Guidelines on Chronic Pelvic Pain

D. Engeler (chair), A.P. Baranowski, J. Borovicka, P. Dinis-Oliveira, S. Elneil, J. Hughes, E.J. Messelink, A. van Ophoven, Y. Reisman, A.C. de C. Williams

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1. INTRODUCTION

1.1 The Guideline

Chronic pelvic pain (CPP) is a prevalent condition which can present a major challenge to health care providers due to its complex aetiology and poor response to therapy.
Chronic pelvic pain is a multifactorial condition and therefore, quite often, poorly managed. Management requires knowledge of all pelvic organ systems and their association with other systems and conditions, including musculoskeletal, neurologic, urologic, gynaecologic and psychological aspects, promoting a multidisciplinary approach.

The European Association of Urology (EAU) Guidelines Working Group for Chronic Pelvic Pain prepared this guidelines document to assist urologists and medical professionals from associated specialties, such as gynaecologists, psychologists, gastroenterologists and sexologists, in assessing the evidence-based management of CPP and to incorporate evidence-based recommendations into their every-day clinical practice.

*1.1.1 **Panel composition***

The panel of experts responsible for this document include urologists, a neuro-urologist, consultants in pain medicine, a gynaecologist, a psychologist, a gastroenterologist and a sexologist.

*1.1.2 **Publication history***

The EAU Guidelines on Chronic Pelvic Pain were first published in 2003 (1) which formed the basis of a scientific publication in European Urology in 2004 (2). Also, in the 2003 edition the concept of Chronic Pelvic Pain Syndromes (CPPS) was introduced, which is now referred to as “pain as a disease process”.

Partial updates of the CPP guidelines were published in 2008 and formed the basis for another scientific publication in European Urology in the year 2010 (3,4).

For the update in 2012 the panel focussed on:

1. restructuring the text to emphasise the significance of holistic management of CPP;
2. addressing the changes in the management of CPPS based on the concept of pain as a disease process.

A complete update of the guidelines is foreseen in 2014.

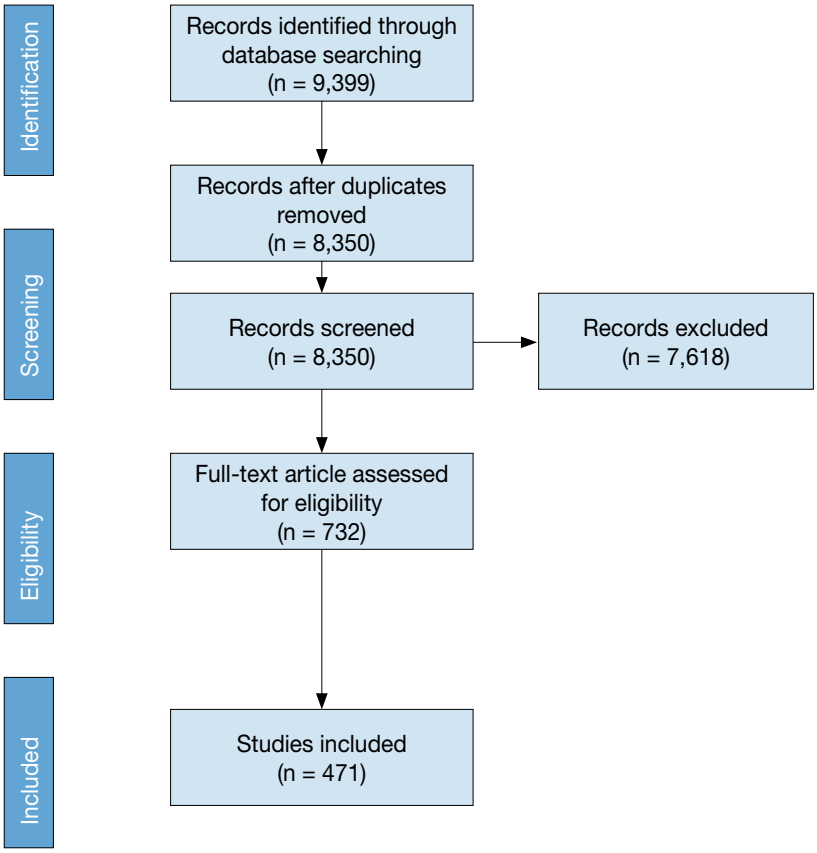
As a result, two new chapters were added; Chapter 5 ‘Gastrointestinal aspects of chronic pelvic pain’ and Chapter 7 ‘Sexological aspects of chronic pelvic pain.

A quick reference document presenting the main findings of these CPP guidelines (pocket guidelines) is also available and has been updated. All texts, alongside scientific publications, can be viewed and downloaded for personal use at the EAU website: http://www.uroweb.org/guidelines/online-guidelines/.

1.2 Methodology

The full text update is based on a systematic review of literature using the Embase and Medline databases, the Cochrane Central Register of controlled trials and the PsycInfo and Bandolier databases to identify the best evidence from RCTs, Level of Evidence 1 (LE: 1), according to the rating schedule adapted from the Oxford Centre for Evidence-based Medicine Levels of Evidence (Table 1) (5). Where no (LE: 1) literature could be identified the search was moved down to the next lower level on the rating scale. Extensive use of free text ensured the sensitivity of the searches, resulting in a substantial body of literature to scan. Searches covered the period January 1995 and May 2011 and were restricted to English language publications.

Flowdiagram update procedure



*1.2.1 Level of evidence and grade of guideline recommendations**

References used in the text have been assessed according to their level of evidence (Table 1), and recommendations have been graded (Table 2) according to the Oxford Centre for Evidence-based Medicine Levels of Evidence (5). 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. (5)*

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 (6-8).

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. (5)*

1.2.2 ***Formal review***

A formal review was carried out prior to publication by a multidisciplinary team of international experts, covering the different fields of expertise described in these guidelines.

1.3 Acknowledgements

The expert panel should like to express their gratitude to professor Magnus Fall, former chairman and patriarch of the CPP panel who established the foundation of these guidelines, the current expert panel can now build on.

The support provided by research scientist Drs. J. Krabshuis has proved to be highly valuable in enhancing the methodological quality of this publication.

1.4 References

1. Fall M, Baranowksi AP, Fowler CJ, et al. EAU Guidelines on Chronic Pelvic Pain 2003. http://www.uroweb.org/guidelines/online-guidelines/
2. Fall M, Baranowski AP, Fowler CJ, et al. EAU Guidelines on Chronic Pelvic Pain. Eur Urol 2004;46:681-689. http://www.uroweb.org/guidelines/online-guidelines/
3. Fall M, Baranowksi AP, Elneil S, et al. EAU Guidelines on Chronic Pelvic Pain 2010. http://www.uroweb.org/guidelines/online-guidelines/
4. Fall M, Baranowski AP, Elneil S, et al. EAU guidelines on chronic pelvic pain. Eur Urol. 2010 Jan;57(1):35-48 http://www.ncbi.nlm.nih.gov/pubmed/19733958
5. Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2009). Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998. Updated by Jeremy Howick March 2009. http://www.cebm.net/index.aspx?o=1025 [Access date November 2012]
6. Atkins D, Best D, Briss PA, et al. GRADE Working Group. Grading quality of evidence and strength of recommendations. BMJ 2004 Jun 19;328(7454):1490. http://www.ncbi.nlm.nih.gov/pubmed/15205295
7. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidenceand strength of recommendations. BMJ 2008;336(7650):924-6. http://www.ncbi.nlm.nih.gov/pubmed/18436948
8. Guyatt GH, Oxman AD, Kunz R, et al. GRADE Working Group. Going from evidence torecommendations. BMJ 2008 May 10;336(7652):1049-51. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2376019/?tool=pubmed

2. CHRONIC PELVIC PAIN

2.1 Introduction to chronic urogenital pain syndromes

Over the years much of the focus for CPP has been on peripheral-end-organ mechanisms, such as inflammatory or infective conditions. However, both animal and clinical research have indicated that many of the mechanisms for the CPP syndromes are based within the central nervous system (CNS). Although a peripheral stimulus such as infection may initiate the start of a CPP condition, the condition may become self-perpetuating as a result of CNS modulation, independent of the original cause. As well as pain, these central mechanisms are associated with several other sensory, functional, behavioural and psychological phenomena. It is this collection of phenomena that forms the basis of the pain syndrome diagnosis and individual phenomena need to be addressed in their own right through multispecialty and multidisciplinary care.

Although ongoing peripheral organ pathology can produce persistent and chronic pain, the main focus of these guidelines is on CPP syndromes in which no peripheral ongoing pathology (such as infection or neoplastic disease) is detected. The main exception is when pain is due to peripheral nerve damage, which will be discussed in chapter 6.

2.2 Pain mechanisms - pain as a disease process

Chronic pelvic pain mechanisms may involve:

1. Ongoing acute pain mechanisms (1) (such as those associated with inflammation or infection), which may involve somatic or visceral tissue.
2. Chronic pain mechanisms, which especially involve the CNS (2).
3. Emotional, cognitive, behavioural and sexual responses and mechanisms (3-6).These are covered in chapter 7 and 8.

Table 3 illustrates some of the differences between the somatic and visceral pain mechanisms. They underlie some of the mechanisms that may produce the classical features of visceral pain; in particular, referred pain and hyperalgesia.

Table 3: Comparison between visceral and somatic pain

	Visceral pain	**Somatic pain**
Effective painful stimuli	Stretching and distension, producing poorly localised pain.	Mechanical, thermal, chemical and electrical stimuli, producing well localised pain.
Summation	Widespread stimulation produces significantly magnified pain.	Widespread stimulation produces a modest increase in pain.
Autonomic involvement	Autonomic features (e.g., nausea and sweating) frequently present.	Autonomic features less frequent.
Referred pain	Pain perceived at a site distant to the cause of the pain is common.	Pain is relatively well localised but well recognised.
Referred hyperalgesia	Referred cutaneous and muscle hyperalgesia is common, as is involvement of other visceral organs.	Hyperalgesia tends to be localised.
Innervation	Low density, unmyelinated C fibres and thinly myelinated A∂ fibres.	Dense innervation with a wide range of nerve fibres.
Primary afferent physiology	Intensity coding. As stimulation increases afferent firing increases with an increase in sensation and ultimately pain.	Two fibre coding. Separate fibres for pain and normal sensation.
Silent afferents	50-90% of visceral afferents are silent until the time they are switched on. These fibres are very important in the central sensitisation process.	Silent afferents present, but form a lower percentage.

Central mechanisms	Play an important part in the hyperalgesia, viscero-visceral, viscero-muscular and musculo-visceral hyperalgesia. Sensations not normally perceived become perceived and non-noxious sensations become painful.	Responsible for the allodynia and hyperalgesia of chronic somatic pain.
Abnormalities of function	Central mechanisms associated with visceral pain may be responsible for organ dysfunction.	Somatic pain associated with somatic dysfunction, e.g., muscle spasm.
Central pathways and representation	As well as classical pathways, there is evidence for a separate dorsal horn pathway and central representation.	Classical pain pathways.

2.2.1 Ongoing peripheral visceral pain mechanisms as a cause of CPP

In most cases of CPP, ongoing tissue trauma, inflammation or infection is not present (7-10). However, conditions that produce recurrent trauma, infection or ongoing inflammation may result in CPP in a small proportion of cases. It is for this reason that the early stages of assessment include looking for these pathologies (11). Once excluded, ongoing investigations for these causes are rarely helpful and indeed may be detrimental.

When acute pain mechanisms are activated by a nociceptive event, as well as direct activation of the peripheral nociceptor transducers, sensitisation of those transducers may also occur, thus magnifying the afferent signalling. Afferents that are not normally active may also become activated by the change, that is, there may be activation of the so-called silent afferents. Although these are mechanisms of acute pain, the increased afferent signalling is often a trigger for the chronic pain mechanisms that maintain the perception of pain in the absence of ongoing peripheral pathology (see below) (12,13).

There are a number of mechanisms by which the peripheral transducers may exhibit an increase in sensibility.

1. Modification of the peripheral tissue, which may result in the transducers being more exposed to peripheral stimulation.
2. There may be an increase in the chemicals that stimulates the receptors of the transducers (14).
3. There are many modifications in the receptors that result in them being more sensitive.

In general, the effect of 1 and 2 is to lower the threshold and the effect of 3 is to increase responsiveness to external stimuli.

Some of the chemicals responsible for the above changes may be released from those cells associated with inflammation, but the peripheral nervous system may also release chemicals in the form of positive and inhibitory loops (Table 4) (15).

Table 4: Mechanisms in the periphery that affect nociceptor response to a nociceptive stimulus

Nerve growth factor (NGF)	May activate primary afferents directly, but also indirectly such as through bradykinin (16). The result is an increase in response of the primary afferents, with multiple action potentials being generated in response to a stimulus, as opposed to just one or two. The TrkA-NGF complex formed on the afferent neurons may also be transmitted centrally where it may alter gene expression. Such long-term gene modification may underlie some of the mechanisms of chronic NGF-induced hypersensitivity.
Adenosinetriphosphate (ATP)	Is thought to be released in increased amounts from certain viscera when stimulated by noxious stimuli. As well as this increased ATP producing an increased stimulation of its receptors, when inflammation is present, the ATP receptors have their properties changed so that there is an increased response per unit of ATP contributing to the nociceptor activation. ATP is thought to act on P2X3 purine receptors, which are found on visceral afferents and small-diameter dorsal root ganglion (DRG) neurons.
Substance P and other neurokinins (17)	Act on afferent tachykinin receptors, such as TRPV1, which is a transducer for noxious heat and protons, and are thought to play a primary role in inflammatory hyperalgesia.

Voltage-gated ion channels	E.g., tetrodotoxin-resistant sodium channel, NaV1.8 are also implicated in peripheral sensitisation. These channels open or close in response to changes in membrane potential. Changes in potassium and calcium voltage-gated channels may also underlie a part of the mechanism responsible for peripheral sensitisation.
Second messenger pathways	Within the primary afferents enable amplification of peripheral messages that they receive. In general, these pathways are balanced by others that are responsible for reducing any activation. During chronic pain, these mechanisms may become imbalanced.

2.2.2 ***Central sensitisation - spinal and higher mechanisms of visceral pain***

There are essentially three processes at the spinal cord level that are involved in central sensitisation (17). Changes in existing protein activity (post-translational processing) are the earliest (within minutes); however, changes in genetic transcription of proteins and even structural changes in neuron connectivity may also have roles to play. These latter changes may occur within days (18).

The chemicals involved in the early phase include several neurotransmitters such as glutamate, substance P, calcitonin gene-related peptide (CGRP), prostaglandin E2 and brain-derived neurotrophic factor (BDNF) (15).

Increased levels of glutamate, due to recurrent afferent nociceptive fibre activity, remove the magnesium ion block of N-methyl-D-aspartate (NMDA). This allows calcium ions to enter the secondary afferents with enhanced depolarisation. Glutamate also binds to amino-methylene-phosphonic acid (AMPA), which may be another pathway by which it increases intracellular calcium. Other transmitters/modulators released centrally include: substance P, which acts on neural kinin receptors; PGE2, which binds to endogenous prostanoid receptors; and BDNF, which acts on tyrosine kinase B receptors and all of these may also increase intracellular calcium.

The calcium ions act to lower the threshold for second-order neuron firing, with increased signalling being transmitted to the higher centres. The second important feature of this increase in calcium ions is inpost-translational processing; this usually involves the addition of phosphate groups to amino acids by kinases. Phosphorylation can dramatically alter the properties of a protein, typically lowering the threshold at which channels open, but also, the channels remain open for longer. The result is that a stimulus produces a magnified evoked response in these neurons.

2.2.3 ***Spinal mechanisms and visceral hyperalgesia***

Central sensitisation (18) is responsible for a decrease in threshold and increase in response duration and magnitude of dorsal horn neurons. It is associated with an expansion of the receptive field. As a result, sensitisation increases signalling to the CNS and amplifies what we perceive from a peripheral stimulus. As an example, for cutaneous stimuli, light touch would not normally produce pain, however, when central sensitisation is present, light touch may be perceived as painful (allodynia). In visceral hyperalgesia (so called because the afferents are primarily small fibres), visceral stimuli that are normally subthreshold and not usually perceived may be perceived. For instance, with central sensitisation, stimuli that are normally subthreshold may result in a sensation of fullness and a need to void the bladder or to defecate. Stimuli normally perceived may be interpreted as pain and stimuli that are normally noxious may be magnified (true hyperalgesia) with an increased perception of pain. As a consequence, one can see that many of the symptoms of the bladder pain syndrome (BPS) (formally known as interstitial cystitis (IC) and irritable bowel syndrome (IBS)) may be explained by central sensitisation. A similar explanation exists for the muscle pain of fibromyalgia.

2.2.4 ***Supraspinal modulation of pain perception***

It is important to appreciate that nociception is the process of transmitting to centres involved in perception information about a stimulus that has the potential to cause tissue damage. Pain is far more complex and involves activation of the nociceptive pathways but also the emotional response. Pain is defined by the International Association for the Study of Pain (IASP) as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (19). The brain may affect the modulation of pain pathways at the spinal cord level.

2.2.5 ***Higher centre modulation of spinal nociceptive pathways***

It is now well accepted that there are both descending pain-inhibitory and descending pain-facilitatory pathways that originate from the brain (20).

The midbrain periaqueductal grey (PAG) plays an important part in spinal modulation. It receives inputs from centres associated with thought and emotion. Projections from the PAG (via several relay systems) to the dorsal horn can inhibit nociceptive messages from reaching conscious perception by spinal mechanisms. The PAG and its associated centres may also be involved in diffuse noxious inhibitory control (DNIC). DNIC is when a nociceptive stimulus, in an area far from the receptive fields of a second nociceptive stimulus, can prevent or reduce pain from that second area. This is thought to be the mechanism for the paradigm of counter-irritation.

Several neurotransmitters and neuromodulators are involved in descending pain-inhibitory pathways. The main contenders are the opioids, 5-hydroxytryptamine and noradrenaline.

The pathways and chemicals for the facilitatory modulation are even less well understood, but the mechanisms are well accepted.

2.2.6 ***Neuromodulation and psychology***

Psychological processes of emotions, thought and behaviour involve networks rather than distinct centres. Some of these processes are sophisticated and others fundamental in evolutionary terms, and their interaction with pain processing is complex. As indicated above, many of the areas involved in relevant psychological processes interact with the PAG, and this is therefore one mechanism by which they may influence pain transmission at the spinal level.

At the spinal level, visceral nociception is dependent upon a system of intensity coding. In the viscera, primary afferents for normal sensations and nociception appear to be the same small fibres arriving at the spinal cord, and the difference between a normal and a noxious message depends upon the number of afferent signals transmitted to the dorsal horn (as opposed to the dual fibre, A/C fibre for nociception and A for light touch, seen in somatic tissue). It is thought that psychological modulation can alter intensity coding more easily than dual-fibre coding, and hence, pain perception.

Various psychological processes affect pain neuromodulation at the higher level. Inhibiting or facilitating both the nociceptive signal reaching the consciousness and appraisal and interpretation of that signal; they will also modulate the response to the nociceptive message and hence the pain experience. Further, descending pathways represent cognitive, emotional and behavioural states at spinal and peripheral levels.

Functional Magnetic Resonance Imaging (FMRI) has indicated that the psychological modulation of visceral pain probably involves multiple pathways. For instance, mood and attentional focus probably act through different areas of the brain when involved in reducing pain (21).

This psychological modulation may act to reduce nociception within a rapid time frame but may also result in long-term vulnerability to chronic visceral pain, through long-term potentiation. This involvement of higher centre learning may be at both a conscious and subconscious level, and is clearly significant in the supratentorial neuroprocessing of nociception and pain. Long-term potentiation (22) may also occur at any level within the nervous system, so that pathways for specific or combinations of stimuli may become established, resulting in an individual being vulnerable to perceiving sensations that would not normally be experienced as painful.

Stress is an intrinsic or extrinsic force that threatens the homeostasis of an organism and can be physical or psychological. Stress induces an adaptive response that involves the endocrine, autonomic nervous and immune systems, and these systems in turn appear to have feedback loops. Stress can modify the nervous system by long-term potentiation so that there are long-term actual or potential changes within these systems. It is this process that may be responsible for the effect of early life and significant adverse life events associated with chronic pain syndromes. It is through all of these factors that stress can play a significant role in nociceptive and pain neuromodulation, with the increased experience of pain as well as the more general effect that stress may have on coping resources (23). Significant adverse life events include, rape, sexual abuse, sexual trauma and sexual threat, such as during internment or torture. These events may produce long-term physical changes in the CNS (biological response), as well as having an effect on a patient's, emotional, cognitive, behavioural and sexual responses (24-26).

2.2.7 ***Autonomic nervous system***

The role of the autonomic nervous system in chronic pain is poorly understood, however, there is good evidence that damaged afferent fibres may develop a sensitivity to sympathetic stimulation, both at the site of injury and more centrally, particularly the dorsal horns. In visceral pain, the efferent output of the CNS may be

influenced by central changes (again, those changes may be throughout the neuraxis), and such modification of the efferent message may produce significant end-organ dysfunction. These functional abnormalities can have a significant effect on quality of life (QoL) and must be managed as appropriate.

2.2.8 ***Endocrine system***

The endocrine system is involved in visceral function. Significant life events, and in particular, early life events may alter the development of the hypothalamic-pituitary-adrenal axis and the chemicals released. Increased vulnerability to stress may occur following such events and is thought to be partly due to increased corticotrophin-releasing hormone (CRH) gene expression. Upregulation of CRH has been implicated in several pain states such as rectal hypersensitivity to rectal distension. This model suggests an action of CRH on mast cells.

A range of stress-related illnesses have been suggested, with IBS and BPS being examples. There is also evidence accumulating to suggest that the sex hormones also modulate both nociception and pain perception.

2.2.9 ***Genetics and chronic pain***

An individual who has had one chronic pain syndrome is more likely to develop another. Family clusters of pain conditions are also observed and animals can be bred that are more prone to an apparent chronic pain state. A whole range of genetic variations have been described that may explain the pain in certain cases; many of these are to do with subtle changes in transmitters and their receptors. However, the picture is more complicated in that development, environment and social factors also influence the situation.

2.3 Clinical paradigms and CPP

2.3.1 ***Referred pain***

Referred pain is frequently observed and its identification is important for diagnosis and treatment. Referral is usually somatic to somatic, or visceral to somatic. However, there is no reason why pain cannot also be perceived within the area of an organ with the nociceptive signal having arisen from a somatic area. Referred pain may occur as a result of several mechanisms but the main theory is one of convergence-projection. In the convergence-projection theory, as an example, afferent fibres from the viscera and the somatic site of referred pain converge onto the same second order projection neurons. The higher centres receiving messages from these projection neurons are unable to separate the two possible sites from the origin of the nociceptive signal (9,13,27).

2.3.2 ***Referred pain to somatic tissues with hyperalgesia in the somatic tissues***

Hyperalgesia refers to an increased sensitivity to normally painful stimuli. In patients that have passed a renal stone, somatic muscle hyperalgesia is frequently present, even a year after expulsion of the stone. Pain to non-painful stimuli (allodynia) may also be present in certain individuals. Somatic tissue hyperaesthesia is associated with urinary and bilary colic, IBS, endometriosis, dysmenorrhoea, and recurrent bladder infection. Vulvar pain syndromes are examples of cutaneous allodynia that, in certain cases, may be associated with visceral pain syndromes, such as BPS. Referred pain with hyperalgesia is thought to be due to central sensitisation of the converging viscero-somatic neurones. Central sensitisation also stimulates efferent activity that could explain the trophic changes that are often found in the somatic tissues.

2.3.3 ***Muscles and pelvic pain***

In the urogenital pain syndromes muscle tenderness and trigger points may be implicated as a source of pain. Central mechanisms are of great importance in the pathogenesis of this muscle hyperalgesia. The muscles involved may be a part of the spinal, abdominal or pelvic complex of muscles. It is not unknown for adjacent muscles of the lower limbs and the thorax to become involved. Pain may be localised to the trigger points but is more often associated with classical referral patterns. As well as trigger points, inflammation of the attachments to the bones (enthesitis) and of the bursa (bursitis) may be found (28-30).

Certain postures affect the different muscles in different ways, and as a consequence, may exacerbate or reduce the pain. Stress has been implicated as both an initiator of pelvic myalgia and as a maintenance factor. As a result, negative sexual encounters may also have a precipitating effect (23).

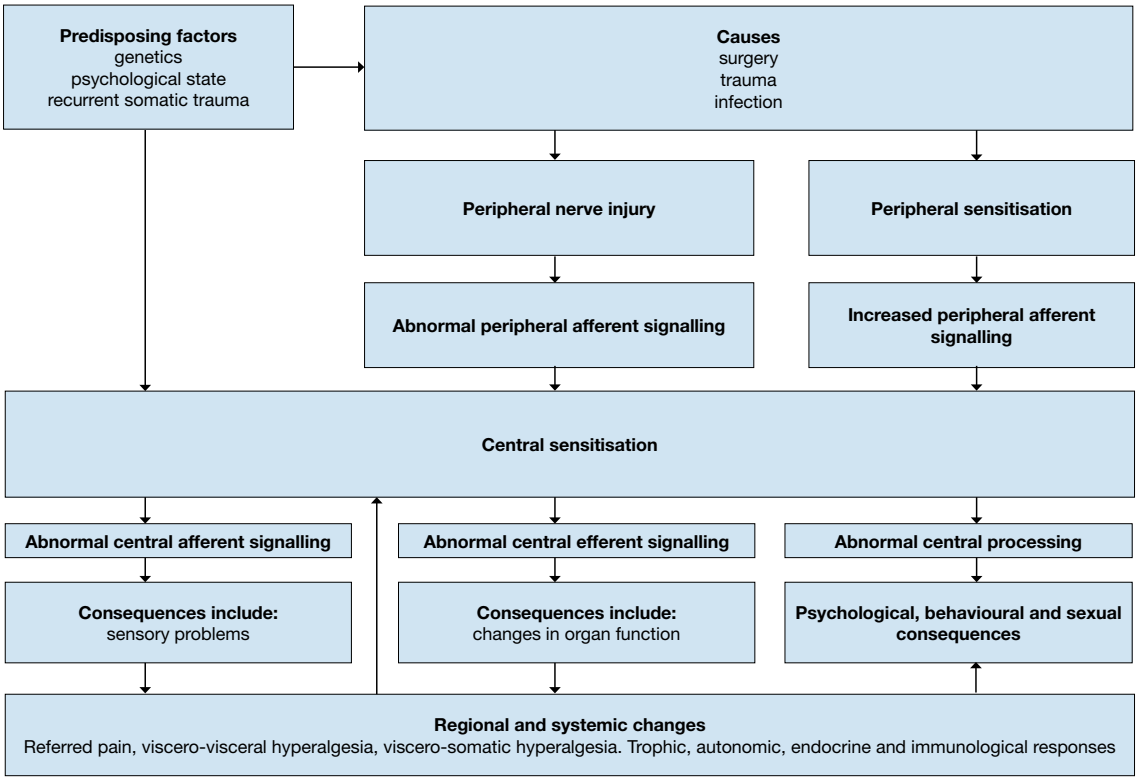
2.3.4 ***Visceral hyperalgesia***

The increased perception of stimuli in the viscera is known as visceral hyperalgesia, and the underlying mechanisms are thought to be responsible for IBS, BPS and dysmenorrhoea. The mechanisms involved are often acute afferent input (e.g., due to infection) followed by long-term central sensitisation.

2.3.5 *Viscero-visceral hyperalgesia*

Viscero-visceral hyperalgesia is thought to be due to two or more organs with converging sensory projections and central sensitisation. For instance, overlap of bladder and uterine afferents or uterine and colon afferents.

Figure 1: Predisposing factors, cause, central en peripheral mechanisms



2.4 Definitions of CPP terminology

2.4.1 *Classification*

Much debate over the classification of CPP has occurred, is ongoing and will continue in the future. Classification involves three aspects of defining a condition, phenotyping, terminology and taxonomy.

2.4.2 *Phenotyping*

Phenotyping is describing the condition. For example, chronic bladder pain may be associated with the presence of Hunner's ulcers and glomerulation on cystoscopy, whereas other bladder pain conditions may have a normal appearance on cystoscopy. These are two different phenotypes. The same is true for IBS, which may be subdivided into that with primarily diarrhoea or that with constipation. Phenotyping is based upon mechanisms when they are known (e.g., infection, ischaemic, autoimmune, or neuropathic). In the absence of well-defined mechanisms, describing the condition by its symptoms, signs and, where possible, by investigations, has been demonstrated to have clinical and research validity in many situations. When pain is the main symptom and pain as a disease process is considered the cause, the condition is often referred to as a pain syndrome - a well-defined collection of symptoms, signs and investigation results associated with pain mechanisms and pain perception as the primary complaint.

2.4.3 *Terminology*

Terminology is the words that are used within classification, both to name the phenotype and within the definition of the phenotype. Examples of names for phenotypes associated with the bladder include interstitial cystitis, painful bladder syndrome or BPS. The EAU, the International Society for the study of BPS (ESSIC), the International Association for the Study of Pain (IASP) and several other groups now prefer the term bladder pain syndrome. In the pain syndromes, the role of the nervous system in generating the sensations is thought to be pivotal, but the term syndrome is also holistic and takes into account the emotional, cognitive, behavioural, sexual and functional consequences of the chronic pain.

When defining the phenotype, the terminology used in that definition must also be clear and if necessary defined. One of the most important guiding principles is that spurious terminology should be avoided. Terms that end in "itis" in particular should be avoided unless infection and or inflammation is proven and considered

to be the cause of the pain (7). It must be appreciated that end-organ inflammation may be secondary and neurogenic in origin and not a primary cause of the pain.

2.4.4 ***Taxonomy***

Taxonomy places the phenotypes into a relationship hierarchy. The EAU approach subdivides CPP into conditions that are pain syndromes and those that are non-pain syndromes. The latter are conditions that have well-recognised pathology (e.g., infection, neuropathy or inflammation), whereas the former syndromes do not and pain as a disease process is the mechanism. Other terms for the non-pain syndromes include "classical conditions", "well-defined conditions" and "confusable diseases". Although the EAU approach deals primarily with urological conditions, this approach to classification can be applied to all conditions associated with pain perception within the pelvis; the classification has been developed to include non-urological pain and was accepted by the IASP for publication in January 2012.

2.5 Classification of CPP syndromes

2.5.1 ***Importance of classification***

It should be obvious to all that a condition cannot be treated unless it is defined. However, the reasons for classifying CPP go far beyond that.

Clues to the mechanism

As a result of systematic phenotypic and taxonomic classification, similarities and differences between conditions become clear. Drawing comparisons between the phenotypes of different disorders allows one to compare disorders such as bladder and bowel pain syndromes, thus facilitating research and treatment.

Guidelines for best treatment options

As conditions become better defined, more specific treatment approaches can be adopted. In particular, there will be a move away from treatments based upon spurious terms (e.g., antibiotics and non-steroidal anti-inflammatory drugs for the "-itis" conditions). Generic treatments aimed at groups of conditions will be more commonplace and based upon research evidence.

Research platform

Only by clearly defining the phenotype being investigated can research be valued or applied in the clinical situation.

Patient needs

A diagnosis, or name, for a set of symptoms can provide patients with a sense of being understood, as well as hope for relief. It may therefore help in acceptance of the problem as chronic, resolution of unfounded fears about its implications (if not life-threatening), and engagement in therapeutic endeavours, as well as in self-management. However, it may also lead to accessing information of variable quality associated with the diagnosis or name, and the possibility of generating new concerns about long-term consequences or about appropriateness of treatment.

Remuneration

In certain countries, having a defined condition is necessary for the patient to receive treatment for their condition.

2.5.2 ***IASP definitions***

Subdividing pain syndromes

There is much debate on the subdivisions of the pain syndromes within the hierarchical taxonomy. The EAU has led the way in this regard and the guiding principles are as follows (31):

1. The pain syndromes are defined by a process of exclusion. In particular, there should be no evidence of infection or inflammation. Investigations by end-organ specialists should thus be aimed at obtaining a differential diagnosis; repeated, unnecessary investigations are detrimental in the management of chronic pain syndromes.
2. A subdivision phenotype should only be used if there is adequate evidence to support its use. For instance, in non-specific, poorly localised pelvic pain without obvious pathology, only the term chronic pelvic pain syndrome (CPPS) should be used. If the pain can be localised to an organ, then a more specific term, such as rectal pain syndrome, may be used. If the pain is localised to multiple organs, then the syndrome is a regional pain syndrome and the term CPPS should once again be considered. As well as defining the patient by a specific end-organ phenotype, there are several other more general descriptors that need to be considered. These are primarily psychological (e.g., cognitive

or emotional), sexual, behavioural and functional. Psychological and behavioural factors are well established to relate to QoL issues and prognosis. In North America a research programme, the MAPP program (Multi-disciplinary Approach to the study of Chronic Pelvic Pain research) has been devised to investigate the importance of these factors and looks at all types of pelvic pain irrespective of the end-organ where the pain is perceived. It also looks at systemic disorder associations, such as the co-occurrence of fibromyalgia, facial pain, or autoimmune disorders.

3. In 2004 this expert panel introduced the concept of managing the polysymptomatic nature of CPP, since then others have developed their own schemes, such as Nickel's UPOINT (32), modified by Magri et al. (33). In the light of these and other publications, the symptom classification table has been updated (Table 5).

The debate in relation to subdividing the pain syndromes remains ongoing. As more information is collected suggesting that the CNS is involved, and indeed may be the main cause of many CPP conditions (e.g., bladder, genitalia, colorectal or myofascial), there is a general tendency to move away from end-organ nomenclature. Whether this is appropriate, only time and good research will tell. To enable such research, it is essential to have a framework of classification within which to work. Any hierarchical taxonomy must be flexible to allow change.

In table 5 the classification has been set up according to the axis system used by IASP. The panel used this table from their first edition and found it very useful for clinical purpose.

Table 5: EAU classification of chronic urogenital pain syndromes

Axis I Region		Axis II System	Axis III End-organ as pain syndrome as identified from Hx, Ex and Ix	Axis IV Referral characteristics	Axis V Temporal characteristics	Axis VI Character	Axis VII Associated symptoms	Axis VIII Psychological symptoms
Chronic pelvic pain	Specific disease associated pelvic pain OR Pelvic pain syndrome	Urological	Prostate	Suprapubic Inguinal Urethral Penile/clitoral Perineal Rectal Back Buttocks Thighs	ONSET Acute Chronic ONGOING Sporadic Cyclical Continuous TIME Filling Emptying Immediate post Late post TRIGGER Provoked Spontaneous	Aching Burning Stabbing Electric	UROLOGICAL Frequency Nocturia Hesitance Dysfunctional flow Urge Incontinence GYNAECOLOGICAL Menstrual Menopause GASTROINTESTINAL Constipation Diarrhoea Bloatedness Urge Incontinence NEUROLOGICAL Dysaesthesia Hyperaesthesia Allodynia Hyperalegesie SEXUOLOGICAL Satisfaction Female dyspareunia Sexual avoidance Erectile dysfunction Medication MUSCLE Function impairment Fasciculation CUTANEOUS Trophic changes Sensory changes	ANXIETY About pain or putative cause of pain Catastrophic thinking about pain DEPRESSION Attributed to pain or impact of pain Attributed to other causes Unattributed PTSD SYMPTOMS Re-experiencing Avoidance
			Bladder					
			Scrotal Testicular Epididymal					
			Penile Urethral					
			Postvasectomy					
		Gynaecological	Vulvar Vestibular Clitoral					
			Endometriosis associated					
			CPPS with cyclical exacerbations					
			Dysmenorrhoea					
		Gastrointestinal	Irritable bowel					
			Chronic anal					
			Intermittent chronic anal					
		Peripheral nerves	Pudendal pain syndrome					
		Sexological	Dyspareunia					
			Pelvic pain with sexual dysfunction					
		Psychological	Any pelvic organ					
		Musculo-skeletal	Pelvic floor muscle Abdominal muscle Spinal					
			Coccyx					

2.5.3 ***Pain syndromes***

The original EAU classification (31) was inspired by the IASP classification (19) and much work around what has become known as "pain as a disease" and its associated psychological, behavioural, sexual and functional correlates. After 10 years work developing the initial ideas, an updated version was accepted by IASP Council for publication in January 2012.

2.5.3.1 Definition of chronic pelvic pain (CPP)

Chronic pelvic pain is chronic or persistent pain perceived* in structures related to the pelvis of either men or women. It is often associated with negative cognitive, behavioural, sexual and emotional consequences as well as with symptoms suggestive of lower urinary tract, sexual, bowel, pelvic floor or gynaecological dysfunction.

[*Perceived indicates that the patient and clinician, to the best of their ability from the history, examination and investigations (where appropriate) has localised the pain as being perceived in the specified anatomical pelvic area.]

In the case of documented nociceptive pain that becomes chronic/persistent through time, pain must have been continuous or recurrent for at least 6 months. That is, it can be cyclical over a 6-month period, such as the cyclical pain of dysmenorrhoea. Six months is arbitrary, however, it was chosen because 3 months was not considered long enough if we include cyclical pain conditions. If non-acute and central sensitisation pain mechanisms are well documented, then the pain may be regarded as chronic, irrespective of the time period.

Cyclical pain is included in the classification and hence dysmenorrhoea needs to be considered as a chronic pain syndrome if it is persistent and associated with negative cognitive, behavioural, sexual, or emotional consequences.

Chronic pelvic pain may be subdivided into conditions with well-defined classical pathology (such as infection or cancer) and those with no obvious pathology. For the purpose of this classification, the term "specific disease-associated pelvic pain" is proposed for the former, and "chronic pelvic pain syndrome" for the latter. The following classification only deals with CPPS.

2.5.3.2 Definition of chronic pelvic pain syndrome

Chronic pelvic pain syndrome (CPPS) is the occurrence of CPP when there is no proven infection or other obvious local pathology that may account for the pain. It is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction. CPPS is a subdivision of CPP.

2.5.3.2.1 Further subdivision of CPPS

Pain perception in CPPS may be focused within a single organ, more than one pelvic organ and even associated with systemic symptoms such as chronic fatigue syndrome, fibromyalgia or Sjögren's syndrome. When the pain is localised to a single organ, some specialists may wish to consider using an end-organ term such as BPS (Table 6). The use of such a phrase with the terminology "syndrome" indicates that, although peripheral mechanisms may exist, CNS neuromodulation may be more important and systemic associations may occur. When the pain is localised to more than one organ site, the term CPPS should be used. Many, including some of the authors of this text, never subdivide by anatomy and prefer to refer to patients with pain perceived within the pelvis and no specific disease process as suffering from CPPS, subdivided by psychological and functional symptoms.

2.5.3.2.2 Psychological considerations for classification

Many CPPSs are associated with a range of concurrent negative psychological, behavioural and sexual consequences that must be described and assessed. Examples that need to be considered are depression, anxiety, fears about pain or its implications, unhelpful coping strategies, and distress in relationships.
Both anxiety and depression can be significant important concomitant symptoms that are relevant to pain, disability and poor QoL. Catastrophic interpretation of pain has been shown to be a particularly salient variable, predicting patients' report of pain, disability, and poor QoL, over and above psychosocial variables such as depression or behavioural factors such as self-reported sexual dysfunction. It is suggested that CPPS sometimes creates a sense of helplessness that can be reported as overwhelming, and may be associated with the refractory nature of the patients' symptoms. It is important to note that many of these biopsychosocial consequences are common to other persistent pain problems but may show varying degrees of salience for any one individual suffering from CPPS. In all patients with CPPS, these consequences must be clearly described as part of the phenotype (where the term phenotype is used to indicate the observable

characteristics of the syndrome).

2.5.3.2.3 Functional considerations for classification
Functional disorders, for the purpose of this document, are pathologies that have arisen secondary to changes in the control mechanisms of an organ or system. That is, they are disorders characterised by disturbance of function. As an example, slow colonic transit is a functional disorder of the bowel - the normal function of the bowel is not occurring as a result of changes in the mechanisms that produce defecation, and hence the bowel control is abnormal. The term is not used in the sense of a psychiatric functional disorder. Many CPPSs are associated with functional abnormalities at a local and even systemic level. These also need to be defined as a part of the phenotype.

Functional pain disorders may not express significant pathology in the organs that appear responsible for the primary symptoms, but they are associated with substantial neurobiological, physiological and sometimes anatomical changes in the CNS.

2.5.3.2.4 Multisystem subdivision
It is recognised that the end-organ where the pain is perceived may not be the centre of pain generation. This classification is based upon the most effective accepted method of classifying and identifying different pain syndromes, that is, by site of presentation. It is argued that keeping the end-organ name in the classification is inappropriate because, in most cases, there are multisystemic causes and effects, with the result that symptoms are perceived in several areas. This is an area in which discussions are ongoing, and despite there being strong arguments for both keeping and dispensing with end-organ classification, the authors have not taken the umbrella approach of referring to all pain perceived in the pelvis as CPPS.

2.5.3.2.5 Dyspareunia
Dyspareunia is defined as pain perceived within the pelvis associated with penetrative sex. It tells us nothing about the mechanism and may be applied to women and men. It is usually applied to penile penetration, but is often associated with pain during insertion of any object. It may apply to anal as well as vaginal intercourse. It is classically subdivided into superficial and deep.

2.5.3.2.6 Perineal pain syndrome
Perineal pain syndrome is a neuropathic-type pain that is perceived in the distribution area of the pudendal nerve, and may be associated with symptoms and signs of rectal, urinary tract or sexual dysfunction. There is no proven obvious pathology. It is often associated with negative cognitive, behavioural, sexual and emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction. Perineal pain syndrome should be distinguished from pudendal neuralgia, which is a specific disease associated with pelvic pain that is caused by nerve damage.

Table 6: Urological pain syndromes

Urological Pain Syndromes - Chapter 3	
Prostate pain syndrome	PPS is the occurrence of persistent or recurrent episodic pain (which is convincingly reproduced by prostate palpation). There is no proven infection or other obvious local pathology. PPS is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction. The term "chronic prostatitis" continues to be equated with that of PPS. In the authors' and others' opinion, this is an inappropriate term, although it is recognised that it has a long history of use. The National Institutes of Health (NIH) consensus (34) includes infection (types I and II), which the authors feel should not be considered under PPS, but as specific disease-associated pelvic pain. The term prostadynia has also been used in the past but is no longer recommended by the expert panel. Please note that some of the authors of the IASP document disagree with this term and suggest that CPPS of the male is used instead of PPS, which has been agreed by the majority.
Bladder pain syndrome	BPS is the occurrence of persistent or recurrent pain perceived in the urinary bladder region, accompanied by at least one other symptom, such as pain worsening with bladder filling and day-time and/or night-time urinary frequency. There is no proven infection or other obvious local pathology. BPS is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction. BPS is believed to represent a heterogeneous spectrum of disorders. There may be specific types of inflammation as a feature in subsets of patients. Localisation of the pain can be difficult by examination, and consequently, another localising symptom is required. Cystoscopy with hydrodistension and biopsy may be indicated to define phenotypes. Recently, ESSIC has suggested a standardised scheme of subclassifications (11) to acknowledge differences and make it easier to compare various studies. Other terms that have been used include "interstitial cystitis", "painful bladder syndrome", and "PBS/IC" or "BPS/IC". These terms are no longer recommended.
Scrotal pain syndrome	Scrotal pain syndrome is the occurrence of persistent or recurrent episodic pain localised within the organs of the scrotum, and may be associated with symptoms suggestive of urinary tract or sexual dysfunction. There is no proven infection or other obvious local pathology. Scrotal pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction. Scrotal pain syndrome is a generic term and is used when the site of the pain is not clearly testicular or epididymal. The pain is not in the skin of the scrotum as such, but perceived within its contents, in a similar way to idiopathic chest pain.
Testicular pain syndrome	Testicular pain syndrome is the occurrence of persistent or recurrent episodic pain perceived in the testes, and may be associated with symptoms suggestive of urinary tract or sexual dysfunction. There is no proven infection or other obvious local pathology. Testicular pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction. Previous terms have included orchitis, orchialgia and orchiodynia. These terms are no longer recommended.
Epididymal pain syndrome	Epididymal pain syndrome is the occurrence of persistent or recurrent episodic pain perceived in the epididymis, and may be associated with symptoms suggestive of urinary tract or sexual dysfunction. There is no proven infection or other obvious local pathology. Epididymal pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction.

Penile pain syndrome	Penile pain syndrome is the occurrence of pain within the penis that is not primarily in the urethra, in the absence of proven infection or other obvious local pathology. Penile pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction.
Urethral pain syndrome	Urethral pain syndrome is the occurrence of chronic or recurrent episodic pain perceived in the urethra, in the absence of proven infection or other obvious local pathology. Urethral pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction. Urethral pain syndrome may occur in men and women.
Postvasectomy scrotal pain syndrome	Postvasectomy scrotal pain syndrome is a scrotal pain syndrome that follows vasectomy. Postvasectomy scrotal pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction. Postvasectomy pain may be as frequent as 1% following vasectomy, possibly more frequent. The mechanisms are poorly understood and it is for that reason considered a special form of scrotal pain syndrome.
Gynaecological Pain Syndromes: external genitalia - Chapter 4	
Vulvar pain syndrome	Vulvar pain syndrome is the occurrence of persistent or recurrent episodic vulvar pain. There is no proven infection or other local obvious pathology. It is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction. Although pain perceived in the vulva was subsumed under sexual disorders in the DSM-IV-R manual for classifying psychiatric disorders, there is no scientific basis for this classification, and pain perceived in the vulva is best understood as a pain problem that usually has psychological consequences. There is no evidence for its classification as a psychiatric disorder. The International Society for the Study of Vulvovaginal Disease (ISSVD) has used the term vulvodynia, where we use the term vulvar pain syndrome. According to the ISSVD, vulvodynia is vulvar pain that is not accounted for by any physical findings. The ISSVD has defined vulvodynia as “vulvar discomfort, most often described as burning pain, occurring in the absence of relevant visible findings or a specific, clinically identifiable, neurologic disorder”. If physical findings are present, the patient is said to have vulvar pain due to a specified cause. The ISSVD has subdivided vulvodynia based on pain location and temporal characteristics of the pain (e.g., provoked or unprovoked). The following definitions are based on that approach.
Generalised vulvar pain syndrome	Generalised vulvar pain syndrome refers to a vulvar pain syndrome in which the pain/burning cannot be consistently and precisely localised by point-pressure mapping via probing with a cotton-tipped applicator or similar instrument. Rather, the pain is diffuse and affects all parts of the vulva. The vulvar vestibule (the part that lies between the labia minora into which the urethral meatus and vaginal introitus open) may be involved but the discomfort is not limited to the vestibule. This pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences. Previous terms have included “dysesthetic vulvodynia” and “essential vulvodynia”, but are no longer recommended.
Localised vulvar pain syndrome	Localised vulvar pain syndrome refers to pain that can be consistently and precisely localised by point-pressure mapping to one or more portions of the vulva. Clinically, the pain usually occurs as a result of provocation (touch, pressure or friction). Localised vulvar pain syndrome can be subdivided into vestibular pain syndrome and clitoral pain syndrome.
Vestibular pain syndrome	Vestibular pain syndrome refers to pain that can be localised by point-pressure mapping to the vestibule or is well perceived in the area of the vestibule.
Clitoral pain syndrome	Clitoral pain syndrome refers to pain that can be localised by point-pressure mapping to the clitoris or is well perceived in the area of the clitoris. Gynaecological system: internal pelvic pain syndromes - Chapter 4.

Endometriosis-associated pain syndrome	Endometriosis-associated pain syndrome is chronic or recurrent pelvic pain in patients with laparoscopically confirmed endometriosis, and the term is used when the symptoms persist despite adequate endometriosis treatment. It is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction. Many patients have pain above and beyond the endometriotic lesions; this term is used to cover that group of patients. Endometriosis may be an incidental finding, is not always painful, and the degree of disease seen laparoscopically does not correlate with severity of symptoms. As with other patients, they often have more than one end-organ involved. It has been suggested that this phenotype should be removed from the classification because the endometriosis may be irrelevant.
CPPS with cyclical exacerbations	CPPS with cyclical exacerbations covers the non-gynaecological organ pain that frequently shows cyclical exacerbations (e.g., IBS or BPS) as well as pain similar to that associated with endometriosis/adenomyosis but where no pathology is identified. This condition is different from dysmenorrhoea, in which pain is only present with menstruation.
Dysmenorrhoea	Dysmenorrhoea is pain with menstruation that is not associated with well-defined pathology. Dysmenorrhoea needs to be considered as a chronic pain syndrome if it is persistent and associated with negative cognitive, behavioural, sexual or emotional consequences.
Musculoskeletal System - Chapter 9	
Pelvic floor muscle pain syndrome	Pelvic floor muscle pain syndrome is the occurrence of persistent or recurrent episodic pelvic floor pain. There is no proven well-defined local pathology. It is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction. This syndrome may be associated with overactivity of or trigger points within the pelvic floor muscles. Trigger points may also be found in several muscles, such as the abdominal, thigh and paraspinal muscles and even those not directly related to the pelvis.
Coccyx pain syndrome	Coccyx pain syndrome is the occurrence of chronic or recurrent episodic pain perceived in the region of the coccyx, in the absence of proven infection or other obvious local pathology. Coccyx pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction. The term “coccydynia” was used but is no longer recommended.
Gastrointestinal Pelvic Pain Syndromes - Chapter 5	
Irritable bowel syndrome	IBS is the occurrence of chronic or recurrent episodic pain perceived in the bowel, in the absence of proven infection or other obvious local pathology. Bowel dysfunction is frequent. IBS is often associated with worry and preoccupation about bowel function, and negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract or gynaecological dysfunction. The above classification is based upon the Rome III Criteria (35): 3 months of continuous or recurring symptoms of abdominal pain or irritation that may be relieved with a bowel movement, may be coupled with a change in frequency, or may be related to a change in stool consistency. Two or more of the following are present at least 25% of the time: change in stool frequency (> 3 bowel movements per day or < 3 per week); noticeable difference in stool form (hard, loose, watery or poorly formed stools); passage of mucus in stools; bloating or feeling of abdominal distension; or altered stool passage (e.g., sensation of incomplete evacuation, straining, or urgency). Extra-intestinal symptoms include: nausea, fatigue, full sensation after even a small meal, and vomiting.

Chronic anal pain syndrome	Chronic anal pain syndrome is the occurrence of chronic or recurrent episodic pain perceived in the anus, in the absence of proven infection or other obvious local pathology. Chronic anal pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction.
Intermittent chronic anal pain syndrome	Intermittent chronic anal pain syndrome refers to severe, brief, episodic pain that seems to arise in the rectum or anal canal and occurs at irregular intervals. This is unrelated to the need to or the process of defecation. It may be considered a subgroup of the chronic anal pain syndromes. It was previously known as "proctalgia fugax" but this term is no longer recommended.

2.6 Conclusions and recommendations: CPP and mechanisms

Conclusions	LE
CPPS mechanisms are well defined and involve mechanisms of neuroplasticity and neuropathic pain.	2
The mechanisms of neuroplasticity and neuropathic pain result in increased perception of afferent stimuli which may produce abnormal sensations as well as pain.	1
End-organ function can also be altered by the mechanisms of neuroplasticity and neuropathic pain, so that symptoms of function can also occur.	1
CPP is associated with a high impact on QoL.	1
The diagnosis of a CPPS as a pain syndrome is essential as it encourages a holistic approach to management with multispecialty and multidisciplinary care.	2

Recommendations	GR
All of those involved in the management of CPP should have an understanding and training in CPPS pain mechanisms.	A
The early assessment of patients should involve not only investigations aimed at specific disease-associated pelvic pain but also assessment of functional, emotional, behavioural, sexual and other quality of life issues, such as effect on work and socialisation.*	A
CPPS patients should be managed in a multispecialty and multidisciplinary environment with consideration of all their symptoms.	A
Future classification should involve consideration of all three recommendations above.	A

CPP = chronic pelvic pain; CPPS = chronic pelvic pain syndrome.
* Instruments for assessment *see* Chapter 8.

2.7 An algorithm for CPP diagnosis and treatment

The algorithm for diagnosing and treating CPP (Figure 2) has been developed to guide a physician through the process from diagnosis to management. A physician should follow the lines by answering the appropriate questions with yes or no. By doing this the clinician will end up at a box that refers to the chapter in this guideline that contains all the information needed.

Because CPP is pain perceived in structures related to the pelvis, it is necessary to approach a patient diagnosed 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. This idea is easily recognised in the algorithm where the division in specific disease associated pain is made on one hand and pelvic pain syndrome on the other.

The algorithm also illustrates that the authors 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.

Every chapter of this guideline shows specific algorithms that assist the clinician in decision making. 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.

Figure 2: An algorithm for diagnosing and managing CPP

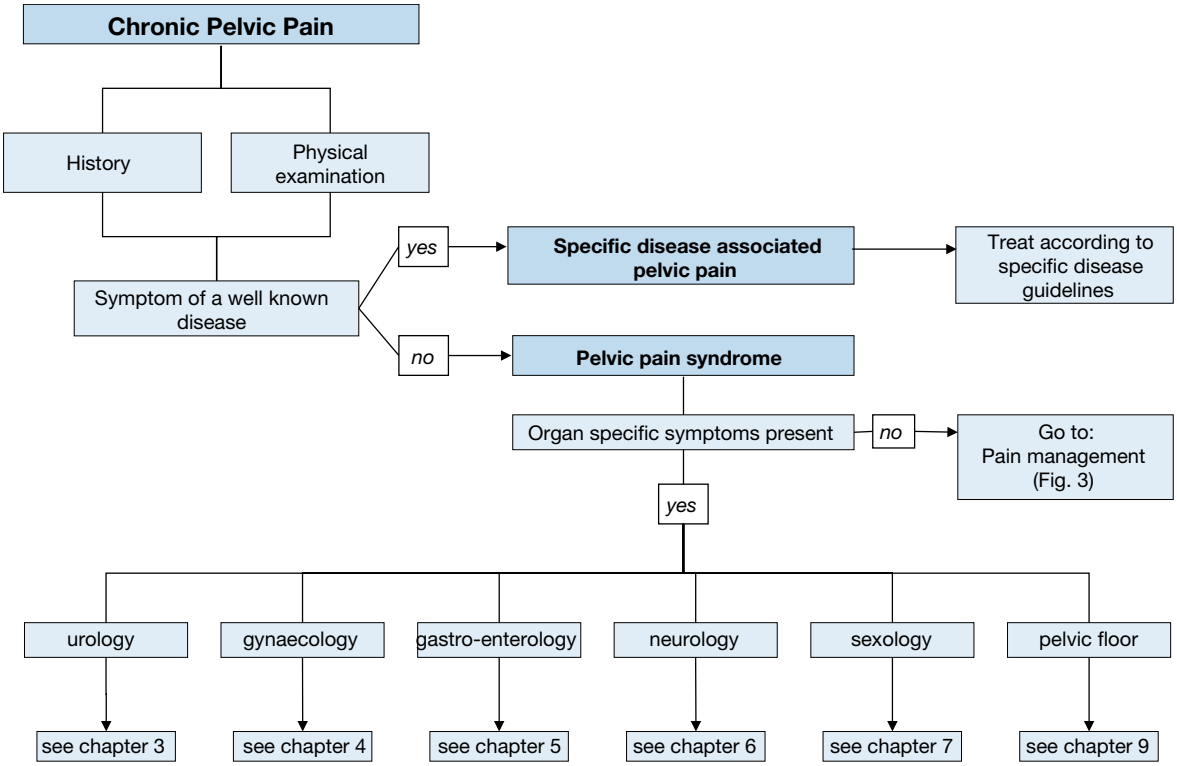


Figure 3: An algorithm for pain management

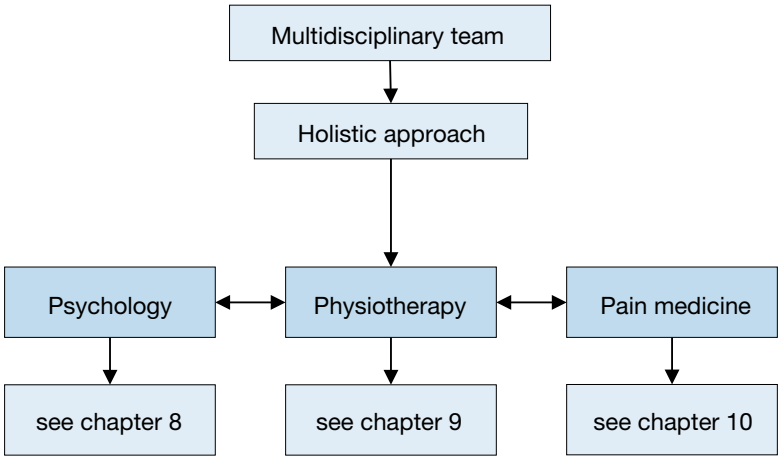


Figure 4: Phenotyping and assessment algorithm for CPP

Phenotyping	Assessment
Urology	Urinary flow, micturition diary, cystoscopy, ultrasound, uroflowmetry
Psychology	History of negative experiences, important loss, coping mechanism, depression
Organ specific	Ask for gynaecological, gastro-intestinal, ano-rectal, sexological complaints Gynaecological examination, rectal examination
Infection	Semen culture and urine culture, vaginal swab, stool culture
Neurological	Ask for neurological complaints (sensory loss, dysaesthesia). Neurological testing during physical examination: sensory problems, sacral reflexes and muscular function
Tender muscle	Palpation of the pelvic floor muscles, the abdominal muscles and the gluteal muscles

2.8 References

1. Linley JE, Rose K, Ooi L, et al. Understanding inflammatory pain: ion channels contributing to acute and chronic nociception. Pflugers Arch. 2010 Apr;459(5):657-69.
http://www.ncbi.nlm.nih.gov/pubmed/20162302
2. McMahon SB, Dmitrieva N, Koltzenburg M, et al. Visceral pain. Br J Anaesth 1995 Aug;75(2):132-144.
http://www.ncbi.nlm.nih.gov/pubmed/7577247
3. Bergeron S, Khalifé S, Glazer HI, et al. Surgical and behavioral treatments for vestibulodynia: two-and-one-half year follow-up and predictors of outcome. Obstet Gynecol. 2008 Jan;111(1):159-66.
http://www.ncbi.nlm.nih.gov/pubmed/18165405
4. Tripp DA, Nickel JC, Wang Y, et al. Catastrophizing and pain-contingent rest predict patient adjustment in men with chronic prostatitis/chronic pelvic pain syndrome. J Pain 2006 Oct;7(10): 697-708.
http://www.ncbi.nlm.nih.gov/pubmed/17018330
5. Tripp DA, Nickel JC, Fitzgerald MP, et al. Sexual functioning, catastrophizing, depression, and pain, as predictors of quality of life in women with interstitial cystitis/painful bladder syndrome. Urology. 2009 May;73(5):987-92.
http://www.ncbi.nlm.nih.gov/pubmed/19394494
6. Nickel JC, Tripp DA, Pontari M, et al. Psychosocial phenotyping in women with interstitial cystitis/ painful bladder syndrome: a case control study. J Urol 2010 Jan;183(1):167-72.
http://www.ncbi.nlm.nih.gov/pubmed/19913812
7. Abrams PA, Baranowski AP, Berger RE, et al. A new classification is needed for pelvic pain syndromes--are existing terminologies of spurious diagnostic authority bad for patients? J Urol 2006 Jun;175(6):1989-90.
http://www.ncbi.nlm.nih.gov/pubmed/16697782
8. Baranowski AP, Abrams P, Berger RE, et al. Urogenital pain--time to accept a new approach to phenotyping and, as a consequence, management. Eur Urol. 2008 Jan;53(1):33-6.
http://www.ncbi.nlm.nih.gov/pubmed/17961909
9. Baranowski AP, Abrams P, et al. (2008). Urogenital Pain in Clinical Practice. New York, Informa Healthcare.
10. Hanno P, Lin A, Nordling J, et al. Bladder Pain Syndrome Committee of the International Consultation on Incontinence. Neurourol Urodyn 2010;29(1):191-198.
http://www.ncbi.nlm.nih.gov/pubmed/20025029
11. van de Merwe JP, Nordling J, Bouchelouche P, et al. Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC proposal. Eur Urol. 2008 Jan;53(1):60-7.
http://www.ncbi.nlm.nih.gov/pubmed/17900797

12. Wesselmann U, Baranowski AP, Börjesson M, et al. EMERGING THERAPIES AND NOVEL APPROACHES TO VISCERAL PAIN. Drug Discov Today Ther Strateg. 2009 Fall;6(3):89-95.
http://www.ncbi.nlm.nih.gov/pubmed/21243067
13. Giamberardino MA, Costantini R, Affaitati G, et al. Viscero-visceral hyperalgesia: characterization in different clinical models. Pain. Pain. 2010 Nov;151(2):307-22.
http://www.ncbi.nlm.nih.gov/pubmed/20638177
14. Pezet S, McMahon SB. Neurotrophins: mediators and modulators of pain. Annu Rev Neurosci. 2006;29:507-38.
http://www.ncbi.nlm.nih.gov/pubmed/16776595
15. Cervero F, Laird JM. Understanding the signaling and transmission of visceral nociceptive events. J Neurobiol. 2004 Oct;61(1):45-54.
http://www.ncbi.nlm.nih.gov/pubmed/15362152
16. Petersen M, Segon von Banchet G, Heppelman B, et al. Nerve growth factor regulates the expression of bradykinin binding sites on adult sensory neurons via the neurotrophin receptor p75.Neuroscience. 1998 Mar;83(1):161-8.
http://www.ncbi.nlm.nih.gov/pubmed/9466406
17. McMahon SB, Jones NG. Plasticity of pain signaling: role of neurotrophic factors exemplified by acid-induced pain. J Neurobiol. 2004 Oct;61(1):72-87.
http://www.ncbi.nlm.nih.gov/pubmed/15362154
18. Nazif O, Teichman JM, Gebhart GF, et al. Neural upregulation in interstitial cystitis. Urology. 2007 Apr;69(4 Suppl):24-33.
http://www.ncbi.nlm.nih.gov/pubmed/17462476
19. Merskey H, Bogduk N. Classification of Chronic Pain. Seattle, IASP press.
20. Melzack R, Coderre TJ, Katz J, et al. Central neuroplasticity and pathological pain. Ann N Y Acad Sci. 2001 Mar;933:157-74.
http://www.ncbi.nlm.nih.gov/pubmed/12000018
21. Fulbright RK, Troche CJ, Skudlarski P, et al. Functional MR imaging of regional brain activation associated with the affective experience of pain. AJR Am J Roentgenol. 2001 Nov;177(5):1205-10.
http://www.ncbi.nlm.nih.gov/pubmed/11641204
22. Rygh LJ, Tjølsen A, Hole K, et al. Cellular memory in spinal nociceptive circuitry. Scand J Psychol. 2002 Apr;43(2):153-9.
http://www.ncbi.nlm.nih.gov/pubmed/12004953
23. Savidge CJ, Slade P. Psychological aspects of chronic pelvic pain. J Psychosom Res. 1997 May;42(5):433-44.
http://www.ncbi.nlm.nih.gov/pubmed/9194016
24. Raphael KG, Widom CS, Lange G. Childhood victimization and pain in adulthood: a prospective investigation. Pain. 2001 May;92(1-2):283-93.
http://www.ncbi.nlm.nih.gov/pubmed/11323150
25. Raphael KG. Childhood abuse and pain in adulthood: more than a modest relationship? Clin J Pain 2005 Sep-Oct;21(5):371-3.
http://www.ncbi.nlm.nih.gov/pubmed/16093741
26. Anda RF, Felitti VJ, Bremner JD, et al. The enduring effects of abuse and related adverse experiences in childhood. A convergence of evidence from neurobiology and epidemiology. Eur Arch Psychiatry Clin Neurosci. 2006 Apr;256(3):174-86.
http://www.ncbi.nlm.nih.gov/pubmed/16311898
27. Vecchiet L, Vecchiet J, Giamberardino MA. Referred Muscle Pain: Clinical and Pathophysiologic Aspects. Curr Rev Pain. 1999;3(6):489-498.
http://www.ncbi.nlm.nih.gov/pubmed/10998708
28. Slocumb JC. Neurological factors in chronic pelvic pain: trigger points and the abdominal pelvic pain syndrome. Am J Obstet Gynecol. 1984 Jul;149(5):536-43.
http://www.ncbi.nlm.nih.gov/pubmed/6234807
29. Taylor DC, Meyers WC, Moylan JA, et al. Abdominal musculature abnormalities as a cause of groin pain in athletes. Inguinal hernias and pubalgia. Am J Sports Med. 1991 May-Jun;19(3):239-42.
http://www.ncbi.nlm.nih.gov/pubmed/1831010
30. Akermark C, Johansson C. Tenotomy of the adductor longus tendon in the treatment of chronic groin pain in athletes. Am J Sports Med. 1992 Nov-Dec;20(6):640-3.
http://www.ncbi.nlm.nih.gov/pubmed/1456357
31. Fall M, Baranowski AP, Fowler CJ, et al. EAU guidelines on chronic pelvic pain. Eur Urol. 2004 Dec;46(6):681-9.
http://www.ncbi.nlm.nih.gov/pubmed/15548433

32. Shoskes DA, Nickel JC, Dolinga R, et al. Clinical phenotyping of patients with chronic prostatitis/ chronic pelvic pain syndrome and correlation with symptom severity.Urology. 2009 Mar;73(3):538-42; discussion 542-3.
http://www.ncbi.nlm.nih.gov/pubmed/19118880
33. Magri V, Wagenlehner F, Perletti G, et al. Use of the UPOINT chronic prostatitis/chronic pelvic pain syndrome classification in European patient cohorts: sexual function domain improves correlations.J Urol 2010 Dec;184(6):2339-45.
http://www.ncbi.nlm.nih.gov/pubmed/20952019
34. Krieger JN, Nyberg L Jr., Nickel JC. NIH consensus definition and classification of prostatitis. JAMA. 1999 Jul;282(3):236-7.
http://www.ncbi.nlm.nih.gov/pubmed/10422990
35. Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disorders. Gastroenterology. 2006 Apr;130(5):1480-91.
http://www.ncbi.nlm.nih.gov/pubmed/16678561

3. UROLOGICAL ASPECTS OF CHRONIC PELVIC PAIN

3.1 Prostate pain syndrome

3.1.1 Introduction

Chronic pain in the region of the prostate has been linked to the term “prostatitis” in the past, although there is a proven bacterial infection in only 10% of the cases (1). The remaining 90% should be classified as prostate pain syndrome (PPS), based on the fact that there is no proven infection or other obvious pathology. If CPP cannot be clearly ascribed to the prostate or another organ of the pelvis, the condition is defined more generally as CPPS, as outlined in Chapter 2.

3.1.2 Definition

Prostate pain syndrome is the occurrence of persistent or recurrent episodic pain in the region of the prostate over at least 3 out of the past 6 months, which is convincingly reproduced by prostate palpation. There is no proven infection or other obvious local pathology. PPS is often associated with negative cognitive, behavioural, sexual, or emotional consequences (2), as well as with symptoms suggestive of lower urinary tract and sexual dysfunction (3,4). According to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) classification, this correlates to CP/CPPS (Cat. III). Laboratory diagnosis goes along 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) (5). At present, there are no clinically relevant diagnostic or therapeutic consequences arising from differentiating inflammatory from non-inflammatory PPS (according to NIH definition), therefore, they are considered here as one entity.

3.1.3 Pathogenesis

Pain is the main symptom in PPS. As a common feature of chronic pain syndromes, no single aetiological explanation has been found. One explanation (6) is that the condition probably occurs in susceptible men exposed to one or more initiating factors, which may be single, repetitive or continuous. Several of these potential initiating factors have been proposed, including infectious, genetic, anatomical, neuromuscular, endocrine, immune (including autoimmune), or psychological mechanisms. These factors may then lead to a peripheral self-perpetuating immunological inflammatory state and/or neurogenic injury, creating acute and then chronic pain. Based on the peripheral and the CNS, sensitisation involving neuroplasticity may lead to a centralised neuropathic pain state (see Chapter 2) (6). This could also explain why tissue damage is not usually found in PPS. There is growing evidence for a neuropathic origin and association with CNS changes of pain in PPS. As outlined earlier, PPS patients have been shown to report higher visual analogue scale scores than controls to short bursts of noxious stimuli to the perineum but not to the anterior thigh (7). This implies an altered sensation in the perineum compared with healthy controls similar to other chronic pain syndromes.

3.1.4 Epidemiology

There is only limited information on the true prevalence of PPS in the population. As a result of significant overlap of symptoms with other conditions (e.g. benign prostate syndrome and BPS), purely symptom-based case definitions may not reflect the true prevalence of PPS (8,9). Prostatitis was diagnosed in 8% of all visits

to urologists and 1% of all primary care physicians annually in the USA (10). In a systematic review of the literature, the population-based prevalence of prostatitis symptoms was found to be 8.2% (range: 2.2-9.7%) (11). In two recent studies not included in this review, prevalence was found to be 2.7% (4) and 2% (12). A prospective Italian survey of visits to a urologist for a physician-assigned diagnosis of prostatitis revealed a prevalence of 12.8%. Among these, ~40% had clinical features of PPS (13). In a self-reported, population-based, cross sectional study of Finnish men aged 20-59 years, the overall lifetime prevalence of prostatitis was as high as 14.2% (14). The risk of prostatitis increased with age (men aged 50-59 years had a 3.1-fold greater risk than those aged 20-39 years). Usual clinical treatment in North American populations has been studied in two studies of sufficient quality. In the follow-up of a cohort of men with PPS-like symptoms based on the NIH Prostatitis Symptom Index (NIH-CPSI) pain and voiding domains, 63% still suffered from persistent symptoms, in contrast to 3% of controls with newly developing symptoms (15). Patients with more severe symptoms were more likely to report symptoms 1 year later. In addition, symptoms substantially improved for up to 6 months follow-up, but then remained unchanged (16).

3.1.5 ***Diagnosis***

Prostate pain syndrome is a symptomatic diagnosis, which is diagnosed from a history of pain perceived in the region of the prostate (convincingly reproduced by prostate palpation), and absence of other lower urinary tract pathology, for a minimum of 3 out of the past 6 months. This implies that specific disease-associated pelvic pain caused by bacterial infection, urogenital cancer, urinary tract disease, urethral stricture, and neurogenic disease of the bladder must be ruled out. A thorough history is an important first step in the evaluation of PPS. It should include type of pain and localisation. Pain is often reported in other pelvic areas outside the prostate such as perineum, rectum, penis, testicles and abdomen (17). In addition, associated lower urinary tract symptoms (LUTS), sexual function, psychological, social and economic factors should be addressed. Determination of the severity of disease, its progression and treatment response can be assessed only by means of a validated symptom-scoring instrument. Quality of life should also be measured because it can be as poor as in acute myocardial infarction, unstable angina pectoris or Crohn's disease (19,20). In a study by Tripp et al. (2) more pain, pain-contingent rest, and urinary symptoms were associated with greater disability (also measured by self-report), and pain was predicted by depression and by catastrophising (helplessness subscale).

Demographic and social support variables were not associated with either pain or adjustment. Reliable, valid indexes of symptoms and QoL are the NIH-CPSI (17) and the International Prostate Symptom Score (I-PSS) (18). 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.

There is no single "gold standard" diagnostic test for PPS, therefore, procedures are on the one hand directed towards identification and exclusion of specific diseases associated with pelvic pain, and on the other hand may be used for phenotypic description. Physical examination including digital rectal examination should be carried out. Muscle tenderness and trigger points in the pelvic floor may be palpated. Measurement of resting urine by ultrasound should exclude incomplete voiding. Prostate-specific antigen testing does not help to diagnose PPS but can exclude prostate cancer in patients at risk.

Laboratory diagnosis has been classically based on the four-glass test for bacterial localisation (21). Besides sterile pre-massage urine (voided bladder urine-2), PPS shows < 10,000 cfu of uropathogenic bacteria in expressed prostatic secretions and insignificant numbers of leukocytes or bacterial growth in ejaculates. However, this test is too complex for use by practising urologists. Diagnostic efficiency may be enhanced cost-effectively by a simple screening procedure, that is, the two-glass test or pre-post-massage test (PPMT) (22). In an extensive analysis of both tests, PPMT was able to indicate the correct diagnosis in > 96% of patients (23). Overall, these tests help only a little in the diagnosis of PPS, because 8% of patients with suggested PPS have been found to have positive prostatic localisation cultures, similar to the percentage of asymptomatic (24).

In PPS, urodynamic studies should be considered in patients with significant LUTS. They may 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 may be dysfunctional (non-relaxing) during voiding (25). As for non-PPS cases, cystoscopy may be considered for further evaluation of micturition symptoms to exclude bladder outlet or urethral pathology, or if haematuria or infection has been found to exclude intravesical pathology.

A general algorithm for assessment and treatment of PPS is shown in Figure 5.

3.1.6 Conclusions and recommendations: assessment/diagnosis PPS

Conclusions	LE
PPS is associated with negative cognitive, behavioural, sexual, or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction.	2b
PPS has no known single aetiology.	3
Pain in PPS involves mechanisms of neuroplasticity and neuropathic pain.	2a
PPS has a high impact on QoL.	2b
Depression and catastrophic thinking are associated with more pain and poorer adjustment.	3
The prevalence of PPS-like symptoms is high in population-based studies (> 2%).	2b
There is significant overlap of symptoms with other conditions.	2b
Reliable instruments assessing symptom severity as well as phenotypic differences exist.	2b

Recommendations	GR
Specific diseases with similar symptoms must be excluded. It is therefore recommended to adapt diagnostic procedures to the patient and to aim at identifying them.	A
After primary exclusion of specific diseases, patients with symptoms according to the above definition should be diagnosed with prostate pain syndrome.	A
A validated symptom and quality of life scoring instrument, such as the NIH-CPSI, should be considered for initial assessment as well as for follow-up.	B
It is recommended to assess prostate pain syndrome associated negative cognitive, behavioural, sexual, or emotional consequences, as well as symptoms of lower urinary tract and sexual dysfunctions.	B

3.1.7 Treatment

There is a large discrepancy in the treatment effects reported in case series and controlled trials that results from a large placebo effect or publication bias. As a result of the multifactorial origin of PPS, one reason for treatment failure in some large randomised placebo-controlled trials may be the heterogeneity of the patient population. Thus, one strategy for improving treatment effects may be stratification of patient phenotypes. A prospective series of phenotypically directed treatment for PPS has shown significant improvement of symptoms and QoL (26). Monotherapeutic strategies for the treatment of PPS may fail (27), therefore, most patients require multimodal treatment aimed at the main symptoms, and taking comorbidity into account. In the past 10 years, results from RCTs have led to advances in standard and novel treatment options.

3.1.7.1 Alpha-blockers

Positive results from RCTs of alpha-blockers, i.e. terazosin (28,29), alfuzosin (30) doxazosin (31,32) and tamsulosin (33) have led to widespread use of alpha-antagonists in the treatment of PPS in recent 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 (33). In contrast, an earlier meta-analysis of nine trials (n = 734) did not show a beneficial effect on pain (34). Moreover, in accordance with an earlier negative report on tamsulosin (35), one adequately powered large placebo-controlled randomised trial of 12 weeks treatment with alfuzosin failed to show any significant difference in the outcome measures, with the exception of the score for ejaculation of the Male Sexual Health Questionnaire scores (showing significant improvement in the alfuzosin group compared to the placebo group, P = 0.04) (36). Regarding safety, this large trial reported similar adverse event rates in the treatment and placebo groups. The most recent in-depth systematic review and network meta-analysis of alpha-blockers (37) has shown significant improvement in symptoms, with standardised mean differences in total symptom, pain, voiding, and QoL scores of -1.7 [95% confidence interval (CI): -1.8 to -0.3], -1.1 (95% CI: -1.8 to -0.3), 1.4 (95% CI: -2.3 to -0.5), and -1.0 (95% CI: -1.8 to 0.2), respectively. In addition, they had a higher rate of favourable response compared to placebo (pooled relative risk of 1.6 (95% CI: 1.1-2.3). However, this finding was associated with publication bias for smaller studies. Overall, alpha-blockers seem to have moderate but significant beneficial effects. This probably is not the case for long-standing PPS patients (36). Future studies should show if longer duration of therapy or some sort of phenotypically directed (e.g. patients with PPS and relevant voiding dysfunction) treatment strategies will improve treatment outcomes.

3.1.7.2 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, leukocyte and antibody status of prostate-specific specimens do not predict antibiotic response in patients with PPS (38), and prostate biopsy culture findings do not differ from those of healthy controls (39). The only randomised placebo-controlled trials of sufficient quality have been done for oral antibiotic treatment with ciprofloxacin (6 weeks) (35), levofloxacin (6 weeks) (40), and tetracycline hydrochloride (12 weeks) (41). These have been analysed in a recently published meta-analysis (37). Although direct meta-analysis has not shown significant differences in outcome measures, network meta-analysis has suggested significant effects in decreasing total symptom scores (-9.8; 95% CI: -15.1 to -4.6), pain scores (-4.4; 95% CI: -7.0 to -1.9), voiding scores (-2.8; 95% CI: -4.1 to -1.6), and QoL scores (-1.9; 95% CI: -3.6 to -0.2) compared with placebo. Overall, antibiotic treatment of PPS is based only on weak evidence. Combination therapy of antibiotics with alpha-blockers has shown even better outcomes in network meta-analysis. However, sample sizes of the studies were relatively small and treatment effects were only modest and most of the time below clinical significance. It may be speculated that patients profiting from treatment have had some unrecognised uropathogens. If antibiotics are used, other therapeutic options should be offered after one unsuccessful course of a quinolone or tetracycline antibiotic over 6 weeks.

3.1.7.3 Anti-inflammatory drugs

For non-steroidal anti-inflammatory drugs, only two RCTs have been published. The first was for rofecoxib, which is no longer on the market; statistical significance over placebo was achieved in some of the outcome measures (42). In the second trial with celecoxib, pain subscore, QoL subscore, and total NIH-CPSI score were in favour of the treatment arm versus placebo, but effects were limited to the duration of therapy (43). A leukotriene antagonist, zafirlukast, has been evaluated in a small randomised placebo-controlled study of patients treated with concomitant doxycycline (44). This study was negative but had a lack of power. For corticosteroids, no significant benefits were shown in a low-power, placebo-controlled, randomised pilot study of a short course of oral prednisolone (45). In a recent meta-analysis, two studies of NSAIDs (40,43) and one with prednisolone (45) were pooled. Anti-inflammatory drugs were 80% more likely to have a favourable response than placebo (total n = 190, RR: 1.8; 95% CI: 1.2-2.6). Overall, a moderate treatment effect has been shown for anti-inflammatory drugs, but larger studies should be done for final confirmation, and long-term side effects have to be taken into account.

3.1.7.4 Opioids

Opioids produce modest pain relief in some patients with refractory PPS, although there are 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 (46). Urologists should use opioids for PPS only in collaboration with pain clinics and with other treatments.

3.1.7.5 5-alpha-reductase inhibitors

Although a few small pilot studies with 5-alpha-reductase inhibitors supported the view that finasteride may improve voiding and pain, the first placebo-controlled randomised trial published in a peer-reviewed journal did not support this, but the study did lack power (47). In another RCT, finasteride provided better amelioration of symptoms compared to saw palmetto over a 1-year period, but lacked a placebo-control arm (48). A 6-month placebo-controlled study showed a non-significant tendency towards better outcome in favour of finasteride, possibly because of a lack of statistical power (49). Based on these data, 5-alpha-reductase inhibitors cannot be recommended for use in PPS.

3.1.7.6 Allopurinol

An RCT of allopurinol was conducted based on the hypothesis that urine reflux intoprostatic ducts causes prostatic inflammation via high concentrations of purine and pyrimidine base-containing metabolites in prostatic secretions (50). However, positive results have not been considered sufficient for recommendation by reviewers of the Cochrane Database (51). In addition, a recent randomised placebo-controlled trial of allopurinol as an adjunct to ofloxacin has not shown any benefit (52).

3.1.7.7 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 (53). An adequately powered randomised placebo-controlled study of Cernilton, another pollen extract, showed clinically significant symptom improvement over a 12-week period in inflammatory PPS patients (NIH Cat. IIIA) (54). The effect was mainly based on a significant effect on pain. Quercetin, a polyphenolic bioflavonoid with documented

antioxidant and anti-inflammatory properties, improved NIH-CPSI scores significantly in a small RCT (55). In contrast, treatment with saw palmetto, most commonly used for benign prostatic hyperplasia, did not improve symptoms over a 1-year period (48). In a systematic review and meta-analysis, patients treated with phytotherapy were found to have significantly lower pain scores than those treated with placebo (37). In addition, overall response rate in network analysis was in favour of phytotherapy (RR: 1.6; 95% CI: 1.1-1.6).

3.1.7.8 Pentosan polysulphate

High-dose oral pentosan polysulphate (3 300 mg/day), as for BPS, is able to improve clinical global assessment and QoL significantly over placebo in men with PPS, suggesting a possible common aetiology (56).

3.1.7.9 Muscle relaxants

Muscle relaxants (diazepam, baclofen) are claimed to be helpful in sphincter dysfunction or pelvic floor/perineal muscle spasm, but there have been only a few prospective clinical trials to support these claims. 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 (32).

3.1.7.10 Pregabalin

Pregabalin is an antiepileptic drug that has been approved for use in chronic postherpetic neuralgia, fibromyalgia, and diabetic neuropathy. In an adequately powered randomised placebo-controlled study, a 6-week course of pregabalin (n = 218) compared to placebo (n = 106) did not result in a significant reduction of NIH-CPSI total score by at least 6 points (57).

3.1.7.11 Botulinum toxin A

Botulinum toxin A (BTX-A) may have pain-alleviating effects through non-neuromuscular action on afferent nociceptive pathways. Local treatment with periurethral injection of BTX-A (200 U) has been tested in a small pilot study with improvement in pain and changes in urethral pressure profile (58). A small randomised placebo-controlled study of perineal skeletal muscle injection (100 U) has been published recently (59). Some effect was found in the global response assessment and the NIH-CPSI pain subdomain score. However, patient number was too low (13 in the BTX-A group and 16 in the placebo group), and follow-up was too short to draw definitive conclusions.

3.1.7.12 Physical treatments

- *Electromagnetic therapy*. In a small, sham-controlled, double-blind study, 4 weeks electromagnetic therapy showed a significant, sustained effect over a 1-year period (60).
- *Microwave thermotherapy.* Significant symptomatic improvement has been reported from heat therapy, for example, transrectal and transurethral thermotherapy (61,62), but there was no sham-control.
- *Extracorporeal shock wave therapy.* A recent sham-controlled double-blind study of four times weekly perineal extracorporeal shock wave therapy (n = 30) showed significant improvement in pain, QoL, and voiding compared to the control group (n = 30) over 12 weeks (63). Confirmatory studies are awaited because of an absent placebo-effect, which is very unusual in PPS trials.
- *Electroacupuncture.* In a small three-arm randomised trial, electroacupuncture was superior to sham treatment and advice and exercise alone (64). In a recent prospective case series of 6 weeks of weekly electroacupuncture of 97 patients with PPS, 92% showed significant improvement in total NIH-CPSI score. Based on these studies, no definitive conclusion can be drawn.
- *Posterior tibial nerve stimulation.* One sham-controlled medium-sized study (n = 89) demonstrated significant improvement in total NIH-CPSI score and visual analogue scale for pain (65).
- *Myofascial physical therapy.* A randomised feasibility trial of myofascial physical therapy including PPS (n = 21) and patients with BPS showed a clinical benefit compared to global therapeutic massage (66). In the PPS group alone, there was no difference in the effect between the two treatment arms.

3.1.7.13 Surgical management

Surgical management, including transurethral incision of the bladder neck, radical transurethral resection of the prostate, or in particular, radical prostatectomy, has a very limited role and requires an additional, specific indication. In addition, the treatment effect of transurethral needle ablation of the prostate (TUNA) was only comparable to sham treatment in two small randomised trials (67,68).

3.1.7.14 Psychological treatment

It is of note that QoL decreases as symptoms increase. Given prediction of QoL by psychological problems

(depression and catastrophising in particular), this means that psychological status should also be targeted in treatment, and the development of a psychologically focused treatment for patients refractory to drug treatment has been noted by the authors of the summary findings from the NIH Chronic Prostatitis Collaborative Research Network studies (69). There are no RCTs of psychological treatment for men with CPP, but Tripp et al. (70) have completed a feasibility trial, which represents the only known account of psychological treatment. Their 8-h intervention improved pain, catastrophising, and QoL, but not depression or some urinary symptoms. Details concerning appropriate treatment content and delivery are contained in Chapter 8.

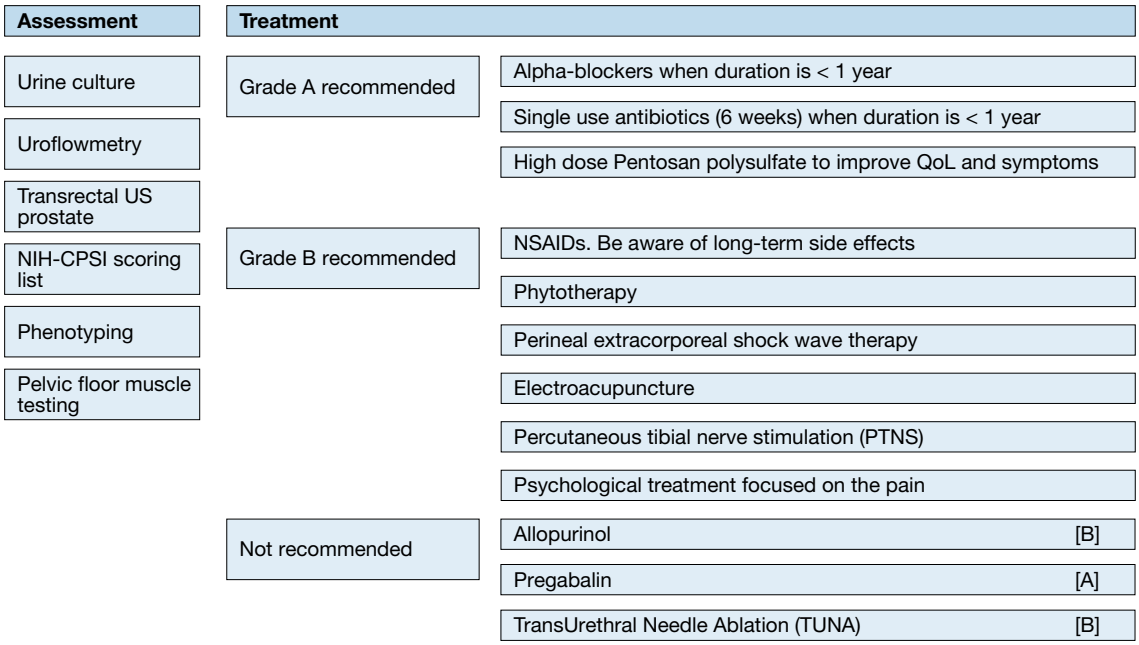
3.1.8 ***Conclusions and recommendations: treatment of PPS***

Conclusions	**LE**
Monotherapeutic treatment regimens in PPS may fail.	3
Phenotypically directed treatment may improve treatment success.	3
Alpha-blockers have moderate treatment effect regarding total pain-, voiding-, and QoL scores in PPS.	1a
Antimicrobial therapy has a moderate effect on total pain-, voiding-, and QoL scores in PPS.	1a
NSAIDs have moderate overall treatment effects on PPS.	1a
There are insufficient data on the effectiveness of steroids in PPS.	2b
There are insufficient data on the effectiveness of opioids in PPS.	4
There are insufficient data on the effectiveness of 5-alpha-reductase inhibitors in PPS.	2b
There are insufficient data on the effectiveness of allopurinol in PPS.	2b
Phytotherapy has some beneficial effect on pain and overall favourable treatment response in PPS.	1a
Pentosan polysulphate improves global assessment and QoL score in PPS.	1b
There are insufficient data on the effectiveness of muscle relaxants in PPS.	2b
Pregabalin is not effective for the treatment of PPS.	1b
BTX-A injection into the pelvic floor may have a modest effect in PPS.	2b
There are only limited data on the effectiveness of electromagnetic therapy in PPS.	2b
There are only limited data on the effectiveness of microwave thermotherapy in PPS.	3
Perineal extracorporeal shock wave therapy probably is effective for the treatment of PPS.	1b
There are limited data on the effectiveness of electroacupuncture for the treatment of PPS.	2b
Posterior tibial nerve stimulation is probably effective for the treatment of PPS.	1b
There are insufficient data on the effectiveness of myofascial physical therapy for the treatment of PPS.	2b
There are limited data on lack of effectiveness of TUNA of the prostate for PPS.	2b
There are insufficient data supporting the use of other surgical treatments, such as transurethral incision of the bladder neck, transurethral resection of the prostate, or radical prostatectomy in patients with PPS.	3
Cognitive behavioural therapy designed for PPS may improve pain, and QoL.	3

Recommendations	GR
Consider multimodal and phenotypically directed treatment options for PPS.	B
Alpha-blockers are recommended for patients with a duration of PPS < 1 year.	A
Single use of antimicrobial therapy (quinolones or tetracyclines) is recommended in treatment-naïve patients over a minimum of 6 weeks with a duration of PPS < 1 year.	A
NSAIDs are recommended for use in PPS, but long-term side effects have to be considered.	B
Allopurinol is not recommended for use in PPS.	B
Phytotherapy might be used in patients with PPS.	B
Consider high-dose pentosan polysulphate to improve symptoms and quality of life in PPS.	A
Pregabalin is not recommended for use in PPS.	A
Perineal extracorporeal shock wave therapy might be considered for the treatment of PPS.	B
Electroacupuncture might be considered for the treatment of PPS.	B
Posterior tibial nerve stimulation might be considered for the treatment of PPS.	B
TUNA of the prostate is not recommended for the treatment of PPS.	B
For PPS with significant psychological distress, psychological treatment focussed on PPS should be attempted.	B

PPS = prostate pain syndrome; TUNA = transurethral needle ablation.

Figure 5: Assessment and treatment algorithm for PPS



3.1.9 References

1. de la Rosette JJ, Hubregtse MR, Meuleman EJ, et al. Diagnosis and treatment of 409 patients with prostatitis syndromes. Urology 1993 Apr;41(4):301-7. http://www.ncbi.nlm.nih.gov/pubmed/8470312
2. Tripp DA, Nickel JC, Wang Y, et al. Catastrophizing and pain-contingent rest predict patient adjustment in men with chronic prostatitis/chronic pelvic pain syndrome. J Pain 2006 Oct;7(10):697-708. http://www.ncbi.nlm.nih.gov/pubmed/17018330
3. Walz J, Perotte P, Hutterer G, et al. Impact of chronic prostatitis-like symptoms on the quality of life in a large group of men. BJU Int 2007 Dec;100(6):1307-11. http://www.ncbi.nlm.nih.gov/pubmed/17941922
4. Marszalek M, Wehrberger C, Hochreiter W, et al. Symptoms suggestive of chronic pelvic pain syndrome in an urban population: prevalence and associations with lower urinary tract symptoms and erectile function. J Urol 2007 May;177(5):1815-9. http://www.ncbi.nlm.nih.gov/pubmed/17437827

5. Nickel JC. Prostatitis: myths and realities. Urology. 1998 Mar;51(3):362-6.
http://www.ncbi.nlm.nih.gov/pubmed/9510337
6. Nickel JC, Baranowski AP, Pontari M, et al. Management of men diagnosed with chronic prostatitis/chronic pelvic pain syndrome who have failed traditional management. Rev Urol. 2007 Spring;9(2):63-72.
http://www.ncbi.nlm.nih.gov/pubmed/17592539
7. Yang CC, Lee JC, Kromm BG, et al. Pain sensitization in male chronic pelvic pain syndrome: why are symptoms so difficult to treat? J Urol 2003 Sep;170(3):823-6.
http://www.ncbi.nlm.nih.gov/pubmed/12913708
8. Barry MJ, Link CL, McNaughton-Collins MF, et al. Overlap of different urological symptom complexes in a racially and ethnically diverse, community-based population of men and women. BJU Int 2008 Jan;101(1):45-51.
http://www.ncbi.nlm.nih.gov/pubmed/17868419
9. Roberts RO, Jacobson DJ, Girman CJ, et al. Low agreement between previous physician diagnosed prostatitis and national institutes of health chronic prostatitis symptom index pain measures.J Urol 2004 Jan;171(1):279-83.
http://www.ncbi.nlm.nih.gov/pubmed/14665894
10. Collins MM, Stafford RS, O'Leary MP, et al. How common is prostatitis? A national survey of physician visits.J Urol 1998 Apr;159(4):1224-8.
http://www.ncbi.nlm.nih.gov/pubmed/9507840
11. Krieger JN, Lee SW, Jeon J, et al. Epidemiology of prostatitis. Int J Antimicrob Agents. 2008 Feb;31 Suppl 1:S85-90.
http://www.ncbi.nlm.nih.gov/pubmed/18164907
12. Ferris JA, Pitts MK, Richters J, et al. National prevalence of urogenital pain and prostatitis-like symptoms in Australian men using the National Institutes of Health Chronic Prostatitis Symptoms Index. BJU Int 2010 Feb;105(3):373-9.
http://www.ncbi.nlm.nih.gov/pubmed/19549116
13. Rizzo M, Marchetti F, Travaglini A, et al. Prevalence, diagnosis and treatment of prostatitis in Italy: A prospective urology outpatient practice study. BJU Int 2003 Dec;92(9):955-9.
http://www.ncbi.nlm.nih.gov/pubmed/14632854
14. Mehik A, Hellström P, Lukkarinen O, et al. Epidemiology of prostatitis in Finnish men: a population-based cross-sectional study. BJU Int 2000 Sep;86(4):443-8.
http://www.ncbi.nlm.nih.gov/pubmed/10971269
15. Nickel JC, Siemens DR, Nickel KR, et al. The patient with chronic epididymitis: Characterization of an enigmatic syndrome. J Urol 2002 Apr;167(4):1701-4.
http://www.ncbi.nlm.nih.gov/pubmed/11912391
16. Turner JUA, Ciol MA, Von Korff M, et al. Prognosis of patients with new prostatitis/pelvic pain syndrome episodes.J Urol 2004 Aug;172(2):538-41.
http://www.ncbi.nlm.nih.gov/pubmed/15247724
17. Litwin MS, McNaughton-Collins M, Fowler FJ Jr, et al. The National Institutes of Health chronic prostatitis symptom index: development and validation of a new outcome measure. Chronic Prostatitis Collaborative Research Network. J Urol 1999 Aug;162(2):369-75.
http://www.ncbi.nlm.nih.gov/pubmed/10411041
18. Mebust WK, Bosch R, Donovan J, et al. Symptom evaluation, quality of life and sexuality. In: Cockett ATK, Khoury S, Aso Y, et al. *Proceedings of the 2ndConsultation on Benign Prostatic Hyperplasia* (BPH), Paris. Channel Islands: Scientific Communication International Ltd, 1993, pp. 131-138.
19. Wenninger K, Heiman JR, Rothman I, et al. Sickness impact of chronic nonbacterial prostatitis and its correlates. J Urol 1996 Mar;155(3):965-8.
http://www.ncbi.nlm.nih.gov/pubmed/8583619
20. McNaughton Collins M, Pontari MA, O'Leary MP, et al. Chronic Prostatitis Collaborative Research Network. Quality of life is impaired in men with chronic prostatitis: the Chronic Prostatitis Collaborative Research Network. J Gen Intern Med 2001 Oct;16(10):656-62.
http://www.ncbi.nlm.nih.gov/pubmed/11679032
21. Meares EM, Stamey TA. Bacteriologic localization patterns in bacterial prostatitis and urethritis. Invest Urol 1968 Mar;5(5):492-518. [no abstract available]
http://www.ncbi.nlm.nih.gov/pubmed/4870505
22. Nickel JC. The Pre and Post Massage Test (PPMT): a simple screen for prostatitis. Tech Urol 1997 Spring;3(1):38-43.
http://www.ncbi.nlm.nih.gov/pubmed/9170224

23. Nickel JC, Shoskes D, Wang Y, et al. How does the pre-massage and postmassage 2-glass test compare to the Meares-Stamey 4-glass test in men with chronic prostatitis/chronic pelvic pain syndrome? J Urol 2006 Jul;176(1):119-24.
http://www.ncbi.nlm.nih.gov/pubmed/16753385
24. Nickel JC, Pontari M, Moon T, et al. Rofecoxib Prostatitis Investigator Team. A randomized, placebo controlled, multicenter study to evaluate the safety and efficacy of rofecoxib in the treatment of chronic nonbacterial prostatitis. J Urol 2003 Apr;169(4):1401-5.
http://www.ncbi.nlm.nih.gov/pubmed/12629372
25. Zermann DH, Ishigooka M, Doggweiler R, et al. Neurourological insights into the etiology of genitourinary pain in men. J Urol 1999 Mar;161(3):903-8.
http://www.ncbi.nlm.nih.gov/pubmed/10022711
26. Shoskes DA, Nickel JC, Kattan MW. Phenotypically Directed Multimodal Therapy for Chronic Prostatitis/Chronic Pelvic Pain Syndrome: A Prospective Study Using UPOINT. Urology 2010 Jun;75(6):1249-53.
http://www.ncbi.nlm.nih.gov/pubmed/20363491
27. Nickel JC, Narayan P, McKay J, et al. Treatment of chronic prostatitis/chronic pelvic pain syndrome with tamsulosin: a randomized double blind trial. J Urol 2004 Apr;171(4):1594-7.
http://www.ncbi.nlm.nih.gov/pubmed/15017228
28. Cheah PY, Liong ML, Yuen KH, et al. Terazosin therapy for chronic prostatitis/chronic pelvic pain syndrome: a randomized, placebo controlled trial. J Urol 2003 Feb;169(2):592-6.
http://www.ncbi.nlm.nih.gov/pubmed/12544314
29. Gül O, Eroglu M, Ozok U. Use of terazosine in patients with chronic pelvic pain syndrome and evaluation by prostatitis symptom score index. Int Urol Nephrol 2001;32(3):433-6.
http://www.ncbi.nlm.nih.gov/pubmed/11583367
30. Mehik A, Alas P, Nickel JC, et al. Alfuzosin treatment for chronic prostatitis/chronic pelvic pain syndrome: a prospective, randomized, double-blind, placebo-controlled, pilot study. Urology 2003 Sep;62(3):425-9.
http://www.ncbi.nlm.nih.gov/pubmed/12946740
31. Evliyaoglu Y, Burgut R. Lower urinary tract symptoms, pain and quality of life assessment in chronic non-bacterial prostatitis patients treated with alpha-blocking agent doxazosin; versus placebo. Int Urol Nephrol 2002;34(3):351-6.
http://www.ncbi.nlm.nih.gov/pubmed/12899226
32. Tugcu V, Tasci AI, Fazlioglu, Gurbuz G, Ozbek E, Sahin S, Kurtulus F, Cek M. A placebo-controlled comparison of the efficiency of triple- and monotherapy in category III B chronic pelvic pain syndrome (PPS). Eur Urol 2007 Apr;51(4):1113-7; discussion 1118.
http://www.ncbi.nlm.nih.gov/pubmed/17084960
33. Nickel JC, Downey J, Pontari MA, et al. A randomized placebo-controlled multicentre study to evaluate the safety and efficacy of finasteride for male chronic pelvic pain syndrome (category IIIA chronic nonbacterial prostatitis). BJU Int 2004 May;93(7):991-5.
http://www.ncbi.nlm.nih.gov/pubmed/15142149
34. Yang G, Wei Q, Li H, et al. The effect of alpha-adrenergic antagonists in chronic prostatitis/ chronic pelvic pain syndrome: a meta-analysis of randomized controlled trials. J Androl 2006 Nov-Dec;27(6):847-52.
http://www.ncbi.nlm.nih.gov/pubmed/16870951
35. Alexander RB, Propert KJ, Schaeffer AJ, et al. Ciprofloxacin or tamsulosin in men with chronic prostatitis/chronic pelvic pain syndrome: a randomized, double-blind trial. Ann Intern Med. 2004 Oct 19;141(8):581-9.
http://www.ncbi.nlm.nih.gov/pubmed/15492337
36. Nickel JC, Krieger JN, McNaughton-Collins M, et al. Chronic Prostatitis Collaborative Research Network. Alfuzosin and symptoms of chronic prostatitis-chronic pelvic pain syndrome. N Engl J Med 2008 Dec 18;359(25):2663-73.
http://www.ncbi.nlm.nih.gov/pubmed/19092152
37. Anothaisintawee, AttiaJ, Nickel JC, et al. Management of chronic prostatitis/chronic pelvic pain syndrome: A systematic review and network meta-analysis. JAMA. 2011 Jan 5;305(1):78-86.
http://www.ncbi.nlm.nih.gov/pubmed/21205969
38. Nickel JC, Downey J, Johnston B, et al. Canadian Prostatitis Research Group. Predictors of patient response to antibiotic therapy for the chronic prostatitis/chronic pelvic pain syndrome: a prospective multicenter clinical trial. J Urol 2001 May;165(5):1539-44.
http://www.ncbi.nlm.nih.gov/pubmed/11342913

39. Lee JC, Muller CH, Rothman I, et al. Prostate biopsy culture findings of men with chronic pelvic pain syndrome do not differ from those of healthy controls. J Urol 2003 Feb;169(2):584-7.
http://www.ncbi.nlm.nih.gov/pubmed/12544312
40. Nickel JC, Pontari M, Moon T, et al. Rofecoxib Prostatitis Investigator Team. A randomized, placebo controlled, multicenter study to evaluate the safety and efficacy of rofecoxib in the treatment of chronic nonbacterial prostatitis. J Urol 2003 Apr;169(4):1401-5.
http://www.ncbi.nlm.nih.gov/pubmed/12629372
41. Zhou Z, Hong L, Shen X, et al. Detection of Nanobacteria Infection in Type III Prostatitis. Urology 2008 Jun;71(6):1091-5.
http://www.ncbi.nlm.nih.gov/pubmed/18538692
42. Nickel JC, Downey J, Clark J, et al. Levofloxacin for chronic prostatitis/chronic pelvic pain syndrome in men: A randomized placebo-controlled multicenter trial. Urology 2003 Oct;62(4):614-7.
http://www.ncbi.nlm.nih.gov/pubmed/14550427
43. Zhao WP, Zhang ZG, Li XD, et al. Celecoxib reduces symptoms in men with difficult chronic pelvic pain syndrome (Category IIIA). Braz J Med Biol Res. 2009 Oct;42(10):963-7.
http://www.ncbi.nlm.nih.gov/pubmed/19787151
44. Goldmeier D, Madden P, McKenna M, et al. Treatment of category III A prostatitis with zafirlukast: A randomized controlled feasibility study. Int J STD AIDS. 2005 Mar;16(3):196-200.
http://www.ncbi.nlm.nih.gov/pubmed/15829018
45. Bates SM, Hill VA, Anderson JB, et al. A prospective, randomized, double-blind trial to evaluate the role of a short reducing course of oral corticosteroid therapy in the treatment of chronic prostatitis/ chronic pelvic pain syndrome. BJU Int 2007 Feb;99(2):355-9.
http://www.ncbi.nlm.nih.gov/pubmed/17313424
46. Nickel JC. Opioids for chronic prostatitis and interstitial cystitis: lessons learned from the 11th World Congress on Pain. Urology 2006 Oct;68(4):697-701. [no abstract available]
http://www.ncbi.nlm.nih.gov/pubmed/17070334
47. Leskinen M, Lukkarinen O, Marttila T. Effects of finasteride in patients with inflammatory chronic pelvic pain syndrome: a double-blind, placebo-controlled, pilot study. Urology 1999 Mar;53(3):502-5.
http://www.ncbi.nlm.nih.gov/pubmed/10096374
48. Kaplan SA, Volpe MA, Te AE. A prospective, 1-year trial using saw palmetto versus finasteride in the treatment of category III prostatitis/chronic pelvic pain syndrome. J Urol 2004 Jan;171:284-8.
http://www.ncbi.nlm.nih.gov/pubmed/14665895
49. Nickel JC, Downey J, Ardern D, et al. Failure of a monotherapy strategy for difficult chronic prostatitis/ chronic pelvic pain syndrome. J Urol 2004 Aug;172(2):551-4.
http://www.ncbi.nlm.nih.gov/pubmed/15247727
50. Persson BE, Ronquist G, Ekblom M. Ameliorative effect of allopurinol on nonbacterial prostatitis: a parallel double-blind controlled study. J Urol 1996 Mar;155(3):961-4.
http://www.ncbi.nlm.nih.gov/pubmed/8583618
51. McNaughton CO, Wilt T. Allopurinol for chronic prostatitis. Cochrane Database Syst Rev 2002;(4):CD001041.
http://www.ncbi.nlm.nih.gov/pubmed/12519549
52. Ziaee AM, Akhavizadegan H, Karbakhsh M. Effect of allopurinol in chronic nonbacterial prostatitis: a double blind randomized clinical trial. Int Braz J Urol 2006 Mar-Apr;32(2):181-6.
http://www.ncbi.nlm.nih.gov/pubmed/16650295
53. Elist J. Effects of pollen extract preparation Prostat/Poltit on lower urinary tract symptoms in patients with chronic nonbacterial prostatitis/chronic pelvic pain syndrome: a randomized, double-blind, placebo-controlled study. Urology 2006 Jan;67(1):60-3.
http://www.ncbi.nlm.nih.gov/pubmed/16413333
54. Wagenlehner FME, Schneider H, Ludwig M, et al. A Pollen Extract (Cernilton) in Patients with Inflammatory Chronic Prostatitis-Chronic Pelvic Pain Syndrome: A Multicentre, Randomised, Prospective, Double-Blind, Placebo-Controlled Phase 3 Study. Eur Urol. 2009 Sep;56(3):544-51.
http://www.ncbi.nlm.nih.gov/pubmed/19524353
55. Shoskes DA, Zeitlin SI, Shahed A, et al. Quercetin in men with category III chronic prostatitis: A preliminary prospective, double-blind, placebo-controlled trial. Urology 1999 Dec;54(6):960-3.
http://www.ncbi.nlm.nih.gov/pubmed/10604689
56. Nickel JC, Forrest JB, Tomera K, et al. Pentosan polysulfate sodium therapy for men with chronic pelvic pain syndrome: a multicenter, randomized, placebo controlled study. J Urol 2005 Apr;173(4):1252-5.
http://www.ncbi.nlm.nih.gov/pubmed/15758763

57. Pontari MA, Krieger JN, Litwin MS, et al. Pregabalin for the treatment of men with chronic prostatitis/chronic pelvic pain syndrome: A randomized controlled trial. Arch Intern Med. 2010 Sep 27;170(17):1586-93.
http://www.ncbi.nlm.nih.gov/pubmed/20876412
58. Zermann D, Ishigooka M, Schubert J. Perisphincteric injection of botulinum toxin type A. A treatment option for patients with chronic prostatic pain? Eur Urol. 2000 Oct;38(4):393-9.
http://www.ncbi.nlm.nih.gov/pubmed/11025376
59. Gottsch HP, Yang CC, Berger RE. A pilot study of botulinum toxin A for male chronic pelvic pain syndrome. Scand J Urol Nephrol 2010 Nov 9. Scand J Urol Nephrol 2011 Feb;45(1):72-6.
http://www.ncbi.nlm.nih.gov/pubmed/21062115
60. Rowe E, Smith C, Laverick L, et al. A prospective, randomized, placebo controlled, double-blind study of pelvic electromagnetic therapy for the treatment of chronic pelvic pain syndrome with 1 year of followup. J Urol 2005 Jun;173(6):2044-7.
http://www.ncbi.nlm.nih.gov/pubmed/15879822
61. Montorsi F, Guazzoni G, Bergamaschi F, et al. Is there role for transrectal microwave hyperthermia of the prostate in the treatment of abacterial prostatitis and prostatodynia? Prostate 1993;22(2):139-46.
http://www.ncbi.nlm.nih.gov/pubmed/8456052
62. Kastner C, Hochreiter W, Huidobro C, et al. Cooled transurethral microwave thermotherapy for intractable chronic prostatitis-results of a pilot study after 1 year. Urology 2004 Dec;64(6):1149-54.
http://www.ncbi.nlm.nih.gov/pubmed/15596188
63. Zimmermann R, Cumpanas A. Miclea F, et al. Extracorporeal Shock Wave Therapy for the Treatment of Chronic Pelvic Pain Syndrome in Males: A Randomised, Double-Blind, Placebo-Controlled Study. Eur Urol. 2009 Sep;56(3):418-24.
http://www.ncbi.nlm.nih.gov/pubmed/19372000
64. Lee SH, Lee BC. Electroacupuncture Relieves Pain in Men With Chronic Prostatitis/Chronic Pelvic Pain Syndrome: Three-arm Randomized Trial. Urology 2009 May;73(5):1036-41.
http://www.ncbi.nlm.nih.gov/pubmed/19394499
65. Kabay S, Kabay SC, Yucel M, et al. Efficiency of posterior tibial nerve stimulation in category IIIB chronic prostatitis/chronic pelvic pain: A sham-controlled comparative study. Urol Int. 2009;83(1):33-8.
http://www.ncbi.nlm.nih.gov/pubmed/19641356
66. FitzGerald MP, Anderson RU, Potts J, et al. Randomized Multicenter Feasibility Trial of Myofascial Physical Therapy for the Treatment of Urological Chronic Pelvic Pain Syndromes. J Urol 2009 Aug;182(2):570-80.
http://www.ncbi.nlm.nih.gov/pubmed/19535099
67. Leskinen MJ, Kilponen A, Lukkarinen O, et al. Transurethral needle ablation for the treatment of chronic pelvic pain syndrome (category III prostatitis): a randomized, sham-controlled study urology 2002 Aug;60(2):300-4.
http://www.ncbi.nlm.nih.gov/pubmed/12137830
68. Aaltomaa S, Ala-Opas M. The effect of transurethral needle ablation on symptoms of chronic pelvic pain syndrome--a pilot study. Scand J Urol Nephrol 2001 Apr;35(2):127-31.
http://www.ncbi.nlm.nih.gov/pubmed/11411655
69. Nickel JC, Alexander RB, Anderson R, et al. Category III chronic prostatitis/chronic pelvic pain syndrome: insights from the National Institutes of Health Chronic Prostatitis Collaborative Research Network studies.Curr Urol Rep. 2008 Jul;9(4):320-7.
http://www.ncbi.nlm.nih.gov/pubmed/18765132
70. Tripp DA, Nickel JC, Katz L. A feasibility trial of a cognitive-behavioural symptom management program for chronic pelvic pain for men with refractory chronic prostatitis/chronic pelvic pain syndrome.Can Urol Assoc J. 2011 Oct;5(5):328-32.
http://www.ncbi.nlm.nih.gov/pubmed/22031613

3.2 Bladder pain syndrome

3.2.1 Introduction

Interstitial cystitis (IC) 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 Hunner at the beginning of the last century (2,3). Subsequent research (4-6) has shown that IC encompassed a heterogeneous spectrum of disorders, with different endoscopic and histopathological presentations, with inflammation an important feature in only a subset of patients. To embrace all patients suffering from bladder pain, the terms painful bladder syndrome (PBS) or BPS have been suggested as more accurate when referring to pain in the bladder region, while assuming IC with Hunner's lesion as a specific type of chronic inflammation of the bladder (7,8). The term BPS was put forward by the International Society for the Study of BPS (ESSIC) and will be used in

these guidelines. In accordance Classic IC (Hunner's lesion and inflammation) will be referred to as BPS type 3 C (See Chapter 2, section 2.4 'Definitions of CPP terminology').

3.2.2 ***Definition***

Although generally accepted, the NIDDK criteria provide only a minimum framework to establish the diagnosis and have been felt to be too restrictive for clinical use (9-12). Recently, the ESSIC has suggested a standardised scheme of diagnostic criteria (13) to make it easier to compare different studies. BPS was preferred as the general term to match the current taxonomy of chronic pain syndromes.

3.2.3 ***Diagnosis***

Bladder pain syndrome should be diagnosed on the basis of pain, pressure or discomfort associated with the urinary bladder, accompanied by at least one other symptom, such as daytime and/or night-time increased urinary frequency, the exclusion of confusable diseases as the cause of symptoms, and if indicated, cystoscopy with hydrodistension and biopsy (Table 7) (8).

Table 7: ESSIC classification of types of BPS according to the results of cystoscopy with hydrodistension and 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]Lesion per Fall's definition with/without glomerulations
[c]Histology showing inflammatory infiltrates and/or detrusor mastocytosis and/or granulation tissue and/or intrafascicular fibrosis.

Beyond subtyping, recent work has indicated the need to phenotype BPS patients. The - Urinary, Psychosocial, Organ Specific, Inflammation, Neurological/Systemic, Tenderness - UPOINT phenotyping system classifies patients according to clinically relevant domains, facilitating the use and appraisal of multimodal therapies (14).

3.2.4 ***Pathogenesis***

Current thought implicates an initial unidentified insult to the bladder, triggering inflammatory, endocrine and neural phenomena (15-17). This may happen in patients with an underlying systemic defect. In fact, BPS is similar and frequently precedes, coexists or follows other so-called functional somatic syndromes (FSSs), occurring predominantly in women, with pain as the main symptom, no abnormal laboratory or anatomical findings, and exacerbated by stress, namely fibromyalgia (FM), IBS and chronic fatigue syndrome (CFS) (17-19). At the bladder level, multiple aetiological or pathophysiological mechanisms have been and are still sought after.

No infection has as yet been implicated (20-25). BPS patients and controls have equal UTI frequency (18,26). Nevertheless, UTI and urgency are significantly more frequent during childhood and adolescence, in patients who later develop BPS in adulthood (27). Pancystitis, with associated perineural inflammatory infiltrates, is an essential part of BPS type 3 C (23), but is scant in non-ulcer BPS (6). There is a 10-fold increase in the mast cell count in bladder tissue from patients with BPS type 3 C compared with controls. Mast-cell-secreted mediators (28,29) can indeed induce symptoms and findings of BPS type 3 C (30). In non-ulcer BPS, however, the mast cell count is normal or only slightly increased (6,29,31,32).

Cystoscopic and biopsy findings in both ulcer and non-ulcer BPS are consistent with defects in the urothelial glycosaminoglycan (GAG) layer, which might expose the submucosal nerve filaments to noxious urine components (33-37). Furthermore, urinary uronate, and sulphated GAG levels are increased in patients with severe BPS (38). Uroplakin III-delta 4, caveolin-1, acid-sensing channels 2a and 3, muscarinic (M2-5) and purinergic receptors (P2X2 and P2X1), bradykinin B1 receptor, and cannabinoid receptor CB1 are also

upregulated and bladder urothelial sensitivity to carbachol enhanced in urothelial cells of BPS patients (39-41). In contrast, tight junction proteins zona occludens-1, junctional adherins molecule -1, and occludin genes are downregulated. Luminal nitric oxide (NO) urinary levels and inducible NO synthetase activity (iNOS) are increased in BPS patients (42). Urinary NO is significantly increased in ulcer patients and decreases with treatment, but not in non-ulcer BPS patients (43). iNOS-dependent NO production may have a role in urothelial dysfunction (44). Altogether, these data further point to increased urothelial permeability. Moreover, constituents of urine may exert a cytotoxic effect (45), especially in situations such as altered urothelial barrier or existence of unsialylated Tamm-Horsefall protein observed in BPS (46,47). Along with altered gene regulation, post translational epigenetic conditioning through micro RNA interference with messenger RNA transcription, may perpetuate the answer to aggression mode, induced on urethelial cells by an initial insult (39,48).

Microvascular alterations are present in BPS. Despite unaltered number of microvessels, the ratio of mature to total vessels is significantly lower (49) and decreased bladder perfusion upon filling is observed in BPS patients (50). Adding to that, proangiogenic vascular endothelial growth factor and hypoxia inducible factor (HIF)-1 expression is increased in the urothelium of BPS patients (49,51).

Involvement of neurogenic inflammation as the trigger to a cascade of events in BPS has been confirmed by multiple observations documenting its occurrence, followed by neuroplasticity and neuronal sensitisation, both in the peripheral and CNS of BPS patients. Thus, bladder sensory nerve fibres can induce bladder wall events through neurogenic inflammation sparked by an initial insult, as well as pain regionalisation and centralisation. In fact, several data have shown enhanced bladder peripheral nerve density and increased peripheral neuromediator release, along with neurotrophin and nerve fibre receptor increases, especially in sensory and sympathetic nerves. Furthermore, besides cytokines from umbrella cells, activation of mast cells in close proximity to nerve terminals can be influenced by oestradiol as well as corticotrophin-releasing hormone (52-58). Regionalisation of pain is observed frequently in BPS patients (59). Moreover, autonomic responses and CNS processing of afferent stimuli are altered in patients with BPS (55,60,61).

Some of the clinical and histopathological characteristics are similar to autoimmune phenomena. However, only some BPS patients demonstrate autoantibodies, immune deposits or complement activation (62-69). Of note, differing T-cell infiltrates and B-cell nodules are seen in BPS type 3 C (70).

3.2.5 ***Epidemiology***

Reports of the prevalence of BPS have varied greatly, along with the diagnostic criteria and populations studied. Recent reports generally show higher figures than earlier ones, ranging from 0.06% to 30% (71-80) There is a female predominance of about 10:1 (4,71,81,82) but contrary to prior belief, possibly no difference in race or ethnicity (83-85). The relative proportions of classic and non-ulcer disease are unclear. Incidence in various studies has ranged from 5 to 50% (5,12,86,87).

Evidence that BPS may have a genetic component has been presented in several studies, but may contribute to less than one third of total variation in susceptibility for BPS, with the remainder being environmental (19,88-91).

BPS has significant economic costs. Direct annual costs in the USA have been estimated to be $750 million (92).

3.2.6 ***References***

1. Skene AJC. Diseases of the bladder and urethra in women. New York: William Wood 1887;167. http://www.archive.org/stream/diseasesofbladd00sken
2. Hunner GL. A rare type of bladder ulcer in women: report of cases. Boston Med Surg J 1915;172: 660-4.
3. Hunner G. Elusive ulcer of the bladder: further notes on a rare type of bladder ulcer with report of 25 cases. Am J Obstet 1918;78:374-95.
4. Hand JR. Interstitial cystitis: report of 223 cases (204 women and 19 men). J Urol 1949 Feb;61(2): 291-310. http://www.ncbi.nlm.nih.gov/pubmed/18111850
5. Messing EM, Stamey TA. Interstitial cystitis: early diagnosis, pathology, and treatment. Urology 1978 Oct;12(4):381-92. http://www.ncbi.nlm.nih.gov/pubmed/213864

6. Fall M, Johansson SL, Aldenborg F. Chronic interstitial cystitis: a heterogeneous syndrome. J Urol 1987 Jan;137(1):35-8.
http://www.ncbi.nlm.nih.gov/pubmed/3795363
7. Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Subcommitte of the International Continence Society. Am J Obstet Gynecol 2002 Jul;187(1):116-26.
http://www.ncbi.nlm.nih.gov/pubmed/12114899
8. van de Merwe JP, Nordling J, Bouchelouche P, et al. Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC poposal. Eur Urol 2008 Jan;53(1):60-7.
http://www.ncbi.nlm.nih.gov/pubmed/17900797
9. Gillenwater JY, Wein AJ. Summary of the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases Workshop on Interstitial Cystitis, National Institutes of Health, Bethesda, Maryland, August 28-29,1987. J Urol 1988 Jul;140(1):203-6. [no abstract available]
http://www.ncbi.nlm.nih.gov/pubmed/3379688
10. Hanno PM, Landis JR, Matthews-Cook Y, et al. The diagnosis of interstitial cystitis revisited: lessons learned from the National Institutes of Health Interstitial Cystitis Database study. J Urol 1999 Feb;161(2):553-7.
http://www.ncbi.nlm.nih.gov/pubmed/9915447
11. Erickson DR, Belchis DA, Dabbs DJ. Inflammatory cell types and clinical features of interstitial cystitis. J Urol 1997 Sep;158(3 Pt 1):790-3.
http://www.ncbi.nlm.nih.gov/pubmed/9258082
12. Peeker R, Fall M. Toward a precise definition of interstitial cystitis: further evidence of differences in classic and nonulcer disease. J Urol 2002 Jun;167(6):2470-2.
http://www.ncbi.nlm.nih.gov/pubmed/11992059
13. Nordling J, Anjum FH, Bade JJ, et al. Primary evaluation of patients suspected of having interstitial cystitis (IC). Eur Urol 2004 May;45(5):662-9.
http://www.ncbi.nlm.nih.gov/pubmed/15082211
14. Nickel JC, Shoskes D, Irvine-Bird K. Clinical phenotyping of women with interstitial cystitis/painful bladder syndrome: a key to classification and potentially improved management. J Urol 2009 Jul;182(1):155-60.
http://www.ncbi.nlm.nih.gov/pubmed/19447429
15. Elbadawi A. Interstitial cystitis: a critique of current concepts with a new proposal for pathologic diagnosis and pathogenesis. Urology 1997 May;49(5A Suppl):14-40.
http://www.ncbi.nlm.nih.gov/pubmed/9145999
16. Okragly AJ, Niles AL, Saban R, et al. Elevated tryptase, nerve growth factor,neurotrophin-3 and glial cell line-derived neurotrophic factor levels in theurine of interstitial cystitis and bladder cancer patients. J Urol 1999 Feb;161(2):438-41.
http://www.ncbi.nlm.nih.gov/pubmed/9915421
17. Warren JW, Wesselmann U, Morozov V, et al. Numbers and types of non bladder syndromes as risk factors for interstitial cystitis/painful bladder syndrome. Urology 2011 Feb;77(2):313-9.
http://www.ncbi.nlm.nih.gov/pubmed/21295246
18. Nickel JC, Shoskes DA, Irvine-Bird K. Prevalence and impact of bacteriuria and/or urinary tract infection in interstitial cystitis/painful bladder syndrome. Urology 2010 Oct;76(4):799-803.
http://www.ncbi.nlm.nih.gov/pubmed/20573386
19. Talati A, Ponniah K, Strug LJ, et al. Panic disorder, social anxiety disorder, and a possible medical syndrome previously linked to chromosome 13.Biol Psychiatry 2008 Mar 15;63(6):594-601.
http://www.ncbi.nlm.nih.gov/pubmed/17920564
20. Domingue GJ, Ghoniem GM, Bost KL, et al. Dormant microbes in interstitial cystitis. Erratum in: J Urol 1996;155:298. J Urol 1995 Apr;153(4):1321-6.
http://www.ncbi.nlm.nih.gov/pubmed/7869536
21. Lynes WL, Sellers RG, Dairiki Shortliffe LM. The evidence for occult bacterial infections as a cause for interstitial cystitis. J Urol 1989;141:268A (abstr 393).
22. Hukkanen V, Haarala M, Nurmi M, et al. Viruses and interstitial cystitis: adenovirus genomes cannot be demonstrated in urinary bladder biopsies. Urol Res 1996;24(4):235-8.
http://www.ncbi.nlm.nih.gov/pubmed/8873382
23. Fall M, Johansson SL, Vahlne A. A clinicopathological and virological study of interstitial cystitis. J Urol 1985 May;133(5):771-3.
http://www.ncbi.nlm.nih.gov/pubmed/2985831

24. Duncan JL, Schaeffer AJ. Do infectious agents cause interstitial cystitis? Urology 1997 May;49(5A Suppl):48-51.
http://www.ncbi.nlm.nih.gov/pubmed/9146001
25. Al-Hadithi HN, Williams H, Hart CA, et al. Absence of bacterial and viral DNA in bladder biopsies from patients with interstitial cystitis/chronic pelvic pain syndrome. J Urol 2005 Jul;174(1):151-4.
http://www.ncbi.nlm.nih.gov/pubmed/15947607
26. Warren JW, Brown V, Jacobs S, et al. Urinary Tract Infection and Inflammation at Onset of Interstitial Cystitis/Painful bladder Syndrome. Urology 2008 Jun;71(6):1085-90.
http://www.ncbi.nlm.nih.gov/pubmed/18538691
27. Peters KM, Killinger KA, Ibrahim IA. Childhood symptoms and events in women with interstitial cystitis/painful bladder syndrome. Urology 2009 Feb;73(2):258-62.
http://www.ncbi.nlm.nih.gov/pubmed/19036420
28. Agarwal M, Dixon RA. A study to detect Helicobacter pylori in fresh and archival specimens from patients with interstitial cystitis, using amplification methods. BJU Int 2003 Jun;91(9):814-6.
http://www.ncbi.nlm.nih.gov/pubmed/12780839
29. Peeker R, Enerback L, Fall M, et al. Recruitment, distribution and phenotypes of mast cells in interstitial cystitis. J Urol 2000 Mar;163(3):1009-15.
http://www.ncbi.nlm.nih.gov/pubmed/10688040
30. Richter B, Roslind A, Hesse U, et al. YKL-40 and mast cells are associated with detrusor fibrosis in patients diagnosed with bladder pain syndrome/interstitial cystitis according to the 2008 criteria of the European Society for the Study of Interstitial Cystitis.Histopathology. 2010 Sep;57(3):371-83.
http://www.ncbi.nlm.nih.gov/pubmed/20840668
31. Dundore PA, Schwartz AM, Semerjian H. Mast cell counts are not useful in the diagnosis of nonulcerative interstitial cystitis. J Urol 1996 Mar;155(3):885-7.
http://www.ncbi.nlm.nih.gov/pubmed/8583599
32. Wyndaele JJ, Van Dyck J, Toussaint N. Cystoscopy and bladder biopsies in patients with bladder pain syndrome carried out following ESSIC guidelines. Scand J Urol Nephrol 2009;43(6):471-5.
http://www.ncbi.nlm.nih.gov/pubmed/19707951
33. Johansson SL, Fall M. Clinical features and spectrum of light microscopic changes in interstitial cystitis. J Urol 1990 Jun;143(6):1118-24.
http://www.ncbi.nlm.nih.gov/pubmed/2342171
34. Anderström CR, Fall M, Johansson SL. Scanning electron microscopic findings in interstitial cystitis. Br J Urol 1989 Mar;63(3):270-5.
http://www.ncbi.nlm.nih.gov/pubmed/2702424
35. Fellows GJ, Marshall DH. The permeability of human bladder epithelium to water and sodium. Invest Urol 1972 Jan;9(4):339-44. [no abstract available]
http://www.ncbi.nlm.nih.gov/pubmed/5058772
36. Parsons CL, Mulholland SG. Successful therapy of interstitial cystitis with pentosanpolysulfate. J Urol 1987 Sep;138(3):513-6.
http://www.ncbi.nlm.nih.gov/pubmed/2442417
37. Parsons CL, Lilly JD, Stein P. Epithelial dysfunction in nonbacterial cystitis (interstitial cystitis). J Urol 1991 Apr;145(4):732-5.
http://www.ncbi.nlm.nih.gov/pubmed/2005689
38. Lokeshwar VB, Selzer MG, Cerwinka WH, et al. Urinary uronate and sulfated glycosaminoglycan levels: markers for interstitial cystitis severity. J Urol 2005 Jul;174(1):344-9.
http://www.ncbi.nlm.nih.gov/pubmed/15947687
39. Sánchez-Freire V, Blanchard MG, Burkhard FC, et al. Acid-Sensing Channels in Human Bladder: Expression, Function and Alterations During Bladder Pain Syndrome. J Urol 2011 Oct;186(4):1509-16.
http://www.ncbi.nlm.nih.gov/pubmed/21855903
40. Gupta GN, Lu S, Gold MS, et al. Bladder Urothelial Cells From Patients With Interstitial Cystitis Have an Increased Sensitivity to Carbachol. Neurourol Urodyn. 2009;28(8):1022-7.
http://www.ncbi.nlm.nih.gov/pubmed/19283864
41. Lin XC, Zhang QH, Zhou P, et al. Caveolin-1 may participate in the pathogenesis of bladder pain syndrome/interstitial cystitis. Urol Int. 2011;86(3):334-9.
http://www.ncbi.nlm.nih.gov/pubmed/21335944
42. Ehrén I, Hosseini A, Lundberg JO, et al. Nitric oxide: a useful gas in the detection of lower urinary tract inflammation. J Urol 1999 Aug;162(2):327-9.
http://www.ncbi.nlm.nih.gov/pubmed/10411031

43. Logadottir YR, Ehren I, Fall M, et al. Intravesical nitric oxide production iscriminates between classic and nonulcer interstitial cystitis. J Urol 2004 Mar;171(3):1148-50; discussion 50-1.
http://www.ncbi.nlm.nih.gov/pubmed/14767289
44. Birder LA, Wolf-Johnston A, Buffington CA, et al. Altered inducible nitricoxide hase expression and nitric oxide production in the bladder of cats with feline interstitial cystitis. J Urol 2005 Feb;173(2): 625-9.
http://www.ncbi.nlm.nih.gov/pubmed/15643277
45. Parsons CL, Bautista SL, Stein PC, et al. Cyto-injury factors in urine: a possible mechanism for the development of interstitial cystitis. J Urol 2000 Oct;164(4):1381-4.
http://www.ncbi.nlm.nih.gov/pubmed/10992419
46. Hang L, Wullt B, Shen Z, et al. Cytokine repertoire of epithelial cells lining the human urinary tract. J Urol 1998 Jun;159(6):2185-92.
http://www.ncbi.nlm.nih.gov/pubmed/9598567
47. Parsons CL, Stein P, Zupkas P, et al. Defective Tamm-Horsfall protein in patients with interstitial cystitis. J Urol 2007 Dec;178(6):2665-70.
http://www.ncbi.nlm.nih.gov/pubmed/17945284
48. Sanchez Freire V, Burkhard FC, Kessler TM, et al. MicroRNAs may mediate the down-regulation of neurokinin-1 receptor in chronic bladder pain syndrome. Am J Pathol 2010 Jan;176(1):288-303.
http://www.ncbi.nlm.nih.gov/pubmed/20008142
49. Kiuchi H, Tsujimura A, Takao T, et al. Increased vascular endothelial growth factor expression in patients with bladder pain syndrome/interstitial cystitis: its association with pain severity and glomerulations. BJU Int 2009 Sep;104(6):826-31.
http://www.ncbi.nlm.nih.gov/pubmed/19298410
50. Pontari MA, Hanno PM, Ruggieri MR. Comparison of bladder blood flow in patients with and without interstitial cystitis. J Urol 1999 Aug;162(2):330-4.
http://www.ncbi.nlm.nih.gov/pubmed/10411032
51. Lee JD, Lee MH. Increased Expression of Hypoxia-inducible Factor-1 and Vascular Endothelial Growth Factor Associated With Glomerulation Formation in Patients With Interstitial Cystitis. Urology 2011 Oct;78(4):971.e11-5.
http://www.ncbi.nlm.nih.gov/pubmed/21813166
52. Abdel-Mageed AB, Ghoniem GM. Potential role of rel/nuclear factor-kappaB in the pathogenesis of interstitial cystitis. J Urol 1998 Dec;160(6 Pt 1):2000-3.
http://www.ncbi.nlm.nih.gov/pubmed/9817309
53. Abdel-Mageed A, Ghoniem G, Human I, et al. Induction of proinflammatory cytokine gene expression by NF-kappaB in human bladder epithelial (T-24) cells: possible mechanism for interstitial cystitis. J Urol 1999;161(Suppl):28.
54. Hohenfellner M, Nunes L, Schmidt RA, et al. Interstitial cystitis: increased sympathetic innervation and related neuropeptide synthesis. J Urol 1992 Mar;147(3):587-91.
http://www.ncbi.nlm.nih.gov/pubmed/1538434
55. Twiss CO, Kilpatrick L, Triaca V, et al. Evidence for central hyperexitability in patients with interstitial cystitis. J Urol 2007 Jun;177(4):49.
http://www.icsoffice.org/Abstracts/Publish/45/000009.pdf
56. Theoharides TC, Pang X, Letourneau R, et al. Interstitial cystitis: a neuroimmunoendocrine disorder. Ann N Y Acad Sci 1998 May;840:619-34.
http://www.ncbi.nlm.nih.gov/pubmed/9629289
57. Okragly AJ, Niles AL, Saban R, et al. Elevated tryptase, nerve growth factor, neurotrophin-3 and glial cell line-derived neurotrophic factor levels in the urine of interstitial cystitis and bladder cancer patients. J Urol 1999 Feb;161(2):438-41; discussion 441-2.
http://www.ncbi.nlm.nih.gov/pubmed/9915421
58. Boucher W, Kempuraj D, Michaelian M, et al. Corticotropin-releasing hormone-receptor 2 is required for acute stress-induced bladder vascular permeability and release of vascular endothelial growth factor. BJU Int 2010 Nov;106(9):1394-9.
http://www.ncbi.nlm.nih.gov/pubmed/20201838
59. Warren JW, Langenberg P, Greenberg P, et al. Sites of pain from interstitial cystitis/painful bladder syndrome. J Urol 2008 Oct;180(4):1373-7.
http://www.ncbi.nlm.nih.gov/pubmed/18707715
60. Yilmaz U, Liu YW, Berger RE, et al. Autonomic nervous system changes in men with chronic pelvic pain syndrome. J Urol 2007 Jun;177(6):2170-4; discussion 2174.
http://www.ncbi.nlm.nih.gov/pubmed/17509311

61. Elbadawi AE, Light JK. Distinctive ultrastructural pathology of nonulcerative interstitial cystitis: new observations and their potential significance in pathogenesis. Urol Int 1996;56(3):137-62.
http://www.ncbi.nlm.nih.gov/pubmed/8860736
62. Oravisto KJ, Alfthan OS, Jokinen EJ. Interstitial cystitis. Clinical and immunological findings. Scand J Urol Nephrol 1970;4(1):37-42. [no abstract available]
http://www.ncbi.nlm.nih.gov/pubmed/5314306
63. Jokinen EJ, Alfthan OS, Oravisto KJ. Antitissue antibodies in interstitial cystitis. Clin Exp Immunol 1972 Jul;11(3):333-9.
http://www.ncbi.nlm.nih.gov/pubmed/4114472
64. Ochs RL, Stein TW Jr, Peebles CL, et al. Autoantibodies in interstitial cystitis. J Urol 1994 Mar;151(3):587-92.
http://www.ncbi.nlm.nih.gov/pubmed/8308964
65. Tan EM. Antinuclear antibodies: diagnostic markers for autoimmune diseases and probes for cell biology. Adv Immunol 1989;44:93-151. [no abstract available]
http://www.ncbi.nlm.nih.gov/pubmed/2646863
66. von Muhlen CA, Tan EM. Autoantibodies in the diagnosis of systemic rheumatic diseases. Semin Arthritis Rheum 1995 Apr;24(5):323-58.
http://www.ncbi.nlm.nih.gov/pubmed/7604300
67. Ochs RL. Autoantibodies and interstitial cystitis. Clin Lab Med 1997 Sep;17(3):571-9.
http://www.ncbi.nlm.nih.gov/pubmed/9316774
68. Mattila J. Vascular immunopathology in interstitial cystitis. Clin Immunol Immunopathol 1982 Jun;23(3):648-55. [no abstract available]
http://www.ncbi.nlm.nih.gov/pubmed/6981479
69. Mattila J, Linder E. Immunoglobulin deposits in bladder epithelium and vessels in interstitial cystitis: possible relationship to circulating anti-intermediate filament autoantibodies. Clin Immunol Immunopathol 1984 Jul;32(1):81-9.
http://www.ncbi.nlm.nih.gov/pubmed/6733983
70. Harrington DS, Fall M, Johansson SL. Interstitial cystitis: bladder mucosa lymphocyte immunophenotyping and peripheral blood flow cytometry analysis. J Urol 1990 Oct;144(4):868-71.
http://www.ncbi.nlm.nih.gov/pubmed/2204728
71. Oravisto KJ. Epidemiology of interstitial cystitis. Ann Chir Gynaecol Fenn 1975;64(2):75-7.
http://www.ncbi.nlm.nih.gov/pubmed/1137336
72. Held PJ, Hanno PM, Wein AJ. In: Hanno PM, Staskin DR, Krane RJ, Wein AJ, eds. Interstitial Cystitis. Epidemiology of interstitial cystitis. London: Springer Verlag, 1990, pp. 29-48.
73. Bade JJ, Rijcken B, Mensink HJ. Interstitial cystitis in The Netherlands: prevalence, diagnostic criteria and therapeutic preferences. J Urol 1995 Dec;154(6):2035-7; discussion 2037-8.
http://www.ncbi.nlm.nih.gov/pubmed/7500452
74. Jones CA, Harris MA, Nyberg L. Prevalence of interstitial cystitisin the United States, Proc Am Urol Ass J Urol 1994;151(Suppl):423A.
75. Curhan GC, Speizer FE, Hunter DJ, et al. Epidemiology of interstitial cystitis: a population based study. J Urol 1999 Feb;161(2):549-52.
http://www.ncbi.nlm.nih.gov/pubmed/9915446
76. Leppilahti M, Sairanen J, Tammela TL, et al. Finnish Interstitial Cystitis-Pelvic Pain Syndrome Study Group. Prevalence of clinically confirmed interstitial cystitis in women: a population based study in Finland. J Urol 2005 Aug;174(2):581-3.
http://www.ncbi.nlm.nih.gov/pubmed/16006902
77. Temml C, WehrbergerC, Riedl C, et al. Prevalence and correlates for interstitial cystitis symptoms in women participating in a health screening project. Eur Urol. 2007 Mar;51(3):803-8; discussion 809.
http://www.ncbi.nlm.nih.gov/pubmed/16979286
78. Burkman RT.Chronic pelvic pain of bladder origin: epidemiology, pathogenesis and quality of life. J Reprod Med 2004 Mar;49(3 Suppl):225-9.
http://www.ncbi.nlm.nih.gov/pubmed/15088860
79. Roberts RO, Bergstralh EJ, Bass SE, et al. Incidence of physician-diagnosed interstitial cystitis in Olmsted County: a community-based study. BJU Int 2003 Feb;91(3):181-5.
http://www.ncbi.nlm.nih.gov/pubmed/12581000
80. Parsons CL, Tatsis V. Prevalence of interstitial cystitis in young women. Urology 2004 Nov;64(5): 866-70.
http://www.ncbi.nlm.nih.gov/pubmed/15533465
81. Greenberg E, Barnes R, Stewart S, et al. Transurethral resection of Hunner's ulcer. J Urol 1974 Jun;111(6):764-6. [no abstract available]
http://www.ncbi.nlm.nih.gov/pubmed/4830879

82. Koziol JA. Epidemiology of interstitial cystitis. Urol Clin North Am 1994 Feb;21(1):7-20. http://www.ncbi.nlm.nih.gov/pubmed/8284848
83. Berry SH, Elliott MN, Suttorp M, et al. Prevalence of symptoms of bladder pain syndrome/interstitial cystitis among adult females in the United States. J Urol 2011 Aug;186(2):540-4. http://www.ncbi.nlm.nih.gov/pubmed/21683389
84. Barry MJ, Link CL, McNaughton-Collins MF, et al. Boston Area Community Health (BACH) Investigators. Overlap of different urological symptom complexes in a racially and ethnically diverse, community-based population of men and women. BJU Int 2008 Jan;101(1):45-51. http://www.ncbi.nlm.nih.gov/pubmed/17868419
85. Song Y, Zhang W, Xu B, et al. Prevalence and correlates of painful bladder syndrome symptoms in Fuzhou Chinese women. Neurourol Urodyn. 2009;28(1):22-5. http://www.ncbi.nlm.nih.gov/pubmed/18671294
86. Parsons CL. Interstitial cystitis: clinical manifestations and diagnostic criteria in over 200 cases. Neurourol Urodynam 1990;9:241. http://onlinelibrary.wiley.com/doi/10.1002/nau.1930090302/abstract
87. Koziol JA, Adams HP, Frutos A. Discrimination between the ulcerous and the nonulcerous forms of interstitial cystitis by noninvasive findings. J Urol 1996 Jan;155(1):87-90. http://www.ncbi.nlm.nih.gov/pubmed/7490906
88. Parsons CL, Zupkas P, Parsons JK. Intravesical potassium sensitivity in patients with interstitial cystitis and urethral syndrome. Urology 2001 Mar;57(3):428-32; discussion 432-3. http://www.ncbi.nlm.nih.gov/pubmed/11248610
89. Warren J, Jackson T, Meyers D, et al. Fishbein/interstitial cystitis association (ICA) survey of interstitial cystitis among family members of ICA members: preliminary analysis. Urology 2001 Jun;57(6 Suppl 1): 126-7. [no abstract available] http://www.ncbi.nlm.nih.gov/pubmed/11378121
90. Warren JW, Keay SK, Meyers D, et al. Concordance of interstitial cystitis in monozygotic and dizygotic twin pairs. Urology 2001 Jun;57(6 Suppl 1):22-5. http://www.ncbi.nlm.nih.gov/pubmed/11378045
91. Altman D, Lundholm C, Milsom I, et al. The genetic and environmental contribution to the occurrence of bladder pain syndrome: an empirical approach in a nationwide population sample. Eur Urol. 2011 Feb;59(2):280-5. http://www.ncbi.nlm.nih.gov/pubmed/21056533
92. Clemens JQ, Meenan RT, Rosetti MC et al. Costs of interstitial cystitis in a managed care population. Urology 2008 May;71(5):776-80. http://www.ncbi.nlm.nih.gov/pubmed/18329077

3.2.7 ***Association with other diseases***

An association has been reported between BPS and non-bladder syndromes (NBSs) - IBS, FM, CFS, vulvodynia, depression, panic disorders, migraine, sicca syndrome, temporomandibular joint disorder, allergy, asthma, systemic lupus erythematosus, inflammatory bowel disease (1-7). Risk of BPS correlates with a number of NBSs in each patient (8). Recent work showing non-ulcer BPS to have significantly more FM, migraine, temporomandibular joint disorder and depression than ulcer patients emphasises the need for subtyping (9).

3.2.8 ***Diagnosis***

The diagnosis of BPS is one of exclusion, using symptoms, examination, urine analysis, cystoscopy with hydrodistension, and biopsy (Figure 6).

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

- Pain, pressure or discomfort perceived to be related to the bladder, 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 (10-14).
- Pain is aggravated by food or drink (13).

The differences between the two BPS subtypes, BPS type 3 C and non-ulcer, include clinical presentation, age distribution (15), molecular features (16-22), which may be discriminated non-invasively (23), and response to treatment (24-27). BPS type 3 C is a highly damaging inflammation that often leads to a small-capacity fibrotic bladder or upper urinary tract outflow obstruction. This type of progression is not observed in non-ulcer disease (14,28). Endoscopically, BPS type 3 C displays reddened mucosal areas often associated with small vessels radiating towards a central scar, sometimes covered by a small clot or fibrin deposit - the

Hunner lesion (14). The scar ruptures with increasing bladder distension, producing a characteristic waterfall-type of bleeding. There is a strong association between BPS type 3 C and reduced bladder capacity under anaesthesia (14,29,30).

Cystoscopy
Non-ulcer disease 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 has shown that there is no difference in the cystoscopic appearance between patients with non-ulcer disease and women without bladder symptoms about to undergo tubal ligation (31). The observation of glomerulations may however not always be constant over time (32).

Some authors maintain that cystoscopy with hydrodistension provides little useful information in addition to the history and physical examination findings (33,34). In contrast, others have found a strong correlation between pain and cystoscopic findings in patients with untreated BPS, and this difference from the results of other studies may have been due to treatment effects (35). Glomerulations may be involved in the disease mechanism, because such findings are highly associated with overexpression of angiogenic growth factors in the bladder and neovascularisation (36). A recent pilot study has demonstrated feasibility of bladder distension and biopsy under local anaesthesia (37). ESSIC believes objective findings are important and that a standardised scheme of diagnostic criteria would help improve the uniformity and comparability of different studies (38).

Biopsies are helpful in establishing or supporting the clinical diagnosis of both classic and non-ulcer types of the disease (17,38-41). 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 BPS (41), but recent reports have suggested that it lacks discriminating power (42,43). A modified test using less concentrated solution has been suggested. This test, although painless in contrast to the original procedure, decreases the maximum cystometric volume in 90% of patients with BPS, but not in controls (44). Furthermore, it has been suggested that the potassium sensitivity test can help to predict the response to GAG treatment (45).

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 (46).

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. Antiproliferative factor, heparin-binding epidermal growth factor-like growth factor, uroplakin III delta-4 mRNA, and YKL-40 have all presented as potential candidates (47-49). NO is interesting because of its ability to discriminate classic from non-ulcer disease with minimal invasiveness. However, all putative markers to date have yet to be validated (50).

3.2.9 ***BPS in children and males***
According to NIDDK criteria, children aged < 18 years is an exclusion criterion. However, occasional cases of BPS of both subtypes have been identified in patients under this age (51). There is increasing evidence that children aged 2-11 may also be affected, although prevalence figures are low (52). Thus, BPS cannot be excluded on the basis of age.
It has been argued that PPS and BPS are inter-related (53,54). However, differences in urinary markers suggest that BPS and PPS are different disorders with distinct pathophysiology (55).

3.2.10 *Conclusions and recommendations: assessment and diagnosis BPS*

Conclusions	LE
BPS has no known single aetiology.	3
Pain in BPS does not correlate with bladder cystoscopic or histologic findings.	2a
BPS Type 3 C is not surely distinguishable by non-invasive means.	2a
Ulcer non-ulcer disease ratios of BPS are highly variable between studies.	2a
The prevalence of BPS-like symptoms is high in population-based studies.	2a
BPS associated non-bladder diseases are extremely prevalent, differ in BPS subtypes and correlate with BPS risk.	2a
BPS has a high impact on quality of life.	2a
There is significant overlap of symptoms with other conditions.	2a
Reliable instruments assessing symptom severity as well as phenotypical differences exist.	2a

Recommendations	GR
Specific diseases with similar symptoms have to be excluded. It is therefore recommended to adapt diagnostic procedures to each patient and aim at identifying them.	A
After primary exclusion of specific diseases, patients with symptoms according to the above definition should be diagnosed with BPS by subtype and phenotype.	A
A validated symptom and quality of life scoring instrument should be considered for initial assessment as well as for follow-up.	B
BPS associated non-bladder diseases should be assessed systematically.	A
BPS associated negative cognitive, behavioural, sexual, or emotional consequences should be assessed.	A

BPS = Bladder pain syndrome.

3.2.11 *References*

1. Warren J, Jackson T, Meyers D, et al. Fishbein/interstitial cystitis association (ICA) survey of interstitial cystitis among family members of ICA members: preliminary analysis. Urology 2001 Jun;57(6 Suppl 1):126-7. [no abstract available]
   http://www.ncbi.nlm.nih.gov/pubmed/11378121
2. Warren JW, Howard FM, Cross RK, et al. Antecedent nonbladder syndromes in case-control study of interstitial cystitis/painful bladder syndrome. Urology 2009 Jan;73(1):52-7.
   http://www.ncbi.nlm.nih.gov/pubmed/18995888
3. Alagiri M, Chottiner S, Ratner V, et al. Interstitial cystitis: unexplained associations with other chronic disease and pain syndromes. Urology 1997 May;49(5A Suppl):52-7.
   http://www.ncbi.nlm.nih.gov/pubmed/9146002
4. Clauw DJ, Schmidt M, Radulovic D, et al. The relationship between fibromyalgia and interstitial cystitis. J Psychiatr Res 1997 Jan-Feb;31(1):125-31.
   http://www.ncbi.nlm.nih.gov/pubmed/9201654
5. Erickson DR, Morgan KC, Ordille S, et al. Nonbladder related symptoms in patients with interstitial cystitis. J Urol 2001;166(2):557-61 Aug; discussion 561-2.
   http://www.ncbi.nlm.nih.gov/pubmed/11458068
6. Weissman MM, Gross R, Fyer A, et al. Interstitial Cystitis and Panic Disorder - A Potential Genetic Syndrome. Arch Gen Psych 2004;61:273-9.
   http://archpsyc.ama-assn.org/cgi/content/abstract/61/3/273
7. Buffington CA. Comorbidity of interstitial cystitis with other unexplained clinical conditions. J Urol 2004 Oct;172(4 Pt 1):1242-8.
   http://www.ncbi.nlm.nih.gov/pubmed/15371816
8. Warren JW, Wesselmann U, Morozov V, et al. Numbers and types of nonbladder syndromes as risk factors for interstitial cystitis/painful bladder syndrome. Urology 2011 Feb;77(2):313-9.
   http://www.ncbi.nlm.nih.gov/pubmed/21295246

9. Peters KM, Killinger KA, Mounayer MH, et al. Are ulcerative and nonulcerative interstitial cystitis/ painful bladder syndrome 2 distinct diseases? A study of coexisting conditions. Urology 2011 Aug;78(2):301-8.
http://www.ncbi.nlm.nih.gov/pubmed/21703668
10. Bullock AD, Becich MJ, Klutke CG, et al. Experimental autoimmune cystitis: a potential murine model for ulcerative interstitial cystitis. J Urol 1992 Dec;148(6):1951-6.
http://www.ncbi.nlm.nih.gov/pubmed/1433651
11. Dodd LG, Tello J. Cytologic examination of urine from patients with interstitial cystitis. Acta Cytol 1998 Jul-Aug;42(4):923-7.
http://www.ncbi.nlm.nih.gov/pubmed/9684578
12. Erickson DR, Davies MF. Interstitial cystitis. Int Urogynecol J Pelvic Floor Dysfunct 1998;9(3):174-83.
http://www.ncbi.nlm.nih.gov/pubmed/9745978
13. Warren JW, Brown J, Tracy JK, et al. Evidence-based criteria for pain of interstitial cystitis/painful bladder syndrome in women. Urology 2008 Mar;71(3):444-8.
http://www.ncbi.nlm.nih.gov/pubmed/18342184
14. Fall M, Johansson SL, Aldenborg F. Chronic interstitial cystitis: a heterogeneous syndrome. J Urol 1987 Jan;137(1):35-8.
http://www.ncbi.nlm.nih.gov/pubmed/3795363
15. Peeker R, Fall M. Toward a precise definition of interstitial cystitis: further evidence of differences in classic and nonulcer disease. J Urol 2002 Jun;167(6):2470-2.
http://www.ncbi.nlm.nih.gov/pubmed/11992059
16. Dundore PA, Schwartz AM, Semerjian H. Mast cell counts are not useful in the diagnosis of nonulcerative interstitial cystitis. J Urol 1996 Mar;155(3):885-7.
http://www.ncbi.nlm.nih.gov/pubmed/8583599
17. Johansson SL, Fall M. Clinical features and spectrum of light microscopic changes in interstitial cystitis. J Urol 1990 Jun;143(6):1118-24.
http://www.ncbi.nlm.nih.gov/pubmed/2342171
18. Harrington DS, Fall M, Johansson SL. Interstitial cystitis: bladder mucosa lymphocyte immunophenotyping and peripheral blood flow cytometry analysis. J Urol 1990 Oct;144(4):868-71.
http://www.ncbi.nlm.nih.gov/pubmed/2204728
19. Peeker R, Aldenborg F, Haglid K, et al. Decreased levels of S-100 protein in non-cer interstitial cystitis. Scand J Urol Nephrol 1998 Dec;32(6):395-8.
http://www.ncbi.nlm.nih.gov/pubmed/9925003
20. Twiss CO, Kilpatrick L, Triaca V, et al. Evidence for central hyperexitability in patients with interstitial cystitis. J Urol 2007 Jun;177(4):49.
http://www.icsoffice.org/Abstracts/Publish/45/000009.pdf
21. Koziol JA, Clark DC, Gittes RF, et al. The natural history of interstitial cystitis: a survey of 374 patients. J Urol 1993 Mar;149(3):465-9.
http://www.ncbi.nlm.nih.gov/pubmed/8437248
22. Enerbäck L, Fall M, Aldenborg F. Histamine and mucosal mast cells in interstitial cystitis. Agents Actions 1989 Apr;27(1-2):113-6.
http://www.ncbi.nlm.nih.gov/pubmed/2750582
23. Koziol JA, Adams HP, Frutos A. Discrimination between the ulcerous and the nonulcerous forms of interstitial cystitis by noninvasive findings. J Urol 1996 Jan;155(1):87-90.
http://www.ncbi.nlm.nih.gov/pubmed/7490906
24. Hanno PM. Amitriptyline in the treatment of interstitial cystitis. Urol Clin North Am 1994 Feb;21(1): 89-91.
http://www.ncbi.nlm.nih.gov/pubmed/8284851
25. Fall M, Lindström S. Transcutaneous electrical nerve stimulation in classic and nonulcer interstitial cystitis. Urol Clin North Am 1994 Feb;21(1):131-9.
http://www.ncbi.nlm.nih.gov/pubmed/8284836
26. Peeker R, Haghsheno MA, Holmang S, et al. Intravesical bacillus Calmette-Guerin and dimethyl sulfoxide for treatment of classic and nonulcer interstitial cystitis: a prospective, randomized doubleblind study. J Urol 2000 Dec;164(6):1912-1915; discussion 1915-6.
http://www.ncbi.nlm.nih.gov/pubmed/11061879
27. Fritjofsson A, Fall M, Juhlin R, et al. Treatment of ulcer and nonulcer interstitial cystitis with sodium pentosanpolysulfate: a multicenter trial. J Urol 1987 Sep;138(3):508-12.
http://www.ncbi.nlm.nih.gov/pubmed/2442416
28. Lechevallier E. Interstitial cystitis. Prog Urol 1995 Feb;5(1):21-30. [Article in French]
http://www.ncbi.nlm.nih.gov/pubmed/7719356

29. Peeker R, Fall M. Toward a precise definition of interstitial cystitis: further evidence of differences in classic and nonulcer disease. J Urol 2002 Jun;167(6):2470-2.
http://www.ncbi.nlm.nih.gov/pubmed/11992059
30. Messing E, Pauk D, Schaeffer A, et al. Associations among cystoscopic findings and symptoms and physical examination findings in women enrolled in the Interstitial Cystitis Data Base (ICDB) Study. Urology 1997 May;49(5A Suppl):81-5.
http://www.ncbi.nlm.nih.gov/pubmed/9146006
31. Waxman JA, Sulak PJ, Kuehl TJ. Cystoscopic findings consistent with interstitial cystitis in normal women undergoing tubal ligation. J Urol 1998 Nov;160(5):1663-7.
http://www.ncbi.nlm.nih.gov/pubmed/9783927
32. Shear S, Mayer R. Development of glomerulations in younger women with interstitial cystitis. Urology.2006 Aug;68(2):253-6.
http://www.ncbi.nlm.nih.gov/pubmed/16904429
33. Ottem DP, Teichman JM. What is the value of cystoscopy with hydrodistension for interstitial cystitis? Urology 2005 Sep;66(3):494-9.
http://www.ncbi.nlm.nih.gov/pubmed/16140064
34. Cole EE, Scarpero HM, Dmochowski RR. Are patient symptoms predictive of the diagnostic and/or therapeutic value of hydrodistention? Neurourol Urodyn 2005;24(7):638-42.
http://www.ncbi.nlm.nih.gov/pubmed/16208660
35. Lamale LM, Lutgendorf SK, Hoffman AN, et al. Symptoms and cystoscopic findings in patients with untreated interstitial cystitis. Urology 2006 Feb;67(2):242-5.
http://www.ncbi.nlm.nih.gov/pubmed/16442603
36. Tamaki M, Saito R, Ogawa O, et al. Possible mechanisms inducing glomerulations in interstitialcystitis: relationship between endoscopic findings and expression of angiogenic growth factors. J Urol 2004 Sep;172(3):945-8.
http://www.ncbi.nlm.nih.gov/pubmed/15311005
37. Nordling J, Anjum FH, Bade JJ, et al. Primary evaluation of patients suspected of having interstitial cystitis (IC). Eur Urol 2004 May;45(5):662-9.
http://www.ncbi.nlm.nih.gov/pubmed/11992059
38. Aihara K, Hirayama A, Tanaka N, et al. Hydrodistension under local anesthesia for patients with suspected painful bladder syndrome/interstitial cystitis: safety, diagnostic potential and therapeutic efficacy. Int J Urol 2009 Dec;16(12):947-52.
http://www.ncbi.nlm.nih.gov/pubmed/19817916
39. Johansson SL, Fall M. Pathology of interstitial cystitis. Urol Clin North Am 1994 Feb;21(1):55-62.
http://www.ncbi.nlm.nih.gov/pubmed/8284845
40. Geurts N, Van Dyck J, Wyndaele JJ. Bladder pain syndrome: do the different morphological and cystoscopic features correlate? Scand J Urol Nephrol 2011 Feb;45(1):20-3.
http://www.ncbi.nlm.nih.gov/pubmed/20846081
41. Parsons CL, Greenberger M, Gabal L, et al. The role of urinary potassium in the pathogenesis and diagnosis of interstitial cystitis. J Urol 1998 Jun;159(6):1862-6;discussion 1866-7.
http://www.ncbi.nlm.nih.gov/pubmed/9598476
42. Chambers GK, Fenster HN, Cripps S, et al. An assessment of the use of intravesical potassium in the diagnosis of interstitial cystitis. J Urol 1999 Sep;162(3 Pt 1):699-701.
http://www.ncbi.nlm.nih.gov/pubmed/10458346
43. Grégoire M, Liandier F, Naud A, et al. Does the potassium stimulation test predict cystometric, cystoscopic outcome in interstitial cystitis? J Urol 2002 Aug;168(2):556-7.
http://www.ncbi.nlm.nih.gov/pubmed/12131308
44. Daha LK, Riedl CR, Hohlbrugger G, et al. Comparative assessment of maximal bladder capacity, 0.9%NaCl versus 0.2 M Kcl, for the diagnosis of interstitial cystitis: a prospective controlled study. J Urol 2003 Sep;170(3):807-9.
http://www.ncbi.nlm.nih.gov/pubmed/12913704
45. Gupta SK, Pidcock L, Parr NJ. The potassium sensitivity test: a predictor of treatment response in interstitial cystitis. BJU Int 2005 Nov;96(7):1063-6.
http://www.ncbi.nlm.nih.gov/pubmed/16225529
46. Lubeck DP, Whitmore K, Sant GR, et al. Psychometric validation of the O'leary-Sant interstitial cystitis symptom index in a clinical trial of pentosan polysulfate sodium. Urology 2001 Jun; 57(6 Suppl 1): 62-6.
http://www.ncbi.nlm.nih.gov/pubmed/11378052

47. Zeng Y, Wu XX, Homma Y, et al. Uroplakin III-delta4 messenger RNA as a promising marker to identify nonulcerative interstitial cystitis. J Urol 2007 Oct;178(4 Pt 1):1322-7; discussion 1327. http://www.ncbi.nlm.nih.gov/pubmed/17698128
48. Richter B, Roslind A, Hesse U, et al. YKL-40 and mast cells are associated with detrusor fibrosis in patients diagnosed with bladder pain syndrome/interstitial cystitis according to the 2008 criteria of the European Society for the Study of Interstitial Cystitis. Histopathology 2010 Sep;57(3):371-83. http://www.ncbi.nlm.nih.gov/pubmed/20840668
49. Keay S, Kleinberg M, Zhang CO, et al. Bladder epithelial cells from patients with interstitial cystitis produce an inhibitor of heparin-binding epidermal growth factor-like growth factor production. J Urol 2000 Dec;164(6):2112-8. http://www.ncbi.nlm.nih.gov/pubmed/11061938
50. Logadottir YR, Ehren I, Fall M, et al. Intravesical nitric oxide production iscriminates between classic and nonulcer interstitial cystitis. J Urol 2004 Mar;171(3):1148-50; discussion 50-1. http://www.ncbi.nlm.nih.gov/pubmed/14767289
51. Close CE, Carr MC, Burns MW, et al. Interstitial cystitis in children. J Urol 1996 Aug;156(2 Pt 2):860-2. http://www.ncbi.nlm.nih.gov/pubmed/8683802
52. Mattox TF. Interstitial cystitis in adolescents and children: a review. J Pediatr Adolesc Gynecol 2004Feb;17(1):7-11. http://www.ncbi.nlm.nih.gov/pubmed/15010032
53. Miller JL, Rothman I, Bavendam TG, et al. Prostatodynia and interstitial cystitis: one and the same? Urology 1995 Apr;45(4):587-90. http://www.ncbi.nlm.nih.gov/pubmed/7716839
54. Pontari MA. Chronic prostatitis/chronic pelvic pain syndrome and interstitial cystitis: are they related? Curr Urol Rep 2006 Jul;7(4):329-34. http://www.ncbi.nlm.nih.gov/pubmed/16930505
55. Keay S, Zhang CO, Chai T, et al. Antiproliferative factor, heparin-binding epidermal growth factor-like growth factor, and epidermal growth factor in men with interstitial cystitis versus chronic pelvic pain syndrome. Urology 2004 Jan;63(1):22-6. http://www.ncbi.nlm.nih.gov/pubmed/14751340

3.2.12 ***Medical treatment***

Analgesics. Pain is often a dominant symptom, therefore, many patients try commonly used analgesics at some stage of the disease. However, pain relief is disappointing because the visceral pain experienced in BPS responds poorly to analgesic drugs. No systematic studies have been conducted 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 (1). BPS is a chronic disease, therefore, long-term opioids should be used only exceptionally and under close surveillance.

Corticosteroids. Reports on outcome with corticosteroid therapy have been both promising (2) and discouraging (3). Soucy et al. (4) have suggested a trial of prednisone (25 mg daily for 1-2 months, afterwards reduced to the minimum required for symptom relief) in patients with severe ulcerative BPS, which is otherwise unresponsive to conventional treatment. The side effects of steroids can be very serious, making it difficult to justify their use.

Antiallergics. Mast cells may play a role in BPS. Histamine is one of the substances released by mast cells. Histamine receptor antagonists have been used to block the H1 (5) as well as the H2 (6) receptor subtypes, 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 (7). 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, which usually resolve after a period of treatment. In the first series using hydroxyzine, > 90% of patients showed improvement across the whole range of symptoms. Interestingly, improvement was noted in associated symptoms including migraine, IBS and allergies (5).

Although these initial results were supported by a further uncontrolled study (5,8), a prospective RCT of hydroxyzine or sodium pentosan polysulphate compared to placebo failed to show a statistically significant effect (9). 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, probably via mechanisms such as blockade of acetylcholine receptors, inhibition of reuptake of released serotonin and noradrenalin, and blockade of histamine H1 receptors. It is also an anxiolytic agent (10). Several reports have indicated amelioration after oral amitriptyline (11-13). In a prospective RCT, 48 patients were treated for 4 months with amitriptyline (14).

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, whereas frequency and functional bladder capacity improved, but not significantly. In a subsequent, prospective, open-label study (15), 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 28 patients fulfilling NIDDK criteria and those with a clinical diagnosis of BPS. Anticholinergic side effects (mouth dryness and weight gain) were common and considered to be a drawback of amitriptyline. A multicentre, randomised, double-blind, placebo-controlled clinical trial comparing amitriptyline and placebo plus behavioural modification in 273 patients concluded that amitriptyline may be beneficial at ≥ 50 mg/daily (16). In clinical practice drowsiness is also a limiting factor with amitriptyline and a lower starting dose of 10 mg is often suggested. Nortriptyline is sometimes considered in place of amitriptyline when drowsiness is the limiting factor.

Pentosan polysulphate sodium (Elmiron) has been evaluated in double-blind, placebo-controlled studies. Pentosan polysulphate sodium is thought to substitute for a defect in the GAG layer. Subjective improvement of pain, urgency, frequency, but not nocturia, has been reported in patients taking the drug compared to placebo (17,18). In an open multicentre study, pentosan polysulphate sodium had a more favourable effect in BPS type 3 C than in non-ulcer disease (19). The normal dose is 150-200 mg twice daily between meals. However, absorption is incomplete. An RCT has compared 300 mg pentosan polysulphate sodium with evaluated dosages of 600 and 900 mg in 380 BPS patients. Mean ICSI scores improved significantly for all dosages (20). 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 pentosan polysulphate sodium and hydroxyzine against placebo failed to demonstrate a statistically significant outcome for either drug, although the former approached statistical significance ($P = 0.064$) (9). Combination therapy showed the highest response rate of 40% compared to 13% with placebo. For patients with an initial minor response to pentosan polysulphate sodium, additional subcutaneous administration of heparin appeared to be helpful (21).

Antibiotics have a limited role in the treatment of BPS. A prospective pilot RCT 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, whereas 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 (22).

Immunosuppressants. Azathioprine, 50-100 mg daily, was given to 38 patients, resulting in disappearance of pain in 22 and urinary frequency in 20 (23). Cyclosporin A (CyA) (24) and methotrexate (25) were initially evaluated in open studies, with a good effect on pain, but a limited effect on urgency and frequency.

More recent studies of CyA have reported promising results (26,27). In 23 patients, daily voiding, 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 a few months of discontinuing CyA.

In a subsequent randomised study (27), 64 patients fulfilling the NIH criteria were randomised to 1.5 mg/kg CyA twice daily or low-dose (3x 100 mg) pentosan polysulphate sodium for 6 months. CyA was superior to pentosan polysulphate 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% (pentosan polysulphate sodium) ($P < 0.001$). However, there were more adverse events in the CyA arm (including induced hair growth, gingival pain and hyperplasia, paraesthesia in the extremities, abdominal pain, flushing, muscle pain and shaking), and only 29 patients completed the 6 months 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 concomitant therapeutics, such as opioids. Two patients with BPS showed improved functional capacity and received adequate pain control when gabapentin was added to their regimen (28). In an uncontrolled dose-escalation protocol with 21 chronic genitourinary pain patients (29), 10 improved with gabapentin at 6 months. The study included eight BPS 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 (30). 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 postherpetic neuralgia. Studies on BPS are still lacking.

Suplatast tosilate (IPD-1151T) is an oral immunoregulator that suppresses helper-T-cell-mediated allergic processes. Fourteen women with BPS 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, IgE and urinary T cells (31). Comparative controlled data are unavailable.

Quercetin is a bioflavonoid that may be effective in male pelvic pain syndrome. It was first tested in a small open-label study of 29 patients, with hopeful results (32). Theoharides et al. (33) have studied 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 BPS 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.

3.2.12.1 References

1. Nickel JC. Opioids for chronic prostatitis and interstitial cystitis: lessons learned from the 11th World Congress on Pain. Urology 2006 Oct;68(4):697-701.
   http://www.ncbi.nlm.nih.gov/pubmed/17070334
2. Badenoch AW. Chronic interstitial cystitis. Br J Urol 1971 Dec;43(6):718-21. [no abstract available]
   http://www.ncbi.nlm.nih.gov/pubmed/5159574
3. Pool TL. Interstitial cystitis: clinical considerations and treatment. Clin Obstet Gynecol 1967 Mar;10(1):185-91. [no abstract available]
   http://www.ncbi.nlm.nih.gov/pubmed/6021011
4. Soucy F, Grégoire M. Efficacy of prednisone for severe refractory ulcerative interstitial cystitis. J Urol 2005 Mar;173(3):841-3; discussion 843.
   http://www.ncbi.nlm.nih.gov/pubmed/15711286
5. Theoharides TC. Hydroxyzine in the treatment of interstitial cystitis. Urol Clin North Am 1994 Feb;21(1):113-9.
   http://www.ncbi.nlm.nih.gov/pubmed/8284834
6. Seshadri P, Emerson L, Morales A. Cimetidine in the treatment of interstitial cystitis. Urology 1994 Oct;44(4):614-6.
   http://www.ncbi.nlm.nih.gov/pubmed/7941209
7. Theoharides TC. Hydroxyzine for interstitial cystitis. J Allergy Clin Immunol 1993 Feb;91(2):686-7. [no abstract available]
   http://www.ncbi.nlm.nih.gov/pubmed/8436783
8. Theoharides TC, Sant GR. Hydroxyzine therapy for interstitial cystitis. Urology 1997 May;49(5A Suppl):108-10.
   http://www.ncbi.nlm.nih.gov/pubmed/9146011
9. Sant GR, Propert KJ, Hanno PM, et al. Interstitial Cystitis Clinical Trials Group. A pilot clinical trial of oral pentosan polysulfate and oral hydroxyzine in patients with interstitial cystitis. J Urol 2003 Sep;170(3):810-5.
   http://www.ncbi.nlm.nih.gov/pubmed/12913705
10. Baldessarini RJ. Drugs and the treatment of psychiatric disorders. In: Gilman A, Gooman L, Rall T, eds. The Pharmacological Basis of Therapeutics. 7th ed. New York: Macmillan, 1985, pp. 387-445.
11. Hand JR. Interstitial cystitis: report of 223 cases (204 women and 19 men). J Urol 1949 Feb;61(2):291-310. [no abstract available]
    http://www.ncbi.nlm.nih.gov/pubmed/18111850
12. Hanno PM, Buehler J, Wein AJ. Use of amitriptyline in the treatment of interstitial cystitis. J Urol 1989 Apr;141(4):846-8.
    http://www.ncbi.nlm.nih.gov/pubmed/2926877
13. Kirkemo AK, Miles BJ, Peters JM. Use of amitriptyline in interstitial cystitis. J Urol 1990;143 (Suppl):279A.

14. van Ophoven A, Pokupic S, Heinecke A, et al. A prospective, randomized, placebo controlled, doubleblind study of amitriptyline for the treatment of interstitial cystitis. J Urol 2004 Aug;172(2):533-6.
http://www.ncbi.nlm.nih.gov/pubmed/15247722
15. van Ophoven A, Hertle L. Long-term results of amitriptyline treatment for interstitial cystitis. J Urol 2005 Nov;174(5):1837-40.
http://www.ncbi.nlm.nih.gov/pubmed/16217303
16. Foster HE Jr, Hanno PM, Nickel JC, et al. Interstitial Cystitis Collaborative Research Network. Effect of amitriptyline on symptoms in treatment naïve patients with interstitial cystitis/painful bladder syndrome. J Urol 2010 May;183(5):1853-8.
http://www.ncbi.nlm.nih.gov/pubmed/20303115
17. Mulholland SG, Hanno P, Parsons CL, et al. Pentosan polysulfate sodium for therapy of interstitial cystitis. A double-blind placebo-controlled clinical study. Urology 1990 Jun;35(6):552-8.
http://www.ncbi.nlm.nih.gov/pubmed/1693797
18. Hwang P, Auclair B, Beechinor D, et al. Efficacy of pentosan polysulfate in the treatment of interstitial cystitis: a meta-analysis. Urology 1997 Jul;50(1):39-43.
http://www.ncbi.nlm.nih.gov/pubmed/9218016
19. Fritjofsson A, Fall M, Juhlin R, et al. Treatment of ulcer and nonulcer interstitial cystitis with sodium pentosanpolysulfate: a multicenter trial. J Urol 1987 Sep;138(3):508-12.
http://www.ncbi.nlm.nih.gov/pubmed/2442416
20. Nickel JC, Barkin J, Forrest J, et al. Elmiron Study Group. Randomized, double-blind, dose-ranging study of pentosan polysulfate sodium for interstitial cystitis. Urology 2005 Apr;65(4):654-8.
http://www.ncbi.nlm.nih.gov/pubmed/15833501
21. van Ophoven A, Heinecke A, Hertle L. Safety and efficacy of concurrent application of oral pentosan polysulfate and subcutaneous low-dose heparin for patients with interstitial cystitis. Urology 2005 Oct;66(4):707-11.
http://www.ncbi.nlm.nih.gov/pubmed/16230121
22. Warren JW, Horne LM, Hebel JR, et al. Pilot study of sequential oral antibiotics for the treatment of interstitial cystitis. J Urol 2000 Jun;163(6):1685-8.
http://www.ncbi.nlm.nih.gov/pubmed/10799160
23. Oravisto KJ, Alfthan OS. Treatment of interstitial cystitis with immunosuppression and chloroquine derivatives. Eur Urol 1976;2(2):82-4.
http://www.ncbi.nlm.nih.gov/pubmed/971677
24. Forsell T, Ruutu M, Isoniemi H, et al. Cyclosporine in severe interstitial cystitis. J Urol 1996 May;155(5):1591-3.
http://www.ncbi.nlm.nih.gov/pubmed/8627830
25. Moran PA, Dwyer PL, Carey MP, et al. Oral methotrexate in the management of refractory interstitial cystitis. Aust N Z J Obstet Gynaecol 1999 Nov;39(4):468-71.
http://www.ncbi.nlm.nih.gov/pubmed/10687766
26. Sairanen J, Forsell T, Ruutu M. Long-term outcome of patients with interstitial cystitis treated with low dose cyclosporine A. J Urol 2004 Jun;171(6 Pt 1):2138-41.
http://www.ncbi.nlm.nih.gov/pubmed/15126772
27. Sairanen J, Tammela TL, Leppilahti M, et al. Cyclosporine A and pentosan polysulfate sodium for the treatment of interstitial cystitis: a randomized comparative study. J Urol 2005 Dec;174(6):2235-8.
http://www.ncbi.nlm.nih.gov/pubmed/16280777
28. Hansen HC. Interstitial cystitis and the potential role of gabapentin. South Med J 2000 Feb;93(2): 238-42.
http://www.ncbi.nlm.nih.gov/pubmed/10701800
29. Sasaki K, Smith CP, Chuang YC, et al. Oral gabapentin (neurontin) treatment of refractory genitourinary tract pain. Tech Urol 2001 Mar;7(1):47-9.
http://www.ncbi.nlm.nih.gov/pubmed/11272678
30. Sonnett TE, Setter SM, Campbell RK. Pregabalin for the treatment of painful neuropathy. Expert Rev Neurother 2006 Nov;6(11):1629-35.
http://www.ncbi.nlm.nih.gov/pubmed/17144773
31. Ueda T, Tamaki M, Ogawa O, et al. Improvement of interstitial cystitis symptoms and problems that developed during treatment with oral IPD-1151T. J Urol 2000 Dec;164(6):1917-20.
http://www.ncbi.nlm.nih.gov/pubmed/11061880
32. Katske F, Shoskes DA, Sender M, et al. Treatment of interstitial cystitis with a quercetin supplement. Tech Urol 2001 Mar;7(1):44-6.
http://www.ncbi.nlm.nih.gov/pubmed/11272677

33. Theoharides TC, Sant GR. A pilot open label study of Cystoprotek in interstitial cystitis. Int J Immunopathol Pharmacol 2005 Jan-Mar;18(1):183-8. http://www.ncbi.nlm.nih.gov/pubmed/15698523

3.2.13 ***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 BPS patients, cost, and risk of infection.

Local anaesthetics. There are sporadic reports of successful treatment of BPS with intravesical lidocaine (1,2). Alkalisation of lidocaine before intravesical application improves pharmacokinetics (3). 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 alkalinised lidocaine [40,000 U heparin, 2% lidocaine (160 mg), and 3 mL 8.4% sodium bicarbonate] (4). One hundred and two adult patients (99 women) with a clinical diagnosis of BPS were randomised from 19 centres in the USA and Canada to receive a daily intravesical instillation of alkalinised lidocaine or placebo (double-blind), for 5 consecutive days. Treated patients had significant sustained symptom relief for up to 1 month (5).

Pentosan polysulphate 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 (6) was performed in 20 patients, of whom 10 received intravesical pentosan polysulphate sodium (300 mg in 50 mL 0.9% saline) twice weekly for 3 months, and 10 received placebo.
At 3 months, four patients in the pentosan polysulphate sodium group and two in the placebo group achieved significant symptomatic relief. Bladder capacity showed a significant increase only in patients treated with pentosan polysulphate sodium. At 18 months, symptoms were relieved in eight patients, who were still receiving pentosan polysulphate sodium instillation, and in four patients not receiving the drug. In another study, a total of 41 women diagnosed with BPS were randomised to receive a combination of intravesical plus oral pentosan polysulphate sodium (21 in treatment group) or intravesical placebo plus oral pentosan polysulphate sodium (20 in placebo group) for 6 weeks. All subjects continued to receive oral pentosan polysulphate sodium for a further 12 weeks. At week 18, the treatment group showed significant improvement in all health-related QoL domains compared to baseline ($P <$ or $= 0.01$), whereas the placebo group showed significant improvement in only three domains, ($P <$ or $= 0.05$) compared to baseline (7).

Intravesical heparin has been proposed as a coating agent. In an open, prospective, uncontrolled trial (8), 48 BPS patients received instillations of 10,000 U in 10 mL sterile water three times weekly for 3 months. In over half of the patients, intravesical heparin controlled the symptoms, with continued improvement after 1 year of therapy. Kuo (9) reported another uncontrolled trial of intravesical heparin (25,000 U twice weekly for 3 months) in women with frequency-urgency syndrome and a positive potassium test. The study included 10 patients with BPS, of whom eight reported symptomatic improvement. Baykal et al. (10) have evaluated intravesical heparin plus dorsal tibial nerve stimulation in 10 refractory BPS 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 (11). After week 24, effectiveness decreased, but there was no significant toxicity. Nordling et al. (12) and Kallestrup et al. (13) have reported a 3-year follow-up of a 3-month, prospective, non-randomised study evaluating the effect of intravesical hyaluronic acid on BPS 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 (14) has demonstrated a similar favourable effect of hyaluronic acid on pain reduction. Forty-eight patients with typical symptoms and a positive potassium (0.4 M) sensitivity test were treated 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 $C_{max} < 30\%$ compared to patients with a reduction of $< 30\%$ with 0.2 M KCl solution ($P = 0.003$). Long-term effects were investigated in a study of 70 patients previously treated with hyaluronan. Of the 70 patients initially treated, 48 were available for evaluation. Of these, 50% reported complete remission with no further therapy. Another 41.7% of patients with symptom recurrence improved after retreatment (15).

Chondroitin sulphate. Intravesical chondroitin sulphate (16) demonstrated beneficial effects in patients with a

positive potassium stimulation test, in two non-randomised, uncontrolled, open-label pilot studies. Steinhoff (17) treated 18 patients with 40 mL instilled intravesically once weekly for 4 weeks and then once monthly 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 (18), 24 refractory patients with BPS 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. A more concentrated 2.0% solution was needed in eight patients to maintain results.

Sixty-five patients with BPS were treated in a prospective, randomised, double-blind, inactive vehicle-controlled, 12-week study (6 weeks treatment, followed by 6 weeks follow-up). At the primary endpoint analysis (week 7), 22.6% of the vehicle control group were responders compared with 39.4% of the active therapy group, however, the difference was not significant, probably due to underpowering of the study (19,20).

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, which is believed to be an important trigger of the inflammatory process. It has been tested empirically and found to alleviate symptoms in BPS. Dimethyl sulphoxide is now a standard treatment. In a controlled crossover trial (21), 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 1-2 months (22). Rössberger et al. (23) have evaluated the discomfort and long-term effects of DMSO instillations in a total of 28 patients. Side effects were no 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 UTIs or shortly after bladder biopsy. It temporarily causes a garlic-like odour. There is a case report in which DMSO treatment may have caused pigmented eye lens deposits (24), therefore, ophthalmic review should be considered during treatment.

Bacillus Calmette Guérin (BCG). The tuberculosis BCG vaccine is used for its immunomodulatory properties in the intravesical treatment of superficial bladder carcinoma. In 1997, a small prospective, double-blind pilot study showed that intravesical BCG demonstrated a 60% response rate versus 27% in the placebo group in 30 patients who received six weekly instillations of Tice strain BCG or placebo (25). In a subsequent 24-33-month follow-up study, eight of the nine responders reported BPS symptom amelioration. BCG did not worsen symptoms in non-responders (26). However, these results are at variance with two controlled trials. In a prospective, double-blind crossover trial of BCG and DMSO (27), BCG treatment failed to demonstrate any benefit. Another randomised, placebo-controlled, double-blind trial of 260 refractory BPS patients (28) 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 (29), 156 non-responders from both groups were offered treatment with open-label BCG. The low response rate (18%) for BCG in this series and the results of the same group's (Interstitial Cystitis Clinical Trials Group; ICCTG) follow-up on the responders, which found no differences, have substantiated the argument against the routine use of BCG for BPS (30).

Vanilloids disrupt sensory neurons (31). Resiniferatoxin (RTX) is an ultrapotent analogue of the chilli pepper extract capsaicin, causing less pain on instillation and therefore no anaesthesia. Chen et al. (32) have investigated RTX tolerability (0.05 or 0.10 μM) in 22 BPS 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 (33), RTX significantly reduced mean frequency, nocturia, and pain scores by about 50%. In another study of seven patients with detrusor hyper-reflexia, RTX improved urinary frequency, incontinence and bladder capacity (34). In a small open-label study with single-dose RTX in patients with frequency and urgency (35), RTX significantly improved LUTS, urodynamic parameters, and QoL for up to 6 months. These results are in contrast with an RCT in 163 BPS patients randomly assigned to receive a single intravesical dose of 50 mL of either placebo or RTX (0.01, 0.05 or 0.10 μM) (36). 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 have been reported from a prospective study on multiple intravesical instillations of RTX (37) (0.01 μM once weekly for 4 weeks). Among 12 patients (one drop-out for severe pain), the overall satisfaction 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. A prospective, randomised, double-blind, crossover study was performed in 26 women, who received instillations with various pH values. There was no evidence that changes in urinary pH affected the pain associated with BPS (38).

3.2.13.1 References

1. Giannakopoulos X, Champilomatos P. Chronic interstitial cystitis. Successful treatment with intravesical lidocaine. Arch Ital Urol Nefrol Androl 1992 Dec;64(4):337-9. http://www.ncbi.nlm.nih.gov/pubmed/1462157
2. Asklin B, Cassuto J. Intravesical lidocaine in severe interstitial cystitis. Case report. Scand J Urol Nephrol 1989;23(4):311-2. http://www.ncbi.nlm.nih.gov/pubmed/2595329
3. Henry R, Patterson L, Avery N, et al. Absorption of alkalized intravesical lidocaine in normal and inflamed bladders: a simple method for improving bladder anaesthesia. J Urol 2001 Jun;165(6 Pt 1):1900-3. http://www.ncbi.nlm.nih.gov/pubmed/11371877
4. Parsons CL. Successful downregulation of bladder sensory nerves with combination of heparin and alkalinized lidocaine in patients with interstitial cystitis. Urology 2005 Jan;65(1):45-8. http://www.ncbi.nlm.nih.gov/pubmed/15667861
5. Nickel JC, Moldwin R, Lee S, et al. Intravesical alkalinized lidocaine (PSD597) offers sustained relief from symptoms of interstitial cystitis and painful bladder syndrome. BJU Int 2009 Apr;103(7):910-8. http://www.ncbi.nlm.nih.gov/pubmed/19021619
6. Bade JJ, Laseur M, Nieuwenburg A, et al. A placebo-controlled study of intravesical pentosanpolysulphate for the treatment of interstitial cystitis. Br J Urol 1997 Feb;79(2):168-71. http://www.ncbi.nlm.nih.gov/pubmed/9052464
7. Davis EL, El Khoudary SR, Talbott EO, et al. Safety and efficacy of the use of intravesical and oral pentosan polysulfate sodium for interstitial cystitis: a randomized double-blind clinical trial.J Urol 2008 Jan;179(1):177-85. http://www.ncbi.nlm.nih.gov/pubmed/18001798
8. Parsons CL, Housley T, Schmidt JD, et al. Treatment of interstitial cystitis with intravesical heparin. BrJ Urol 1994 May;73(5):504-7. http://www.ncbi.nlm.nih.gov/pubmed/8012771
9. Kuo HC. Urodynamic results of intravesical heparin therapy for women with frequency urgency syndrome and interstitial cystitis. J Formos Med Assoc 2001 May;100(5):309-14. http://www.ncbi.nlm.nih.gov/pubmed/11432309
10. Baykal K, Senkul T, Sen B, et al. Intravesical heparin and peripheral neuromodulation on interstitial cystitis. Urol Int 2005;74(4):361-4. http://www.ncbi.nlm.nih.gov/pubmed/15897705
11. Morales A, Emerson L, Nickel JC, et al. Intravesical hyaluronic acid in the treatment of refractory interstitial cystitis. Urology 1997 May;49(5A Suppl):111-3. http://www.ncbi.nlm.nih.gov/pubmed/9146012
12. Nordling J, Jørgensen S, Kallestrup E. Cystistat for the treatment of interstitial cystitis: a 3-year followup study. Urology 2001 Jun;57(6 Suppl 1):123. [no abstract available] http://www.ncbi.nlm.nih.gov/pubmed/11378112
13. Kallestrup EB, Jørgensen S, Nordling J, et al. Treatment of interstitial cystitis with Cystistat: a hyaluronic acid product. Scand J Urol Nephrol 2005;39(2):143-7. http://www.ncbi.nlm.nih.gov/pubmed/16032779
14. Daha LK, Riedl CR, Lazar D, et al. Do cystometric findings predict the results of intravesical hyaluronic acid in women with interstitial cystitis? Eur Urol 2005 Mar;47(3):393-7; discussion 397. http://www.ncbi.nlm.nih.gov/pubmed/15716206
15. Engelhardt PF, Morakis N, Daha LK, et al. Long-term results of intravesical hyaluronan therapy in bladder pain syndrome/interstitial cystitis. Int Urogynecol J Pelvic Floor Dysfunct 2011 Apr;22(4): 401-5. http://www.ncbi.nlm.nih.gov/pubmed/20938644
16. Palylyk-Colwell E. Chondroitin sulfate for interstitial cystitis. Issues Emerg Health Technol 2006 May(84);1-4. http://www.ncbi.nlm.nih.gov/pubmed/16724430

17. Steinhoff G. The efficacy of chondroitin sulfate 0.2% in treating interstitial cystitis. Can J Urol 2002 Feb;9(1):1454-8.
http://www.ncbi.nlm.nih.gov/pubmed/11886599
18. Sorensen RB. Chondroitin sulphate in the treatment of interstitial cystitis and chronic inflammatory disease of the urinary bladder. Eur Urol 2003;Suppl 2:16-8.
http://www.journals.elsevierhealth.com/periodicals/eursup/article/PIIS1569905603000368/abstract
19. Nickel JC, Egerdie B, Downey J, et al. A real-life multicentre clinical practice study to evaluate the efficacy and safety of intravesical chondroitin sulphate for the treatment of interstitial cystitis. BJU Int 2009 Jan;103(1):56-60.
http://www.ncbi.nlm.nih.gov/pubmed/18778342
20. Nickel JC, Egerdie RB, Steinhoff G, et al. A multicenter, randomized, double-blind, parallel group pilot evaluation of the efficacy and safety of intravesical sodium chondroitin sulfate versus vehicle control in patients with interstitial cystitis/painful bladder syndrome. Urology 2010 Oct;76(4):804-9.
http://www.ncbi.nlm.nih.gov/pubmed/20494413
21. Perez-Marrero R, Emerson LE, Feltis JT. A controlled study of dimethyl sulfoxide in interstitial cystitis. J Urol 1988 Jul;140(1):36-9.
http://www.ncbi.nlm.nih.gov/pubmed/3288775
22. Sant GR, LaRock DR. Standard intravesical therapies for interstitial cystitis. Urol Clin North Am 1994 Feb;21(1):73-83.
http://www.ncbi.nlm.nih.gov/pubmed/8284849
23. Rössberger J, Fall M, Peeker R. Critical appraisal of dimethyl sulfoxide treatment for interstitial cystitis:discomfort, side-effects and treatment outcome. Scand J Urol Nephrol 2005;39(1):73-7.
http://www.ncbi.nlm.nih.gov/pubmed/15764276
24. Rowley S, Baer R. Lens deposits associated with RIMSO-50 (dimethylsulphoxide). Eye 2001 Jun;15(Pt 3):332-3.
http://www.ncbi.nlm.nih.gov/pubmed/11450733
25. Peters K, Diokno A, Steinert B, et al. The efficacy Of intravesical Tice strain bacillus Calmette-Guerin in the treatment of interstitial cystitis: a double-blind, prospective, placebo controlled trial. J Urol 1997 Jun;157(6):2090-4.
http://www.ncbi.nlm.nih.gov/pubmed/9146587
26. Peters KM, Diokno AC, Steinert BW, et al. The efficacy of intravesical bacillus Calmette-Guerin in the treatment of interstitial cystitis: long-term followup. J Urol 1998 May;159(5):1483-6; discussion1486-7.
http://www.ncbi.nlm.nih.gov/pubmed/9554338
27. Peeker R, Haghsheno MA, Holmang S, et al. Intravesical bacillus Calmette-Guerin and dimethyl sulfoxide for treatment of classic and nonulcer interstitial cystitis: a prospective, randomized doubleblind study. J Urol 2000 Dec;164(6):1912-1915; discussion 1915-6.
http://www.ncbi.nlm.nih.gov/pubmed/11061879
28. Mayer R, Propert KJ, Peters KM, et al. Interstitial Cystitis Clinical Trials Group. A randomized controlled trial of intravesical bacillus calmette-guerin for treatment refractory interstitial cystitis. J Urol 2005 Apr;173(4):1186-91.
http://www.ncbi.nlm.nih.gov/pubmed/15758738
29. Propert KJ, Mayer R, Nickel JC, et al. Interstitial Cystitis Clinical Trials Group. Did patients with interstitial cystitis who failed to respond to initial treatment with bacillus Calmette-Guerin or placebo in a randomized clinical trial benefit from a second course of open label bacillus Calmette-Guerin? J Urol 2007 Sep;178(3 Pt 1):886-90.
http://www.ncbi.nlm.nih.gov/pubmed/17631335
30. Propert KJ, Mayer R, Nickel JC, et al. Interstitial Cystitis Clinical Trials Group. Followup of patients with interstitial cystitis responsive to treatment with intravesical bacillus Calmette-Guerin or placebo. J Urol 2008 Feb;179(2):552-5.
http://www.ncbi.nlm.nih.gov/pubmed/18082224
31. Chancellor MB. RTX exotoxins. Urology 2001 Jun;57(6 Suppl 1):106-7. [no abstract available]
http://www.ncbi.nlm.nih.gov/pubmed/11378069
32. Chen TY, Corcos J, Camel M, et al. Prospective, randomized, double-blind study of safety and tolerability of intravesical resiniferatoxin (RTX) in interstitial cystitis (IC). Int Urogynecol J Pelvic Floor Dysfunct 2005 Jul-Aug;16(4):293-7.
http://www.ncbi.nlm.nih.gov/pubmed/15818465
33. Lazzeri M, Beneforti P, Spinelli M, et al. Intravesical resiniferatoxin for the treatment of hypersensitive disorder: a randomized placebo controlled study. J Urol 2000 Sep;164(3 Pt 1):676-9.
http://www.ncbi.nlm.nih.gov/pubmed/10953124

34. Silva C, Avelino A, Souto-Moura C, et al. A light- and electron-microscopic histopathological study of human bladder mucosa after intravesical resiniferatoxin application. BJU Int 2001 Sep;88(4):355-60. http://www.ncbi.nlm.nih.gov/pubmed/11564021
35. Apostolidis A, Gonzales GE, Fowler CJ. Effect of intravesical Resiniferatoxin (RTX) on lower urinary tract symptoms, urodynamic parameters, and quality of life of patients with urodynamic increased bladder sensation. Eur Urol 2006 Dec;50(6):1299-305. http://www.ncbi.nlm.nih.gov/pubmed/16697519
36. Payne CK, Mosbaugh PG, Forrest JB, et al. ICOS RTX Study Group (Resiniferatoxin Treatment for Interstitial Cystitis). Intravesical resiniferatoxin for the treatment of interstitial cystitis: a randomized, double-blind, placebo controlled trial. J Urol 2005 May;173(5):1590-4. http://www.ncbi.nlm.nih.gov/pubmed/15821499
37. Peng CH, Kuo HC. Multiple intravesical instillations of low-dose resiniferatoxin in the treatment of refractory interstitial cystitis. Urol Int 2007;78(1):78-81. http://www.ncbi.nlm.nih.gov/pubmed/17192738
38. Nguan C, Franciosi LG, Butterfield NN, et al. A prospective, double-blind, randomized cross-over study evaluating changes in urinary pH for relieving the symptoms of interstitial cystitis. BJU Int 2005 Jan;95(1):91-4. http://www.ncbi.nlm.nih.gov/pubmed/15638902

3.2.14 ***Interventional treatments***

Bladder distension. A frequently cited report by Bumpus (1) 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 (2) and Longacre (3) were just as vague during the 1930s. In 1957, an uncontrolled retrospective study was presented by Franksson (4), 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 have reported contradictory results. Dunn et al. (5) have claimed to have achieved complete absence of symptoms in 16/25 patients during a mean follow-up of 14 months using the Helmstein method (6), in which an intravesical balloon is distended at the level of systolic blood pressure for 3 h. Bladder rupture occurred in two cases. These results disagree with those of Badenoch (7), who failed to note any improvement in 44/56 patients after hydrodistension. Twenty years later, McCahy (8) rejected balloon hydrodistension because of inefficacy and a complication rate of 20%. In the recent literature, bladder necrosis following hydrodistension has been extremely rare (9).

In 2002, Glemain et al. (10) reported an uncontrolled study on 65 BPS patients treated by 3 h 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 > 150 mL.

Ottem and Teichmann reported a retrospective study of 84 BPS patients (11), and 56% reported short-lived improvement from hydrodistension. Rose et al. have investigated bladder distension using electromotive drug administration (EMDA) (12,13), 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. (14) have reported on repeated hydrodistension in 52 BPS patients (NIH criteria). Under epidural anaesthesia, the bladder was repeatedly distended to maximal capacity and distension was repeated on the following day for 30 min. Five patients were classified as good responders, 30 as moderate and 17 as poor. Overall, hydrodistension was effective for ~70% of patients for > 3 months, without serious complications.

According to a study by Erickson et al. (15), 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 (16), 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, scientific justification is scarce. It represents a diagnostic tool, but has a limited therapeutic role.

EMDA enhances tissue penetration of ionised drugs by iontophoresis. When adapted for the bladder, EMDA uses a transurethral anode and a suprapubic skin cathode. EMDA is expensive and has been the subject of uncontrolled studies only.

Six BPS patients were treated with EMDA using lidocaine (1.5%) and 1:100,000 adrenaline in aqueous solution, while the bladder was dilated to maximum tolerance (17). Significant bladder enlargement was achieved and voiding symptoms and pain decreased. In four patients, the results were reported as durable. Rosamilia et al. (18) treated 21 women using EMDA with lidocaine and dexamethasone, followed by bladder distension. 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. (19) 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 (20) has described TUR of a 1-cm ulcer in a woman who experienced symptom resolution for 1 year. Subsequently, Greenberg et al. (21) have reported 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 < 1 year and efficacy was not superior to non-surgical treatment.

In another series of 30 BPS type C patients (22), complete TUR of visible lesions resulted in an initial disappearance of pain in all patients and a decrease in frequency in 21. 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 has reported the largest series of patients with BPS type C treated by complete TUR of all visible ulcers (23). A total of 259 TURs were performed on 103 patients. Ninety-two patients experienced amelioration, with symptom relief lasting > 3 years in 40% of patients, and most of the remaining patients responded well to subsequent TUR.

Transurethral application of the (Nd-YAG) laser is suggested as an alternative to TUR for endoscopic treatment in BPS. Shanberg et al. (24) have treated 5 refractory BPS patients, 4 of whom demonstrated cessation of pain and frequency within several days. Follow-up at 3-15 months revealed no relapse, except for mild recurrent voiding symptoms. This series was extended to 76 patients treated at two institutions (25). 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 BPS type C underwent ablative Nd-YAG laser ablation of Hunner's ulcers (26). All patients showed symptom improvement within a few days, without complications. At 23 months, mean pain and urgency scores, nocturia and voiding intervals improved significantly. However, relapse in 11 patients required up to four additional treatments. Controlled studies are still lacking. Endourological resection is not applicable to non-ulcer BPS.

Botulinum toxin A (BTX-A) may have an antinociceptive effect on bladder afferent pathways, producing both symptomatic and urodynamic improvements (27). Thirteen BPS patients were injected with 100-200 IU of BTX-A (abobotulinumtoxin A or onabotulinumtoxin A) into 20-30 sites submucosally in the trigone and floor of the bladder. Overall, nine (69%) patients noted 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 those in another study of BTX-A (onabotulinumtoxin A) in 10 patients with BPS (28). One hundred units were injected suburothelially into 20 sites in five patients, while 100 U were injected into the trigone in the remaining five. None of the patients became symptom-free; two showed only limited improvement in bladder capacity and pain score.

To ascertain effect of repeat injections a total of 13 patients were followed up for 2 years, while 58 injections were administered with a mean of 4.8 ± 0.8 injections per patient. The mean interval between two consecutive injections was 5.25 ± 0.75 months. At 1 and 4 months follow-up, 10 patients reported a subjective improvement. Mean VAS scores, mean daytime and night-time urinary frequency decreased significantly. The three non-responders to the first intravesical treatment session underwent further treatment 3 months later with satisfactory results. At 1 and 2 years follow-up, the beneficial effects persisted in all patients (29).

In an RCT, the difference between hydrodistension and hydrodistension plus intravesical BTX-A (onabotulinumtoxin A) was analysed. Of the 67 patients, 44 were divided in two groups: one received 200 U and the other 100 U, and cystoscopic hydrodistension was performed after 2 weeks. The remaining 23 patients received hydrodistension only. There was symptomatic improvement in all groups. However, in the hydrodistension group, 70% had returned to their previous symptoms after the first month, while in the BTX-A-

treated groups, there was improvement of VAS, functional bladder capacity and cystometric bladder capacity at 3 months. At 12 and 24 months, the results in the active group were 55 and 30% versus 26 and 17% in the hydrodistension group (30).

Trigonal-only injection seems effective and long-lasting because 87% of patients (n = 23) reported improvement after a 3-month follow-up period in a study by Pinto et al. Over 50% referred continuity of the beneficial effect 9 months after the first treatment. When retreatment was needed, similar results were obtained. The authors concluded that this treatment is safe, effective and can be repeated (31).

Hyperbaric oxygen (HBO). In a prospective pilot study, six patients underwent 30 sessions of 100% HBO inhalation and were followed up for > 15 months. Four patients rated the therapeutic result as excellent or good, while two showed only short-term amelioration (32). In a subsequent double-blind, sham-controlled study (33), 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 patients. Disadvantages include high costs, limited availability of treatment sites and time-consuming treatment.

Neuromodulation. In the first prospective, single-blind, crossover trial of sacral nerve stimulation (SNS) versus pudendal nerve stimulation (PNS) for patients with BPS (n = 22), PNS gave an overall 59% improvement in symptoms, whereas SNS gave an overall 44% improvement ($P = 0.05$). Most patients who tested both a sacral and pudendal electrode chose PNS as the better site. Follow-up showed marked improvements in voiding variables and validated BPS symptom questionnaires. Over 90% of patients treated with neuromodulation stated that they would undergo implantation again (34).

Long-term results were verified in a retrospective study of 78 patients treated from 1994 to 2008. Permanent sacral neuromodulation implantation was performed in patients who showed at least 50% improvement in their symptoms with a temporary peripheral nerve evaluation test. Median follow-up was 61.5 (SD± 27.7 months). Good long-term success of sacral neuromodulation was seen in 72% of the patients. The explantation rate was 28%. The most frequent reason for explantation was poor outcome (54% of the failed patients). The revision rate was 50% (35).

In another observational, retrospective, case-controlled review (January 2002-March 2004), 34 female patients underwent permanent device implants. Mean pre-/postoperative pelvic pain and urgency/frequency scores were 21.61 ± 8.6/9.22 ± 6.6 ($P < 0.01$), and mean pre-/postoperative visual analogue pain scale (VAPS) scores were 6.5 ± 2.9/2.4 ± 1.1 ($P < 0.01$). Mean follow-up was 86 ± 9.8 months. Sacral neuromodulation showed adequate improvement for the symptoms of refractory BPS. Reoperation rate was 25% (36).

3.2.14.1 References

1. Bumpus HCJ. Interstitial cystitis: its treatment by overdistension of the bladder. Med Clin North Am 1930;13:1495-8.
2. Ormond JK. Interstitial cystitis. J Urol 1935;33:576-82.
3. Longacre JJ. The treatment of contracted bladder with controlled tidal irrigation. J Urol 1936;36:25-33.
4. Franksson C. Interstitial cystitis: a clinical study of fifty-nine cases. Acta Chir Scand 1957 May;113(1):51-62. [no abstract available] http://www.ncbi.nlm.nih.gov/pubmed/13443727
5. Dunn M, Ramsden PD, Roberts JB, et al. Interstitial cystitis, treated by prolonged bladder distension. Br J Urol 1977;49(7):641-5. http://www.ncbi.nlm.nih.gov/pubmed/597701
6. Helmstein K. Treatment of bladder carcinoma by a hydrostatic pressure technique. Report on 43 cases. Br J Urol 1972 Aug;44(4):434-50. [no abstract available] http://www.ncbi.nlm.nih.gov/pubmed/5070147
7. Badenoch AW. Chronic interstitial cystitis. Br J Urol 1971 Dec;43(6):718-21. [no abstract available] http://www.ncbi.nlm.nih.gov/pubmed/5159574
8. McCahy PJ, Styles RA. Prolonged bladder distension: experience in the treatment of detrusor overactivity and interstitial cystitis. Eur Urol 1995;28(4):325-7. http://www.ncbi.nlm.nih.gov/pubmed/8575501
9. Zabihi N, Allee T, Maher MG, et al. Bladder necrosis following hydrodistention in patients with interstitial cystitis. J Urol 2007 Jan;177(1):149-52; discussion 152. http://www.ncbi.nlm.nih.gov/pubmed/17162025

10. Glemain P, Rivière C, Lenormand L, et al. Prolonged hydrodistention of the bladder for symptomatic treatment of interstitial cystitis: efficacy at 6 months and 1 year. Eur Urol 2002 Jan;41(1):79-84.
http://www.ncbi.nlm.nih.gov/pubmed/11999471
11. Ottem DP, Teichman JM. What is the value of cystoscopy with hydrodistension for interstitial cystitis? Urology 2005 Sep;66(3):494-9.
http://www.ncbi.nlm.nih.gov/pubmed/16140064
12. Rose AE, Azevedo KJ, Payne CK. Office bladder distention with electromotive drug administration (EMDA) is equivalent to distention under general anesthesia (GA). BMC Urol 2005 Nov;5:14.
http://www.ncbi.nlm.nih.gov/pubmed/16300684
13. Rose AE, Payne CK, Azevedo K. Pilot study of the feasibility of in-office bladder distention using electromotive drug adminstration (EMDA). Neurourol Urodyn 2005;24(3):254-60.
http://www.ncbi.nlm.nih.gov/pubmed/15747341
14. Yamada T, Murayama T, Andoh M. Adjuvant hydrodistension under epidural anesthesia for interstitial cystitis. Int J Urol 2003 Sep;10(9):463-8; discussion 469.
http://www.ncbi.nlm.nih.gov/pubmed/12941123
15. Erickson DR, Kunselman AR, Bentley CM, et al. Changes in urine markers and symptoms after bladder distention for interstitial cystitis. J Urol 2007 Feb;177(2):556-60.
http://www.ncbi.nlm.nih.gov/pubmed/17222633
16. Cole EE, Scarpero HM, Dmochowski RR. Are patient symptoms predictive of the diagnostic and/or therapeutic value of hydrodistention? Neurourol Urodyn 2005;24(7):638-42.
http://www.ncbi.nlm.nih.gov/pubmed/16208660
17. Gürpinar T, Wong HY, Griffith DP. Electromotive administration of intravesical lidocaine in patients with interstitial cystitis. J Endourol 1996 Oct;10(5):443-7.
http://www.ncbi.nlm.nih.gov/pubmed/8905491
18. Rosamilia A, Dwyer PL, Gibson J. Electromotive drug administration of lidocaine and dexamethasone followed by cystodistension in women with interstitial cystitis. Int Urogynecol J Pelvic Floor Dysfunct 1997;8(3):142-5.
http://www.ncbi.nlm.nih.gov/pubmed/9449586
19. Riedl CR, Knoll M, Plas E, et al. Electromotive drug administration and hydrodistention for the treatment of interstitial cystitis. J Endourol 1998 Jun;12(3):269-72.
http://www.ncbi.nlm.nih.gov/pubmed/9658301
20. Kerr WS Jr. Interstitial cystitis: treatment by transurethral resection. J Urol 1971 May;105(5):664-6. [no abstract available]
http://www.ncbi.nlm.nih.gov/pubmed/4397018
21. Greenberg E, Barnes R, Stewart S, et al. Transurethral resection of Hunner's ulcer. J Urol 1974 Jun;111(6):764-6.
http://www.ncbi.nlm.nih.gov/pubmed/4830879
22. Fall M. Conservative management of chronic interstitial cystitis: transcutaneous electrical nerve stimulation and transurethral resection. J Urol 1985 May;133(5):774-8.
http://www.ncbi.nlm.nih.gov/pubmed/3872946
23. Peeker R, Aldenborg F, Fall M. Complete transurethral resection of ulcers in classic interstitial cystitis. Int Urogynecol J Pelvic Floor Dysfunct 2000;11(5):290-5. [no abstract available]
http://www.ncbi.nlm.nih.gov/pubmed/11052564
24. Shanberg AM, Baghdassarian R, Tansey LA. Treatment of interstitial cystitis with the neodymium-YAG laser. J Urol 1985 Nov;134(5):885-8.
http://www.ncbi.nlm.nih.gov/pubmed/3840538
25. Malloy TR, Shanberg AM. Laser therapy for interstitial cystitis. Urol Clin North Am 1994 Feb; 21(1): 141-4.
http://www.ncbi.nlm.nih.gov/pubmed/8284837
26. Rofeim O, Hom D, Freid RM, et al. Use of the neodymium: yag laser for interstitial cystitis: a prospective study. J Urol 2001 Jul;166(1):134-6.
http://www.ncbi.nlm.nih.gov/pubmed/11435840
27. Smith CP, Radziszewski P, Borkowski A, et al. Botulinum toxin a has antinociceptive effects in treating interstitial cystitis. Urology 2004 Nov;64(5):871-5; discussion 875.
http://www.ncbi.nlm.nih.gov/pubmed/15533466
28. Kuo HC. Preliminary results of suburothelial injection of botulinum a toxin in the treatment of chronic interstitial cystitis. Urol Int 2005;75(2):170-4.
http://www.ncbi.nlm.nih.gov/pubmed/16123573

29. Giannantoni A, Mearini E, Del Zingaro M, et al.Two-year efficacy and safety of botulinum a toxin intravesical injections in patients affected by refractory painful bladder syndrome. Curr Drug Deliv 2010 Jan;7(1):1-4.
http://www.ncbi.nlm.nih.gov/pubmed/19863481
30. Kuo HC, Chancellor MB. Comparison of intravesical botulinum toxin type A injections plus hydrodistention with hydrodistention alone for the treatment of refractory interstitial cystitis/painful bladder syndrome. BJU Int 2009 Sep;104(5):657-61.
http://www.ncbi.nlm.nih.gov/pubmed/19338543
31. Pinto R, Lopes T, Frias B, et al. Trigonal injection of botulinum toxin A in patients with refractory bladder pain syndrome/interstitial cystitis. Eur Urol 2010 Sep;58(3):360-5.
http://www.ncbi.nlm.nih.gov/pubmed/20227820
32. van Ophoven A, Rossbach G, Oberpenning F, et al. Hyperbaric oxygen for the treatment of interstitial cystitis: long-term results of a prospective pilot study. Eur Urol 2004 Jul;46(1):108-13.
http://www.ncbi.nlm.nih.gov/pubmed/15183555
33. van Ophoven A, Rossbach G, Pajonk F, et al. Safety and efficacy of hyperbaric oxygen therapy for the treatment of interstitial cystitis: a randomized, sham controlled, double-blind trial. J Urol 2006 Oct;176(4 Pt 1):1442-6.
http://www.ncbi.nlm.nih.gov/pubmed/16952654
34. Peters KM, Feber KM, Bennett RC. A prospective, single-blind, randomized crossover trial of sacral vs pudendal nerve stimulation for interstitial cystitis. BJU Int 2007 Oct;100(4):835-9.
http://www.ncbi.nlm.nih.gov/pubmed/17822464
35. Gajewski JB, Al-Zahrani AA. The long-term efficacy of sacral neuromodulation in the management of intractable cases of bladder pain syndrome: 14 years of experience in one centre. BJU Int 2011 Apr;107(8):1258-64.
http://www.ncbi.nlm.nih.gov/pubmed/20883483
36. Marinkovic SP, Gillen LM, Marinkovic CM. Minimum 6-year outcomes for interstitial cystitis treated with sacral neuromodulation. Int Urogynecol J Pelvic Floor Dysfunct 2011 Apr;22(4):407-12.
http://www.ncbi.nlm.nih.gov/pubmed/20848271

3.2.15 ***Treatments of limited efficacy and absence of recent publications***

Cimetidine. The H2-blocker cimetidine has been reported to improve symptoms in BPS (1). 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 (2).

Prostaglandins. Misoprostol is a prostaglandin that regulates various immunological cascades. Twenty-five BPS patients received 600 µg/day misoprostol 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% (3).

L-Arginine. Oral treatment with l-arginine, the substrate for NO synthase, has been reported to decrease BPS-related symptoms (4-6). Nitric oxide level has been shown to be elevated in patients with BPS (7). However, others could not demonstrate either symptomatic relief or change in NO production after treatment (8,9).

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 (10). 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 40 mg/day duloxetine over 8 weeks (11). 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.

Clorpactin is a detergent of hypochloric acid previously used to treat BPS (12-16). Due to high complication rates (14-17), clorpactin instillations can no longer be recommended.

3.2.15.1 References

1. Dasgupta P, Sharma SD, Womack C, et al. Cimetidine in painful bladder syndrome: a histopathological study. BJU Int 2001 Aug;88(3):183-6. http://www.ncbi.nlm.nih.gov/pubmed/11488726
2. Thilagarajah R, Witherow RO, Walker MM. Oral cimetidine gives effective symptom relief in painful bladder disease: a prospective, randomized, double-blind placebo-controlled trial. BJU Int 2001 Feb;87(3):207-12. http://www.ncbi.nlm.nih.gov/pubmed/11167643
3. Kelly JD, Young MR, Johnston SR, et al. Clinical response to an oral prostaglandin analogue in patients with interstitial cystitis. Eur Urol 1998;34(1):53-6. http://www.ncbi.nlm.nih.gov/pubmed/9676414
4. Korting GE, Smith SD, Wheeler MA, et al. A randomized double-blind trial of oral L-arginine for treatment of interstitial cystitis. J Urol 1999 Feb;161(2):558-65. http://www.ncbi.nlm.nih.gov/pubmed/9915448
5. Wheeler MA, Smith SD, Saito N, et al. Effect of long-term oral L-arginine on the nitric oxide synthase pathway in the urine from patients with interstitial cystitis. J Urol 1997 Dec; 158(6):2045-50. http://www.ncbi.nlm.nih.gov/pubmed/9366309
6. Smith SD, Wheeler MA, Foster HE Jr, et al. Improvement in interstitial cystitis symptom scores during treatment with oral L-arginine. J Urol 1997 Sep;158(3 Pt 1):703-8. http://www.ncbi.nlm.nih.gov/pubmed/9258064
7. Lundberg JO, Ehren I, Jansson O, et al. Elevated nitric oxide in the urinary bladder in infectious and noninfectious cystitis. Urology 1996 Nov;48(5):700-2. http://www.ncbi.nlm.nih.gov/pubmed/8911512
8. Ehren I, Lundberg JO, Adolfsson J, et al. Effects of L-arginine treatment on symptoms and bladder nitric oxide levels in patients with interstitial cystitis. Urology 1998 Dec;52(6):1026-9. http://www.ncbi.nlm.nih.gov/pubmed/9836549
9. Cartledge JJ, Davies AM, Eardley I. A randomized double-blind placebo-controlled crossover trial of the efficacy of L-arginine in the treatment of interstitial cystitis. BJU Int 2000 Mar;85(4):421-6. http://www.ncbi.nlm.nih.gov/pubmed/10691818
10. Barbalias GA, Liatsikos EN, Athanasopoulos A, et al. Interstitial cystitis: bladder training with intravesical oxybutynin. J Urol 2000 Jun;163(6):1818-22. http://www.ncbi.nlm.nih.gov/pubmed/10799190
11. van Ophoven A, Hertle L. The dual serotonin and noradrenaline reuptake inhibitor duloxetine for the treatment of interstitial cystitis: results of an observational study. J Urol 2007 Feb;177(2):552-5. http://www.ncbi.nlm.nih.gov/pubmed/17222632
12. O'Conor VJ. Clorpactin WCS-90 in the treatment of interstitial cystitis. Q Bull Northwest Univ Med Sch 1955;29(4):293-5. [no abstract available] http://www.ncbi.nlm.nih.gov/pubmed/13273619
13. Wishard WN Jr, Nourse MH, Mertz JH. Use of Clorpactin WCS 90 for relief of symptoms due to interstitial cystitis. J Urol 1957 Mar;77(3):420-3. [no abstract available] http://www.ncbi.nlm.nih.gov/pubmed/13417272
14. Messing EM, Freiha FS. Complication of Clorpactin WCS90 therapy for interstitial cystitis. Urology 1979 Apr;13(4):389-92. http://www.ncbi.nlm.nih.gov/pubmed/219578
15. Murnaghan GF, Saalfeld J, Farnworth RH. Interstitial cystitis - treatment with Clorpactin WCS 90. Br J Urol 1970 Dec;42(6):744. [no abstract available] http://www.ncbi.nlm.nih.gov/pubmed/5491939
16. von Heyden B, Schmid HP. [Intravesical therapy of interstitial cystitis.] Urologe A 2000 Nov;39(6): 542-4. http://www.ncbi.nlm.nih.gov/pubmed/11138274
17. Hanno P. Interstitial cystitis and related diseases. In: Walsh PC, Retik AB, Stamey TA, Vaughan ED, eds. Campbell's Urology Philadelphia: WB Saunders Co., 1998, pp. 648.

3.2.16 ***Non-pharmacological treatments***

Behavioural bladder training techniques are attractive for BPS patients with predominant symptoms of frequency/urgency but hardly any pain. Parsons et al. (1) included 21 selected BPS patients in a protocol that 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. (2) 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 93 min and daily

micturition was 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 patients (3). In an analysis of the Interstitial Cystitis Data Base (ICDB) cohort study, special diets were among the five most commonly used therapies (4). Bade et al. (5) have found that BPS patients consume significantly fewer calories, less 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 BPS (6).

A study of the metabolism of the arylalkylamines (tryptophan, tyrosine, tyramine and phenylalanine) in 250 patients revealed an inability to synthesise normal amounts of serotonin and MHPG 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 patients with nutrition-related exacerbations, calcium glycerophosphate was reported to ease food-related flares (7). The observed efficacy seems little better than would be expected with placebo.

Overall, dietary management is a common self-care strategy in BPS and offers a cost-effective therapeutic approach. Comprehensive instructions on how to identify individual trigger foods are given in the IC-Network Patient Handbook (8). However, scientific data are limited and dietary restriction alone does not produce complete symptomatic relief.

Acupuncture. In non-curable and agonising diseases like BPS, 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 (9). 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 (10).

In a non-randomised comparison in women with urethral syndrome, 128 treated by acupuncture and traditional Chinese medicine were compared with 52 treated by western medicine as controls. Efficacy rates and urodynamic parameters were significantly better in the acupuncture group (11). In contrast, in a prospective study on the effect of acupuncture in BPS (12), 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 (13,14), there are no scientific data on its effect on BPS symptoms.

Physiotherapy. General body exercise may be beneficial in some BPS patients (15). An uncontrolled trial of transvaginal manual therapy of the pelvic floor musculature (Thiele massage) in 21 BPS patients with high-tone dysfunction of the pelvic floor resulted in significant improvement on several assessment scales (16). Langford et al. (17) have prospectively examined the role of specific levator ani trigger point injections in 18 women with CPP. Each trigger point was identified by intravaginal palpation and injected with 5 mL of a mixture of 10 mL 0.25% bupivacaine, 10 mL 2% lidocaine and 1 mL (40 mg) triamcinolone. Thirteen (72%) women improved with the first trigger point injection, with six (33%) women being completely pain-free.

Intravaginal electrical stimulation was applied to 24 women with CPP in the form of ten 30-min applications, two or three times weekly. 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 ($P = 0.0005$) (18).

3.2.16.1 References

1. Parsons CL, Koprowski PF. Interstitial cystitis: successful management by increasing urinary voiding intervals. Urology 1991 Mar;37(3):207-12.
   http://www.ncbi.nlm.nih.gov/pubmed/2000675
2. Chaiken DC, Blaivas JG, Blaivas ST. Behavioral therapy for the treatment of refractory interstitial cystitis. J Urol 1993 Jun;149(6):1445-8.
   http://www.ncbi.nlm.nih.gov/pubmed/8501784
3. Webster DC, Brennan T. Use and effectiveness of physical self-care strategies for interstitial cystitis. Nurse Pract 1994 Oct;19(10):55-61.
   http://www.ncbi.nlm.nih.gov/pubmed/7529390

4. Rovner E, Propert KJ, Brensinger C, et al. Treatments used in women with interstitial cystitis: the interstitial cystitis data base (ICDB) study experience. The Interstitial Cystitis Data Base Study Group. Urology 2000 Dec;56(6):940-5.
http://www.ncbi.nlm.nih.gov/pubmed/11113737
5. Bade JJ, Peeters JM, Mensink HJ. Is the diet of patients with interstitial cystitis related to their disease? Eur Urol 1997;32(2):179-83.
http://www.ncbi.nlm.nih.gov/pubmed/9286650
6. Gillespie L. Metabolic appraisal of the effects of dietary modification on hypersensitive bladder symptoms. Br J Urol 1993 Sep;72(3):293-7.
http://www.ncbi.nlm.nih.gov/pubmed/8220989
7. Bologna RA, Gomelsky A, Lukban JC, et al. The efficacy of calcium glycerophosphate in the prevention of food-related flares in interstitial cystitis. Urology 2001 Jun;57(6 Suppl 1):119-20. [no abstract available]
http://www.ncbi.nlm.nih.gov/pubmed/11378102
8. Osborne JH, Manhattan D, Laumnn B. IC and Diet. In: Osborne JH, ed. The Interstitial Cystitis Network Patient Handbook. Chapter 5. Santa Rosa, CA, USA: The Interstitial Cystitis Network, 1999;pp. 43-62. [access date November 2012]
9. Chang PL. Urodynamic studies in acupuncture for women with frequency, urgency and dysuria. J Urol 1988 Sep;140(3):563-6.
http://www.ncbi.nlm.nih.gov/pubmed/3411675
10. Chang PL, Wu CJ, Huang MH. Long-term outcome of acupuncture in women with frequency, urgency and dysuria. Am J Chin Med 1993;21(3-4):231-6.
http://www.ncbi.nlm.nih.gov/pubmed/8135166
11. Zheng H, Wang S, Shang J, et al. Study on acupuncture and moxibustion therapy for female urethral syndrome. J Tradit Chin Med 1998 Jun;18(2):122-7.
http://www.ncbi.nlm.nih.gov/pubmed/10437230
12. Geirsson G, Wang YH, Lindström S, et al. Traditional acupuncture and electrical stimulation of the posterior tibial nerve. A trial in chronic interstitial cystitis. Scand J Urol Nephrol 1993;27(1):67-70.
http://www.ncbi.nlm.nih.gov/pubmed/8493470
13. Lynch DF Jr. Empowering the patient: hypnosis in the management of cancer, surgical disease and chronic pain. Am J Clin Hypn 1999 Oct;42(2):122-30.
http://www.ncbi.nlm.nih.gov/pubmed/10624023
14. Barber J. Incorporating hypnosis in the management of chronic pain. In: Barber J, Adrian C, eds. Psychological Approaches in the Management of Pain. New York: Brunner/Mazel, 1982; pp. 60-83.
15. Karper WB. Exercise effects on interstitial cystitis: two case reports. Urol Nurs 2004 Jun;24(3):202-4.
http://www.ncbi.nlm.nih.gov/pubmed/15311489
16. Oyama IA, Rejba A, Lukban JC, et al. Modified Thiele massage as therapeutic intervention for female patients with interstitial cystitis and high-tone pelvic floor dysfunction. Urology 2004 Nov;64(5):862-5.
http://www.ncbi.nlm.nih.gov/pubmed/15533464
17. Langford CF, Udvari Nagy S, Ghoniem GM. Levator ani trigger point injections: An underutilized treatment for chronic pelvic pain. Neurourol Urodyn 2007;26(1):59-62.
http://www.ncbi.nlm.nih.gov/pubmed/17195176
18. de Oliveira Bernardes N, Bahamondes L. Intravaginal electrical stimulation for the treatment of chronic pelvic pain. J Reprod Med 2005 Apr;50(4):267-72.
http://www.ncbi.nlm.nih.gov/pubmed/15916211

3.2.17 ***Surgical treatment***

When all efforts fail to relieve disabling symptoms, surgical removal of the diseased bladder is the ultimate option (1-4). 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 (5). Sporadic reports that unresected BPS bladders cease to cause symptoms when excluded from the flow or urine are scarce (6,7).

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 (8-16), ileocaecum (15-22), right colon (8,16,23), and sigmoid (10,12,13,18,22). Substituting gastric segments (24,25) 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 (12). In 1977, Bruce et al. achieved satisfactory relief of BPS symptoms by ileocystoplasty and colocystoplasty in eight patients (10). Dounis and Gow have reported seven BPS patients whose pain and frequency were considerably improved after supratrigonal cystectomy with ileocaecal augmentation (26).

In 1991, Kontturi et al. used segments of colon and sigmoid colon in 12 cases (22). 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. have reported a series of eight patients undergoing supratrigonal cystectomy with ileocaecocystoplasty.

Although symptoms resolved in two patients, treatment failure in another six necessitated secondary cystectomy and ileal conduit formation (17).

Linn et al. (27) have followed six BPS patients after supratrigonal cystectomy with ileocaecal augmentation for a period of 30 months, and have reported that all patients were symptom-free and voided spontaneously.

In 2002, Van Ophoven et al. (1) reported the long-term results of trigone-preserving cystectomy and consecutive orthotopic substitution enteroplasty in 18 women with BPS, 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, because 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-up, the debate on the outcome of BPS patients undergoing cystectomy continues and results vary greatly between different surgeons and patient populations.

Chakravarti et al. (28) presented a retrospective review of 11 patients, who had undergone a trigone-preserving orthotopic substitution caecocystoplasty for intractable BPS Type 3 C 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 postoperative 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 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. (29) have 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 with a clinical diagnosis of BPS. The BPS 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 to be a contraindication for enterocystoplasty.

In contrast, Navalón et al. (30) have reported a 32-month follow-up of four women with refractory BPS who underwent supratrigonal cystectomy with orthotopic substitution ileocystoplasty. 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 postoperative period. All patients reported high satisfaction with the outcome.

Subtrigonal cystectomy. Although less popular, subtrigonal cystectomy has also been reported (27,31-34). 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 (35).

In contrast, Linn et al. have 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-catheterisation to support voiding of the ileocaecal augmentate (27). A recent report on female sexuality after cystectomy and orthotopic ileal neobladder (36) describes eight patients. Pain was relieved in all eight, but only one regained a normal sexual life postoperatively.

Selecting patients and technique. BPS 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 several 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 is 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 preoperative cystoscopy and bladder capacity as a prognostic parameter for operative success (7). Responders and failures following orthotopic substitution differed in mean preoperative bladder capacity (200 vs. 525 mL, respectively) (17). These findings have been supported by Peeker et al. (37), who found that patients with end-stage BPS Type 3 C had excellent results following ileocystoplasty, whereas patients with non-ulcer disease were not helped. These results have recently been confirmed by another study from the same institution.

A retrospective analysis of 47 patients fulfilling the NIH criteria, who underwent reconstructive surgery using various techniques during 1978-2003 (38), 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 still ranks first in current US practice trends in surgical BPS therapy (39). 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 who develop recurrent pain in the augmented bladder or continent pouch after enterocystoplasty or continent urinary diversion, Elzawahri (40) has recommended retubularisation 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 (41). Reconstructive surgery for refractory BPS 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 preoperative evaluation, with an emphasis on assessment to determine the relevant disease location and subtype.

A summary of the treatment options for BPS, including LE and GR is given in the next section. Figure 6 and 7 are algorithms for the diagnosis and therapy of BPS based on the information discussed above.

3.2.18 ***Conclusions and recommendations: treatment of BPS***

Conclusions	**LE**
None of the present existing treatments have effect on all BPS subtypes or phenotypes.	4
Conventional analgesics have little efficacy. Opioids are effective in controlling BPS pain.	2b
Corticosteroids are not recommended as long-term treatment.	3
Hydroxyzine has limited efficacy shown in RCT and is effective in associated non bladder diseases.	1b
Limited data exist on effectiveness of cimetidine in BPS.	2b
Amitriptyline is effective in pain and related symptoms of BPS.	1b
Oral pentosanpolysulphate sodium is effective in pain and related symptoms of BPS.	1a
Oral pentosanpolysulphate sodium plus subcutaneous heparin is effective in pain and related symptoms of BPS especially in patients initially low responders to pentosanpolysulphate sodium alone.	1b
Only limited data exist on the effectiveness of antibiotics in the treatment of BPS.	2b
Insufficient data for the effectiveness of prostaglandins in BPS exist. Adverse effects are frequent.	3
Global response on cyclosporin A was superior to pentosanpolysulphate sodium, but associated with more adverse effects.	1b
Duloxetin has shown no effect and tolerability is poor.	2b
Oxybutynin has limited effect in BPS pain, but data are scant.	3
Only insufficient data exist for the effectiveness of gabapentin in BPS.	3
Only insufficient data exist for the effectiveness of suplatast tosilate in BPS.	3
Preliminary data showed effectiveness of quercetin alone and in multimodal uncontrolled studies.	3
Intravesical lidocaine plus sodium bicarbonate is effective in the short term.	1b
Intravesical pentosanpolysulphate sodium is effective based on limited data and may enhance effect of oral treatment.	1b
There are limited data on the effectiveness of intravesical heparin.	3
Intravesical hyaluronic acid may have long term effects in BPS patients with positive intravesical modified KCl test.	2b

Intravesical chondroitin sulphate may be effective according to non-randomised studies. Published RCTs are underpowered.	2b
Intravesical DMSO is effective in the treatment of BPS, but side effects have to be considered.	1b
Intravesical submucosal BTX-A injection plus hydrodistension has sustained and significantly improved effect over hydrodistension alone.	1b
Only limited data exist on the effectiveness of BTX-A injection into detrusor or trigone.	3
Data on effectiveness of intravesical vanilloids are contradictory. Largest of RCTs without efficacy.	1b
Intravesical Bacillus Calmette Guérin (BCG) is not effective in BPS.	1b
Intravesical clorpactin has insufficient data to support effectiveness and high complication rates.	3
There is only insufficient data to support effectiveness of bladder distension.	3
Scarce data indicate electromotive drug administration may have a beneficial effect in patient subsets.	3
Transurethral resection (Coagulation and laser) may be effective in BPS type 3 C.	3
Sacral neuromodulation may be effective in BPS.	3
Pudendal nerve stimulation is superior to sacral nerve stimulation for the treatment of BPS.	1b
Bladder training may be effective in patients with predominant urinary symptoms and little pain.	3
Manual and physical therapy may have limited effects.	3
Avoidance of some food and drink avoids pain triggering.	3
Acupuncture: data contradictory.	3
Psychological therapy may be effective in ameliorating coping with disease.	3
No definitive conclusion on the effectiveness of surgical organ removal for BPS can be drawn based on large variability results in reported series.	3

Recommendations	**GR**
Offer subtype and phenotype-oriented therapy for the treatment of BPS.	A
Multimodal behavioural, physical and psychological techniques should always be considered alongside oral or invasive treatments for BPS.	A
Opioids might be used in BPS in disease flare-ups. Long-term application solely if all treatments failed.	C
Corticosteroids are not recommended as long-term treatment.	C
Offer hydroxyzine for the treatment of BPS.	A
Consider cimetidine as valid oral option before invasive treatments.	B
Administer amitriptyline for use in BPS.	A
Offer oral pentosanpolysulphate sodium for the treatment of BPS.	A
Treatment with oral pentosanpolysulphate sodium plus subcutaneous heparin is recommended especially in low responders to pentosanpolysulphate sodium alone.	A
Antibiotics can be offered when infection is present or highly suspected.	C
Prostaglandins are not recommended. Insufficient data on BPS, adverse effects considerable.	C
Cyclosporin A might be used in BPS but adverse effects are significant and should be carefully considered.	B
Duloxetin is not recommended for BPS treatment.	C
Oxybutynin might be considered for the treatment of BPS.	C
Gabapentin might be considered in oral treatment of BPS.	C
Administer intravesical lidocain plus sodium bicarbonate prior to more invasive methods.	A
Administer intravesical pentosanpolysulphate sodium before more invasive treatment alone or combined with oral pentosanpolysulphate sodium.	A
Consider intravesical heparin before more invasive measures alone or in combination treatment.	C
Consider intravesical hyaluronic acid before more invasive measures.	B
Consider intravesical chondroitin sulphate before more invasive measures.	B
Administer intravesical DMSO before more invasive measures.	A
Consider intravesical bladder wall and trigonal injection of BTX-A if intravesical instillation therapies failed.	C
Administer submucosal injection of BTX-A plus hydrodistension if intravesical instillation therapies failed.	A

Intravesical therapy with Bacillus Calmette Guérin is not recommended in BPS.	A
Intravesical therapy with clorpactin is not recommended in BPS.	A
Intravesical therapy with vanilloids is not recommended in BPS.	C
Bladder distension is not recommended as a treatment of BPS.	C
Electromotive drug administration might be considered before more invasive measures.	C
Consider transurethral resection (or coagulation or laser) of bladder lesions, but in BPS type 3 C only.	B
Neuromodulation might be considered before more invasive interventions.	B
Consider bladder training in patients with little pain.	B
Consider manual and physical therapy in first approach.	B
Consider diet avoidance of triggering substances.	C
Accupuncture is not recommended.	C
Consider psychological therapy in multimodal approach.	B
All ablative organ surgery should be last resort for experienced and BPS knowledgeable surgeons only.	A

DMSO = dimethyl sulphoxide; BPS = bladder pain syndrome.

Figure 6: Diagnosis and therapy of BPS

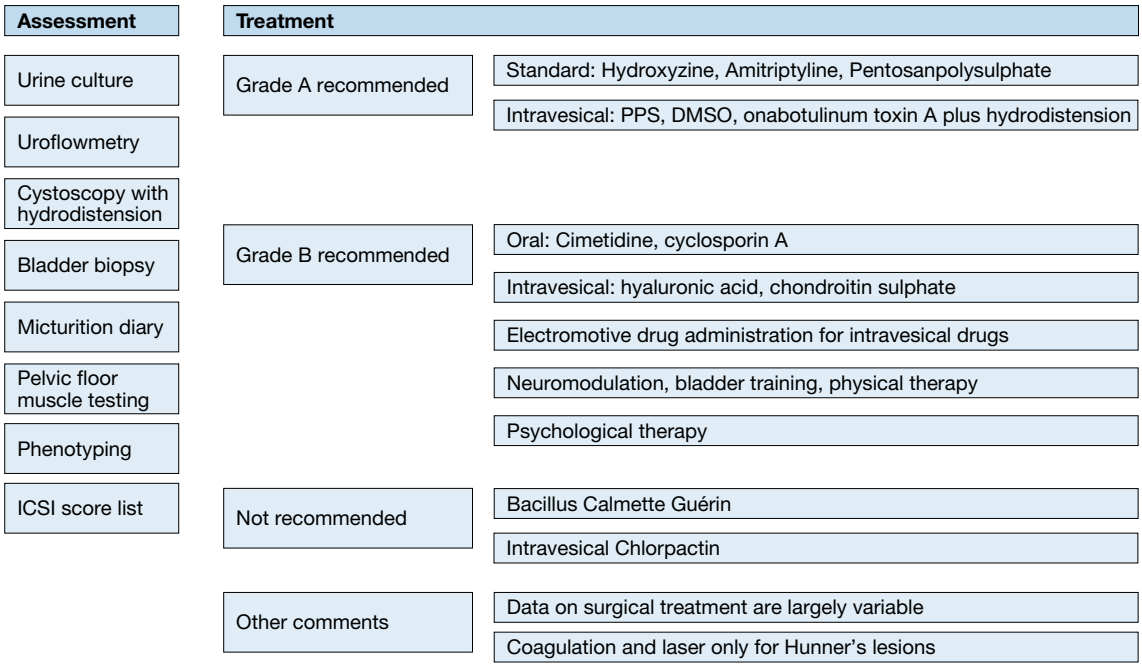
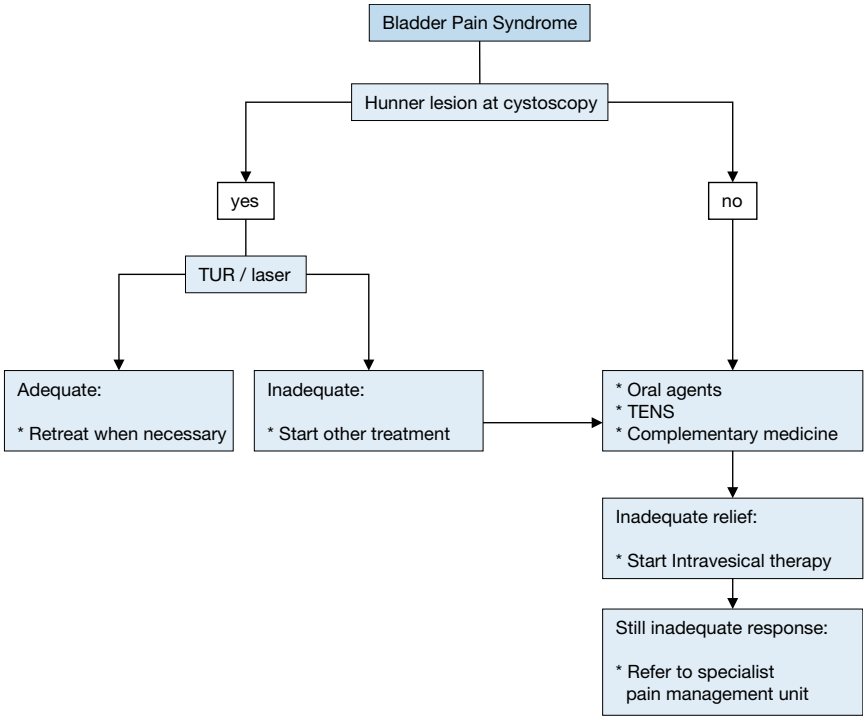


Figure 7: Algorithm for BPS Type 3 C



3.2.19 ***References***

1. van Ophoven A, Oberpenning F, Hertle L. Long-term results of trigone-preserving orthotopic substitution enterocystoplasty for interstitial cystitis. J Urol 2002 Feb;167(2 Pt 1):603-7. http://www.ncbi.nlm.nih.gov/pubmed/11792927
2. Loch A, Stein U. [Interstitial cystitis. New aspects in diagnosis and therapy]. Urologe A 2004 Sep;43(9):1135-46. [Article in German] http://www.ncbi.nlm.nih.gov/pubmed/15322757
3. Oberpenning F, van Ophoven A, Hertle L. [Chronic interstitial cystitis.] Deutsches Ärzteblatt 2002, 99:204-8. [Article in German]
4. Oberpenning F, Van Ophoven A, Hertle L. Interstitial cystitis: an update. Curr Opin Urol 2002 Jul;12(4):321-32. http://www.ncbi.nlm.nih.gov/pubmed/12072654
5. Warwick R, Ashkan M. The functional results of partial, subtotal and total cystoplasty with special reference to ureterocecocystoplasty, selective sphincterotomy and cystoplasty. Br J Urol 1967 Feb;39(1):3-12. [no abstract available] http://www.ncbi.nlm.nih.gov/pubmed/5336762
6. Messing EM, Stamey TA. Interstitial cystitis: early diagnosis, pathology, and treatment. Urology 1978 Oct;12(4):381-92. http://www.ncbi.nlm.nih.gov/pubmed/213864
7. Freiha FS, Faysal MH, Stamey TA. The surgical treatment of intractable interstitial cystitis. J Urol 1980 May;123(5):632-4. http://www.ncbi.nlm.nih.gov/pubmed/7420547
8. Badenoch AW. Chronic interstitial cystitis. Br J Urol 1971 Dec;43(6):718-21. [no abstract available] http://www.ncbi.nlm.nih.gov/pubmed/5159574
9. Awad SA, Al-Zahrani HM, Gajewski JB, et al. Long-term results and complications of augmentation ileocystoplasty for idiopathic urge incontinence in women. Br J Urol 1998 Apr;81(4):569-73. http://www.ncbi.nlm.nih.gov/pubmed/9598629
10. Bruce PT, Buckham GJ, Carden AB, et al. The surgical treatment of chronic interstitial cystitis. Med J Aust 1977 Apr;1(16):581-2. http://www.ncbi.nlm.nih.gov/pubmed/875802
11. Christmas TJ, Holmes SA, Hendry WF. Bladder replacement by ileocystoplasty: the final treatment for interstitial cystitis. Br J Urol 1996 Jul;78(1):69-73. http://www.ncbi.nlm.nih.gov/pubmed/8795403

12. von Garrelts B. Interstitial cystitis: thirteen patients treated operatively with intestinal bladder substitutes. Acta Chir Scand 1966 Oct;132(4):436-43. [no abstract available]
http://www.ncbi.nlm.nih.gov/pubmed/5972716
13. Guillonneau B, Toussaint B, Bouchot O, et al. [Treatment of interstitial cystitis with sub-trigonal cystectomy and enterocystoplasty.] Prog Urol 1993 Feb;3(1):27-31. [Article in French]
http://www.ncbi.nlm.nih.gov/pubmed/8485591
14. Koskela E, Kontturi M. Function of the intestinal substituted bladder. Scand J Urol Nephrol 1982;16(2):129-33.
http://www.ncbi.nlm.nih.gov/pubmed/7123162
15. Shirley SW, Mirelman S. Experiences with colocystoplasties, cecocystoplasties and ileocystoplasties in urologic surgery: 40 patients. J Urol 1978 Aug;120(2):165-8.
http://www.ncbi.nlm.nih.gov/pubmed/671623
16. Webster GD, Maggio MI. The management of chronic interstitial cystitis by substitution cystoplasty. J Urol 1989 Feb;141(2):287-91.
http://www.ncbi.nlm.nih.gov/pubmed/2913346
17. Nielsen KK, Kromann-Andersen B, Steven K, et al. Failure of combined supratrigonal cystectomy and Mainz ileovcecocystoplasty in intractable interstitial cystitis: is histology and mast cell count a reliable predictor for the outcome of surgery? J Urol 1990 Aug;144(2 Pt 1):255-8; discussion 258-9.
http://www.ncbi.nlm.nih.gov/pubmed/2374189
18. Hradec EA. Bladder substitution: indications and results in 114 operations. J Urol 1965 Oct;94(4): 406-17. [no abstract available]
http://www.ncbi.nlm.nih.gov/pubmed/5320331
19. DeJuana CP, Everett JC Jr. Interstitial cystitis: experience and review of recent literature. Urology 1977 Oct;10(4):325-9.
http://www.ncbi.nlm.nih.gov/pubmed/919117
20. Utz DC, Zincke H.The masquerade of bladder cancer in situ as interstitial cystitis. J Urol 1974 Feb;111(2):160-1. [no abstract available]
http://www.ncbi.nlm.nih.gov/pubmed/4810754
21. Whitmore WF 3rd, Gittes RF. Reconstruction of the urinary tract by cecal and ileocecal cystoplasty:review of a 15-year experience. J Urol 1983 Mar;129(3):494-8. [no abstract available]
http://www.ncbi.nlm.nih.gov/pubmed/6834531
22. Kontturi MJ, Hellström PA, Tammela TL, et al. Colocystoplasty for the treatment of severe interstitial cystitis. Urol Int 1991;46(1):50-4.
http://www.ncbi.nlm.nih.gov/pubmed/2024372
23. Seddon JM, Best L, Bruce AW. Intestinocystoplasty in treatment of interstitial cystitis. Urology 1977 Nov;10(5):431-5.
http://www.ncbi.nlm.nih.gov/pubmed/919133
24. Leong CH. Use of the stomach for bladder replacement and urinary diversion. Ann R Coll Surg Engl 1978 Jul;60(4):283-9.
http://www.ncbi.nlm.nih.gov/pubmed/666231
25. Singla A, Galloway N. Early experience with the use of gastric segment in lower urinary tract reconstruction in adult patient population. Urology 1997 Oct;50(4):630-5.
http://www.ncbi.nlm.nih.gov/pubmed/9338749
26. Dounis A, Gow JG. Bladder augmentation-a long-term review. Br J Urol 1979 Aug;51(4):264-8.
http://www.ncbi.nlm.nih.gov/pubmed/466001
27. Linn JF, Hohenfellner M, Roth S, et al. Treatment of interstitial cystitis: comparison of subtrigonal and supratrigonal cystectomy combined with orthotopic bladder substitution. J Urol 1998 Mar;159(3): 774-8.
http://www.ncbi.nlm.nih.gov/pubmed/9474146
28. Chakravarti A, Ganta S, Somani B, et al. Caecocystoplasty for intractable interstitial cystitis: long-term results. Eur Urol 2004 Jul;46(1):114-7.
http://www.ncbi.nlm.nih.gov/pubmed/15183556
29. Blaivas JG, Weiss JP, Desai P, et al. Long-term followup of augmentation enterocystoplasty and continent diversion in patients with benign disease. J Urol 2005 May;173(5):1631-4.
http://www.ncbi.nlm.nih.gov/pubmed/15821519
30. Navalón Verdejo P, Ordoño Domínguez F, De la Torre Abril L, et al. [Orthotopic bladder substitution in the treatment of interstitial cystitis.] Arch Esp Urol 2005 Sep;58(7):605-10. [Article in Spanish]
http://www.ncbi.nlm.nih.gov/pubmed/16294782

31. Bejany DE, Politano VA. Ileocolic neobladder in the woman with interstitial cystitis and a small contracted bladder. J Urol 1995 Jan;153(1):42-3.
http://www.ncbi.nlm.nih.gov/pubmed/7966787
32. Nurse DE, McCrae P, Stephenson TP, et al.The problems of substitution cystoplasty. Br J Urol 1988 May;61(5):423-6.
http://www.ncbi.nlm.nih.gov/pubmed/3395801
33. Lotenfoe RR, Christie J, Parsons A, et al. Absence of neuropathic pelvic pain and favorable psychological profile in the surgical selection of patients with disabling interstitial cystitis. J Urol 1995 Dec;155(6):2039-42.
http://www.ncbi.nlm.nih.gov/pubmed/7500453
34. Hughes OD, Kynaston HG, Jenkins BJ, et al. Substitution cystoplasty for intractable interstitial cystitis. Br J Urol 1995 Aug;76(2):172-4.
http://www.ncbi.nlm.nih.gov/pubmed/7663907
35. Nurse DE, Parry JR, Mundy AR. Problems in the surgical treatment of interstitial cystitis. Br J Urol 1991 Aug;68(2):153-4.
http://www.ncbi.nlm.nih.gov/pubmed/1822961
36. Volkmer BG, Gschwend JE, Herkommer K, et al. Cystectomy and orthotopic ileal neobladder: the impact on female sexuality. J Urol 2004 Dec;172(6 Pt 1):2353-7.
http://www.ncbi.nlm.nih.gov/pubmed/15538266
37. Peeker R, Aldenborg F, Fall M. The treatment of interstitial cystitis with supratrigonal cystectomy and ileocystoplasty: difference in outcome between classic and nonulcer disease. J Urol 1998 May;159(5):1479-82.
http://www.ncbi.nlm.nih.gov/pubmed/9554337
38. Rössberger J, Fall M, Jonsson O, et al. Long-term results of reconstructive surgery in patients with bladder pain syndrome/interstitial cystitis: subtyping is imperative. Urology 2007 Oct;70(4):638-42.
http://www.ncbi.nlm.nih.gov/pubmed/17991529
39. Gershbaum D, Moldwin R. Practice trends for the management of interstitial cystitis. Urology 2001 Jun;57(6 Suppl 1):119.
http://www.ncbi.nlm.nih.gov/pubmed/11378100
40. Elzawahri A, Bissada NK, Herchorn S, et al. Urinary conduit formation using a retubularized bowel from continent urinary diversion or intestinal augmentations: ii. Does it have a role in patients with interstitial cystitis? J Urol 2004 Apr;171(4):1559-62.
http://www.ncbi.nlm.nih.gov/pubmed/15017220
41. Shaikh A, Ahsan S, Zaidi Z. Pregnancy after augmentation cystoplasty. J Pak Med Assoc 2006 Oct;56(10):465-7.
http://www.ncbi.nlm.nih.gov/pubmed/17144396

3.3 Genital pain syndrome

3.3.1 ***Scrotal pain syndrome***

Scrotal pain syndrome is the occurrence of persistent or recurrent episodic pain localised within the organs of the scrotum, and may be associated with symptoms suggestive of urinary tract or sexual dysfunction. There is no proven infection or other obvious local pathology. Scrotal pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction. Scrotal pain syndrome is a generic term and is used when the site of the pain is not clearly testicular or epididymal. The pain is not in the skin of the scrotum as such, but perceived within its contents, in a similar way to idiopathic chest pain.

3.3.2 ***Pathogenesis***

The pathogenesis of chronic scrotal pain is diverse and in most cases unknown. Pain in the scrotum can be divided into direct pain localised in the scrotum, or referred pain coming from another place or system in the body. The problem is that we cannot always make that division in clinical practice. Direct pain is located in the testes, epididymis, inguinal nerves or the vas deferens.

3.3.2.1 Testicular pain syndrome

Testicular pain syndrome is the occurrence of persistent or recurrent episodic pain perceived in the testes, and may be associated with symptoms suggestive of urinary tract or sexual dysfunction. There is no proven infection or other obvious local pathology. Testicular pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction. Previous terms have included orchitis, orchialgia and orchiodynia. These terms are no longer recommended.

3.3.2.2 Epididymal pain syndrome

Epididymal pain syndrome is the occurrence of persistent or recurrent episodic pain perceived in the epididymis, and may be associated with symptoms suggestive of urinary tract or sexual dysfunction. There is no proven infection or other obvious local pathology. Epididymal pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction.

Structural abnormalities of the epididymis can be visualised using ultrasound. Patients with multiple cysts may have pain caused by the compression that these cysts exert on the epididymis. Another local entity is chronic epididymitis (1). Chronic epididymis may be associated with signs of inflammation: inflammatory or obstructive chronic epididymitis (2).

3.3.2.3 Nerves

The ilioinguinal and genitofemoral nerves are the most prominent afferent nerves for the scrotum (3). The inguinal nerves are especially important. It is generally accepted that pain after inguinal surgery (hernia) is a consequence of damage to the nerves inside the spermatic cord (4). This is based on the anatomical knowledge that all nerves involved in testicular pain merge in the spermatic cord (5). This fact has consequences for the choice of treatment. The pudendal nerve supplies the skin of the perineum and the posterior side of the scrotum. Pain in this area is pathognomic for pudendal neuropathy.

3.3.2.4 Postvasectomy pain syndrome

Postvasectomy scrotal pain syndrome is a scrotal pain syndrome that follows vasectomy. Postvasectomy scrotal pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction. Postvasectomy pain may be as frequent as 1% following vasectomy, possibly more frequent. The mechanisms are poorly understood and it is for that reason considered a special form of scrotal pain syndrome. Pathogenetically, it is thought that postvasectomy pain is caused by the fact that the vas deferens is no longer patent. This may lead to congestion in the epididymis which in turn gives rise to pain because of dilatation of hollow structures (6). Incidence of postvasectomy pain is 2-20% among all men who have undergone a vasectomy (7). In men with postvasectomy pain, only 2-6% have a VAS score > 5 (8). In a large cohort study of 625 men, the likelihood of scrotal pain after 6 months was 14.7%. The mean pain severity on a VAS score was 3.4/10. In the pain group, 0.9% had quite severe pain, noticeably affecting their daily life. In this cohort, different techniques were used to perform the vasectomy. The risk of scrotal pain was significantly lower in the no-scalpel vasectomy group, at 11.7% compared with 18.8% in the scalpel group (9).

3.3.2.5 Post-inguinal hernia repair

Chronic pain after inguinal hernia surgery is a well recognised phenomenon. An international working group has set up guidelines for prevention and management of postoperative chronic pain following inguinal hernia surgery. They have stated that the most important way of preventing pain is to identify and preserve all three inguinal nerves (10). Chronic scrotal pain is a complication of hernia repair, but in trials, it is seldom reported or it is put under the term chronic pain (not specified). In studies that have explicitly mentioned scrotal pain, there was a difference in incidence between laparoscopic and open hernia repair. In almost all studies, the frequency of scrotal pain was significantly higher in the laparoscopic than in the open group (4,11-13). In one particular study, there was no difference at 1 year but after 5 years, the open group had far fewer patients with scrotal pain (14).

3.3.2.6 Referred pain

Growing knowledge of pain mechanisms has taught us that pain felt in organ A can be caused by dysfunction of structure B. The best known referred pain is of myofascial origin, especially the trigger points (see Chapter 9). Problems inside the bladder or abdominal cavity can also give rise to pain in the scrotal area. When making a treatment plan for patients with scrotal pain, it is important to remember this phenomenon.

3.3.3 ***Diagnosis***

A physical examination is mandatory in patients with scrotal pain. Gentle palpation of each component of the scrotum is performed to search for masses and painful spots. A rectal examination is done to look for prostate abnormalities and to examine the pelvic floor muscles. Scrotal ultrasound has limited value in finding the cause of the pain. In > 80% of patients, ultrasound does not show abnormalities that have clinical implications (15,16). If physical examination is normal, ultrasound can be performed to reassure the patient that there is no pathology that needs therapy (mainly surgery). Ultrasound can be used to diagnose hydroceles, spermatoceles, cysts and varicoceles. When abnormalities such as cysts are seen, this may play a role in therapeutic decision making. In general practice, it seems that many urologists are performing ultrasound examination in almost all

patients. Swiss urologists, for instance, perform it in 93% of cases (17).

3.3.4 ***Treatment***

Treatment of chronic scrotal pain is based on the principles of treating chronic pain syndromes, described throughout these guidelines. It is becoming increasingly clear that advances in the nonsurgical management of testicular pain are mainly based on the emergence of pain relief as a specialty. Knowing this, it seems obvious that referring to a multidisciplinary pain team or pain centre should be considered in an early phase of the consultation (18). By doing this, surgery can be postponed or even avoided.

3.3.4.1 Conservative treatment

For conservative treatment, apart from pharmacotherapy, myofascial therapy by specialised physiotherapists should be considered. The pelvic floor muscles should be tested and will often be found overactive, which means that they contract when relaxation is needed. An overactive pelvic floor should be treated with physiotherapy (19-21). More specific myofascial trigger points are found in the pelvic floor, but also in the lower abdominal musculature. Treatment consists of applying pressure to the trigger point and stretching the muscle (22,23) (see Chapter 9).

3.3.4.2 Surgery

In a survey among Swiss urologists, it was found that 74% would do an epididymectomy, 7% an inguinal orchiectomy, and 6% a denervation (17). In the literature, there is consensus on postponing surgery until there is no other option. The only treatment that seems to be effective is microsurgical denervation. Epididymectomy is a choice in selected cases and orchiectomy is the last resort.

3.3.4.1.1 Microsurgical denervation

Considering the fact that all the nerves for the scrotal organs merge into the spermatic cord, it seems reasonable to cut all these nerves in patients with pain. All the studies that have been done were cohort studies but their success rates were high. The size of effect was so remarkable that it is recommended that randomised studies are performed to obtain better proof. The three cohort studies that are found were consistent in the indication criteria, the diagnostic methods applied, and the surgical approach used. All had a follow-up of at least 20 months. They included patients with chronic scrotal pain who did not respond to conservative treatment. Ultrasound showed no abnormalities and a spermatic cord block showed pain relief of > 50%. The surgical approach is inguinal. The cord is transected in such a way that all identifiable arterial structures, including testicular, cremasteric, deferential arteries and lymphatic vessels are left intact. The surgery is performed under magnification by loupe or microscope. Complete relief of pain is achieved in 71-96% and partial relief in 9-17%. This means that 12-15% had no relief of pain after denervation. The complication of testicular atrophy was seen in 3-7% of the operated patients (24-26). There is no difference in success based on the cause of pain. The laparoscopic route for denervation seems feasible but the results are unclear (27).

3.3.4.1.2 Epididymectomy

There is to date no hard evidence available, but expert opinion is clear that epididymectomy should be reserved for patients who have undergone denervation but still have pain. Epididymectomy shows different results in various groups of patients. Epididymectomy shows the best results in patients with pain after vasectomy, or pain on palpation of the epididymis and when ultrasound shows multiple cysts. Patients with chronic epididymitis show bad results with epididymectomy.

The percentage of patients that are cured ranges from 50 to 92% (1,6,28-30). These results are also from cohort studies but the fact that assessment can help in predicting the chance of success makes further studies worthwhile. One study in our search has yielded different results, namely, that postvasectomy patients fared worse and that ultrasound did not help in predicting the result of the operation. No reason was found for this result (9).

3.3.4.1.3 Orchiectomy

Orchiectomy is seen as the last resort in patients with intrascrotal pain, who do not respond to any other treatment. There have been no studies than can help in making a rational decision on whether to perform orchiectomy.

3.3.4.1.4 Vasovasostomy

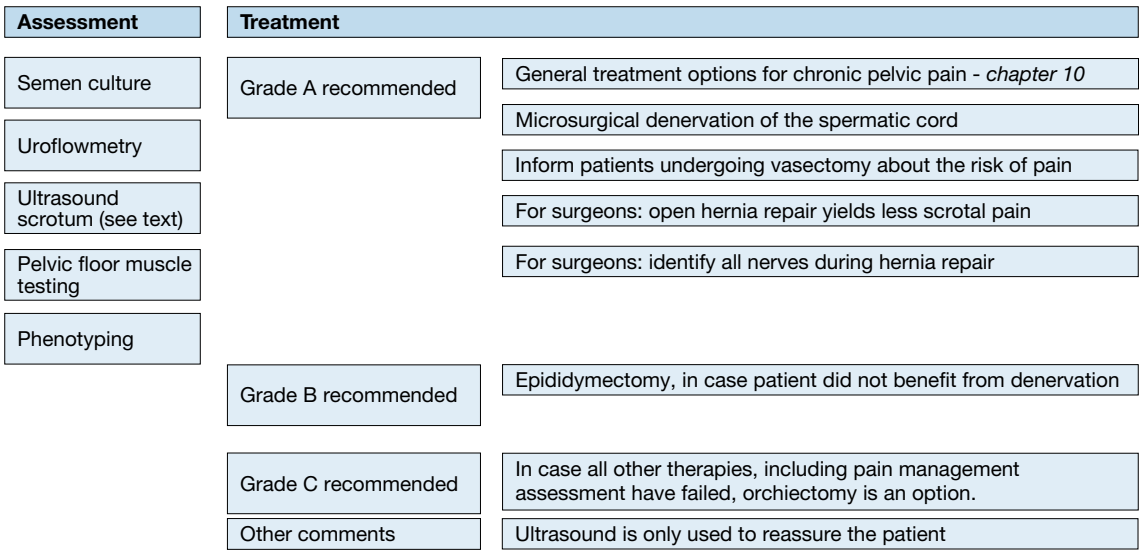
In postvasectomy pain syndrome, a vasovasostomy might help to overcome the obstruction and thereby improve the pain. Some studies have shown good results but the quality of these studies was limited. Results are as high as 69-84% (31,32).

3.3.5 *Conclusions and recommendations: scrotal pain syndrome*

Conclusions	LE
The nerves in the spermatic cord play an important role in scrotal pain.	2b
Ultrasound of the scrotal content is not of help in diagnostics nor treatment of scrotal pain.	2b
Postvasectomy pain is seen in a substantial number of men undergoing vasectomy.	2b
Scrotal pain is more often noticed after laparoscopic then after open inguinal hernia repair.	1b
Microsurgical denervation of the spermatic cord is an effective therapy for scrotal pain syndrome.	2b
Vasovasostomy is effective in postvasectomy pain.	2b
Orchiectomy is the last resort in treating scrotal pain syndrome.	4

Recommendations	GR
Start with general treatment options for chronic pelvic pain (see chapter 10).	A
Inform about the risk of postvasectomy pain when counselling patients planned for vasectomy.	A
To reduce the risk of scrotal pain, open instead of laparoscopic inguinal hernia repair is recommended.	A
It is recommended that during inguinal hernia repair all the nerves in the spermatic cord are identified.	A
For patients who are treated surgically, microsurgical denervation of the spermatic cord is recommended.	A
For patients who do not benefit from denervation it is recommended to perform epididymectomy.	B
We recommend that orchiectomy should not be done, unless all other therapies, including pain management assessment have failed.	C

Figure 8: Assessment and treatment algorithm for scrotal pain syndrome



3.3.6 *References*

1. Padmore DE, Norman RW, Millard OH. Analyses of indications for and outcomes of epididymectomy. J Urol 1996 Jul;156(1):95-6. http://www.ncbi.nlm.nih.gov/pubmed/8648848
2. Nickel JC, Siemens DR, Nickel KR, et al. The patient with chronic epididymitis: characterization of an enigmatic syndrome. J Urol 2002 Apr;167(4):1701-4. http://www.ncbi.nlm.nih.gov/pubmed/11912391
3. Rab M, Ebmer AJ, Dellon AL. Anatomic variability of the ilioinguinal and genitofemoral nerve:implications for the treatment of groin pain. Plast Reconstr Surg 2001 Nov;108(6):1618-23. http://www.ncbi.nlm.nih.gov/pubmed/11711938
4. Eklund A, Montgomery A, Bergkvist L, et al. Chronic pain 5 years after randomized comparison of laparoscopic and Lichtenstein inguinal hernia repair. Br J Surg. 2010 Apr;97(4):600-8. http://www.ncbi.nlm.nih.gov/pubmed/20186889

5. Heidenreich A, Olbert P, Engelmann UH. Management of chronic testalgia by microsurgical testicular denervation. Eur Urol. 2002 Apr;41(4):392-7.
http://www.ncbi.nlm.nih.gov/pubmed/12074809
6. Sweeney P, Tan J, Butler MR, et al. Epididymectomy in the management of intrascrotal disease: a critical reappraisal. Br J Urol 1998 May;81(5):753-5.
http://www.ncbi.nlm.nih.gov/pubmed/9634056
7. Nariculam J, Minhas S, Adeniyi A, et al. A review of the efficacy of surgical treatment for andpathological changes in patients with chronic scrotal pain. BJU Int 2007 May;99(5):1091-3.
http://www.ncbi.nlm.nih.gov/pubmed/17244279
8. Manikandan R, Srirangam SJ, Pearson E, et al. Early and late morbidity after vasectomy: a comparison of chronic scrotal pain at 1 and 10 years. BJU Int 2004 Mar;93(4):571-4.
http://www.ncbi.nlm.nih.gov/pubmed/15008732
9. Leslie TA, Illing RO, Cranston DW, et al. The incidence of chronic scrotal pain after vasectomy: aprospective audit. BJU Int 2007 Dec;100(6):1330-3.
http://www.ncbi.nlm.nih.gov/pubmed/17850378
10. Alfieri S, Amid PK, Campanelli G, et al. International guidelines for prevention and management of post-operative chronic pain following inguinal hernia surgery. Hernia. 2011 Jun;15(3):239-49.
http://www.ncbi.nlm.nih.gov/pubmed/21365287
11. Andersson B, Hallén M, Leveau P, et al. Year: 2004. Laparoscopic extraperitoneal inguinal hernia repair versus open mesh repair: a prospective randomized controlled trial. Surgery 2003 May; 133(5):464-72.
http://www.ncbi.nlm.nih.gov/pubmed/12773973
12. Wright D, Paterson C, Scott N, et al. Five-year follow-up of patients undergoing laparoscopic or open groin hernia repair: A randomized controlled trial. Ann Surg. 2002 Mar;235(3):333-7.
http://www.ncbi.nlm.nih.gov/pubmed/11882754
13. Hallén M, Bergenfelz A, Westerdahl J. Laparoscopic extraperitoneal inguinal hernia repair versus open mesh repair: long-term follow-up of a randomized controlled trial.Surgery. 2008 Mar;143(3):313-7.
http://www.ncbi.nlm.nih.gov/pubmed/18291251
14. Grant AM, Scott NW, O'Dwyer PJ, et al. Five-year follow-up of a randomized trial to assess pain and numbness after laparoscopic or open repair of groin hernia.Br J Surg. 2004 Dec;91(12):1570-4.
http://www.ncbi.nlm.nih.gov/pubmed/15515112
15. van Haarst EP, van Andel G, Rijcken TH, et al. Value of diagnostic ultrasound in patients with chronicscrotal pain and normal findings on clinical examination. Urology 1999 Dec;54(6):1068-72.
http://www.ncbi.nlm.nih.gov/pubmed/10604710
16. Lau MW, Taylor PM, Payne SR. The indications for scrotal ultrasound. Br J Radiol. 1999 Sep;72(861):833-7.
http://www.ncbi.nlm.nih.gov/pubmed/10645188
17. Strebel RT, Leippold T, Luginbuehl T, et al. Chronic scrotal pain syndrome: management among urologists in Switzerland. Eur Urol. 2005 Jun;47(6):812-6.
http://www.ncbi.nlm.nih.gov/pubmed/15925078
18. Messelink EJ. The pelvic pain centre. World J Urol 2001 Jun;19(3):208-12.
http://www.ncbi.nlm.nih.gov/pubmed/11469609
19. Cornel EB, van Haarst EP, Schaarsberg RW, et al. The effect of biofeedback physical therapy in menwith Chronic Pelvic Pain Syndrome Type III. Eur Urol 2005 May;47(5):607-11.
http://www.ncbi.nlm.nih.gov/pubmed/15826751
20. Hetrick DC, Glazer H, Liu YW, et al. Pelvic floor electromyography in men with chronic pelvic painsyndrome: a case-control study. Neurourol Urodyn 2006;25(1):46-9.
http://www.ncbi.nlm.nih.gov/pubmed/16167354
21. Rowe E, Smith C, Laverick L, et al. A prospective, randomized, placebo controlled, double-blind studyof pelvic electromagnetic therapy for the treatment of chronic pelvic pain syndrome with 1 year offollowup. J Urol 2005 Jun;173(6):2044-7.
http://www.ncbi.nlm.nih.gov/pubmed/15879822
22. Anderson RU, Wise D, Sawyer T, et al. Integration of myofascial trigger point release and paradoxicalrelaxation training treatment of chronic pelvic pain in men. J Urol 2005 Jul;174(1):155-60.
http://www.ncbi.nlm.nih.gov/pubmed/15947608
23. Srinivasan AK, Kaye JD, Moldwin R. Myofascial dysfunction associated with chronic pelvic floor pain: management strategies. Curr Pain Headache Rep 2007 Oct;11(5):359-64.
http://www.ncbi.nlm.nih.gov/pubmed/17894926

24. Strom KH, Levine LA. Microsurgical denervation of the spermatic cord for chronic orchialgia: long-term results from a single center. J Urol 2008 Sep;180(3):949-53. http://www.ncbi.nlm.nih.gov/pubmed/18639271
25. Levine LA, Matkov TG. Microsurgical denervation of the spermatic cord as primary surgical treatment of chronic orchialgia. J Urol 2001 Jun;165(6 Pt 1):1927-9. http://www.ncbi.nlm.nih.gov/pubmed/11371883
26. Heidenreich A, Olbert P, Engelmann UH. Management of chronic testalgia by microsurgical testicularderenervation. Eur Urol 2002 Apr;41(4):392-7. http://www.ncbi.nlm.nih.gov/pubmed/12074809
27. Cadeddu JA, Bishoff JT, Chan DY, et al. Laparoscopic testicular denervation for chronic orchalgia. J Urol 1999 Sep;162(3 Pt 1):733-5; discussion 735-6. http://www.ncbi.nlm.nih.gov/pubmed/10458355
28. Granitsiotis P, Kirk D. Chronic testicular pain: an overview. Eur Urol 2004 Apr;45(4):430-6. http://www.ncbi.nlm.nih.gov/pubmed/15041105
29. Sweeney CA, Oades GM, Fraser M, et al. Does surgery have a role in management of chronic intrascrotal pain? Urology 2008 Jun;71(6):1099-102. http://www.ncbi.nlm.nih.gov/pubmed/18436286
30. Calleary JG, Masood J, Hill JT. Chronic epididymitis: is epididymectomy a valid surgical treatment? Int J Androl. 2009 Oct;32(5):468-72. http://www.ncbi.nlm.nih.gov/pubmed/18380787
31. Nangia AK, Myles JL, Thomas AJ Jr. Vasectomy reversal for the postvasectomy pain syndrome: aclinical and histological evaluation. J Urol 2000 Dec;164(6):1939-42. http://www.ncbi.nlm.nih.gov/pubmed/11061886
32. Myers SA, Mershon CE, Fuchs EF. Vasectomy reversal for treatment of the postvasectomy pain syndrome. J Urol 1997 Feb;157(2):518-20. http://www.ncbi.nlm.nih.gov/pubmed/8996346

3.4 Urethral pain syndrome

3.4.1 ***Definition***

Urethral pain syndrome is the occurrence of chronic or recurrent episodic pain perceived in the urethra, in the absence of proven infection or other obvious local pathology. Urethral pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction. Urethral pain syndrome may occur in men and women.

3.4.2 ***Pathogenesis***

Based on the definition, there is no well-known pathogenetic mechanism responsible for urethral pain syndrome. There are no data available to answer the question: “how common is dysuria in the presence of negative rigorous investigation of the bladder and urethra?” Some suggestions have been proposed. The intimate relation of the urethra with the bladder (both covered with urothelium) makes it plausible that pathology seen in the bladder is also found in the urethra and causes the same symptoms. This is the case in classifying urethral pain syndrome as a form of BPS. It is obvious that what might cause pain in the bladder could be responsible for urethral pain. Mechanisms thought to be basic for BPS also apply to the urethra. This means that the specific testing with potassium is used to support the theory of epithelial leakage (1,2). Urethral syndrome is supposed to be the same as BPS in that the epithelium is leaking, thereby causing pain.

Another possible mechanism is the neuropathic hypersensitivity following urinary tract infection (3). Symptoms recorded in patients with urethral pain syndrome can also be classified as referred pain from other organs or from the myofascial system. Attention to the phenomenon of referred pain is important. See Chapter 9 for more on the myofascial origin of the pain.

The relationship with gynaecological and obstetric aspects is unclear. In a small group of patients with urethral pain, it has been found that grand multiparity and delivery without episiotomy were more often seen in patients with urethral syndrome, using univariate analysis (4).

3.4.3 ***Treatment***

There is no specific treatment that can be advised. Management should be multidisciplinary and multimodal (5). Laser therapy of the trigonal region may be a specific treatment. One trial comparing two forms of laser reported good results, but did not compare with sham treatment (6). The majority of publications on treatment of urethral pain syndrome have come from psychologists. In a 2007 review of treatment, Kaur and Arunkalaivanan have concluded that “treatment at its best” is by “behavioural therapy including biofeedback, meditation, bladder retraining, and hypnosis has been used with some success”, but no reference is given,

and no trials of these arose from the search (3). Baldoni et al. (7) have reported high rates of anxiety and depression, and worsening of symptoms related to stress in patients with urethral pain syndrome The only treatment trial found was by Baldoni et al. The psychological model that he used is not entirely clear: they have described how “in some cases” psychotherapy enables patients to recognise “the emotional implications” of their urinary problem, leading to both physical and psychological improvement. “Emotional implications” could mean either emotional consequences, consistent with a cognitive behavioural model of chronic pain in which those consequences, rather than the pain itself, are targeted to improve QoL, or it could mean implications for - exposure of - emotional conflict or similar psychological disorder, which is presumed to be the aetiology of the urethral pain.

Baldoni et al. recruited 36 female patients diagnosed with urethral syndrome in an Italian urology clinic after negative urography, cystoscopy and urine culture, and urodynamic examination. Thirteen women were randomly selected for psychotherapy, but the method was not blind or free of possible bias. Psychotherapy was 12-16 weekly 1-h sessions, with additional fortnightly group discussion, and focused on associations between urinary symptoms and emotion. Four patients were also prescribed low-dose antidepressants. The control group received usual care but no psychological treatment.

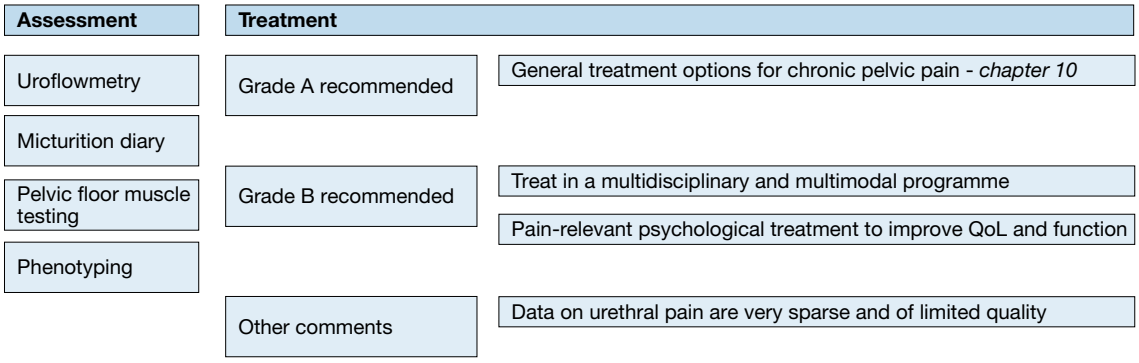
Assessment of symptoms at 6 months and four years after the end of treatment (with loss of two patients from each arm) showed substantial improvement in total urinary symptoms and additionally in pelvic pain, with 9/11 psychotherapy patients with normal levels of urinary function at 6 months, and 8/11 with normal levels at 4 years. Control patients were unchanged at both follow-up points. The trial had significant weaknesses; in particular, the non-blind assignment to treatment condition, the non-standardised measures, and, for the purposes of this review, the combination of all urinary symptoms so that treatment effects on pain were obscured. The authors have noted that the lack of any credible intervention with controls makes it difficult to conclude that it was the particular treatment, rather than the general provision of treatment, which brought about recorded improvement. However, the results can be taken as encouraging the trial of psychological methods, using orthodox outcome measures and more rigorous methodology.

3.4.4 Conclusions and recommendations: urethral pain syndrome

Conclusions	**LE**
Urethral pain syndrome may be a part of BPS.	2a
Urethral pain may be neuropathic hypersensitivity following urinary tract infection.	2b
There is no specific treatment for urethral pain syndrome.	4
In patients with significant distress associated with bladder or urethral symptoms, psychological treatment may be worth using to reduce distress and thereby improve function and quality of life.	4

Recommendations	**GR**
Start with general treatment options for chronic pelvic pain (see chapter 10).	A
It is recommended that patients with urethral pain syndrome are treated in a multidisciplinary and multimodal programme.	B
When patients are distressed, it is recommended to refer them for pain-relevant psychological treatment to improve function and quality of life.	B

Figure 9: Assessment and treatment algorithm for urethral pain syndrome



3.4.5 ***References***

1. Parsons CL, Zupkas P, Parsons JK. Intravesical potassium sensitivity in patients with interstitialcystitis and urethral syndrome. Urology 2001 Mar;57(3):428-32; discussion 432-3. http://www.ncbi.nlm.nih.gov/pubmed/11248610
2. Parsons CL. The role of a leaky epithelium and potassium in the generation of bladder symptoms in interstitial cystitis/overactive bladder, urethral syndrome, prostatitis and gynaecological chronic pelvic pain. BJU Int 2011 Feb;107(3):370-5. http://www.ncbi.nlm.nih.gov/pubmed/21176078
3. Kaur H, Arunkalaivanan AS. Urethral pain syndrome and its management. Obstet Gynecol Surv 2007May;62(5):348-51; quiz 353-4. http://www.ncbi.nlm.nih.gov/pubmed/17425813
4 Gürel H, Gürel SA, Atilla MK. Urethral syndrome and associated risk factors related to obstetrics and gynecology.Eur J Obstet Gynecol Reprod Biol. 1999 Mar;83(1):5-7. http://www.ncbi.nlm.nih.gov/pubmed/10221602
5. Yoon SM, Jung JK, Lee SB, et al. Treatment of female urethral syndrome refractory to antibiotics. Yonsei Med J. 2002 Oct;43(5):644-51. http://www.ncbi.nlm.nih.gov/pubmed/12402379
6. Costantini E, Zucchi A, Del Zingaro M, et al. Treatment of urethral syndrome: a prospective randomized study with Nd:YAG laser. Urol Int. 2006;76(2):134-8. http://www.ncbi.nlm.nih.gov/pubmed/16493214
7. Baldoni F, Baldaro B, Trombini G. Psychotherapeutic perspectives in urethral syndrome. Stress Medicine 1995;11:79-84. http://onlinelibrary.wiley.com/doi/10.1002/smi.2460110115/abstract

4. GYNAECOLOGICAL ASPECTS OF CHRONIC PELVIC PAIN

4.1 Introduction

Chronic pelvic pain in urological and gynaecological practice is often complex and difficult to treat. The aim is to try and determine a remediable cause and treat it using the most effective available therapy. However, in 30% of cases, no cause is ever determined and this presents a therapeutic challenge to the attendant physician (1).

4.2 Clinical history

Taking a detailed medical history is essential to making a diagnosis. 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.

4.3 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. Clinical pelvic examination should be a single digit examination if possible, but in most cases a gentle double digit examination is tolerable and sometimes necessary. The usual bimanual examination can generate severe pain so the examiner must proceed with caution. The examination of a woman with CPP can be very difficult, and many authors recommend that it should be directed to the determination of cutaneous allodynia along the dermatomes of the abdomen (T11-L1) and the perineum (S3). The degree of tenderness of the muscles and on the perineum (perineal body, levators and obturator internus) should be determined.

4.3.1 ***Investigations***

Vaginal and endocervical swabs to exclude infection are mandatory and cervical cytology screening is advisable. Pelvic imaging, using ultrasound scanning or magnetic resonance, can provide useful information about pelvic anatomy and pathology. Any areas of tenderness detected can provide information related to the possible presence of current or pre-existing visceral disease (2,3). Laparoscopy is perhaps the most useful

invasive investigation to exclude gynaecological pathology (4,5) and to assist in the differential diagnosis of CPP in women (6). Often, it is combined with cystoscopy (7,8) and/or proctoscopy to help identify the site of multi-compartment pain.

Psychological considerations around laparoscopy
There have been three diverse studies of laparoscopy. Elcombe et al. have shown, by comparing waiting time for laparoscopy, that there was a distinct and lasting improvement in pain consequent on laparoscopy, which was greater than the gradual improvement without further treatment before or after laparoscopy. Improvement was related to beliefs about pain and its meaning in terms of serious disease, and not to medical variables (9).

In another study, showing women a photograph of their pelvic contents taken during laparoscopy, during postlaparoscopy feedback, did not improve pain ratings or beliefs about pain more than feedback without a photograph (10).

Peters et al. compared standard clinical care of patients with CPP (where organic causes of pelvic pain were excluded first and diagnostic laparoscopy was routinely performed, before attention being given to other causes such as psychological disturbances) with a second group, where an integrated approach was chosen from the beginning (equal attention was given to somatic, psychological, dietary, environmental, and physiotherapeutic factors and laparoscopy was not routinely performed) (11). Both groups were similar with respect to clinical characteristics of the patients and the severity of their pain as assessed by various pain parameters. Evaluation of the pain 1 year after the institution of treatment revealed that the integrated approach improved pelvic pain significantly more often than the standard approach for three out of four pain parameters. Though laparoscopy played no important role in the treatment of pelvic pain it was found to be an essential tool to rule out any organic cause for the pain. Equal attention to both organic and other causative factors from the beginning of therapy is more likely to result in a reduction of pelvic pain than just using a standard approach (11). Pain and function improved somewhat more in the integrated group, but scoring was not standardised and hard to interpret.

4.4 Pain associated with well-defined conditions

4.4.1 ***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 (6). Secondary dysmenorrhoea suggests the development of a pathological process and it is essential to exclude endometriosis (5), adenomyosis (12) and pelvic infection.

Treatment
Reassurance and an explanation of the cause of dysmenorrhoea are usually helpful, together with the use of simple analgesics, followed by non-steroidal anti-inflammatory drugs (NSAIDs) (13), which are particularly helpful if they are started before the onset of each menstrual cycle. NSAIDs are effective in dysmenorrhoea, probably because of their effects on prostaglandin synthetase.

Suppression of ovulation using oral contraceptive tablets (either combined or progesterone only) or the use of a levo-norgestrol intra-uterine device reduces dysmenorrhoea dramatically in most cases and may be used as a therapeutic test. As a result of the chronic nature of the condition, potentially addictive analgesics should be avoided and multidisciplinary pain management strategies, including psychology should be engaged.

4.4.2 ***Infection***

In premenopausal women, a history of pelvic inflammatory disease (PID) must be excluded. Swabs to exclude infections with organisms such as chlamydia and gonorrhoea, as well as vaginal and genital tract pathogens (14), should be taken. Patients' sexual contacts need to be traced in all cases with a positive culture. If there is any doubt about the diagnosis, laparoscopy may be helpful.

Pelvic inflammatory disease can cause the same clinical findings as endometriosis and can lead to a chronic pain state. Although PID often has a bacterial origin, viral infections such as primary herpes simplex infection need to be excluded because they also present with severe pelvic/vaginal/vulvar pain (15). They are usually associated with ulcerating lesions and inflammation, which may lead to urinary retention (16). Hospitalisation and opiates may be needed to achieve adequate analgesia.

Treatment
Treatment of infection depends on the causative organisms. Subclinical chlamydial infection may lead to tubal pathology, which can result in subfertility in the future. Thus, screening for this organism in sexually active young women is essential to prevent this complication. Standard broad-spectrum antibiotics targeting Gram-

positive and negative organisms are normally recommended. Chronic PID is no longer common in developed countries, but still poses a significant problem for women in developing countries.

4.4.3 ***Endometriosis and adenomyosis***

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 known.

A diagnosis is usually made when a history of secondary dysmenorrhoea and often dyspareunia exists. On examination, there is often tenderness in the lateral vaginal fornices, reduced uterine mobility, tenderness in the recto-vaginal septum, and on occasion, adnexal masses. Laparoscopy is the most useful diagnostic tool (17-19).

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. Adenomyosis is associated with augmented pain during menses. It is diagnosed by an ultrasound scan of the uterus, which often shows cystic dilatation of the myometrium (20).

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 analogues to create an artificial menopause, although the resulting oestrogen deficiency does have marked long-term side effects, such as reduced bone density and osteoporosis. Thus, these drugs are normally only used before surgery to improve surgical outcome and reduce surgical complications in patients with endometriosis. Surgery for endometriosis is challenging and the extensive removal of all endometriotic lesions is often thought to be essential. This is still considered to be controversial, as there is at least one RCT showing no benefit in pain relief in the removal of early endometriosis compared to sham surgery (21,22). Nevertheless, the best results are achieved laparoscopically, by highly trained and skilled laparoscopic surgeons, in specialist centres (19,23).

A multidisciplinary team is 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. In this situation, multidisciplinary pain management strategies, including psychology, should be engaged.

In patients with adenomyosis, there is no curative surgery other than hysterectomy but patients can benefit from hormonal therapy (oral or levo-norgestrol containing intra-uterine devices) and analgesics as outlined above.

4.4.4 ***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.

4.4.5 ***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 (24). This is often due to transient oestrogen deficiency, commonly seen in the postpartum period and during breastfeeding. Denervation of the pelvic floor with re-innervation may also lead to dysfunction and pain.

Treatment

Treatment with a short course of hormone replacement cream can be therapeutically beneficial. However, often reassurance that the situation will improve on the cessation of breastfeeding is also helpful.

4.4.6 ***Pain associated with pelvic organ prolapse and prolapse surgery***

Pelvic organ prolapse is often an asymptomatic condition, unless it is so marked that it causes back strain, vaginal pain and skin excoriation (25). Prolapse is often a disease of older women, and it is often associated with postmenopausal oestrogen deficiency, which may lead to pain associated with intercourse. Hormone replacement therapy is usually helpful in this circumstance. However, in severe cases associated with a “dragging pain”, the only options are specially designed supportive plastic vaginal devices or surgery.

In the past few years, pelvic organ prolapse surgery has gained a new dimension. Most tissue surgery is now augmented by the use of non-absorbable mesh (usually in the form of “mesh kits”) (26-28). Although they may have a role in supporting the vagina, they are also associated with several complications including bladder,

bowel and vaginal trauma (27). In a subset of these patients, chronic pain may ensue, because mesh insertion may cause nerve and muscle irritation (23,24).

Clinical evaluation
It is essential that patients are fully evaluated clinically. They may also benefit from specialised imaging, using contrast mediums if necessary, to identify problematic areas. Most patients can be treated by mesh-excisional surgery (29,30), if appropriate, or multidisciplinary pain management strategies, including psychology, should surgery not be relevant.

4.5 Vaginal and vulvar pain syndromes

Pain in the vagina or the female external genital organs (the vulva, which includes the labia, clitoris, and entrance to the vagina) is most commonly due to infection or trauma. The latter is usually as a consequence of childbirth or surgery. Pain is usually a precedent to dyspareunia.
When the pain persists for > 6 months, it can be diagnosed as “vulvodynia” or “chronic vaginal/vulvar pain syndrome” with no known cause. It is still a poorly understood condition and often many doctors do not recognise it as a real pain syndrome. Many women feel isolated because it remains a difficult condition to treat.

There are two main subtypes of vulvodynia: generalised vulvodynia, where the pain occurs in different areas of the vulva at different times; and vulvar vestibulitis, where the pain is at the entrance of the vagina. In generalised vulvodynia, the pain may be constant or occur occasionally, but touch or pressure does not initiate it, although it may make the pain worse. In vulvar vestibulitis, the pain is described as a burning sensation that comes on only after touch or pressure, such as during intercourse.
The causes of vulvodynia are many and include:

- History of sexual abuse
- History of chronic antibiotic use
- Hypersensitivity to yeast infections, allergies to chemicals or other substances
- Abnormal inflammatory response (genetic and non-genetic) to infection and trauma,
- Nerve or muscle injury or irritation
- Hormonal changes

Although therapeutic options remain limited and require a multidisciplinary pain management approach, with psychological and physiotherapy input, they can be treated effectively with physiotherapy, stretching exercises and even botulinum toxin, though in the case of the latter the evidence is variable.

Psychological treatment of chronic vulvar pain
There are few published accounts of psychological treatment for chronic vulvar pain, distinct from provoked vulvar pain (also known as vulvar vestibulitis, provoked vestibulodynia, or dyspareunia). Three reviews in the past decade, all of provoked as well as chronic vulvar pain, have acknowledged the lack of understanding of aetiology and maintenance of this problem, and emphasise different components of what is known.

Damsted-Peterson et al. have described peripheral and central nervous system changes most consistent with models of chronic pain, as well as local inflammation and pelvic floor tension, and recommend multimodal treatment (31). Lotery et al. have focused on local factors, and recommend education, support, and counselling, but provide no evidence to support these (32). Nanke & Rief have described interaction of physiological, psychological and interpersonal factors, and recommend biofeedback on the basis of uncontrolled studies (33).

The only RCT found has compared cognitive behavioural therapy (CBT), adapted for vulvar pain from a previously published model, with supportive psychotherapy, for a mixed population of women with provoked and chronic vulvar pain (34). CBT consists of behavioural therapy (for sexual problems, increasing general activity, and pain control), relaxation, and cognitive coping skills. Supportive psychotherapy, also for 10 one hour sessions, involves non-directive talking therapy by an accepting and reflective therapist. Follow-up to 1 year has shown that ~40% of patients with both conditions achieve at least 33% (clinically significant) pain relief, with improvement in sexual and emotional function; CBT shows superiority in some outcomes.

4.6 Summary

Pain in association with urinary and gastrointestinal symptoms must be considered carefully. For example, patients with bladder pain quite often present with dyspareunia due to bladder base tenderness, so though the dyspareunia may be the focus it is the bladder component that is the main problem. Similarly, in those with anal pain it may be the evacuatory dysfunction that is the main culprit. Conditions, such as pelvic congestion has been cited as a cause of pelvic pain of unknown aetiology, but this diagnosis is not universally recognised (15,16).

It is only when all the above conditions have been excluded that the physician may declare that the

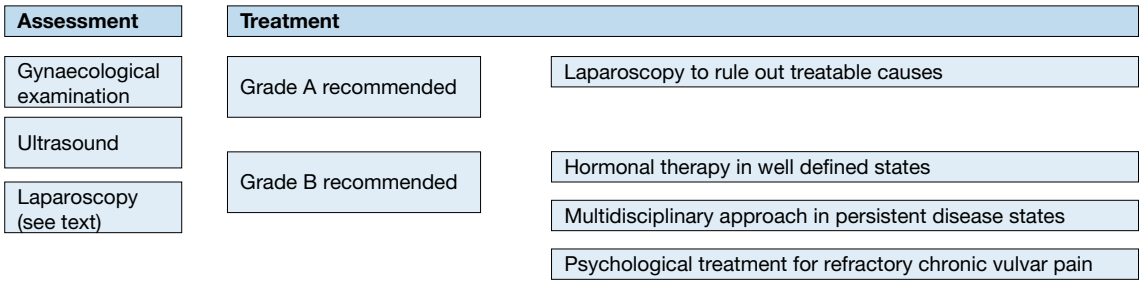
patient has 'unexplained' pelvic pain. Treating these patients remains a challenge for all physicians, but quite clearly the best results are obtained from a multidisciplinary approach that considers all possible causes.

4.6.1 Conclusions and recommendations: gynaecological aspects of chronic pelvic pain

Clinical state		**LE**
Clinical history and examination	Mandatory to making a diagnosis	2a
Investigations	Mandatory to making a diagnosis	2a
	Laparoscopy is well tolerated and does not appear to have negative psychological effects	1b
Pain associated with well-defined conditions	*Dysmenorrhoea: effective therapeutic options*	3
	Infection: effective therapeutic option	3
	Endometriosis: effective therapeutic options including medical and surgical care	1b
	Gynaecological malignancy: effective therapeutic options	3
	Injuries related to childbirth: effective therapeutic options	3
	Pain associated with pelvic organ prolapse: effective therapeutic options	3
Vaginal and vulvar pain syndrome	Diagnosis and therapeutic interventions	3
	Psychological treatment (CBT or supportive psychotherapy) can improve pain and sexual and emotional function	1b

Recommendations	**GR**
All women with pelvic pain should have a full gynaecological history and evaluation, and including laparoscopy is recommended to rule out a treatable cause (e.g. endometriosis).	A
Provide therapeutic options such as hormonal therapy or surgery in well-defined disease states.	B
Provide a multidisciplinary approach to pain management in persistent disease states.	B
Recommend psychological treatment for refractory chronic vulvar pain.	B
Use alternative therapies in the treatment of chronic gynaecological pelvic pain.	C

Figure 10: Assessment and treatment gynaecological aspects in chronic pelvic pain



4.7 References

1. Newham AP, van der Spuy ZM, Nugent F. Laparoscopic findings in women with chronic pelvic pain. S Afr Med J. 1996 Sep;86(9 Suppl):1200-3. http://www.ncbi.nlm.nih.gov/pubmed/9180785
2. Jarrell J, Giamberardino MA, Robert M. Bedside tests of viscera-somatic pain. J Obstet Gynaecol Can 2011 (submitted).
3. Jarrell J. Demonstration of cutaneous allodynia in association with chronic pelvic pain. J Vis Exp. 2009 Jun 23;(28). http://www.ncbi.nlm.nih.gov/pubmed/19550406
4. Howard FM. The role of laparoscopy as a diagnostic tool in chronic pelvic pain. Baillieres Best Pract Res Clin Obstet Gynaecol. 2000 Jun;14(3):467-94. http://www.ncbi.nlm.nih.gov/pubmed/10962637

5. Jacobson TZ, Duffy JM, Barlow D, et al. Laparoscopic surgery for pelvic pain associated with endometriosis. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD001300.
http://www.ncbi.nlm.nih.gov/pubmed/19821276
6. Porpora MG, Gomel V. The role of laparoscopy in the management of pelvic pain in women of reproductive age. Fertil Steril. 1997 Nov;68(5):765-79.
http://www.ncbi.nlm.nih.gov/pubmed/9389799
7. Wyndaele JJ, Van Dyck, J, Toussaint N. Cystoscopy and bladder biopsies in patients with bladder pain syndrome carried out following ESSIC guidelines. Scand J Urol Nephrol 2009;43(6):471-5.
http://www.ncbi.nlm.nih.gov/pubmed/19707951
8. Seracchioli R, Mannini D, Colombo FM, et al. Cystoscopy-assisted laparoscopic resection of extramucosal bladder endometriosis. J Endourol. 2002 Nov;16(9):663-6.
http://www.ncbi.nlm.nih.gov/pubmed/12490020
9. Elcombe S, Gath D, Day A. The psychological effects of laparoscopy on women with chronic pelvic pain. Psychol Med. 1997 Sep;27(5):1041-50.
http://www.ncbi.nlm.nih.gov/pubmed/9300510
10. Onwude JL, Thornton JG, Morley S, et al. A randomised trial of photographic reinforcement during postoperative counselling after diagnostic laparoscopy for pelvic pain. Eur J Obstet Gynecol Reprod Biol. 2004 Jan 15;112(1):89-94.
http://www.ncbi.nlm.nih.gov/pubmed/14687747
11. Peters AA, van Dorst E, Jellis B, et al. A randomized clinical trial to compare two different approaches in women with chronic pelvic pain. Obstet Gynecol. 1991 May;77(5):740-4.
http://www.ncbi.nlm.nih.gov/pubmed/1826544
12. Wassong C, Shah B, Kanayama M, et al. Radiologic findings of pelvic venous congestion in an adolescent girl with angiographic confirmation and interventional treatment. Pediatr Radiol. 2011 Sep 13.
http://www.ncbi.nlm.nih.gov/pubmed/21912968
13. Allen C, Hopewell S, Prentice A, et al. Nonsteroidal anti-inflammatory drugs for pain in women with endometriosis. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD004753.
http://www.ncbi.nlm.nih.gov/pubmed/19370608
14. Ness RB, Soper DE, Holley RL, et al. Effectiveness of inpatient and outpatient treatment strategies for women with pelvic inflammatory disease: results from the Pelvic Inflammatory Disease Evaluation and Clinical Health (PEACH) Randomized Trial. Am J Obstet Gynecol. 2002 May;186(5):929-37.
http://www.ncbi.nlm.nih.gov/pubmed/12015517
15. Corey L, Adams HG, Brown ZA, et al. Genital herpes simplex virus infections: clinical manifestations, course, and complications. Ann Intern Med. 1983 Jun;98(6):958-72.
http://www.ncbi.nlm.nih.gov/pubmed/6344712
16. Young H, Moyes A, McMillan A, et al. Screening for treponemal infection by a new enzyme immunoassay. Genitourin Med. 1989 Apr;65(2):72-8.
http://www.ncbi.nlm.nih.gov/pubmed/2666302
17. Fauconnier A, Chapron C, Dubuisson JB, et al. Relation between pain symptoms and the anatomic location of deep infiltrating endometriosis. Fertil Steril. 2002 Oct;78(4):719-26.
http://www.ncbi.nlm.nih.gov/pubmed/12372446
18. Vercellini P, Crosignani PG, Abbiati A, et al. The effect of surgery for symptomatic endometriosis: the other side of the story. Hum Reprod Update. 2009 Mar-Apr;15(2):177-88.
http://www.ncbi.nlm.nih.gov/pubmed/19136455
19. Vercellini P, Crosignani PG, Somigliana E, et al. Medical treatment for rectovaginal endometriosis: what is the evidence? Hum Reprod. 2009 Oct;24(10):2504-14.
http://www.ncbi.nlm.nih.gov/pubmed/19574277
20. Kaminski P, Gajewska M, Wielgos M, et al. The usefulness of laparoscopy and hysteroscopy in the diagnostics and treatment of infertility. Neuro Endocrinol Lett. 2006 Dec;27(6):813-7.
http://www.ncbi.nlm.nih.gov/pubmed/17187014
21. Jarrell J, Mohindra R, Ross S, et al. Laparoscopy and reported pain among patients with endometriosis. J Obstet Gynaecol Can. 2005 May;27(5):477-85.
http://www.ncbi.nlm.nih.gov/pubmed/16100643
22. Jarrell J, Brant R, Leung W, et al. Women's Pain Experience Predicts Future Surgery for Pain Associated With Endometriosis. J Obstet Gynaecol Can. 2007 Dec;29(12):988-91.
http://www.ncbi.nlm.nih.gov/pubmed/18053384
23. Daniels J, Gray R, Hills RK, et al. Laparoscopic uterosacral nerve ablation for alleviating chronic pelvic pain: a randomized controlled trial. JAMA. 2009 Sep 2;302(9):955-61.
http://www.ncbi.nlm.nih.gov/pubmed/19724042

24. Hay-Smith EJ. Therapeutic ultrasound for postpartum perineal pain and dyspareunia. Cochrane Database Syst Rev. 2000;(2):CD000495.
http://www.ncbi.nlm.nih.gov/pubmed/10796210
25. Roovers JP, van der vaart CH, van der Blom JG, et al. A randomised controlled trial comparing abdominal and vaginal prolapse surgery: effects on urogenital function. BJOG. 2004 Jan;111(1):50-6.
http://www.ncbi.nlm.nih.gov/pubmed/14687052
26. Withagen MI, Vierhout ME, Hendriks JC, et al. Risk factors for exposure, pain, and dyspareunia after tension-free vaginal mesh procedure. Obstet Gynecol. 2011 Sep;118(3):629-36.
http://www.ncbi.nlm.nih.gov/pubmed/21860293
27. Niro J, Philippe AC, Jaffeux P, et al. [Postoperative pain after transvaginal repair of pelvic organ prolapse with or without mesh]. Gynecol Obstet Fertil. 2010 Nov;38(11):648-52. [Article in French]
http://www.ncbi.nlm.nih.gov/pubmed/21030280
28. Lin LL, Haessler AI, Ho MH, et al. Dyspareunia and chronic pelvic pain after polypropylene mesh augmentation for transvaginal repair of anterior vaginal wall prolapse. Int Urogynecol J Pelvic Floor Dysfunct. 2007 Jun;18(6):675-8.
http://www.ncbi.nlm.nih.gov/pubmed/16988779
29. Walid MS, Heaton RL. Laparoscopic apical mesh excision for deep dyspareunia caused by mesh banding in the vaginal apex. Arch Gynecol Obstet. 2009 Sep;280(3):347-50.
http://www.ncbi.nlm.nih.gov/pubmed/19127368
30. Margulies RU, Lewicky_Gaupp C, Fenner DE, et al. Complications requiring reoperation following vaginal mesh kit procedures for prolapse. Am J Obstet Gynecol. 2008 Dec;199(6):678.e1-4.
http://www.ncbi.nlm.nih.gov/pubmed/18845282
31. Damstedt-Petersen C, Boyer SC, et al. Current perspectives in vulvodynia. Womens Health (Lond Engl). 2009 Jul;5(4):423-36.
http://www.ncbi.nlm.nih.gov/pubmed/19586434
32. Lotery HE, McClure N, Galask RP. Vulvodynia. Lancet. 2004 Mar 27;363(9414):1058-60.
http://www.ncbi.nlm.nih.gov/pubmed/15065562
33. Nanke A, R. W. (2004). Biofeedback in somatoform disorders and related syndromes. Current Opinion in Psychiatry 17: 133-138.
34. Masheb RM, Kerns RD, Lozano C, et al. A randomized clinical trial for women with vulvodynia: Cognitive-behavioral therapy vs. supportive psychotherapy. Pain. 2009 Jan;141(1-2):31-40.
http://www.ncbi.nlm.nih.gov/pubmed/19022580

5. GASTROINTESTINAL ASPECTS OF CHRONIC PELVIC PAIN

5.1 Introduction

This chapter describes CPP perceived to be associated with the gastrointestinal tract, which is mainly due to functional disorders and cannot be explained by structural or specific well-defined diseases of the pelvis.

Some points to note:

- There may be a considerable overlap of the gastrointestinal with other pelvic pain syndromes.
- Defined gastrointestinal conditions with specific structural defects and diseases may coexist. Behavioural changes such as straining can lead to organic diseases such as rectal prolapse, solitary rectal ulcer syndrome, or pudendal nerve injury with consecutive faecal incontinence.
- Some structural gastrointestinal abnormalities (e.g., postpartum anal sphincter defects, or small rectoceles) are often observed in asymptomatic individuals and may be coincidental with the gastrointestinal pelvic pain syndrome.
- Different diseases can aggravate previously asymptomatic functional disorders which may become symptomatic such as faecal incontinence in patients with diarrhoea of different origins or anal fissure in patients with dyssynergic defecation.
- Finally, we need to consider that all functional disorders such as anorectal pain are defined on the basis of retrospectively evaluated longstanding symptoms, which ideally would have been registered prospectively with symptom diaries (1,2).

5.2 Clinical history

Functional anorectal disorders are diagnosed by symptoms, supplemented by objective findings. The predominant symptoms patients are interviewed about are discomfort or pain in relation to their bowel habits, daily activities, and eating. A precise history of dysfunctional voiding or defecation should be asked, ideally applying symptom questionnaires for urinary and anorectal symptoms (e.g., Rome III questionnaire for anorectal pain). Excessive straining at most defecations, anal digitations in dyssynergic defecation, and a sensation of anal blockage may be found in patients with chronic anal pain. History of anxiety and depression with impaired QoL is often encountered in anorectal functional disorders and should be evaluated.

5.2.1 ***Clinical examination and investigations***

At clinical examination, perianal dermatitis may be found as a sign of faecal incontinence or diarrhoea. Fissures may be easily overlooked and should be searched thoroughly in patients with anal pain. Rectal digital examination findings may show high or low anal sphincter resting pressure, a tender puborectalis muscle in patients with the levator ani syndrome, and occasionally increased perineal descent. The tenderness during posterior traction on the puborectalis muscle differentiates between Levator Ani Syndrome and Unspecified Functional Anorectal Pain and is used in most studies as the main inclusion criterion. Dyssynergic (paradoxical) contraction of the pelvic muscles when instructed to strain during defecation is a frequent finding in patients with pelvic pain. Attention should be paid to anal or rectal prolapse at straining, and ideally during bimanual examination by the gynaecologist to diagnose an enterocele or cystocele.

5.2.2 ***Diagnostic assessment***

The Rome III criteria for diagnosis of functional anorectal diseases include symptoms for each specific functional disorder as listed below. The gastrointestinal diagnostic assessment should be performed in an interdisciplinary manner, preferably at a pelvic floor centre by a dedicated team and appropriate testing. The most frequently performed investigations are flexible rectosigmoidoscopy or colonoscopy, pelvic ultrasound, anorectal endosonography and anorectal manometry combined with anal EMG and balloon expulsion test. Three-dimensional anorectal ultrasound has become an indispensable readily available tool for the specialised proctologist. Perineal ultrasound offers the advantage of sphincter imaging without insertion of the transducer into the rectum. MRI in conjunction with MR defecography has become the most valuable imaging technique to assess anorectal function dynamically. MRI studies outline simultaneously the anatomy of the pelvic floor and allow us to visualise different structural and functional pathologies, by applying dynamic sequences after filling of the rectum with a viscous contrast medium (e.g., ultrasound gel). The following pathologies can be visualised: pelvic floor descent, an abnormal anorectal angle while squeezing and straining, rectal intussusception, rectocele, enterocele and cystocele. However, limitations of MR defecography are the left lateral position and the limited space for the patient, which may reduce the ability to strain and hereby reduce the sensitivity of the method, underestimating the size of entero-and rectoceles as well as the amount of intussusception. Surgical consultations should be available for all patients, plus referral to an urogynaecologist or urologist when indicated. Biofeedback treatment, botulinum toxin injection, and percutaneous tibial nerve and sacral nerve stimulation should be available as a complementary therapeutic option to medical and surgical treatment.

5.3 Pain associated with well-defined conditions

5.3.1 ***Haemorrhoids***

Chronic pelvic pain is rare in haemorrhoidal disease because endoscopic and surgical treatment is mostly effective in acute disease. The most frequent aetiology of pain without significant bleeding is thrombosed external haemorrhoids or an anal fissure. Haemorrhoidal pain on defecation associated with bleeding is usually due to prolapsed or ulceration of internal haemorrhoids. Anaemia from haemorrhoidal bleeding is rare but may arise in patients on anticoagulation therapy, or those with clotting disorders. Different treatments of haemorrhoids have been evaluated by two systematic Cochrane reviews. Excisional haemorrhoidectomy (EH) has been compared to the less-invasive technique of rubber band ligation (RBL), and has been shown to increase pain, with more complications and time off work. However, despite these disadvantages of EH, complete long-term cure of symptoms is increased by surgery, and minor complications are accepted by patients. RBL is the choice of treatment for grade II haemorrhoids, whereas EH should be reserved for grade III haemorrhoids or recurrence after RBL (3). New stapler techniques of haemorrhoidopexy are associated with a higher long-term risk of recurrence and prolapse compared to conventional EH. Further studies are needed (4).

5.3.2 ***Anal fissure***

Anal fissures are tears in the distal anal canal and induce pain during and after defecation. The pain can last for several minutes to hours. Persistence of symptoms beyond 6 weeks or visible transversal anal sphincter fibres define chronicity. Fissures located off the midline are often associated with specific diseases such as Crohn's

disease or anal cancer. Internal anal sphincter spasms and ischaemia are associated with chronic fissures. Medical therapy with nitrates and calcium channel blockers resulting in sphincter relaxation is effective (5). Botulinum A toxin injection is indicated for fissures that are refractory to topical nitrates. Surgery with lateral internal sphincterotomy is the most studied procedure but carries the risk of postoperative faecal incontinence, and may be replaced by fissure excision combined with botulinum toxin or anal advancement flap.

5.3.3 ***Proctitis***

Abdominal and pelvic pain in patients with inflammatory bowel disease and proctitis are often difficult to interpret. Faecal calprotectin may help to differentiate between inflammation and functional pain, to spare steroids. Tricyclic antidepressants at low dose can be effective in this situation when acute exacerbation has been ruled out (6,7).

5.3.4 ***Constipation***

Constipation is usually not associated with CPP but is often associated with and may induce increased pelvic discomfort and psychological distress. Dyssynergic defecation is the most common aetiology and responsible for 50% of causes of constipation. Dyssynergia describes an overactivity of pelvic floor muscles during defecation and the partial or complete inability to relax voluntarily pelvic floor muscles. Stool diaries and physiological testing followed by biofeedback treatment when indicated have been established as standard care in randomised controlled trials (8).

5.4 Chronic anal pain syndrome

5.4.1 ***Diagnostic criteria for chronic anal pain syndrome (chronic proctalgia) according to the Rome III criteria are as follows and must include all of the following:***

1. Chronic or recurrent rectal pain or aching.
2. Episodes last at least 20 min.
3. Exclusion of other causes of rectal pain such as ischaemia, inflammatory bowel disease, cryptitis, intramuscular abscess and fissure, haemorrhoids, prostatitis, and coccygodynia.

These criteria should be fulfilled for the past 3 months with symptom onset at least 6 months before diagnosis (2).

The chronic anal pain syndrome includes the above diagnostic criteria and exhibits exquisite tenderness during posterior traction on the puborectalis muscle. This common and debilitating condition is frustrating to treat. Pathophysiology of pain is thought to be due to overactivity of the pelvic floor muscles. Chiarioni et al. have recently published an RCT demonstrating that biofeedback treatment was superior to electrogalvanic stimulation and massage for treatment of the levator ani syndrome. One hundred and fifty-seven patients who had at least weekly rectal pain were investigated, but only patients with tenderness on traction of the pelvic floor showed a significant treatment benefit. Eighty-seven percent of patients with tenderness of the puborectalis muscle (Rome II: Highly likely Levator Ani Syndrome) reported adequate relief after one month of biofeedback versus 45% for electrogalvanic stimulation, and 22% for massage. These results were maintained at 12 months with adequate relief after nine sessions of biofeedback in 58% of the whole group (Rome II: Highly likely and Possible Levator Ani Syndrome), after galvanic stimulation in 27% and massage in 21% of patients. As previously described in dyssynergic defecation, the ability to expel a 50-ml water-filled balloon and to relax pelvic floor muscles after biofeedback treatment were predictive of a favourable therapeutic outcome (9). The pathophysiology of the chronic anal pain syndrome is therefore similar to that of dyssynergic defecation, and this favours the role of the pelvic floor muscles in the pathophysiology of both conditions. Other treatment modalities have been less successful.

5.4.2 ***Botulinum toxin in pelvic pain***

Chronic pelvic pain associated with spasm of the levator ani muscles and treatment of the puborectalis and pubococcygeus muscle by botulinum toxin appears to be promising in some women, as shown in a pilot study (n = 12). The inclusion criteria were dependent only on vaginal manometry with overactivity of the pelvic floor muscles, defined as a vaginal resting pressure > 40 cm H_2O. Although dyspareunia and dysmenorrhoea improved, non-menstrual pelvic pain scores were not significantly ameliorated (10). In the following double-blinded, randomised, placebo-controlled trial, the same group defined pelvic floor myalgia according to the two criteria of tenderness on contraction and hypertension (> 40 cm H_2O) and included 60 women. In this larger study, non-menstrual pelvic pain was significantly improved compared to that treated with placebo (VAS score 51 vs. 22; P = 0.009). It was concluded therefore that botulinum toxin is effective for reducing pelvic-floor-muscle associated pain with acceptable adverse effects such as occasional urinary and faecal stress incontinence (11).

However, recently, a small RCT failed to show any benefit of botulinum toxin, and sacral nerve stimulation has been reported to be somewhat beneficial in an uncontrolled study, showing improvement in less than half the patients (12,13).

5.4.3 ***Intermittent chronic anal pain syndrome (proctalgia fugax) consists of all the following diagnostic criteria, which should be fulfilled for 3 months and before 3 months:***

1. Recurrent episodes of pain localised to the anus or lower rectum.
2. Episodes last from several seconds to minutes.
3. There is no anorectal pain between episodes.

Stressful life events or anxiety may precede the onset of the intermittent chronic anal pain syndrome. The attacks may last from a few seconds to as long as 30 min. The pain may be cramping, aching or stabbing and may become unbearable. However, most patients do not report it to their physicians and pain attacks occur less than five times a year in 51% of patients. Due to the short duration of the episodes, medical treatment and prevention is often not feasible. Inhaled beta-2 adrenergic agonist salbutamol was effective in an RCT in patients with frequent symptoms and shortened pain duration (14). Other treatment options are topic diltiazem and botulinum toxin (15). However, there is still some controversy as regards the duration of pain of intermittent chronic and chronic anal pain syndrome and RCTs do often use different definitions extending the pain duration in order to better evaluate the study-drug action.

5.5 Summary

Chronic pelvic pain is an interdisciplinary entity needing multispecialty and multidisciplinary diagnostic assessment by a gastroenterologist, urologist, gynaecologist and pain teams as appropriate, with the input of physicians, psychologists and physiotherapists amongst others. Anorectal pain is investigated best by endoscopic and functional testing to rule out structural disease that can be treated specifically. Chronic pelvic pain due to functional disorders remains a therapeutic challenge that may respond to biofeedback therapy, electrogalvanic syndrome and botulinum toxin in the case of levator ani syndrome and defecatory defects associated with pelvic pain.

5.5.1 ***Conclusions and recommendations: anorectal pain syndrome***

Conclusions on functional anorectal pain	**LE**
Tenderness on traction is the main criterion of the chronic anal pain syndrome.	1a
Biofeedback is the preferred treatment for the chronic anal pain syndrome.	1a
Electrogalvanic stimulation is less effective than biofeedback.	1b
Botulinum toxin is efficient in CPP with spasms.	1b
Sacral neurostimulation is effective in pelvic pain.	3
Inhaled salbutamol is effective in intermittent chronic anal pain syndrome.	3

Recommendations for functional anorectal pain	**GR**
Functional testing is recommended in patients with anorectal pain.	A
Biofeedback treatment is recommended in patients with pelvic pain and dyssynergic defecation.	A
Botulinum toxin and electrogalvanic stimulation can be considered in the chronic anal pain syndrome.	B
Sacral neuromodulation is recommended in the chronic anal pain syndrome.	C
Inhaled salbutamol is recommended in the intermittent chronic anal pain syndrome.	C

Figure 11: Assessment and treatment algorithm for anorectal pain syndrome

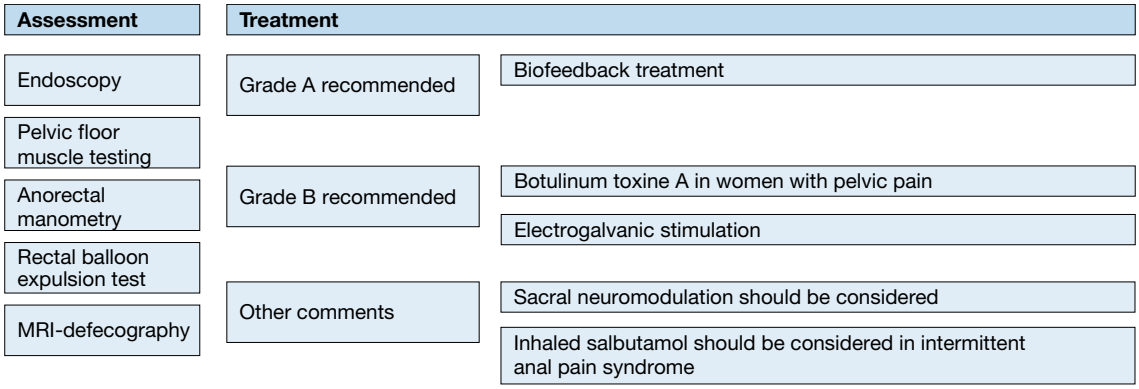
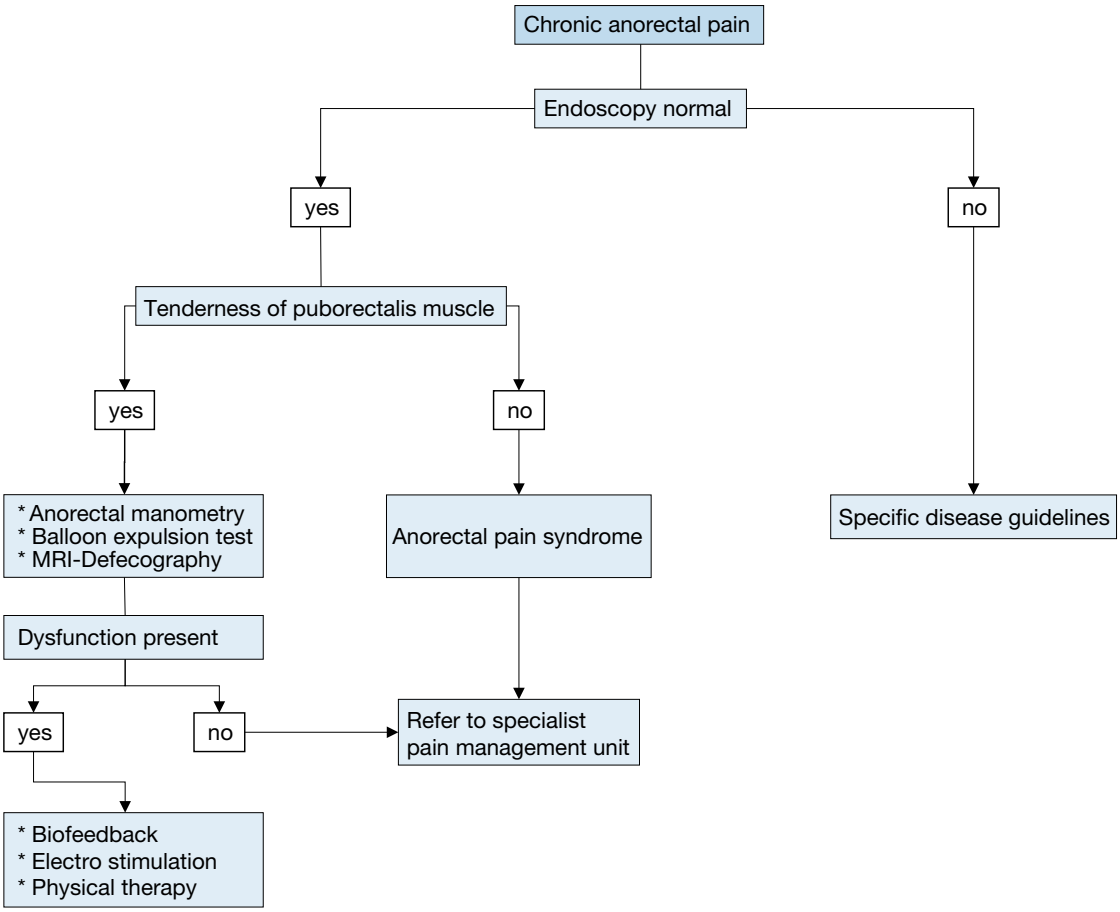


Figure 12: Diagnosis algorithm for chronic anorectal pain



5.6 References

1. Whitehead WE, Bharucha AE. Diagnosis and treatment of pelvic floor disorders: what's new and what to do. Gastroenterology. 2010 Apr;138(4):1231-5. [no abstract available] http://www.ncbi.nlm.nih.gov/pubmed/20176023
2. Bharucha AE, Wald A, Enck P, et al. Functional anorectal disorders. Gastroenterology. 2006 Apr;130(5):1510-8. http://www.ncbi.nlm.nih.gov/pubmed/16678564
3. Shanmugam V, Thaha MA, Rabindranath KS, et al. Rubber band ligation versus excisional haemorrhoidectomy for haemorrhoids. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD005034. http://www.ncbi.nlm.nih.gov/pubmed/16034963
4. Jayaraman S, Colquhoun PH, Malthaner RA. Stapled versus conventional surgery for hemorrhoids. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD005393. http://www.ncbi.nlm.nih.gov/pubmed/17054255
5. Nelson R. Non surgical therapy for anal fissure. Cochrane Database Syst Rev. 2003;(4):CD003431. http://www.ncbi.nlm.nih.gov/pubmed/14583976

6. Keohane J, O'Mahony C, O'Mahony L, et al. Irritable bowel syndrome-type symptoms in patients with inflammatory bowel disease: a real association or reflection of occult inflammation? Am J Gastroenterol. 2010 Aug;105(8):1788.
http://www.ncbi.nlm.nih.gov/pubmed/20389294
7. Halpert A, Dalton CB, Diamant NE, et al. Clinical response to tricyclic antidepressants in functional bowel disorders is not related to dosage. Am J Gastroenterol. 2005;100:664-71.
http://www.ncbi.nlm.nih.gov/pubmed/15743366
8. Rao SS, Valestin J, Brown CK, et al. Long-term efficacy of biofeedback therapy for dyssynergic defecation: randomized controlled trial. Am J Gastroenterol. 2010 Apr;105(4):890-6.
http://www.ncbi.nlm.nih.gov/pubmed/20179692
9. Chiarioni G, Nardo A, Vantini I, et al. Biofeedback is superior to electrogalvanic stimulation and massage for treatment of levator ani syndrome. Gastroenterology. 2010 Apr;138(4):1321-9.
http://www.ncbi.nlm.nih.gov/pubmed/20044997
10. Jarvis Sk, Abbott JA, Lenart MB, et al. Pilot study of botulinum toxin type A in the treatment of chronic pelvic pain associated with spasm of the levator ani muscles. Aust N Z J Obstet Gynaecol. 2004 Feb;44(1):46-50.
http://www.ncbi.nlm.nih.gov/pubmed/15089868
11. Abbott JA, Jarvis SK, Lyons SD, et al. Botulinum toxin type A for chronic pain and pelvic floor spasm in women: a randomized controlled trial. Obstet Gynecol. 2006 Oct;108(4):915-23.
http://www.ncbi.nlm.nih.gov/pubmed/17012454
12. Rao SS, Paulson J, Mata M, et al. Clinical trial: effects of botulinum toxin on levator ani syndrome—a double-blind, placebo controlled study. Aliment Pharmacol Ther. 2009 May 1;29(9):985-91.
http://www.ncbi.nlm.nih.gov/pubmed/19222415
13. Falletto E, Masin A, Lolli P, et al. Is sacral nerve stimulation an effective treatment for chronic idiopathic anal pain? Dis Colon Rectum. 2009 Mar;52(3):456-62.
http://www.ncbi.nlm.nih.gov/pubmed/19333046
14. Eckardt VF, Dodt O, Kanzler G, et al. Treatment of proctalgia fugax with salbutamol inhalation. Am J Gastroenterol. 1996 Apr;91(4):686-9.
http://www.ncbi.nlm.nih.gov/pubmed/8677929
15. Atkin GK, Suliman A, Vaizey CJ. Patient characteristics and treatment outcome in functional anorectal pain. Dis Colon Rectum. 2011 Jul;54(7):870-5.
http://www.ncbi.nlm.nih.gov/pubmed/21654255

6. PERIPHERAL NERVE PAIN SYNDROMES

6.1 Neuropathic pain

Much has been written on the subject of peripheral neuropathic pain (1-4) including its diagnosis and treatment. There are some fundamental principles that are worth considering:

1. Nerve injury is associated with changes both within the peripheral nervous system (PNS) and the central neural axis including the higher centres. These changes serve to produce an increasing disparity between stimulus and response (Chapter 2).
2. In the PNS, nerve damage may produce a neuroma that can provide a source of ongoing afferent central activity. The neuroma may be discreet and palpable to touch or en-passage and not palpable. Neuromas are sensitive and respond to: compression (e.g., by the surrounding tissue or digital pressure), temperature change and adrenergic stimulation. Sympathetic nerve fibres can grow into neuromas as well as the associated dorsal root ganglia, which may result in sensitivity to body adrenaline changes such as through mood and environment with subsequent changes in pain.
3. Windup is a progressive increase in centrally elicited action potentials per unit peripheral stimulus. A severe acute insult or a chronic repeated stimulus may result in a transient windup phenomenon becoming permanent through immediate gene activation and neurochemical and structural neuronal changes within the CNS. These long-term changes in central sensitisation are associated with dysfunction of the afferent sensory nervous system and perception, as well as efferent motor, vasomotor and pseudomotor activity within the pathways of the injured nerve (5).
4. These central changes may result in abnormal afferent processing for nerves other than those originally damaged, so that increased perception (pain, allodynia and hyperaesthesia) from an area greater than the expected pattern may occur. In the case of tissues with innervation that overlaps with an injured nerve, somatic and visceral hypersensitivity (e.g., sensory urge with increased frequency of

voiding/evacuation) may be perceived from those tissues.

Essentially, what may be considered a simple nerve injury may be magnified by the CNS so that a whole region may be involved and a non-specific regional pain syndrome may arise. There is also a suggestion that involvement of both the peripheral and CNS in the control of the endocrine and immunological system may also become abnormal. Certainly, there is a complex interaction between nerve injury, emotional well being, disability and widespread pain. A proportion of patients go on to develop chronic fatigue syndrome, fibromyalgia and immunological disorders (6-8).

6.2 Anatomy

When considering pelvic pain mechanisms, nerves associated with the pelvis/genitalia are generally divided into thoraco-lumbar and sacral root afferents. The hypogastric plexus is mixed autonomic (sympathetic and parasympathetic) and may contain afferents associated with pain.

6.2.1 The anterior groin nerves

The **iliohypogastric nerve** arises from L1 and its anterior branch supplies the skin above the pubis; its lateral cutaneous branch is distributed to the anterolateral part of the buttock.
The **ilioinguinal** nerve is smaller than the iliohypogastric nerve; it also arises from L1 and is distributed to the skin of the groin and mons pubis.
The **genitofemoral** nerve arises from L1 and L2. It passes through the psoas muscle, then down it to emerge through the deep inguinal ring. Its genital branch supplies the cremaster muscle and a part of the anterior and lateral scrotum. The femoral branch passes close to the external iliac artery, the deep circumflex iliac artery and the femoral artery to be distributed to the upper part of the femoral triangle. The two branches of the femoral branch may separate at any level, therefore, sensory phenomena associated with nerve damage depend upon the level of the lesion and individual variability.
The **lateral cutaneous** nerve of the thigh arises from L2 and L3 and eventually leaves the abdomen behind or through the inguinal ligament at a variable distance medial to the anterior superior iliac spine. In the thigh, it divides into an anterior branch that supplies the anterolateral skin of the thigh, approximately 10 cm down from the inguinal ligament to the knee. The posterior branch supplies the skin more laterally from the greater trochanter, down to the mid-thigh.
The **obturator nerve** arises from L2-L4, descends through the psoas muscle, runs around the pelvis in close proximity to the obturator internus muscle and obturator vessels, and leaves the pelvis via the obturator foramen. This nerve has significant motor innervation, and its cutaneous branch is distributed primarily to the skin on the medial aspect of the knee.

6.2.2 The posterior subgluteal triangle nerves

The posterior triangle area is the area defined superiorly by the upper border of the piriformis, inferiorly by the lower border of quadratus femoris, laterally by the greater trochanter and medially by and lateral border of the sacrum, the lateral borders of the sacrotuberal ligament and ischeal tuberosity. This region contains the sciatic nerve, posterior femoral cutaneous nerve (which branches into the posterior cutaneous perineal branch and the cluneal nerves), the nerve to the obturator internus muscle, and the pudendal nerve. These nerves pass deep to the piriformis muscle and superficial to the superiour gemellus and obturator internus muscles. Injury in this area may damage one or more of these nerves (Figure 13) (9-15).

6.2.3 Branches of the pudendal nerve

The **pudendal nerve** has its origins at the S2-S4 levels. S2 and S3 also contribute to the sciatic nerve and S4 to the coccygeal plexus and the annoccoccygeal nerves.
The pudendal nerve has three main branches: the **inferior anorectal nerve**, the **superficial perineal nerve** (which terminates as cutaneous branches in the perineum and posterior aspect of the scrotum), and the **deep perineal nerve**, which is distributed to the pelvic structures (innervating parts of the bladder, prostate and urethra). This branch terminates as the dorsal nerve of the penis/clitoris, which innervates the glans.
In addition to sensory branches, the pudendal nerve provides motor innervation to anal and urethral sphincters, as well as to the bulbospongiosus and ischiocavernous muscles (involved in the bulbocavernosal response, orgasm and ejaculation). Autonomic fibres also pass with the pudendal nerve and are derived from the presacral parasympathetic as well as sympathetic fibres via the hypogastric plexi.

6.2.4 Anatomical relations of the pudendal nerve (Figure 13)

The anatomy may be variable, however, the three roots that form the pudendal nerve usually merge anterior to the sacrum and inferior to the piriformis muscle.

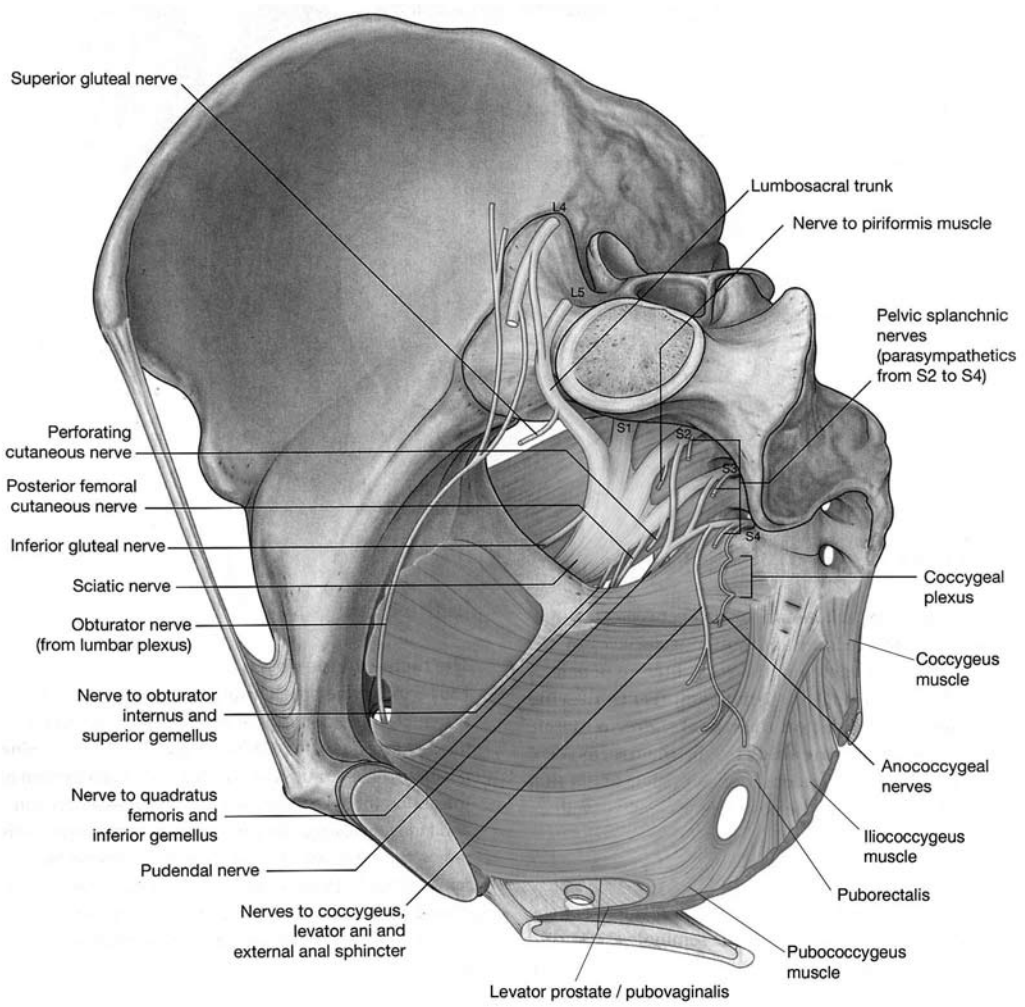
The pudendal nerve leaves the pelvis via the greater sciatic notch to enter the subgluteal region. In the

posterior subgluteal triangle (the area bordered by the inferior edge of the piriformis muscle, the sarotuberous ligament medially and the upper border of the rectus femoris muscle inferiorly), the nerve emerges from under the inferior border of the piriformis muscle with its associated pudendal artery and veins; it is medial to the nerve innervating the obturator internus muscle, which is medial to the posterior femoral cutaneous nerve (which divides into its cutaneous branch but also the inferior cluneal nerves and perineal nerves), which is medial to the sciatic nerve. These anatomical relations are important for neurotracing techniques used for nerve blocks and because symptoms in those nerve territories also help with diagnosis (16-20).

The pudendal nerve leaves the subgluteal region as it wraps around the superficial surface of the ischeal spine/sacrospinal ligament to re-enter the pelvis (9,10) via the lesser sciatic notch (between the more ventral sacrospinal ligament and the more dorsal sacrotuberal ligaments). This occurs 15% of the time at the enthesis of the spine and the ligament; 75% of the time, it is more medial, and 10% of the time, it wraps around the spine. The sacrotuberal ligament may have a sharp superior border, be wide, and as a result, close to the spinosacral ligament, or be divided with the pudendal nerve passing through it. All of these features may predispose to nerve injury.
As the pudendal nerve re-enters the pelvis below the levator muscles, it runs within a fascial canal medial to the internal obturator muscle (Alcock's canal).

The inferior anorectal branch may never be a true branch of the pudendal nerve, and may have its origins directly from the sacral roots. As a consequence, pain associated with pudendal nerve injury may not involve the anorectal area. Similarly, pain may only be perceived in the anorectal area if the main pudendal nerve is not involved. In 11% of cases, the inferior anorectal nerve pierces the sacrospinal ligament, possibly increasing the risk of entrapment. Other variations of the anorectal branch exist with the nerve branching off from the main pudendal nerve at any point in the gluteal region or within the pelvis. In 56% of cases, the pudendal nerve is a single trunk as it re-enters the pelvis. Some people have two or three pudendal nerve trunks.

Figure 13: Anatomical relations of the pudendal nerve



Source: Drake, Vogel, & Mitchell: GRAY's ANATOMY FOR STUDENTS, 2004 Elsevier Inc.

6.2.5 *Afferent nerves and the genitalia*

- The afferents from the skin of the genitals pass via a complex of multiple sensory nerves and this makes the anatomical diagnosis of nerve injury as a cause of pain difficult.
- The anterolateral part of the scrotum/labia majora has afferents associated with the genitofemoral nerve primarily; there may also be some involvement of the ilioinguinal and iliohypogastric nerves.
- The posterior scrotal/labia branches of the pudendal nerve transmit sensation from the posterior scrotum/labia majora.
- The penis shaft is innervated on its dorsal surface by the genitofemoral, ilioinguinal and iliohypogastric nerves, and the ventral surface by the perineal branches of the posterior femoral cutaneous nerve and cutaneous branches of the pudendal nerve.
- The glans penis/clitoris is associated with the dorsal nerve of the penis/clitoris, the terminal branch of the pudendal nerve.
- All the nerves that are associated with the scrotum may also receive afferents from the testes, although classically, the nerves from the testes are usually associated with the genitofemoral nerve (thoracolumbar as opposed to sacral roots).
- The superficial branches of the pudendal's superficial perineal nerve and the perineal branch of the posterior femoral cutaneous nerve receive afferents from the perineal skin.
- Deeper afferents from the perineum and from some of the pelvic organs pass to the pudendal nerve via its deep perineal branch.

6.2.6 *Afferents in the autonomic plexus*

The pelvic plexus is associated with both the parasympathetic and sympathetic nerves, and as well as afferents associated with these pathways, afferents may travel back to the sacral and thoracolumbar roots with these autonomic nerves. Sites for injury and possible intervention may thus include: the ganglion impar, superior hypogastric plexus, inferior hypogastric plexus, and lumbar sympathetic trunk, as well as more central spinal root areas.

6.3 Aetiology of nerve damage

6.3.1 *Anterior groin nerves - aetiology of nerve damage*

The primary afferents of the anterior groin nerves enter the spinal cord at the thoracolumbar level (T10 to L3). Thoracolumbar spinal pathology and any pathology along the course of the nerve may result in neuropathic pain in the distribution of these nerves. As well as neoplastic disease, infection and trauma, surgical incisions and postoperative scarring may result in nerve injury (21-23).

6.3.2 *Pudendal neuralgia - aetiology of nerve damage*

Anatomical variations

Anatomical variations may predispose the patient to developing pudendal neuralgia over time or with repeated low-grade trauma (such as sitting for prolonged periods of time or cycling) (9,10).

The pudendal nerve may be damaged due to local anatomical variation at the level of:

1. The piriformis muscle. For example, as part of a piriformis syndrome: in some cases, the nerve may pass through the muscle and hence be trapped; or in other cases, muscle hypertrophy or spasm is implicated.
2. The sacrospinal/sacrotuberous ligaments, possibly accounting for 42% of cases.
3. Within Alcock's canal (medial to the obturator internus muscle, within the fascia of the muscle), possibly accounting for 26% of cases.
4. Multiple levels in 17% of cases.

The site of injury determines the site of perceived pain and the nature of associated symptoms (e.g., the more distal the damage, the less likely the anal region will be involved).

6.3.3 *Surgery*

In orthopaedic hip surgery, pressure from the positioning of the patient, where the perineum is placed hard against the brace, can result in pudendal nerve damage (24,25). The surgery itself may also directly damage the nerve. Pelvic surgery such as sacrospinous colpopexy is clearly associated with pudendal nerve damage in some cases (26,27). In many types of surgery, including colorectal, urological and gynaecological, pudendal nerve injury may be implicated.

6.3.4 ***Trauma***

Fractures of the sacrum or pelvis may result in pudendal nerve/root damage and pain. Falls and trauma to the gluteal region may also produce pudendal nerve damage if associated with significant tissue injury or prolonged pressure.

6.3.5 ***Cancer***

Tumours in the presacral space must be considered. Tumours invading the pudendal nerve may occur and there may also be damage from surgery for pelvic cancer (13).

6.3.6 ***Birth trauma***

This is more difficult to be certain about (12). The pudendal neuralgia of birth trauma is thought to resolve in most cases over a period of months. However, rarely, it appears to continue as painful neuropathy. Multiple pregnancies and births may predispose to stretch neuropathy in later life.

6.3.7 ***Elderly women***

Child birth (28) and repeated abdominal straining associated with chronic constipation (29) are thought to predispose elderly women to postmenopausal pelvic floor descent and stretching of the pudendal nerve with associated pain. Changes in the hormone status may also be a factor.

In the Urogenital Pain Management Centre, the commonest associations with pudendal neuralgia appear to be: history of pelvic surgery; prolonged sitting (especially young men working with computer technology); and postmenopausal older women. Trauma- and cancer-related pain is less frequent, cycling whereas classical appears to be rarely seen.

6.4 Diagnosis for pudendal neuralgia

6.4.1 ***Differential diagnosis of other disorders***

Other forms of neuropathic pain (30,31).

As well as the pudendal nerve, there are several other nerves that may mimic the symptoms of pudendal neuralgia if they are damaged.

Inferior cluneal nerve. This is a branch of the posterior femoral cutaneous nerve. This nerve is prone to injury in the ischial region. Cluneal nerve injury produces a sensation of pain perceived more laterally than that for pudendal neuralgia.

Sacral nerve roots. The S2-S4 nerve roots may be involved. This is an important differential diagnosis as tumours must be excluded.

Cauda equina syndrome. Lumbar spinal pathology involving the cauda equina may result in an intractable neuropathic pain.

Ilioinguinal, iliohypogastric and genitofemoral nerves. Injury to these nerves or their roots may occur from thoracolumbar pathology, abdominal posterior wall conditions, surgery, and entrapment in the groin. The pain may extend into the groin, anterior perineum and scrotum/labia majorum. If the femoral branch of the genitofemoral nerve is involved, pain may extend into the inner thigh.

Referred spinal pain

Pain from thoracolumbar pathology may refer to the groin. Spinal pain may become associated with muscle hyperalgesia and trigger points. The muscle associated pain may spread to involve a range of muscles, including the pelvic floor muscles with resultant pelvic pain.

Musculoskeletal disorders

Trigger points associated with localised tenderness and pain may be detected in the piriformis, obturator internus, levator ani, bulbocavernosal and ischeocavernosal muscles, as well as the gluteal, adductor, rectus abdominus and spinal muscles. All of these may refer the pain to or close to the pelvis.

Pathology of the joints (sacroiliac, pubic symphysis, hip and spinal) may also refer into the pelvis.

Coccyx pain syndrome, a painful coccyx may occur for a number of reasons (Chapter 2).

6.4.2 ***Clinical presentation of pudendal neuralgia***

6.4.2.1 Age

There is a wide age range, as one would expect with a condition that has so many potential causes. There is a suggestion that, the younger the patient, the better the prognosis. Essentially, the sooner the diagnosis is made, as with any compression nerve injury, the better the prognosis, and older patients may have a more protracted problem (32-34).

6.4.2.2 Sex
Six out of ten cases are observed in women.

6.4.2.3 History
A proportion of patients will be able to relate the onset of pain to an acute event such as surgery, sepsis or trauma, and occasionally, cycling for a prolonged period. Chronic injury is more frequent, such as associated with sitting for prolonged periods over time. Many will be idiopathic.

The pain is classically perceived in the perineum from anus to clitoris/penis. However, less-specific pain distribution may occur, and this may be due to anatomical variation, involvement of branches of the nerve rather that the main nerve, CNS central sensitisation, and consequently, the involvement of other organs and systems in a regional pain syndrome. Other nerves in the vicinity may also be involved, for example, inferior cluneal nerve and perineal branches of the posterior femoral cutaneous nerve. The musculoskeletal system may become involved, confusing the pain picture as aches and pains develop in the muscles due to immobility and disability, possibly magnified by the CNS changes.

Burning is the most predominant adjective used to describe the pain. Crushing and electric may also be used, indicating the two components - a constant pain often associated with acute sharp episodes. Many patients may have the feeling of a swelling or foreign body in the rectum or perineum, often described as a golf or tennis ball. The term pain has different meanings to patients and some would rather use the term discomfort or numbness.

Aggravating factors include any cause of pressure being applied, either directly to the nerve or indirectly to other tissue, resulting in pudendal traction. Allodynia is pain on light touch due to involvement of the CNS, and may make sexual contact and the wearing of clothes difficult. These patients often remain standing, and as a consequence, develop a wide range of other aches and pains. Soft seats are often less well tolerated, whereas sitting on a toilet seat is said to be much better tolerated. If unilateral, sitting on one buttock is common. The pain may be exacerbated by bowel or bladder evacuation.

6.4.2.4 Associated features
Pudendal nerve damage may be associated with a range of sensory phenomena. In the distribution of the nerve itself, as well as unprovoked pain; the patient may have paraesthesia (pins and needles); dysaesthesia (unpleasant sensory perceptions usually but not necessarily secondary to provocation, such as the sensation of running cold water); allodynia (pain on light touch); or hyperalgesia (increased pain perception following a painful stimulus, including hot and cold stimuli). Similar sensory abnormalities may be found outside of the area innervated by the damaged nerve, particularly for the visceral and muscle hyperalgesia.

The cutaneous sensory dysfunction may be associated with superficial dispareunia, but also irritation and pain associated with clothes brushing the skin. There may also be a lack of sensation and pain may occur in the presence of numbness. Visceral hypersensitivity may result in an urge to defecate or urinate. This is usually associated with voiding frequency, with small amounts urine being passed. Pain on visceral filling may occur. Anal pain and loss of motor control may result in poor bowel activity, with constipation and/or incontinence. Ejaculation and orgasm may also be painful or reduced.

Many of those suffering from pudendal neuralgia complain of fatigue and generalised muscle cramps, weakness and pain. Being unable to sit is a major disability, and over time, patients struggle to stand and they often become bedbound. The immobility produces generalised muscle wasting, and minimal activity hurts. As a consequence of the widespread pain and disability, patients often have emotional problems, and in particular, depression. Patients with CPP are also often anxious and have the tendency to catastrophise. Depression, catastrophising and disability are all poor prognostic markers.

Cutaneous colour may change due to changes in innervation but also because of neurogenic oedema. The patient may describe the area as swollen due to this oedema, but also to the lack of afferent perception.

6.4.2.5 Clinical examination
A full clinical examination of the spinal, muscular, nervous and urogenital systems is necessary to aid in diagnosis of pudendal neuralgia, especially to detect signs indicating another pathology. Often, there is little to find in pudendal neuralgia and frequently findings are non-specific. The main pathognomonic features are the signs of nerve injury in the appropriate neurological distribution, for example, allodynia or numbness. Tenderness in response to pressure over the pudendal nerve may aid the clinical diagnosis. This may be elicited by per rectal or per vaginal examination and palpation in the region of the ischeal spine and/or Alcock's

canal. Muscle tenderness and the presence of trigger points in the muscles may confuse the picture. Trigger points may be present in a range of muscles, both within the pelvis (levator ani and obturator internus muscles) or externally (e.g., the piriformis, adductors, rectus abdominus or paraspinal muscles).

6.4.2.6 Investigations

Magnetic resonance imaging scans of the pelvis are usually normal although some practitioners claim them to be useful (35,36). However, MRI scans of the pelvis and spine (mid thoracic to coccyx) are considered essential to help with the differential diagnosis of pudendal neuralgia. Electrophysiological studies may reveal signs of perineal denervation, increased pudendal nerve latency, or impaired bulbocavernosal reflex (25,34,37-39). However, for an abnormality to be detected, significant nerve damage is probably necessary. Pain may be associated with limited nerve damage, therefore, these investigations are often normal in patients thought to have pudendal neuralgia.

6.5 Management of pain associated with nerve damage

The approach to managing a patient with pain following nerve damage is similar irrespective of the nerve involved. There is a suggestion that early treatment has a better prognosis. The general principles are covered in chapter 10 of this document.

6.5.1 ***Pudendal neuralgia and injections***

The role of injections may be divided into two. First, an injection of local anaesthetic and steroid at the sight of nerve injury may produce a therapeutic action. The possible reasons for this are related to the fact that steroids may reduce any inflammation and swelling at the site of nerve irritation, but also because steroids may block sodium channels and reduce irritable firing from the nerve. The second possible benefit of local infiltration is diagnostic. It has already been indicated that when the pudendal nerve is injured there are several sites where this may occur. Differential block of the pudendal nerve helps to provide information in relation to the site where the nerve may be trapped (16-20,35,40-44).

Infiltration at the ischeal spine requires the use of a nerve stimulator/locator. Both motor (anal contraction) and sensory endpoints may be noted. The anatomical endpoint may be localised by fluoroscopy, computed tomography (CT) guidance, or the use of ultrasound. Ultrasound avoids any form of radiation, whereas CT guidance involves a significant amount of radiation. Currently, fluoroscopy is probably the imaging technique most frequently used because it is readily available to most anaesthetists that perform the block.

Currently, infiltration of the pudendal nerve within Alcock's canal is primarily undertaken with the use of CT. As well as injecting around the pudendal nerve, specific blocks of other nerves arising from the pelvis may be performed. Similarly, trigger point injections into tender areas within muscles may also be considered. Pulsed radiofrequency stimulation has also been suggested as a treatment (45).

6.5.2 ***Pudendal neuralgia and surgery***

Decompression of an entrapped or injured nerve is a routine approach and probably should apply to the pudendal nerve as it applies to all other nerves. There are several approaches and the approach of choice probably depends upon the nature of the pathology. The most traditional approach is the transgluteal approach; however, a transperineal approach may be an alternative, particularly if the nerve damage is thought to be related to previous pelvic surgery (11,14,33,35,46-48).

Currently, there has been only one prospective randomised study (11). This suggests that, if the patient has had the pain for < 6 years, 66% of patients will see some improvement with surgery (compared to 40% if the pain has been present for > 6 years). Surgery is by no means the answer for all patients. On talking to patients that have undergone surgery, providing the diagnosis was clear-cut, most patients are grateful to have undergone surgery but many still have symptoms that need management.

6.5.3 ***Pudendal neuralgia and neuromodulation***

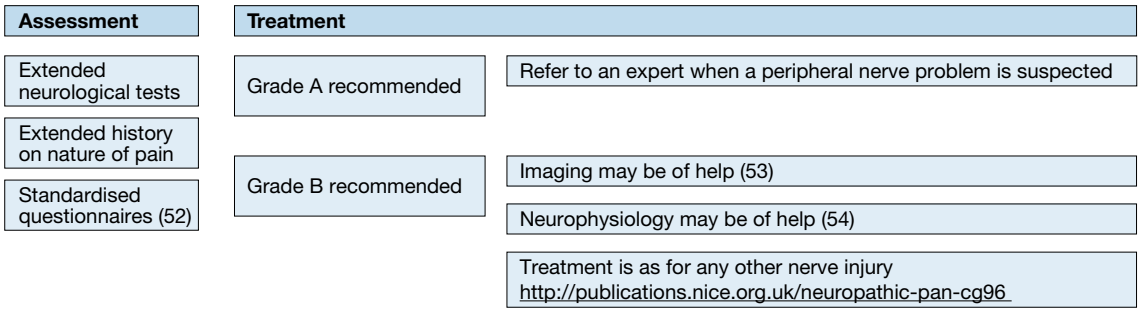
Pudendal neuralgia represents a peripheral nerve injury and as such should respond to neuromodulation by implanted pulse generators. However, it is important that the stimulation is perceived in the same site as the perceived pain. Spinal cord stimulation (SCS) may be effective for thoraco-lumbar afferents. However, it is difficult to obtain appropriate stimulation from SCS for the sacral nerves including pudendal. There is limited experience with sacral root stimulation and as a result stimulation for pudendal neuralgia should only be undertaken in specialised centres and in centres that can provide multidisciplinary care (49-51).

6.6 Conclusions and recommendations: pudendal neuralgia

Conclusions	LE
Multiple sensory and functional disorders within the region of the pelvis/urogenital system may occur as a result of injury to one or more of many nerves. The anatomy is complex.	2
There is no single aetiology for the nerve damage and the symptoms and signs may be few or multiple.	1
Investigations are often normal.	2
The peripheral nerve pain syndromes are frequently associated with negative cognitive, behavioural, sexual, or emotional consequences.	1
There are multiple treatment options with varying levels of evidence.	1

Recommendations	GR
It is important to rule out confusable diseases.	A
If a peripheral nerve pain syndrome is suspected, early referral should occur to an expert in the field, working within a multidisciplinary team environment.	B
Imaging and neurophysiology may help with the diagnosis, but the gold standard investigation is an image and nerve locator guided local anaesthetic injection.	B
Neuropathic pain guidelines are well established. Standard approaches to management of neuropathic pain should be utilised.	A

Figure 14: Assessment and treatment algorithm for peripheral nerve pain syndrome



6.7 References

1. Treede RD, Jensen TS, Campbell JN, et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. Neurology 2008 Apr 29;70(18):1630-5. http://www.ncbi.nlm.nih.gov/pubmed/18003941
2. Jensen TS, Madsen CS, Finnerup NB. Pharmacology and treatment of neuropathic pains. Curr Opin Neurol. 2009 Oct;22(5):467-74. http://www.ncbi.nlm.nih.gov/pubmed/19741531
3. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. J Pain 2009 Sep;10(9):895-926. http://www.ncbi.nlm.nih.gov/pubmed/19712899
4. Jensen TS, Baron R, Haanpää, et al. A new definition of neuropathic pain. Pain. 2011 Oct;152(10):2204-5. [no abstract available] http://www.ncbi.nlm.nih.gov/pubmed/21764514
5. Goebel, A. (2011). Complex regional pain syndrome in adults. Rheumatology (Oxford). 2011 Oct;50(10):1739-50. http://www.ncbi.nlm.nih.gov/pubmed/21712368
6. Goebel, A, Baranowski A, Maurer K, et al. Intravenous immunoglobulin treatment of the complex regional pain syndrome: a randomized trial. Ann Intern Med. 2010 Feb 2;152(3):152-8. http://www.ncbi.nlm.nih.gov/pubmed/20124231
7. Nickel JC, Tripp DA, Pontari M, et al. Interstitial cystitis/painful bladder syndrome and associated medical conditions with an emphasis on irritable bowel syndrome, fibromyalgia and chronic fatigue syndrome. J Urol 2010 Oct;184(4):1358-63. http://www.ncbi.nlm.nih.gov/pubmed/20719340

8. Warren JW, Wesselmann U, Morozov V, et al. Numbers and types of nonbladder syndromes as risk factors for interstitial cystitis/painful bladder syndrome. Urology 2011 Feb;77(2):313-9. http://www.ncbi.nlm.nih.gov/pubmed/21295246
9. Antolak SJ Jr, Hough DM, Pawlina W. et al. Anatomical basis of chronic pelvic pain syndrome: the ischial spine and pudendal nerve entrapment. Med Hypotheses. 2002 Sep;59(3):349-53. http://www.ncbi.nlm.nih.gov/pubmed/12208168
10. Mahakkanukrauh P, Surin P, Vaidhayakarn P. Anatomical study of the pudendal nerve adjacent to the sacrospinous ligament. Clin Anat. 2005 Apr;18(3):200-5. http://www.ncbi.nlm.nih.gov/pubmed/15768420
11. Robert R, Labat JJ, Bensignor M, et al. Decompression and transposition of the pudendal nerve in pudendal neuralgia: a randomized controlled trial and long-term evaluation. Eur Urol. 2005 Mar;47(3):403-8. http://www.ncbi.nlm.nih.gov/pubmed/15716208
12. Ashton-Miller JA, DeLancey JO. Functional anatomy of the female pelvic floor. Ann N Y Acad Sci. 2007 Apr;1101:266-96. http://www.ncbi.nlm.nih.gov/pubmed/17416924
13. Moszkowicz D, Alsaid B, Bessede T, et al. Where does pelvic nerve injury occur during rectal surgery for cancer? Colorectal Dis. 2011 Dec;13(12):1326-34. http://www.ncbi.nlm.nih.gov/pubmed/20718836
14. Robert R, Labat JJ, Khalfallah M, et al. [Pudendal nerve surgery in the management of chronic pelvic and perineal pain]. Prog Urol. 2010 Nov;20(12):1084-8. [Article in French] http://www.ncbi.nlm.nih.gov/pubmed/21056388
15. Filippiadis DK, Velonakis G, Mazioti A, et al. CT-guided percutaneous infiltration for the treatment of Alcock's neuralgia. Pain Physician. 2011 Mar-Apr;14(2):211-5. http://www.ncbi.nlm.nih.gov/pubmed/21412375
16. Bolandard, F, Bazin JE. Nerve stimulator guided pudendal nerve blocks. Can J Anaesth. Canada. 52: 773; author reply 773-774. [no abstract available] http://www.ncbi.nlm.nih.gov/pubmed/16103396
17. Naja MZ, Al-Tannir MA, Maaliki H, et al. Nerve-stimulator-guided repeated pudendal nerve block for treatment of pudendal neuralgia. Eur J Anaesthesiol. 2006 May;23(5):442-4. [no abstract available] http://www.ncbi.nlm.nih.gov/pubmed/16573866
18. Wey PF, Lions C, Rimmelé T, et al. [Nerve stimulator guided pudendal nerve block for postoperative analgesia. An evaluation of professional practice]. Ann Fr Anesth Reanim. France. 26: 1087-1088. [no abstract available] [Article in French] http://www.ncbi.nlm.nih.gov/pubmed/17961968
19. Peng PW, Tumber PS. Ultrasound-guided interventional procedures for patients with chronic pelvic pain - a description of techniques and review of literature. Pain Physician. 2008 Mar-Apr;11(2):215-24. http://www.ncbi.nlm.nih.gov/pubmed/18354713
20. Kim S, Song S, Paek O, et al. Nerve-stimulator-guided pudendal nerve block by pararectal approach. Colorectal Dis. 2012 May;14(5):611-5. http://www.ncbi.nlm.nih.gov/pubmed/21752174
21. Matejcik V. Anatomical variations of lumbosacral plexus. Surg Radiol Anat. 2010 Apr;32(4):409-14. http://www.ncbi.nlm.nih.gov/pubmed/19696958
22. Hahn L. Treatment of ilioinguinal nerve entrapment - a randomized controlled trial. Acta Obstet Gynecol Scand. 2011 Sep;90(9):955-60. http://www.ncbi.nlm.nih.gov/pubmed/21615360
23. Klaassen Z, Marshall E, Tubbs RC, et al. Anatomy of the ilioinguinal and iliohypogastric nerves with observations of their spinal nerve contributions. Clin Anat. 2011 May;24(4):454-61. http://www.ncbi.nlm.nih.gov/pubmed/21509811
24. Goldet R, Kerdraon J, Amarenco G. [Traction on the orthopedic table and pudendal nerve injury. Importance of electrophysiologic examination]. Rev Chir Orthop Reparatrice Appar Mot. 1998 Oct;84(6):523-30. [Article in French] http://www.ncbi.nlm.nih.gov/pubmed/9846326
25. Amarenco G, Ismael SS, Bayle B, et al. Electrophysiological analysis of pudendal neuropathy following traction. Muscle Nerve. 2001 Jan;24(1):116-9. http://www.ncbi.nlm.nih.gov/pubmed/11150974
26. Alevizon SJ, Finan MA. Sacrospinous colpopexy: management of postoperative pudendal nerve entrapment. Obstet Gynecol. 1996 Oct;88(4 Pt 2):713-5. http://www.ncbi.nlm.nih.gov/pubmed/8841264

27. Fisher HW, Lotze PM. Nerve injury locations during retropubic sling procedures. Int Urogynecol J. 2011 Apr;22(4):439-41.
http://www.ncbi.nlm.nih.gov/pubmed/21060989
28. Kapoor DS, Thakar R, Sultan AH. Combined urinary and faecal incontinence. Int Urogynecol J Pelvic Floor Dysfunct. 2005 Jul-Aug;16(4):321-8.
http://www.ncbi.nlm.nih.gov/pubmed/15729476
29. Amarenco G, Kerdraon J, Lanoe Y. [Perineal neuropathy due to stretching and urinary incontinence. Physiopathology, diagnosis and therapeutic implications]. Ann Urol (Paris). 1990;24(6):463-6. [Article in French]
http://www.ncbi.nlm.nih.gov/pubmed/2176777
30. Darnis B, Robert R, Labat JJ, et al. Perineal pain and inferior cluneal nerves: anatomy and surgery. Surg Radiol Anat. 2008 May;30(3):177-83.
http://www.ncbi.nlm.nih.gov/pubmed/18305887
31. Labat JJ, Robert R, Delavierre D, et al. [Symptomatic approach to chronic neuropathic somatic pelvic and perineal pain]. Prog Urol. 2010 Nov;20(12):973-81. [Article in French]
http://www.ncbi.nlm.nih.gov/pubmed/21056374
32. Robert R, Prat-Pradal D, Labat JJ, et al. Anatomic basis of chronic perineal pain: role of the pudendal nerve. Surg Radiol Anat. 1998;20(2):93-8.
http://www.ncbi.nlm.nih.gov/pubmed/9658526
33. Shafik A. Pudendal canal syndrome as a cause of vulvodynia and its treatment by pudendal nerve decompression. Eur J Obstet Gynecol Reprod Biol. 1998 Oct;80(2):215-20.
http://www.ncbi.nlm.nih.gov/pubmed/9846672
34. Labat JJ, Riant T, Robert R, et al. Diagnostic criteria for pudendal neuralgia by pudendal nerve entrapment (Nantes criteria). Neurourol Urodyn. 2008;27(4):306-10.
http://www.ncbi.nlm.nih.gov/pubmed/17828787
35. Filler AG. Diagnosis and treatment of pudendal nerve entrapment syndrome subtypes: imaging, injections, and minimal access surgery. Neurosurg Focus. 2009 Feb;26(2):E9.
http://www.ncbi.nlm.nih.gov/pubmed/19323602
36. Insola A, Granata G, Padua L. Alcock canal syndrome due to obturator internus muscle fibrosis. Muscle Nerve. 2010 Sep;42(3):431-2.
http://www.ncbi.nlm.nih.gov/pubmed/20665515
37. Lee JC, Yang CC, Kromm BG, et al. Neurophysiologic testing in chronic pelvic pain syndrome: a pilot study. Urology 2001 Aug;58(2):246-50.
http://www.ncbi.nlm.nih.gov/pubmed/11489711
38. Lefaucheur JP, Labat JJ, Amarenco G, et al. What is the place of electroneuromyographic studies in the diagnosis and management of pudendal neuralgia related to entrapment syndrome? Neurophysiol Clin. 2007 Aug-Sep;37(4):223-8.
http://www.ncbi.nlm.nih.gov/pubmed/17996810
39. Labat JJ, Delavierre D, Sibert L, et al. [Electrophysiological studies of chronic pelvic and perineal pain]. Prog Urol. 2010 Nov;20(12):905-10. [Article in French]
http://www.ncbi.nlm.nih.gov/pubmed/21056364
40. Thoumas, D, Leroi AM, Mauillon J, et al. Pudendal neuralgia: CT-guided pudendal nerve block technique. Abdom Imaging. 1999 May-Jun;24(3):309-12.
http://www.ncbi.nlm.nih.gov/pubmed/10227901
41. Kovacs P, Gruber H, Piegger J, et al. New, simple, ultrasound-guided infiltration of the pudendal nerve: ultrasonographic technique. Dis Colon Rectum. 2001 Sep;44(9):1381-5.
http://www.ncbi.nlm.nih.gov/pubmed/11584221
42. Antolak SJ Jr, Antolak CM. Therapeutic pudendal nerve blocks using corticosteroids cure pelvic pain after failure of sacral neuromodulation. Pain Med. 2009 Jan;10(1):186-9.
http://www.ncbi.nlm.nih.gov/pubmed/19222779
43. Rigaud J, Riant T, Delavierre D, et al. [Somatic nerve block in the management of chronic pelvic and perineal pain]. Prog Urol. 2010 Nov;20(12):1072-83. [Article in French]
http://www.ncbi.nlm.nih.gov/pubmed/21056387
44. Romanzi L. Techniques of pudendal nerve block. J Sex Med. 2010 May;7(5):1716-9. [no abstract available]
http://www.ncbi.nlm.nih.gov/pubmed/20537059
45. Rhame EE, Levey KA, Ghraibo CG. Successful treatment of refractory pudendal neuralgia with pulsed radiofrequency. Pain Physician. 2009 May-Jun;12(3):633-8.
http://www.ncbi.nlm.nih.gov/pubmed/19461829

46. Bautrant E, de Bisschop E, Vaini-Elies V, et al. [Modern algorithm for treating pudendal neuralgia: 212 cases and 104 decompressions]. J Gynecol Obstet Biol Reprod (Paris). 2003 Dec;32(8 Pt 1):705-12. [Article in French]
http://www.ncbi.nlm.nih.gov/pubmed/15067894
47. Possover M, Baekelandt J, Flaskamp C, et al. Laparoscopic neurolysis of the sacral plexus and the sciatic nerve for extensive endometriosis of the pelvic wall. Minim Invasive Neurosurg. 2007 Feb;50(1):33-6.
http://www.ncbi.nlm.nih.gov/pubmed/17546541
48. Robert R, Labat JJ, Riant T, et al. Neurosurgical treatment of perineal neuralgias. Adv Tech Stand Neurosurg. 2007;32:41-59.
http://www.ncbi.nlm.nih.gov/pubmed/17907474
49. Mayer RD, Howard FM. Sacral nerve stimulation: neuromodulation for voiding dysfunction and pain. Neurotherapeutics. 2008 Jan;5(1):107-13.
http://www.ncbi.nlm.nih.gov/pubmed/18164489
50. Carmel M, Lebel M, Tu le M. Pudendal nerve neuromodulation with neurophysiology guidance: a potential treatment option for refractory chronic pelvi-perineal pain. Int Urogynecol J. 2010 May;21(5):613-6.
http://www.ncbi.nlm.nih.gov/pubmed/20012596
51. Marcelissen T, Van Kerrebroeck P, de Wachter S. Sacral neuromodulation as a treatment for neuropathic clitoral pain after abdominal hysterectomy. Int Urogynecol J. 2010 Oct;21(10):1305-7.
http://www.ncbi.nlm.nih.gov/pubmed/20386879
52. Horowitz SH. The diagnostic workup of patients with neuropathic pain. Med Clin North Am. Jan 2007;91(1):21-30.
http://www.ncbi.nlm.nih.gov/pubmed/17164102
53. Kim S, Choi JY, Huh YM, et al. Role of magnetic resonance imaging in entrapment and compressive neuropathy - what,where, and how to see the peripheral nerves on the musculoskeletal magnetic resonance image: part 1. Overview and lower extremity. Eur Radiol. Jan 2007;17(1):139-149.
http://www.ncbi.nlm.nih.gov/pubmed/16572334
54. Labat JJ, Delavierre D, Sibert L, et al. [Electrophysiological studies of chronic pelvic and perineal pain]. Prog Urol. Vol 20. France: 2010 Elsevier Masson SAS; 2010:905-910. [Article in French]
http://www.ncbi.nlm.nih.gov/pubmed/21056364

7. SEXOLOGICAL ASPECTS OF CHRONIC PELVIC PAIN

7.1 Introduction

In general, human sexuality has three aspects - sexual function, sexual self-concept, and sexual relationships. Pain can affect self-esteem, one's ability to enjoy sex and relationships. Healthy sexuality is a positive and life-affirming part of being human. The capacity to experience optimal comfort and satisfaction in sexual expression also requires basic physical abilities. Essentially, these include intact sensory and motor processes, and the ability to move with ease.

Chronic pain may hinder the ability to move freely, and thus, may limit the positions one can get into to have sex. Second, chronic pain may affect the ability to respond sexually and conversely; in CPP the sex act can be associated with pain that can be inhibiting. Research on male sexual dysfunction highlights the importance of considering partners and the impact that male sexual problems have on their partners. Sexual dysfunction occurs in an interpersonal context and has implications for both partners in a relationship. Chronic pain also impacts the sexual and interpersonal functioning of couples; declines in sexual activity and reduced relationship satisfaction have been noted among patients with chronic pain and their partners (1,2).

It is recommended that a biopsychosocial model of CPPS should be incorporated into future research, and that research considers the role that sexual and relationship variables may play in couples' adjustment.

The sexual-response cycle is divided into five phases: desire, arousal (excitement), plateau, orgasm and resolution. They are actually all part of a continuous process of sexual response. There is much variation among individuals, as well as between different sexual events and there are different models to describe the sexual responses (3).

During the sexual response cycle, the different phases are controlled by a different part of the brain and spinal cord. In each of these phases chronic pain and CPP in particular can cause disturbances (4).

- The Desire Phase begins in the "pleasure centres" of the brain and controls a person's sexual appetite or drive. Pain or even the fear of pain can decrease desire, making the person uninterested in sex. In some cases, however, having sex may actually help to relieve pain.
- The Arousal Phase is associated with the swelling of the blood vessels in a man's penis and in a woman's labia, vagina, and clitoris. This swelling causes an erection in the penis and in the clitoris and release of lubricating fluids. If a person experiences pain at the time of becoming excited, the excitement may be reversed, in a man the penis will become limp and in a woman the lubrication will stop, leading to dryness.
- The Orgasm Phase describes a genital reflex controlled by the spinal cord, which causes the genital muscles to contract, involuntarily releasing sexual tension and swelling that build up during the excitement phase. In some cases, pain prevents people from reaching this phase.

7.2 General considerations

Pelvic pain in women (5) and in men (6) is associated with significant sexual dysfunction. While chronic pain impacts all aspects of functioning, including work, family relationships, and social activities, the most frequent complaint cited by patients with CPP is sexual dysfunction (7). Factors contributing to sexual dysfunction in patients with chronic pain are multifactorial and contextual (8), and may be related to comorbidity with depression (9,10), use of antidepressant medications (11), and relationship satisfaction (12), among many other factors. There are reports of increased rates of past sexual abuse which may have negative impact on sexual function (13,14). Chronic pelvic pain may have a higher association with sexual dysfunction than other types of chronic pain. CPP specifically involves areas intimately connected to sexuality, which may negatively impact one's body image and sexual self-esteem (15), and also affects both partners in the relationship (16).

7.3 Pelvic floor involvement in sexual function and dysfunction

The pelvic floor of the male appears to have some impact on sexual function, although its exact role is unclear. Erection is a neurovascular event in which the smooth and striated musculature of the corpora cavernosa and pelvic floor play a role in facilitating and maintaining the erection (17). In ejaculation and orgasm the rhythmic contraction of the bulbocavernous and ischiocavernous muscles is perceived as pleasurable. Ejaculation is controlled by the sympathetic nervous system and performed with help of the pelvic floor muscles. Controlling the pelvic floor muscles may delay the onset of ejaculation through an active relaxation of the pelvic floor muscles. This is a learned technique, which may be mastered using pelvic floor biofeedback. Pelvic floor exercise and biofeedback for the treatment of both erectile dysfunction (ED) and premature ejaculation (PE) have been reported on in the literature.

Early studies maintained that strong pelvic floor muscles in women, particularly the ischiocavernous muscle that attaches to the clitoral hood, were crucial for adequate genital arousal and attainment of orgasm (18), and that weak muscles may provide insufficient activity necessary for vaginal friction or blood flow, and inhibit orgasmic potential (19). It has also been proposed that sexual pleasure is enhanced for both partners by genital responses provided by contraction of the levator ani (20). It stands to reason, therefore, that better control over pelvic floor muscle contraction and relaxation could improve sexual function.

However, few studies are available to support this notion. In a Scandinavian randomised controlled study pelvic floor muscle training has been demonstrated to improve QoL and sexual function in women with urinary stress incontinence (20). In a Turkish study, improvement in sexual desire, performance during coitus, and achievement of orgasm were reported in women (n = 42) who received pelvic floor muscle re-education (21).

The effectiveness of physical therapy in treating sexual pain disorders has been reported upon in the literature as well. Retrospective studies have reported on a success rate of 77% (22,23). Goetsch recently reported her findings that physical therapy may serve as important adjunct to surgery for "vulvar vestibulitis" (vulvar pain syndrome) (24).

7.4 Chronic pelvic pain and sexual dysfunction of the male

In the BACH study, Hu et al. found that men who reported having experienced sexual, physical, or emotional abuse had increased odds (1.7 compared to 3.3) for symptoms suggestive of PPS. The authors suggested that clinicians may wish to screen for abuse in men presenting with symptoms suggestive of PPS. Conversely, clinicians may wish to inquire about pelvic pain in patients who have experienced abuse (25).

A key feature of PPS is chronic pain. Chronic pain and its treatment can impair our ability to express sexuality. In a study in England 73% of patients with chronic pain had some degree of sexual problems as result of the pain (8). These problems can occur because of several factors. Psychological factors like decrease in self-esteem, depression and anxiety can contribute to loss of libido. Physiological factors like fatigue, nausea

and pain itself can cause sexual dysfunction. Pain medications (opioids, and the selective serotonin reuptake inhibitors, SSRI) can also decrease libido (26) and delay ejaculation.

The evaluation of the effects of PPS on sexual function should take into consideration the adverse effects of drug therapy of PPS on sexuality, as well as the more interesting direct interactions between the PPS symptoms and disorders of libido, erectile function and ejaculation.

The number of studies on the effects of CPP on sexual function is limited. Sexual dysfunction is often ignored because of a lack of standardised measurements. At the present, the most commonly used tool is the international index of erectile function (IIEF) questionnaire (27). Post-ejaculation pain is not mentioned in this questionnaire.

In the 1980s an association between PPS and sexual dysfunction was postulated (28). This study reported a high incidence of decreased libido in patients with PPS, and they also concluded that this syndrome should be viewed as a psychosomatic disorder. Whereas psychology may play a role in the genesis of the pain, nowadays, we would say there is little evidence to support PPS as being a psychiatric disorder, but rather a biopsychological disorder in certain cases. For more information on this issue see Chapter 3.1.
In 2 reviews the relation between PPS and health status, with influence on sexual activity, were addressed (29,30).

In a Chinese study of men with PPS 1768 males completed the questionnaires. The overall prevalence of sexual dysfunction was 49%. Erectile dysfunction is the most investigated sexual dysfunction in PPS patients. The reported prevalence of ED ranges from 15.1% to 48%, varying with the evaluation tools and populations (31,32). Erectile dysfunction was prevalent in 27.4% of Italian men aged 25-50 (33), 15.2% among Turkish men (significantly higher than control group) (34) and 43% among Finnish men with PPS (35). The prevalence of ED was found to be higher in young men with PPS than in the general population.

According to other studies men with pelvic pain had higher chance of suffering from ED (36,37). Recently, a significant correlation between “chronic prostatitis”, PPS symptoms (measured by NIH-CPSI) and ED (measured by IIEF) was confirmed (38), while other studies using the same questionnaires were not able to confirm such a correlation (27,39). Some studies also report ejaculatory dysfunction, mainly premature ejaculation (6,22,31,32). According to the definition set up by the International Society for Sexual Medicine, PE is “a male sexual dysfunction characterised by ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration, and inability to delay ejaculation on all or nearly all vaginal penetrations” (40). The reported prevalence of PE varies widely in PPS patients, but unlike ED the prevalence does not increase with age (32).

A study from Turkey concerning the interaction between PPS and premature ejaculation (PE) according to intravaginal ejaculation latency time showed that 77% of men with PPS suffered from PE (34). Screponi et al. reported the high incidence of prostatic inflammation symptoms in men with PE (41). Premature ejaculation associated with PPS is hypothesised to be caused by infection or inflammation, thus treatment with antibiotics should reduce PE symptoms. In 2 studies antibiotic treatment has shown a significant increase in patients IELT (intravaginal ejaculation latency time). Despite these improvements, the mean IELT was still very low and questionable. Before these results can be recommended, further placebo controlled studies are mandatory (42,43).

Furthermore, there are reports which highlight the appearance of ejaculatory pain in patients with PPS (44), while some studies suggested PPS symptoms improvement by increased ejaculatory frequency and sexual activity (45,46).

The presence of pelvic pain may increase the risk for erectile dysfunction independently of age (47). On the other hand, cross-sectional data suggest no improvement of lower urinary tract symptoms (LUTS) by an increased frequency of ejaculation (30). In a study bridging the gap between LUTS and ED, Muller and Mulhall have speculated on the negative impact of PPS on QoL, leading to consecutive impairment of erectile function (48). Although mental distress and impaired QoL related to illness could contribute to sexual dysfunction observed in patients with PPS, the presence of erectile and ejaculatory disorders is more frequently related to symptoms and imaging suggestive of a more severe inflammatory condition (6). These arguments are important for the understanding of the close relationship between CPP symptoms, disturbed sexuality, impact on QoL, and psychological implications including depression (29-32,49).

Sexual dysfunction heightens anger, frustration and depression, all of which place a strain on the relationship and the partner. The female partners of men with sexual dysfunction and depression often present with similar symptoms including pain upon intercourse and depressive symptoms. Men with PPS have reported a high frequency of sexual relationship dissolution and psychological symptoms, such as depression and suicidal thinking (29,48). Prostate pain syndrome patients reported greater sexual and relationship problems: 45% reported an increase in pain during or following intercourse, and many reported avoiding sexual relationships for fear of spreading an infection to their partner (50). On the other hand, Smith et al. found that men with PPS did not report significant decrease of sexual satisfaction compared to control. The results of the

study suggested that while men with PPS and their partners may experience some sexual difficulties, PPS may not have a large negative impact on patients' intimate relationships (51). Aubin et al. found that men appeared open to the initiation of sex and assumed their partners were sexually satisfied (52).

There is a consensus that therapeutic strategies reducing symptoms, especially against pelvic pain, are of relevance in relation to changes of sexuality. On the other hand, having sex and intimacy can yield positive experiences that will reduce the pain. The CNS plays an important role in this mechanism.

7.5 Chronic pelvic pain and sexual dysfunction of the female

Chronic pelvic pain is a clinical condition that results from the complex interactions of physiological and psychological factors and has a direct impact on the social, marital, and professional lives of women. Chronic pelvic pain leads to substantial impairment in QoL and several sexual dysfunctions (53-56).

It seems reasonable to expect that pain, extreme fatigue, depressive mood and pain drugs will affect women's sexuality. Women with pain may report a variety of sexual problems ranging from decreased pleasure and frequency of intercourse, superficial or deep dyspareunia, and problems in reaching orgasm to a total aversion toward sexual intimacy of any kind. Ter Kuile et al. found in their study that women with CPP reported significantly more pain, depression, and anxiety symptoms and were physically more impaired than women in the control group. In comparison with controls, women with CPP reported significantly more sexual avoidance behaviour, non-sensuality, and complaints of "vaginismus" (57).

Chronic pelvic pain is more directly associated with sexual dysfunction than chronic pain at other sites. In one study of CPP patients' feelings and beliefs about their pain or illness, 40 out of 64 participants cited sexual dysfunction as one of the chief problems the illness had caused, making it the most frequent complaint (58). Collett and colleagues (59) also found that patients with CPP reported more sexual problems than women with any other type of chronic pain problem.

The quality of intimate relationships is closely connected with sexual function (60). Satisfaction with the sexual relationship appears to be associated with higher marital functioning (61). In addition to its relationship with marital dissatisfaction, sexual dissatisfaction is related to sexual dysfunction. In cases in which one partner suffers from chronic pain, the ability of both partners to cope with the pain and the extent to which partners are supportive of the chronic pain sufferer have been found to be a predictor of sexual functioning (61).

In community-based studies in the UK (7), New Zealand (54) and Australia (62), a substantially larger proportion of the women with CPP reported dyspareunia (varying between 29% and 42%) than women without CPP (varying between 11% and 14%). Only a few studies have investigated sexual problems within clinical populations (59,63,64). The study of Veritt et al. shows that all of the sexual function domains (desire, arousal, lubrication, orgasm, satisfaction, and pain) were significantly lower in women with CPP than in women without CPP (64). In line with the results of the community based studies, patients with CPP reported more sexual problems such as dyspareunia, problems with desire or arousal and lubrication than women without CPP (63-65).

One study of patients enrolled in chronic pain treatment programs in England has reported that 73% had pain-related sexual problems (8). Approximately two-thirds of patients in another study have reported reduced frequency in their sexual relations as a result of CPP (66).

One study demonstrated that CPP patients reported worse sexual function with regard to desire, arousal, lubrication, orgasm, satisfaction, and more frequent and severe pain with vaginal penetration than women without sexual dysfunction (67).

Maruta et al. interviewed 50 chronic pain sufferers and their spouses, of whom 78% of the pain sufferers and 84% of partners described deterioration, including cessation of their sex life (1). In another study, in patients with back pain, half reported decreased frequency of sex since the onset of chronic pain (8)

The female sexual function index (FSFI) has been developed as a brief, multidimensional self-report instrument for assessing the key dimensions of sexual function in women, which includes desire, subjective arousal, lubrication, orgasm, satisfaction, and pain. The study of Veritt FF et al. showed that when FSFI was used women with CPP reported worse sexual function in all subscales and total score than did women without CPP; the largest differences between women with CPP and without CPP were seen for the domains of pain and arousal; the correlations of FSFI corresponded well to each other; the total score and the subscales of the FSFI had high levels of internal consistency and test-retest reliability when assessed in a sample of women with CPP; and finally, that the FSFI showed good ability to discriminate between women with and without CPP (67).

Some studies report a significant association between sexual abuse before the age of 15 years and later CPP (13). It is suggested that there is increased frequency of sexual abuse or trauma history, anxiety and depression in women with CPP (68-72). While the study of Fry et al. with 164 women with CPP show that child sexual abuse did not apparently differ in prevalence from that in the general population, which must throw into question previous assertions about its widespread and general role in CPP.

7.6 Treatment of sexual dysfunctions and CPP

Couples often benefit from early referral for relationship and sexual counselling during their treatment course (73). Specific behavioural strategies for women who have urogenital complaints and female sexual dysfunction often include exploring alternatives to sexual intercourse (manual or oral pleasuring), different coital positions (female superior or side lying), and pacing, such as limiting thrusting to less than that that causes. Planning for the time of intercourse is important, and scheduling a clinic visit after intercourse might be useful to identify specific sites and causes of postcoital flares. Other behavioural changes involve pre- and postcoital voiding, application of ice packs to the genital or suprapubic area (73,74), and use of vaginal dilators before penile penetration. An alternative is to use natural dilators such as different fingers or sex toys. Hypoallergenic non-irritating lubricants can be used to reduce vulvar, urethra, and vaginal friction, and women with signs of vulvovaginal atrophy may benefit from introital application of minimally absorbed locally applied oestrogen cream (75). In patients with an overactive pelvic floor, referral for physical therapy, myofascial release, and internal pelvic floor muscle massage may offer relief (4).

7.7 In summary

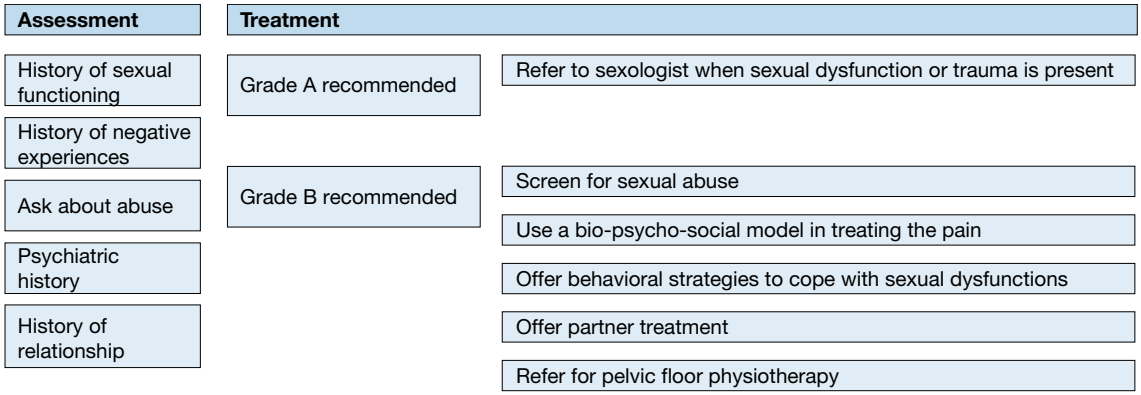
Problems with sexual functioning resulting from CPP have to be addressed and assessed by the health care professional. The attention directed toward these patients must be focused not only on the disease but also on the woman as a whole. As treatment solely of the underlying disease is not acceptable, the care of these suffering women should also address the emotional, sexual, and social problems that the disease causes.

7.8 Conclusions and recommendations: sexological aspects in CPP

Conclusions	**LE**
Chronic pain can lead to decline in sexual activity and satisfaction and may reduce relationship satisfaction.	2a
Patients who reported having sexual, physical or emotional abuse show a higher rate of reporting symptoms of PPS.	2b
Sexual dysfunctions are prevalent in patient with PPS.	2b
In men with PPS the most prevalent sexual complaints are erectile dysfunction and ejaculatory dysfunction.	3
In females with CPPS all sexual function domains are lower. The most reported dysfunctions are sexual avoidance, dyspareunia and “vaginismus”.	2a
Vulvar pain syndrome is associated with BPS.	3
Women with BPS suffer significantly more from fear of pain, dyspareunia and less desire.	2a
Pelvic floor muscle function is involved in the excitement and orgasm phases of sexual response.	3
Chronic pain can cause disturbances in each of the sexual response cycle phases.	2b
Pelvic floor muscle physical therapy may offer relief of pain and reduction in sexual complaints.	2b

Recommendations	**GR**
Patients presenting with symptoms suggestive for chronic pelvic pain syndrome, should be screened for abuse, without suggesting a causal relation with the pain.	B
The biopsychosocial model should be applied in the evaluation of the effect of chronic pelvic pain syndrome on the sexual function of the patient.	B
The biopsychosocial model should be incorporated in research in the role of chronic pelvic pain in sexual dysfunction.	B
Offer behavioural strategies to the patient and his/her partner to cope with sexual dysfunctions.	B
Training of the pelvic floor muscles is recommended to improve quality of life and sexual function.	B

Figure 15: Assessment and treatment algorithm for sexological aspects in chronic pelvic pain



7.9 References

1. Maruta T, Osborne D, Swanson DW et al. Chronic pain patients and spouses. Marital and sexual adjustment. Mayo Clin Proc 1981 May;56(5):307-10. http://www.ncbi.nlm.nih.gov/pubmed/7230895
2. Flor H, Turk DC, Scholtz OB. Impact of chronic pain on the spouse: Marital, emotional and physical consequences. J Psychosom Res 1987;31(1):63-71. http://www.ncbi.nlm.nih.gov/pubmed/3820147
3. Human sexuality (5° ed). MASTERS William, JOHNSON Virginia, KOLODNY Robert. © 1995-2011 LAVOISIER S.A.S.
4. Rosenbaum TY, Owens A. The role of pelvic floor physical therapy in the treatment of pelvic and genital pain-related sexual dysfunction. J Sex Med 2008 Mar;5(3):513-23. http://www.ncbi.nlm.nih.gov/pubmed/18304280
5. Randolph ME, Reddy DM. Sexual functioning in women with chronic pelvic pain: The impact of depression, support, and abuse. J Sex Res 2006 Feb;43(1):38-45. http://www.ncbi.nlm.nih.gov/pubmed/16817066
6. Trinchieri A, Magri V, Cariani L et al. Prevalence of sexual dysfunction in men with chronic prostatitis/ chronic pelvic pain syndrome. Arch Ital Urol Androl 2007 Jun;79(2):67-70. http://www.ncbi.nlm.nih.gov/pubmed/17695411
7. Zondervan KT, Yudkin PL, Vessey MP et al. The prevalence of chronic pelvic pain in women in the United Kingdom: A systematic review. Br J Obstet Gynaecol 1998 Jan;105(1):93-9. http://www.ncbi.nlm.nih.gov/pubmed/9442169
8. Ambler N, Williams AC, Hill P et al. Sexual difficulties of chronic pain patients. Clin J Pain 2001 Jun;17(2):138-45. http://www.ncbi.nlm.nih.gov/pubmed/11444715
9. Averill PM, Novy DM, Nelson DV et al. Correlates of depression in chronic pain patients: A comprehensive examination. Pain 1996 Apr;65(1):93-100. http://www.ncbi.nlm.nih.gov/pubmed/8826495
10. Philipp M, Delini-Stula A, Baier D et al. Assessment of sexual dysfunction in depressed patients and reporting attitudes in routine daily practice: Results of the postmarketing observational studies with moclobemide, a reversible MAO-A inhibitor. Int J Psychiatry Clin Pract 1999;3:257-64.
11. Ferguson JM. The effects of antidepressants on sexual functioning in depressed patients: A review. J Clin Psychiatry 2001;62 Suppl 3:22-34. http://www.ncbi.nlm.nih.gov/pubmed/11229450
12. Coates R, Ferroni EA. Sexual dysfunction and marital disharmony as a consequence of chronic lumbar spinal pain. Sex Marital Ther 1991;6:65-9.
13. Lampe A, Solder E, Ennemoser A et al. Chronic pelvic pain and previous sexual abuse. Obstet Gynecol 2000 Dec;96(6):929-33. http://www.ncbi.nlm.nih.gov/pubmed/11084180
14. Rellini A, Meston CM. Sexual abuse and female sexual dysfunction: Clinical implications. Urodinamica 2004;14:80-3.
15. Heinberg LJ, Fisher BJ, Wesselmann U et al. Psychological factors in pelvic/urogenital pain: The influence of site of pain versus sex. Pain 2004 Mar;108(1-2):88-94. http://www.ncbi.nlm.nih.gov/pubmed/15109511

16. Smith KB, Tripp D, Pukall C et al. Predictors of sexual and relationship functioning in couples with chronic prostatitis/chronic pelvic pain syndrome. J Sex Med 2007 May;4(3):734-44.
http://www.ncbi.nlm.nih.gov/pubmed/17451490
17. McMahon CG, Abdo C, Incrocci L et al. Disorders of orgasm and ejaculation in men. J Sex Med 2004 Jul;1(1):58-65.
http://www.ncbi.nlm.nih.gov/pubmed/16422984
18. Graber B, Kline-Graber G. Female orgasm: Role of the pubococcygeus muscle. J Clin Psychiatry 1979 Aug;40(8):348-51.
19. Shafik A. The role of the levator ani muscle in evacuation, sexual performance, and pelvic floor disorders. Int Urogynecol J Pelvic Floor Dysfunct 2000 Dec;11(6):361-76.
http://www.ncbi.nlm.nih.gov/pubmed/11147745
20. Bo K, Talseth T, Vinsnes A. Randomized controlled trial on the effect of pelvic floor muscle training on quality of life and sexual problems in genuine stress incontinent women. Acta Obstet Gynecol Scand 2000 Jul;79(7):598-603.
http://www.ncbi.nlm.nih.gov/pubmed/10929962
21. Beji NK, Yalcin O, Erkan HA. The effect of pelvic floor training on sexual function of treated patients. Int Urogynecol J Pelvic Floor Dysfunct 2003 Oct;14(4):234-8.
http://www.ncbi.nlm.nih.gov/pubmed/14530833
22. Anderson, Wise D, Sawyer T et al. Sexual dysfunction in men with CP/CPPS: Improvement after trigger point release. Paradoxical relaxation training.J Urol 2006 Oct;176(4 Pt 1):1534-8.
http://www.ncbi.nlm.nih.gov/pubmed/16952676
23. Bergeron S, Brown C, Lord MJ et al. Physical therapy for vulvar vestibulitis syndrome: A retrospective study. J Sex Marital Ther 2002 May-June;28(3):183-92.
http://www.ncbi.nlm.nih.gov/pubmed/11995597
24. Goetsch MF. Surgery combined with muscle therapy for dyspareunia from vulvar vestibulitis: An observational study. J Reprod Med 2007 Jul;52(7):597-603.
http://www.ncbi.nlm.nih.gov/pubmed/17847757
25. Hu JC, Link CL, McNaughton-Collins M et al. The Association of Abuse and Symptoms Suggestive of Chronic Prostatitis/Chronic Pelvic Pain Syndrome: Results from the Boston Area Community Health Survey. J Gen Intern Med 2007 Nov;22(11):1532-7.
http://www.ncbi.nlm.nih.gov/pubmed/17763912
26. Fleming MP, Paice JA. Sexuality and chronic pain. Journal of Sex Education and Therapy 2001.26:204-214.
27. Rosen RC, Riley A, Wagner G et al. The international index of erectile function (IIEF): A multidimensional scale for assessment of erectile dysfunction. Urology 1997 Jun;49(6):822-30.
http://www.ncbi.nlm.nih.gov/pubmed/9187685
28. Keltikangas-Jarvinen L, Jarvinen H, Lehtonen T. Psychic disturbances in patients with chronic prostatis. Ann Clin Res. 1981 Feb;13(1):45-9.
http://www.ncbi.nlm.nih.gov/pubmed/7195683
29. Berghuis JP, Heiman JR, Rothman I et al. Psychological and physical factors involved in chronic idiopathic prostatitis. J Psychosom Res. 1996 Oct;41(4):313-25.
http://www.ncbi.nlm.nih.gov/pubmed/8971661
30. Jacobsen SJ, Jacobson DJ, Rohe DE et al. Frequency of sexual activity and prostatic health: fact or fairy tale? Urology 2003 Feb;61(2):348-53.
http://www.ncbi.nlm.nih.gov/pubmed/12597946
31. Lee SW, Liong ML, Yuen KH et al. Adverse impact of sexual dysfunction in chronic prostatitis/chronic pelvic pain syndrome. Urology 2008 Jan;71(1):79-84.
http://www.ncbi.nlm.nih.gov/pubmed/18242370
32. Liang CZ, Zhang XJ, Hao ZY et al. Prevalence of sexual dysfunction in Chinese men with chronic prostatitis. BJU Int 2004 Sep;94(4):568-70.
http://www.ncbi.nlm.nih.gov/pubmed/15329114
33. Bartoletti R, Cai T, Mondaini N et al. Prevalence, incidence estimation, risk factors and characterization of chronic prostatitis/chronic pelvic pain syndrome in urological hospital outpatients in Italy: Results of a multicenter case-control observational study. J Urol 2007 Dec;178(6):2411-5.
http://www.ncbi.nlm.nih.gov/pubmed/17937946
34. Gonen M, Kalkan M, Cenker A et al. Prevalence of premature ejaculation in Turkish men with chronic pelvic pain syndrome. J Androl 2005 Sep-Oct;26(5):601-3.
http://www.ncbi.nlm.nih.gov/pubmed/16088036

35. Mehik A, Hellstrom P, Sarpola A et al. Fears, sexual disturbances and personality features in men with prostatitis: A population-based cross-sectional study in Finland. BJU Int 2001 Jul;88(1):35-8.
http://www.ncbi.nlm.nih.gov/pubmed/11446842
36. Weidner W, Wagenlehner FM, Marconi M et al. Acute bacterial prostatitis and chronic prostatitis/ chronic pelvic pain syndrome: andrological implications. Andrologia. 2008 Apr;40(2):105-12.
http://www.ncbi.nlm.nih.gov/pubmed/18336460
37. O'Leary MP, Fowler FJ, Lenderking WR et al. A brief male sexual function inventory for urology. Urology 1995 Nov;46(5):697-706.
http://www.ncbi.nlm.nih.gov/pubmed/7495124
38. Qiu YC, Xie CY, Zeng XD et al. Investigation of sexual function in 623 patients with chronic prostatitis. Zhonghua Nan Ke Xue. 2007 Jun;13(6):524-6. [Article in French]
http://www.ncbi.nlm.nih.gov/pubmed/17615977
39. Davis SN, Binik YM, Carrier S: Sexual dysfunction and pelvic pain in men: A male sexual pain disorder? J Sex Marital Ther 2009; 35:182-205.
40. McMahon CG, Abdo C, Incrocci L et al. Disorders of orgasm and ejaculation in men. J Sex Med 2004 Jul;1(1):58-65.
http://www.ncbi.nlm.nih.gov/pubmed/16422984
41. Screponi E, Carosa E, Di Stasi SM et al. Prevalence of chronic prostatitis in men with premature ejaculation. Urology 2001 Aug;58(2):198-202.
http://www.ncbi.nlm.nih.gov/pubmed/11489699
42. Hennenfent BR, Feliciano AE. Changes in white blood cell counts in men undergoing thrice-weekly prostatic massage, microbial diagnosis and antimicrobial therapy for genitourinary complaints. Br J Urol 1998 Mar;81(3):370-6.
http://www.ncbi.nlm.nih.gov/pubmed/9523654
43. El-Nashaar A, Shamloul R. Antibiotic treatment can delay ejaculation in patients with premature ejaculation and chronic bacterial prostatitis. J Sex Med 2007 Mar;4(2):491-6.
http://www.ncbi.nlm.nih.gov/pubmed/17367444
44. Ilie CP, Mischianu DL, Pemberton RJ. Painful ejaculation. BJU international 2007 Jun;99(6):1335-9.
http://www.ncbi.nlm.nih.gov/pubmed/17346279
45. Shoskes DA, Landis JR, Wang Y et al. Impact of post-ejaculatory pain in men with category III chronic prostatitis/chronic pelvic pain syndrome. J Urol 2004 Aug;172(2):542-7.
http://www.ncbi.nlm.nih.gov/pubmed/15247725
46. Weidner W, Ludwig M, Miller J. Therapy in male accessory gland infection--what is fact, what is fiction? Andrologia. 1998;30 Suppl 1:87-90. [no abstract available]
http://www.ncbi.nlm.nih.gov/pubmed/9629448
47. Marszalek M, Wehrberger C, Temml C et al. Chronic Pelvic Pain and Lower Urinary Tract Symptoms in Both Sexes: Analysis of 2749 Participants of an Urban Health Screening Project. Eur Urol. 2009 Feb;55(2):499-507.
http://www.ncbi.nlm.nih.gov/pubmed/18395963
48. Muller A, Mulhall JP. Sexual dysfunction in the patient with prostatitis. Curr Opin Urol. 2005 Nov;15(6):404-9.
http://www.ncbi.nlm.nih.gov/pubmed/16205492
49. Tripp DA, Nickel JC, Ross S et al. Prevalence, symptom impact and predictors of chronic prostatitislike symptoms in Canadian males aged 16-19 years. BJU international 2009 Apr;103(8):1080-4.
http://www.ncbi.nlm.nih.gov/pubmed/19007369
50. Egan KJ, Krieger JL. Psychological problems in chronic prostatitis patients with pain. Clinical Journal of Pain 1994 Sep;10(3):218-26.
http://www.ncbi.nlm.nih.gov/pubmed/7833580
51. Smith KB, Pukall CF, Tripp DA, Nickel JC. Sexual and Relationship Functioning in Men with Chronic Prostatitis/Chronic Pelvic Pain Syndrome and Their Partners. Arch Sex Behav 2007;36:301-311.
http://www.ncbi.nlm.nih.gov/pubmed/17186130
52. Aubin S, Berger RE, Heiman JR, Ciol MA: The association between sexual function, pain, and psychological adaptation of men diagnosed with chronic pelvic pain syndrome type III. J Sex Med 2008;5:657-667.
http://www.ncbi.nlm.nih.gov/pubmed/18208504
53. Gunter J. Chronic pelvic pain: An integrated approach to diagnosis and treatment. Obstet Gynecol Surv 2003 Sep;58(9):615-23.
http://www.ncbi.nlm.nih.gov/pubmed/12972837

54. Grace V, Zondervan K. Chronic pelvic pain in women in New Zealand: Comparative well-being, comorbidity, and impact on work and other activities. Health Care Women Int 2006 Aug;27(7):585-99. http://www.ncbi.nlm.nih.gov/pubmed/16844672
55. Latthe P, Latthe M, Say L, Gulmezoglu M et al. WHO systematic review of prevalence of chronic pelvic pain: A neglected reproductive health morbidity. BMC Public health 2006 Jul 6;6:177. http://www.ncbi.nlm.nih.gov/pubmed/16824213
56. Pearce C, Curtis M. A multidisciplinary approach to self care in chronic pelvic pain. Br J Nurs 2007 Jan 25-Feb 7;16(2):82-5. http://www.ncbi.nlm.nih.gov/pubmed/17353816
57. ter Kuile MM, Weijenborg PTM, Spinhoven P. Sexual functioning in women with chronic pelvic pain: The role of anxiety and depression. J Sex Med 2010 May;7(5):1901-10. http://www.ncbi.nlm.nih.gov/pubmed/19678881
58. Fry RPW, Crisp AH, Beard RW. Patients' illness models in chronic pelvic pain. Psychother Psychosom 1991;55(2-4):158-63. http://www.ncbi.nlm.nih.gov/pubmed/1891563
59. Collett BJ, Cordle CJ, Stewart CR et al. A comparative study of women with chronic pelvic pain, chronic nonpelvic pain and those with no history of pain attending general practitioners. Br J Obstet Gynecol 1998 Jan;105(1):87-92. http://www.ncbi.nlm.nih.gov/pubmed/9442168
60. McCabe MP, Jupp JJ. Intercorrelations among general arousability, emerging and current sexual desire, and severity of sexual dysfunction in women. Psychol Rep. 1989 Aug;65(1):147-54. http://www.ncbi.nlm.nih.gov/pubmed/2780925
61. Flor H, Kerns RD, Turk DC. The role of spouse reinforcement, perceived pain, and activity levels of chronic pain patients. J Psychosoma Res 1987;31(2):251-9. http://www.ncbi.nlm.nih.gov/pubmed/3585827
62. Pitts MK, Ferris JA, Smith AM et al. Prevalence and correlates of three types of pelvic pain in a nationally representative sample of Australian women. Med J Aust 2008 Aug 4;189(3):138-43. http://www.ncbi.nlm.nih.gov/pubmed/18673099
63. Florido J, Perez-Lucas R, Navarrete L. Sexual behavior and findings on laparoscopy or laparotomy in women with severe chronic pelvic pain. Eur J Obstet Gynecol Reprod Biol 2008 Aug;139(2):233-6. http://www.ncbi.nlm.nih.gov/pubmed/18403089
64. Verit FF, Verit A, Yeni E. The prevalence of sexual dysfunction and associated risk factors in women with chronic pelvic pain: A cross-sectional study. Arch Gynecol Obstet 2006 Aug;274(5):297-302. http://www.ncbi.nlm.nih.gov/pubmed/16705463
65. Phillips NA. The clinical evaluation of dyspareunia. Int J Impot Res 1998 May;10 Suppl 2:S117-20. http://www.ncbi.nlm.nih.gov/pubmed/9647973
66. Paice J. Sexuality and chronic pain. Am J Nurs 2003 Jan;103(1):87-9. [no abstract available] http://www.ncbi.nlm.nih.gov/pubmed/12544064
67. Verit FF, Verit A. Validation of the Female Sexual Function Index in women with chronic pelvic pain. J Sex Med 2007 Nov;4(6):1635-41. http://www.ncbi.nlm.nih.gov/pubmed/17888066
68. Roelofs K, Spinhoven P. Trauma and medically unexplained symptoms towards an integration of cognitive and neurobiological accounts. Clin Psychol Rev 2007 Oct;27(7):798-820. http://www.ncbi.nlm.nih.gov/pubmed/17728032
69. McGowan LPA, Clark-Carter DD, Pitts MK. Chronic pelvic pain: A meta-analytic review. Psychol Health 1998;13:937-51.
70. Leonard LM, Follette VM. Sexual functioning in women reporting a history of child abuse. Review of the empirical literature and clinical implications. Annu Rev Sex Res 2002;13:346-88. http://www.ncbi.nlm.nih.gov/pubmed/12836736
71. Angst J. Sexual problems in healthy and depressed persons. Int Clin Psychopharmacol 1998 Jul;13 Suppl 6:S1-4. http://www.ncbi.nlm.nih.gov/pubmed/9728667
72. Walker EA, Katon WJ, Hansom J, et al. Psychiatric diagnoses and sexual victimization in women with chronic pelvic pain. Psychosomatics 36:531-540, 1995. http://www.ncbi.nlm.nih.gov/pubmed/7501783
73. Kellogg-Spadt S, Whitmore KE. Role of the female urologist/urogynecologist. In: Goldstein I, Meston CM, Davis SR, Traish AM, eds. Women's sexual function and dysfunction: Study, diagnosis and treatment. Vol. 17. London: Taylor and Francis; 2006:708-14.

74. Webster DC, Brennan T. Use and effectiveness of sexual self-care strategies for interstitial cystitis. Urol Nurs 1995 Mar;15(1):14-22. http://www.ncbi.nlm.nih.gov/pubmed/7792618
75. Hayes RD, Bennett CM, Fairley CK et al. What can prevalence studies tell us about female sexual difficulty and dysfunction? J Sex Med 2006 Jul;3(4):589-95. http://www.ncbi.nlm.nih.gov/pubmed/16839314

8. PSYCHOLOGICAL ASPECTS OF CHRONIC PELVIC PAIN

This chapter first addresses general issues concerning the psychological contribution to pelvic pain and its presenting problems, and assessment and treatment, and then it describes the same areas in relation to CPP in women. This is by far the area with the greatest psychological contribution to pelvic and urogenital pain, and exemplifies many of the problems raised in the first part of the chapter.

8.1 Understanding the psychological components of pain

8.1.1 Neurophysiology of pain

Models that integrate the psychological factors consistently found to be relevant in the maintenance of persistent pelvic and urogenital pain with current neurobiological understanding of pain are few but of high quality. Symptom-related anxiety and central pain amplification may be measurably linked, as in IBS (1). Bajaj et al. (2) have demonstrated central sensitisation in symptomatic endometriosis, and this model is more extensively dealt with in Chapter 4. The various mechanisms of facilitation, amplification, and failure of inhibition, mean that there should be no expectation of a simple relationship between physical findings, pain experienced, and resulting distress and restriction of activities. Difficulty disengaging even from expected painful stimuli, undergone voluntarily and within tolerable levels, is characteristic in people struggling with chronic pain (3). However, difficult as it is to relieve chronic pain, the pain system is plastic and treatment attempts are not entirely unsuccessful.

8.1.2 Sexual abuse and trauma

Many studies have reported high rates of childhood sexual abuse in adults with persistent pain, usually in hospital care samples, and particularly by women with pelvic pain (4). However, all these studies are retrospective, and there appears to be a relationship between poor study quality and likelihood of reporting this association (5). 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 years to establish a definite history, comparing those with such a history with demographically matched classmates (6). The conclusions of this study were 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; however, 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 for which no major pathology is found 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 studies or careful comparisons rather than, as in many published studies, comparing women with a history of sexual abuse and CPP with women without either (7). No studies have been found about sexual or physical abuse in childhood and pelvic pain in men, although it is evident that they suffer other adverse effects on psychological and physical health (8,9).

8.1.3 Interpreting psychological differences

An important review (7) 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 have critically examined 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.

In summary, women with pelvic pain often have other 'medically unexplained' symptoms, and current or 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. Studies that invoke 'medically unexplained' or 'psychosomatic' or 'somatoform' disorders do not engage with current understanding of pain, such as viscerovisceral cross sensitisation in relation to multiple pain sites (10), referring instead to a dualistic model in which absence of physical findings is taken to indicate psychological origins of the complaint of pain (11,12). At the extreme, pain is overshadowed by diagnosis as a sexual problem ('dyspareunia') when pain is in fact the central problem and not contingent only on sexual activity (13).

8.2 Psychological assessment of pain

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 the meaning of pain to the individual.

Anxiety probably refers to fears of missed pathology as the cause of pain (cancer being foremost among these) and to uncertainties about the possibilities of treatment and the likely prognosis if treated or untreated. A question such as that suggested by Howard (14), "What do you believe or fear is the cause of your pain?" is more suitable than a general anxiety questionnaire.

Depression is also commonly found in men and women with persistent pelvic pain (15). In a study comparing men and women with low back pain, and women with pelvic pain and men with urogenital pain (16), it was found that, when differences in age and pain duration and severity were taken into account, there were no differences in depression according to pain site, and pain site predicted disability.

However, there is a risk when using diagnostic or standard assessment instruments of attributing pain-related problems to neurovegetative signs of depression (17,18). As Stones et al. (19) has cautioned: "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" (p416).

Pain ratings themselves may be predicted by cognitive and emotional variables (20). Furthermore, target outcomes of pain severity, distress and disability co-vary only partly, and improvement in one does not necessarily imply improvement in the others. Therefore, it is particularly important when the primary outcome is pain to anchor its meaning in a study such as that by Gerlinger et al. (21), who determined clinically important differences in pain in relation to overall satisfaction with treatment.

There are many measures of restricted function, or disability, most suited to musculosketal pain and mobility problems rather than the difficulties of the individual with pelvic or urogenital pain. Some include one or more items related to sexual activity, but there has perhaps been an over-emphasis on the effects of pain on sexual performance, although the overall relationship may be more important (22).

In the Cochrane review of pelvic pain in women (23), the outcomes of pharmacotherapy, surgery and physical therapy trials consist of pain scores (patient-rated and physican-estimated); functional measures such as urinary peak flow rate (for persistent pelvic pain in men); examination findings such as pelvic tenderness (women); and uptake of further treatment following the trial treatment. A few trials have included QoL, but none have measured mood change. This indicates a general but mistaken assumption that improvement in pain leads to resolution of other problems. Furthermore, if all treatments sampled the same domains of pain in their evaluation, comparison across treatments, by medical personnel and patients, would be more easily achieved (24). Suggested instruments for assessment in each of these domains can be found in the consensus paper by Turk et al. (25).

8.3 Psychological issues in the treatment of pain

Provision of information that is personalised and responsive to the presenting problem and the concerns of the patient, conveying belief and concern, is a powerful way to allay anxiety (26). It can be helpful to provide additional written information or direct the patient to reliable sources. Many practitioners rely on locally produced material or pharmaceutical products of variable quality, although they endorse the need for independent materials for patients (27).

Ideally, treatment arises from general principles and practice in the field of chronic pain, with specific study of the population of concern and design of appropriate treatment trials (28). The field of pelvic pain shows a curious phenomenon whereby few of the mainstream psychologically based treatments are subjected to trials and published, but instead there are often rather idiosyncratic versions of treatment components, or combinations of interventions, published in single, often underpowered trials. It is hard to conclude anything from these, as is seen in the psychological treatment section of several other chapters.

Psychological interventions may be directed at the pain itself, with the intended outcome of reducing pain and its consequent impact on life, or adjustment to pain, with improved mood and function and reduced health care use, with or without pain reduction. The major psychologically based treatment that improves adjustment, which is aimed more at reducing distress and disability than pain, is cognitive behavioural therapy,

for which there have been > 10 systematic reviews (29), although its effects may be small and maintenance in the longer term is uncertain. For less disabled and distressed patients, this can be delivered in part over the internet (30). A systematic review of short-term psychodynamic psychotherapy (31) has reported similar improvements in "somatic disorders", which often includes pelvic pain, although it was not among the trials reviewed. Pain-focused interventions, again with no trials in pelvic pain, have been subjected to systematic review, including hypnotherapy (32) and autogenic training (33).

However, all these systematic reviews suffer from heterogeneity among the trials, shortcomings in trial methodology, and little longer term follow-up to establish maintenance of treatment gains. The crucial question, of what works best for whom, is unanswered and possibly unanswerable given the complexity of variables, outcomes, and the difficulties in standardising treatments.

8.4 Female pelvic pain

8.4.1 ***Psychological risk factors in development and maintenance of pelvic pain***

A thorough review from nearly 15 years ago (34) argues against division of aetiology into organic versus psychogenic, and concludes that, given the methodological problems of many studies, the evidence for sexual abuse as a risk factor is uncertain. A large review and meta-analysis of risk factors, including physical pathology, psychological distress, and sexual abuse (35) drew mainly on retrospective studies, which introduced various biases. Pelvic pain and distress may be variously related, each as the consequence of the other, or arising independently.

The only systematic review (5) of risk factors for chronic non-cyclical pelvic pain in women included the following as well as medical variables: sexual or physical abuse (ORs from 1.51 to 3.49); psychological problems such as anxiety (OR: 2.28, 95% CI: 1.41- 3.70) and depression (OR: 2.69, 95% CI: 1.86-3.88); hysteria, i.e., multiple somatic problems (OR: 4.83, 95% CI: 2.50-9.33); and psychosomatic symptoms (OR: 8.01, 95% CI: 5.16-12.44). The terms hysteria and psychosomatic symptoms can best be understood as multiple somatic symptoms not associated with or indicative of any serious disease process, and personality variables are not reliably associated with pelvic pain in women. Although some of these risk factors are doubtless interrelated - history of sexual abuse and depression, for instance - such effects cannot be disentangled from the studies available.

Issues of early trauma such as childhood sexual or physical abuse as a risk factor are addressed in more detail earlier in this chapter, but it is important to say that better quality studies, including one prospective study using court records of childhood abuse (6), have reported a weaker or no relationship, or not one which is specific to pelvic pain (5,36-38). However, another systematic review (9) has concluded that there is some evidence for a specific relationship between rape and CPP (and also with fibromyalgia and functional gastrointestinal disorders). It is also important to recognise the possible role of recent sexual assault on the presentation of pelvic pain (4,39).

There have been fewer studies of maintenance of or recovery from pelvic pain in relation to psychological factors. Weijenborg et al. (40) have found that, in 25% of women treated surgically, recovery from pelvic pain over a mean 3 years follow-up was not predicted by pain variables at baseline, nor by a general measure of psychological distress or sociodemographic variables, or reports of childhood sexual abuse.

Studies that have described pelvic pain as medically unexplained or psychosomatic, due to the lack of physical findings, have been discarded. This is because such a distinction is unhelpful and is not informed by our understanding of pain mechanisms (11). When diagnostic investigations are used to assign symptoms to physical and mental origins, with no suggested connection between them, and with interest only in the former type of symptoms, explanations are often experienced by women as scepticism about the reality or severity of the pain (41). This can undermine the therapeutic relationship between the patient and the doctor (42). Ehlert et al. (43) have found that women with pelvic pain with and without laparoscopic findings do not differ from one another; only from pain-free controls, as anticipated by Savidge & Slade (7). Distress, described in the patient's terms or within a psychodiagnostic framework, is best understood in the context of pain and the meaning of pain to the individual (7). In a large primary care study, Zondervan et al. (44) have noted the tendency to attribute pelvic pain without obvious pathology to a psychological cause, and that it is increasingly recognised as unhelpful; depression and anxiety are common in any chronic pain, not pelvic pain alone. They have found that restriction by pain does not distinguish between women who do and do not seek health care, and that there may be an anxiety-related cause of the pain in both groups.

8.4.2 ***Psychological assessment of pelvic pain***

Anxiety and post-traumatic stress symptoms are common in some women with CPP (44,45), and may account for substantial variance in health status and treatment use. Negative investigative findings do not necessarily resolve women's anxieties about what might be causing pain (26). Depression may be related to pain in various ways, as described above. Until measures are available that are adequately standardised in patients with

pain, anxiety and distress may be best assessed by questions about concerns about the cause of pain, its implications, and its consequences for everyday life (46).

Reference to the studies of the IMMPACT group (24) is recommended for guidance on outcome measures suitable for pain trials.

8.4.3 ***Psychological factors in treatment of persistent pelvic pain***

Untreated, there is a significant rate of symptom improvement. In one study, 25% of patients reported recovery (nearly half with total recovery) over a 3-4-year period, and neither pain nor distress at baseline, nor intervention received, was found to be associated with recovery (40). This recovery rate should be borne in mind when interpreting results of treatment trials.

There is one Cochrane systematic review and meta-analysis of treatments for pelvic pain, excluding that due to endometriosis, IBS, and chronic PID (47). All treatments were included (although the update protocols split surgical from non-surgical (48), and outcomes were mainly pain scores, QoL, and resource use, including health care resources. The 14 treatment trials included counselling, psychoeducation, reassurance, and emotional disclosure, as well as a multicomponent pain management programme. The authors concluded in favour of educational counselling combined with ultrasound scanning, which improved pain and mood; and a multidisciplinary rehabilitative approach including surgery, pharmacotherapy, physiotherapy, and psychosocial intervention, which improved function but not pain. Emotional disclosure (a stress reduction method) through writing brought about a small improvement in some pain scores.

Several other reviews make positive comments on psychological involvement (49), and recommend addressing psychological concerns from the outset rather than after other treatment has failed. Psychological interventions may be directed at the pain itself, with the intended outcome of reducing pain and its consequent impact on life (1), or at adjustment to pain, with improved mood and function and reduced health care use, with or without pain reduction (2).

In the first category are relaxation and biofeedback methods of controlling and decreasing pain by reducing muscle tension, and this is applied in mainly uncontrolled trials to pelvic floor retraining both in men and women. The only RCT applied a specific type of cognitively enhanced physical therapy to overall muscle tension, but not to the pelvic floor, combined with normal gynaecological treatment compared with gynaecological treatment alone (50). Pain was reduced by 50% and motor function improved in various aspects by 10 h of physical therapy, with particular attention to tension and relaxation and to the thoughts and emotions that interfere with balanced posture and movement.

In the second category, 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. A systematic review and meta-analysis which shows a good outcome for mixed chronic pain or back pain groups across pain experience, mood, coping, and activity, cannot with confidence be extrapolated to women with pelvic pain alone (51). The only RCTs in CPP used elements of this approach in combination with medroxyprogesterone acetate (MPA) or placebo (52). Combination of MPA and psychological therapy outperformed other treatment methods in the long-term, with nearly three quarters of women reporting > 50% pain relief.

Several single treatments with benefits in other chronic pain or chronic health problems have been tried in pelvic pain. Norman et al. have compared emotional disclosure by writing about pain with writing about positive events as a control (53). The differences were small but in favour of emotional disclosure on one measure of pain appraisal, particularly in women with more distress at baseline. Given the extent of problems associated with pelvic pain, this intervention on its own is unlikely to produce much change, but could be combined with other components described above.

In a different intervention, Fenton et al. have conducted a small RCT of transcranial direct current stimulation compared to sham stimulation (54). Pain reduction was greater in the treatment group, in the first week only, as was reduction in disability.

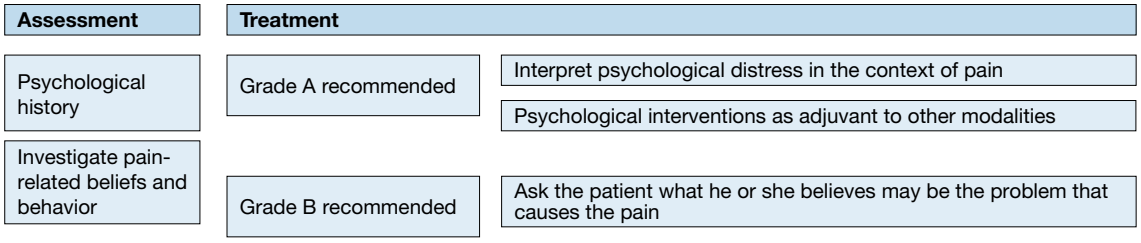
8.5 Conclusions and recommendations: psychological aspects of CPP

Conclusions	**LE**
There is no evidence that distress generates complaints of pelvic pain, or that multiple symptoms suggest unreality of pain.	2b
Current or recent sexual abuse should be assessed as possible contributory factors in pelvic pain.	2a
Psychological intervention in general can produce benefits in pain, mood, and quality of life, depending on its content and focus.	1a
Psychologically informed physical therapy can improve pain and function.	1b

Combined exercise and cognitive behavioural therapy with medroxyprogesterone acetate can reduce pain in a majority of women with pelvic pain.	1b
Transcranial direct current stimulation may reduce pain in the short term.	1b

Recommendations	GR
Psychological distress is common in pelvic pain in women, but should be interpreted in the context of pain.	A
Ask the patient what she thinks may be wrong to cause pain, to allow the opportunity to inform and reassure as appropriate.	B
Try psychological interventions in combination with medical and surgical treatment, or alone.	A

Figure 16: Assessment and treatment algorithm for psychological aspects of chronic pelvic pain



8.6 References

1. Berman SM, Naliboff BD, Suyenobu B, et al. Reduced brainstem inhibition during anticipated visceral pain correlates with enhanced brain response to the visceral stimulus in women with irritable bowel syndrome. J Neurosci. 2008 Jan;28(2):349-59. http://www.ncbi.nlm.nih.gov/pubmed/18184777
2. Bajaj P, Bajaj P, Madsen H, et al. Endometriosis is associated with central sensitisation: a psychophysical controlled study. J Pain 2003 Sep;4(7):372-80. http://www.ncbi.nlm.nih.gov/pubmed/14622679
3. Eccleston C, Crombez G. Worry and chronic pain: a misdirected problem solving model. Pain. 2007 Dec 5;132(3):233-6. [no abstract available] http://www.ncbi.nlm.nih.gov/pubmed/17961924
4. Hilden M, Schei B, Swahnberg K, et al. A history of sexual abuse and health: a Nordic multicentre study. BJOG. 2004 Oct;111(10):1121-7. http://www.ncbi.nlm.nih.gov/pubmed/15383115
5. Latthe P, Mignini L, Gray R, et al. Factors predisposing women to chronic pelvic pain: systematic review. BMJ. 2006 Apr;332(7544):749-55. http://www.ncbi.nlm.nih.gov/pubmed/16484239
6. Raphael KG, Widom CS, Lange G. Childhood victimization and pain in adulthood: a prospective investigation. Pain. 2001 May;92(1-2):283-93. http://www.ncbi.nlm.nih.gov/pubmed/11323150
7. Savidge CJ, Slade P. Psychological aspects of chronic pelvic pain. Journal of J Psychosom Res. 1997 May;42(5):433-44. http://www.ncbi.nlm.nih.gov/pubmed/9194016
8. Leserman J. Sexual abuse history: prevalence, health effects, mediators, and psychological treatment. Psychosom Med. 2005 Nov-Dec;67(6):906-15. http://www.ncbi.nlm.nih.gov/pubmed/16314595
9. Paras ML, Murad MH, Chen LP, et al. Sexual abuse and lifetime diagnosis of somatic disorders. A systematic review and meta-analysis. JAMA. 2009 Aug;302(5):550-61. http://www.ncbi.nlm.nih.gov/pubmed/19654389
10. Malykhina AP. Neural mechanisms of pelvic organ cross-sensitisation. Neuroscience. 2007 Nov;149(3):660-72. http://www.ncbi.nlm.nih.gov/pubmed/17920206
11. Grace VM. Pitfalls of the medical paradigm in chronic pelvic pain. Baillieres Best Pract Res Clin Obstet Gynaecol. 2000 Jun;14(3):525-39. http://www.ncbi.nlm.nih.gov/pubmed/10962640
12. Sharpe M, Carson A. 'Unexplained' somatic symptoms, functional syndromes, and somatization: do we need a paradigm shift? Ann Intern Med. 2001 May;134(9 Pt 2):926-30. http://www.ncbi.nlm.nih.gov/pubmed/11346330

13. Binik YM. The DSM diagnostic criteria for dyspareunia. Arch Sex Behav. 2010 Apr;39(2):292-303.
http://www.ncbi.nlm.nih.gov/pubmed/19830537
14. Howard FM. Chronic pelvic pain. Obstet Gynecol. 2003 Mar;101(3):594-611.
http://www.ncbi.nlm.nih.gov/pubmed/12636968
15. Fitzgerald MP, Link CL, Litman HJ, et al. Beyond the lower urinary tract: the association of urologic and sexual symptoms with common illnesses. Eur Urol. 2007 Aug;52(2):407-15.
http://www.ncbi.nlm.nih.gov/pubmed/17382458
16. Heinberg LJ, Fisher BJ, Wesselman U, et al. Psychological factors in pelvic/urogenital pain: the influence of site of pain versus sex. Pain. 2004 Mar;108(1-2):88-94.
http://www.ncbi.nlm.nih.gov/pubmed/15109511
17. Pincus T, Williams A. Models and measurements of depression in chronic pain. J Psychosom Res 1999 Sep;47:211-219.
http://www.ncbi.nlm.nih.gov/pubmed/10576470
18. Lorencatto C, Petta CA, Navarro MJ, et al. Depression in women with endometriosis with and without chronic pelvic pain. Acta Obstet Gynecol Scand. 2006;85(1):88-92.
http://www.ncbi.nlm.nih.gov/pubmed/16521687
19. Stones RW, Selfe SA, Fransman S, et al. Psychosocial and economic impact of chronic pelvic pain. Baillieres Best Pract Res Clin Obstet Gynaecol. 2000 Jun;14(3):415-31.
http://www.ncbi.nlm.nih.gov/pubmed/10962635
20. Tripp DA, Nickel JC, Wang Y, et al. Catastrophizing and pain-contingent rest predict patient adjustment in men with chronic prostatitis/chronic pelvic pain syndrome. J Pain 2006 Oct;7 (10): 697-708.
http://www.ncbi.nlm.nih.gov/pubmed/17018330
21. Gerlinger C, Schumacher U, Faustman T, et al. Defining a minimally clinically important difference for endometriosis-associated pelvic pain measured on a visual analog scale: analyses of two placebo-controlled, randomized trials. Health Qual Life Outcomes. 2010 Nov 24;8:138.
http://www.ncbi.nlm.nih.gov/pubmed/21106059
22. Smith KB, Pukall CF. A systematic review of relationship adjustment and sexual satisfaction among women with provoked vestibulodynia. J Sex Res. 2011 Mar;48(2-3):166-91.
http://www.ncbi.nlm.nih.gov/pubmed/21409713
23. Stones W, Cheong YC, Howard FM. Interventions for treating chronic pelvic pain in women (review). Cochrane Database Syst Rev. 2000;(4):CD000387.
http://www.ncbi.nlm.nih.gov/pubmed/11034686
24. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain. 2005 Jan;113(1-2):9-19.
http://www.ncbi.nlm.nih.gov/pubmed/15621359
25. Turk DC, Dworkin RH, Allen RR, et al. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. Pain. 2003 Dec;106(3):337-45.
http://www.ncbi.nlm.nih.gov/pubmed/14659516.
26. McGowan L, Luker K, Creed F, et al. 'How do you explain a pain that can't be seen?': The narratives of women with chronic pelvic pain and their disengagement with the diagnostic cycle. Br J Health Psychol. 2007 May;12(Pt 2):261-74.
http://www.ncbi.nlm.nih.gov/pubmed/17456285
27. EAU Survey: What do you tell your patients?
http://www.uroweb.org/news/?act=showfull&aid=246
28. Nickel JC, Tripp D, Teal V, et al. Interstitial Cystitis Collaborative Trials Group. Journal of Urology 2007;177:1832-1836.
http://www.ncbi.nlm.nih.gov/pubmed/17437831
29. Eccleston C, Williams AC, Morley S. Psychological therapies for the management of chronic pain (excluding headache) in adults. Cochrane Database Syst Rev. 2009 Apr;(2):CD007407.
http://www.ncbi.nlm.nih.gov/pubmed/19370688
30. Macea DD, Gajos K, Daglia Calil YA, et al. The efficacy of web-based cognitive behavioral interventions for chronic pain: a systematic review and meta-analysis. Journal of Pain 2010 Oct;11: 917-929.
http://www.ncbi.nlm.nih.gov/pubmed/20650691
31. Abbass A, Kisely S, Kroenke K. Short-term psychodynamic psychotherapy for somatic disorders. Psychother Psychosom. 2009;78(5):265-74.
http://www.ncbi.nlm.nih.gov/pubmed/19602915

32. Flammer E, Alladin A. The efficacy of hypnotherapy in the treatment of psychosomatic disorders: meta-analytical evidence. Int J Clin Exp Hypn. 2007 Jul;55(3):251-74.
http://www.ncbi.nlm.nih.gov/pubmed/17558717
33. Stetter F, Kupper S. Autogenic training: a meta-analysis of clinical outcome studies. Appl Psychophysiol Biofeedback. 2002 Mar;27(1):45-98.
http://www.ncbi.nlm.nih.gov/pubmed/12001885
34. Fry RP, Crisp AH, Beard RW. Sociopsychological factors in chronic pelvic pain: a review. J Psychosom Res. 1997 Jan;42(1):1-15.
http://www.ncbi.nlm.nih.gov/pubmed/9055210
35. Zondervan K, Barlow DH. Epidemiology of chronic pelvic pain. Baillieres Best Pract Res Clin Obstet Gynaecol. 2000 Jun;14(3):403-14.
http://www.ncbi.nlm.nih.gov/pubmed/10962634
36. Raphael KG, Chandler HK, Ciccone DS. Is childhood abuse a risk factor for chronic pain in adulthood? Curr Pain Headache Rep. 2004 Apr;8(2):99-110.
http://www.ncbi.nlm.nih.gov/pubmed/14980144
37. Davis MA, Luecken LJ, Zautra AJ. Are reports of childhood abuse related to the experience of chronic pain in adulthood? A meta-analytic review of the literature. Clin J Pain 2005 Sep-Oct;21(5):398-405.
http://www.ncbi.nlm.nih.gov/pubmed/16093745
38. Maniglio R. The impact of child sexual abuse on health: a systematic review of reviews. Clin Psychol Rev. 2009 Nov;29(7):647-57.
http://www.ncbi.nlm.nih.gov/pubmed/19733950
39. Campbell R, Lichty LF, Sturza M, et al. Gynecological health impact of sexual assault. Res Nurs Health. 2006 Oct;29(5):399-413.
http://www.ncbi.nlm.nih.gov/pubmed/16977640
40. Weijenborg PT, Greeven A, Dekker FW, et al. Clinical course of chronic pelvic pain in women. Pain. 2007 Nov;132 Suppl 1:S117-23.
http://www.ncbi.nlm.nih.gov/pubmed/17689866
41. Savidge CJ, Slade P, Steward P, et al. Women's perspectives on their experiences of chronic pelvic pain and medical care. J Health Psychol 1998 Jan;3(1):103-16.
http://www.ncbi.nlm.nih.gov/pubmed/22021346
42. Price J, Farmer G, Harris J, et al. Attitudes of women with chronic pelvic pain to the gynaecological consultation: a qualitative study. BJOG. 2006 Apr;113(4):446-52.
http://www.ncbi.nlm.nih.gov/pubmed/16489938
43. Ehlert U, Heim C, Hellhammer DH. Chronic pelvic pain as somatoform disorder. Psychother Psychosom. 1999 Mar-Apr;68(2):87-94.
http://www.ncbi.nlm.nih.gov/pubmed/10026460
44. Zondervan KT, Yudkin PL, Vessey MP, et al. The community prevalence of chronic pelvic pain in women and associated illness behaviour. Br J Gen Pract. 2001 Jul;51(468):541-7.
http://www.ncbi.nlm.nih.gov/pubmed/11462313
45. Meltzer-Brody S, Leserman J, Zolnoun D, et al. Trauma and posttraumatic stress disorder in women with chronic pelvic pain. Obstet Gynecol. 2007 Apr;109(4):902-8.
http://www.ncbi.nlm.nih.gov/pubmed/17400852
46. Allaire C, Taenzer P. History-taking, physical examination and psychological assessment. In: Jarrell JF, Vilos GJ (editors) Consensus guidelines for the management of chronic pelvic pain. J Obstet Gynaecol Can. 2005 Sep;27(9):869-910. [Article in English, French]
http://www.ncbi.nlm.nih.gov/pubmed/19830953
47. Stones RW, Mountfield J. Interventions for treating chronic pelvic pain in women. Cochrane Database Syst Rev. 2000;(4):CD000387.
http://www.ncbi.nlm.nih.gov/pubmed/11034686
48. Cheong YC, Smotra G, Farquhar C. Non surgical interventions for the management of chronic pelvic pain. Protocol. Cochrane Library 2010; issue 11.
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008797/abstract
49. Bordman R, Jackson B. Below the belt. Approach to chronic pelvic pain. Can Fam Physician. 2006 Dec;52(12):1556-62.
http://www.ncbi.nlm.nih.gov/pubmed/17279236
50. Haugstad GK, Haugstad TS, Kirste UM, et al. Mensendieck somatocognitive therapy as treatment approach to chronic pelvic pain: Results of a randomized controlled intervention study. Am J Obstet Gynecol. 2006 May;194(5):1303-10.
http://www.ncbi.nlm.nih.gov/pubmed/16647914

51. Morley SJ, Eccleston C, Williams ACdeC. Systematic review and meta-analysis of randomised controlled trials of cognitive behaviour therapy and behaviour therapy for chronic pain in adults, excluding headache. Pain. 1999 Mar;80(1-2):1-13. http://www.ncbi.nlm.nih.gov/pubmed/10204712
52. Farquhar CM, Rogers V, Franks S, et al. A randomized controlled trial of medroxyprogesterone acetate and psychotherapy for the treatment of pelvic congestion. Br J Obstet Gynaecol. 1989 Oct;96(10):1153-62. http://www.ncbi.nlm.nih.gov/pubmed/2531611
53. Norman SA, Lumley MA, Dooley JA, et al. For whom does it work? Moderators of the effects of written emotional disclosure in a randomized trial among women with chronic pelvic pain. Psychosom Med. 2004 Mar-Apr;66(2):174-83. http://www.ncbi.nlm.nih.gov/pubmed/15039501
54. Fenton BW, Palmieri PA, Boggio P, et al. A preliminary study of transcranial direct current stimulation for the treatment of refractory pelvic pain. Brain Stimul. 2009 Apr;2(2):103-7. http://www.ncbi.nlm.nih.gov/pubmed/20633407

9. PELVIC FLOOR FUNCTION AND CHRONIC PELVIC PAIN

9.1 Introduction

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

9.2 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. 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. Contraction of the pelvic floor muscles results in inward movement of the perineum and upward movement of the pelvic organs. In many situations, other muscles such as the abdominal, adductor and 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 stools. Contractions also form a defence against introduction of foreign objects into the anus or vagina, and in women, they can protect against sexual penetration. Additionally, detrusor muscle inhibition occurs in parallel with pelvic floor muscle contraction. Pelvic floor muscle contractions play an important role in sexual function. During the arousal phase, pelvic floor muscle contractions are used to increase vasocongestion.

During the final phase of the sexual response cycle, a series of involuntary contractions is associated with the physical sensations of orgasm. 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. Relaxation of the pelvic floor muscles is needed for voiding, defecation and for sexual intercourse. The muscles of the pelvic floor are integrated in the total muscular girdle of the pelvis, yielding the stability needed for bearing the trunk. Instability in its turn leads to compensatory pelvic floor muscle (over) activity.

9.3 Dysfunction

Pelvic floor dysfunction should be classified according to “The standardisation of terminology of pelvic floor muscle function and dysfunction” (1). This is an international multidisciplinary report from the International Continence Society. By palpation of the pelvic floor muscles, the contraction and relaxation are qualified. Voluntary contraction can be absent, weak, normal or strong, and voluntary relaxation can be absent, partial or complete. 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.

Normal pelvic floor muscles relax during urination and contract during coughing. Overactive pelvic floor muscles do not relax during micturition, defecation or during sex and cause dysfunctional voiding, overactive bladder, constipation and dyspareunia (2). Underactive pelvic floor muscles do not contract sufficiently to keep the patient dry. Non-functioning pelvic floor muscles do not show any activity whatsoever and can cause every type of pelvic organ dysfunction.

Overactivity tends to develop over a protracted period, with many causes. A psychological mechanism that is thought to play a role is that contraction of the pelvic floor muscles closes some of the exits of the body (anus and vagina), and helps to keep urine and stool inside. It gives women a defence mechanism against unwanted vaginal penetration of any type. The pelvic floor muscles also help to postpone micturition, which can be of benefit in a social or working environment. In summary, the pelvic floor muscles assist in adaptation to different situations in life.

9.4 Pelvic floor muscles and myofascial pain

Chronic pelvic pain can simply be a form of myalgia, due to misuse of muscles, in this case, the pelvic floor muscles. Studies in the field of chronic prostatitis support the idea that patients with CPP have more muscle spasm and increased muscle tone and pain when palpating the pelvic floor muscles (3). Muscle relaxation can diminish spasm and pain (4). Repeated or chronic muscular overload can activate trigger points in the muscle. A report from the Chronic Prostatitis Cohort Study showed that 51% of patients with prostatitis and only 7% of controls had any muscle tenderness. Tenderness in the pelvic floor muscles was only found in the CPP group (5).

9.4.1 ***Muscular aspects***

The relationship between muscular dysfunction (especially overactivity) and pelvic pain has been found in several studies. Rectal pain treated with pelvic floor muscle therapy is only relieved when patients learn to relax their pelvic floor muscles (6). The vast majority (92.2%) of men visiting a tertiary centre for pelvic pain had dysfunction of the pelvic floor muscles. This finding was true regardless of evidence of inflammation (prostatitis or cystitis) (7). This relationship has been found in chronic prostatitis (8), BPS (9) and vulvar pain (10). Dysfunction of the pelvic floor directly affects function of the pelvic viscera and vice versa. Both systems can act as the primary signal to the spinal cord, with a cascade of reactions ascending to the CNS as a result. The muscle itself ends up with a diminished length, leading to restrictions even when it is in a relaxed state.

9.4.2 ***Neurological aspects***

In 1999, the first ideas about the neurological aspects of the pelvic floor muscles in relation to CPP were published. The probability of CNS breakdown in the regulation of pelvic floor function was suggested as a mechanism for development of CPP. Of the patients presenting with pelvic pain, 88% had poor to absent pelvic floor function (11). Basic studies on the role of neurogenic inflammation have also elucidated some important phenomena. Irritation of the prostate, bladder and pelvic floor muscles results in expression of C-fos-positive cells in the CNS. There appears to be convergence of afferent information onto central pathways. Once the central changes have become established, they become independent of the peripheral input that initiated them (12).

9.4.3 ***Myofascial trigger points***

Repeated or chronic muscular overload can activate trigger points in the muscle. Trigger points are defined as hyperirritable spots within a taut band. Other criteria for trigger points are: recognition of the pain as ‘familiar’, and pain on stretching the muscle. Apart from pain, trigger points prevent full lengthening of the muscle, thereby restricting the range of movement. Pain as a result of these trigger points is aggravated by specific movements and alleviated by certain positions. Positions and movements in which the shortened muscle is stretched are painful. Patients know which activities and postures influence pain. Trigger points can be located within the pelvic floor muscles and in adjacent muscles such as the abdominal, gluteal and ileopsoas muscles.

Pain is aggravated by pressure on the trigger point (e.g., pain related to sexual intercourse). Pain also worsens after sustained or repeated contractions (e.g., pain related to voiding or defecation).

9.5 Diagnostics of pelvic floor muscle function

Diagnosing pelvic floor muscle function in patients with CPP starts by taking a complete functional history of the pelvic organ function. The following items certainly should be addressed: lower urinary tract function, anorectal function, sexual function, gynaecological items, presence of pain and psycho-social aspects.

9.5.1 ***Physical examination***

After taking a history, physical examination should be done. Special attention must be paid to the abdominal, inguinal and genital areas, but also to the pelvic alignment. The patient should be asked to point at the location of maximal pain and at the secondary pain points. Palpation of the abdomen with special attention to the muscles may yield pain points that are important for making a treatment plan. A vaginal or rectal examination should be performed to assess the function of the pelvic floor muscles, according to the ICS report. This assessment has been tested and shows satisfactory face validity and intra-observer reliability. It can therefore be considered suitable for use in clinical practice (13). Rectal examination is a good way to test the pelvic floor muscle function in men (14).

9.5.2 ***Electromyography and pressure measurement (EMG)***

Additional examination can be done using electromyography. This is preferably done using an intravaginal or intra-anal probe. This measures the electrical activity of the pelvic floor muscles as a group. It does not reveal anything about the efficacy of the contraction or relaxation. There is good correlation between digital palpation and intravaginal surface EMG (15). To measure the effect of pelvic floor muscle contraction, a pressure probe can be used. The measurement of anal pressure is reliable (16). Performance of EMG in different positions gives more insight into the properties of the pelvic floor. Electromyography is one of the most used input methods for biofeedback. Intraluminal pressure can also be used for this purpose.

9.5.3 ***Imaging***

Anatomical imaging of the pelvic floor muscles can be done using MRI. It is still debatable whether MRI can be of help in diagnosing pudendal entrapment. Functional imaging can be done using techniques such as video-urodynamics (pelvic floor muscles in relation to bladder function) or defecography (pelvic floor muscles in relation to defecation). The reason for this is to exclude disease-specific pain. Repeated imaging studies may be detrimental for the patient because they emphasise somatic causes of the pain.

9.5.4 ***Myofascial trigger points***

There is no accepted reference standard for the diagnosis of trigger points. Data on the reliability of physical examination are conflicting. Reliability is relatively good for tenderness and for recognisable referred pain. It is lower for taut band recognition and local twitch response. The reliability improves when examination is done by experts, who are specially trained in diagnosing trigger points. Other techniques are used for diagnosing trigger points but none have become standard. Among these are imaging techniques and EMG (17).

In a cohort study of 72 men with CPP, the relationship between the locations of the trigger point and the referred pain was examined. Ninety percent of the patients showed tenderness in the puborectalis muscle and 55% in the abdominal wall muscles. Of the patients in whom trigger points were found in the puborectalis, 93% reported pain in the penis and 57% in the suprapubic region. Patients with trigger points in the abdominal muscles reported pain in the penis (74%), perineum (65%) and rectum (46%) (18).

9.6 Treatment of pelvic floor muscle pain

Treating pelvic floor overactivity and myofascial trigger points should be considered in the management of CPP. Treatment should be done by specialised physiotherapists who are trained not only in the musculoskeletal aspects of pain, but also in the psychological mechanisms and the role of the CNS in chronic pain.

9.6.1 ***Pelvic floor muscle exercise***

For patients with CPP and dysfunction of the pelvic floor muscles, it is very helpful to learn how to relax the muscles when the pain starts. By doing this, the circle of pain-spasm-pain can be interrupted. In the case of shortened muscles, relaxation alone is not enough. Stretching of the muscle is mandatory to regain length and function. Studies on physical therapy for pelvic floor pain syndrome have been sparse. A single blinded RCT with myofascial physical therapy and general massage was carried out in patients with prostate or bladder pain. The global response rate to treatment with massage was significantly better in the prostate than in the bladder pain group (57% vs. 21%). In the prostate pain group, there was no difference between the two

treatment arms. In the bladder pain group, myofascial treatment did significantly better than the massage. Massage only improved complaints in the prostate pain group. The fact that the prostate pain group consisted of only men is mentioned as a possible confounding factor (19).

9.6.2 ***Biofeedback and electrostimulation***

Biofeedback can be helpful in the treatment of pelvic floor pain in the process of recognising the action of the muscles. Visualising the action of the pelvic floor muscles by using biofeedback is an eye opener to many patients. Biofeedback should always be used in consultation with the patient. Special care should be taken when there is a history of negative physical or sexual experiences. The numbers of patients in most studies concerning biofeedback have been small but the results are promising. In a cohort study, 31 patients with CPPS participating in a pelvic floor biofeedback re-education programme were followed. The mean chronic prostatitis symptom index decreased from 23.6 to 11.4. They also measured the pelvic floor muscle activity by EMG using an anal probe. The resting amplitude was taken as a parameter for the ability to relax the pelvic floor muscles. This parameter was 4.9 μV at the start and 1.7 μV at the end of the treatment, so the relaxation improved markedly. There was also a correlation between the decline in EMG values and improvement in prostatitis symptom score (20).

In a study among patients with levator ani syndrome, biofeedback was found to be the most effective therapy. Other modalities used were electrostimulation and massage. Adequate relief was reported by 87% in the biofeedback group, 45% for electrostimulation, and 22% for massage (6). A review on biofeedback in pelvic floor dysfunction has shown that biofeedback is better than placebo or sham treatment. An odds ratio of 5.8 favouring biofeedback has been calculated based on three studies (21).

9.6.3 ***Myofascial trigger point release***

The treatment of myofascial trigger points has different options. There are three groups of treatment: (1) manual therapy: pressure and release, compression, spray and stretch; (2) dry needling: putting a solid filiform needle directly in the trigger point, repeatedly and in an up and down pecking motion; and (3) wet needling: injection of lidocaine or botulinum toxin into the trigger point. The evidence for all the different treatments is weak. In most studies, no significant difference between these techniques has been found. One problem is that most of the studies were small and heterogeneous with regard to the patients and methods. This is especially true for comparing any technique with sham or placebo treatment. For manual therapy, central trigger points are treated by stretching the muscle because this inactivates it. Trigger points lying in the attachment of the muscle to the bone are treated using direct manual therapy.

Other well-known techniques such as biofeedback and neuromuscular stimulation have been used in the treatment of trigger points. There is no evidence that manual techniques are more effective than no treatment (22). In most studies of dry needling, it has been compared with wet needling. Different systematic reviews have come to the conclusion that, although there is an effect of needling on pain, it is neither supported nor refuted that this effect is better than placebo (23). Other reviews have concluded that the same is true for the difference between dry and wet needling (24,25).

9.6.4 ***Botulinum A toxin***

Botulinum A toxin (BTX-A) is an inhibitor of acetylcholine release at the neuromuscular junction and has a paralysing effect on striated muscles. BTX-A has been injected into trigger points. It is more expensive than lidocaine and has not been proven to be more effective (26). Reviews do not support the injection of BTX-A into trigger points (27).

Pelvic floor muscle overactivity plays a role in CPP. BTX-A, as a muscle relaxant, can be used to reduce the resting pressure in the pelvic floor muscles. In women with high resting pressure in the pelvic floor muscles, it has been found that BTX-A lowers this pressure significantly. The magnitude of reduction was significantly higher than that in the placebo group. On the pain score (VAS), no intergroup differences were found in this relatively small randomised study (28). BTX-A can also be injected at the sphincter level to improve urination or defecation. Relaxation of the urethral sphincter alleviates the bladder problems and secondarily the spasm. In a cohort study of 13 patients with CPP, BTX-A was injected into the external urethral sphincter. Subjectively, 11 patients reported a substantial change in pain symptoms, from 7.2 to 1.6 on a visual analogue scale (29).

9.6.5 *Pain management*

The physiotherapist is part of the pain management team, together with the pain doctor and the psychologist. The therapeutic options for physiotherapists may not be the same in every country. Physiotherapists can either specifically treat the pathology of the pelvic floor muscles, or more generally treat myofascial pain if it is part of the pelvic pain syndrome.

9.7 Conclusions and recommendations: pelvic floor function

Conclusions	LE
The ICS classification is suitable for clinical practice.	2a
Overactivity of the pelvic floor muscles is related to chronic pelvic pain, prostate, bladder and vulvar pain.	2a
The overactivity of the pelvic floor muscles is an input to the central nervous system causing central sensitisation.	2b
There is no accepted standard for diagnosing myofascial trigger points.	2a
There is a relation between the location of trigger point and the region where the pain is perceived.	3
Myofascial treatment is effective in prostate- and bladder pain syndrome.	1b
Biofeedback improves the outcome of myofascial therapy for pelvic floor dysfunction.	1a
Trigger point release is effective in treating muscle and referred pain, but there is no preference from one method over another.	1a

Recommendations	GR
The use of the ICS classification on pelvic floor muscle function and dysfunction is recommended.	A
In patients with chronic pelvic pain syndrome it is recommended to actively look for the presence of myofascial trigger points.	B
In patients with chronic pelvic pain syndrome it is recommended to apply pelvic floor muscle treatment as first line treatment.	B
Apply pelvic floor muscle treatment as first line treatment in patients with chronic pelvic pain syndrome.	A
When myofascial trigger points are found treatment by pressure or needling is recommended.	A

Figure 17: Assessment and treatment pelvic floor function

Assessment	Treatment	
Palpation of the muscles	Grade A recommended	Use the International Continence Society classification of dysfunction
Testing of pelvic floor function		Use biofeedback in combination with muscle exercises
Pelvic floor muscle EMG		Treat myofascial trigger points using pressure or needling
Test for myofascial trigger points	Grade B recommended	Look actively for the presence of myofascial trigger points
History of all the involved organs		Apply pelvic floor muscle therapy as first line treatment
Standardised questionnaires	Other comments	The role and options of a physiotherapist may difffer between countries

9.8 References

1. Messelink EJ, Benson T, Berghmans B et al. Standardisation of terminology of pelvic floor muscle function and dysfunction: report from the pelvic floor clinical assessment group of the International Continence Society. Neurourol Urodyn. 2005;24(4):374-80. http://www.ncbi.nlm.nih.gov/pubmed/15977259
2. Messelink EJ. The overactive bladder and the role of the pelvic floor muscles. BJU Int 1999 Mar;83Suppl 2:31-5. http://www.ncbi.nlm.nih.gov/pubmed/10210602

3. Hetric DC, Ciol MA, Rothman I, et al. Musculoskeletal dysfunction in men with chronic pelvic pain syndroime type III: a case-control study. J Urol 2003 Sep;170(3):828-31.
http://www.ncbi.nlm.nih.gov/pubmed/12913709
4. Clemens JQ, Nadler RB, Schaeffer AJ, et al. Biofeedback, pelvic floor re-education, and bladder training for male chronic pelvic pain syndrome. Urology 2000 Dec 20;56(6):951-5.
http://www.ncbi.nlm.nih.gov/pubmed/11113739
5. Shoskes DA, Berger R, Elmi A.,et al. Muscle tenderness in Men with Chronic Prostatitis/Chronic Pelvic Pain syndrome: The Chronic Prostatitis Cohort Study. J Urol 2008 Feb;179(2):556-60.
http://www.ncbi.nlm.nih.gov/pubmed/18082223
6. Chiarioni G, Nardo A, Vantini I, et al. Biofeedback Is Superior to Electrogalvanic Stimulation and Massage for Treatment of Levator Ani Syndrome. Gastroenterology. 2010 Apr;138(4):1321-9.
http://www.ncbi.nlm.nih.gov/pubmed/20044997
7. Zermann DH, Ishigooka M, Doggweiler R, Schmidt RA. Chronic prostatitis: a myofascial pain syndrome? Infect Urol 1999;12:84-6.
http://www.prostatitis.org/myofascial.html
8. Shoskes DA, Berger R, Elmi A, et al. Muscle tenderness in Men with Chronic Prostatitis/Chronic Pelvic Pain syndrome: The Chronic Prostatitis Cohort Study. J Urol 2008 Feb;179(2):556-60.
http://www.ncbi.nlm.nih.gov/pubmed/18082223
9. Peters KM. Prevalence of Pelvic floor dysfunction in patients with Interstitial Cystitis. Urology 2007 Jul;70(1):16-8.
http://www.ncbi.nlm.nih.gov/pubmed/17656199
10. Reissing ED, Brown C, Lord MJ, et al. Pelvic floor muscle functioning in women with vulvar vestibulitis syndrome. J Psychosom Obstet Gynaecol. 2005 Jun;26(2):107-13.
http://www.ncbi.nlm.nih.gov/pubmed/16050536
11. Zermann DH, Ishigooka M, Doggweiler R, et al. Neurourological insights into the etiology of genitourinary pain in men. J Urol 1999 Mar;161(3):903-8.
http://www.ncbi.nlm.nih.gov/pubmed/10022711
12. Ishigooka M, Zermann DH, Doggweiler, et al. Similarity of distributions of spinal C-fos and plasma extravasation after acute chemical irritation of the bladder and the prostate. J Urol 2000 Nov;164(5):1751-6.
http://www.ncbi.nlm.nih.gov/pubmed/11025764
13. Slieker-ten Hove MC, Pool-Goudzwaard AL, Eijkemans MJ, et al. Face validity and reliability of the first digital assessment scheme of pelvic floor muscle function conform the new standardized terminology of the International Continence Society. Neurourol Urodyn. 2009;28(4):295-300.
http://www.ncbi.nlm.nih.gov/pubmed/19090583
14. Wydaele JJ, Van Eetvelde B. Reproducibility of digital testing of the pelvic floor muscles in men. Arch Phys Med Rehabil. 1996 Nov;77(11):1179-81.
http://www.ncbi.nlm.nih.gov/pubmed/8931532
15. Romanzi LJ, Polaneczky M, Glazer HI. Simple test of pelvic muscle contraction during pelvic examination: correlation to surface electromyography. Neurourol Urodyn. 1999;18(6):603-12.
http://www.ncbi.nlm.nih.gov/pubmed/10529708
16. Dorey G, Swinkels A. Test Retest Reliability of Anal Pressure Measurements in Men with Erectile Dysfunction. Urol Nurs. 2003 Jun;23(3):204-12.
http://www.ncbi.nlm.nih.gov/pubmed/12861738
17. Lucas N, Macaskill P, Irwig L, et al. Reliability of physical examination for diagnosis of myofascial trigger points: a systematic review of the literature. Clin J Pain 2009 Jan;25(1):80-9.
http://www.ncbi.nlm.nih.gov/pubmed/19158550
18. Anderson RU, Sawyer T, Wise D, et al. Painful myofascial trigger points and pain sites in men with chronic prostatitis/chronic pelvic pain syndrome. J Urol 2009 Dec;182(6):2753-8.
http://www.ncbi.nlm.nih.gov/pubmed/19837420
19. FitzGerald MP, Anderson RU, Potts J, et al. Randomized multicenter feasibility trial of myofascial physical therapy for the treatment of urological chronic pelvic pain syndromes. J Urol 2009 Aug;182(2):570-80.
http://www.ncbi.nlm.nih.gov/pubmed/19535099
20. Cornel EB, van Haarst EP, Schaarserg RW, et al. The effect of biofeedback physical therapy in men with chronic pelvic pain syndrome type III. Eur Urol. 2005 May;47(5):607-11.
http://www.ncbi.nlm.nih.gov/pubmed/15826751
21. Koh CE, Young CJ, Young JM, et al. Systematic review of randomized controlled trials of the effectiveness of biofeedback for pelvic floor dysfunction. Br J Surg. 2008 Sep;95(9):1079-87.
http://www.ncbi.nlm.nih.gov/pubmed/18655219

22. de las Penas CF, Sohrbeck Campo M, Fernandez Carnero J, et al. Manual therapies in myofascial trigger point treatment: a systematic review.
23. Tough EA, White AR, Cummings TM, et al. Acupuncture and dry needling in the management of myofascial trigger point pain: a systematic review and meta-analysis of randomised controlled trials. Eur J Pain 2009 Jan;13(1):3-10. http://www.ncbi.nlm.nih.gov/pubmed/18395479
24. Cummings TM, White AR. Needling therapies in the management of myofascial trigger point pain: a systematic review. Arch Phys Med Rehabil. 2001 Jul;82(7):986-92. http://www.ncbi.nlm.nih.gov/pubmed/11441390
25. Scott NA, Guo B, Barton PM, et al. Trigger point injections for chronic non-malignant musculoskeletal pain: a systematic review. Pain Med. 2009 Jan;10(1):54-69. http://www.ncbi.nlm.nih.gov/pubmed/18992040
26. Kamanli A, Kaya A, Ardicoglu O, et al. Comparison of lidocaine injection, botulinum toxin injection, and dry needling to trigger points in myofascial pain syndrome. Rheumatol Int. 2005 Oct;25(8):604-11. http://www.ncbi.nlm.nih.gov/pubmed/15372199
27. Ho KY, Tan KH. Botulinum toxin A for myofascial trigger point injection: a qualitative systematic review. Eur J Pain 2007 Jul;11(5):519-27. http://www.ncbi.nlm.nih.gov/pubmed/17071119
28. Abbott JA, Jarvis SK, Lyons SD, et al. Botulinum toxin type A for chronic pain and pelvic floor spasm in women: a randomized controlled trial. Obstet Gynecol. 2006 Oct;108(4):915-23. http://www.ncbi.nlm.nih.gov/pubmed/17012454
29. Zermann D, Ishigooka M, Schubert J, et al. Perisphincteric injection of botulinum toxin type A. A treatment option for patients with chronic prostatic pain? Eur Urol. 2000 Oct;38(4):393-9. http://www.ncbi.nlm.nih.gov/pubmed/11025376

10. GENERAL TREATMENT OF CHRONIC PELVIC PAIN

10.1 Introduction

Chronic pelvic pain is well defined and involves multiple mechanisms as described in previous chapters. The management requires a holistic approach with biological, psychological and social components. This chapter looks solely at general treatments and should be used as part of a management plan including the interventions suggested in the specific chapters.

Despite the developments in basic science, there has not been the same in pharmacological intervention. It is recognised that there are often central mechanisms involved in CPP. This chapter looks at general treatments for pain (both peripheral and central) and not the specific treatments mentioned in the Chapters 2 and 6.

Despite the frequency of CPP, relatively few studies have specifically looked at the medications used in CPP patients (1). As a result, a wider look at the literature has been undertaken, including the agents used for central and neuropathic pain. Further specific research is required in this group of patients.

The agents concerned are divided for ease of description. Combinations often provide a greater benefit than individual agents. They may also allow lower dosages of each agent and thus minimise the side effects.

The aim of using these drugs is to allow patients to improve their QoL. This is best measured by assessing their function as well as pain severity. If the addition of these agents does not allow this, then they should be withdrawn. Unfortunately, the failure of one agent to provide benefit does not mean that there is an alternative. If the benefit is limited by side effects, then the lowest effective dose should be found (by dose titration). In some circumstances, patients can tolerate a higher level of pain and have fewer side effects.

If the use of simple analgesics fails to provide adequate benefit, then one should consider using the neuropathic agents, and if there is no improvement, consider involving a specialist pain management centre with an interest in pelvic pain.

10.2 Simple analgesics

Paracetamol (acetaminophen)

Paracetamol is a well-tolerated analgesic in a class of its own. This is an antipyretic analgesic with a central

mechanism of action (2). It is often available over the counter without prescription. There is evidence that paracetamol is beneficial in managing somatic and arthritic pain. (3-5). There is little evidence for its use in CPP, but it should be considered if it has not already been tried.

Non-steroidal anti-inflammatory agents (NSAIDs)
This is a group of agents that include salicylic acid. They have had significant publicity over recent years. They are anti-inflammatory, antipyretic analgesics that act by inhibiting the enzyme cyclo-oxygenase (COX). They have a peripheral effect, hence their use in painful conditions involving peripheral or inflammatory mechanisms.

They are commonly used for pelvic pain because many are available over the counter and are usually well tolerated. The evidence for their benefit is often weak or non-existent. It should be remembered that they do have side effects, which may be significant. There is no good evidence to suggest one NSAID over another for pelvic pain.

For pelvic pain in which inflammatory processes are considered to be involved, such as dysmenorrhoea (6), NSAIDs are more effective than placebo and paracetamol, but with a higher incidence of side effects. For pelvic pain in which central mechanisms may be incriminated, such as endometriosis (7), then the evidence is lacking for NSAIDs despite their common use.

Guidelines for use of NSAIDs and COX-2 selective agents have been developed. They have more side effects than paracetamol, including indigestion, headaches and drowsiness.

At a practical level, NSAIDs could be considered as analgesics for patients with pelvic pain. They should be tried (having regard for the cautions and contraindications for use) and the patient reviewed for improvement in function as well as analgesia. If this is not achieved, or there are side effects, then the NSAID should be stopped.

Neuropathic analgesics
This is a group of agents that are not simple analgesics but are used to modulate neuropathic or centrally mediated pain. There are several classes used with a recognised benefit in pain medicine. They are taken on a regular basis rather than as required. They all have side effects that limit their use in some patients.

In the UK, the National Institute for Health and Clinical Excellence (NICE) has reviewed the pharmacological management of neuropathic pain (8). There is further guidance in progress for the management of neuropathic pain in the non-specialist setting.

Not all the agents have a licence for use in pain management but there is a history and evidence to demonstrate their benefit. The evidence for treatment of CPP is lacking but is present for other painful conditions. For this chapter, most of the evidence is from non-pelvic pain sources. The general method for using these agents is by titrating the dose against benefit and side effects. The aim is for patients to have an improvement in their QoL, which is often best assessed by alterations in their function. Side effects frequently limit the use of these agents. It is common to use these agents in combinations but studies comparing different agents against each other or in combination are lacking.

*10.2.1 **Antidepressants***

10.2.1.1 Tricyclic antidepressants

This is a group of drugs with multiple mechanisms of action. They have a long history of use in pain medicine and have been subjected to a Cochrane review (9). This suggests that they are effective for neuropathic pain with numbers needed to treat (NNT) of approximately three.

Amitriptyline is the most commonly used member of this group at doses from 10 to 75 mg/day (sometimes rising to 150 mg/day). This is titrated against benefit or side effects and taken at night (8). Nortriptyline and imipramine are often used as alternatives.

10.2.1.2 Other antidepressants

Venlafaxine is a serotonin and noradrenalin reuptake inhibiter (SNRI). It does not have a license for managing neuropathic pain but there is evidence of its benefit in chronic pain (8). There are cautions particularly in patients with heart disease. This is a drug best used by those familiar with its use.

Duloxetine is a newer SNRI antidepressant. It is used for depression, urinary stress incontinence and neuropathic pain. There is moderately strong evidence for a benefit in diabetic neuropathy and fibromyalgia at a dose of 60 mg/day (10). Side effects are common and may result in its discontinuation.

Selective serotonin reuptake inhibitors (SSRIs) are antidepressants with fewer side effects. They are effective for depression, but there have been insufficient studies to demonstrate their benefit in pelvic or neuropathic pain (9,11,12).

10.2.2 ***Anticonvulsants***

This group of drugs are commonly used in the management of neuropathic pain. There have been general studies as well as some looking more particularly at pelvic pain. Individual agents have been systematically reviewed. Their use is suggested in the NICE Neuropathic Guidelines (8).

Carbamazepine has a long history of use in neuropathic pain. Evidence exists for its benefit (13). It should be remembered that the trials have tended to be of short duration, showing only moderate benefit. There are side effects; some of which may be serious. With more recently developed agents becoming available, with fewer serious side effects, carbamazepine is no longer a first-choice agent.

Gabapentin is commonly used for neuropathic pain and has been systematically reviewed (14). It provides good quality relief with NNT of approximately six. This is a more conservative estimate than in previous reports. Side effects are common, notably drowsiness, dizziness and peripheral oedema. These effects do limit compliance but are often tolerated by patients. The doses involved were all greater than 1.2 g/day. For upper dose levels, reference should be made to local formularies, and many clinicians do not routinely exceed 2.4 g/day in divided doses (most commonly three times daily).

One study of women with CPP has suggested that gabapentin alone or in combination with amitriptyline provides better analgesia then amitriptyline alone (15).

Pregabalin is another commonly used neuromodulator. There is good evidence for its efficacy in some neuropathic conditions but the NNT varies depending on the condition (16). The dose for benefit is in the range of 300 to 600 mg/day. The same systematic review has found that doses less than 150 mg/day are unlikely to provide benefit. As with gabapentin, side effects are relatively common and may not be tolerated by patients.

Other anticonvulsants are available but not commonly used for managing pain.

10.2.3 ***Other agents***

Other agents can be used in the management of neuropathic pain but are best limited to those that are specialists in the management of pain and familiar with their use. They tend to be considered after the standard options have been exhausted. As with all good pain management, they are used as part of a comprehensive management plan.

Topical capsaicin has been used for neuropathic pain either by repeated low-dose (0.075%) administration or more recently as a single high dose (8%). Topical application (usually to an area of hyperaesthesia or allodynia) is more inconvenient than for other medications, and capsaicin does cause initial heat on application. Skin sensitivity is a limiting factor and may not be well tolerated. A systematic review has suggested there may be benefit in some patients (17). Care should be taken to ensure that unused cream or that washed off the hands following application is not inadvertently transferred to other areas of skin or mucous membranes.

Antipsychotics have been used and despite limited research, a systematic review has suggested that further research should be undertaken on the atypical antipsychotics, which have fewer side effects and are better tolerated than the older antipsychotics (18).

10.3 Opioids

Opioids are used for chronic non-malignant pain and may be beneficial for a small number of patients. Often patients will stop taking oral opioids due to side effects or insufficient analgesia (19).

They should only be used in conjunction with a management plan and with consultation between clinicians experienced in their use. It is suggested that a pain management unit should be involved along with the patient and their primary care physician.

There are well established guidelines for the use of opioids in pain management as well as considering the potential risks (20). There is also information available online for patients (21,22).

Opioid rotation is used in palliative care and to some extent in non-cancer pain. The evidence is clinical, largely anecdotal, or from small trials and is not convincing (23). The rational is that if a patient has significant side effects and inadequate analgesia to one opioid then swapping to another agent may be better tolerated.

There are several agents available in the group. They can be divided into weak (e.g., codeine, dihydrocodeine and tramadol) or strong opioids (e.g., morphine, oxycodone, fentanyl and hydromorphone).

Oral administration is preferable, but if poorly tolerated, a percutaneous (patch) route may have advantages. More invasive approaches are less commonly used and within the realms of specialist units.
Side effects are common and require active management. This is particularly true of constipation with some interesting developments on methods for managing it.

There is a growing understanding of opioid-induced hyperalgesia; a situation in which patients taking opioids, paradoxically, become more sensitive to painful stimuli (24). This is another reason for these drugs to be used in a controlled fashion for long-term management of non-malignant pain.

10.3.1 ***Recommendations for use of opioids in chronic/non-acute urogenital pain***

Recommendations
All other reasonable treatments must have been tried and failed.
The decision to instigate long-term opioid therapy should be made by an appropriately trained specialist in consultation with another physician (including the patients and their family doctor).
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.
The patient should undergo a trial of opioids.
The dose required needs to be calculated by careful titration.
The patient should be made aware (and possibly give written consent): • That opioids are strong drugs and associated with addiction and dependency. • Opioids will normally only be prescribed from one source (preferably the family doctor). • The drugs will be prescribed for fixed periods of time and a new prescription will not be available until the end of that period. • The patient may 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. • Inappropriate aggressive behaviour associated with demanding the drug will not be accepted. • Hospital specialist review will normally occur at least once a year. • The patient may be requested to attend a psychiatric/psychological review. 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.
Morphine is the first-line opioid, 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.

10.3.2 ***Morphine***

There is no compelling evidence that one opioid is better than another. Morphine is the traditional gold standard and the opioid with which many physicians are most familiar. The aim is to use a slow or sustained release preparation starting with a low dose and titrating the dose every 3 days to 1 week against improvement in both function and pain. Side effects should also be monitored and managed accordingly. Particular attention should be paid to the management of constipation.

10.3.3 ***Other opioid agents***

There are a variety of agents available and some are mentioned below, giving an idea of the options available.

Transdermal fentanyl may be considered when oral preparations are restricted (e.g., iliostomy). It may also be beneficial when there are intolerable side effects from other opioids.

Methadone has a long record of use as an opioid. There is a theoretical advantage of benefit with its N-methyl-D-aspartate receptor (NMDA) antagonist activity. This may be particularly relevant in neuropathic pain (25).

Oxycodone may have greater efficacy than morphine in some situations, such as hyperalgesic states including visceral pain (26).

Analgesics with a dual mode of action may have a role in the management of chronic pain. Tramadol is an established analgesic with dual effects on opioid receptors and serotonin release. More recently, a new agent, tapentadol, has been released with opioid action and noradrenalin reuptake inhibition. It is too early to assess its real value in the armamentarium for pain management.

10.4 Nerve blocks

Nerve blocks for pain management are usually carried out by specialists in pain medicine and as part of a broader management plan (27). They may have a diagnostic or therapeutic role.

Textbooks have been written on the subject and practitioners using them should be trained in appropriate patient selection, indications, risks and benefits. Many such interventions also require understanding and expertise in using imaging techniques to perform the blocks accurately.

Diagnostic blocks can be difficult to interpret due to the complex nature of the mechanisms underlying the painful condition or syndrome. Sustained but limited benefit may lead to more permanent procedures (e.g., neurolytic block or radiofrequency procedures). Neurolytic blocks in particular should only be considered by practitioners experienced in their use and with the full understanding of the patient because complications can be disastrous.

There is a weak evidence base for these interventions for chronic non-malignant pain.

10.5 Transcutaneous electrical nerve stimulation (TENS)

Despite the popularity of TENS and the number of trials undertaken, a systematic review has been unable to provide good evidence for or against its use in the management of chronic pain (28). It is clear that further more rigorous trials should be undertaken to provide some clarity for a commonly used intervention.

10.6 Neuromodulation in pelvic pain syndromes

The role of neuromodulation in the management of pelvic pain should only be considered by specialists in pelvic pain management. These techniques are only used as part of a broader management plan and require regular follow-up.

The research base is developing and the techniques broadening [e.g., spinal cord stimulation (SCS), sacral root stimulation, dorsal root ganglion stimulation or peripheral nerve stimulation]. These are expensive interventions and thus many of the patients involved are refractory to other therapies. It is thus inappropriate to provide a detailed review of these techniques for this publication.

In the UK, guidance has been published for SCS in neuropathic pain (29). This emphasises the comments above. This guidance suggests a trial period of stimulation before full implementation.

Neuromodulation is still finding its role in pelvic pain management. There has been growing evidence in small case series or pilot studies, but more detailed research is required (30). Its role in overactive bladder and faecal incontinence is more robust but is limited for pain.

10.7 Summary

Chronic pelvic pain is a common complaint that is well defined and involves multiple mechanisms. Some of the conditions have clear management pathways but many do not. In these CPP syndromes, a holistic multidisciplinary team approach is required with active patient involvement.

This chapter focuses on general treatment of CPP, mainly drug therapy, and comments on other more invasive techniques. The latter are used in combination with other modalities. Many are aimed at management of neuropathic pain or conditions in which central mechanisms are implicated.

At this stage in management, the involvement of trained clinicians with expertise in chronic pain management should be considered. Centres with a particular interest in pelvic pain do exist and involve clinicians from several specialties along with other health care professionals (e.g., physiotherapy, psychology, nursing and occupational therapy).

With any of the agents above, the aim is to assess pain relief, improvement in function, and side effects. This should be done regularly while titrating and optimising drug dose. If there is no benefit, then the drug should be withdrawn.

Neuropathic agents are frequently used and often in combination. There is significant inter-patient variability in effect. Use is often limited by side effects that may be worse than any pain reduction.

Opioid drugs are used in this group of patients. Their role is limited and they should only be started in consultation with all parties involved (including the patient's family practitioner). National guidelines exist and should be followed. There is growing understanding of the limitations of opioid use, and more recently, the paradoxical situation of opioid-induced hyperalgesia.

10.8 Recommendations for the medical and interventional treatment of CPP

Agent	Pain Type	LE	GR	Comment
Paracetamol	Somatic pain	1a	A	Evidence based on arthritic pain with good benefit
NSAIDs	Pelvic pain with inflammatory process (e.g. dysmenorrhoea)	1a	A	Good evidence for their use
Antidepressants including tricyclic antidepressants, duloxetine and venlafaxine	Neuropathic pain	1a	A	Effective. No specific evidence for CPP
Anticonvulsants gabapentin, pregabalin	Neuropathic pain, fibromyalgia	1a	A	Effective
Gabapentin	Women with CPP	2b	B	Effective
Topical capsaicin	Neuropathic pain	1a	A	Some evidence of benefit
Opioids	Chronic non-malignant pain	1a	A	Beneficial in a small number of patients
Nerve blocks		3	C	Have a role as part of a broad management plan
TENS		1b	B	There is no good evidence for or against the use of TENS. Data covered chronic pain not just CPP and was insufficient regarding long-term treatment effects.
Neuromodulation	Pelvic pain	3	C	Role developing with increasing research

TENS = transcutaneous electrical nerve stimulation; CPP = chronic pelvic pain

Figure 18: Algorithm for general analgesic treatment of chronic pelvic pain

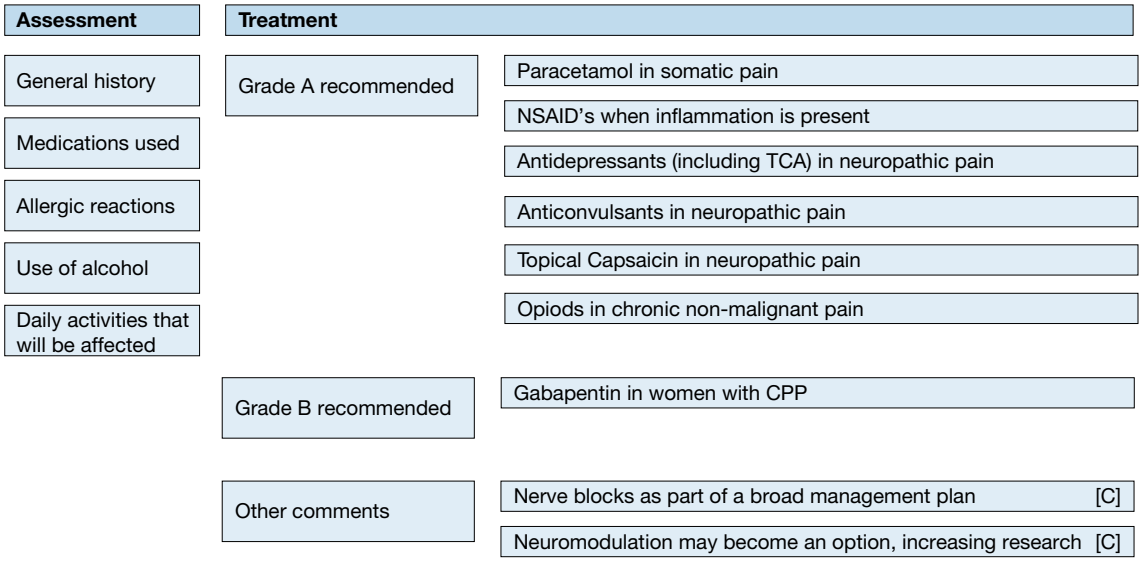
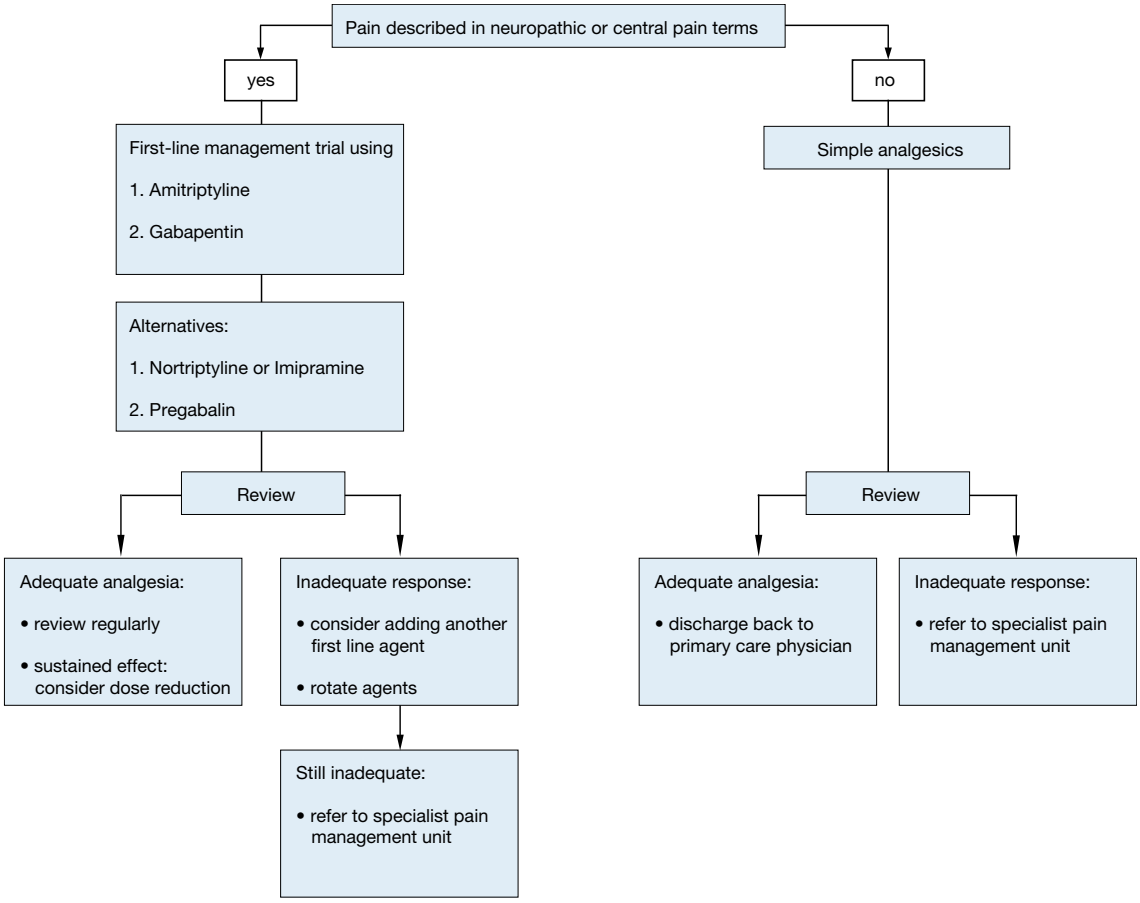


Figure 19: General management algorithm



10.9 References

1 Stones W, Cheong Ying C, Howard Fred M, et al. Interventions for treating chronic pelvic pain in women. Cochrane database of systematic reviews [serial on the Internet]. 2005; (2). http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD000387/frame.html.

2 Remy C, Marret E, Bonnet F. State of the art of paracetamol in acute pain therapy.Curr Opin Anaesthesiol. 2006 Oct;19(5):562-5. http://www.ncbi.nlm.nih.gov/pubmed/16960492

3 Roelofs PD, Deyo RA, Koes BW, et al. Non-steroidal anti-inflammatory drugs for low back pain. Spine (Phila Pa 1976). 2008 Jul 15;33(16):1766-74. http://www.ncbi.nlm.nih.gov/pubmed/18580547

4 Towheed T, Maxwell L, Judd MG, et al. Acetaminophen for osteoarthritis. Cochrane Cochrane Database Syst Rev. 2006 Jan 25;(1):CD004257. http://www.ncbi.nlm.nih.gov/pubmed/16437479

5 Altman RD, Zinsenheim JR, Temple AR, et al. Three-month efficacy and safety of acetaminophen extended-release for osteoarthritis pain of the hip or knee: a randomized, double-blind, placebo-controlled study. Osteoarthritis Cartilage. 2007 Apr;15(4):454-61. http://www.ncbi.nlm.nih.gov/pubmed/17142063

6. Marjoribanks J, Proctor M, Farquhar C, et al. Nonsteroidal anti-inflammatory drugs for dysmenorrhoea. Cochrane Database Syst Rev. 2010 Jan;(1):CD001751. http://www.ncbi.nlm.nih.gov/pubmed/20091521

7. Allen C, Hopewell S, Prentice A, et al. Nonsteroidal anti-inflammatory drugs for pain in women with endometriosis. Cochrane Database Syst Rev. 2009 Apr;(2):CD004753. http://www.ncbi.nlm.nih.gov/pubmed/19370608

8. NICE clinical guideline 96. Neuropathic pain. The pharmacological management of neuropathic pain in adults in non-specialist settings. http://guidance.nice.org.uk/CG96

9. Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. Cochrane Database Syst Rev. 2007 Oct 17;(4):CD005454.
http://www.ncbi.nlm.nih.gov/pubmed/17943857
10. Lunn MP, Hughes RA, Wiffen PJ. Duloxetine for treating painful neuropathy or chronic pain. Cochrane Database Syst Rev. 2009 Oct;(4):CD007115.
http://www.ncbi.nlm.nih.gov/pubmed/19821395
11. Lee RA, West RM, Wilson JD. The response to sertraline in men with chronic pelvic pain syndrome. Sex Transm Infect. 2005 Apr;81(2):147-9.
http://www.ncbi.nlm.nih.gov/pubmed/15800093
12. Engel CC Jr, Walker EA, Engel AL, et al. A randomized, double-blind crossover trial of sertraline in women with chronic pelvic pain. J Psychosom Res. 1998 Feb;44(2):203-7.
http://www.ncbi.nlm.nih.gov/pubmed/9532549
13. Wiffen PJ, Derry S, Moore RA, et al. Carbamazepine for acute and chronic pain in adults. Cochrane Database Syst Rev. 2011 Jan;(1):CD005451.
http://www.ncbi.nlm.nih.gov/pubmed/21249671
14. Moore RA, Wiffen PJ, Derry S, et al. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev. 2011 Mar;(3):CD007938.
http://www.ncbi.nlm.nih.gov/pubmed/21412914
15. Sator-Katzenschlager SM, Scharbert G, Kress HG, et al. Chronic pelvic pain treated with gabapentin and amitriptyline: a randomized controlled pilot study. Wien Klin Wochenschr. 2005 Nov;117(21-22): 761-8.
http://www.ncbi.nlm.nih.gov/pubmed/16416358
16. Moore RA, Straube S, Wiffen PJ et al. Pregabalin for acute and chronic pain in adults. Cochrane Database Syst Rev. 2009 Jul;(3):CD007076.
http://www.ncbi.nlm.nih.gov/pubmed/19588419
17. Derry S, Lloyd R, Moore RA, et al. Topical capsaicin for chronic neuropathic pain in adults. Cochrane Database Syst Rev. 2009 Oct;(4):CD007393.
http://www.ncbi.nlm.nih.gov/pubmed/19821411
18. Seidel S, Aigner M, Ossege M, et al. Antipsychotics for acute and chronic pain in adults. Cochrane Database Syst Rev. 2008 Oct;(4):CD004844.
http://www.ncbi.nlm.nih.gov/pubmed/18843669
19. Noble M, Treadwell JR, Tregear SJ, et al. Long-term opioid management for chronic noncancer pain. Cochrane Database Syst Rev. 2010 Jan;(1):CD006605.
http://www.ncbi.nlm.nih.gov/pubmed/20091598
20. The British Pain Society. Opioids for persistent pain: Good practice. 2010.
http://www.britishpainsociety.org/book_opioid_main.pdf
21. The British Pain Society. Opioids for persistent pain: Information for patients. 2010.
http://www.britishpainsociety.org/pub_patient.htm
22. The British Pain Society. Pain and problem drug use: Information for patients. 2007.
http://www.britishpainsociety.org/pub_patient.htm
23. Quigley C. Opioid switching to improve pain relief and drug tolerability. Cochrane Database Syst Rev. 2004;(3):CD004847.
http://www.ncbi.nlm.nih.gov/pubmed/15266542
24. Lee M, Silverman SM, Hansen H, et al. A comprehensive review of opioid-induced hyperalgesia. Pain Physician. 2011 Mar-Apr;14(2):145-61.
http://www.ncbi.nlm.nih.gov/pubmed/21412369
25. Sotgiu ML, Valente M, Storchi R, et al. Cooperative N-methyl-D-aspartate (NMDA) receptor antagonism and mu-opioid receptor agonism mediate the methadone inhibition of the spinal neuron pain-related hyperactivity in a rat model of neuropathic pain. Pharmacol Res 2009 Oct;60(4):284-90.
http://www.ncbi.nlm.nih.gov/pubmed/19717013
26. Olesen AE, Staahl C, Arendt-Nielsen L, et al. Different effects of morphine and oxycodone in experimentally evoked hyperalgesia: a human translational study. Br J Clin Pharmacol. 2010 Aug;70(2):189-200.
http://www.ncbi.nlm.nih.gov/pubmed/20653672
27. Baranowski AP, Fall M, Abrams P. Urogenital Pain in Clinical Practice: Taylor and Francis; 2007.
28. Nnoaham KE, Kumbang J. Transcutaneous electrical nerve stimulation (TENS) for chronic pain. Cochrane Database Syst Rev. 2008 Jul;(3):CD003222.
http://www.ncbi.nlm.nih.gov/pubmed/18646088

29. NICE technology appraisal guidance 159. Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin.
http://guidance.nice.org.uk/TA159
30. Fariello JY, Whitmore K. Sacral neuromodulation stimulation for IC/PBS, chronic pelvic pain, and sexual dysfunction. Int Urogynecol J Pelvic Floor Dysfunct 2010 Dec;21(12):1553-8.
http://www.ncbi.nlm.nih.gov/pubmed/20972541

11. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

AMPA	amino-methylene-phosphonic acid
ATP	Adenosinetriphosphate
BCG	Bacillus Calmette Guérin
BDNF	brain-derived neurotrophic factor
BPS	bladder pain syndrome
BTX-A	Botulinum toxin A
CBT	cognitive behavioural therapy
CFS	chronic fatigue syndrome
CGRP	calcitonin gene-related peptide
CI	confidence interval
CNS	central nervous system
CPP	chronic pelvic pain
CPPS	chronic pelvic pain syndrome
CRH	corticotrophin-releasing hormone
CyA	Cyclosporin A
DMSO	Dimethyl sulphoxide
DNIC	diffuse noxious inhibitory control
DRG	dorsal root ganglion
EH	excisional haemorrhoidectomy
ESSIC	European Society for the Study of BPS
FM	fibromyalgia
FSSs	functional somatic syndromes
GAG	glycosaminoglycan
HBO	Hyperbaric oxygen
HIF	hypoxia inducible factor
IASP	Association for the Study of Pain
IBS	irritable bowel syndrome
ICDB	Interstitial Cystitis Data Base
ICSI	Interstitial Cystitis Symptom Index
I-PPS	International Prostate Symptom Score
ISSVD	Society for the Study of Vulvovaginal Disease
LUTS	lower urinary tract symptoms
MAPP	Multi-disciplinary Approach to the study of chronic Pelvic Pain research
MPA	medroxyprogesterone acetate
MRI	magnetic resonance imaging
NBSs	non-bladder syndromes
NGF	nerve growth factor
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health
NIH-CPSI	NIH Prostatitis Symptom Index
NMDA	N-methyl-D-aspartate
NNT	numbers needed to treat
NO	nitric oxide
PAG	periaqueductal grey
PID	pelvic inflammatory disease
PNS	pudendal nerve stimulation
PNS	peripheral nervous system
PPMT	pre-post-massage test
PPS	prostate pain syndrome
QoL	quality of life
RBL	rubber band ligation
RCT	randomised controlled trial
RTX	Resiniferatoxin
TUNA	transurethral needle ablation
TUR	transurethral resection
VAPS	visual analogue pain scale

Conflict of interest

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