved laparoscopically, by highly trained and skilled laparoscopic surgeons, in specialist centres (11). A multidisciplinary team will be required for the treatment of extensive disease, including a pain management team.

The pain associated with endometriosis is often not proportionate to the extent of the condition and, even after extensive removal of the lesions and suppression of the condition, the pain may continue.

## 3.7 Gynaecological malignancy

The spread of gynaecological malignancy of the cervix, uterine body, or ovary will cause pelvic pain depending on the site of spread. Treatment is of the primary condition, but all physicians dealing with pelvic pain must be fully aware of the possibility of gynaecological malignancy.

## 3.8 Injuries related to childbirth

Tissue trauma and soft tissue injuries occurring at the time of childbirth may lead to CPP related to the site of injury. Dyspareunia is a common problem leading to long-term difficulties with intercourse and female sexual dysfunction (12). Denervation of the pelvic floor with re-innervation may also lead to dysfunction and pain. Hypo-oestrogenism, as a result of breast feeding, may also contribute to pelvic floor pain and dysfunction.

Vulval pain and psychosexual problems are discussed extensively in other sections of this text.

Post-menopausal oestrogen deficiency may lead to pain associated with intercourse, which will respond to hormone replacement therapy.

## 3.9 Conclusion

Once all the above conditions have been excluded, the gynaecologist may well be left with patients with unexplained pelvic pain. It is imperative to consider pain associated with the urinary and gastrointestinal tract at the same time. For example, patients with bladder pain quite often present with dyspareunia due to bladder base tenderness.

Previously, pelvic congestion has been cited as a course of pelvic pain of unknown aetiology, but this diagnosis is not universally recognised (13,14).

As previously stated in dealing with pelvic pain, the best results will be obtained from a multidisciplinary approach that considers all possible causes.

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# 4. NEUROLOGICAL ASPECTS

## 4.1 Physiology of the urogenital system

The fused somatic and autonomic innervation of the pelvic organs reflects the human need to integrate urogenital functions into our social existence. Proper bladder control is essential for everyday life, while sexual behaviour is an activity upon which depend intimate relationships and the continuation of the species. Physiological functioning of the bladder and sexual organs therefore requires intact innervation, which extends from the frontal lobes of the cortex to the distant pelvic plexi.

The integration of the sympathetic, parasympathetic, and somatic innervation in both female and male urogenital tracts is complex. Sympathetic innervation arises from the thoracolumbar outflow, while parasympathetic outflow and somatic innervation originate from the sacral segments of the spinal cord. Afferent nerves travel retrogradely with all three innervating systems. Integration of inputs from the different levels of central and peripheral innervation occurs in plexi, from which nerves arise to innervate pelvic organs. The sacral (predominantly somatic) and the pelvic (predominantly parasympathetic) plexus are intimately linked, with sympathetic connections from the superior and inferior hypogastric plexus.

The sacral plexus innervates the perineum, uterus in the female and the penis in the male, through the pudendal nerve. The parasympathetic fibres arise from S2 to S4 to synapse with the ganglia in the pelvic plexus, which are located in the adventitia around the bladder base and in the bladder wall, and from which comes visceral innervation to the bladder and the internal genital organs. The superior hypogastric plexus (sympathetic), situated at the sacral promontory, is the origin of the left and right hypogastric nerves.

## 4.2 Physiology of the bladder

The urinary bladder is a reservoir whose functions are simply storage and emptying. However, these functions are only accomplished by an extensive and complex innervation that co-ordinates the activity of the striated muscles of the pelvic floor and the various effector organs making up the lower urinary tract (LUT) (1).

### *4.2.1 **Bladder filling***

Most of the time, the bladder is a low-pressure storage system, which accommodates urine entering from the ureters. The walls of the ureters contain smooth muscle arranged in spiral, longitudinal and circular bundles. They pass obliquely through the bladder wall thereby preventing reflux of urine into the ureters during a bladder contraction.

Under normal circumstances, urine entering the bladder does not cause an increase in intravesical pressure. The smooth muscle of the bladder wall (the detrusor muscle) exhibits plasticity when stretched. The relationship between detrusor pressure and bladder filling can be studied by performing subtracted cystometry, where the pressure difference between two fluid-filled catheters inserted into the bladder and the rectum is determined. A plot of these values against the volume of fluid infused is seen in Figure 6. In health, the detrusor pressure remains almost flat, as fluid fills the bladder that can normally accommodate around 500mL.

Detrusor muscle fibres condense in the region of the bladder neck, forming a well-defined circular collar in the male, and an obliquely/ longitudinally orientated muscle coalescing into the urethral wall in the female. The bladder neck therefore forms a proximal sphincter, which is more evident in the male than in the female, and which is thought to be important in preventing retrograde ejaculation.

Striated muscle comprises the external urethral sphincter, which forms a U-shape around the urethra with some fibres completely encircling it anteriorly, so that as the muscle contracts, the urethra becomes occluded. During the storage phase, continence is maintained by the high resistance offered by the bladder neck and urethra, together with the integrity of the external urethral sphincter (Figure 7). Tonic firing of pudendal motor units of the external urethral sphincter and pelvic floor ensure that a higher pressure is maintained within the urethra than within the bladder. Furthermore, dampening of the parasympathetic innervation of the detrusor by the activation of sympathetic efferents via a sacral to thoracolumbar intersegmental reflex pathway (2) prevents the bladder from contracting spontaneously or involuntarily, the so-called ‘storage reflex’. This reflex not only inhibits the detrusor, but also causes contraction of the bladder neck and the proximal urethra. The situation is reversed when micturition is initiated (see below).

### *4.2.2 **Afferent innervation of the bladder***

Sensations of bladder fullness are conveyed to the spinal cord in the pelvic and hypogastric nerves (3). The afferent components of these nerves contain myelinated ( Aδ) and unmyelinated (C) axons. The Aδ fibres respond to passive distension and active contraction (3) and thus convey information about bladder filling. The C-fibres, insensitive to bladder filling under physiological conditions (therefore termed ‘silent’ C-fibres) respond primarily to noxious stimuli such as chemical irritation of the urothelium (4) or cooling (5). The cell bodies of both these classes of axons are located in the dorsal root ganglia (DRG) at the level of S2 – S3 and T11 – L2 spinal segments. Bladder afferent activity enters the spinal cord through the dorsal horn and ascends rostrally to higher brain centres involved in bladder control (see below).

In the urinary bladder, sensory nerves have been identified in the suburothelial layer (predominantly in

the bladder neck) as well as in the detrusor muscle (6-9). They form a plexus in the suburothelium with some terminal fibres possibly projecting into the urothelium (10-12). Afferent fibres also originate from the trigone and urethra and run in the hypogastric and pudendal nerves respectively.

The response of the bladder to stretch has been extensively investigated and recently a population of cells located in the suburothelial layer of the bladder, called myofibroblasts (13), have been identified. They may act as stretch sensory receptors.

#### *4.2.3* ***Efferent innervation of the bladder***

The LUT receives innervation from both the parasympathetic and the sympathetic branches of the autonomic nervous system. The pelvic nerves (arising from the parasympathetic pelvic plexus) cause contraction of the detrusor which effects bladder emptying, whereas parasympathetic innervation of the outflow tract exerts an inhibitory effect resulting in relaxation of the bladder neck and urethra (14). The sympathetic fibres are derived from the T11-T12 and L1-L2 in the spinal cord and run through either the inferior mesenteric ganglia or the hypogastric nerve, or pass through the paravertebral chain to enter the pelvic nerves at the base of the bladder and the urethra. The predominant effect of the sympathetic innervation is inhibition of the parasympathetic pathways at local or spinal level and mediation of contraction of the outflow tract.

The somatic nerve supply to the pelvic floor musculature and part of the urethra originates at S2 – S4 and is conveyed peripherally by the pudendal nerves. A distinct, medially placed motor nucleus at the same spinal level (Onuf's nucleus) supplies axons that innervate the external urethral sphincter.

#### *4.2.4* ***Central control of micturition***

Efficient storage and emptying of the bladder requires co-ordinated action of the detrusor and outflow tract. Storage control is achieved in infancy, but voiding is determined by the perceived state of bladder fullness and the social environment (15). The spinal reflexes involved in storage and micturition are relatively simple and are controlled by higher brain centres. Functional brain imaging has shown that a wide complex of brain networks control the processes of bladder storage (16,17) and voiding (18,19), which ultimately results in the activation or inhibition of the pontine micturition centre.

It is from here that direct pathways descend to the sacral spinal cord and modulate the parasympathetic outflow to the detrusor and co-ordinate the somatic innervation to the external urethral sphincter (20). A desire to void is generated when the bladder volume reaches capacity (approximately 500 mL in humans) (21), but a micturition reflex is only triggered if higher cortical function assesses the situation as appropriate for voiding. Complete emptying is ensured by the resultant detrusor contraction, which is maintained throughout voiding (achieved by the detrusor's unique ability to sustain near-maximal force generation in the face of significant length change [22]), and concomitant relaxation of the outflow tract.

#### *4.2.5* ***Physiology of the genital organs***

The female reproductive organs are comprised of the vagina and vulva, important for sexual function, and the ovaries and uterus, necessary for ovulation and reproduction. The uterus is made up of a fibromuscular lower body or cervix and a muscular upper body, which is lined by a hormonally sensitive endometrial layer. The latter responds to the complex monthly hormonal cycle mediated by the hypothalamic-pituitary-ovarian axis acting in tandem with neurological control.

*Innervation*. Female reproductive organs are innervated in a topographic fashion by afferents which pass retrogradely to the pelvic or hypogastric plexus (23). The afferent nerves contribute to uterine and vaginal perceptions (nociception) that are modified by the reproductive status (24). These plexi communicate with the higher brain centres (the hypothalamus (25), the hippocampus and the limbic system) via the spinal cord, dorsal column nuclei, and the solitary nucleus.

The vagina, a highly expandable fibromuscular tube, receives sensory fibres from the pudendal nerve (the perineal and posterior labial branches) and the ilioinguinal nerve. The blood vessels of the smooth muscle of the vaginal walls are supplied by autonomic fibres from the inferior hypogastric plexuses. The clitoris, which is considered homologous to the penis, is also composed of erectile tissue with two miniature corpora cavernosa. Covered with a prepuce, the free end of the clitoris, the glans, is highly sensitive to sexual stimulation. Sexual excitement induces vascular smooth muscle relaxation, (26) mediated by substances such as vasoactive intestinal peptide (VIP) (27) and nitric oxide, and resulting in increased pelvic blood flow, clitoral and labial engorgement, and transudative vaginal lubrication. This sexual response is due, as in the male, to parasympathetic activity, and at orgasm, there is repeated contraction of the perineal skeletal muscle, supplied by the perineal branch of the pudendal nerve.

Women with complete spinal cord injury at the mid-thoracic level show perceptual responses to vaginal and/or cervical self-stimulation (e.g. pain suppression and sexual response, including orgasm), with increased activity in the solitary tract nucleus (28).

*Menstruation*. Animal studies have shown that the rat uterus is directly innervated by both autonomic and sensory nerves, including adrenergic (29) and cholinergic (30), as well as by different peptidergic fibres containing VIP, substance P, calcitonin-gene-related peptide, and galanin (31,32). Uterine innervation undergoes profound remodelling during puberty, pregnancy, and after delivery. However, the extent to which uterine innervation may change during the menstrual cycle is uncertain (33,34).

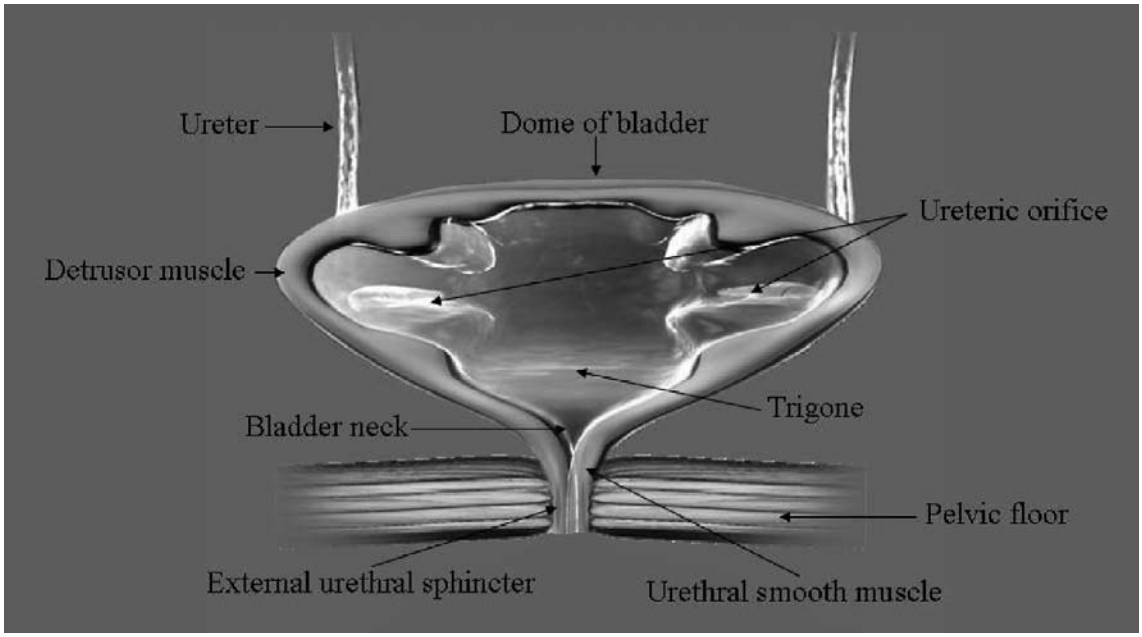
The human uterus is under direct control of the hormonal cycle, which influences the innervation of the uterine arteries (cholinergic, adrenergic, and peptidergic), and regulates the spontaneous contractile activity of the smooth muscle of vessel walls, as well as the motor responses of these tissues to different vasoactive substances (35). A hormonal disturbance may cause dysfunctional bleeding by changing vessel growth as well as vascular and myometrial smooth muscle activity (36). An example of the latter is primary dysmenorrhoea, when there is an increased secretion of vasopressin (35), which acts on type V1 vasopressin receptors of the uterus, causing myometrial hyperactivity and vasoconstriction, with resultant uterine ischemia and pain.

*Pregnancy and parturition*. In the pregnant uterus, the motor and sensory innervation undergoes a profound denervation process, although the changes do not affect all types of nerves. Immunocytochemical studies have indicated that myometrial and perivascular VIP-containing fibres disappear at the end of pregnancy (37). In contrast, SP-containing primary afferent neurons do not degenerate during pregnancy (38). At the end of pregnancy, the numbers of both myometrial and perivascular adrenergic nerves are decreased in the rat (39,40) in the guinea pig (41,42), and in humans (43). The whole autonomic uterine innervation therefore undergoes substantial remodelling during pregnancy.

*Urogenital pain*. The innervation of the pelvis shows great convergence, demonstrating the existence of extensive cross-system, viscero-visceral interactions within the CNS, which, while organised for coherent bodily functioning, serve as a substrate by which pathophysiology in one organ can influence physiology and responses to pathophysiology in other organs (24). Some cross-system effects reported in the literature include bladder inflammation, reducing the rate of uterine contractions and the effects of drugs on the uterus (44) and colon inflammation, producing signs of inflammation in an otherwise healthy bladder and uterus. The pathophysiology of one pelvic organ influences the physiology of another is poorly understood, but improved knowledge and understanding of the convergence of peripheral and central innervation of the pelvis may have considerable clinical relevance.

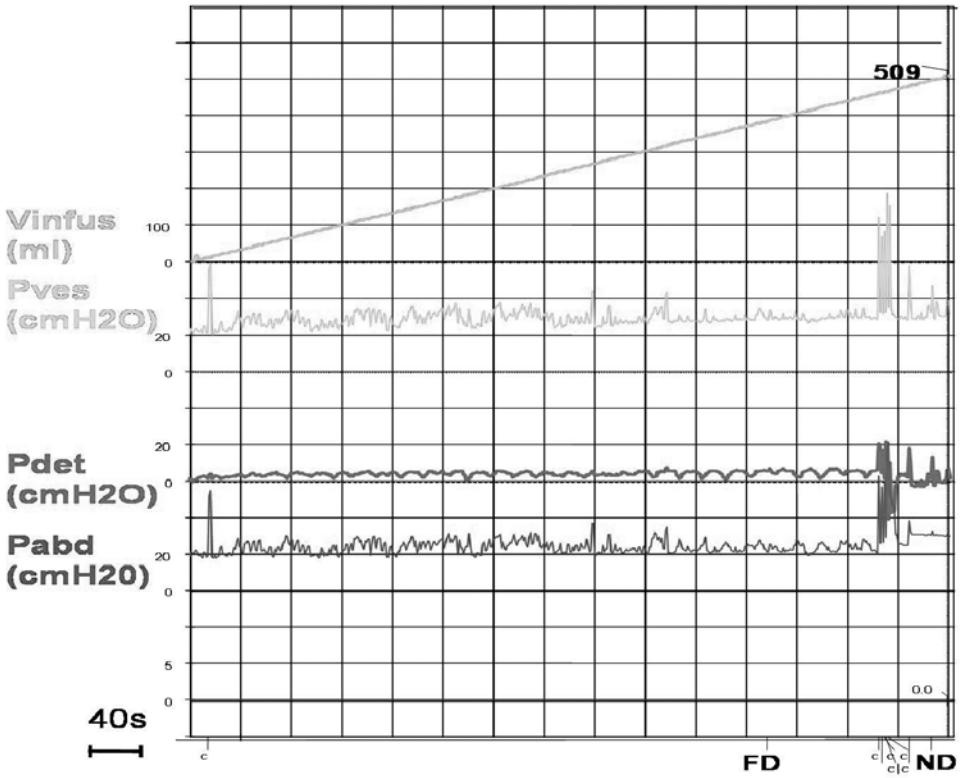
*Conclusion*. The rich and complex innervation of the bladder and genital organs, which enables their physiological function, appears also to be a potential substrate for neural pain. Perhaps pain results when autonomic innervation becomes ‘confused’.

**Figure 6: Effector organs making up the lower urinary tract (LUT)**




This is a representation of the female LUT. In the male, the prostate gland is situated around the external urethral sphincter (With permission of Mr. Vinal Kalsi).

**Figure 7: Subtraction cystometry showing typical bladder function**




*Pabd = intra-abdominal pressure measured with a rectal catheter; Pves = measured intravesical pressure; Pdet = detrusor pressure; Pdet = Pves-Pabd; Vinfus = infusion volume, 50 mL/min.*

The detrusor pressure remains less than 10 $cmH_20$ until the first desire to void (FD) is reached, which is accompanied by a small rise in the pressure tracing. There is a concomitant rise in vesical pressure; however, there is no rise in intra-abdominal pressure. The pressure rise is due to contraction of the detrusor; however, it is small due to the compliant properties of the bladder. The normal desire to void (ND) is soon accompanied by cystometric capacity (about 500 mL), at which time a void will be initiated. The undulations seen on the traces are a result of interference due to respiration.

### 4.3 Sexual dysfunction in men and women

Various classifications of sexual dysfunction have been proposed, the most recent being one which included hypoactive sexual desire, or disorders of sexual desire, sexual arousal, orgasms, or sexual pain (45). Many of these disorders are common amongst the general population: the Male Massachusetts study showing an increasing prevalence of erectile dysfunction (ED) with age so that of a group of men aged 60-70 almost 60% had ED to a greater or lesser extent (46). The prevalence of FSD has been estimated to be between 25%-63%, the figure depending on the definition used and population studies. Amongst groups of patients with neurological disease the prevalence of all types of disorder is even higher, although precise figures are not known.

Neurological causes of sexual dysfunction include cortical disease, spinal cord trauma, stroke, epilepsy, multiple sclerosis, radical pelvic surgery, and many more conditions. As the aetiology is diverse, so is the pathophysiology with damage to the thoraco-lumbar outflow in men during extensive surgery affecting ejaculation to damage of the hypothalamus and pituitary, following head injury, resulting in hypopituitarism and a concomitant de-sensitisation of the genital region.

The treatment in men and women with neurological or non-neurological disease includes pelvic floor exercises and electrical stimulation feedback with cognitive therapy. Male sexual dysfunction is discussed in detail within these guidelines.

Female sexual dysfunction is less easy to treat, but is affected by problems in the male, and it is now recommended that evaluation of the female should be addressed within the context of the couple in a sexual medicine clinic. Identifying and treating general medical conditions is vital to the effective management of both men and women. In addition to neurological related dysfunction in young women, pelvic floor dysfunction,

as a consequence of childbirth, must be taken into account as the importance of the menopause in the older woman. Despite the fact that hormone replacement therapy has been used extensively and effectively, there is still a small sub-set of women in whom this is not enough. In this group the libido is affected greatly and the use of testosterone products have been found to be important. Pharmacotherapy, like the PDE-5 inhibitors in men, has not been found to be useful in women.

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# 5. NEUROGENIC CONDITIONS

## 5.1 Introduction

It is clearly important for the patient to have been thoroughly examined by a urologist or gynaecologist and local pelvic pathology excluded. Once a structural cause has been eliminated, a neurological opinion is often sought, with the prime aim of the neurologist being to exclude any form of conus or sacral root pathology. MRI is the investigation of choice to show both neural tissue and surrounding structures.

If all examinations and investigations fail to reveal an abnormality, the diagnosis is likely to be one of the focal pain syndromes. These are persistent or recurrent or episodic pains referred to specific pelvic organs in the proven absence of infection, malignancy, or other obvious pathology (see Table 3). Although these are well-recognised conditions, their pathophysiology is not understood. However, it seems likely that the problems relate in some way to the combined visceral, autonomic, and somatic innervation of the pelvic organs.

## 5.2 Pudendal nerve entrapment

Chronic compression of the pudendal nerve in the ischiorectal fossa may result in a perineal pain located either anteriorly in the vagina or vulval region, or posteriorly in the anorectal region. The ICS has used the following definition, ‘perineal pain is felt: in the female, between the posterior fourchette (posterior lip of the introitus) and the anus, and in the male, between the scrotum and the anus’ (1).

The pain may include unpleasant sensations of numbness or a burning sensation, and may be exacerbated by sitting and relieved by standing. Neurological examination of the perineum is normal. If tested, the sacral reflexes are present and anal sphincter tone is normal. Neurophysiological examination is said to be helpful is some cases; sacral reflex latency (using electrical stimulation of the dorsal nerve of the clitoris and recording muscle activity in the perineum) and the pudendal nerve distal motor latency using the St Marks

Stimulator has been recommended. These investigations require specialist neurophysiological expertise.

Pudendal nerve neuropathy is likely to be a probable diagnosis if the pain is unilateral, has a burning quality and is exacerbated by unilateral rectal palpation of the ischial spine, with delayed pudendal motor latency on that side only. However, such cases account for only a small proportion of all those presenting with perineal pain. Proof of diagnosis rests on pain relief following decompression of the nerve in Alcock's canal and is rarely achieved. The value of the clinical neurophysiological investigations is debatable; some centres in Europe claim that the investigations have great sensitivity (1,2), while other centres, which also have a specialised interest in pelvic floor neurophysiology, have not identified any cases. Further information may be gained by a diagnostic nerve block or MRI investigation.

### 5.3 Other neurogenic conditions

Other pelvic floor clinical neurophysiological investigations are more helpful in identifying changes of denervation and re-innervation. Lesions causing such disorders are usually associated with bladder and/or sexual dysfunction rather than isolated urogenital pain.

A major defect of the clinical neurophysiological investigations currently available is that they examine mostly large myelinated nerve fibre function rather than the unmyelinated and small myelinated fibres, which subserve autonomic innervation, pelvic organ sensation and pain (3).

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# 6. PELVIC FLOOR FUNCTION AND DYSFUNCTION

### 6.1 Introduction

The pelvic floor is made up of muscles and fascia. The muscles usually function as a composite, though the anterior and posterior components may act in isolation. The pelvic floor has three functions: support, contraction, and relaxation.

### 6.2 Function

In its resting state, the pelvic floor supports the bladder and the urethra in the anterior compartment, the uterus and the vagina in the middle compartment, and the rectum and the anus in the posterior compartment. The integrity of the support function depends on the anatomical position of the muscles, on the resting 'tone' and on the integrity of the fascia (1). As with all skeletal muscles, tone is maintained by the efferent nerve fibres, and may vary with hormonal status (menstrual cycle, pregnancy, and menopause).

The support activated during a rise in intra-abdominal pressure is different from that at rest. When intra-abdominal pressure rises, the pelvic floor muscles must respond with a contraction occurring simultaneously or before the pressure rise. The latter is termed an anticipatory 'response' or feed-forward loop (2). Electromyography recordings show tonic motor unit activity at rest, with phasic recruitment of large motor units in response to coughing.

A contraction of the pelvic floor muscles results in an inward movement of the perineum and an upward movement of the pelvic organs. In many situations, other muscles such as the abdominal muscles, the adductor muscles, and the gluteal muscles also contract. There are two types of contraction that can be distinguished: a voluntary contraction, resulting from impulses arising in the cerebral cortex, and a reflex contraction. These contractions not only maintain support of the pelvic organs, they close the urethra, anus and vagina, thus avoiding loss of urine or stool, and affording women a defensive mechanism. Additionally, detrusor inhibition occurs in parallel with pelvic floor muscle contraction.

A contraction of the pelvic floor muscles must have sufficient strength. Strength results from muscle capacity and neurogenic drive, reflected in the frequency of excitation and the number of activated motor units. An increase in muscle strength is achieved through the recruitment of more motor units. A contraction must be

rapidly effective and remain so for a certain period (endurance).

Pelvic floor contractions play an important role in sexual function. During the arousal phase, pelvic floor muscle contractions are used to increase vasocongestion. During the last phase of the sexual response cycle, a series of involuntary contractions is associated with the physical sensations of orgasm (3).

Pelvic floor muscle relaxation results in a decrease or termination of the squeezing of the urethra, vagina and anus. The perineum and the pelvic organs return to their anatomical resting position. Pelvic floor muscle relaxation is the result of inhibition of tonically active motor units. Relaxation of the pelvic floor muscles is needed for voiding, defecation, and for sexual intercourse.

### 6.3 Dysfunction

Pelvic floor dysfunction should be classified according to 'The standardisation of terminology of pelvic floor muscle function and dysfunction' (4). This is an international multidisciplinary report from the ICS. As in all ICS standardisation documents, this is based on the triad of symptom, sign, and condition. Symptoms are what the patient tells you; signs are found by physical examination. By palpation of the pelvic floor muscles, the contraction and relaxation are qualified. The voluntary contraction can be absent, weak, normal, or strong. The voluntary relaxation can be absent, partly, or completely. The involuntary contraction and relaxation is absent or present.

Based on these signs, pelvic floor muscles can be classified as follows:

- non-contracting pelvic floor;
- non-relaxing pelvic floor;
- non-contracting, non-relaxing pelvic floor.

Based on symptoms and signs, the following conditions are possible:

- normal pelvic floor muscles;
- overactive pelvic floor muscles;
- underactive pelvic floor muscles;
- non-functioning pelvic floor muscles.

An example is as follows:

- *Symptom*: pain in the perineal region;
- *Sign:* non-relaxing pelvic floor (no relaxation, neither voluntary nor involuntary);
- *Condition*: overactive pelvic floor muscles.

An underactive pelvic floor means that the muscles do not contract when they need to. In practice, this leads to incontinence of urine or stool. An overactive pelvic floor means that the pelvic floor muscles do not relax when they should. This may result in complaints like low flow rates and constipation (5). Another symptom of overactivity is CPP and more specific dyspareunia.

Overactivity tends to develop over a protracted period, with many causes. In most cases, there is the problem of limited access to a toilet on demand, leading to postponement of voiding by contraction of the pelvic floor muscles. When they do eventually have the time to void, detrusor power is lacking. They start to use abdominal straining which results, through the guarding reflex, in contraction of the pelvic muscles (6).

Why an overactive pelvic floor causes pain has only partly been elucidated (7). A muscle that is continuously contracting will ache. Nerves that pass through the pelvic floor may be compressed, and vessels to the penis and scrotum may be obstructed. Both mechanisms will lead to pelvic pain. A contracting pelvic floor will increase afferent input to the sacral spinal cord, the pons and the cerebral cortex. In response, the CNS may modify efferent signals to the pelvis. This change in efferent activity may further aggravate the situation (8).

### 6.4 Myofascial trigger points

Repeated or chronic muscular overload can activate trigger points in the muscle. Trigger points are defined as hyperirritable spots associated with a hypersensitive palpable nodule in a taut band (9). Trigger points are painful on compression and give rise to characteristic referred pain and motor dysfunction. They prevent full lengthening of the muscles, they weaken the muscle and they lead to pain that is very recognisable for the patient.

Pain as a result of these trigger points is aggravated by specific movements and alleviated by certain positions. Patients know what activities and postures influence the pain. Trigger points can be located within the pelvic floor muscle (10). In a case of pelvic floor muscle trigger points, a patient will sit down cautiously, often on one buttock. Rising after a period of sitting will cause pain. Pain will be aggravated by pressure on the trigger point (e.g. pain related to sexual intercourse). Pain will also get worse after sustained or repeated contractions (e.g. pain related to voiding or defecation). On physical examination, trigger points can be

palpated and compression will give local and referred pain. In patients with CPP, trigger points are often found in muscles related to the pelvis like abdominal, gluteal and piriformis muscle.

## 6.5 Therapy

Treating pelvic floor overactivity should be considered in the management of CPP (11). There are a number of methods, taught by specialised physiotherapists, which can be used to improve the function and co-ordination of the pelvic floor muscles. The use of biofeedback by means of pelvic floor muscle electromyography should be considered because it might help the patient to understand the dysfunction of the pelvic floor muscles. This understanding will improve the result of the treatment.

Central trigger points are treated by stretching the muscle, which inactivates them. However, trigger points lying in the attachment of the muscle to the bone respond better to direct manual therapy. Muscle exercises are helpful, e.g. voluntary contractions followed by complete relaxation. Pressure on the trigger points and subsequent release is also effective (12,13). Stretching of the muscle will be more effective after pain relief by direct pressure on the trigger point. Injecting the trigger points with a local anaesthetic will show that the trigger points are really causing the pain; its will give an acute relief of pain and will unblock the muscle so that stretching becomes possible.

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# 7. PSYCHOLOGICAL FACTORS IN PERSISTENT CHRONIC PELVIC PAIN

## 7.1 Introduction

This section describes the evidence for psychological factors, which play a part in the development or maintenance of persistent pelvic pain, in adjustment to pain, and in treatments including psychologically-based treatments.

The function of pain, particularly acute pain, is to demand action to stop or minimise damage, and to protect the injured part to promote healing. When pain persists without ongoing damage or disease, or after the damage has healed, it appears to have no such function. However, it can disrupt daily life and cause distress, particularly since the person with pain tends to use the acute pain model, and to fear damage, disease, and prolonged suffering. Cognitive and emotional processes are integral in pain processing (1,2). Psychological and social factors are involved as risk factors for the development of persistent pain from acute pain, in adaptation to pain, and in the decision to seek and to adhere (or not) to recommended treatment for the pain.

## 7.2 Psychological models of pain

A fully integrated model of pain, as described above, with changes in excitatory and inhibitory mechanisms at peripheral and central level, and changes in cortical and subcortical processing of pain, but not defined by tissue damage or disease severity, does not correspond well with the model of somatisation, or somatoform pain.

This model assumes that pain can be partitioned into distinct biological and psychological processes which, added together, constitute the presenting complaint, and that absence of significant physical signs constitutes evidence for substantial psychological causation (3,4). This has been a particularly prominent model in pelvic pain, at least in women.

In fact, multiple models co-exist, often poorly specified. One model, unsubstantiated by psychiatric diagnostic systems, rules that pain is inauthentic if it is not supported by clinical signs and that the pain is therefore a covert expression of distress or psychological disorder. This model relies on a dualism, which has no place in scientific medicine and is unacceptable to most patients. Another model, commoner in psychodynamically informed systems, constructs pain (perhaps without physical signs, but not defined by their absence) as an expression of an unconscious conflict or source of distress.

Several models are compatible with our understanding of physiological processes as it has developed since Melzack and Wall's (1965) work (1). Psychophysiological reactivity, built on stress models, describes the activation of systems for defence against physical or psychological stress. Prolonged stress leads to repeated alerting and depletion of systems involved. This was demonstrated by Flor et al. (1992) (5), using electromyography in back muscles, in response to psychological/social stressors. This may be a mechanism for the production of pain in pelvic floor muscles, even if it is not the primary cause of pelvic pain. Pelvic floor overactivity is now the subject of investigation and treatment attempts (see Sections 2.5 and 6.5). In addition, Link et al. (2007) (6) have proposed an association between trauma (sexual and physical abuse in childhood) and bladder activity and urinary symptoms, presumably mediated by stress mechanisms.

The cognitive-behavioural model classically took pain as a starting point, and described modulation of the experience of pain, and reaction to it, in terms of cognition, emotion and behaviour. There are reliable associations between certain beliefs or types of belief, and associated behaviour and/or emotions, including extensive evidence for the importance of psychological factors in determining the level of pain experienced, levels of disability and restriction due to pain, levels of distress, and extent of healthcare use (2,7), demonstrated either in specific pain problems, such as back pain or fibromyalgia, or for mixed persistent pain populations, but with few studies in pelvic pain populations.

Psychological factors are better researched and described than social factors, and both suffer from overlapping constructs which neither fall into clear hierarchies of organisation nor map well on to processes and pathways in the brain. Among the better established ones are attention (8) and fear and associated avoidance patterns (9).

The cognitive and behavioural model is compatible with the psychophysiological reactivity model. More recently, it has been extended by reference to neurotransmitters common to pain or to other symptoms, including urinary symptoms (10) and to mood pathways; and to dysregulation across multiple systems producing a range of 'medically unexplained symptoms', which concomitantly occur with mood disorders at a higher level than chance in individuals and in their first-degree relatives (11,12).

Psychological models, particularly cognitive and behavioural models, when integrated with a biomedical model, are described as biopsychosocial models.

## 7.3 Methodology

Both PubMed and PsychInfo were searched to access trials published in psychology journals not covered by medical databases, with a search covering the last 10 years, since psychological trials tend to take longer to run and to reach publication than medical and other clinical trials. The Cochrane database was also searched.

## 7.4 Psychological factors in assessment of pelvic pain

A careful review by Savidge and Slade (1997) (13) of CPP in women identifies as problematic the notion that women without physical findings to which pain can be causally attributed differ in psychological characteristics from women with physical findings. They critically examine the methodologies of studies purporting to show such differences, and the bias introduced by sampling and by unsuitable measures; they argue for better methodology in replication of these studies, particularly those sampling life events, and for greater use of idiographic methods. However, the report of anxiety, depression, and sexual problems is sufficiently common for these to be important in assessment and in planning treatment. Distress, described in the patient's terms or within a psychodiagnostic framework, is best understood in the context of pain and of the meaning of pain to the individual.

### *7.4.1* ***Psychological risk factors in the development of pelvic pain and adaptation to it***

There is one systematic review (14) of risk factors for CPP in women: there appears to be no equivalent systematic review of pelvic pain in men. For non-cyclical pelvic pain in women, Latthe et al. drew on 40 studies (n = 20,040). Of the 48 risk factors included in the studies, pain was associated with (biomedical factors) pelvic pathology, miscarriage, and heavy menstrual flow; and (psychological factors):

- lifetime drug and alcohol abuse (OR 4.61, 95%; CI 1.09-19.38);
- sexual or physical abuse (OR 1.51-3.49);
- psychological problems: anxiety (OR 2.28; 95% CI 1.41-3.70); depression (OR 2.69; 95% CI 1.86-3.88); multiple somatic problems (OR 4.83; 95% CI 2.50-9.33 and OR 8.01; 95% CI 5.16-12.44): the terms 'hysteria' and 'psychosomatic symptoms' are used but can best be understood as multiple somatic symptoms not associated with or indicative of any serious disease process.

Personality variables, length of education, and marital status were not reliably associated with pelvic pain in women. Interrelationships, such as between history of sexual abuse and depression, for instance, cannot be disentangled from the studies available.

A meta-analysis (15) confirms the reported association in retrospective studies between the report of childhood sexual abuse by adults and persistent pain; often this concerns childhood sexual abuse and pelvic pain (16). However, these studies are retrospective; interestingly, Latthe et al. (14) found poor quality papers were more likely to report this association than better quality ones. The only prospective investigation into the relationship between childhood sexual abuse, physical abuse or neglect, and 'medically unexplained pain' including pelvic pain, used court records concerning sexual abuse before the age of 11 to establish a definite history, comparing those with such a history with demographically matched classmates (17). It concluded that physically and sexually abused individuals were not at risk for increased pain symptoms. Although those individuals with pain problems as adults were more likely to report earlier sexual or physical abuse or neglect, this did not correspond with the established early history of abuse. The correlation between childhood victimisation and pain symptoms is less straightforward than previously thought, and may be more about retrospective explanatory frameworks used by women for pain which is 'medically unexplained' than about occurrence or extent of abuse.

In particular, findings of depression and/or post-traumatic stress disorder in adult women reporting childhood sexual abuse are common, with or without pain. Disentangling the influences and inferences requires prospective study or suitable comparison groups. See Savidge and Slade (1997) (13) for an excellent critique. Within pelvic pain populations, worthwhile studies can be done without comparison. For example, Poleshuck et al. (2005) (18) found that, in women with pelvic pain attending a clinic, the report of physical or sexual abuse in childhood was associated with greater psychological distress than in women without, but there were no differences in pain experience, or physical or social function. In summary, women with pelvic pain often have other 'medically unexplained' symptoms, and current or a lifetime anxiety and depression disorder; they may have a history of physical or sexual abuse in childhood but the significance of this for pelvic pain is unclear.

The report of pelvic pain appears to be more common after rape (19), and recent sexual assault should be considered, particularly if the woman expresses distress.

No studies were found of sexual or physical abuse in childhood and pelvic pain in men.

### *7.4.2* ***Anxiety***

Findings of anxiety are common in samples of women with CPP (20), as are above-threshold scores on screening instruments for post-traumatic stress disorder (21).

In the latter study, higher post-traumatic stress disorder scores were associated with, and contributed

up to 10% unique variance to, poorer health status and more surgery visits. However, anxiety is likely to refer to pain being caused by fears of missed pathology, particularly cancer, and to uncertainties about treatment and the likely prognosis, treated or untreated.

Medical consultations and investigations are particular sources of anxiety, but also a focus of hopes of progress towards resolution of the problem. In a study of women with pelvic pain (22), laparoscopy was followed by a substantial reduction in pain, the size of which was predicted by beliefs about pain and about the seriousness of the woman's condition. Women with higher levels of pain at baseline and higher estimates of the seriousness of their condition reported greater pain reduction.

However, anxieties are not only about the possibility of serious pathology. Stones et al. (2000) reported that women with pelvic pain usually understand that nothing life-threatening has been or is likely to be found, but still want a diagnosis or explanation of the pain (23). Evidence from in-depth studies of women with pelvic pain underline the fact that they want to be assessed in terms of the effects of pain on their lives, to feel understood and have the pain legitimised. They hope for an explanation, and reassurance about the cause of pain and about the possibilities of treating it (24). When they feel disbelieved, and the emphasis is on the absence of physical findings rather than on their experience of pain, they are likely to feel invalidated and to drop out of treatment dissatisfied (25).

There appear to be no similar studies of men's concerns when consulting for persistent pelvic pain.

#### *7.4.3* ***Depression and catastrophising***

Depression or depressed mood is also commonly found in both men and women with persistent pelvic pain (10), and has been reliably associated with urological symptoms (not necessarily painful) (10). However, this association may be no greater than in other persistent pain groups (26), when the comparison group is from a pain sample not from the healthy population.

In addition, there is an important methodological question to be asked of any study using diagnostic or standard assessment instruments, which is how symptoms have been attributed, many of which in depression are understood as neurovegetative signs. The core of clinical depression is negativity about the self. This describes relatively few people with persistent pain, who characteristically state that it is pain, not the self, at the base of their problem (27). Stones et al. (2000) suggested that 'psychological distress may be a consequence and not a cause of persistent pain: while identification of depression is important as part of treatment, caution is required before attribution of causality' (p. 416) (23).

Psychological factors contributing to adjustment to CPP/prostatitis in men was investigated in a large North American cohort study (28). Overall pain severity, sensory, and affective aspects of pain was predicted by catastrophising, particularly the helplessness dimension; pain distress was also predicted by depression. Impact of pain on activity was predicted by urinary symptoms, pain, and taking pain-contingent rest. An earlier study (28) has shown the importance of pain and depression for predicting lower QoL in men with chronic prostatitis/pelvic pain.

#### *7.4.4* ***Impact of pain***

The impact of pain has been investigated almost entirely in terms of sexual problems. Women with pelvic pain reported these at a higher rate than did patients with other chronic pain disorders in a small UK study (29), with most reporting loss of interest in sex, dyspareunia, and pain following sexual intercourse. A much larger sample of women seeking healthcare, three-quarters for pelvic pain, yielded significantly lower QoL scores than age-sex norms and widespread dissatisfaction with sexual activities, which was attributed to the pelvic problems (30). A small study of men with CPP (31) showed that pain severity predicted poorer sexual functioning, although this was less important than relationship variables.

There are short measures available to assess the impact of pain on the patient's life. The Brief Pain Inventory (http://www.mdanderson.org/education-and-research/departments-programs-and-labs/departments-and-divisions/symptom-research/symptom-assessment-tools/BPI_UserGuide.pdf) consists of four 0 to 10 numerical scales for pain (current, average, worst, least) and seven scales for interference with specific aspects of life: general activity, mood, walking ability, normal work, relationships with other people, sleep, and enjoyment of life (32). A higher total score indicates greater pain and interference by pain with life. The EuroQoL is a quality-of-life scale (www.euroqol.org) available in various European languages and free for non-commercial use (33). It provides questions asking about mobility, self-care, pain, usual activities, and psychological status. There are also two questions on the impact of urinary symptoms and one on QoL within the NIH Chronic Prostatitis Symptom Scale, CPSI (34).

### **7.5 Summary: assessment recommendations** (Table 14)

A psychologist (or equivalent) is not required for this level of assessment, but access to regular discussion with a psychologist enables the clinician to interpret better the results of assessment.

### *7.5.1* ***Anxiety***

It is important to obtain the patient's view of what is wrong or of what the patient is worried might be causing pain and other symptoms. Investment in establishing a trusting therapeutic relationship with the patient pays off when these questions are asked. Howard et al. (2003) suggest asking the patient, 'what do you believe or fear is the cause of your pain?' (35).

Investigations and results of examination should be explained clearly, in terms of what they can show, what they did or didn't show, and how this helps the investigations, attempts at diagnosis, or plans for treatment. This requires an adequate model of pain. Brief reassurance alone provides (at best) short-term relief of anxiety, after which the patient returns to seek help with the problem and the anxiety.

### *7.5.2* ***Depression***

If the patient admits a depressed mood and attributes it to pain, it may be that the patient is interpreting information about and experience of pain and other symptoms in catastrophic ways. Good information can counteract this (as in anxiety). It may also be that the pain has had a serious impact on the patient's life; roles and satisfactions are lost because of pain, but can return with effective treatment. Encouragement to consider how to recover valued activities, with or without some pain relief, is helpful but the patient may require advice on how to do this from a pain management team.

### *7.5.3* ***Sexual and physical abuse in childhood***

It is important to consider the possibility of physical and sexual abuse when taking the history, but disclosure can be difficult before a therapeutic relationship is established. It is not clear that pain, which the patient attributes to childhood sexual or physical abuse, should be managed any differently. Any disclosure of current physical or sexual abuse should be referred immediately to appropriate health, social, or welfare services.

## **7.6 Psychological factors in treatment of pelvic pain** (Table 15)

Untreated, there is a significant likelihood of symptom improvement. A follow-up study of women with pelvic pain referred to a clinic showed that 25% reported recovery (nearly half of them total recovery) over the 3 to 4 intervening years. However, neither pain nor distress at baseline, nor intervention received, was found to be associated with recovery (36).

Other sections cover the various physical (surgical, pharmacological, physiotherapeutic) interventions for male and female pelvic pain, and their outcomes. Psychological interventions may be directed:

1. At the pain itself, with the intended outcome of pain reduction and consequent reduction of impact of pain on life, or;
2. At adjustment to pain, with the intended outcome of improved mood and function and reduced healthcare use, with or without pain reduction.

The first category of interventions includes relaxation and biofeedback methods of controlling and decreasing pain by reducing muscle tension. Such methods are being applied to pelvic floor retraining, both in men (37,38) and women, sometimes alongside other physical therapies (see Section 6.5). The only RCT has been of a specific type of cognitively enhanced physical therapy applied to overall muscle tension, not to the pelvic floor. This Norwegian study (39) tested 'mensendieck somatocognitive therapy' combined with normal gynaecological treatment versus gynaecological treatment alone in women with CPP. Pain was reduced by 50% and motor function improved by 10 hours of physical therapy, with particular attention to tension and relaxation, and the thoughts and emotions that interfere with balanced posture and movement.

In the second category of interventions (see above), multicomponent pain management, involving education, physical retraining, behavioural change and increasing activity, relaxation, and cognitive therapy, is often applied to mixed groups of chronic pain patients, including those with pelvic pain, but there have been no RCTs of pelvic pain groups. There is a systematic review and meta-analysis (40), showing good outcome for mixed or back pain groups across pain experience, mood, coping, and activity. There is no reason to believe this does not apply to pelvic pain patients, but a trial of pelvic pain management alone is lacking.

The Cochrane database holds one systematic review and meta-analysis of treatments for pelvic pain, excluding pain due to endometriosis, irritable bowel syndrome, and chronic pelvic inflammatory disease (41). Treatment inclusion was broad: medical, surgical, physical, psychological, lifestyle, and complementary and alternative. Outcomes were mainly pain scores, QoL and use of resources, including health care resources. This review, updated in 2005, includes 14 treatment trials covering pharmacotherapy; surgery; chiropractic; magnet therapy; counselling, psychoeducation, reassurance, and emotional disclosure; and a multicomponent pain management programme. Most trials were small, so the review covers 1,133 patients in all. Nine were of good methodological quality, but outcomes were mainly change in pain and other symptoms, with few including scales for mood (2), pain beliefs (1) or impact of pain (2).

From a psychological point of view, a minority of the trials in the Cochrane systematic review is of interest. The authors conclude in favour of educational counselling combined with ultrasound scan, which

improved pain and mood; and a multidisciplinary rehabilitative approach, including surgery, pharmacotherapy, physiotherapy, and psychosocial intervention, which improved function but not pain. A selective serotonin reuptake inhibitor antidepressant made no improvement in pain but improved function. Consultation using a photograph taken during laparoscopy had no effect; emotional disclosure (a stress reduction method) through writing brought about very small improvement in some pain scores.

It is regrettable that outcome measures correspond relatively poorly between studies with broadly similar aims, i.e. to restore the patient to a more normal lifestyle and better physical and psychological health. A review paper assessing outcome measures for chronic pain clinical trails stresses the significance of measuring mood change. Mood change is a particular issue since, intentionally or not, any intervention, and even a good consultation, can bring about cognitive, emotional, and/or behavioural change. Enabling the patient to understand what is causing the pain, and therefore the implications of the pain for everyday life and longer-term life goals, can be a major influence on the patient's successful management of pain. Furthermore, if all treatments sampled the same domains of pain in their evaluation, comparison across treatments, by medical personnel and by patients, would be more easily achieved (42).

**Table 14: Psychological factors in the assessment of CPP**

| Assessment | LE | GR | Comment |
|---|---|---|---|
| Anxiety about cause of pain:<br>• 'Are you worried about what might be causing your pain?' | 1a | C | Studies of women only: men'sanxieties not studied |
| Depression attributed to pain:<br>• 'How has the pain affected your life?'<br>• 'How does the pain make you feel emotionally?' | 1a | C | Studies of women only: men's anxieties not studied |
| Multiple physical symptoms/ general health | 1a | C | |
| History of sexual or physical abuse | 1a | C | Current/recent abuse may be more important |

**Table 15: Physical and psychological treatment in the management of CPP**

| Treatment | LE | GR | Comment |
|---|---|---|---|
| Tension-reduction; relaxation, for pain reduction | 1b | C | Relaxation +/- biofeedback +/- physical therapy; mainly male pelvic pain |
| Multidisciplinary pain management for well-being | 1a | A | Pelvic pain patients treated with psychology-based pain management; few specific pelvic pain trials |

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# 8. GENERAL TREATMENT OF CHRONIC PELVIC PAIN

There is very little specific evidence for the role of analgesic and co-analgesic drugs in CPP, with one systematic review in women suggesting that further research is required (1). As CPP is thought to be modulated by similar mechanisms to those of somatic, visceral, and neuropathic pain, the evidence below has been derived from the general chronic pain literature. This section has divided the drugs into their broad classes for ease of reading and reference.

Many of the agents will be familiar to chronic pain clinicians and their involvement with difficult cases will help in the development of individualised pain management plans. Some drugs discussed below are best used by clinicians experienced in their use. The use of drugs for specific urogenital conditions is covered by the guidelines for that condition. This chapter looks at the general considerations for patients within the commonly used drug classes.

The evidence grading is the same as elsewhere in the EAU guidelines, looking at outcome of treatment. Recommendations are based on the likely benefit to a patient in terms of pain or improved QoL rather than on the basis of disease modification. Table 16 provides an overview of available treatments together with evidence levels and graded recommendations.

## 8.1 Simple analgesics

### *8.1.1 **Paracetamol***

Paracetamol should be considered on its own. It has analgesic and antipyretic activity and is used in acute and chronic painful conditions (2). There is evidence for its use in somatic pain and arthritic pain in particular (3,4) but the benefits are limited. There is little evidence about its role in CPP.

### *8.1.2 **Acidic antipyretic analgesics***

The classical NSAIDs fall into this group and include salicylic acid. They are known to act on the cyclo-oxygenase (COX) enzyme. The early NSAIDs tended to have little selectivity for COX-2 over COX-1, and are therefore said to be associated with more side effects than the newer COX-2 selective inhibitors. The COX-1 enzyme is mainly involved in normal 'housekeeping' functions, such as mediating gastric mucosal integrity, and renal and platelet function. Blocking the COX-1 enzyme is the cause of the platelet, gastric and renal complications that can occur with NSAIDs. It has been suggested that the COX-2 enzyme is inducible as a result of tissue damage, and that it is the main enzyme involved in inflammation and peripheral sensitisation of nociceptors. As a result, the analgesic efficacy of COX-2 selective drugs should be as good as that of the non-selective drugs. This, however, has been disputed (5). More recent studies and reviews including those form the European and US drug advisory bodies highlight the cardiovascular risks associated with COX-2 selective agents (6-8). The risk for cardiac risk is clear for COX-2 agents and classical NSAIDs may also be incriminated (9). Thus, selective COX-2 agents should not be prescribed in patients with increased risk of cardiovascular disease including congestive cardiac failure.

There is very little evidence for NSAIDs to be used in the management of CPP and even less evidence for COX-2 selective drugs. Most analgesic studies have investigated dysmenorrhoea, in which NSAIDs were found to be superior to placebo and possibly paracetamol (10).

For practical purposes the NSAIDs may be divided into:

- non-selective, low potency (e.g. salicylic acid, ibuprofen, mefenamic acid);
- non-selective, high potency (e.g. ketoprofen, diclofenac, ketorolac);
- COX-2 selective drugs (e.g. celecoxib, etoricoxib).

*8.1.3 Guidelines for use of NSAIDs and COX-2 selective agents*

- Non-selective, low potency NSAIDs should be used in the first instance. They are most likely to be of help if there is an inflammatory component to the pain. More potent NSAIDs should be reserved for those conditions in which the low potency drugs have been tried and failed to produce significant benefit.
- COX-2 selective drugs should be used with caution as an alternative to the non-selective drugs where there is an increased risk of gastric complications. They should be avoided in patients with known cardiovascular disease.
- NSAIDs should be taken with food and consideration must be given to the use of gastric protective agents.
- The benefits of the NSAIDs must be demonstrated to outweigh the risks.
- All NSAIDs are contraindicated in active gastrointestinal ulceration/bleeding and renal disease. They may exacerbate asthma and produce fluid retention.
- Even if stronger analgesics such as opioids are added, the NSAIDs can be continued as they are likely to have a synergistic action improving pain control above and beyond that obtained with opioids alone (11).
- Paracetamol should be considered as an alternative to, or given with, NSAIDs as it is well tolerated with few side effects.

## 8.2 Neuropathic analgesics

### *8.2.1 **Tricyclic antidepressants***

There is very little evidence in CPP for tricyclic antidepressants in humans. What data is available includes these drugs as options in treatment (12-14). A study in cats does suggest that tricyclics may have a role in the management of cystitis (15). Most studies involve neuropathic pain. If there is a suggestion of nerve injury or central sensitisation, the algorithm outlined in Figure 8 should be considered.

Saarto and Wiffen (16) reviewed antidepressants for neuropathic pain. They concluded that tricyclics are effective for neuropathic pain with limited evidence for the selective serotonin reuptake inhibitor antidepressant drugs and insufficient evidence for other antidepressants. The study suggests that HIV-related pain does not respond and further work is required with regard to more specific conditions.

Tricyclic antidepressants tend to be used in lower dosages than those required for treating depression. Amitriptyline is used up to a dose of 150 mg once daily.

### *8.2.2 **Anticonvulsants***

These drugs have been used in the management of pain for many years. Whereas there is little evidence to support the use of anticonvulsants in the management of genitourinary pain, they should be considered if there is a suggestion of neuropathic pain or central sensitisation. There is no role for these drugs in acute pain (17).

Gabapentin has been introduced for pain management and has undergone a systematic review by Wiffen (18). It is said to have fewer serious side effects compaired to the older anticonvulsants and in some countries is licensed for use in chronic neuropathic pain. There are claims that it produces a more natural sleep state at night than antidepressants.

The evidence (for neuropathic pain) does not demonstrate any superiority for gabapentin over carbamazepine (17). The numbers needed to harm (for minor harm) is 2.5 for gabapentin and 3.7 for carbamazepine. Many practitioners, however, would not use carbamazepine as a first-line anticonvulsant in pain management because of its potentially serious side effects (blood, hepatic or skin disorders).

Carbamazepine and other anticonvulsants (e.g. phenytoin or valproate) have been used for neuropathic pain but are best reserved for practioners familiar with their use.

### *8.2.3 **N-methyl-D-aspartate (NMDA) antagonists***

The NMDA receptor channel complex is known to be an important channel for the development and maintenance of chronic pain. It is felt to be particularly important when there is evidence of central sensitisation and opioid tolerance (19-23). These are the phenomena that alter signal transmission within the nervous system so that non-painful stimuli may become painful (allodynia) and pain from a painful stimulus is magnified (hyperalgesia). NMDA antagonists have been used in the management of neuropathic pain (24).

Ketamine has been useful in several chronic pain states including peripheral neuropathies with allodynia, stump and phantom pain, central pain, and cancer-related pain, with and without a neurological component, but its long-term role remains unclear (25).

Ketamine has been used as a general anaesthetic for over 30 years. It has also been used as an intravenous analgesic in burns units and accident and emergency units. Ketamine is thought to act primarily at the NMDA receptor, though it may also have action at sodium channels and opioid (kappa and mu) receptors (23). Difficult urogenital pains may therefore be helped by ketamine if there is evidence of nerve injury or central sensitisation.

Ketamine is not licensed for use in chronic pain and like the opioids has been used as a street drug of

addiction. Ketamine should only be started by an experienced practitioner trained in its use. Similar care to that of opioids must be taken if a patient is to be managed at home.

#### *8.2.4* ***Sodium channel blockade***

In a significant number of patients with urogenital pain, nerve injury and neuropathic changes are thought to play a role. These may be associated with a reduction in some sodium channels and the development of novel sodium channels. As a result, injured afferents become prone to generating more prolonged and higher frequency discharges, with a reduced refractory period. These changes in the characteristics of sodium channels are thought to underlie the mechanisms of mechanosensitivity, thermosensitivity and chemosensitivity (26). They may be involved in some visceral hyperalgesia.

Human studies have demonstrated that intravenous lidocaine reduces neuropathic pain and sensory phenomena, such as allodynia (27). A positive lidocaine challenge may be followed by repeated infusions of lidocaine and the benefit from a single infusion may be prolonged.

A role for the oral analogue, mexiletine, has also to be defined (28); a positive response to intravenous lidocaine does not always indicate that mexiletine will work.

Challapalli et al. have reviewed the role of local anaesthetic agents in neuropathic pain. They are safe and better than placebo and as effective as other analgesics. Further research is needed into specific painful conditions and outcome measures to assess whether pain relief is clinically significant (29). Again, these agents are being used outside their licence and are best instituted by clinicians familiar with them.

## 8.3 Opioids

There is now a general acceptance that opioids have a role in the management of chronic non-malignant pain (30). Studies have tended to be short term and a systematic review concluded that further research is required into the long-term use of opioids (31). The use of opioids in urogenital pain is poorly defined. Their use in neuropathic pain remains equivocal but a meta-analysis suggests clinically important benefits (32). The authors emphasise that more research is needed ino long-term outcomes and side effects. There is also evidence suggesting that opioids may produce different responses with different types of pain (33).

Generally, slow-release preparations are preferred for chronic pain. Side effects are common but rarely serious. If, however, a particular agent causes side effects and clinical benefit, rotating to another opioid may be beneficial. Titrating the dose should be closely monitored to assess both benefit and side effects. Rotating from one opioid to another also requires close monitoring as there are no exact dose equivalents. General guidelines for the use of opioids in chronic pain have been published (34,35). The following guidelines are suggested, but the clinician involved should be familiar with the use of opioids in non-malignant pain.

#### *8.3.1* ***Guidelines for the use of opioids in chronic/non-acute urogenital pain***

1. All other reasonable treatments must have been tried and failed.
2. The decision to instigate long-term opioid therapy should be made by an appropriately trained specialist in consultation with another physician (preferably the patient's family doctor).
3. Where there is a history or suspicion of drug abuse, a psychiatrist or psychologist with an interest in pain management and drug addiction should be involved.
4. The patient should undergo a trial of opioids.
5. The dose required needs to be calculated by careful titration.
6. The patient should be made aware (and possibly give written consent):
   - I. That opioids are strong drugs and associated with addiction and dependency.
   - II. The opioids will normally only be prescribed from one source (preferably the family doctor).
   - III. The drugs will be prescribed for fixed periods of time and a new prescription will not be available until the end of that period.
   - IV. The patient will be subjected to spot urine and possibly blood checks to ensure that the drug is being taken as prescribed and that non-prescribed drugs are not being taken.
   - V. Inappropriate aggressive behaviour associated with demanding the drug will not be accepted.
   - VI. Hospital specialist review will normally occur at least once a year.
   - VII. The patient may be requested to attend a psychiatric/psychology review.
   - VIII. Failure to comply with the above may result in the patient being referred to a drug dependency agency and the use of therapeutic, analgesic opioids being stopped.
7. Morphine is the first-line drug, unless there are contraindications to morphine or special indications for another drug. The drug should be prescribed in a slow-release/modified release form. Short-acting preparations are undesirable and should be avoided where possible. Parenteral dosing is undesirable and should be avoided where possible.

### *8.3.2* ***Morphine***

There is no compelling evidence that one opiate is better than another. Morphine is the traditional gold standard and the opioid many physicians are most familiar with. In an acute situation, the daily morphine requirement may be calculated by titration of rapid-release morphine. In chronic pain situations, starting with a low dose of slow-release morphine and titrating the dose every 3 days to 1 week is adequate.

### *8.3.3* ***Transdermal fentanyl***

Transdermal fentanyl is used when oral absorption is restricted or when the patient suffers with intolerable side effects from other opioids. Patients with rapid bowel transit times (e.g. iliostomy) may find transdermal preparations beneficial. Patches are generally changed every 72 hours.

### *8.3.4* ***Methadone***

Methadone is a strong analgesic with a long track record of use. It has opioid and NMDA-antagonistic activity (24). It is suggested that further work is needed to look at its role in neuropathic pain (33). Its use is supported as a fourth-line agent in treating neuropathic pain in a consensus document by the Canadian Pain Society (36). Rotating from other opioids to methadone is not an exact science because dosing ratios are not clearly understood (37). Metabolite accumulation and cardiac side effects can be a problem. A practitioner familiar with its use as an analgesic should prescribe methadone.

### *8.3.5* ***Oxycodone***

A slow-release preparation is available with evidence suggesting its benefit in neuropathic pain. Evidence suggests that oxycodone has benefits over morphine in some experimentally induced visceral pains (38). The pharmacology of oxycodone is different to morphine in experimental neuropathic states (39). An RCT has also demonstrated a role for oxycodone in neuropathic pain (diabetic neuropathy) (40).

### *8.3.6* ***Other opioids and opioid-like agents***

Other opioids are available as slow- or modified-release preparations. They may be useful for opiate rotation if side effects or tolerance is a problem.

Buprenorphine and pentazocine both have agonist and antagonist properties and can induce withdrawal symptoms in patients used to opioids. Naloxone may only partly reverse respiratory depression. Buprenorphine topical patches are now available and may offer a similar advantage to topical fentanyl.

Codeine and dihydrocodeine are effective for the relief of mild-to-moderate pain. They are limited by side effects (notably constipation) and genetic variance of metabolism that affects analgesic efficacy. Approximately 10% of individuals will not effectively metabolise codeine resulting in inadequate analgesia (41).

Tramadol produces analgesia by two mechanisms, an opioid effect and an enhancement of serotoninergic and adrenergic pathways (42,43). It has fewer typical opioid side effects (especially less respiratory depression, less constipation and less addiction potential) and is available in a slow-release preparation. A Cochrane review suggests that there is a role for tramadol in neuropathic pain management (44).

**Figure 8: Guidelines for the use of neuropathic analgesics**

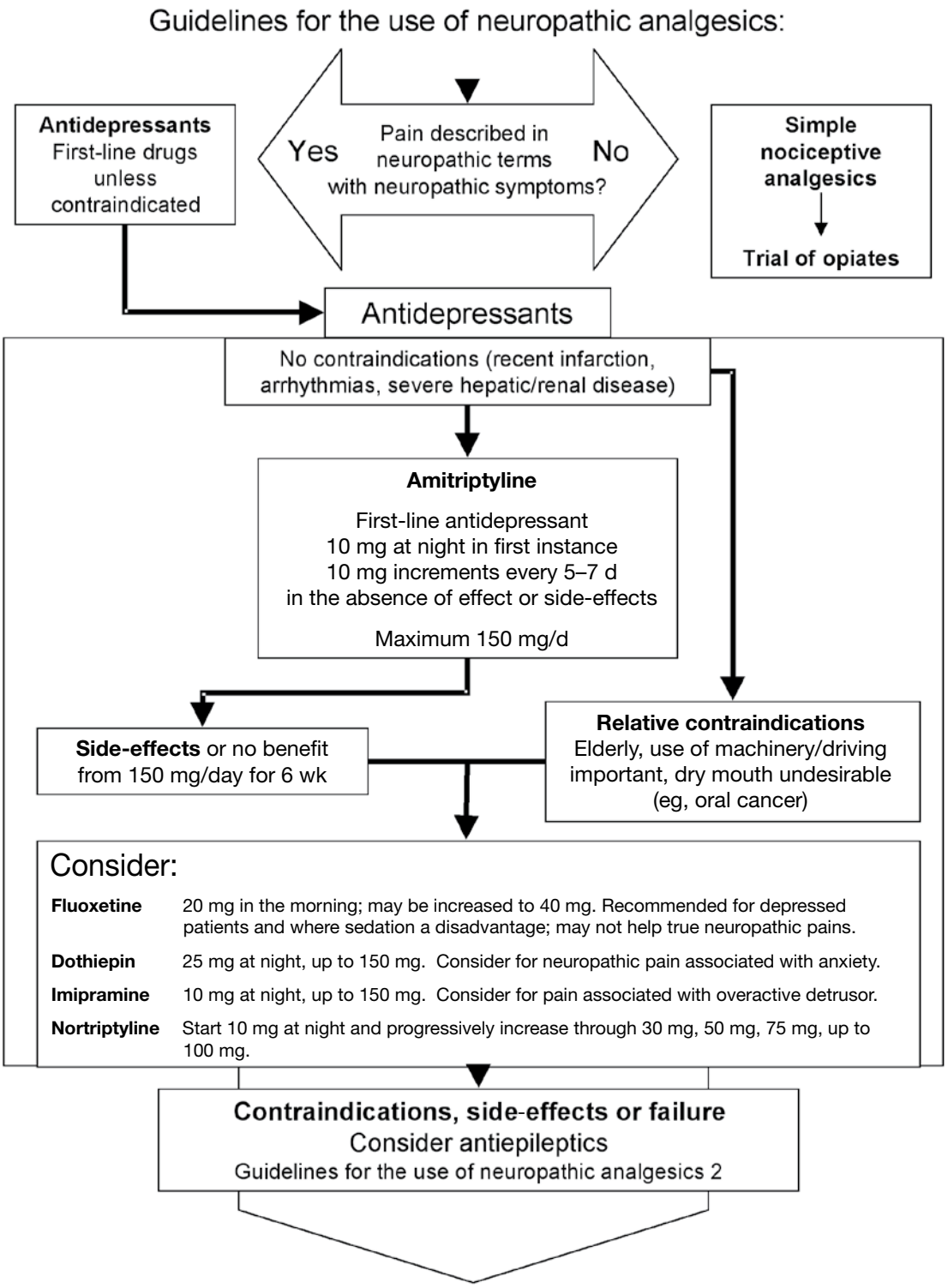

**Table 16: Pharmacological treatment of CPP**

| Type of pain | LE | GR | Comment |
|---|---|---|---|
| Paracetamol for somatic pain | 1b | A | Benefit is limited and based on arthritic pain |
| COX-2 antagonists | 1b | A | Avoid in patients with cardiovascular risk factors |
| NSAIDs for dysmenorrhoea | 1a | B | Better than placebo but unable to distinguish between different NSAIDs |
| Tricyclic antidepressants | 1a | A | Neuropathic pain |
| Tricyclic antidepressants | 3 | C | Evidence suggests pelvic pain is similar to neuropathic pain |
| Anticonvulsants Gabapentin | 1a | A | For neuropathic pain |
| Opioids for chronic non malignant pain | 1a | A | Limited long-term data<br>Should only be used by clinicians experienced in their use |
| Opioids for neuropathic pain | 1a | A | Benefit is probably clinically significant<br>Caution with use, as above |

*COX = cyclo-oxygenase; NSAID = non-steroidal anti-inflammatory drug.*

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### 8.5 Nerve blocks

Neural blockade for pain management is usually carried out by a consultant in pain medicine with an anaesthetic background. Textbooks have been written on the techniques employed and individual specialists using neural blockade must be well versed in assessment of the patient, the indications for specific procedures, and the general and specific risks associated with the procedures, as well as possible advantages.

Procedures may be performed for diagnostic reasons, therapeutic benefit or possibly both. Diagnostic blocks can be difficult to interpret and a clear understanding of the many mechanisms by which a block may be acting must be understood. Temporary but consistent responses to nerve blocks may lead a specialist to proceed with a neurolytic nerve block or to a pulsed radiofrequency neuromodulation procedure. Neurolytic nerve blocks are rarely indicated for a benign process, and to proceed with a neurolytic nerve block may result in disastrous results.

Published guidelines emphasise that all nerve blocks should be performed with appropriate attention to safety, including the presence of skilled support staff and appropriate monitoring and resuscitation equipment. The use of block needles, nerve location devices and imaging (i.e. X-ray image intensifier, ultrasound or CT) appropriate for the procedure is essential.

The evidence base for nerve blocks is not strong (1-5), but suggests that:

- Peripheral nerve blocks, such as ilioinguinal/iliohypogastric/genitofemoral, may be useful in the management of neuropathic pain associated with nerve damage, such as following hernia repairs.
- Blocks around the spermatic cord may be useful diagnostically prior to testicular denervation.
- Lumbar (L1) sympathetic blocks may be helpful in the management of testicular pain, renal pain and possibly a range of pelvic pain conditions with afferents that pass via the L1 level.
- Pudendal nerve blocks may be useful in the management of pudendal nerve injury related pain and possibly pelvic floor muscle spasm. Where pudendal neuralgia is suspected, pudendal nerve blocks may have a diagnostic role. Multiple other nerves close to the pudendal nerve may also be associated with neuropathic symptoms and differential nerve blocks using neurotracing may be of help in understanding the process'.
- Pre-sacral blocks and the ganglion Impar block may have a role in the management of pelvic pathology, particularly cancer pain.
- Sacral root nerve blocks may be helpful in the diagnosis of those conditions that might respond to sacral root stimulation.

The above list is not exhaustive and readers are advised to look at the major textbooks in this area (6).

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## 8.6 Transcutaneous electrical nerve stimulation (TENS)

The rationale behind using surface electrical nerve stimulation to relieve pain is the stimulation of myelinated afferents and thus activation of segmental inhibitory circuits. Urinary frequency may also be reduced. The favoured explanation of TENS draws on the gate-control theory of pain (1). Nevertheless, TENS may directly elicit reflex effects and influence autonomous functions. For example, relaxation of the bronchial muscles (2), the coronary arteries (3) and the urinary bladder have been observed in response to TENS (4).

TENS involves the use of a pulse generator with an amplifier and electrodes. The pulses may be delivered continuously or as trains of varying duration. Continuous stimulation seems to be preferable when treating pain.

The stimulation pulses used may have different properties. Square-wave pulses are notably effective in activating the nerve fibres and are most frequently used. Biphasic pulses are preferable as the zero net charge flow of this pulse helps to reduce electrochemical reactions at the electrode contact sites. Nevertheless, technical simplification has led to the use of unipolar rectangular pulses in many devices, apparently with few complications. The stimulus intensity required to activate a peripheral nerve varies with the pulse duration. In terms of charge transfer for a threshold effect, short pulses (0.1 ms) are most effective, but at the expense of higher pulse amplitudes (5). For most applications of nerve stimulation, the pulse frequency is a crucial variable. The frequencies used during TENS vary widely, from 1 Hz to 100 Hz. There are no systematic evaluation data to guide optimal electrical settings for TENS in urological practice.

Standard electrodes are made of carbon rubber. These are strong, flexible, durable, and cheap, but must be attached by adhesive tape. Self-adhesive electrodes have been developed. These are especially advantageous for people with sensitive skin, but they are expensive. The size of the electrode has a bearing on the current density – a minimum of 4 $cm^2$ has been recommended for TENS (6). The electrode-skin impedance should be reduced by application of a generous layer of electrolyte gel to promote good contact under the entire electrode.

The stimulus intensity required to elicit sensory appreciation varies between individuals. The maximum

tolerable intensity just below pain threshold should be used. While it is plausible that electrode positioning will affect the result of treatment, this property has not been evaluated. In BPS/IC, suprapubic (7,8), vaginal-anal (4,9) and tibial nerve sites (10,11) have been tested, all with some success.

Counselling of the patient before the start of the treatment is necessary. A specially trained nurse with the time necessary to communicate the technical instructions is a good option. The patient should be confident with the feeling of strong stimulation and view self-treatment without fear. The induction time for TENS to produce analgesia varies widely. The effect is cumulative. Since onset and progression are usually rather slow in IC, the standard recommendation so far has been 0.5-2 hours of treatment twice daily. The duration of an individual treatment session depends on the severity of pain.

#### *8.6.1* ***Results of suprapubic TENS in BPS/IC***

Observations are scant. In the largest study published so far, 60 patients, 33 with classic IC and 27 with non-ulcer disease, were treated by suprapubic TENS (6). The electrodes were positioned about 10-15 cm apart, immediately above the pubic symphysis. They were attached by a long strip of adhesive tape going halfway around the body to enable the patient to be ambulant during stimulation. Follow-up ranged from 9 months to 17 years. Patients who responded reported more marked effects on bladder pain than on micturition frequency. Of the patients with classic IC, 54% were helped by the treatment. The outcome of TENS was less favourable in non-ulcer IC. Of 27 patients with non-ulcer IC, only 26% benefited from the treatment.

The present experience of electrical stimulation is based on open studies. There are difficulties in designing controlled studies of TENS, since the treatment is based on administration of stimulation of high intensity, at specific sites, over a very long period of time. Another problem is that it is not possible to measure pain precisely. Therefore, it is difficult to assess the efficacy of TENS in BPS/IC with accuracy.

Several controlled studies of post-operative pain have shown TENS to be superior to sham stimulation (12). TENS has also been shown to reduce the amount of halothane required to maintain adequate anaesthesia during hand surgery in unconscious patients, in whom psychological influences have been eliminated (13). The beneficial effect of TENS on classic IC clearly exceeds the level of the placebo effect observed in drug studies of IC (54% versus 13-20%) (14,15).

### 8.7 Sacral neuromodulation in pelvic pain syndromes

Sacral neuromodulation (SNS) has been shown to have benefits in patients with refractory motor urge incontinence (16,17), urinary retention, and CPP (18-20). Neuropathic pain and complex regional pain syndromes may also be treated successfully with neurostimulation applied to dorsal columns and peripheral nerves (21).

The mechanisms of action are the subject of many hypotheses, with very little evidence to support any particular one. The hypotheses include:

- blocking of pain transmission by direct effects in the spinothalamic tracts;
- activation of descending inhibitory pathways;
- effects on central sympathetic systems;
- segmental inhibition through coarse fibre activation and brain stem loops;
- inhibition by increasing gamma-aminobutyric acid levels in the dorsal horn;
- thalamocortical mechanisms masking the nociceptive input (21,22).

Sacral root neuromodulation was introduced in the mid-1980s as a means of regaining bladder control in the face of disturbed function (23). Based on the neurophysiology of the bladder and urethra, it is a minimally invasive tool that bridges the gap between conservative options and invasive surgical procedures. The data on clinical applications are drawn exclusively from observational studies.

Sacral root neuromodulation draws on the observation that electrical stimulation of sacral nerves modulates neural reflexes of the pelvis (24). Acceptable application of the stimuli is the challenge. Neurostimulation of S3 or S4 sacral nerves using a transforamenal approach is a viable option for patients with refractory urinary voiding disorders.

Recently, SNS has also been investigated in IC. In an initial report on six patients (25), percutaneous neurostimulation significantly improved frequency, pain and urgency towards normal values, while urinary markers for IC were normalised. Maher et al. (26) reported a favourable response with significant improvement in pelvic pain, daytime frequency, nocturia, urgency and voided volume in 15 women with IC.

Because pelvic pain syndromes are viewed as a manifestation of disturbed neural function, patients with refractory pelvic floor dysfunction and pelvic pain have been treated with SNS and benefit has been reported (27). Sacral neuromodulation for CPP has been based on promising data from pilot studies and prospective, placebo-controlled studies are now justified.

### *8.7.1* ***References***


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# 9. ABBREVIATIONS USED IN THE TEXT

*This list is not comprehensive for the most common abbreviations*

| | |
|---|---|
| ABP | acute bacterial prostatitis |
| BCG | Bacillus Calmette-Guérin |
| BPS | bladder pain syndrome |
| BTX-A | Botulinum Toxin A |
| CBP | chronic bacterial prostatitis |
| CFU | colony-forming units |
| CNS | central nervous system |
| COX | cyclo-oxygenase |
| CP/CPPS | chronic prostatitis associated with chronic pelvic pain syndrome |
| CPP(S) | chronic pelvic pain (syndrome) |
| CPSI | chronic Prostatitis Symptom Index |
| CT | computed tomography |
| CyA | cyclosporin A |
| DMSO | dimethyl sulphoxide |
| DRE | digital rectal examination |
| DRG | dorsal root ganglia |
| EAU | European Association of Urology |
| ED | erectile dysfunction |
| EMDA | electromotive drug administration |
| EPS | expressed prostatic secretions |
| ESSIC | European Society for the Study of IC/PBS |
| FD | first desire to void |
| GAG | glycosaminoglycan |
| GI | gastrointestinal |
| GR | grade of recommendation |
| HBO | hyperbaric oxygen |
| IASP | International Association for the Study of Pain |
| IC | interstitial cystitis |
| ICA | Interstitial Cystitis Association |
| ICDB | Interstitial Cystitis Data Base |
| ICS | International Continence Society |
| ICSI | Interstitial Cystitis Symptom Index (also known as the O'Leary Sant Symptom Index) |
| IL-6 | interleukin-6 |
| I-PSS | International Prostate Symptom Score |
| ISSVD | International Society for the Study of Vulvovaginal Disease |
| LE | level of evidence |
| LHRH | luteinising hormone releasing hormone |
| LUT | lower urinary tract |
| LUTS | lower urinary tract symptoms |
| MRI | magnetic resonance imaging |
| ND | normal desire to void |
| Nd-YAG | neodymium-yttrium-aluminium-garnet |
| NIDDK | National Institute of Diabetes and Digestive and Kidney Diseases |
| NIH | National Institutes of Health |
| NMDA | N-methyl-D-aspartate |
| NSAIDs | non-steroidal anti-inflammatory drugs |
| PBS | painful bladder syndrome |
| PCA | prostate cancers |
| PFM | pelvic floor muscles |
| PPMT | pre- and post-massage test |
| PPS | prostate pain syndrome |
| PSA | prostate specific antigen |
| PUGO | IASP special interest group, Pain of Urogenital Origin |
| PVR | post-void residual urine |
| QoL | quality of life |
| RCT | randomised controlled trial |
| RTX | resiniferatoxin |

| | |
|---|---|
| SNS | sacral neuromodulation |
| SPIN | Specialists in Pain International Network |
| TENS | transcutaneous electrical nerve stimulation |
| TRUS | transrectal ultrasonography |
| TUNA | transurethral needle ablation of the prostate |
| TUR | transurethral resection |
| VAS | visual analogue scale |
| VB2 | pre-prostatic massage urine |
| VB3 | post-prostatic massage urine |
| VIP | vasoactive intestinal peptide |
| WBC | white blood cells |
| WHO | World Health Organization |

**Conflict of interest**
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