

# EAU Guidelines on Chronic Pelvic Pain

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# 1. INTRODUCTION

## 1.1 Aim

These European Association of Urology (EAU) Guidelines on Chronic Pelvic Pain play an important role in the process of consolidation and improvement of care for patients with pelvic pain and associated lower abdominal pain. From both literature and daily practice, it has become clear that lower abdominal and pelvic pain are areas still under development. These Guidelines have been recognised as a cornerstone for important developments that have taken place in the past years.

These Guidelines aim to expand the awareness of caregivers in the field of abdominal and pelvic pain, and to assist those who treat patients with abdominal and pelvic pain in their daily practice. The Guidelines are a useful instrument not only for urologists, but also for gynaecologists, surgeons, physiotherapists, psychologists and pain doctors.

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

## 1.2 Structure and scope

The Panel wishes to take advantage of modern methods of delivering Guidelines information to clinicians. In 2016, a stepped information structure was made, in alignment with stepped-care protocols, using new digital information sources like websites and Apps to aid this process. Furthermore, the Guidelines were changed according to the template used in all other non-oncology Guidelines of the EAU, while recognising that structuring Guidelines on chronic pain is different from structuring one on another subject. A multidisciplinary approach is of utmost importance and demands a broad view. In 2016, the Guidelines were rewritten to be centred around pain instead of being organ centred. It is partly theoretical to show the importance of using this pain-centred approach. The biggest part, however, deals with the practical approach to diagnostics, treatment and management of patients with abdominal and pelvic pain.

## 1.3 Publication history

The EAU Guidelines on Chronic Pelvic Pain were first published in 2003. This formed the basis of a 2004 scientific publication [1]. In the 2003 edition of these Guidelines, the concept of chronic pelvic pain syndromes was introduced, which is now referred to as “pain as a disease process”. In 2008, a limited update of the Guidelines was published and formed the basis of another scientific publication in 2010 [2]. In the 2014 edition, minor revisions were made. For the 2015 edition, the Panel critically reviewed chronic primary bladder pain syndrome (PBPS), which is now a comprehensive part of the Guidelines. The fact that this part was so extensive, shows that the roots of talking about abdominal pain and pelvic pain lies in the bladder, and interstitial cystitis was one of the first subjects addressed that talked about pain in urology. The Panel illustrated this in a 2013 publication [3]. In the 2025 edition, minor updates were made to the definition of PBPS in Section 1.5 ‘Terminology’ and to patient education in Chapter 5. The next update of the EAU Guidelines on Chronic Pelvic Pain will be published in 2027.

## 1.4 Available publications

Alongside the full text version of the EAU Guidelines on Chronic Pelvic Pain, a quick reference document (Pocket Guidelines) is available. This reference document is an abridged version that may require consultation together with the full text version. It follows the update cycle of the underlying full texts. All documents are accessible on the EAU website: <https://uroweb.org/guidelines/chronic-pelvic-pain>. An EAU Guidelines App for iOS and Android devices is also available, containing the Pocket Guidelines, interactive algorithms and calculators, clinical decision support tools, Guidelines cheat sheets and links to the extended Guidelines.

## 1.5 Panel composition

The Panel of experts responsible for the Guidelines include five urologists (one of whom has a subspecialisation in neuro-urology and one is a sexologist), three consultants in pain medicine, a uro-gynaecologist, a psychologist, a gastroenterologist, a pelvic physiotherapist, a health scientist and (clinical) epidemiologist and two patient representatives. All experts involved in the production of this document have submitted potential conflict of interest statements, which can be viewed on the EAU website: <https://uroweb.org/guidelines/chronic-pelvic-pain/panel>.

## 1.6 Terminology

### *Definitions of chronic pelvic pain terminology*

#### **Classification**

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

#### **Phenotyping**

Phenotyping is describing the condition. For example, chronic bladder pain may be associated with the presence of Hunner's lesions and glomerulations on cystoscopy, whereas other bladder pain conditions may have a normal appearance on cystoscopy. These are two different phenotypes. The same is true for irritable bowel syndrome (IBS), which may be sub-divided into that associated primarily with 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, characterising the condition by its symptoms and signs, and – where possible – by investigative findings, has shown to have clinical and research validity in many contexts. 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. The 11<sup>th</sup> revision of the World Health Organization (WHO) International Classification of Diseases (ICD-11) uses the term chronic primary pain to distinguish these conditions from pain associated with another diagnosis that the WHO refers to as chronic secondary pain (see below).

#### **Terminology**

Terminology is the word(s) 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 PBPS. The EAU, the International Society for the study of PBPS (known as ESSIC), the International Association for the Study of Pain (IASP) and several other groups have preferred the term PBPS. 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 comprehensive and considers the emotional, cognitive, behavioural, sexual and functional consequences of 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. Particularly, terms that end in "itis" should be avoided unless infection and/or inflammation is proven and considered to be the cause of the pain [4]. End-organ inflammation may be secondary and neurogenic in origin, and not a primary cause of the pain.

#### **Taxonomy**

Taxonomy places the phenotypes into a relationship hierarchy. The EAU approach subdivides chronic pelvic pain into conditions that are pain syndromes with no obvious diagnosis; chronic primary pelvic pain syndromes (CPPPS) (consistent with ICD-11 chronic primary pain); 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" and the ICD-11 chronic secondary pain. 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.

### *Classification of chronic pelvic pain*

#### **Importance of classification**

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

#### **Clues to the mechanism**

As a result of systematic phenotypic and taxonomic classifications, similarities and differences between conditions become clear. Drawing comparisons between the phenotypes of different disorders allows comparison between 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 to the clinical situation.

### **Patient needs**

A diagnosis or name for a set of symptoms can provide patients with a sense of being understood and hope for relief. It may help in acceptance of the problem as chronic, resolution of unfounded fears about its implications (if not life-threatening), engagement in therapeutic endeavours, and assist in self-management. However, it may result in accessing information of varying quality related to the diagnosis or name and could raise new concerns about long-term consequences or the suitability of treatment.

### **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 [1]:

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 therefore 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 CPPPS 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, also potentially with the term primary added. If the pain is localised to multiple organs, then the syndrome is a regional pain syndrome and the term CPPPS 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 factors which relate to quality of life (QoL) issues and prognosis. A North American research program, the MAPP program (Multidisciplinary 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 (FM), facial pain or autoimmune disorders.
3. In 2004, the Panel introduced the concept of managing the polysymptomatic nature of CPPPS. Since then, others have developed their own schemes, such as Nickel's UPOINT [5], modified with the addition of a sexual dysfunction domain [6]. Considering these and other publications, the symptom classification table has been updated (Table 1).

The debate in relation to subdividing the pain syndromes continues. As more information is collected suggesting that the central nervous system (CNS) is involved and may be the main cause of many CPPPS conditions (e.g. bladder, genitalia, colorectal or myofascial), there is a general tendency to move away from end-organ nomenclature. Only time and good research will determine whether this is appropriate. 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 for change.

#### ***ICD classification: purpose and uses***

The WHO ICD is the foundation for the identification of health trends and statistics globally, and the international standard for reporting diseases and health conditions. It is the diagnostic classification standard for all clinical and research purposes. It defines the universe of diseases, disorders, injuries and other related health conditions, listed in a comprehensive and hierarchical fashion [7]. The latest version, ICD-11, has been available since January 2022 for member states to report with.

The ICD-11 classification for the first time included chronic pain (“chronic pain is pain that persists or recurs for longer than three months”) and divided the coding into chronic primary pain (“chronic primary pain is multifactorial: biological, psychological and social factors contribute to the pain syndrome”) and a number of chronic secondary pain conditions (related to cancer, post-surgical, musculoskeletal, visceral, neuropathic, headache/orofacial, other).

The significance of the inclusion of chronic pain as a condition within the ICD-11 should not be underestimated. There are, however, unresolved issues regarding this classification, such as when a condition ends and pain persists, does the term chronic secondary pain become chronic primary pain [8, 9]?

The Panel have changed the EAU terminology previously used in these Guidelines to show conformity with ICD-11 definitions. This will include changing terminology used in originally cited works.

The classification has been set up according to the axis system used by IASP.

**Table 1: EAU classification of chronic pelvic 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	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 Hesitancy Dysfunctional flow Urgency Incontinence	ANXIETY About pain or putative cause of pain  Catastrophic thinking about pain
		Bladder					
Chronic secondary pelvic pain syndrome, formally known as specific disease associated pelvic pain	Gynaecological	Scrotal Testicular Epididymal	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 Hesitancy Dysfunctional flow Urgency Incontinence	ANXIETY About pain or putative cause of pain  Catastrophic thinking about pain
		Penile Urethral					
Chronic primary pelvic pain syndrome, formally known as pelvic pain syndrome	Gastrointestinal	Post-vasectomy	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 Hesitancy Dysfunctional flow Urgency Incontinence	ANXIETY About pain or putative cause of pain  Catastrophic thinking about pain
		Vulvar Vestibular Clitoral					
Chronic primary pelvic pain syndrome, formally known as pelvic pain syndrome	Gastrointestinal	Endometriosis associated	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 Hesitancy Dysfunctional flow Urgency Incontinence	ANXIETY About pain or putative cause of pain  Catastrophic thinking about pain
		CPPPS with cyclical exacerbations					
Chronic primary pelvic pain syndrome, formally known as pelvic pain syndrome	Gastrointestinal	Dysmenorrhoea	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 Hesitancy Dysfunctional flow Urgency Incontinence	ANXIETY About pain or putative cause of pain  Catastrophic thinking about pain
		Irritable bowel					
Chronic primary pelvic pain syndrome, formally known as pelvic pain syndrome	Gastrointestinal	Chronic anal	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 Hesitancy Dysfunctional flow Urgency Incontinence	ANXIETY About pain or putative cause of pain  Catastrophic thinking about pain
		Intermittent chronic anal					
Chronic primary pelvic pain syndrome, formally known as pelvic pain syndrome	Gastrointestinal	Pudendal pain syndrome	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 Hesitancy Dysfunctional flow Urgency Incontinence	ANXIETY About pain or putative cause of pain  Catastrophic thinking about pain
		Dyspareunia					
Chronic primary pelvic pain syndrome, formally known as pelvic pain syndrome	Gastrointestinal	Pelvic pain with sexual dysfunction	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 Hesitancy Dysfunctional flow Urgency Incontinence	ANXIETY About pain or putative cause of pain  Catastrophic thinking about pain
		Any pelvic organ					
Chronic primary pelvic pain syndrome, formally known as pelvic pain syndrome	Gastrointestinal	Pelvic floor muscle	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 Hesitancy Dysfunctional flow Urgency Incontinence	ANXIETY About pain or putative cause of pain  Catastrophic thinking about pain
		Abdominal muscle					
Chronic primary pelvic pain syndrome, formally known as pelvic pain syndrome	Gastrointestinal	Spinal	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 Hesitancy Dysfunctional flow Urgency Incontinence	ANXIETY About pain or putative cause of pain  Catastrophic thinking about pain
		Coccyx					
Chronic primary pelvic pain syndrome, formally known as pelvic pain syndrome	Gastrointestinal	Hip muscle	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 Hesitancy Dysfunctional flow Urgency Incontinence	ANXIETY About pain or putative cause of pain  Catastrophic thinking about pain

CPPPS = chronic primary pelvic pain syndrome; Hx = history; Ex = examination; Ix = investigation; PTSD = post-traumatic stress disorder.

## **Pain syndromes**

The original EAU Guidelines classification [1] was inspired by the IASP classification [10] and much work around what has become known as “pain as a disease” and its associated psychological, behavioural, sexual, social and organ function aspects. After ten years of work developing the initial ideas, an updated version was accepted by the IASP Council for publication in January 2012.

### **EAU Definition of chronic pelvic pain**

Chronic pelvic pain is chronic or persistent pain perceived\* in structures related to the pelvis of either males or females. It is often associated with negative cognitive, behavioural, sexual and emotional consequences, as well as with symptoms suggestive of lower urinary tract (LUT), 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], have localised the pain as being discerned in a 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 three months (in accordance with ICD-11). For cyclical pain, a longer period of more than six months may be appropriate. Cyclical pain is included in the classification, particularly if there is evidence of central sensitisation, and dysmenorrhoea (hormonally dependent) 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 but still including biological mechanisms. For the EAU’s classification, the term “specific disease-associated pelvic pain” has been accepted for the former, and “chronic pelvic pain syndrome” for the latter. In the ICD-11, the former is called chronic secondary pelvic pain, and the latter chronic primary pelvic pain.

The following classification only deals with CPPPS.

### **EAU Definition of chronic primary pelvic pain syndrome**

Chronic primary pelvic pain syndrome is the occurrence of chronic pain 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 LUT, sexual, bowel or gynaecological dysfunction. Chronic primary pelvic pain syndrome is a subdivision of chronic pelvic pain. Throughout this text, chronic pelvic pain syndrome is replaced with CPPPS if it is appropriate.

### **Further subdivision of chronic primary pelvic pain syndrome**

Pain perception in CPPPS may be focused within a single organ, more than one pelvic organ, and even associated with systemic symptoms such as chronic fatigue syndrome (CFS), FM 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 bladder pain syndrome (Table 2), also using the term primary. 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 generic term CPPPS should be used. Many, including some of the Panel members, never subdivide by anatomy and prefer to refer to patients with pain perceived within the pelvis and no specific disease process, as suffering from CPPPS, subdivided by psychological and functional symptoms.

### **Psychological considerations for classification**

Many CPPPSs 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 significantly important concomitant symptoms that are relevant to pain, disability and poor QoL. Catastrophic interpretation of pain is a particularly salient variable, predicting patients’ report of pain, disability, and poor QoL beyond other psychosocial variables, such as depression or behavioural factors, like self-reported sexual dysfunction. Many of these biopsychosocial consequences are common to other persistent pain problems but may show varying degrees of importance for an individual suffering from CPPPS. In all patients with CPPPS, 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) [11].

### Functional considerations for classification

For the purposes of these Guidelines, functional disorders 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 because of changes in the mechanisms that produce defecation, and therefore bowel control is altered. The term is not used in the sense of a psychiatric functional disorder. Many CPPPSs 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 include 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.

### 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 and 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 Panel have not taken the umbrella approach of referring to all pain perceived in the pelvis as chronic pelvic pain syndrome, primary or secondary.

### 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 females and males. 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.

### Primary perineal pain syndrome

Primary 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 LUT, sexual, bowel or gynaecological dysfunction. Primary perineal pain syndrome should be distinguished from pudendal neuralgia, which is a specific disease associated with perineal pain that is caused by nerve damage.

**Table 2: Chronic primary pelvic pain syndromes (the term primary can be included in any of the following)**

Urological pain syndromes	
<b>Primary prostate pain syndrome</b>	Primary prostate pain syndrome 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. Primary prostate pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of LUT and sexual dysfunction. The term "chronic prostatitis" continues to be equated with that of PPPS. In the authors' and others' opinion, this is an inappropriate term, although it is recognised that it has a long history of use. The NIH consensus [12] includes infection (types I and II), which the authors feel should not be considered under PPPS, but as specific disease-associated pelvic pain. The term prostaticodynia has also been used in the past but is no longer recommended by the Panel. Some of the authors of the IASP document disagree with this term and suggest that CPPPS of the male is used instead of PPPS, which has been agreed by the majority.

<b>Primary bladder pain syndrome</b>	Primary bladder pain syndrome 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 daytime and/or night-time urinary frequency. There is no proven infection or other obvious local pathology. Primary bladder pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of LUT and sexual dysfunction. Primary bladder pain syndrome represents a heterogeneous spectrum of symptoms, including primarily functional or sensory presentations. 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. The ESSIC have suggested a standardised scheme of subclassifications [13] 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 “PBPS/IC”. These terms are no longer recommended.
<b>Primary scrotal pain syndrome</b>	Primary scrotal pain syndrome is the occurrence of persistent or recurrent episodic pain localised to the scrotum or the structure within it and may be associated with symptoms suggestive of LUT or sexual dysfunction. There is no proven infection or other obvious local pathology. Primary scrotal pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences. Primary 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.
<b>Primary testicular pain syndrome</b>	Primary testicular pain syndrome is the occurrence of persistent or recurrent episodic pain perceived in the testes and may be associated with symptoms suggestive of LUT or sexual dysfunction. There is no proven infection or other obvious local pathology. Primary testicular pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences. Previous terms have included orchitis, orchialgia and orchiodynia. These terms are no longer recommended.
<b>Primary epididymal pain syndrome</b>	Primary epididymal pain syndrome is the occurrence of persistent or recurrent episodic pain perceived in the epididymis and may be associated with symptoms suggestive of LUT or sexual dysfunction. There is no proven infection or other obvious local pathology. Primary epididymal pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences.
<b>Primary penile pain syndrome</b>	Primary 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. Primary penile pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of LUT and sexual dysfunction.
<b>Primary urethral pain syndrome</b>	Primary 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. Primary urethral pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of LUT, sexual, bowel or gynaecological dysfunction. Primary urethral pain syndrome may occur in males and females.
<b>Post-vasectomy scrotal pain syndrome</b>	Post-vasectomy scrotal pain syndrome is a scrotal pain syndrome that follows vasectomy. Post-vasectomy scrotal pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of LUT and sexual dysfunction. The mechanisms are poorly understood and for that reason it is considered by some to be a special form of primary scrotal pain syndrome.

<b>Primary gynaecological pain syndromes: external genitalia</b>	
<b>Primary vulvar pain syndrome</b>	Primary 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 LUT, sexual, bowel or gynaecological dysfunction. Although pain perceived in the vulva was included 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 ISSVD has used the term vulvodynia, whereas these Guidelines use the term primary 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 sub-divided vulvodynia based on pain location and temporal characteristics of the pain (e.g. provoked or unprovoked). The following definitions are based on that approach.
<b>Primary generalised vulvar pain syndrome</b>	Primary 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 diffused 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 these are no longer recommended.
<b>Primary localised vulvar pain syndrome</b>	Primary 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 because of provocation (touch, pressure or friction). Primary localised vulvar pain syndrome can be subdivided into primary vestibular pain syndrome and primary clitoral pain syndrome.
<b>Primary vestibular pain syndrome</b>	Primary 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.
<b>Primary clitoral pain syndrome</b>	Primary 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.
<b>Gynaecological system: internal pelvic pain syndromes</b>	
<b>Endometriosis-associated pain syndrome</b>	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 LUT, 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. It has been suggested that this phenotype should be removed from the classification because the endometriosis may be irrelevant.
<b>Chronic primary pelvic pain syndrome with cyclical exacerbations</b>	Chronic primary pelvic pain syndrome with cyclical exacerbations covers the non-gynaecological organ pain that frequently shows cyclical exacerbations (e.g. IBS or PBPS) as well as pain like 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.
<b>Primary dysmenorrhoea</b>	Primary dysmenorrhoea is pain with menstruation that is not associated with well-defined pathology. Dysmenorrhoea needs to be considered as a chronic primary pain syndrome if it is persistent and associated with negative cognitive, behavioural, sexual or emotional consequences.

<b>Gastrointestinal pelvic pain syndromes</b>	
<b>Irritable bowel syndrome</b>	Irritable bowel syndrome is the occurrence of chronic, or recurrent, episodic (abdominal) pain associated with defecation or change in bowel habits. In routine diagnostic examination, obvious anatomic or physiologic abnormalities are absent. Bowel dysfunction (e.g. constipation) is frequent. Irritable bowel syndrome is often associated with worry and pre-occupation about bowel function, and negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of LUT or gynaecological dysfunction. The classification is based upon the Rome IV criteria [14]. Recurrent abdominal pain on average at least one day per week in the last three months. Symptom onset at least six months prior to diagnosis. The pain is associated with at least two or more of the following criteria: related to defecation; associated with a change in frequency of stool; or a change in form of stool. Depending on the predominant stool form, based on the Bristol Stool Scale, IBS can be subdivided into IBS with predominant constipation (IBS-C), predominant diarrhoea (IBS-D), and with mixed bowel habits (IBS-M). Patients whose bowel habits don't fit in one of the above categories are classified as IBS unclassified (IBS-U). Extra-intestinal symptoms include: nausea, fatigue, full sensation after even a small meal, and vomiting.
<b>Chronic primary anal pain syndrome</b>	Chronic primary 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 primary anal pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of LUT, sexual, bowel or gynaecological dysfunction.
<b>Intermittent chronic primary anal pain syndrome</b>	Intermittent chronic primary 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 sub-group of the chronic primary anal pain syndromes. It was previously known as "proctalgia fugax" but this term is no longer recommended.
<b>Musculoskeletal system</b>	
<b>Primary pelvic floor muscle pain syndrome</b>	Primary 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 LUT, sexual, bowel or gynaecological dysfunction. This syndrome may be associated with over-activity 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.
<b>Primary coccyx pain syndrome</b>	Primary 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. Primary coccyx pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of LUT, sexual, bowel or gynaecological dysfunction. The term "coccydynia" was used but is no longer recommended.
<b>Chronic pain post-surgery</b>	
<b>Chronic post-surgical pain syndrome</b>	The definition of CPSP is chronic pain that develops or increases in intensity after a surgical procedure and persists beyond the healing process, that is, at least three months after the surgery. There is a separate category for this in the ICD-11 classification.

CPSP = chronic post-surgical pain; DSM-IV-R = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Revised; ESSIC = International Society for the Study of Bladder Pain Syndrome; IBS = irritable bowel syndrome; IC = interstitial cystitis; ISSVD = The International Society for the Study of Vulvovaginal Disease; LUT = lower urinary tract; NIH = National Institutes of Health; PBS = painful bladder syndrome; PBPS = primary bladder pain syndrome; PPPS = primary prostate pain syndrome.

## 2. METHODOLOGY

### 2.1 Data identification

Information regarding the search strategy and a list of associations endorsing the EAU Guidelines is available online: <https://uroweb.org/guidelines/chronic-pelvic-pain/publications-appendices>.

Recommendations within the Guidelines are developed by the Panels to prioritise clinically important care decisions. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates) and the nature and variability of patient values and preferences. This decision process, which can be reviewed in the strength rating forms that accompany each Guideline recommendation, addresses several key elements:

1. the overall quality of the evidence which exists for the recommendation [15]
2. the magnitude of the effect (individual or combined effects)
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study-related factors)
4. the balance between desirable and undesirable outcomes
5. the impact and certainty of patient values and preferences on the intervention.

Strong recommendations typically indicate a high degree of evidence quality and/or a favourable balance of benefit to harm and patient preference. Weak recommendations typically indicate availability of lower quality evidence, and/or equivocal balance between benefit and harm, and uncertainty or variability of patient preference [16].

The 2012 full text update was 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 randomised controlled trials (RCTs) (Level of Evidence 1 [LE: 1]) according to the rating schedule adapted from the Oxford Centre for Evidence-based Medicine Levels of Evidence. 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. The 2012 scoping search covered the period January 1995 to July 2011 and was restricted to English language publications. In 2017, a scoping search for the previous five years was performed, and the Guidelines were updated accordingly. In 2021, a new section was included on post-surgical pain syndrome. From January 2022, the WHO ICD-11 has been available for member states to report with and the classifications in these Guidelines were amended accordingly. In 2024, a scoping search for the previous three years was performed and the Guidelines were updated accordingly.

### 2.2 Peer review

This document was subject to peer review prior to publication in 2021.

## 3. EPIDEMIOLOGY, AETIOLOGY AND PATHOPHYSIOLOGY

### 3.1 Chronic visceral pain

#### Definition of pain

Pain is defined as an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage (IASP Taxonomy) [17].

#### Introduction to chronic pelvic primary pain syndromes

Over the years much of the focus for CPPPS has been on peripheral end-organ mechanisms, such as inflammatory or infective conditions. However, research has indicated that many of the mechanisms for the CPPPSs are based within the CNS. Although a peripheral stimulus such as infection may initiate the start of a CPPPS condition, the condition may become self-perpetuating because of CNS modulation. 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 form the basis of the pain syndrome diagnosis, and each individual phenomenon needs to be addressed through multispecialty and multidisciplinary care. Although

ongoing peripheral organ pathology can produce persistent and chronic pain, the main focus of these Guidelines is on CPPPSs 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.

#### 3.1.1 **Incidence**

No adequate data on incidence were found.

#### 3.1.2 **Prevalence**

Across the world [18] chronic pain is prevalent, seriously affecting the quality of people's social, family and working lives, with differences between countries attributable to multiple causes, including study methodology. A United Kingdom (UK) study found a prevalence of chronic pelvic pain of 14.8% in females that are 25 years old [19, 20].

#### 3.1.3 **Influence on Quality of Life**

Assessing QoL in pelvic pain patients is challenging due to the complex pathology, the multifaceted nature of the complaints, and the overlap between the different pelvic pain syndromes. Pelvic pain syndromes have an impact in terms of QoL [21], depression, anxiety, impaired emotional functioning, insomnia and fatigue [21, 22]. If these aspects are identified and targeted early in the diagnostic process, the associated pain symptoms may also improve. Addressing comorbidities will help in further improving QoL. Quality of life assessment is therefore important in patients with pelvic pain and should include physical, psychosocial behavioural and emotional aspects, using standardised instruments where possible. In many countries, chronic pain is the leading cause of years lost to disability [18], although these figures are dominated by musculoskeletal pain and headache. Chronic pain is frequently associated with depression and other psychological disorders, reduced capacity to work and perform domestic activities, and substantial use of healthcare services, often with disappointing outcomes.

#### 3.1.4 **Costs**

No adequate data on costs were found.

#### 3.1.5 **Risk factors and underlying causes**

##### 3.1.5.a **Risk factors**

Risk factors include many different factors from various areas, including genetic, psychological state, recurrent physical trauma and endocrine factors.

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 is thought to be partly due to increased corticotrophin-releasing hormone (CRH) gene expression. Up-regulation of CRH has been implicated in several pain states, such as hypersensitivity to rectal distension [23]. This model suggests an action of CRH on mast cells. A range of stress-related illnesses have been suggested, for example, IBS and bladder pain syndrome [24, 25]. There is evidence accumulating to suggest that the sex hormones also modulate both nociception and pain perception [26]. Stress can also produce long-term biological changes which may form the relation between chronic pain syndromes and significant early life and adverse life events [27]. Asking the patient about these events is important as it influences their psychological well-being [28, 29].

Genetics also play a role in assessing the risk of developing chronic pain. An individual who has one chronic pain syndrome is more likely to develop another. Family clusters of pain conditions are also observed. A 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 complex, as developmental, environmental and social factors also play a contributory role. Evidence that PBPS may have a genetic component has been presented in several identical twin studies, but genetics may contribute to less than one third of total variation in susceptibility to PBPS [30, 31].

Studies about integrating the psychological factors of CPPPSs are few, but the quality is high. Psychological factors are consistently found to be relevant in the maintenance of persistent pelvic and urogenital pain [32]. Beliefs about pain contribute to the experience of pain [33] and symptom-related anxiety and central pain amplification may be measurably linked. Worrying about pain and perceived stress predict worsening of urological chronic pain over a year [32, 34]. Central sensitisation has been demonstrated in a small study of symptomatic endometriosis [35] and central changes are evident in association with dysmenorrhoea and is increasingly recognised as a risk for female pelvic pain [36]. The various mechanisms of CNS facilitation,

amplification and failure of inhibition mean that there is no simple relationship between physical findings, pain experience and resulting distress and restriction of activities. Division of aetiology into organic versus psychogenic is unscientific. Diagnoses that assign female pain to psychological origins due to scepticism about the reality or severity of their pain [20, 37] undermines any therapeutic relationship [38]. Pelvic pain and distress is related [39] in both males and females [40]; as are painful bladder and distress [34]. In a large population-based study of males, CPPPS was associated with prior anxiety disorder [41]. The only systematic review [42] of risk factors for chronic non-cyclical pelvic pain in females identified, in addition to medical variables: sexual or physical abuse (Odds ratio [OR]: 1.51–3.49); psychological problems, such as anxiety (OR: 2.28; 95% Confidence Interval [CI]: 1.41–3.70) and depression (OR: 2.69; 95% CI: 1.86–3.88); multiple hysteria (OR: 4.83; 95% CI: 2.50–9.33); and psychosomatic symptoms (OR: 8.01; 95% CI: 5.16–12.44).

Many studies have reported high rates of childhood sexual abuse in adults with persistent pain, particularly in females with pelvic pain [43]. It is hard to establish a causal role for sexual abuse or trauma history, anxiety or depression in females with CPPPS [44, 45], as the attribution of current pain to past sexual or physical abuse is associated both with current depression [46] and with current overall physical health [47]. There is some evidence for a specific relationship between rape and CPPPS (and with FM and functional gastrointestinal disorders) [48]; and recent sexual assault may prompt presentation of pelvic pain [43, 49]. Few studies have examined the association between childhood sexual or physical abuse in relation to pelvic pain in males, although it has known adverse effects on health [48], but males who reported having experienced sexual, physical or emotional abuse had increased odds (3.3 vs. 1.7) for symptoms suggestive of CPPPS [50]. Both sexes should be screened for sexual abuse when presenting with symptoms suggestive of CPPPS, and clinicians should inquire about pelvic pain in patients who have experienced abuse [50].

### 3.1.5.b Underlying causes

The mechanisms that serve as an underlying cause for chronic pelvic pain are:

1. Ongoing acute pain mechanisms [51] (such as those associated with inflammation or infection), which may involve somatic or visceral tissue.
2. Chronic pain mechanisms, which especially involve the CNS [4].
3. Emotional, cognitive, behavioural and sexual responses and mechanisms [52, 53].

Symptoms and signs of neuropathic pain appear to be common in CPPPS patients and assessment of neuropathic pain should be considered in that group of patients, including those with secondary pelvic pain and other pelvic pathologies [54]. Chronic pain mechanisms may include altered resting state neuromotor connectivity, for instance in males with chronic prostatitis/CPPPS [55].

Table 3 illustrates some of the differences between the somatic and visceral pain mechanisms. These 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
<b>Effective painful stimuli</b>	Stretching and distension, producing poorly localised pain.	Mechanical, thermal, chemical and electrical stimuli, producing well localised pain.
<b>Summation</b>	Widespread stimulation produces significantly magnified pain.	Widespread stimulation produces a modest increase in pain.
<b>Autonomic involvement</b>	Autonomic features (e.g. nausea and sweating) frequently present.	Autonomic features less frequent.
<b>Referred pain</b>	Pain perceived at a site distant to the cause of the pain is common.	Pain is relatively well localised and well recognised.
<b>Referred hyperalgesia</b>	Referred cutaneous and muscle hyperalgesia is common, as is involvement of other visceral organs.	Hyperalgesia tends to be localised.
<b>Innervation</b>	Low density, unmyelinated C-fibres and thinly myelinated Aδ fibres.	Dense innervation with a wide range of nerve fibres.

<b>Primary afferent physiology</b>	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.
<b>Silent afferents</b>	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.
<b>Central mechanisms</b>	Play an important part in the hyperalgesia, viscerovisceral, visceromuscular and muscoviceral hyperalgesia.	Sensations not normally perceived become perceived and non-noxious sensations become painful. Responsible for the allodynia and hyperalgesia of chronic somatic pain.
<b>Abnormalities of function</b>	Central mechanisms associated with visceral pain may be responsible for organ dysfunction.	Somatic pain associated with somatic dysfunction, for example, muscle spasm.
<b>Central pathways and representation</b>	As well as classical pathways, there is evidence for a separate dorsal horn pathway and central representation.	Classical pain pathways.

#### Ongoing peripheral pain mechanisms in visceral pain

In most cases of chronic pelvic pain, ongoing tissue trauma, inflammation or infection is absent [56, 57]. However, conditions that produce recurrent trauma, infection or ongoing inflammation may result in chronic pelvic pain in a small proportion of cases. For example, out of a large cohort with acute bacterial prostatitis, 10.5% ended up with a state of CPPPS [58]. It is for this reason that the early stages of assessment include looking for these pathologies. Once excluded, ongoing investigations for these causes are rarely helpful and indeed may be detrimental.

When acute pain mechanisms are triggered by a nociceptive event, direct activation of peripheral nociceptor transducers occurs, and these transducers may also become sensitised, thereby amplifying 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) [59].

There are several 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 stimulate the receptors of the transducers [60].
3. There are many modifications in the receptors that result in them being more sensitive.

In general, the effect of 1 and 2 above is to lower the threshold, and the effect of 3 above 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 positive and inhibitory loops [61, 62].

### **Central sensitisation as a mechanism in visceral pain**

It is important to appreciate that nociception is the process of transmitting information to centres involved in perception of 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. The brain may affect the modulation of pain pathways at the spinal cord level.

Neuronal sensitisation is responsible for a decrease in threshold and an 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. For 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 sub-threshold and not usually perceived, may be perceived and result in a sensation of fullness and a need to void or to defecate. Non-noxious stimuli may be interpreted as pain and stimuli that are normally noxious may be magnified (true hyperalgesia) with an increased perception of pain. Consequently, one can see that many of the symptoms of PBPS and IBS may be explained by central sensitisation. A similar explanation exists for the muscle pain in FM.

It is now well accepted that there are both descending pain-inhibitory and descending pain-facilitatory pathways that originate from the brain [63]. Several neurotransmitters and neuromodulators are involved in descending pain-inhibitory pathways. The main ones are opioids, 5-hydroxytryptamine and noradrenaline.

The autonomic nervous system also plays a role in sensitisation. 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 in 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 QoL and must be appropriately managed.

### **Psychological mechanisms in visceral pain**

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.

Various psychological processes affect pain neuromodulation at a higher level. Inhibiting or facilitating both the strength of the nociceptive signal reaching the consciousness, and appraisal and interpretation of that signal, 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.

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 [64]. 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 [65] may 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 feeling pain from sensations that would not normally be experienced as painful.

An important review [27] of chronic pelvic pain in females dismantled the notion that females without relevant physical findings differ in psychological characteristics from females with relevant physical findings. Females with pelvic pain often have other non-pain somatic symptoms and current or lifetime anxiety and depression disorder [19]; they may have a history of physical or sexual abuse in childhood, but this is of unclear significance. Studies should avoid interpreting the absence of physical findings as evidence for psychological origins of the complaint ('psychosomatic' or 'somatoform' disorders). Pain studies describe multiple processes by which pain may spread across sites or evolve over time, including central sensitisation (see previous section), viscerovisceral cross-sensitisation involving multiple pain sites [66], activation of the hypothalamic-pituitary axis; and dysregulation of serotonergic pathways [67], rendering pain levels responsive to stress. Some pain problems that affect sexual activity are diagnosed as sexual problems (e.g. 'dyspareunia') when pain is the central problem and is not contingent on sexual activity alone [68]. Better integration of sexology and mainstream psychology for pelvic pain in both males and females is needed, building on a biopsychosocial formulation [69, 70].

The term psychosomatic symptoms can best be understood as multiple somatic symptoms not associated with, or indicative of, any serious disease process. Medical and surgical history may also be important [71].

### **Understanding the psychological components of pain**

Psychological processes of emotions, thought and behaviour involve distributed networks, whose interactions with pain processing are complex, producing inhibition and facilitation of signal processing, appraisal and response. Models that integrate psychological factors involved in maintaining persistent pelvic and urogenital pain with current neurobiological understanding of pain are few, but the quality is high (see Section 3.1.5.a).

There is no evidence that females with CPPPS without physical findings are primarily presenting a psychological problem [27]. Anxiety and post-traumatic stress symptoms are common in some females with CPPPS [20, 72] and with vulvar pain [73]. This may account for substantial variance in health status, treatment use and treatment outcome; for instance, female expectations about vulvar pain on penetration-predicted pain, sexual function and sexual satisfaction [74]. Negative investigative findings do not necessarily resolve female anxieties about the cause of pain [75, 76] and anxiety often focuses on what might be 'wrong'. Depression may be related to pain in various ways, as described above. Until adequately standardised measures are available in patients with pain, assessment of anxiety and distress requires questions about the patient's beliefs about the cause of pain, the hope that diagnosis will validate pain, the struggle with unpredictability, and the implications of pain for everyday life [77, 78]. Reference to the studies of the IMMPACT group [79] is recommended for guidance on outcome measures suitable for pain trials.

Stress can modify the nervous system to produce long-term biological changes. These structural changes may be responsible for significant early life and adverse life events which are associated later with chronic pain syndromes [29]. The patient should be asked about adverse life events that may produce these biological responses and affect general psychological well-being [29, 80].

#### **3.1.5.c Clinical paradigms in visceral pain**

##### **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 because of several mechanisms but the main theory is one of convergence-projection. In the convergence-projection theory, 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 [59].

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 biliary colic, IBS, endometriosis, dysmenorrhoea and recurrent bladder infections. Primary vulvar pain syndromes are examples of cutaneous allodynia that, in certain cases, may be associated with visceral pain syndromes, such as PBPS. Referred pain with hyperalgesia is thought to be due to central sensitisation of the converging viscerosomatic neurons. Central sensitisation also stimulates efferent activity that could explain the trophic changes that are often found in the somatic tissues.

##### **Musculo-skeletal system 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. Adjacent musculature of the lower limbs and thorax may also become involved. Pain may be localised to the trigger points, but it is more often associated with classical referral patterns. In addition to trigger points, inflammation of the ligaments and tendons to the bones (enthesitis) and of the bursa (bursitis) may be found [81]. Certain postures affect the different muscles in different ways and may exacerbate or reduce the pain. As with negative sexual encounters, stress has been implicated as both an initiator of pelvic myalgia and as a maintenance factor.

##### **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, PBPS and dysmenorrhoea. The mechanisms involved are often acute afferent input (e.g. due to infection) followed by long-term central sensitisation. 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.

## **3.2 Pelvic pain**

### **3.2.1 Incidence**

No adequate data on incidence were found.

### **3.2.2 Prevalence**

#### **3.2.2.a Primary prostate pain syndrome**

There is limited information on the true prevalence of primary prostate pain syndrome (PPPS) in the population. As a result of significant overlap of symptoms with other conditions (e.g. benign prostatic enlargement and PBPS), purely symptom-based case definitions may not reflect the true prevalence of PPPS [82, 83]. In the literature, population-based prevalence of prostatitis symptoms ranges from 2.2-14.2% [84, 85]. The risk of prostatitis increases with age (males aged 50-59 years have a 3.1-fold greater risk than those aged 20-39 years).

#### **3.2.2.b Primary bladder pain syndrome**

Reports of PBPS prevalence have varied greatly, along with the diagnostic criteria and populations studied. Reports range from 0.06-20% [86-92]. There is a female predominance of about ten to one [90] but possibly no difference in race or ethnicity [82, 93, 94]. The relative proportions of Hunner's lesion and non-lesion disease are unclear. Incidence in studies has ranged from 5-50% [95-98]. There is increasing evidence that children under 18 years old may also be affected, although prevalence figures are low; therefore, PBPS cannot be excluded on the basis of age [99].

#### **3.2.2.c Sexual pain syndrome**

In the 1980s, an association between chronic pelvic pain and sexual dysfunction was postulated. In a review, the relationship between PPPS and health status with influence on sexual activity was addressed [100]. In a Chinese study of males with chronic pelvic pain, 1,768 males completed the questionnaires. The overall prevalence of sexual dysfunction was 49%. Erectile dysfunction (ED) is the most investigated sexual dysfunction in PPPS patients. The reported prevalence of ED ranges from 15.1-48%, varying with evaluation tools and populations [101, 102]. Erectile dysfunction was prevalent in 27.4% of Italian males aged 25-50 [103], 15.2% of Turkish males (significantly higher than in the control group) [104] and 43% of Finnish males with PPPS [105]. The prevalence of ED was found to be higher in young males with PPPS than in the general population. A significant correlation between "chronic prostatitis", chronic pelvic pain symptoms (measured by NIH-CPSI) and ED (measured by International Index of Erectile Function [IIEF]) was confirmed, while other studies using the same questionnaires were not able to confirm such a correlation [70, 106]. Some studies also report ejaculatory dysfunction, mainly premature ejaculation [101, 102, 107, 108].

In community-based studies in the UK [109], New Zealand [110] and Australia [111], a substantially larger proportion of females with chronic pelvic pain reported dyspareunia (varying between 29-42%) than females without chronic pelvic pain (varying between 11-14%). Only a few studies have investigated sexual problems within clinical populations [112]. Another study showed that all of the sexual function domains (desire, arousal, lubrication, orgasm, satisfaction, pain) were significantly lower in females with chronic pelvic pain than in females without chronic pelvic pain [112]. A study of patients enrolled in chronic pain treatment programs in England reported that 73% had pain-related sexual problems [113].

#### **3.2.2.d Myofascial pain syndromes**

The relationship between muscular dysfunction (especially over-activity) and pelvic pain has been found in several studies [114]. Rectal pain treated with pelvic floor muscle therapy is only relieved when patients learn to relax their pelvic floor muscles [115, 116]. The vast majority (92.2%) of males 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) [117]. This relationship has been found in chronic prostatitis [118], PBPS [119] and vulvar pain [120]. 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 shortened, leading to restrictions even in a relaxed state.

### **3.2.3 Influence on Quality of Life**

Data on the influence on QoL will be included in a future version of the Guidelines.

### **3.2.4 Costs**

No adequate data on costs were found.

### 3.2.5 **Risk factors and underlying causes**

The risk factors are unspecific for most of the pain syndromes in the pelvic area. These are described in Section 3.1.5.a. The underlying causes, including the mechanisms for the different clinical pain syndromes are described here.

#### 3.2.5.a **Primary prostate pain syndrome**

Pain is the main symptom in PPPS. As a common feature of primary chronic pain syndromes, no single aetiological explanation has been found. One explanation is that the condition probably occurs in susceptible males 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. A study showed that chronic but not acute histological inflammation of the prostate was significantly associated with symptomatic progression [121]. Based on the peripheral and the CNS, sensitisation involving neuroplasticity may lead to a centralised neuropathic pain state. This could also explain why tissue damage is not usually found in PPPS. There is growing evidence for a neuropathic origin and association with CNS changes of pain in PPPS, and anxiety appears to be a risk factor for its development [41].

#### 3.2.5.b **Primary bladder pain syndrome**

An initial unidentified insult to the bladder leading to urothelial damage, neurogenic inflammation and pain is thought to be a trigger of PBPS. However, PBPS might be a local manifestation of a systemic disorder. No infection has yet been implicated. Nevertheless, in patients with PBPS in adulthood, urinary infections are significantly more frequent during childhood and adolescence [122]. Experimental induction of chronic pelvic pain by O-antigen deficient bacterial strains supports the bacterial hypothesis [123]. Pancystitis with associated perineural inflammatory infiltrates and mast cell count increase is an essential part of PBPS type 3C [124], but is rare in non-lesion PBPS [29, 64, 125, 126]. Cystoscopic and biopsy findings in both lesion and non-lesion PBPS are consistent with defects in the urothelial glycosaminoglycan (GAG) layer, which might expose submucosal structures to noxious urine components [127-131] and a consequent cytotoxic effect [132, 133]. Studies indicate that autonomic dysfunction with sympathetic predominance may be implicated in PBPS [134, 135].

An association has been reported between PBPS and non-bladder syndromes such as FM, CFS, IBS, vulvodynia, depression, panic disorders, migraine, sicca syndrome, temporomandibular joint disorder, allergy, asthma and systemic lupus erythematosus [136-141]. Psychological comorbidities, especially depression, has been found to be related to symptom severity [136]. Risk of PBPS correlates with a number of non-bladder syndromes in each patient [142]. Studies have shown non-lesion PBPS is associated with significantly greater comorbidity, including FM, migraine, temporomandibular joint disorder and depression compared with PBPS type 3C, emphasising the need for subtyping [143].

Early-stage research also suggests that PBPS may have a distinct gene expression pattern that may provide novel targets for future therapies [144, 145]. Furthermore, lower-level evidence has implicated urinary microbiome dysbiosis and sympathetic nervous system imbalance in PBPS pathology [146-149].

#### 3.2.5.c **Primary scrotal pain syndrome**

Often scrotal pain is not associated with any specific pathology. Pain is perceived in the testes, epididymis or vas deferens. As the ilioinguinal, genitofemoral and pudendal nerves innervate the scrotum [150], any pathology or intervention at the origin or along the course of these nerves may result in pain perceived in the scrotum [151]. Two special forms of scrotal pain syndrome can be described.

The first is post-vasectomy scrotal pain syndrome which occurs following vasectomy. The mechanisms are poorly understood, and for that reason, it is considered by some to be a special form of primary scrotal pain syndrome. Incidence of post-vasectomy pain is 2-20% among all males who have undergone a vasectomy. In males with post-vasectomy pain, 2-6% have a Visual Analogue Scale (VAS) score > 5 [152]. In a large cohort study of 625 males, the likelihood of scrotal pain after six 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 post-vasectomy pain was significantly lower in the no-scalpel vasectomy group (11.7% vs. 18.8% in the scalpel group) [153].

The second special form of scrotal pain is post-inguinal hernia repair pain. It is seen as 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 [151, 154]. In one particular study, there was no difference at one year but after five years, the open group had far fewer patients with scrotal pain [155]. Inguinal hernia repair can lead to chronic post-surgical pain (CPSP) in up to 10% of patients at six months [156] and may present with groin and/or scrotal pain. Testicular injury is uncommon (< 1%) but if associated with pain, orchidectomy can lead to symptomatic relief in two-thirds of patients [157]. Careful identification and preservation of nerves is associated with a reduced risk of chronic pain.

#### 3.2.5.d Primary urethral pain syndrome

Several mechanisms for the development of primary urethral pain syndrome have been proposed. The intimate relationship of the urethra with the bladder (both covered with urothelium) suggests that primary urethral pain syndrome may be a form of PBPS. Mechanisms thought to be basic for PBPS may also apply to the urethra. This means that the specific testing with potassium has been used to support the theory of epithelial leakage [158, 159]. Another possible mechanism is neuropathic hypersensitivity following urinary tract infection. The relationship with gynaecological and obstetric aspects is unclear. In a small group of patients with urethral pain, it was found that grand multiparity and delivery without episiotomy were more often seen in patients with urethral syndrome, based on univariate analysis [160].

#### 3.2.5.e Primary vaginal and vulvar pain syndromes

Pain in the vagina or the female external genital organs is often due to infection or trauma resulting from childbirth or surgery. Pain is usually a precedent to dyspareunia. When the pain persists for more than three months, it can be diagnosed as primary vulvar pain syndrome previously known as “vulvodynia” or “chronic vaginal pain” with no known cause. It is still a poorly understood condition, and therefore difficult to treat.

There are two main sub-types of primary vulvar pain syndrome: generalised, where the pain occurs in different areas of the vulva at different times; and focal, where the pain is at the entrance of the vagina. In primary generalised vulvar pain syndrome, the pain may be constant or occur occasionally, but touch or pressure do not initiate it, although it may make the pain worse. In primary focal vulvar pain syndrome, the pain is described as a burning sensation that comes on only after touch or pressure, such as during intercourse.

The possible causes of primary vulvar pain syndrome involve a complex interplay between affective, behavioural and interpersonal factors, such as:

- history of physical or sexual abuse
- history of chronic antibiotic use
- hypersensitivity to yeast infections or allergies to chemicals or other substances
- abnormal inflammatory response (genetic and non-genetic) to infection and trauma
- nerve or muscle injury or irritation
- psychological factors, such as depressive symptoms, anxiety, pain-related fear and catastrophising [161, 162]
- hormonal changes.

#### 3.2.5.f Chronic pelvic pain and prolapse/incontinence mesh

Continence and prolapse mesh implants were developed as simple, flexible polypropylene plastic acting as a scaffold to treat stress urinary incontinence (SUI) and uterovaginal prolapse. These were deemed easy to insert, but no credence was given to how safe they were, whether they could be removed should they cause complications, or what to do should they not be effective [163, 164]. Most meshes took less than an hour to implant surgically and most patients were treated as day cases, enabling them to be discharged promptly and resume their daily activities. Therefore, rather than undergo complex traditional surgery, females were offered permanent mesh implants, particularly in the treatment of SUI where it was considered to be the gold standard [165, 166]. However, over the last few years, the insertion of mesh has come with significant ‘health and safety warnings’ [167, 168].

For many, mesh was initially seen not just as an effective treatment but as a permanent one. Complications were not thought to be a significant issue and the figure of 1-3% was often quoted. However, we now know the complication rate was closer to 10% [169]. This included chronic pain [170, 171]; chronic infections [172]; erosion into the surrounding organs, including the vagina, urethra and bladder; as well as nerve and musculoskeletal damage affecting mobility [170, 171, 173, 174]. All had a significant impact on patients’ QoL.

As a result of severely debilitating complications following mesh implantation [170], the field of mesh removal medicine and surgery emerged [175].

Early recognition of possible mesh complications is very important. It is normal to wake up in some degree of discomfort after any surgery. However, if pain after surgery is very severe and much more than expected after this type of surgery, it can signal added trauma to the surrounding organs during the procedure. Most pain is often managed with analgesia, but some patients might not fully respond to therapy. If the pain is difficult to treat and does not improve over time, it may become necessary to remove the mesh. Leaving a painful mesh in the pelvis can lead to chronic pelvic pain. The precise mechanism is unknown, but it is thought to be a 'neuro-inflammatory' process [176], as has been proposed in hernia mesh neuralgia. The impact of the mesh, regardless of site, appears to be similar.

#### 3.2.5.g Chronic post-surgical pain

Chronic pain may develop following surgical procedures and has a significant impact on the individual. The ICD-11 has classified CPSP as a chronic pain condition. The definition of CPSP is chronic pain that develops or increases in intensity after a surgical procedure and persists beyond the healing process, that is, at least three months after the surgery [177].

Chronic post-surgical pain may occur in a significant number of patients and is more common following certain types of surgery than others. Procedures with a higher risk of CPSP include limb amputation (30-85%), thoracotomy (5-65%) and mastectomy (11-57%) [178].

Risk factors for CPSP include several pre-, peri-, and postoperative factors. In a prospective cohort of patients undergoing laparoscopy and laparotomies, younger age, female sex, chronic pain preoperatively elsewhere, higher number of previous operations, use of opioids, and a higher postoperative pain score have been found to be associated with a higher risk of CPSP. Older age, malignant indication for surgery, a higher preoperative mental health score, and the use of epidural analgesia in addition to general anaesthesia were protective [179, 180].

There are several procedures specific to the abdomen and pelvis that are associated with an increased risk of chronic pain post-surgery, including bariatric procedures, inguinal hernia repair, vasectomy, hysterectomy and caesarean section. Adhesions are a common cause of chronic abdominal pain but despite this, a systematic review identified only low-level evidence to help guide management of affected individuals [181].

The estimated prevalence of CPSP following bariatric surgery is 30% [182]. In affected individuals, careful assessment that may include laparoscopy could identify a treatable cause (such as adhesions, mesenteric defect or cholecystitis) and lead to a significant reduction in postoperative pain [183].

Inguinal hernia repair can lead to CPSP in up to 10% of patients at six months [156] and may present with groin and/or scrotal pain. The incidence of post-vasectomy pain ranges from 2-20% [152, 184]. The risk is significantly lower following the no scalpel technique [153].

The incidence of post-surgical pain following hysterectomy is difficult to determine as pain is a common indication of the operation. When defined as CPSP, rates are estimated at 28-30% [185, 186]. Careful case selection and management of patient expectation is therefore important.

The frequency of caesarean sections has increased over time. A meta-analysis has shown a significant incidence of CPSP both at three months and at more than twelve months (15% and 11%, respectively) [187], therefore careful counselling is needed in non-emergency cases.

#### 3.2.5.h Ketamine uropathy and chronic pelvic pain

Ketamine is an N-Methyl-D-aspartate acid receptor antagonist that is used as a dissociative anaesthetic agent and in pain management. Recreational ketamine use, especially in young adults, is rising across Europe with increasing relevance to chronic pain services. The European Drug Agency reported that between 2019 and 2023, treatment for ketamine misuse in the European Union more than quadrupled [188], and in 2024, ketamine use in 16-24 year olds was 2.9% in England and Wales [189].

Ketamine uropathy develops from repeated recreational exposure. Proposed mechanisms include direct urothelial toxicity, disruption of the GAG layer, microvascular injury and neurogenic inflammation leading to an ulcerative cystitis that progresses to fibrosis, a contracted bladder and dilated upper tracts [190,

191]. Cystoscopy reveals ulceration, erythema and a markedly reduced bladder capacity [190]. Upper tract involvement (hydronephrosis, ureteric strictures) can develop with progression to renal impairment if left untreated [192, 193]. After a latent period, over a quarter of regular Ketamine users experience urinary symptoms. Symptoms correlate with dose and duration, and include severe suprapubic/bladder pain, dysuria, haematuria, frequency, urgency and nocturia.

### 3.2.5.i Associated conditions in pelvic pain syndromes

#### **Nerve damage**

Spinal pathology and any pathology along the course of the nerve involved may result in neuropathic pain in the distribution of these nerves. Neoplastic disease, infection, trauma, surgical incisions and postoperative scarring may result in nerve injury [194].

In the literature, pudendal neuralgia is the most often mentioned form of nerve damage. Anatomical variations may predispose a patient to developing pudendal neuralgia over time or with repeated low-grade trauma (such as sitting for prolonged periods of time or cycling) [195, 196].

The pudendal nerve may be damaged 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 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.
5. The site of injury determines the location 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).

The clinical presentation depends on different factors. As expected, there is a wide age range with a condition that has so many potential causes. It is suggested that the younger the patient, the better the prognosis. As with any compression nerve injury, the sooner the diagnosis is made, the better the prognosis; older patients may have a more protracted problem [197]. Six out of ten cases are observed in females. Some special situations can be listed:

- 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 [198-200]. The surgery itself may also directly damage the nerve. Pelvic surgery, such as sacrospinous fixation, is clearly associated with pudendal nerve damage in some cases [201]. In many types of surgery, including colorectal, urological and gynaecological, pudendal nerve injury may be implicated.
- 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.
- Tumours in the pre-sacral space must be considered. Tumours invading the pudendal nerve may occur and there may also be damage from surgery for pelvic cancer [202, 203].
- The pudendal neuralgia of childbirth 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. This is more difficult to establish with certainty [204, 205].
- Childbirth and repeated abdominal straining associated with chronic constipation [206] are thought to predispose elderly females 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 Urogenital Pain Management Centres, the most common associations with pudendal neuralgia appear to be history of pelvic surgery, prolonged sitting, and postmenopausal status in older females.

#### **Sexual dysfunction**

Chronic pelvic pain is a clinical condition that results from complex interactions of physiological and psychological factors and has a direct impact on the social, personal and professional lives of males and females.

### *Males*

Chronic pain as well as its treatment can impair the ability to express sexuality. In a study conducted in England, 73% of patients with any chronic pain had some degree of sexual problems because of the pain [113]. These problems can occur because of several factors. Psychological factors like pain catastrophising, a decrease in self-esteem, depression, and anxiety can contribute to the problem severity [207]. Physiological factors like fatigue, nausea and pain itself can cause sexual dysfunction. Pain medications (opioids, and the selective serotonin reuptake inhibitors [SSRIs]) can also decrease libido [208] and delay ejaculation. The number of studies on the effects of CPPPS on sexual function is limited. Sexual dysfunction is often ignored because of a lack of standardised measurements. At present, the most commonly used tool is the IIEF questionnaire [106].

The presence of pelvic pain may increase the risk for ED, independent of age [209]. On the other hand, cross-sectional data suggest no improvement of lower urinary tract symptoms (LUTS) by an increased frequency of ejaculation [210]. Although mental distress and impaired QoL related to illness could contribute to sexual dysfunction observed in patients with PPPS, the presence of erectile and ejaculatory disorders is more frequently related to symptoms suggestive of a more severe inflammatory condition [108]. These arguments are important for the understanding of the close relationship between CPPPS symptoms, disturbed sexuality, impact on QoL, and psychological implications, including depression and more failure-anticipation thoughts [100-102, 210-212]. Sexual dysfunction heightens anger, frustration and depression, all of which place a strain on the patients' relationships. The partners of males with sexual dysfunction and depression often present with similar symptoms, including pain upon intercourse and depressive symptoms. Males with CPPPS have reported a high frequency of sexual relationship dissolution and psychological symptoms, such as depression and suicidal ideation [100, 213]. On the other hand, it was found that males with PPPS did not report significantly decreased sexual satisfaction compared to controls [214]. There is consensus that therapeutic strategies reducing symptoms of pelvic pain are of relevance in relation to changes in sexual function. Also, intimacy and having sex can yield positive experiences that will reduce the pain. The CNS plays an important role in this mechanism.

### *Females*

Chronic pelvic pain leads to substantial impairment in QoL and several sexual dysfunctions [215]. It seems reasonable to expect that pain, extreme fatigue, depressive mood and pain drugs will affect female sexuality. Females with CPPPS reported significantly more pain, depression and anxiety symptoms, and were physically more impaired than females in the control group. In comparison with controls, females with CPPPS reported significantly more sexual avoidance behaviour, non-sensuality, and complaints of "vaginismus" [216]. Patients with CPPPS reported more sexual problems than females with any other type of chronic pain problem [217]. The quality of intimacy in relationships is closely connected with sexual function [218]. Satisfaction with sexual relationships appears to be associated with higher marital functioning [219]. In addition, sexual dissatisfaction is related to sexual dysfunction. When 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 [219].

In another study, approximately two-thirds of patients reported reduced frequency in their sexual relations as a result of CPPPS [220]. One study found that patients with CPPPS reported poorer sexual function – including reduced desire, arousal, lubrication, orgasm and satisfaction – and experienced more frequent and severe pain during vaginal penetration compared with females without CPPPS [221]. In an interview with 50 chronic pain sufferers and their spouses, 78% of the pain sufferers and 84% of partners described deterioration, including cessation, of sexual activity [222]. In a study of patients with back pain, half reported decreased frequency of sex since the onset of chronic pain [113]. 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 females, which includes desire, subjective arousal, lubrication, orgasm, satisfaction and pain. Using the FSFI, females with CPPPS reported lower sexual function in all subscales and total score than females without CPPPS. The largest differences between females with or without CPPPS were seen for the domains of pain and arousal. 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 females with CPPPS. The FSFI also showed good ability to discriminate between females with or without CPPPS [221].

### **Myofascial pain**

Myalgia is too often overlooked as a form of chronic pelvic pain. The pelvic floor and adjacent muscles are used in an abnormal way. Studies in the field of chronic prostatitis support the idea that patients with CPPPS have more muscle spasm and increased muscle tone, and report pain when the pelvic floor muscles are palpated [223]. Learning pelvic floor muscle relaxation techniques can diminish spasm and pain [224]. Repeated or

chronic muscular overload can activate trigger points in the pelvic floor muscles. A report from the Chronic Prostatitis Cohort Study found that 51% of patients with prostatitis had muscle tenderness, compared with 7% of controls. Tenderness in the pelvic floor muscles was only found in the CPPPS group [118].

The first ideas about the neurological aspects of the pelvic floor muscles in relation to chronic pelvic pain were published in 1999. The possibility of CNS changes in the regulation of pelvic floor function was suggested as a mechanism for development of CPPPS. Of the patients presenting with pelvic pain, 88% had poor to absent pelvic floor muscle function [117].

Repeated or chronic muscular overload can activate trigger points in the muscle. Trigger points are defined as hyper-irritable 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 because 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 iliopsoas 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 of pelvic floor muscles (e.g. pain related to voiding or defecation).

### **3.3 Abdominal aspects of pelvic pain**

#### **3.3.1 Incidence**

Epidemiological data on IBS and CPPPS are scarce [225]. Chronic pelvic pain has been shown to be one of the most common functional disorders in females of reproductive age. In 1999, the monthly incidence rate of CPPPS was 1.58/1000 [226].

#### **3.3.2 Prevalence**

Using a vague definition of continuous or episodic pain situated below the umbilicus over six months, a study reported that CPPPS was one of the most common diagnoses in primary care units in Great Britain [226]. The monthly prevalence rate of CPPPS in this study was 21.5/1,000, with an annual prevalence of 38.3/1,000. The prevalence rates increase significantly with older age and vary significantly between regions in the UK. In a sample of American householders, the overall prevalence of anorectal pain was 11.6% for functional anorectal pain and 6.6% for levator ani syndrome. The difference between male and female was small (11.1 vs. 12.1%) [227]. Irritable bowel syndrome is associated with common gynaecologic problems (endometriosis, dyspareunia and dysmenorrhoea) [228]. In females who presented with abdominal pain to the gynaecologic clinic or were scheduled for laparoscopy due to CPPPS, 50% had symptoms of IBS [229]. In a survey from Olmsted County, 20% of females reported CPPPS and 40% of those met the criteria for IBS [230]. This overlap of CPPPS and IBS was associated with an increased incidence of somatisation. In a prospective, controlled study, only psychosocial variables (but not gynaecological surgical procedure) predicted the development of pain, without a difference in the incidence of IBS [231]. Clinical features of pelvic floor dysfunction, gynaecological factors, and psychological symptoms are associated with disordered anorectal function in patients with IBS, but do not predict physiological anorectal testing.

#### **3.3.3 Influence on health-related Quality of Life**

There is little known on health-related quality of life (HRQoL) in patients with CPPPS. There is a need to develop validated disease-specific HRQoL instruments for CPPPS in addition to sound measurement properties. More data are available for patients with IBS treated at referral centres who exhibit HRQoL scores comparable to those of patients with other common conditions such as diabetes, end-stage renal disease, and inflammatory bowel disease [232]. Subgroups of IBS with predominance of diarrhoea or constipation show no difference in HRQoL. Multivariate analysis shows that HRQoL in patients with IBS is affected by sex and psychological conditions.

#### **3.3.4 Costs**

Costs combine direct healthcare costs and societal costs (productivity loss), such as under-performance and absenteeism from work. The annual costs to society can be calculated by using the average population earnings. In Germany, direct care costs are estimated at €791 and societal costs €995 per patient with IBS per year, which may be comparable to patients with CPPPS [233].

#### **3.3.5 Risk factors & underlying causes**

Risk factors are covered in Section 3.1.5.

### 3.4 Summary of evidence and recommendations for chronic primary pelvic pain syndrome and pain mechanisms

Summary of evidence	LE
Chronic primary pelvic pain syndrome 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 be altered by the mechanisms of neuroplasticity so that symptoms of function can also occur.	1
The diagnosis of a CPPPS as a pain syndrome is essential, as it encourages a holistic approach to management with multi-specialty and multidisciplinary care.	2

Recommendations	Strength rating
All of those involved in the management of chronic pelvic pain should have knowledge of peripheral and central pain mechanisms.	Strong
The early assessment of patients with chronic pelvic pain should involve investigations aimed at excluding disease-associated pelvic pain.	Strong
Assess functional, emotional, behavioural, sexual and other quality of life issues, such as effect on work and socialisation, early in patients with chronic pelvic pain and address these issues as well as the pain.	Strong
Build up relations with colleagues to be able to manage chronic primary pelvic pain syndrome comprehensively in a multi-specialty and multidisciplinary environment with consideration of all the patient's symptoms.	Strong

## 4. DIAGNOSTIC EVALUATION

### 4.1 General evaluation

#### 4.1.1 History

History is very important for the evaluation of patients with chronic pelvic pain. Pain syndromes are symptomatic diagnoses, which are derived from a history of pain perceived in the region of the pelvis and absence of other pathology for a minimum of three months. This implies that specific disease-associated pelvic pain caused by bacterial infection, cancer, drug-induced pathology (e.g. ketamine use) [234], primary anatomical or functional disease of the pelvic organs, and neurogenic disease must be ruled out.

#### 4.1.1.a Anxiety, depression and overall function

Distress is best understood in the context of pain and of the meaning of pain to the individual and is best assessed ideographically rather than normatively. Almost all diagnostic measures and standardised instruments of anxiety and depression are designed for people without significant physical problems, so are difficult to interpret in chronic pelvic pain [235].

Anxiety about pain often refers to fears of missed pathology (particularly cancer) as the cause of pain [33], or to uncertainties about treatment and prognosis. This can drive healthcare seeking behaviour. The question: "What do you believe or fear is the cause of your pain?" has been suggested [236]. Anxiety may also concern urinary urgency and frequency that are problematic in social settings.

Depression or depressed moods are common in chronic pain [237], often related to losses consequent to chronic pain (work, leisure activities, social relationships, etc.). Due to the lack of suitable assessment instruments, it is better to ask a simple question such as "How does the pain affect you emotionally?". If the answer gives cause for concern about the patient's emotional state, further assessment should be undertaken by an appropriately qualified healthcare professional.

Most measures of restricted function are designed primarily for musculoskeletal pain and may emphasise mobility problems rather than the difficulties of the individual with pelvic or urogenital pain. A promising specific measure, UPOINT, was introduced and in a later version the sexual aspects were added [238]. However, it may underassess relevant psychological variables [40]. Generic QoL measures are helpful. If such an instrument is not already used, the Brief Pain Inventory [239] provides a broad and economical assessment of interference of pain with various aspects of life, and is available in multiple languages. For further suggested instruments see [240].

#### 4.1.1.b Urological aspects

Pain may be associated with urological symptoms. A detailed history of LUT functions should be taken. Dysfunctions of the LUT may exacerbate symptoms, as pain may interfere with the function of the LUT. Micturition in all its aspects should be addressed. Special attention should be paid to the influence of micturition on the experience of pain.

#### Primary prostate pain syndrome

Primary prostate pain syndrome is diagnosed from a history of pain perceived in the region of the prostate (convincingly reproduced by prostate palpation) and absence of other LUT pathology for a minimum of three months. As mentioned above, specific disease-associated pelvic pain must be ruled out. A thorough history is an important first step in the evaluation of PPPS. 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 [46]. In addition, associated LUT symptoms, 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 (see Section 4.2.1). These subjective outcome measures are recommended for the basic evaluation and therapeutic monitoring of patients in urological practice.

#### Primary bladder pain syndrome

PBPS 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 4) [13]. A targeted drug history should be obtained, with ketamine uropathy considered in young patients presenting with otherwise unexplained LUTS and suprapubic or bladder pain.

The nature of pain in PBPS is key to disease definition and typically includes:

1. pressure, pain, or discomfort perceived to be related to the bladder, intensifying with increasing bladder content
2. located suprapubically, sometimes radiating to the groins, vagina, rectum or sacrum
3. relieved by voiding but soon returns [241, 242]
4. aggravated by food or drink [242].

Primary bladder pain syndrome type 3 can lead to a small capacity fibrotic bladder with or without upper urinary tract outflow obstruction.

#### 4.1.1.c Gynaecological aspects

A detailed medical history outlining the nature, frequency and site of pain, as well as its relationship to precipitating factors and the menstrual cycle, may help define the aetiology. A menstrual and sexual history, including a history of sexually transmitted diseases, vaginal discharge, as well as previous sexual trauma, is mandatory along with an up-to-date cervical cancer screening. A history of obstetric and/or gynaecological surgery is also warranted, particularly if devices such as synthetic mesh were used.

#### 4.1.1.d Gastrointestinal aspects

The predominant symptoms that 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 taken, ideally applying symptom questionnaires for urinary and anorectal symptoms (e.g. Rome IV criteria 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.

Diagnostic criteria for primary chronic anal pain syndrome (chronic proctalgia) according to the Rome IV criteria are as follows and must include all of the following: chronic or recurrent rectal pain or aching; episodes last at least 30 minutes; and exclusion of other causes of rectal pain, such as ischaemia, inflammatory bowel disease, cryptitis, intramuscular abscess and fissure, haemorrhoids, prostatitis and coccyx pain syndrome. These criteria should be fulfilled for the past three months with symptom onset at least six months before diagnosis [14, 243].

Primary chronic anal pain syndrome includes the above diagnostic criteria and exhibits exquisite tenderness during posterior traction on the puborectalis muscle (previously called "levator ani syndrome"). Pathophysiology of pain is thought to be due to over-activity of the pelvic floor muscles and probably rectoanal incoordination.

Primary intermittent chronic anal pain syndrome (proctalgia fugax) consists of all the following diagnostic criteria, which should be present for three months: recurrent episodes of pain localised to the anus or lower rectum; episodes last from several seconds to minutes; and there is no anorectal pain between episodes. Stressful life events or anxiety may precede the onset of intermittent chronic anal pain syndrome. The attacks may last from a few seconds to as long as 30 minutes. 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.

#### 4.1.1.e Peripheral nerve aspects

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 than 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 developing 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 meaning to different patients, and some would rather use the term discomfort or numbness.

Aggravating factors include any type 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, consequently, develop a wide range of other aches and pains. Soft seats are often not 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.

Pudendal nerve damage may be associated with a range of sensory phenomena: in the distribution of the nerve itself as well as unprovoked pain; 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 visceral and striated muscle hyperalgesia.

The cutaneous sensory dysfunction may be associated with superficial dyspareunia, 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 of 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.

#### 4.1.1.f Myofascial aspects

When taking a history from a patient with pelvic pain, it is important to address the function of all the organs in the pelvic area. The following items should certainly be addressed: LUT function, anorectal function, sexual function, gynaecological items, presence of pain and psychosocial aspects. A diagnosis of pelvic floor dysfunction cannot be made on history alone. However, pelvic floor muscle dysfunction may be suspected when two or more pelvic organs are affected, such as a combination of LUTS and bowel symptoms.

#### 4.1.2 Physical evaluation

The clinical examination often serves to confirm or refute the initial impressions gained from a good history. The examination should be aimed at specific questions where the outcome of the examination may change management. Prior to an examination, best practice requires the medical practitioner to explain what will happen and what the aims of the examination are to the patient. Consent to the examination should occur during that discussion and should cover an explanation around the aim to maintain modesty as appropriate and, if necessary, why there is a need for rectal and/or vaginal examination. Finally, the risk of exacerbating the pain should form a part of that request. A record of the discussion should be noted. The possibility of the presence of a chaperone should be discussed with the patient. As well as a local examination, a general musculoskeletal and neurological examination should be considered and undertaken as an integral part of the assessment. Following the examination, it is good practice to ask the patient if they had any concerns relating to the conduct of the examination and that discussion should be noted.

There is no specific diagnostic test for CPPPS, therefore, procedures are directed towards identification and exclusion of specific diseases associated with pelvic pain and may be used for phenotypic description. Abdominal and pelvic examination to exclude gross pelvic pathology and demonstrate the site of tenderness is essential. It is important to look for abnormalities in muscle function.

Examination of the external genitalia is a part of the evaluation. In patients with scrotal pain, gentle palpation of each component of the scrotum is performed to search for masses and painful spots. The penis and urethra may be palpated in a similar way. Many authors recommend assessment of the cutaneous allodynia along the dermatomes of the abdomen (T11-L1) and the perineum (S3); the degree of tenderness should be recorded. The bulbocavernosus reflex in males may also provide useful information concerning the intactness of the pudendal nerves. Clinical pelvic examination should be a single digit examination, if possible. The usual bimanual examination can generate severe pain, and the examiner must proceed with caution. A rectal examination is performed to assess prostate abnormalities in male patients, including pain on palpation, and to examine the rectum and the pelvic floor muscles with respect to muscle tenderness, trigger points, and the ability to contract and relax these muscles.

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 for thoroughly in patients with anal pain. A rectal digital examination may show high or low anal sphincter resting pressure, a tender puborectalis muscle in patients with 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 combined rectal and vaginal examination to diagnose pelvic organ prolapse.

A full clinical examination of the musculo-skeletal, 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 findings are frequently 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 clinical diagnosis [244]. This may be elicited by per rectal or per vaginal examination and palpation in the region of the ischial spine and/or Alcock's canal. Muscle tenderness and the presence of trigger points in the muscles may complicate the clinical 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 abdominis or paraspinal muscles).

## 4.2 Supplemental evaluation

If history is suggestive of LUT, gynaecological, anorectal or other disease of known aetiology, the diagnostic work-up should follow the respective Guidelines.

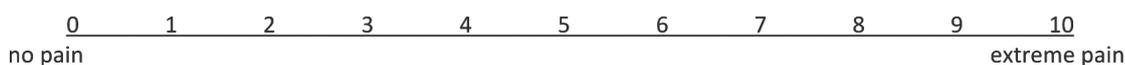
#### 4.2.1 **Assessing pelvic pain and related symptoms**

Determination of the severity of pain and associated symptoms, its progression and treatment response can be assessed only by means of a reliable and validated symptom-scoring instrument. These subjective outcome measures are recommended for the basic evaluation and therapeutic monitoring of patients. Pain should always be assessed at presentation and to identify progression and treatment response (see below). In addition to assessment in the clinic, the patient can maintain a daily record (pain diary). This may need to include other relevant variables such as voiding, sexual activity, activity levels or analgesic use. Increased attention to patient-reported outcomes gives prominence to patients' views on their disease. Pain diaries, in patients' own environments, improve data quality.

Quality of life should also be measured because it can be very poor compared to other chronic diseases [245, 246]. In a study, 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) [53].

Where the primary outcome of treatment is pain relief, it is valuable to agree upon a clinically useful level of relief before starting treatment [247]. The most reliable methods are:

- a five-point verbal scale: none, mild, moderate, severe, very severe pain
- a VAS score from one to ten
- an eleven-point numerical scale (as below).



Pain assessment ratings are not independent of cognitive and emotional variables [52]. Target outcomes of pain severity, distress and disability co-vary only partly, and improvement in one does not necessarily imply improvement in the others. When the primary outcome is pain, its meaning should be anchored in discussion of clinically important difference [247].

#### **Primary prostate pain syndrome**

Reliable, valid indices of symptoms and QoL are the NIH-CPSI [248] and the International Prostate Symptom Score (I-PSS) [249].

#### **Primary bladder pain syndrome**

Symptom scores may help to assess the patient and act as outcome measures. The O'Leary-Sant Symptom Index, also known as the Interstitial Cystitis Symptom Index (ICSI), was validated in a large study [250].

#### **Gastrointestinal questionnaire**

Functional anorectal pain disorders (anorectal pelvic pain) are defined and characterised by duration, frequency and quality of pain. More complex questionnaires are used in the setting of IBS. The validated IBS Symptom Severity Scale (IBS-SSS) includes the broadest measurement of pain-related aspects [251, 252]. However, as different instruments measure different endpoints of chronic abdominal pain in IBS, a comparison of published studies is often impossible.

#### **Sexual function assessment**

In males, the most frequent effect on sexual function are ED and premature ejaculation. These can be evaluated by proper questionnaires, namely IIEF and Premature Ejaculation Diagnostic Tool (PEDT). In comparison with controls, females with chronic pelvic pain reported significantly more sexual avoidance behaviour, non-sensuality and complaints of "vaginismus" [206]. The FSFI has been developed as a brief, multidimensional self-report instrument for assessing the key dimensions of sexual function in females, which includes desire, subjective arousal, lubrication, orgasm, satisfaction and pain [253]. The corresponding evidence in males is lacking.

#### 4.2.2 **Focused myofascial evaluation**

Pelvic floor muscle testing can be done by a clinician, but a consultation of the pelvic floor by a physiotherapist is a good alternative. Both should have appropriate training in pelvic assessment. A vaginal or rectal examination is performed to assess the function of the pelvic floor muscles, according to the International Continence Society (ICS) report. This assessment has been tested and shows satisfactory validity and intra-observer reliability. It can therefore be considered suitable for use in clinical practice [254]. Rectal examination is a good way to test the pelvic floor function in males [255]. There is a growing number of reports on the use of

ultrasound (US) in establishing the function of the pelvic floor muscles. The exact place in the diagnostic setting needs to be addressed in the future [256]. In a cohort study of 72 males with chronic pelvic pain, 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%) [257]. In addition, a broad musculoskeletal (tender point) evaluation, including muscles outside the pelvis, helps to diagnose the myofascial pain aspects of the pelvic pain in phenotyping pelvic pain patients [258, 259].

#### 4.2.3 **Neurological**

##### **Injections**

An injection of local anaesthetic and steroid at the site of nerve injury may be diagnostic. Differential block of the pudendal nerve helps to provide information in relation to the site where the nerve may be trapped [260, 261]. Infiltration at the ischial spine requires the use of a nerve stimulator/locator. Both motor (anal contraction) and sensory endpoints may be noted. The anatomical target may be localised by fluoroscopy, computed tomography (CT) guidance, or the use of US. An US avoids any form of radiation, whereas CT guidance involves a significant amount of radiation. As well as injecting around the pudendal nerve, specific blocks of other nerves arising from the pelvis may be performed.

##### **Electrophysiological studies**

These may reveal signs of perineal denervation, increased pudendal nerve latency, or impaired bulbocavernosus reflex [262, 263]. 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.

#### 4.2.4 **Imaging**

Ancillary studies should be performed according to appropriate guidelines for exclusion of diseases with known aetiology presenting with symptoms identical to those of chronic pelvic pain syndrome. Once the latter diagnosis is established, studies can be useful to assess functional abnormalities and phenotype conditions such as PBPS and primary chronic anal pain syndrome.

##### **Ultrasound**

Ultrasound has limited value but may reassure patients. However, over-investigating may be detrimental.

##### **Magnetic resonance imaging**

Magnetic resonance (MR) neurography has been increasingly used in specialised centres for the diagnosis of the location (proximal vs. peripheral) and degree (total vs. partial) of nerve injury in the peripheral nervous system, earlier and with higher specificity than conduction studies. This may show benefits for CPPPS in the coming years.

##### **Magnetic resonance defecating proctogram**

Magnetic resonance imaging in conjunction with MR defecography has become the most valuable imaging technique to assess anorectal function dynamically. Magnetic resonance imaging studies simultaneously outline the anatomy of the pelvic floor and visualise different structural and functional pathologies by applying dynamic sequences after filling of the rectum with a viscous contrast medium (e.g. US 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 or supine position and the limited space for the patient, which may reduce the ability to strain and thereby reduce the sensitivity of the method, underestimating the size of entero- and rectoceles as well as the amount of intussusception.

##### **Functional neuroimaging**

Functional magnetic resonance imaging (fMRI) is currently being re-evaluated as a research tool and some groups have raised issues around over interpretation [264]. With regards to pain, fMRI findings may represent a pain matrix or may represent non-specific threat processing [265]. Currently, this Panel cannot recommend fMRI as a clinical tool [266].

#### 4.2.5 **Laboratory tests**

##### **Microbiology tests**

###### **Primary prostate pain syndrome**

Laboratory diagnosis of prostatitis has been classically based on the four-glass test for bacterial localisation [267]. Besides sterile pre-massage urine (voided bladder urine-2), PPPS shows < 103cfu/mL 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 cost-effectively enhanced by a simple screening procedure, that is, the two-glass test or pre-post-massage test (PPMT) [268, 269]. Overall, these tests help only a little in the diagnosis of PPPS, because 8% of patients with suggested PPPS have been found to have positive prostatic localisation cultures, similar to the percentage of asymptomatic males [270].

###### **Primary bladder pain syndrome**

Urine dipstick and urine culture (including culture for tuberculosis if sterile pyuria) are recommended in all patients suspected of having PBPS. Urine cytology is also recommended in risk groups.

###### **Gynaecological aspects of chronic pelvic pain**

Vaginal and endocervical swabs to exclude infection are recommended. In specific cases, imaging may be required to help rule out a defined pathology, such as sacral neuropathy in endometriosis [271].

#### 4.2.6 **Invasive tests**

##### **Anorectal pain**

Anorectal manometry with sensory testing (pressure volume measurement: barostat) may be useful to diagnose dyssynergic defecation and hypersensitivity of the rectum that are typical for patients with CPPPS and IBS. Anorectal manometry and the ballon expulsion test (BET) may also help to predict the response to biofeedback therapy in levator ani syndrome [115]. In patients with anorectal pain, flexible rectosigmoidoscopy or colonoscopy should be considered to rule out coincidental colorectal pathology.

##### **Laparoscopy for females**

Laparoscopy is perhaps the most useful invasive investigation to exclude gynaecological pathology [272, 273] and to assist in the differential diagnosis of CPPPS in females [274, 275]. Often, it is combined with cystoscopy [276, 277] and/or proctoscopy to help identify the site of multi-compartment pain.

##### **Psychological considerations around laparoscopy**

Three very different studies of laparoscopy suggest that it can improve pain through resolving concerns about serious disease [278]. Integrating somatic and psychological assessment from the start rather than dealing with psychological concerns only after excluding organic causes of pelvic pain is helpful [279].

##### **Cystoscopy and bladder biopsy**

Despite controversy on the diagnostic and follow-up value of cystoscopy in PBPS [280-284], the Panel are of the view that objective findings are important for diagnosis, prognosis and ruling out other treatable conditions (a standardised scheme of diagnostic criteria will also contribute to uniformity and comparability of different studies) [285]. Endoscopically, PBPS type 3 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's lesion [241]. The scar ruptures with increasing bladder distension, producing a characteristic waterfall type of bleeding. There is a strong association between PBPS type 3 and reduced bladder capacity under anaesthesia [286]. Non-lesion disease displays a normal bladder mucosa at initial cystoscopy. The development of glomerulations after hydrodistension is considered to be a positive diagnostic sign although it can be observed without PBPS [287]. Biopsies are helpful in establishing or supporting the clinical diagnosis of both classic and non-lesion types of the disease [127, 158, 285, 288, 289]. Important differential diagnoses to exclude, by histological examination, are carcinoma *in situ* and tuberculous cystitis [290].

**Table 4: ESSIC classification of PBPS types according to results of cystoscopy with hydrodistension and biopsies [13]**

	Cystoscopy with hydrodistension			
	Not done	Normal	Glomerulations <sup>a</sup>	Hunner lesion <sup>b</sup>
Biopsy				
Not done	XX	1X	2X	3X
Normal	XA	1A	2A	3A
Inconclusive	XB	1B	2B	3B
Positive <sup>c</sup>	XC	1C	2C	3C

<sup>a</sup>Cystoscopy: glomerulations grade 2-3.

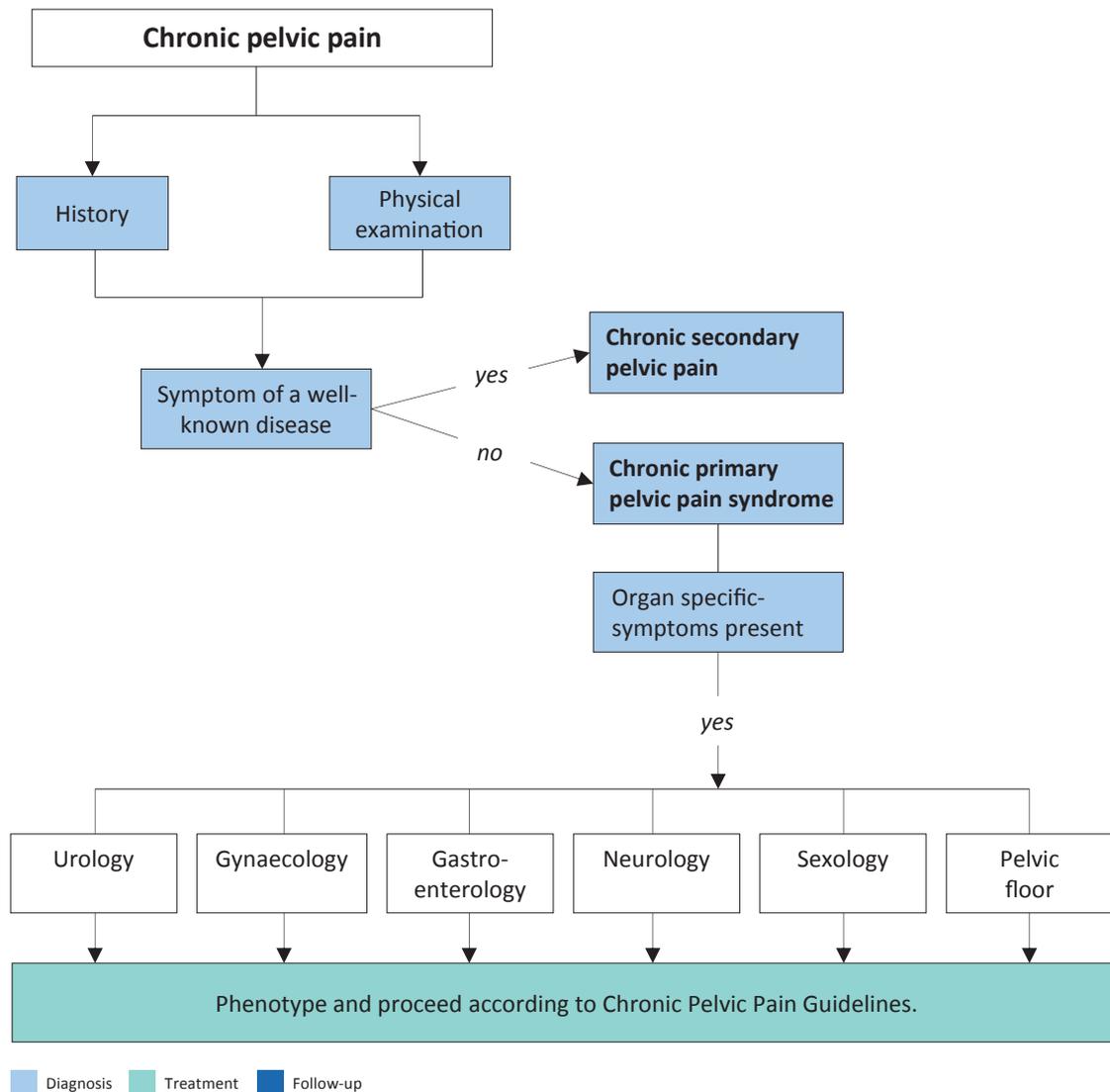
<sup>b</sup>Lesion per Fall's definition with/without glomerulations.

<sup>c</sup>Histology showing inflammatory infiltrates and/or detrusor mastocytosis and/or granulation tissue and/or intrafascicular fibrosis.

ESSIC = International Society for the Study of Bladder Pain Syndrome; PBPS = primary bladder pain syndrome.

### 4.3 Diagnostic algorithm

**Figure 1: Diagnosing chronic pelvic pain**



**Figure 2: Phenotyping of pelvic pain - UPOINT classification**

Phenotyping	Assessment
Urology	Urinary flow, micturition diary, cystoscopy, ultrasound, uroflowmetry.
Psychology	Anxiety about pain, depression and loss of function, history of negative sexual experiences.
Organ specific	Ask for gynaecological, gastro-intestinal, ano-rectal, sexual 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.
Sexological	Erectile function, ejaculatory function, post-orgasmic pain.

#### 4.4 Other painful conditions without a urological cause

##### Dysmenorrhoea

Menstrual pain or ‘dysmenorrhoea’ may be primary or secondary. Primary dysmenorrhoea classically begins at the onset of ovulatory menstrual cycles and tends to decrease following childbirth [274]. Secondary dysmenorrhoea suggests the development of a pathological process, such as endometriosis [273], adenomyosis or pelvic infection, which need to be excluded.

##### Infection

In premenopausal females, a history of pelvic inflammatory disease (PID) must be excluded. A patient’s sexual history should be taken along with swabs to exclude chlamydia and gonorrhoea infection. Bacterial and viral genital tract pathogens should also be excluded [291] as this can cause severe pelvic/vaginal/vulvar pain [292] and are associated with ulcerating lesions and inflammation, which may lead to urinary retention [293]. If there is any doubt about the diagnosis, laparoscopy may be helpful, as one of the differential diagnoses is endometriosis.

##### Endometriosis and adenomyosis

The incidence of endometriosis is rising in the developed world. It has widespread impact on female lives [294], with pain more important than physical findings in determining QoL [295]. The precise aetiology is unknown, but an association with infertility is recognised [296]. A diagnosis is usually made when a history of secondary dysmenorrhoea and/or dyspareunia exists [297]. On examination, there is often tenderness in the lateral vaginal fornices, reduced uterine mobility, tenderness in the rectovaginal septum and, on occasion, adnexal masses. Laparoscopy is the most useful diagnostic tool [298]. Adenomyosis is associated with augmented pain during menses [299]. It is diagnosed by an US of the uterus, which often shows cystic dilatation of the myometrium [300].

##### Gynaecological malignancy

The spread of gynaecological malignancy of the cervix, uterine body or ovary will cause pelvic pain depending on the site of spread.

##### Injuries related to childbirth

Trauma occurring at the time of childbirth may lead to chronic pelvic pain related to the site of injury [301]. Female sexual dysfunction is perhaps the most common presenting problem [302], though increasingly females are reporting other symptoms such as pelvic girdle pain and other genito-pelvic pain of different aetiology [303]. There is often a transient problem with oestrogen deficiency in the post-partum period and during breastfeeding, which can compound this condition. Denervation of the pelvic floor can similarly compound the condition [304].

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

Pelvic-organ prolapse is often asymptomatic, unless it is so marked that it causes back pain, vaginal pain and skin excoriation [305]. Prolapse is often a disease of older females and it is often associated with postmenopausal oestrogen deficiency that may lead to pain associated with intercourse. Prolapse surgery has entailed the use of non-absorbable mesh (usually in the form of “mesh kits”). Although these may have a role in supporting the vagina, it is also associated with several complications including bladder, bowel and vaginal trauma [306], chronic pain [307], and neuropathy [308]. Patients need to be fully evaluated and may need specialised imaging, using contrast mediums if necessary, to make a diagnosis of the possible cause of the pain [309-312].

### **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 prolapse or ulceration of internal haemorrhoids. Anaemia from haemorrhoidal bleeding is rare but may arise in patients on anti-coagulation therapy, or those with clotting disorders.

### **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 six 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.

### **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.

### **Irritable bowel syndrome**

Although IBS can be associated with pelvic pain, the Panel consider a full discussion of this topic beyond the scope of these Guidelines. Several high-quality clinical guidelines address this topic [243, 313].

## **4.5 Summary of evidence and recommendations for diagnostic evaluation**

### **4.5.1 Diagnostic evaluation - general**

<b>Summary of evidence</b>	<b>LE</b>
Clinical history and examination are mandatory when making a diagnosis.	2a

<b>Recommendation</b>	<b>Strength rating</b>
Take a full history and evaluate to rule out a treatable cause in all patients with chronic pelvic pain.	Strong

### **4.5.2 Diagnostic evaluation of primary prostate pain syndrome**

<b>Summary of evidence</b>	<b>LE</b>
Primary prostate pain syndrome is associated with negative cognitive, behavioural, sexual, or emotional consequences, as well as with symptoms suggestive of LUT and sexual dysfunction.	2b
Primary prostate pain syndrome has no known single aetiology.	3
Pain in PPPS involves mechanisms of neuroplasticity and neuropathic pain.	2a
Primary prostate pain syndrome has a high impact on QoL.	2b
Depression and catastrophic thinking are associated with more pain and poorer adjustment.	3
The prevalence of PPPS-like symptoms is high in population-based studies (> 2%).	2b
Reliable instruments assessing symptom severity as well as phenotypic differences exist.	2b

Recommendations	Strength rating
Adapt diagnostic procedures to the patient. Exclude specific diseases with similar symptoms.	Strong
Use a validated symptom and Quality of Life scoring instrument, such as the National Institutes of Health Chronic Prostatitis Symptom Index, for initial assessment and follow-up.	Strong
Assess primary prostate pain syndrome-associated negative cognitive, behavioural, sexual or emotional consequences, as well as symptoms of lower urinary tract and sexual dysfunctions.	Strong

#### 4.5.3 *Diagnostic evaluation of primary bladder pain syndrome*

Summary of evidence	LE
Primary bladder pain syndrome has no known single aetiology.	3
Pain in PBPS does not correlate with bladder cystoscopy or histologic findings.	2a
Primary bladder pain syndrome type 3C can only be confirmed by cystoscopy and histology.	2a
Lesion/non-lesion disease ratios of PBPS are highly variable between studies.	2a
The prevalence of PBPS-like symptoms is high in population-based studies.	2a
Primary bladder pain syndrome occurs at a level higher than chance with other pain syndromes.	2a
Primary bladder pain syndrome has an adverse impact on QoL.	2a
Reliable instruments assessing symptom severity as well as phenotypical differences exist.	2a

Recommendations	Strength rating
Perform general anaesthetic rigid cystoscopy in patients with bladder pain to subtype and rule out confusable disease.	Strong
Diagnose patients with symptoms according to the European Association of Urology definition, after primary exclusion of specific diseases, with primary bladder pain syndrome (PBPS) by subtype and phenotype.	Strong
Assess PBPS-associated non-bladder diseases systematically.	Strong
Assess PBPS-associated negative cognitive, behavioural, sexual or emotional consequences.	Strong
Use a validated symptom and Quality of Life scoring instrument for initial assessment and follow-up.	Strong

#### 4.5.4 *Diagnostic evaluation of scrotal pain syndrome*

Summary of evidence	LE
The nerves in the spermatic cord play an important role in scrotal pain.	2b
Ultrasound of the scrotal contents does not aid in diagnosis or treatment of scrotal pain.	2b
Post-vasectomy pain is seen in a substantial number of males undergoing vasectomy.	2b
Scrotal pain is more often noticed after laparoscopic than after open inguinal hernia repair.	1b

#### 4.5.5 *Diagnostic evaluation of urethral pain syndrome*

Summary of evidence	LE
Primary urethral pain syndrome may be a part of PBPS.	2a
Urethral pain involves mechanisms of neuroplasticity and neuropathic pain.	2b

#### 4.5.6 *Diagnostic evaluation of gynaecological aspects chronic pelvic pain*

Summary of evidence	LE
Laparoscopy is well-tolerated and does not appear to have negative psychological effects.	1b

Recommendations	Strength rating
Take a full uro-gynaecological history in those who have had a continence or prolapse non-absorbable mesh inserted and consider specialised imaging of the mesh.	Strong
Refer to a gynaecologist following complete urological evaluation if there is a clinical suspicion of a gynaecological cause for pain. Laparoscopy should be undertaken in accordance with gynaecological guidelines.	Strong

#### 4.5.7 Diagnostic evaluation of anorectal pain syndrome

Summary of evidence	LE
Tenderness on traction is the main criterion of the chronic anal pain syndrome.	1a

Recommendation	Strength rating
Anorectal function tests are recommended in patients with anorectal pain.	Strong

#### 4.5.8 Diagnostic evaluation of nerves to the pelvis

Summary of evidence	LE
Multiple sensory and functional disorders within the region of the pelvis/urogenital system may occur because 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

Recommendations	Strength rating
Rule out confusable diseases, such as neoplastic disease, infection, trauma and spinal pathology.	Strong
If a peripheral nerve pain syndrome is suspected, refer early to an expert in the field, working within a multidisciplinary team environment.	Weak
Imaging and neurophysiology help diagnosis, but image- and nerve-locator-guided local anaesthetic injection is preferable.	Weak

#### 4.5.9 Diagnostic evaluation of sexological aspects in chronic pelvic pain

Summary of evidence	LE
Chronic pain can lead to decline in sexual activity and satisfaction and may reduce relationship satisfaction.	2a
Males who reported having sexual, physical or emotional abuse show a higher rate of reporting symptoms of CPPPS.	2b
Sexual dysfunctions are prevalent in males with PPPS.	2b
In males with PPPS, the most prevalent sexual complaints are ED and ejaculatory dysfunction.	3
In females with CPPPS, all sexual function domains are lower. The most reported dysfunctions are sexual avoidance, dyspareunia and "vaginismus".	2a
Vulvar pain syndrome is associated with PBPS.	2a
Females with PBPS suffer significantly more from fear of pain, dyspareunia and decreased 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

Recommendation	Strength rating
Screen patients presenting with symptoms suggestive of chronic primary pelvic pain syndrome for abuse, without suggesting a causal relation with the pain.	Weak

#### 4.5.10 *Diagnostic evaluation of psychological aspects of chronic pelvic pain*

Summary of evidence	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 are possible contributory factors in pelvic pain.	2a

Recommendations	Strength rating
Assess patient psychological factors related to the pain, for example, pain-related fear, anxiety and depressive symptoms.	Strong
Ask patients what they think is the cause of their pain and other symptoms to allow the opportunity to inform and reassure.	Strong

#### 4.5.11 *Diagnostic evaluation of pelvic floor function*

Summary of evidence	LE
The ICS classification is suitable for clinical practice.	2a
Over-activity of the pelvic floor muscles is related to chronic pelvic pain, prostate, bladder and vulvar pain.	2a
Over-activity of the pelvic floor muscles is an input to the CNS 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

Recommendations	Strength rating
Use the International Continence Society classification on pelvic floor muscle function and dysfunction.	Strong
In patients with chronic primary pelvic pain syndrome, actively look for the presence of myofascial trigger points.	Weak

## 5. MANAGEMENT

The management of chronic pelvic pain is based on a biopsychosocial model. This is a holistic approach where patient engagement is fundamental. Communicating empathy and understanding is a prerequisite for patient engagement, which in turn facilitates treatment adherence and improves psychological well-being [77, 314]. Empathic communication should therefore be integrated at all stages in the management of chronic pelvic pain.

Single interventions, including psychology, physiotherapy, drugs and more invasive interventions, need to be considered within a broader personalised management strategy, including self-management. All potential interventions should be explored in collaboration with the patient, aiming for a shared understanding of the potential and realistic outcomes, where benefits, risks and efforts are weighed against each other, and against the possibility of no treatment.

### Patient education

Communicating empathy, legitimisation and understanding is particularly important for patient education. Patient education, defined as learning about diseases, symptoms, comorbidities and their management to improve health [315], shared learning and understanding form the basis of discussions about treatment options in chronic pelvic pain. Exploring the patient's worries, preferences, questions and concerns, and establishing what the patient believes is the cause of pain, are the first steps for personalising patient education according to needs.

Patient education has been categorised into pain science education (“how pain works”) and pain management education (“how to manage pain”) [316]. These two aspects should be customised based on the patient’s needs and requests. For many patients, recommendations for further learning from evidence-based resources is valuable to enhance health literacy. When developing educational resources, it is essential to consider educational, cultural, linguistic and socioeconomic diversity to ensure they are accessible and effective for all individuals. Clinicians can direct patients towards trustworthy and helpful resources. These may be published by public healthcare and by patient charities and organisations, and might include audio-visual resources such as podcasts, video clips and interactive content. This is important to ensure clear understanding of the risks, benefits and potential consequences of the available options [317]. This will empower patients to make informed decisions that reflect their personal values. Deliberate and personalised patient education and enhanced patient engagement will facilitate shared decision-making. Shared decision-making is the integration of clinical expertise and the patient’s (and/or carer and families) personal preferences, values and choices [318], which is ethically imperative and should be prioritised. The process underpins self-management and may provide better outcomes and prevention of relapse [319].

### **Treatment philosophy**

Providing information that is personalised and responsive to the patient’s problems, conveying belief and concern, is a powerful way to allay anxiety [320]. Additional written information or direction to reliable sources of information is useful; practitioners tend to rely on locally produced material or pharmaceutical products of variable quality while endorsing the need for independent materials for patients.

## **5.1 Conservative management**

### **5.1.1 Physical therapy**

The physiotherapist is part of the pain management team (including doctors, psychologists and nurses). 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. In most studies that look at the effect of physiotherapy in pelvic pain, treatment of the pelvic floor is only part of the pain management. In a review about physiotherapy in females with pelvic pain, it was concluded that recommendations for physiotherapy should be given with caution [321]. The review found six RCTs, of which three showed level 1b evidence with low risk of bias. One of these three found that Mensendieck somatocognitive therapy showed a pain reduction after one year follow-up of 64%. This approach consists of myofascial relaxation and tension, improving posture and movement in combination with cognitive behaviour therapy [322].

### **Pelvic floor muscle pain**

Treating pelvic floor over-activity and myofascial trigger points should be considered in the management of chronic pelvic pain. 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.

For patients with chronic pelvic pain 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 body 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 massage. Massage only improved complaints in the prostate pain group. The fact that gender distribution was different in each group is mentioned as a possible confounding factor [323]. A RCT of 84 patients with PPPS comparing so-called conventional therapy ( $\alpha$ -blockers, anti-inflammatory drugs and sitz baths) with biofeedback and pelvic floor muscle relaxation therapy, demonstrated an improvement in both groups after three months, but three months after the end of treatment, the effects only persisted in the biofeedback and pelvic floor muscle relaxation therapy patients [324].

### **Myofascial trigger point release**

Treatment of myofascial trigger points can be done by manual therapy, dry needling and wet needling. The evidence for all the different treatments is weak, with most studies showing no significant difference between these techniques, though most studies were small and heterogeneous with regards to the patients and methods. There is no evidence that manual techniques are more effective than no treatment [325]. Most studies of dry needling have 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 [326].

### **Physiotherapy in primary bladder pain syndrome**

Transvaginal manual therapy of the pelvic floor musculature (Thiele massage) in PBPS patients with high-tone dysfunction of the pelvic floor significantly improved several assessment scales [327]. The role of specific levator ani trigger point injections in females with chronic pelvic pain has been studied [328]. Each trigger point was identified by intravaginal palpation and injected with bupivacaine, lidocaine and triamcinolone. Seventy two percent of females improved with the first trigger point injection, with 33% being completely pain-free. Efficacy and safety of pelvic floor myofascial physical therapy have been compared with global therapeutic massage in females with PBPS; the global response assessment rate was 59% and 26%, respectively. Pain, urgency and frequency ratings, and symptoms decreased in both groups during follow-up, and did not differ significantly between the groups. This suggests that myofascial physical therapy is beneficial in females with PBPS [329].

### **Primary anal pain syndrome**

An RCT demonstrated that biofeedback treatment was superior to electrogalvanic stimulation and massage of the levator muscle for treating chronic primary anal pain syndrome [115]. 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. In patients with tenderness of the puborectalis muscle (Rome II: "Highly likely levator ani syndrome"), 87% 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 50mL water-filled balloon and to relax pelvic floor muscles after biofeedback treatment were predictive of a favourable therapeutic outcome [115]. The pathophysiology of the chronic primary anal pain syndrome is therefore like 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.

### **Treatment of sexual dysfunctions and chronic pelvic pain**

Couples often benefit from early referral for relationship and sexual counselling during their treatment course [330]. It needs to be remembered that sexual difficulties will arise because of pelvic pain syndromes as well as those disorders potentially being primary. Specific behavioural strategies for females 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 the activity to less than that which causes pain. 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 post-coital flares. The corresponding evidence in males is lacking, but similar principles would apply. Other behavioural changes involve pre- and post-coital voiding, application of ice packs to the genital or suprapubic area [330, 331], and increased use of vaginal dilators, fingers or sex toys. Lubricants can also be used and females with signs of vulvovaginal atrophy may benefit from oestrogen cream [332]. Optimising the pelvic floor muscle is indicated when dysfunction is present and will relieve the pain [333-335].

### **Other physical therapy interventions**

#### **Electromagnetic therapy**

A small, sham-controlled, double-blind study of four weeks showed a significant, sustained effect over a one-year period for CPPPS [336].

#### **Microwave thermotherapy**

In uncontrolled studies, significant symptomatic improvement has been reported from heat therapy, for example, transrectal and transurethral thermotherapy [337, 338].

#### **Extracorporeal shockwave therapy**

A small sham-controlled, double-blind study of four times weekly perineal extracorporeal shockwave therapy (n = 30) in males with CPPPS showed significant improvement in pain, QoL and voiding compared to the control group (n = 30) over 12 weeks [339]. Two other randomised sham-controlled studies have been published, one comparing ten treatment sessions over two weeks (n = 40 vs. n = 40) [340], another with four times weekly treatments (n = 20 vs. n = 20) [341]. Both concluded there was a significant effect in terms of total NIH-CPSI score and pain at 12 weeks. No long-term effects at 24 weeks could be shown in a published follow-up study of the second [342]. A Cochrane review of non-pharmacological interventions for chronic pelvic pain reported a reduction in symptoms following treatment compared with control and concluded that extracorporeal shockwave therapy may improve symptoms without an increase in adverse events [343]. In addition, a systematic review and meta-analysis concluded that extracorporeal shockwave therapy is effective

for the improvement of pain and QoL, but long-term efficacy was non-significant [344]. Publications have shown a potential role for external shock wave lithotripsy applied to the bladder. In an RCT enrolling 54 patients, improvement in the VAS > 3 was 57.1% versus 19.0% (ESWT vs. placebo;  $p = 0.011$ ), at 12 weeks post-treatment. However, the primary endpoint did not reach significance [345].

### **Acupuncture**

An RCT comparing acupuncture ( $n = 50$ ) versus sham-controlled ( $n = 50$ ) once weekly treatment for six weeks, showed significant long-lasting improvement at 24 weeks in terms of response rate and overall symptom scores [346]. Another RCT showed a significant effect for a follow-up of 32 weeks [347]. Two systematic reviews and meta-analyses were published in 2016 analysing seven RCTs with a total of 471 participants comparing acupuncture to sham-control or oral medical treatment [348, 349]. Both concluded that acupuncture was effective and safe, significantly reducing total NIH-CPSI scores compared to sham or medical treatment, and should be considered as a treatment option. This is in line with the conclusion of a Cochrane review [343] on non-pharmacological treatment options. In a large multicentre RCT comparing acupuncture ( $n = 220$ ) with sham acupuncture ( $n = 220$ ) in patients with PPPS over a period of eight weeks (20 sessions), a superior improvement of symptoms was shown in the acupuncture group with durable effects 24 weeks after treatment [350]. In a published systematic review and meta-analysis of only high-quality trials (JADAD score  $\geq 4$ ), it was concluded that acupuncture was superior to sham acupuncture in terms of pain score, NIH-CPSI score, QoL score, urinary symptom and efficacy rate [351].

### **Posterior tibial nerve stimulation**

See section 5.3.2, Neuromodulation.

### **Transcutaneous electrical nerve stimulation**

See section 5.3.2, Neuromodulation.

#### **5.1.2 Psychological therapy**

Psychological interventions may be directed at pain itself or at adjustment to pain in terms of function and mood and reduced healthcare use, with or without pain reduction. Ideally, treatment follows general principles and practice in the field of chronic pain [352, 353] but these have been neglected in pelvic pain. Three systematic reviews and meta-analyses of the few heterogeneous trials of psychologically based treatment for pelvic pain [354-356] found benefits for pain comparable to those from pharmacotherapy over a few months, but this was not sustained at follow-up. Exposure to pain-related fears in females with chronic pelvic pain proved superior to manual therapy in reducing those fears and overall pain disability, albeit assessed only by self-report [357]. The importance of multidisciplinary treatment is emphasised by several reviews [40, 358, 359] of intervention for diverse chronic pains, but standard multicomponent psychologically-based programmes for pelvic pains are mostly in the pilot stages [360], with mixed findings so far [361]. For primary focal vulvar pain syndrome, multimodal physiotherapy integrating psychological components has shown beneficial effects, although more research on the effects of psychological therapy and multicomponent psychologically-based programmes is needed in this patient group [362]. For less disabled and distressed patients, treatment can be delivered remotely [363, 364].

#### **5.1.3 Dietary treatment**

Scientific data are limited and dietary restriction alone does not produce significant symptomatic relief; however, consider the involvement of a dietician.

## **5.2 Pharmacological management**

### **5.2.1 Drugs for chronic primary pelvic pain syndrome**

In this Section, the evidence available for specific CPPPSs is presented. More generic use is discussed in Section 5.2.2. 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, for example, PPPS, one reason for treatment failure in some large placebo-controlled RCTs, may be the heterogeneity of the patient population. One strategy for improving treatment effects may be stratification of patient phenotypes. A prospective series of phenotypically directed treatment for CPPPS has shown significant improvement of symptoms and QoL [365]. Monotherapeutic strategies for the treatment of CPPPS may fail [366], therefore, most patients require multimodal treatment aimed at the main symptoms, and taking comorbidity into account. In the past ten years, results from RCTs have led to advances in standard and novel treatment options.

### 5.2.1.a Mechanisms of action

Mechanisms of action are discussed as appropriate under the drugs headings below.

### 5.2.1.b Comparisons of agents used in pelvic pain syndromes

#### **Primary prostate pain syndrome**

##### **Anti-inflammatory drugs**

For non-steroidal anti-inflammatory agents (NSAIDs), a trial with celecoxib reported that the pain sub-score, QoL sub-score, and total NIH-CPSI score were in favour of the treatment arm versus placebo, but effects were limited to the duration of therapy [367]. In a meta-analysis, two studies of NSAIDs [270, 367] and one with prednisolone [368] were pooled. Anti-inflammatory drugs were 80% more likely to have a favourable response than placebo. In an updated network meta-analysis with more restrictive inclusion criteria regarding documented outcome measures but a wider spectrum of drugs (including GAGs, phytotherapy and tanezumab), a significant effect on total NIH-CPSI scores and treatment response rates could be demonstrated. A 2019 Cochrane systematic review concluded that anti-inflammatories may reduce prostatitis symptoms compared to placebo [369]. Overall, a moderate treatment effect has been shown for anti-inflammatory drugs, but larger studies are needed for confirmation, and long-term side effects must be considered.

##### **$\alpha$ -blockers**

Positive results from RCTs of the  $\alpha$ -blockers terazosin [370, 371], alfuzosin [372], doxazosin [373, 374], tamsulosin [375, 376] and silodosin [377] have led to widespread use of  $\alpha$ -antagonists in the treatment of PPPS in recent years. Whereas one systematic review and meta-analysis did not report a relevant effect of  $\alpha$ -blockers due to study heterogeneity [378], another network meta-analysis of  $\alpha$ -blockers [377] showed significant improvement in total symptoms, pain, voiding and QoL scores. In addition, it had a higher rate of favourable response compared to placebo (relative risk [RR]: 1.4; 95% CI: 1.1–1.8;  $p = 0.013$ ). However, treatment responsiveness, that is, clinically perceptible or significant improvement, may be lower than expected from the change in mean symptom scores. Overall,  $\alpha$ -blockers seem to have moderate but significant beneficial effects. This probably is not the case for long-standing PPPS patients [379]. A 2019 Cochrane systematic review reported an uncertain treatment effect of  $\alpha$ -blockers on “prostatitis” symptoms, and little to no difference in sexual dysfunction, QoL, anxiety and depression [369]. Future studies should show if longer duration of therapy or phenotypically directed (e.g. patients with PPPS and relevant voiding dysfunction) treatment strategies will improve treatment outcomes.

##### **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 four to six weeks or even longer. Culture, leukocyte and antibody status of prostate-specific specimens do not predict antibiotic response in patients with PPPS [380], and prostate biopsy culture findings do not differ from those of healthy controls [381]. The only placebo-controlled RCTs of sufficient quality have been done for oral antibiotic treatment with ciprofloxacin (six weeks) [382], levofloxacin (six weeks) [383], and tetracycline hydrochloride (12 weeks) [384]. These studies have been analysed in meta-analyses [377, 385]. Although direct meta-analysis has not shown significant differences in outcome measures, network meta-analysis has suggested significant effects in decreasing total symptom, pain, voiding, and QoL scores compared with placebo. Combination therapy of antibiotics with  $\alpha$ -blockers has shown even better outcomes in network meta-analysis. Despite significant improvement in symptom scores, antibiotic therapy did not lead to statistically significant higher response rates [385]. In addition, the sample sizes of the studies were relatively small and treatment effects only modest, mostly below clinical significance. It may be speculated that patients profiting from treatment had some unrecognised uropathogens. A Cochrane systematic review reported that antibiotics may reduce “prostatitis” symptoms compared to placebo [369]. If antibiotics are used, other therapeutic options should be offered after one unsuccessful course of a quinolone or tetracycline antibiotic over six weeks. In addition, it is very important that unnecessary antibiotic use is avoided and local resistance patterns are considered. In this regard, the relevant recommendations of the EAU Guidelines on Urological Infections should be followed [386].

##### **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 RCT published in a peer-reviewed journal did not support this, although the study lacked power [387]. In another RCT, finasteride provided better amelioration of symptoms compared to saw *palmetto* over a one-year period but lacked a placebo-control arm [388]. A six-month placebo-controlled study showed a non-significant tendency towards better outcome in favour of finasteride, possibly because of a lack

of statistical power [376]. A Cochrane review concluded that finasteride probably reduces prostatitis symptoms compared to placebo [369]. The NIH-CPSI scores decreased significantly in a subgroup of males enrolled in a prostate cancer risk reduction study treated with dutasteride compared to placebo [377]. Patients (n = 427; age 50 to 75; with elevated prostate-specific antigen [PSA]) were included if they had significant “prostatitis like” symptoms at baseline. Based on the evidence, 5- $\alpha$ -reductase inhibitors cannot be recommended for use in PPPS in general, but symptom scores may be reduced in a restricted group of older males with an elevated PSA [377].

### **Phytotherapy**

Phytotherapy applies scientific research to the practice of herbal medicine. An adequately powered placebo-controlled RCT of a pollen extract (Cernilton<sup>®</sup>) showed clinically significant symptom improvement over a 12-week period in inflammatory PPPS patients (NIH Cat. IIIA) [389]. The effect was mainly based on a significant effect on pain. Another pollen extract (DEPROX 500) has been shown to significantly improve total symptoms, pain and QoL compared to ibuprofen [390]. A RCT of patients treated with pollen extract suppositories (n = 70) versus oral ibuprofen (n = 71) over a period of ten days found a clinically significant effect up to six months of follow-up, including fewer adverse events in the pollen extract group [391]. A systematic review and meta-analysis of pollen extract for the treatment of PPPS showed significant improvement in overall QoL [392]. As an adjunct to  $\alpha$ -blocker therapy, cernitin pollen extract proved superior to tadalafil in terms of pelvic pain and discomfort [393]. Quercetin, a polyphenolic bioflavonoid with documented antioxidant and anti-inflammatory properties, improved NIH-CPSI scores significantly in a small RCT [394]. In a large, multicentre trial of 221 patients over 12 weeks, *saw palmetto* extract (*Serenoa repens*) led to statistically significant improvement in the NIH-CPSI total score and sub-scores compared to placebo [395]. In a systematic review and meta-analysis, patients treated with phytotherapy were found to have significantly lower pain scores than those treated with placebo [377]. In addition, overall RR in network meta-analysis was in favour of phytotherapy (RR: 1.6; 95% CI: 1.1–1.6).

**Pregabalin** is an anti-epileptic drug that has been approved for use in neuropathic pain. In an adequately powered placebo-controlled RCT, which was the only report included in a published Cochrane review [396], a six-week course of pregabalin (n = 218) compared to placebo (n = 106) did not result in a significant reduction of NIH-CPSI total score [397]. This may have a role in selected patients and should be used in accordance with Section 5.2.2.

**Pentosane polysulphate** is a semi-synthetic drug manufactured from beech-wood hemicellulose. One study using oral high-dose (3 x 300mg/day) demonstrated a significant improvement in clinical global assessment and QoL over placebo in males with PPPS, suggesting a possible common aetiology [398].

**Muscle relaxants** (diazepam, baclofen) are claimed to be helpful in sphincter dysfunction or pelvic floor/perineal muscle spasm, but there have been few prospective clinical trials to support these claims. In one RCT, a triple combination of a muscle relaxant (thiocolchicoside), an anti-inflammatory drug (ibuprofen) and an  $\alpha$ -blocker (doxazosin) was effective in treatment-naïve patients, but not superior to an  $\alpha$ -blocker alone [374].

**Botulinum toxin type A (BTX-A)** for the treatment of CPPPS is an off-label use, but a systematic review identified two RCTs and one non-randomised comparative study assessing intraprostatic BTX-A injections (100-200 units) for treatment of PPPS [399]. All three papers used the NIH-CPSI to score pain. Although two of the studies reported a statistically significant reduction in pain, incomplete data and differences in dose and study methodology precluded calculation of a summary effect estimate for BTX-A-related improvement in pain. No definitive conclusions could be drawn from the review.

**Zafirlukast**, a leukotriene antagonist, and prednisone failed to show a benefit in two low-power placebo-controlled studies [368, 400]. A placebo-controlled phase IIa study of tanezumab, a humanised monoclonal antibody that specifically inhibits the pain mediating neurotrophin (a nerve growth factor), failed to demonstrate significant effect [401] and should only be used in clinical trials.

### **Allopurinol**

There is insufficient evidence for the use of allopurinol in PPPS [402, 403].

## **Primary bladder pain syndrome**

### **Treatments of significant value for primary bladder pain syndrome**

#### **Antihistamines**

Mast cells may play a role in PBPS. Histamine is one of the substances released by mast cells. Histamine receptor antagonists have been used to block the H1 and H2 receptor subtypes, with variable results. A prospective placebo-controlled RCT of hydroxyzine or oral pentosane polysulphate did not show a significant effect [404].

#### **Amitriptyline**

Amitriptyline is a tricyclic antidepressant. Several reports have indicated improvement of PBPS symptoms after oral amitriptyline. Amitriptyline has been shown to be beneficial when compared with placebo plus behavioural modification [405]. Drowsiness is a limiting factor with amitriptyline; nortriptyline is sometimes considered instead.

#### **Pentosane polysulphate**

Pentosane polysulphate is a semi-synthetic drug manufactured from beech wood hemicellulose. Subjective improvement of pain, urgency, frequency, but not nocturia, has been reported [406, 407]. Pentosane polysulphate had a more favourable effect in PBPS type 3C than in non-lesion disease [408]. Response was not dose dependent but related more to treatment duration. At 32 weeks, about half the patients responded. Combination therapy showed a RR of 40% compared to 13% with placebo. For patients with an initial minor response to pentosane polysulphate, additional subcutaneous heparin was helpful [409, 410].

#### **Immunosuppressants**

Azathioprine treatment has resulted in disappearance of pain and urinary frequency [411]. Initial evaluation of methotrexate [412] showed good analgesic effect but limited efficacy for urgency and frequency. Corticosteroids are not recommended in the management of patients with PBPS because of a lack of evidence.

#### **Intravesical treatments**

Intravesical drugs are administered due to poor oral bioavailability establishing high drug concentrations within the bladder, with few systemic side effects. Disadvantages include the need for intermittent catheterisation (which can be painful in PBPS patients), cost and risk of infection.

- **Local anaesthetics**

There are sporadic reports of successful treatment of PBPS with intravesical lidocaine [413, 414]. Alkalinisation of lidocaine improves its pharmacokinetics [415]. Combination of heparin, lidocaine and sodium bicarbonate gave immediate symptom relief in 94% of patients and sustained relief after two weeks in 80% of patients [416]. Intravesical instillation of alkalinised lidocaine or placebo for five consecutive days resulted in significantly sustained symptom relief for up to one month [417].

- **Hyaluronic acid and chondroitin sulphate**

These are described to repair defects in the GAG layer. Even though intravesical GAG replenishment has been in use for about twenty years for PBPS/IC, most of the studies are uncontrolled and with a small number of patients. Based on the studies available, there are differences by virtue of substance classes, whether they are natural GAG layer components, dosage formulations, or concentrations. An RCT seems to reinforce the case for GAG layer replenishment, however it lacks a placebo arm [418]. A meta-analysis confirms usefulness of GAG layer replenishment [412]. However, most retrieved studies are non-randomised and with scarce numbers.

- **Intravesical heparin**

Primary bladder pain syndrome patients were treated with heparin for three months, and over half had control of symptoms, with continued improvement after one year of therapy [419]. Intravesical heparin plus peripheral neuromodulation in patients with refractory PBPS was studied and it was shown that voiding frequency, pain score and maximum cystometric capacity were significantly better after two and 12 months [420].

- **Hyperbaric oxygen**

This has a moderate effect on a small subgroup of PBPS patients. Disadvantages include high cost, limited availability of treatment sites, and time-consuming treatment [409].

## **Treatments of limited value for primary bladder pain syndrome**

### **Cimetidine**

There are limited data to suggest that cimetidine improves symptoms of PBPS in the short-term. Compared with placebo for three months, cimetidine significantly improved symptom scores, pain and nocturia, although the bladder mucosa showed no histological changes in either group [421].

### **Prostaglandins**

Misoprostol is a prostaglandin that regulates various immunological cascades. After three months of treatment with misoprostol, 14 out of 25 patients had significantly improved, with 12 showing a sustained response after a further six months [422]. The incidence of adverse drug effects was 64%.

### **L-Arginine**

Oral treatment with the nitric oxide (NO) synthase substrate L-arginine was suggested to decrease PBPS-related symptoms. However, no symptomatic relief or change in NO production could be shown after treatment [423, 424].

**Oxybutynin** is an anti-cholinergic drug used in overactive detrusor dysfunction. Intravesical oxybutynin combined with bladder training improves functional bladder capacity, volume at first sensation, and cystometric bladder capacity [425]. However, an effect on pain has not been reported.

**Duloxetine** is a serotonin-noradrenaline re-uptake inhibitor antidepressant with a licence for the management of neuropathic pain. It did not significantly improve symptoms of PBPS [426]. Administration was safe. Based on these preliminary data, duloxetine cannot be recommended for treatment of PBPS.

**Phosphodiesterase type 5 inhibitors (PDE5Is) inhibitors** are drugs currently used for ED. In an RCT, it improved all parameters evaluated at 12 weeks, but at 24 weeks results were not consistent for pain VAS score [427]. Using a PDE5I, theoretically, the activation of C-fibre is decreased, bladder afferent activity is reduced, and detrusor muscle tone relaxes.

### **Primary scrotal pain syndrome**

Treatment of primary scrotal pain syndrome is based on the principles of treating chronic pain syndromes, as described throughout these Guidelines.

In males with pain post-inguinal hernia repair, there is limited evidence from case series showing that neurectomy of the damaged nerves can lead to symptomatic benefit [187, 428].

For scrotal pain post-vasectomy, affected males may find that reversal of the vasectomy can cure symptoms, especially in those in whom patency is achieved [429]. In a prospective RCT, pulsed radio frequency to the ilioinguinal and genitofemoral nerves is associated with high rates of symptomatic improvement (80%) but follow-up was limited to three months [430]. The evidence for epididymectomy is poor but if considered, is less likely to provide benefit if the epididymis has a normal sonographic appearance [431].

### **Chronic gynaecological pain**

It is difficult to compare the wide variation of drugs from an efficacy and safety perspective as these have such diverse uses/indications. In gynaecological patients whose chronic pelvic pain is not attributable to any well-defined condition, it is often difficult to identify a therapeutic pathway other than a multidisciplinary approach to chronic abdominopelvic pain management. A Cochrane review suggests there may be some evidence (moderate) supporting the use of progestogens [354]. Though efficacious, physicians need to be knowledgeable of progestogenic side effects (e.g. weight gain, bloatedness - the most common adverse effects) that can stop some patients from accepting such medication. Gonadotropin-releasing hormone (GnRH), such as goserelin, are also thought to help such pain. However, when compared with progestogens, the efficacy remains limited. The quality of evidence is generally low and drawn from single studies [354]. Gonadotropin-releasing hormone binds to specific receptors on pituitary gonadotrophs, leading to desensitisation and consequently to suppressed gonadotropin secretion. By contrast, GnRH antagonists compete with GnRH for receptors, thus gonadotrophin secretion, which may be beneficial in certain clinical applications, such as reducing the size of fibroids, endometrial bleeding and endometriosis [432].

## **Pelvic floor, abdominal and chronic anal pain**

### **Botulinum toxin type A (pelvic floor)**

Pelvic floor muscle overactivity plays a role in CPPPS. Botulinum toxin type A as a muscle relaxant, can be used to reduce the resting pressure of the pelvic floor muscles and injection of the puborectalis and pubococcygeus muscles has been used to treat spasm of the levator ani. A pilot study of 12 females with pelvic floor muscle overactivity, as defined by a vaginal resting pressure > 40cm H<sub>2</sub>O on vaginal manometry, reported a reduction in resting pressure with improvement in dyspareunia and dysmenorrhoea, but no significant changes in non-menstrual pelvic pain scores [433]. A systematic review including three RCTs comparing BTX-A with saline injections into the pelvic floor found no benefit in pain scores at six months follow-up despite a reduction in pelvic floor pressure [399].

Botulinum toxin type A has been injected into trigger points. It is more expensive than lidocaine and has not been proven to be more effective [434]. Reviews do not support the injection of BTX-A into trigger points [435].

Botulinum toxin type A can also be injected at the sphincter level to improve urination or defecation. Relaxation of the urethral sphincter alleviates bladder problems and secondarily the spasm. In a cohort study of 13 patients with CPPPS, BTX-A was injected into the external urethral sphincter. Subjectively, 11 patients reported a substantial change in pain symptoms, from a score of 7.2 to 1.6 on a VAS [436].

### **Intermittent chronic primary anal pain syndrome**

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 [437]. Other treatment options are topic diltiazem and BTX-A [438]. However, there is still some controversy regarding the duration of pain of intermittent chronic and chronic primary anal pain syndrome. Randomised controlled trials often use different definitions, extending the pain duration (with a shift to chronic pain) to include more patients and to better evaluate the study-drug action.

### **Abdominal pain associated with irritable bowel syndrome**

Linaclotide, a minimally absorbed peptide guanylate cyclase-C agonist, at a dose of 290 $\mu$ g once daily significantly improved abdominal pain (48.9% vs. 34.5% placebo-treated) and bowel symptoms associated with IBS with constipation over 26 weeks of treatment [439]. Diarrhoea was the most common adverse event in patients treated with linaclotide (4.5%). Although it is known to overlap with IBS pelvic pain, effect on the latter was not assessed in this study.

In a Cochrane meta-analysis, antispasmodics had a beneficial effect for improvement of abdominal pain compared to placebo (58% vs 46%) in IBS [440]. In a meta-analysis of nine RCTs, peppermint oil showed improvement in abdominal pain in patients with IBS [441].

#### **5.2.2 Analgesics**

If the use of simple analgesics fails to provide adequate benefit, consider using neuropathic agents, and if there is no improvement, consider involving a specialist pain management centre with an interest in pelvic pain. Chronic pelvic pain is well defined and involves multiple mechanisms as described in previous sections.

The management requires a holistic approach with biological, psychological and social components. Few studies have specifically looked at medications used in CPPPS [442], therefore, a wider look at the literature has been undertaken and further specific research is required. The agents concerned are divided for ease of description. Combinations often provide a greater benefit than individual agents [443]. They may also allow lower individual dosages and thus minimise 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 use of these agents does not allow this, then they should be withdrawn. The failure of one agent does not exclude potential benefit of an alternative. If the benefit is limited by side effects, then the lowest effective dose should be found (by dose titration). Sometimes, patients will prefer a higher level of pain and have fewer side effects.

##### **5.2.2.a Mechanisms of action**

Mechanisms of action are discussed as appropriate under the drug headings below.

### 5.2.2.b Comparisons within and between groups in terms of efficacy and safety

#### **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 [444]. It is often available over the counter without prescription. A review questions its routine use as a first-line analgesic based on inadequate evidence of efficacy in many pain conditions, including dysmenorrhoea [445]. It will not be effective for all patients and individual responses should be reviewed when deciding on longer term use.

#### **Non-steroidal anti-inflammatory agents**

These agents are anti-inflammatory, antipyretic analgesics that act by inhibiting the enzyme cyclooxygenase (COX). They have a peripheral effect, hence their use in conditions involving peripheral or inflammatory mechanisms. They are commonly used for pelvic pain; many are available over the counter and are usually well-tolerated. There is insufficient evidence to suggest one NSAID over another for pelvic pain. 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.

The evidence for their benefit in chronic pelvic pain is weak or non-existent and is often limited by side effects. For pelvic pain in which inflammatory processes are considered important, such as dysmenorrhoea [446], 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 [447], evidence is lacking for NSAIDs despite their common use.

At a practical level, if NSAIDs are considered, they should be tried (having regard for the cautions and contraindications) and the patient reviewed for improvement in function as well as analgesia. If this is not achieved, or side effects are limiting, then they should be withdrawn.

#### **Neuromodulators**

These agents are not simple analgesics but are used to modulate neuropathic or centrally mediated pain. There are several classes commonly used with recognised benefits in pain medicine. They are taken on a regular basis, and all have side effects that may limit their use and have the potential to be dependence-forming. In the UK, NICE has reviewed the pharmacological management of neuropathic pain [448]. The evidence for treatment of CPPPS 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. It is common to use these agents in combination but studies comparing different agents against each other, or in combination, are lacking. Some of these agents are also used for specific conditions. Early identification of neuropathic pain with a simple questionnaire could facilitate targeted therapy with neuromodulators [54].

#### **Antidepressants**

##### **Tricyclic antidepressants**

The tricyclic antidepressants (TCAs) have multiple mechanisms of action and are frequently limited by their side effects. Tricyclic antidepressants have a long history of use in pain medicine and have been subjected to a Cochrane review [449], suggesting that they are effective for neuropathic pain. Amitriptyline is the most used at doses from 10-75mg/day (sometimes rising to 150mg/day). This is titrated against benefit or side effects and should be taken at night [448]. Nortriptyline and imipramine are used as alternatives.

##### **Other antidepressants**

Duloxetine is a serotonin and noradrenaline reuptake inhibitor (SNRI) antidepressant licensed for use in depression, SUI and neuropathic pain. There is evidence of benefit in diabetic neuropathy and FM at a dose of 60mg/day [450, 451]. Side effects are common and may result in its discontinuation.

##### **Anticonvulsants**

Anticonvulsants are commonly used in the management of neuropathic pain. There are general studies and some look more particularly at pelvic pain. Individual agents have been systematically reviewed. Their use is suggested in the NICE Neuropathic Pain Guidelines [448].

*Carbamazepine* has a long history of use in neuropathic pain. Evidence exists for its benefit [452]. Trials tend to be of short duration, showing only moderate benefit. There are side effects, some of which may be serious. It is no longer a first-choice agent. Other anticonvulsant agents are available with fewer serious side effects.

#### **Gabapentinoids**

There is a growing awareness and evidence of the risk for dependence and misuse of gabapentinoids [453]. A formal assessment of efficacy against benefit and side effects (both pain and QoL) is required with the patient to determine the lowest effective dose and if longer-term treatment is to be used.

*Gabapentin* is commonly used for neuropathic pain and has been systematically reviewed [454, 455]. This demonstrates good evidence for postherpetic neuralgia and diabetic neuropathy but evidence for other neuropathies is limited. A double-blind RCT looking at CPPPS in females with no obvious pathology demonstrated no benefits but higher levels of side effects [455].

*Pregabalin* is a commonly used neuromodulator with good evidence of efficacy in some neuropathic conditions [456]. The dose for benefit is in the range of 300-600mg/day. Evidence for central neuropathic pains is inadequate. Some patients do gain moderate to significant benefit, but most will gain no benefit and then the drug should be discontinued. Other agents can be used in the management of neuropathic pain, but they are best administered by specialists in the management of pain who are 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 multidimensional management plan.

#### **Opioids**

Opioids have been used extensively in the management of chronic non-cancer pain. There is increasing evidence that their role is limited in this population but may be beneficial for a small number of patients at a low dose in a managed setting [457]. There is clear evidence of harm and significant professional, public and political interest. Their use is beneficial for both acute pain and for cancer pain management, particularly towards the end of life.

Often patients will stop taking oral opioids due to side effects or insufficient analgesic effects [458]. There is clear evidence of harm, including effects on the endocrine and immune systems, as well as a growing understanding of opioid-induced hyperalgesia [459]. There is limited guidance on the best method for tapering the dose of opioids with the aim of stopping or finding the lowest effective dose [460].

Opioids should be used only as part of a structured management plan, in consultation with 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. Ensure there are arrangements for formal monitoring, follow-up and review. If opioids are used and the pain remains, then they are not working and should be stopped, even if there is no alternative [459].

The risk of harm increases substantially at doses above 120mg/day morphine-equivalence [459] and guidance suggests regular (at least annual) review for patients with over 50mg/day morphine-equivalence and pain specialist involvement above 90mg/day morphine-equivalence [461].

There are well-established guidelines for the use of opioids in pain management as well as considering the potential risks [459, 461]. Opioid reduction and optimisation should be undertaken where opioids are not providing clear, measurable benefit. There is also information available online for patients [459]. Opioids Aware is a web-based resource (<https://fpm.ac.uk/opioids-aware>) for patients and healthcare professionals, jointly produced by the Faculty of Pain Medicine of Royal College of Anaesthetists and Public Health England, to support prescribing of opioid medicines for pain [459].

#### **Cannabinoids**

There has been increasing interest and changes in national regulations regarding the use of cannabinoids for medicinal use. Regarding pain, the evidence base for the use of cannabinoids is weak [462-464] and further well conducted clinical trials are necessary. This is an area where further guidance and research is likely in the coming years.

## **5.3 Further management**

### **5.3.1 Nerve blocks**

Nerve blocks for pain management are usually carried out by specialists in pain medicine as part of a broader management plan [465]. 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 mechanisms underlying the painful condition or syndrome. Sustained but limited benefit may lead to more permanent procedures (e.g. radiofrequency procedures). There is a weak evidence base for use of these interventions in chronic non-cancer pain [466-469].

#### **Pudendal neuralgia**

The role of injections may be divided into two. First, an injection of local anaesthetic with or without steroids at the site of nerve injury or nerve entrapment may produce a therapeutic action [470, 471]. The second possible benefit 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 [270, 472-474].

Infiltration at the ischial 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, CT guidance, or the use of US – the latter avoids any radiation, whereas CT guidance involves a significant amount of radiation. Fluoroscopy and US guidance imaging are the most frequently used techniques for performing nerve block because it is readily available to most anaesthetists. Pulsed radio frequency lesioning for pudendal neuralgia is being developed with a paper demonstrating potential benefit. Follow-up is short term and further research is required to better elucidate its place in management [475].

### **5.3.2 Neuromodulation**

The role of neuromodulation in the management of pelvic pain should only be considered by specialists in pelvic pain management. These techniques are 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, sacral root stimulation, dorsal root ganglion stimulation or peripheral nerve stimulation). These are expensive interventional techniques for patients that are refractory to other therapies. Neuromodulation is still finding its role in pelvic pain management. There has been growing evidence but more detailed, high-quality research is required [476]. Its role in overactive bladder (OAB) and faecal incontinence is more robust but is limited for pain. Two systematic reviews have evaluated neuromodulation techniques for chronic pelvic pain syndrome [477, 478]. Both studies concluded that neuromodulation may be effective in reducing pain and improving QoL in patients with chronic pelvic pain syndrome; however, studies were of a low quality and long-term results were needed.

#### **Transcutaneous electrical nerve stimulation**

Transcutaneous electrical nerve stimulation (TENS) is a non-invasive technique used in many pain conditions. A systematic review identified 12 studies of TENS in chronic pelvic pain conditions including four RCTs [477]. All RCTs demonstrated a significant reduction in pain following 12 weeks of treatment for pain conditions, including dysmenorrhoea and CPPPS. Pain was also found to improve following TENS for provoked vestibular pain. There was conflicting data regarding improvement of QoL following TENS; where validated questionnaires were used, no significant improvement was found, whereas in trialist-defined studies, an improvement was seen in TENS for dysmenorrhoea and CPPPS. The beneficial effects of a course of TENS may be sustained; one study demonstrating a persistent benefit at 43 months in 73% of males with CPPPS and another demonstrating a prolonged significant improvement in females with provoked vestibular pain at ten months post-treatment. Where reported, there were no adverse events recorded. Transcutaneous electrical nerve stimulation could offer an effective non-invasive treatment option for patients with CPPPS.

#### **Percutaneous tibial nerve stimulation**

Percutaneous tibial nerve stimulation (PTNS) is a minimally invasive technique that can be used in an outpatient setting. Two systematic reviews have shown that PTNS is effective in reducing pain in patients with CPPPS [477, 478]. Three RCTs showed a significant improvement in pain scores and QoL as measured by validated questionnaires. Where recorded, adverse events were rare and minor, including temporary slight pain at application site and haematoma.

### **Sacral nerve stimulation**

Sacral nerve stimulation (SNS) is an invasive technique requiring sedation or general anaesthesia for implantation of a device following trial stimulation. A systematic review identified ten studies of SNS in CPPPS, either retrospective case series or prospective cohort studies and no RCTs. Where reported, a mean of 69% of participants progressed to implantation of device following test stimulation (range 52-91%). All studies reported an improvement in pain, statistically significant in five studies. Quality of life was measured in three studies, and a significant improvement was demonstrated in two of the three studies. There was a large variation in adverse events reported, ranging from 0-50%. Complications not requiring surgical intervention included pain, failure of device, wound infection and seroma. The reoperation rate ranged between 11-50% for complications including lead migration, systemic infection, intrathecal implantation, loss of efficacy and erosion. In clinical practice, a patient should be appropriately counselled regarding the need for a period of trial stimulation and, whilst there may be an improvement in symptoms, this should be weighed against a notable complication rate.

A 2018 systematic review identified 14 studies. In all, 403 patients had undergone percutaneous nerve evaluation and/or SNM stage 1 and 54.8% had progressed to the permanent implantation stage, which is similar to that reported previously. The cause of pain was reported to be IC or bladder pain syndrome in 170 cases (42.2%). Visual Analogue Scale pain scores were available pre- and post-SNM in 210 patients and overall improvement in pain scores was significant. Sacral nerve stimulation is a promising treatment option for refractory chronic pelvic pain. Randomised prospective studies are warranted to compare SNS to other modalities for chronic pelvic pain treatment. Further studies are needed to compare antegrade versus retrograde approaches [479].

### **Other neuromodulation techniques**

A variety of other techniques of neuromodulation for patients with CPPPS were identified by systematic reviews [477, 480]. These techniques include intravaginal electrical stimulation for females with CPPPS, pudendal nerve stimulation for CPPPS, spinal cord stimulation for pudendal neuralgia, transcutaneous interferential electrical stimulation for IBS, electrical acupuncture for dysmenorrhoea, and electrical stimulation/biofeedback and electromagnetic stimulation for males with CPPPS. Whilst an improvement in pain has been reported in these studies, it is noted that they are largely of low quality and further work is needed in this area to enable robust clinical recommendations to be made. Neuromodulation in combination with hormonal treatment in deep endometriosis may have some benefit [481].

#### **5.3.3 Surgery**

##### **Primary bladder pain syndrome**

##### **Bladder distension**

Although bladder hydrodistension is a common treatment for PBPS, the scientific justification is scarce. It can be part of the diagnostic evaluation but has limited therapeutic role [482].

##### **Hydrodistension and Botulinum toxin type A**

Botulinum toxin type A may have an anti-nociceptive effect on bladder afferent pathways, producing symptomatic and urodynamic improvements [483]. Treatment with hydrodistension and hydrodistension plus intravesical BTX-A has been compared [484]. There was symptomatic improvement in all patients. However, in the hydrodistension-only group, 70% returned to their previous symptoms after one month, while in the BTX-A-treated patients, VAS score and functional and cystometric bladder capacity improved at three months. Botulinum toxin type A trigonal-only injection seems effective and long-lasting, as 87% of patients reported improvement after three months follow-up [485]. Over 50% of patients reported continued benefit nine months after the first treatment. When retreatment was needed, similar results were obtained. Up to 59% of patients remain responders after nine treatments. The sustained duration of the effect, despite the increase in the number of procedures, suggests that intratrighonal sensory neurons do not develop tolerance to OnaBotA, even during long periods of administration [472]. Adverse effects of BTX-A administration for IC or PBPS were significantly less than for OAB syndrome, namely in increased post-void residual volumes and decreased voiding efficiency [473]. Randomised controlled trials have reported benefits and long efficacy of BTX-A administration [474, 486-488], but a summary estimate for overall change in pain following BTX-A injections was not possible in a systematic review [399]. Conflicting data on results hinder issuance of a clear recommendation for the use of Botox in PBPS phenotypes [489].

Results of treatment with intravesical plasma rich (PRP) injections are also being explored. A prospective trial showed that patients with global response assessment > 2 had success rates at one month and at three months after the fourth PRP injection (70.6% and 76.7%, respectively). The VAS pain score, frequency and nocturia showed a significant decrease (all  $p < 0.05$ ). However, further studies are needed to validate findings [490].

### **Transurethral resection, coagulation and laser ablation**

Endourological destruction of bladder tissue aims to eliminate urothelial Hunner lesions. Coagulation of glomerulations or petequiae area is not recommended. Since the 1970s, resection and fulguration have been reported to achieve symptom relief, often for more than three years [491-493]. Repeated resection or fulguration treatments should be wisely indicated. A study has shown no difference in therapeutic benefit between transurethral laser ablation or resection [493].

### **Major surgery for primary bladder pain syndrome [494]**

Primary bladder pain syndrome is a benign condition that can severely impact QoL but does not shorten life expectancy. Consequently, major operative procedures are ranked last in the therapeutic algorithm and are only appropriate as a last resort for patients with severe refractory disease. The level of evidence underpinning reconstructive surgery is weak with no consensus regarding the optimal surgical approach. A systematic review with 450 patients (90% female; median age 54.5 years) from 20 eligible studies reported symptomatic improvement in 77.2% of patients, with an overall complication rate of 26.5% and a mortality rate of 1.3% [494]. This complication rate is likely an underestimate, as a third of the procedures did not specify their complication data. All the studies included in the systematic review were retrospective and observational with no control groups. There was also heterogeneity in the diagnostic criteria and outcome measures used. The main surgical options performed comprised:

1. Urinary diversion without cystectomy is performed to minimise the duration and complexity of surgery, and preserve sexual function and fertility, but complications related to the retained bladder commonly occur with the incidence of pyocystitis reported to range between 3.3% and 67%.
2. Subtotal (supratrigonal) cystectomy with substitution cystoplasty is the preferred reconstructive approach, particularly in younger patients [495], and the use of various intestinal segments has been reported [496-498].
3. Total (subtrigonal) cystectomy and orthotopic neobladder formation has the benefit of removing the trigone as a possible disease site but requires ureteric reimplantation. Trigonal disease is reported in 50% of patients and surgical failure has been blamed on the trigone being left in place [499], especially in patients with non-lesion type disease [500, 501]. Incomplete emptying of the orthotopic bladder augmentation is most likely to occur following trigonal resection so intermittent catheterisation may be required [502]. A study on female sexuality after cystectomy and orthotopic ileal neobladder showed pain relief in all patients and improvement in sexual function in females who remained sexually active [503]. Pregnancies with subsequent lower-segment Caesarean section have been reported after ileocystoplasty [504].
4. Cystectomy and ileal conduit formation avoids the increased surgical complexity of a continent urinary diversion and is the favoured approach in patients with significantly impaired renal function. The technique is considered for patients with PBPS who develop recurrent pain in the augmented bladder, continent pouch after enterocystoplasty or continent urinary diversion. Re-tubularisation of a previously used bowel segment to form a urinary conduit has been recommended [505].

Complete removal of the bladder is more likely to lead to symptom improvement compared with leaving part (subtotal cystectomy) or the whole bladder *in situ* [494]. Reports that unresected PBPS bladders cease to induce symptoms after loss of contact with urine are limited [96, 506].

Major surgery should be preceded by thorough preoperative evaluation, with an emphasis on determining the relevant disease location and subtype. If major surgery is being considered, the patient should be referred to a specialist centre experienced in managing CPPPS with a multidisciplinary team approach.

### **Primary prostate pain syndrome**

There is no evidence for surgical management, including transurethral incision of the bladder neck, radical transurethral resection of the prostate or, in particular, radical prostatectomy, in the management of chronic pain in patients with PPPS. A large Chinese RCT of circumcision combined with a triple oral therapy (ciprofloxacin, ibuprofen, tamsulosin) versus oral therapy alone, has been published for patients with PPPS (total n = 774) [507]. It is hypothesised that there may be some immunological interaction via pathogenic antigen presenting cells in the foreskin with CD4+ T-cells causing autoimmunity to the prostate gland. An improvement in total NIH-CPSI score and subdomain scores was reported at 12 weeks. However, despite a large cohort, the study results are questionable because of the weak theoretical background, and a potential large placebo effect lacking a sham-control. In addition, no long-term effectiveness has been reported. Before having an impact on recommendations, the results of this study must be independently confirmed, and the treatment effect must persist.

### **Primary testicular pain syndrome**

Microsurgical denervation of the spermatic cord can be offered to patients with testicular pain. In a long-term follow-up study, patients who had a positive result on blocking the spermatic cord were found to have a good result following denervation [508, 509].

### **Chronic primary anal and abdominal pain syndrome**

Chronic primary anal pain syndrome after stapled procedures, such as haemorrhoidopexy or stapled transanal rectal resection, may respond to excision of the scarred staple line as shown in 21 consecutive patients, with an overall improvement of pain in 85.7% of patients undergoing scar excision surgery [510]. An early scar excision before three to six months after pain onset was associated with better pain relief. Adhesiolysis is still in discussion in the pain management after laparotomy/laparoscopy for different surgical indications in the pelvis and entire abdomen. An RCT has shown that adhesiolysis is associated with an increased risk of operative complications and additional operations, and increased healthcare costs, as compared to laparoscopy alone [511].

### **Primary urethral pain syndrome**

There is no specific treatment that can be recommended. Management should be multidisciplinary and multimodal [512]. 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 [513]. Most publications on treatment of primary urethral pain syndrome have come from psychologists [514, 515].

### **Presumed intra-abdominal adhesions**

In gynaecological patients with CPPPS and presumed adhesions, there is no consensus as to whether adhesiolysis should be performed to improve pain [515].

Extensive surgery for endometriosis is challenging and is still considered to be controversial, as there is at least one RCT showing no benefit in pain relief after the removal of early extensive endometriosis versus sham surgery [273, 516]. Increasingly, treatment algorithms are being developed using a multidisciplinary approach, although thus far, none have been proven clinically [517]. In patients with adenomyosis, the only curative surgery is hysterectomy, but patients can benefit from hormonal therapy and analgesics (see Section 5.2.2).

### **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 selection is largely dependent on the underlying pathology. The most traditional approach is transgluteal; however, a transperineal approach may be an alternative, particularly if the nerve damage is thought to be related to previous pelvic surgery [261, 518-522]. One prospective RCT (transgluteal approach) [521] suggests that, if the patient has had the pain for less than six years, 66% of patients will see some improvement with surgery (vs. 40% if the pain has been present for more than six years). Surgery is not the answer for all patients. On talking to patients that have undergone surgery, provided the diagnosis was clear-cut, most patients were grateful to have undergone surgery but many still have symptoms that need management. This facility may not be available in all countries.

### **Chronic pelvic pain and prolapse/incontinence mesh**

Removing an existing mesh is a complex procedure [523]. Each patient is approached on an individual basis depending on the type of mesh and extent of complications [524]. The complexity of surgery often involves removal of dense scar tissue, reformation of inflamed vaginal skin, and surgical reconstruction of the urethra and bladder [525]. Such surgery requires specialist skills, best provided within a multidisciplinary tertiary setting. Possible complications as a result of this surgical removal include bleeding, infection, damage to surrounding organs and LUTS, persistent chronic pain and recurrent SUI after mesh removal [526].

Although mesh removal is a complex procedure, it is generally associated with beneficial and durable outcomes, particularly with respect to chronic pain [527]. However, the long-term consequences of mesh removal may include chronic persistent pain, autoimmune responses, and complex neuropathies affecting the pelvis and lower limbs [528, 529]. Some of these can be treated effectively using a multidisciplinary pain management approach [530]. In other cases, the residual symptoms may require the input of an immunologist, rheumatologist or other symptom-defined specialist. The alternative to continence and prolapse mesh surgery is dependent on the clinical findings at the time. These include behavioural change, physiotherapy (for SUI and grade I-II uterovaginal prolapse) or native-tissue surgical techniques. Studies have shown that over 70% of patients that committed to physiotherapy for SUI often did not need any further intervention [531]. Many clinicians are reverting to conservative measures first, before reconsidering surgery. Clinicians are also now

retraining in traditional continence surgical techniques that existed in the pre-mesh era, such as the Burch colposuspension and autologous fascial sling, as well as traditional utero-vaginal prolapse techniques such as vaginal hysterectomy, sacrospinous fixation and fascial repair of vaginal wall prolapse.

### **Ketamine uropathy and chronic pelvic pain**

Ketamine cessation is the primary disease-modifying intervention and can result in symptom improvement for many, but established fibrosis and strictures do not reverse [532]. Relapse is common and close coordination with addiction services is critical. In 2024, the British Association of Urological Surgeons issued a detailed consensus statement on the assessment and management of ketamine uropathy [533]. Suggested baseline investigations include urinalysis and urine culture, serum renal and liver function measurements, and a urinary tract US. Three stages of ketamine uropathy are described, with treatment recommendations provided for each stage.

- Stage 1 (inflammatory): Cessation with referral to substance misuse services, oral antimuscarinic or B3 agonists, pentosan polysulphate.
- Stage 2 (structural change): Intravesical instillations, intradetrusor botulinum toxin injections under general anaesthetic.
- Stage 3 (end stage/upper tract compromise): Ongoing monitoring of upper tracts and supporting abstinence, with referral to specialist services for consideration of augmentation cystoplasty or urinary diversion.

With increased availability and uptake in young adults, ketamine uropathy is likely to present a serious challenge for European urology and chronic pelvic pain services. Proactive clinician enquiry, patient education, early intervention and joint working with addiction services will be critical in preventing progression to irreversible uropathy.

## **5.4 Summary of evidence and recommendations: management**

### **5.4.1 Management of primary prostate pain syndrome**

<b>Summary of evidence</b>	<b>LE</b>
Phenotypically directed treatment may improve treatment success.	3
In PPPS, α-blockers have moderate treatment effect regarding total pain, voiding, and QoL scores.	1a
Antimicrobial therapy has a moderate effect on total pain, voiding, and QoL scores in PPPS.	1a
Non-steroidal anti-inflammatory drugs have moderate overall treatment effects on PPPS.	1a
Phytotherapy has some beneficial effect on pain and overall favourable treatment response in PPPS.	1a
Pentosane polysulphate improves global assessment and QoL score in PPPS.	1b
There are insufficient data on the effectiveness of muscle relaxants in PPPS.	2b
Pregabalin is not effective for the treatment of PPPS.	1b
Botulinum toxin type A injection into the pelvic floor (or prostate) may have a modest effect in PPPS.	2b
Acupuncture is superior to sham acupuncture in improving symptoms and QoL.	1a
Posterior tibial nerve stimulation is probably effective for the treatment of PPPS.	1b
Extracorporeal shock wave therapy is probably effective over the short term.	1b
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 PPPS.	3
Cognitive behavioural therapy designed for PPPS may improve pain and QoL.	3

<b>Recommendations</b>	<b>Strength rating</b>
Offer multimodal and phenotypically directed treatment options for primary prostate pain syndrome (PPPS).	Weak
Use antimicrobial therapy (quinolones or tetracyclines) over a minimum of six weeks in treatment-naïve patients with a duration of PPPS less than one year.	Strong
Use α-blockers for patients with a duration of PPPS less than one year.	Strong
Offer high-dose oral pentosane polysulphate in PPPS.	Weak
Offer acupuncture in PPPS.	Strong

Offer non-steroidal anti-inflammatory drugs in PPPS, but long-term side effects must be considered.	Weak
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#### 5.4.2 Management of primary bladder pain syndrome

Summary of evidence	LE
There is insufficient data for the long-term use of corticosteroids in PBPS.	3
Limited data exist on effectiveness of cimetidine in PBPS.	2b
Amitriptyline is effective for pain and related symptoms of PBPS.	1b
Oral pentosane polysulphate is effective for pain and related symptoms of PBPS.	1a
Oral pentosane polysulphate plus subcutaneous heparin is effective for pain and related symptoms of PBPS, especially in initially low responders to pentosane polysulphate alone.	1b
Intravesical lidocaine plus sodium bicarbonate is effective in the short term.	1b
Intravesical pentosane polysulphate is effective, based on limited data, and may enhance oral treatment.	1b
There are limited data on the effectiveness of intravesical heparin.	3
Intravesical chondroitin sulphate may be effective.	2b
There is insufficient data for the use of bladder distension as a therapeutic intervention.	3
Hydrodistension plus BTX-A is superior to hydrodistension alone.	1b
Intravesical bacillus Calmette-Guérin is not effective in PBPS.	1b
Transurethral resection (coagulation and laser) may be effective in PBPS type 3C.	3
Sacral neuromodulation may be effective in PBPS.	3
Pudendal nerve stimulation is superior to sacral neuromodulation for treatment of PBPS.	1b
Avoidance of certain foods and drink may reduce symptoms.	3
Outcome of cystectomy for PBPS is variable.	3

Recommendations	Strength rating
Offer subtype and phenotype-oriented therapy for the treatment of primary bladder pain syndrome (PBPS).	Strong
Always consider offering multimodal behavioural, physical and psychological techniques alongside oral or invasive treatments of PBPS.	Strong
Offer dietary advice.	Weak
Administer amitriptyline for treatment of PBPS.	Strong
Offer oral pentosane polysulphate for the treatment of PBPS.	Strong
Offer oral pentosane polysulphate plus subcutaneous heparin in low responders to pentosane polysulphate alone.	Weak
Do not recommend oral corticosteroids for long-term treatment.	Strong
Offer intravesical hyaluronic acid or chondroitin sulphate before more invasive measures.	Weak
Offer intravesical lidocaine plus sodium bicarbonate prior to more invasive methods.	Weak
Offer intravesical heparin before more invasive measures alone or in combination treatment.	Weak
Do not use bladder distension alone as a treatment of PBPS.	Weak
Consider submucosal bladder wall and trigonal injection of botulinum toxin type A plus hydrodistension if intravesical instillation therapies have failed.	Strong
Offer neuromodulation before more invasive interventions.	Weak
Only undertake ablative and/or reconstructive surgery as the last resort and only by experienced and PBPS-knowledgeable surgeons, following a multidisciplinary assessment including pain management.	Strong
Offer transurethral resection (or coagulation or laser) of bladder lesions, but in PBPS type 3C only.	Strong

#### 5.4.3 Management of scrotal pain syndrome

Summary of evidence	LE
Microsurgical denervation of the spermatic cord is an effective therapy for primary scrotal pain syndrome.	2b
Vasovasostomy is effective in post-vasectomy pain.	2b

Recommendations	Strength rating
Inform about the risk of post-vasectomy pain when counselling patients planned for vasectomy.	Strong
Do open instead of laparoscopic inguinal hernia repair, to reduce the risk of scrotal pain.	Strong
In patients with testicular pain improving after spermatic block, offer microsurgical denervation of the spermatic cord.	Weak

#### 5.4.4 Management of primary urethral pain syndrome

Summary of evidence	LE
There is no specific treatment for primary urethral pain syndrome.	4

#### 5.4.5 Management of gynaecological aspects of chronic pelvic pain

Summary of evidence	LE
Therapeutic options, including pharmacotherapy and surgery, can treat endometriosis effectively.	1b
Psychological treatment (cognitive behaviour therapy or supportive psychotherapy) can improve pain as well as sexual and emotional function in vaginal and vulvar pain syndrome.	1b
Most gynaecological pain conditions (including dysmenorrhea, post-mesh insertion and gynaecological malignancy) can be treated effectively using pharmacotherapy.	3
All other gynaecological conditions (including obstetric injury, pelvic organ prolapse) can be treated effectively with surgery.	2

Recommendations	Strength rating
Involve a gynaecologist to provide therapeutic options, such as hormonal therapy or surgery, in well-defined disease states.	Strong
Provide a multidisciplinary approach to pain management in persistent disease states.	Strong
All patients who have developed complications after mesh insertion should be referred to a multidisciplinary service (incorporating pain medicine and surgery).	Strong

#### 5.4.6 Management of primary anorectal pain syndrome

Summary of evidence	LE
Biofeedback is the preferred treatment for chronic primary anal pain syndrome.	1a
Electro stimulation is less effective than biofeedback.	1b
Available evidence fails to confirm effectiveness of BTX-A in management of chronic primary anal pain syndrome.	3
Percutaneous tibial nerve stimulation is effective in anal pain.	3
Sacral neuromodulation is effective in anal pain.	3
Inhaled salbutamol is effective in intermittent chronic primary anal pain syndrome.	3

Recommendations	Strength rating
Undertake biofeedback treatment in patients with chronic anal pain.	Strong
Offer percutaneous tibial nerve stimulation in chronic primary anal pain syndrome.	Weak
Offer sacral neuromodulation in chronic primary anal pain syndrome.	Weak
Offer inhaled salbutamol in intermittent chronic primary anal pain syndrome.	Weak

#### 5.4.7 *Management of pudendal neuralgia*

Summary of evidence	LE
There are multiple treatment options with varying levels of evidence.	3

Recommendation	Strength rating
Use standard approaches for the management of neuropathic pain. Neuropathic pain guidelines are well-established.	Strong

#### 5.4.8 *Management of sexological aspects in chronic pelvic pain*

Summary of evidence	LE
Pelvic floor muscle physical therapy may offer relief of pain and reduction in sexual complaints.	2b

Recommendations	Strength rating
Offer behavioural strategies to the patient and their partner to reduce sexual dysfunctions.	Weak
Offer pelvic floor muscle therapy as part of the treatment plan to improve quality of life and sexual function.	Weak

#### 5.4.9 *Management of psychological aspects in chronic pelvic pain*

Recommendation	Strength rating
For chronic pelvic pain with significant psychological distress, refer patient for chronic pelvic pain-focused psychological treatment.	Strong

#### 5.4.10 *Management of pelvic floor dysfunction*

Summary of evidence	LE
Myofascial treatment is effective.	1b
Biofeedback improves the outcome of myofascial therapy.	1a

Recommendations	Strength rating
Apply myofascial treatment as first-line treatment.	Weak
Offer biofeedback as therapy adjuvant to muscle exercises, in patients with anal pain due to an overactive pelvic floor.	Strong

#### 5.4.11 *Management of chronic/non-acute urogenital pain by opioids*

Recommendations	Strength rating
Opioids and other drugs of addiction/dependency should only be prescribed following multidisciplinary assessment and only after other reasonable treatments have been tried and failed.	Strong
The decision to instigate long-term opioid therapy should be made by an appropriately trained specialist in consultation with the patient and their family doctor.	Strong
Involve a psychiatrist or psychologist with an interest in pain management and drug addiction where there is a history or suspicion of drug abuse.	Strong

## 6. EVALUATION OF TREATMENT RESULTS

### 6.1 Evaluation of treatment

For patients with chronic primary visceral pain, a visit to the clinician is important because they can ask questions, talk about how the process is going, and have time with a caregiver who understands the nature of their pain. The first evaluation should take place after about six weeks to determine whether the treatment has been successful. When necessary, adaptations are made and a next evaluation is planned.

#### 6.1.1 *Treatment has not been effective*

##### 6.1.1.a **Alternative treatment**

In cases where the treatment initiated did not have enough effect, an alternative approach is advised. The first step is a thorough evaluation of patient or caregiver adherence to the initiated treatment. Ask whether the patient has taken the medication according to the prescription, if there were any side effects, and if there were any changes in pain and function. Adjustment of medication or dose schemes might help. Another important step is to review reports from other healthcare professionals, such as the physiotherapist and psychologist. Has the therapy been followed until the end? What was the opinion of the therapist about the changes that were observed? In cases where the sessions were terminated by the patient, ask why they made that decision. Check if the patient has understood the idea behind the therapy that had been prematurely stopped.

##### 6.1.1.b **Referral to next envelope of care**

If patients and doctors conclude that none of the therapies showed enough effect, then referral to a next envelope of care is advised. The terminology used to describe the nature and specialisation level of centres that provide specialised care for visceral pain patients is not standardised and is country-based. This does not facilitate easy referral schemes. It is advised that patients are referred to a centre that works with a multidisciplinary team and is nationally recognised as being specialised in pelvic pain. Such a centre will re-evaluate what has been done and, when available, provide specialised care.

##### 6.1.1.c **Self-management and shared care**

Patients who find themselves confronted with CPPPS for which there is no specific treatment option available, will have to live with their pain. They will need to manage their pain, meaning that they will have to find a way to deal with the impact of their pain on daily activities in all domains of life. Self-help programmes may be advised and can be of help. The patient may also benefit from shared care, which means a caregiver is available to support self-management strategies. Together with this caregiver, the patient can optimise and use the self-management strategies.

#### 6.1.2 *Treatment has been effective*

In cases where treatment has been effective, attention must be paid to fall-back prevention. If the patient feels the same pain again, it helps to start at an early stage with the self-management strategies that they have learned during the former treatment. By doing so, they will have the best chance of preventing the redevelopment of pelvic pain syndromes.

## 7. REFERENCES

1. Fall, M., *et al.* EAU guidelines on chronic pelvic pain. *Eur Urol*, 2004. 46: 681.  
<https://www.ncbi.nlm.nih.gov/pubmed/15548433>
2. Fall, M., *et al.* EAU guidelines on chronic pelvic pain. *Eur Urol*, 2010. 57: 35.  
<https://www.ncbi.nlm.nih.gov/pubmed/19733958>
3. Engeler, D.S., *et al.* The 2013 EAU guidelines on chronic pelvic pain: is management of chronic pelvic pain a habit, a philosophy, or a science? 10 years of development. *Eur Urol*, 2013. 64: 431.  
<https://www.ncbi.nlm.nih.gov/pubmed/23684447>
4. McMahon, S.B., *et al.* Visceral pain. *Br J Anaesth*, 1995. 75: 132.  
<https://www.ncbi.nlm.nih.gov/pubmed/7577247>
5. Shoskes, D.A., *et al.* Clinical phenotyping of patients with chronic prostatitis/chronic pelvic pain syndrome and correlation with symptom severity. *Urology*, 2009. 73: 538.  
<https://www.ncbi.nlm.nih.gov/pubmed/19118880>
6. Magri, V., *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. 184: 2339.  
<https://www.ncbi.nlm.nih.gov/pubmed/20952019>
7. World Health Organization. International Classification of Diseases (11th Revision). 2018.  
<https://icd.who.int/en>
8. Aziz, Q., *et al.* The IASP classification of chronic pain for ICD-11: chronic secondary visceral pain. *Pain*, 2019. 160: 69.  
<https://www.ncbi.nlm.nih.gov/pubmed/30586073>
9. Hauser, W., *et al.* Taxonomies for chronic visceral pain. *Pain*, 2020. 161: 1129.  
<https://www.ncbi.nlm.nih.gov/pubmed/32032194>
10. Merskey, H., *et al.*, Classification of Chronic Pain. 2nd Edition ed. 1994.  
<https://www.iasp-pain.org/publications/free-ebooks/classification-of-chronic-pain-second-edition-revised/>
11. Afari, N., *et al.* A MAPP Network Case-control Study of Urological Chronic Pelvic Pain Compared With Nonurological Pain Conditions. *Clin J Pain*, 2020. 36: 8.  
<https://www.ncbi.nlm.nih.gov/pubmed/31794439>
12. Krieger, J.N., *et al.* NIH consensus definition and classification of prostatitis. *JAMA*, 1999. 282: 236.  
<https://www.ncbi.nlm.nih.gov/pubmed/10422990>
13. van de Merwe, J.P., *et al.* Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC proposal. *Eur Urol*, 2008. 53: 60.  
<https://www.ncbi.nlm.nih.gov/pubmed/17900797>
14. Mearin, F., *et al.* Bowel Disorders. *Gastroenterology*, 2016.  
<https://www.ncbi.nlm.nih.gov/pubmed/27144627>
15. Phillips, B., *et al.* Oxford Centre for Evidence-based Medicine Levels of Evidence. Updated by Jeremy Howick March 2009. 2009.  
<https://www.cebm.ox.ac.uk/resources/levels-of-evidence/oxford-centre-for-evidence-based-medicine-levels-of-evidence-march-2009>
16. Guyatt, G.H., *et al.* Going from evidence to recommendations. *BMJ*, 2008. 336: 1049.  
<https://www.ncbi.nlm.nih.gov/pubmed/18467413>
17. Raja, S.N., *et al.* The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. *Pain*, 2020. 161: 1976.  
<https://www.ncbi.nlm.nih.gov/pubmed/32694387>
18. Global Burden of Disease Study Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*, 2015. 386: 743.  
<https://www.ncbi.nlm.nih.gov/pubmed/26063472>
19. Ayorinde, A.A., *et al.* Chronic pelvic pain in women of reproductive and post-reproductive age: a population-based study. *Eur J Pain*, 2017. 21: 445.  
<https://www.ncbi.nlm.nih.gov/pubmed/27634190>
20. Zondervan, K.T., *et al.* The community prevalence of chronic pelvic pain in women and associated illness behaviour. *Br J Gen Pract*, 2001. 51: 541.  
<https://www.ncbi.nlm.nih.gov/pubmed/11462313>
21. Baranowski, A.P. Chronic pelvic pain. *Best Pract Res Clin Gastroenterol*, 2009. 23: 593.  
<https://www.ncbi.nlm.nih.gov/pubmed/19647692>

22. Chuang, Y.C., *et al.* Increased risks of healthcare-seeking behaviors of anxiety, depression and insomnia among patients with bladder pain syndrome/interstitial cystitis: a nationwide population-based study. *Int Urol Nephrol*, 2015. 47: 275.  
<https://www.ncbi.nlm.nih.gov/pubmed/25577231>
23. Kano, M., *et al.* Altered brain and gut responses to corticotropin-releasing hormone (CRH) in patients with irritable bowel syndrome. *Sci Rep*, 2017. 7: 12425.  
<https://www.ncbi.nlm.nih.gov/pubmed/28963545>
24. Yueh, H.Z., *et al.* Risk of Autoimmune Diseases in Patients With Interstitial Cystitis/Bladder Pain Syndrome: A Nationwide Population-Based Study in Taiwan. *Front Med (Lausanne)*, 2021. 8: 747098.  
<https://www.ncbi.nlm.nih.gov/pubmed/34616760>
25. Laden, B.F., *et al.* Comorbidities in a Nationwide, Heterogenous Population of Veterans with Interstitial Cystitis/Bladder Pain Syndrome. *Urology*, 2021. 156: 37.  
<https://www.ncbi.nlm.nih.gov/pubmed/33901534>
26. Hellman, K.M., *et al.* Circulating sex steroids and bladder pain sensitivity in dysmenorrhea. *Mol Pain*, 2021. 17: 17448069211035217.  
<https://www.ncbi.nlm.nih.gov/pubmed/34689649>
27. Savidge, C.J., *et al.* Psychological aspects of chronic pelvic pain. *J Psychosom Res*, 1997. 42: 433.  
<https://www.ncbi.nlm.nih.gov/pubmed/9194016>
28. Anda, R.F., *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. 256: 174.  
<https://www.ncbi.nlm.nih.gov/pubmed/16311898>
29. Raphael, K.G., *et al.* Childhood victimization and pain in adulthood: a prospective investigation. *Pain*, 2001. 92: 283.  
<https://www.ncbi.nlm.nih.gov/pubmed/11323150>
30. Tunitsky, E., *et al.* Bladder pain syndrome/interstitial cystitis in twin sisters. *J Urol*, 2012. 187: 148.  
<https://www.ncbi.nlm.nih.gov/pubmed/22088343>
31. Vehof, J., *et al.* Shared genetic factors underlie chronic pain syndromes. *Pain*, 2014. 155: 1562.  
<https://www.ncbi.nlm.nih.gov/pubmed/24879916>
32. Dybowski, C., *et al.* Predictors of pain, urinary symptoms and quality of life in patients with chronic pelvic pain syndrome (CPPS): A prospective 12-month follow-up study. *J Psychosom Res*, 2018. 112: 99.  
<https://www.ncbi.nlm.nih.gov/pubmed/30097143>
33. Roth, R.S., *et al.* Patient beliefs about pain diagnosis in chronic pelvic pain: relation to pain experience, mood and disability. *J Reprod Med*, 2011. 56: 123.  
<https://www.ncbi.nlm.nih.gov/pubmed/21542529>
34. Naliboff, B.D., *et al.* Clinical and Psychosocial Predictors of Urological Chronic Pelvic Pain Symptom Change in 1 Year: A Prospective Study from the MAPP Research Network. *J Urol*, 2017. 198: 848.  
<https://www.ncbi.nlm.nih.gov/pubmed/28528930>
35. Bajaj, P., *et al.* Endometriosis is associated with central sensitization: a psychophysical controlled study. *J Pain*, 2003. 4: 372.  
<https://www.ncbi.nlm.nih.gov/pubmed/14622679>
36. Vincent, K., *et al.* Dysmenorrhoea is associated with central changes in otherwise healthy women. *Pain*, 2011. 152: 1966.  
<https://www.ncbi.nlm.nih.gov/pubmed/21524851>
37. Savidge, C.J., *et al.* Women's Perspectives on their Experiences of Chronic Pelvic Pain and Medical Care. *J Health Psychol*, 1998. 3: 103.  
<https://www.ncbi.nlm.nih.gov/pubmed/22021346>
38. Price, J., *et al.* Attitudes of women with chronic pelvic pain to the gynaecological consultation: a qualitative study. *BJOG*, 2006. 113: 446.  
<https://www.ncbi.nlm.nih.gov/pubmed/16489938>
39. Martin, C.E., *et al.* Catastrophizing: a predictor of persistent pain among women with endometriosis at 1 year. *Hum Reprod*, 2011. 26: 3078.  
<https://www.ncbi.nlm.nih.gov/pubmed/21900393>
40. Riegel, B., *et al.* Assessing psychological factors, social aspects and psychiatric co-morbidity associated with Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS) in men - A systematic review. *Journal of Psychosomatic Research*, 2014. 77: 333.  
<https://pubmed.ncbi.nlm.nih.gov/25300538/>

41. Chung, S.D., *et al.* Association between chronic prostatitis/chronic pelvic pain syndrome and anxiety disorder: a population-based study. *PLoS One*, 2013. 8: e64630.  
<https://www.ncbi.nlm.nih.gov/pubmed/23691256>
42. Latthe, P., *et al.* Factors predisposing women to chronic pelvic pain: systematic review. *BMJ*, 2006. 332: 749.  
<https://www.ncbi.nlm.nih.gov/pubmed/16484239>
43. Hilden, M., *et al.* A history of sexual abuse and health: a Nordic multicentre study. *BJOG*, 2004. 111: 1121.  
<https://www.ncbi.nlm.nih.gov/pubmed/15383115>
44. McGowan, L.P.A., *et al.* Chronic pelvic pain: A meta-analytic review. *Psychol Health*, 1998. 13: 937.  
<https://www.tandfonline.com/doi/abs/10.1080/08870449808407441>
45. Walker, E.A., *et al.* Psychiatric diagnoses and sexual victimization in women with chronic pelvic pain. *Psychosomatics*, 1995. 36: 531.  
<https://www.ncbi.nlm.nih.gov/pubmed/7501783>
46. Nickel, J.C., *et al.* Childhood sexual trauma in women with interstitial cystitis/bladder pain syndrome: a case control study. *Can Urol Assoc J*, 2011. 5: 410.  
<https://www.ncbi.nlm.nih.gov/pubmed/22154637>
47. Schrepf, A., *et al.* Adverse Childhood Experiences and Symptoms of Urologic Chronic Pelvic Pain Syndrome: A Multidisciplinary Approach to the Study of Chronic Pelvic Pain Research Network Study. *Ann Behav Med*, 2018. 52: 865.  
<https://www.ncbi.nlm.nih.gov/pubmed/30212850>
48. Paras, M.L., *et al.* Sexual abuse and lifetime diagnosis of somatic disorders: a systematic review and meta-analysis. *JAMA*, 2009. 302: 550.  
<https://www.ncbi.nlm.nih.gov/pubmed/19654389>
49. Campbell, R., *et al.* Gynecological health impact of sexual assault. *Res Nurs Health*, 2006. 29: 399.  
<https://www.ncbi.nlm.nih.gov/pubmed/16977640>
50. Hu, J.C., *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. 22: 1532.  
<https://www.ncbi.nlm.nih.gov/pubmed/17763912>
51. Linley, J.E., *et al.* Understanding inflammatory pain: ion channels contributing to acute and chronic nociception. *Pflugers Arch*, 2010. 459: 657.  
<https://www.ncbi.nlm.nih.gov/pubmed/20162302>
52. Tripp, D.A., *et al.* Sexual functioning, catastrophizing, depression, and pain, as predictors of quality of life in women with interstitial cystitis/painful bladder syndrome. *Urology*, 2009. 73: 987.  
<https://www.ncbi.nlm.nih.gov/pubmed/19394494>
53. Tripp, D.A., *et al.* Catastrophizing and pain-contingent rest predict patient adjustment in men with chronic prostatitis/chronic pelvic pain syndrome. *J Pain*, 2006. 7: 697.  
<https://www.ncbi.nlm.nih.gov/pubmed/17018330>
54. Whitaker, L.H., *et al.* An Exploratory Study into Objective and Reported Characteristics of Neuropathic Pain in Women with Chronic Pelvic Pain. *PLoS One*, 2016. 11: e0151950.  
<https://www.ncbi.nlm.nih.gov/pubmed/27046128>
55. Kutch, J.J., *et al.* Altered resting state neuromotor connectivity in men with chronic prostatitis/chronic pelvic pain syndrome: A MAPP: Research Network Neuroimaging Study. *Neuroimage Clin*, 2015. 8: 493.  
<https://www.ncbi.nlm.nih.gov/pubmed/26106574>
56. Abrams, P., *et al.* A new classification is needed for pelvic pain syndromes—are existing terminologies of spurious diagnostic authority bad for patients? *J Urol*, 2006. 175: 1989.  
<https://www.ncbi.nlm.nih.gov/pubmed/16697782>
57. Hanno, P., *et al.* Bladder Pain Syndrome Committee of the International Consultation on Incontinence. *Neurourol Urodyn*, 2010. 29: 191.  
<https://www.ncbi.nlm.nih.gov/pubmed/20025029>
58. Yoon, B.I., *et al.* Clinical courses following acute bacterial prostatitis. *Prostate Int*, 2013. 1: 89.  
<https://www.ncbi.nlm.nih.gov/pubmed/24223408>
59. Giamberardino, M.A., *et al.* Viscero-visceral hyperalgesia: characterization in different clinical models. *Pain*, 2010. 151: 307.  
<https://www.ncbi.nlm.nih.gov/pubmed/20638177>
60. Pezet, S., *et al.* Neurotrophins: mediators and modulators of pain. *Annu Rev Neurosci*, 2006. 29: 507.  
<https://www.ncbi.nlm.nih.gov/pubmed/16776595>

61. Cervero, F., *et al.* Understanding the signaling and transmission of visceral nociceptive events. *J Neurobiol*, 2004. 61: 45.  
<https://www.ncbi.nlm.nih.gov/pubmed/15362152>
62. Kobayashi, H., *et al.* Mechanism of pain generation for endometriosis-associated pelvic pain. *Arch Gynecol Obstet*, 2014. 289: 13.  
<https://www.ncbi.nlm.nih.gov/pubmed/24121693>
63. Melzack, R., *et al.* Central neuroplasticity and pathological pain. *Ann N Y Acad Sci*, 2001. 933: 157.  
<https://www.ncbi.nlm.nih.gov/pubmed/12000018>
64. Fulbright, R.K., *et al.* Functional MR imaging of regional brain activation associated with the affective experience of pain. *AJR Am J Roentgenol*, 2001. 177: 1205.  
<https://www.ncbi.nlm.nih.gov/pubmed/11641204>
65. Rygh, L.J., *et al.* Cellular memory in spinal nociceptive circuitry. *Scand J Psychol*, 2002. 43: 153.  
<https://www.ncbi.nlm.nih.gov/pubmed/12004953>
66. Malykhina, A.P. Neural mechanisms of pelvic organ cross-sensitization. *Neuroscience*, 2007. 149: 660.  
<https://www.ncbi.nlm.nih.gov/pubmed/17920206>
67. Sanford, M.T., *et al.* The role of environmental stress on lower urinary tract symptoms. *Curr Opin Urol*, 2017. 27: 268.  
<https://www.ncbi.nlm.nih.gov/pubmed/28376513>
68. Binik, Y.M. The DSM diagnostic criteria for dyspareunia. *Arch Sex Behav*, 2010. 39: 292.  
<https://www.ncbi.nlm.nih.gov/pubmed/19830537>
69. Bergeron, S., *et al.* Genital pain in women: Beyond interference with intercourse. *Pain*, 2011. 152: 1223.  
<https://www.ncbi.nlm.nih.gov/pubmed/21324589>
70. Davis, S.N., *et al.* Sexual dysfunction and pelvic pain in men: a male sexual pain disorder? *J Sex Marital Ther*, 2009. 35: 182.  
<https://www.ncbi.nlm.nih.gov/pubmed/19360518>
71. Leserman, J., *et al.* Identification of diagnostic subtypes of chronic pelvic pain and how subtypes differ in health status and trauma history. *Am J Obstet Gynecol*, 2006. 195: 554.  
<https://www.ncbi.nlm.nih.gov/pubmed/16769027>
72. Meltzer-Brody, S., *et al.* Trauma and posttraumatic stress disorder in women with chronic pelvic pain. *Obstet Gynecol*, 2007. 109: 902.  
<https://www.ncbi.nlm.nih.gov/pubmed/17400852>
73. Iglesias-Rios, L., *et al.* Depression and posttraumatic stress disorder among women with vulvodynia: evidence from the population-based woman to woman health study. *J Womens Health (Larchmt)*, 2015. 24: 557.  
<https://www.ncbi.nlm.nih.gov/pubmed/25950702>
74. Anderson, A.B., *et al.* Associations Between Penetration Cognitions, Genital Pain, and Sexual Well-being in Women with Provoked Vestibulodynia. *J Sex Med*, 2016. 13: 444.  
<https://www.ncbi.nlm.nih.gov/pubmed/26853045>
75. Roth, R.S., *et al.* Psychological factors and chronic pelvic pain in women: a comparative study with women with chronic migraine headaches. *Health Care Women Int*, 2011. 32: 746.  
<https://www.ncbi.nlm.nih.gov/pubmed/21767098>
76. Souza, P.P., *et al.* Qualitative research as the basis for a biopsychosocial approach to women with chronic pelvic pain. *J Psychosom Obstet Gynaecol*, 2011. 32: 165.  
<https://www.ncbi.nlm.nih.gov/pubmed/21919820>
77. Toye, F., *et al.* A meta-ethnography of patients' experiences of chronic pelvic pain: struggling to construct chronic pelvic pain as 'real'. *J Adv Nurs*, 2014. 70: 2713.  
<https://www.ncbi.nlm.nih.gov/pubmed/25081990>
78. Jarrell, J.F., *et al.* Consensus guidelines for the management of chronic pelvic pain. *J Obstet Gynaecol Can*, 2005. 27: 869.  
<https://www.ncbi.nlm.nih.gov/pubmed/19830953>
79. Dworkin, R.H., *et al.* Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain*, 2005. 113: 9.  
<https://www.ncbi.nlm.nih.gov/pubmed/15621359>
80. Awad, S.A., *et al.* Long-term results and complications of augmentation ileocystoplasty for idiopathic urge incontinence in women. *Br J Urol*, 1998. 81: 569.  
<https://www.ncbi.nlm.nih.gov/pubmed/9598629>

81. Slocumb, J.C. Neurological factors in chronic pelvic pain: trigger points and the abdominal pelvic pain syndrome. *Am J Obstet Gynecol*, 1984. 149: 536.  
<https://www.ncbi.nlm.nih.gov/pubmed/6234807>
82. Barry, M.J., *et al.* Overlap of different urological symptom complexes in a racially and ethnically diverse, community-based population of men and women. *BJU Int*, 2008. 101: 45.  
<https://www.ncbi.nlm.nih.gov/pubmed/17868419>
83. Roberts, R.O., *et al.* Low agreement between previous physician diagnosed prostatitis and national institutes of health chronic prostatitis symptom index pain measures. *J Urol*, 2004. 171: 279.  
<https://www.ncbi.nlm.nih.gov/pubmed/14665894>
84. Krieger, J.N., *et al.* Epidemiology of prostatitis. *Int J Antimicrob Agents*, 2008. 31 Suppl 1: S85.  
<https://www.ncbi.nlm.nih.gov/pubmed/18164907>
85. Mehik, A., *et al.* Epidemiology of prostatitis in Finnish men: a population-based cross-sectional study. *BJU Int*, 2000. 86: 443.  
<https://www.ncbi.nlm.nih.gov/pubmed/10971269>
86. Bade, J.J., *et al.* Interstitial cystitis in The Netherlands: prevalence, diagnostic criteria and therapeutic preferences. *J Urol*, 1995. 154: 2035.  
<https://www.ncbi.nlm.nih.gov/pubmed/7500452>
87. Burkman, R.T. Chronic pelvic pain of bladder origin: epidemiology, pathogenesis and quality of life. *J Reprod Med*, 2004. 49: 225.  
<https://www.ncbi.nlm.nih.gov/pubmed/15088860>
88. Curhan, G.C., *et al.* Epidemiology of interstitial cystitis: a population based study. *J Urol*, 1999. 161: 549.  
<https://www.ncbi.nlm.nih.gov/pubmed/9915446>
89. Leppilahti, M., *et al.* Prevalence of clinically confirmed interstitial cystitis in women: a population based study in Finland. *J Urol*, 2005. 174: 581.  
<https://www.ncbi.nlm.nih.gov/pubmed/16006902>
90. Oravisto, K.J. Epidemiology of interstitial cystitis. *Ann Chir Gynaecol Fenn*, 1975. 64: 75.  
<https://www.ncbi.nlm.nih.gov/pubmed/1137336>
91. Roberts, R.O., *et al.* Incidence of physician-diagnosed interstitial cystitis in Olmsted County: a community-based study. *BJU Int*, 2003. 91: 181.  
<https://www.ncbi.nlm.nih.gov/pubmed/12581000>
92. Temml, C., *et al.* Prevalence and correlates for interstitial cystitis symptoms in women participating in a health screening project. *Eur Urol*, 2007. 51: 803.  
<https://www.ncbi.nlm.nih.gov/pubmed/16979286>
93. Berry, S.H., *et al.* Prevalence of symptoms of bladder pain syndrome/interstitial cystitis among adult females in the United States. *J Urol*, 2011. 186: 540.  
<https://www.ncbi.nlm.nih.gov/pubmed/21683389>
94. Song, Y., *et al.* Prevalence and correlates of painful bladder syndrome symptoms in Fuzhou Chinese women. *Neurourol Urodyn*, 2009. 28: 22.  
<https://www.ncbi.nlm.nih.gov/pubmed/18671294>
95. Koziol, J.A., *et al.* Discrimination between the ulcerous and the nonulcerous forms of interstitial cystitis by noninvasive findings. *J Urol*, 1996. 155: 87.  
<https://www.ncbi.nlm.nih.gov/pubmed/7490906>
96. Messing, E.M., *et al.* Interstitial cystitis: early diagnosis, pathology, and treatment. *Urology*, 1978. 12: 381.  
<https://www.ncbi.nlm.nih.gov/pubmed/213864>
97. Parsons, C. Interstitial cystitis: clinical manifestations and diagnostic criteria in over 200 cases. *Neurourol Urodyn*, 1990. 9.  
<https://onlinelibrary.wiley.com/doi/10.1002/nau.1930090302>
98. Peeker, R., *et al.* Toward a precise definition of interstitial cystitis: further evidence of differences in classic and nonulcer disease. *J Urol*, 2002. 167: 2470.  
<https://www.ncbi.nlm.nih.gov/pubmed/11992059>
99. Mattox, T.F. Interstitial cystitis in adolescents and children: a review. *J Pediatr Adolesc Gynecol*, 2004. 17: 7.  
<https://www.ncbi.nlm.nih.gov/pubmed/15010032>
100. Berghuis, J.P., *et al.* Psychological and physical factors involved in chronic idiopathic prostatitis. *J Psychosom Res*, 1996. 41: 313.  
<https://www.ncbi.nlm.nih.gov/pubmed/8971661>

101. Lee, S.W., *et al.* Adverse impact of sexual dysfunction in chronic prostatitis/chronic pelvic pain syndrome. *Urology*, 2008. 71: 79.  
<https://www.ncbi.nlm.nih.gov/pubmed/18242370>
102. Liang, C.Z., *et al.* Prevalence of sexual dysfunction in Chinese men with chronic prostatitis. *BJU Int*, 2004. 93: 568.  
<https://www.ncbi.nlm.nih.gov/pubmed/15008731>
103. Bartoletti, R., *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. 178: 2411.  
<https://www.ncbi.nlm.nih.gov/pubmed/17937946>
104. Gonen, M., *et al.* Prevalence of premature ejaculation in Turkish men with chronic pelvic pain syndrome. *J Androl*, 2005. 26: 601.  
<https://www.ncbi.nlm.nih.gov/pubmed/16088036>
105. Mehik, A., *et al.* Fears, sexual disturbances and personality features in men with prostatitis: a population-based cross-sectional study in Finland. *BJU Int*, 2001. 88: 35.  
<https://www.ncbi.nlm.nih.gov/pubmed/11446842>
106. Rosen, R.C., *et al.* The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology*, 1997. 49: 822.  
<https://www.ncbi.nlm.nih.gov/pubmed/9187685>
107. Anderson, R.U., *et al.* Sexual dysfunction in men with chronic prostatitis/chronic pelvic pain syndrome: improvement after trigger point release and paradoxical relaxation training. *J Urol*, 2006. 176: 1534.  
<https://www.ncbi.nlm.nih.gov/pubmed/16952676>
108. Trinchieri, A., *et al.* Prevalence of sexual dysfunction in men with chronic prostatitis/chronic pelvic pain syndrome. *Arch Ital Urol Androl*, 2007. 79: 67.  
<https://www.ncbi.nlm.nih.gov/pubmed/17695411>
109. Zondervan, K.T., *et al.* The prevalence of chronic pelvic pain in women in the United Kingdom: a systematic review. *Br J Obstet Gynaecol*, 1998. 105: 93.  
<https://www.ncbi.nlm.nih.gov/pubmed/9442169>
110. Grace, V., *et al.* Chronic pelvic pain in women in New Zealand: comparative well-being, comorbidity, and impact on work and other activities. *Health Care Women Int*, 2006. 27: 585.  
<https://www.ncbi.nlm.nih.gov/pubmed/16844672>
111. Pitts, M.K., *et al.* Prevalence and correlates of three types of pelvic pain in a nationally representative sample of Australian women. *Med J Aust*, 2008. 189: 138.  
<https://www.ncbi.nlm.nih.gov/pubmed/18673099>
112. Verit, F.F., *et al.* The prevalence of sexual dysfunction and associated risk factors in women with chronic pelvic pain: a cross-sectional study. *Arch Gynecol Obstet*, 2006. 274: 297.  
<https://www.ncbi.nlm.nih.gov/pubmed/16705463>
113. Ambler, N., *et al.* Sexual difficulties of chronic pain patients. *Clin J Pain*, 2001. 17: 138.  
<https://www.ncbi.nlm.nih.gov/pubmed/11444715>
114. Loving, S., *et al.* Pelvic floor muscle dysfunctions are prevalent in female chronic pelvic pain: a cross-sectional population-based study. *Eur J Pain*, 2014. 18: 1259.  
<https://www.ncbi.nlm.nih.gov/pubmed/24700500>
115. Chiarioni, G., *et al.* Biofeedback is superior to electrogalvanic stimulation and massage for treatment of levator ani syndrome. *Gastroenterology*, 2010. 138: 1321.  
<https://www.ncbi.nlm.nih.gov/pubmed/20044997>
116. Rao, S.S., *et al.* ANMS-ESNM position paper and consensus guidelines on biofeedback therapy for anorectal disorders. *Neurogastroenterol Motil*, 2015. 27: 594.  
<https://www.ncbi.nlm.nih.gov/pubmed/25828100>
117. Zermann, D., *et al.* Chronic prostatitis: a myofascial pain syndrome? *Infect Urol*, 1999. 12: 84.  
<https://zanotowane.pl/1014/7270/>
118. Shoskes, D.A., *et al.* Muscle tenderness in men with chronic prostatitis/chronic pelvic pain syndrome: the chronic prostatitis cohort study. *J Urol*, 2008. 179: 556.  
<https://www.ncbi.nlm.nih.gov/pubmed/18082223>
119. Peters, K.M., *et al.* Prevalence of pelvic floor dysfunction in patients with interstitial cystitis. *Urology*, 2007. 70: 16.  
<https://www.ncbi.nlm.nih.gov/pubmed/17656199>
120. Reissing, E.D., *et al.* Pelvic floor muscle functioning in women with vulvar vestibulitis syndrome. *J Psychosom Obstet Gynaecol*, 2005. 26: 107.  
<https://www.ncbi.nlm.nih.gov/pubmed/16050536>

121. Nickel, J.C., *et al.* Chronic Prostate Inflammation Predicts Symptom Progression in Patients with Chronic Prostatitis/Chronic Pelvic Pain. *J Urol*, 2017. 198: 122.  
<https://www.ncbi.nlm.nih.gov/pubmed/28089730>
122. Peters, K.M., *et al.* Childhood symptoms and events in women with interstitial cystitis/painful bladder syndrome. *Urology*, 2009. 73: 258.  
<https://www.ncbi.nlm.nih.gov/pubmed/19036420>
123. Rudick, C.N., *et al.* O-antigen modulates infection-induced pain states. *PLoS One*, 2012. 7: e41273.  
<https://www.ncbi.nlm.nih.gov/pubmed/22899994>
124. Richter, B., *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. 57: 371.  
<https://www.ncbi.nlm.nih.gov/pubmed/20840668>
125. Dundore, P.A., *et al.* Mast cell counts are not useful in the diagnosis of nonulcerative interstitial cystitis. *J Urol*, 1996. 155: 885.  
<https://www.ncbi.nlm.nih.gov/pubmed/8583599>
126. Peeker, R., *et al.* Recruitment, distribution and phenotypes of mast cells in interstitial cystitis. *J Urol*, 2000. 163: 1009.  
<https://www.ncbi.nlm.nih.gov/pubmed/10688040>
127. Johansson, S.L., *et al.* Clinical features and spectrum of light microscopic changes in interstitial cystitis. *J Urol*, 1990. 143: 1118.  
<https://www.ncbi.nlm.nih.gov/pubmed/2342171>
128. Lokeshwar, V.B., *et al.* Urinary uronate and sulfated glycosaminoglycan levels: markers for interstitial cystitis severity. *J Urol*, 2005. 174: 344.  
<https://www.ncbi.nlm.nih.gov/pubmed/15947687>
129. Parsons, C.L., *et al.* Epithelial dysfunction in nonbacterial cystitis (interstitial cystitis). *J Urol*, 1991. 145: 732.  
<https://www.ncbi.nlm.nih.gov/pubmed/2005689>
130. Parsons, C.L., *et al.* Successful therapy of interstitial cystitis with pentosanpolysulfate. *J Urol*, 1987. 138: 513.  
<https://www.ncbi.nlm.nih.gov/pubmed/2442417>
131. Sanchez-Freire, V., *et al.* Acid-sensing channels in human bladder: expression, function and alterations during bladder pain syndrome. *J Urol*, 2011. 186: 1509.  
<https://www.ncbi.nlm.nih.gov/pubmed/21855903>
132. Hang, L., *et al.* Cytokine repertoire of epithelial cells lining the human urinary tract. *J Urol*, 1998. 159: 2185.  
<https://www.ncbi.nlm.nih.gov/pubmed/9598567>
133. Parsons, C.L., *et al.* Cyto-injury factors in urine: a possible mechanism for the development of interstitial cystitis. *J Urol*, 2000. 164: 1381.  
<https://www.ncbi.nlm.nih.gov/pubmed/10992419>
134. Chelimsky, G., *et al.* Autonomic Testing in Women with Chronic Pelvic Pain. *J Urol*, 2016. 196: 429.  
<https://www.ncbi.nlm.nih.gov/pubmed/27026035>
135. Charrua, A., *et al.* Can the adrenergic system be implicated in the pathophysiology of bladder pain syndrome/interstitial cystitis? A clinical and experimental study. *Neurourol Urodyn*, 2015. 34: 489.  
<https://www.ncbi.nlm.nih.gov/pubmed/24375689>
136. Fischer-Grote, L., *et al.* Comorbidities of bladder pain syndrome in the context of the HITOP distress category: a systematic review and meta-analysis. *Int Urogynecol J*, 2022. 33: 2335.  
<https://www.ncbi.nlm.nih.gov/pubmed/35262767>
137. Alagiri, M., *et al.* Interstitial cystitis: unexplained associations with other chronic disease and pain syndromes. *Urology*, 1997. 49: 52.  
<https://www.ncbi.nlm.nih.gov/pubmed/9146002>
138. Buffington, C.A. Comorbidity of interstitial cystitis with other unexplained clinical conditions. *J Urol*, 2004. 172: 1242.  
<https://www.ncbi.nlm.nih.gov/pubmed/15371816>
139. Erickson, D.R., *et al.* Nonbladder related symptoms in patients with interstitial cystitis. *J Urol*, 2001. 166: 557.  
<https://www.ncbi.nlm.nih.gov/pubmed/11458068>
140. Warren, J.W., *et al.* Antecedent nonbladder syndromes in case-control study of interstitial cystitis/painful bladder syndrome. *Urology*, 2009. 73: 52.  
<https://www.ncbi.nlm.nih.gov/pubmed/18995888>

141. Weissman, M., *et al.* Interstitial Cystitis and Panic Disorder - A Potential Genetic Syndrome. *Arch Gen Psych*, 2004. 61.  
<https://pubmed.ncbi.nlm.nih.gov/14993115/>
142. Warren, J.W., *et al.* Numbers and types of nonbladder syndromes as risk factors for interstitial cystitis/painful bladder syndrome. *Urology*, 2011. 77: 313.  
<https://www.ncbi.nlm.nih.gov/pubmed/21295246>
143. Peters, K.M., *et al.* Are ulcerative and nonulcerative interstitial cystitis/painful bladder syndrome 2 distinct diseases? A study of coexisting conditions. *Urology*, 2011. 78: 301.  
<https://www.ncbi.nlm.nih.gov/pubmed/21703668>
144. Akiyama, Y., *et al.* Molecular Taxonomy of Interstitial Cystitis/Bladder Pain Syndrome Based on Whole Transcriptome Profiling by Next-Generation RNA Sequencing of Bladder Mucosal Biopsies. *J Urol*, 2019. 202: 290.  
<https://www.ncbi.nlm.nih.gov/pubmed/30865573>
145. Akiyama, Y., *et al.* Interstitial cystitis/bladder pain syndrome: The evolving landscape, animal models and future perspectives. *Int J Urol*, 2020. 27: 491.  
<https://www.ncbi.nlm.nih.gov/pubmed/32246572>
146. Choi, H.W., *et al.* Microbiome in urological diseases: Axis crosstalk and bladder disorders. *Investig Clin Urol*, 2023. 64: 126.  
<https://www.ncbi.nlm.nih.gov/pubmed/36882171>
147. Li, K., *et al.* Interplay between bladder microbiota and overactive bladder symptom severity: a cross-sectional study. *BMC Urol*, 2022. 22: 39.  
<https://www.ncbi.nlm.nih.gov/pubmed/35305613>
148. Farmer, M.A., *et al.* Brain White Matter Abnormalities in Female Interstitial Cystitis/Bladder Pain Syndrome: A MAPP Network Neuroimaging Study. *J Urol*, 2015. 194: 118.  
<https://www.ncbi.nlm.nih.gov/pubmed/25711200>
149. Abreu-Mendes, P., *et al.* A Pilot Study of Functional Brain Magnetic Resonance Imaging in BPS/IC Patients: Evidence of Central Sensitization. *Urol Res Pract*, 2024. 50: 53.  
<https://www.ncbi.nlm.nih.gov/pubmed/39115335>
150. Rab, M., *et al.* Anatomic variability of the ilioinguinal and genitofemoral nerve: implications for the treatment of groin pain. *Plast Reconstr Surg*, 2001. 108: 1618.  
<https://www.ncbi.nlm.nih.gov/pubmed/11711938>
151. Eklund, A., *et al.* Chronic pain 5 years after randomized comparison of laparoscopic and Lichtenstein inguinal hernia repair. *Br J Surg*, 2010. 97: 600.  
<https://www.ncbi.nlm.nih.gov/pubmed/20186889>
152. Manikandan, R., *et al.* Early and late morbidity after vasectomy: a comparison of chronic scrotal pain at 1 and 10 years. *BJU Int*, 2004. 93: 571.  
<https://www.ncbi.nlm.nih.gov/pubmed/15008732>
153. Leslie, T.A., *et al.* The incidence of chronic scrotal pain after vasectomy: a prospective audit. *BJU Int*, 2007. 100: 1330.  
<https://www.ncbi.nlm.nih.gov/pubmed/17850378>
154. Hallen, M., *et al.* Laparoscopic extraperitoneal inguinal hernia repair versus open mesh repair: long-term follow-up of a randomized controlled trial. *Surgery*, 2008. 143: 313.  
<https://www.ncbi.nlm.nih.gov/pubmed/18291251>
155. Grant, A.M., *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. 91: 1570.  
<https://www.ncbi.nlm.nih.gov/pubmed/15515112>
156. Alfieri, S., *et al.* Influence of preservation versus division of ilioinguinal, iliohypogastric, and genital nerves during open mesh herniorrhaphy: prospective multicentric study of chronic pain. *Ann Surg*, 2006. 243: 553.  
<https://www.ncbi.nlm.nih.gov/pubmed/16552209>
157. Ronka, K., *et al.* Role of orchiectomy in severe testicular pain after inguinal hernia surgery: audit of the Finnish Patient Insurance Centre. *Hernia*, 2015. 19: 53.  
<https://www.ncbi.nlm.nih.gov/pubmed/23929499>
158. Parsons, C.L. 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. 107: 370.  
<https://www.ncbi.nlm.nih.gov/pubmed/21176078>
159. Parsons, C.L., *et al.* Intravesical potassium sensitivity in patients with interstitial cystitis and urethral syndrome. *Urology*, 2001. 57: 428.  
<https://www.ncbi.nlm.nih.gov/pubmed/11248610>

160. Gurel, H., *et al.* Urethral syndrome and associated risk factors related to obstetrics and gynecology. *Eur J Obstet Gynecol Reprod Biol*, 1999. 83: 5.  
<https://www.ncbi.nlm.nih.gov/pubmed/10221602>
161. Reed, B.D., *et al.* Psychosocial and sexual functioning in women with vulvodynia and chronic pelvic pain. A comparative evaluation. *J Reprod Med*, 2000. 45: 624.  
<https://www.ncbi.nlm.nih.gov/pubmed/10986680>
162. Niedenfuehr, J., *et al.* A scoping review: the psychosocial barriers that exist for people with vulvodynia. *J Sex Med*, 2023. 20: 833.  
<https://www.ncbi.nlm.nih.gov/pubmed/37037784>
163. Gornall, J. How mesh became a four letter word. *Bmj*, 2018. 363: k4137.  
<https://www.ncbi.nlm.nih.gov/pubmed/30305315>
164. Heneghan, C., *et al.* Surgical mesh and patient safety. *BMJ*, 2018. 363: k4231.  
<https://www.ncbi.nlm.nih.gov/pubmed/30305286>
165. Nilsson, C.G. Creating a gold standard surgical procedure: the development and implementation of TVT. *Int Urogynecol J*, 2015. 26: 467.  
<https://www.ncbi.nlm.nih.gov/pubmed/25582086>
166. Waltregny, D. TVT-O: a new gold standard surgical treatment of female stress urinary incontinence? *Eur Urol*, 2013. 63: 879.  
<https://www.ncbi.nlm.nih.gov/pubmed/23352654>
167. NICE, Urinary incontinence and pelvic organ prolapse in women: management: NICE Guideline. 2019.  
<https://www.nice.org.uk/guidance/ng123>
168. Hofner, K., *et al.* [Use of synthetic slings and mesh implants in the treatment of female stress urinary incontinence and prolapse : Statement of the Working Group on Urological Functional Diagnostics and Female Urology of the Academy of the German Society of Urology]. *Urologe A*, 2020. 59: 65.  
<https://www.ncbi.nlm.nih.gov/pubmed/31741004>
169. Keltie, K., *et al.* Complications following vaginal mesh procedures for stress urinary incontinence: an 8 year study of 92,246 women. *Sci Rep*, 2017. 7: 12015.  
<https://www.ncbi.nlm.nih.gov/pubmed/28931856>
170. Wang, C., *et al.* Synthetic mid-urethral sling complications: Evolution of presenting symptoms over time. *Neurourol Urodyn*, 2018. 37: 1937.  
<https://www.ncbi.nlm.nih.gov/pubmed/29464783>
171. Vancaillie, T., *et al.* Pain after vaginal prolapse repair surgery with mesh is a post-surgical neuropathy which needs to be treated - and can possibly be prevented in some cases. *Aust N Z J Obstet Gynaecol*, 2018. 58: 696.  
<https://www.ncbi.nlm.nih.gov/pubmed/29577243>
172. Mellano, E.M., *et al.* The Role of Chronic Mesh Infection in Delayed-Onset Vaginal Mesh Complications or Recurrent Urinary Tract Infections: Results From Explanted Mesh Cultures. *Female Pelvic Med Reconstr Surg*, 2016. 22: 166.  
<https://www.ncbi.nlm.nih.gov/pubmed/26829350>
173. Ubertazzi, E.P., *et al.* Long-term outcomes of transvaginal mesh (TVM) In patients with pelvic organ prolapse: A 5-year follow-up. *Eur J Obstet Gynecol Reprod Biol*, 2018. 225: 90.  
<https://www.ncbi.nlm.nih.gov/pubmed/29680466>
174. Mateu Arrom, L., *et al.* Pelvic Organ Prolapse Repair with Mesh: Mid-Term Efficacy and Complications. *Urol Int*, 2018. 101: 201.  
<https://www.ncbi.nlm.nih.gov/pubmed/29874667>
175. Khatri, G., *et al.* Diagnostic Evaluation of Chronic Pelvic Pain. *Phys Med Rehabil Clin N Am*, 2017. 28: 477.  
<https://www.ncbi.nlm.nih.gov/pubmed/28676360>
176. Bendavid, R., *et al.* A mechanism of mesh-related post-herniorrhaphy neuralgia. *Hernia*, 2016. 20: 357.  
<https://www.ncbi.nlm.nih.gov/pubmed/26597872>
177. Treede, R.D., *et al.* A classification of chronic pain for ICD-11. *Pain*, 2015. 156: 1003.  
<https://www.ncbi.nlm.nih.gov/pubmed/25844555>
178. Schug, S.A., *et al.* Risk stratification for the development of chronic postsurgical pain. *Pain Rep*, 2017. 2: e627.  
<https://www.ncbi.nlm.nih.gov/pubmed/29392241>
179. Strik, C., *et al.* Risk of Pain and Gastrointestinal Complaints at 6Months After Elective Abdominal Surgery. *J Pain*, 2019. 20: 38.  
<https://www.ncbi.nlm.nih.gov/pubmed/30107242>

180. Bouman, E.A., *et al.* Reduced incidence of chronic postsurgical pain after epidural analgesia for abdominal surgery. *Pain Pract*, 2014. 14: E76.  
<https://www.ncbi.nlm.nih.gov/pubmed/23758753>
181. van den Beukel, B.A.W., *et al.* Analgesia in patients with adhesion-related chronic abdominal and pelvic pain after surgery: a systematic review. *Acta Chir Belg*, 2022. 122: 303.  
<https://www.ncbi.nlm.nih.gov/pubmed/33899669>
182. Mala, T., *et al.* Abdominal Pain After Roux-En-Y Gastric Bypass for Morbid Obesity. *Scand J Surg*, 2018. 107: 277.  
<https://www.ncbi.nlm.nih.gov/pubmed/29739280>
183. Alsulaimy, M., *et al.* The Utility of Diagnostic Laparoscopy in Post-Bariatric Surgery Patients with Chronic Abdominal Pain of Unknown Etiology. *Obes Surg*, 2017. 27: 1924.  
<https://www.ncbi.nlm.nih.gov/pubmed/28229315>
184. Nariculum, J., *et al.* A review of the efficacy of surgical treatment for and pathological changes in patients with chronic scrotal pain. *BJU Int*, 2007. 99: 1091.  
<https://www.ncbi.nlm.nih.gov/pubmed/17244279>
185. Han, C., *et al.* Incidence and risk factors of chronic pain following hysterectomy among Southern Jiangsu Chinese Women. *BMC Anesthesiol*, 2017. 17: 103.  
<https://www.ncbi.nlm.nih.gov/pubmed/28800726>
186. Behera, M., *et al.* Laparoscopic findings, histopathologic evaluation, and clinical outcomes in women with chronic pelvic pain after hysterectomy and bilateral salpingo-oophorectomy. *J Minim Invasive Gynecol*, 2006. 13: 431.  
<https://www.ncbi.nlm.nih.gov/pubmed/16962527>
187. Amid, P.K., *et al.* Surgical treatment of chronic groin and testicular pain after laparoscopic and open preperitoneal inguinal hernia repair. *J Am Coll Surg*, 2011. 213: 531.  
<https://www.ncbi.nlm.nih.gov/pubmed/21784668>
188. European Union Drugs Agency, European Drug Report 2025: Trends and Developments. 2025.  
[www.euda.europa.eu](http://www.euda.europa.eu)
189. ONS Centre for Crime and Justice, Drug misuse in England and Wales: year ending March 2024. 2024.  
<https://www.ons.gov.uk/peoplepopulationandcommunity/crimeandjustice/articles/drugmisuseinenglandandwales/yearendingmarch2024>
190. Shahani, R., *et al.* Ketamine-associated ulcerative cystitis: a new clinical entity. *Urology*, 2007. 69: 810.  
<https://www.ncbi.nlm.nih.gov/pubmed/17482909>
191. Chu, P.S., *et al.* 'Street ketamine'-associated bladder dysfunction: a report of ten cases. *Hong Kong Med J*, 2007. 13: 311.  
<https://www.ncbi.nlm.nih.gov/pubmed/17592176>
192. Tam, Y.H., *et al.* One-stop clinic for ketamine-associated uropathy: report on service delivery model, patients' characteristics and non-invasive investigations at baseline by a cross-sectional study in a prospective cohort of 318 teenagers and young adults. *BJU Int*, 2014. 114: 754.  
<https://www.ncbi.nlm.nih.gov/pubmed/24552244>
193. Vizgan, G., *et al.* Ketamine-induced uropathy: A narrative systemic review of surgical outcomes of reconstructive surgery. *BJU Compass*, 2023. 4: 377.  
<https://www.ncbi.nlm.nih.gov/pubmed/37334018>
194. Hahn, L. Treatment of ilioinguinal nerve entrapment - a randomized controlled trial. *Acta Obstet Gynecol Scand*, 2011. 90: 955.  
<https://www.ncbi.nlm.nih.gov/pubmed/21615360>
195. Antolak, S.J., Jr., *et al.* Anatomical basis of chronic pelvic pain syndrome: the ischial spine and pudendal nerve entrapment. *Med Hypotheses*, 2002. 59: 349.  
<https://www.ncbi.nlm.nih.gov/pubmed/12208168>
196. Mahakkanukrauh, P., *et al.* Anatomical study of the pudendal nerve adjacent to the sacrospinous ligament. *Clin Anat*, 2005. 18: 200.  
<https://www.ncbi.nlm.nih.gov/pubmed/15768420>
197. Robert, R., *et al.* Anatomic basis of chronic perineal pain: role of the pudendal nerve. *Surg Radiol Anat*, 1998. 20: 93.  
<https://www.ncbi.nlm.nih.gov/pubmed/9658526>
198. Amarenco, G., *et al.* Electrophysiological analysis of pudendal neuropathy following traction. *Muscle Nerve*, 2001. 24: 116.  
<https://www.ncbi.nlm.nih.gov/pubmed/11150974>

199. Goldet, R., *et al.* [Traction on the orthopedic table and pudendal nerve injury. Importance of electrophysiologic examination]. *Rev Chir Orthop Reparatrice Appar Mot*, 1998. 84: 523.  
<https://www.ncbi.nlm.nih.gov/pubmed/9846326>
200. Polyzois, I., *et al.* Pudendal nerve palsy in trauma and elective orthopaedic surgery. *Injury*, 2013. 44: 1721.  
<https://www.ncbi.nlm.nih.gov/pubmed/24054001>
201. Vodegel, E.V., *et al.* Surgical management of pudendal nerve entrapment after sacrospinous ligament fixation. *BJOG*, 2022. 129: 1908.  
<https://www.ncbi.nlm.nih.gov/pubmed/35289051>
202. Moszkowicz, D., *et al.* Where does pelvic nerve injury occur during rectal surgery for cancer? *Colorectal Dis*, 2011. 13: 1326.  
<https://www.ncbi.nlm.nih.gov/pubmed/20718836>
203. Chen, Z., *et al.* From basic to clinical: Anatomy of Denonvilliers' fascia and its application in laparoscopic radical resection of rectal cancer. *World J Gastrointest Surg*, 2023. 15: 2108.  
<https://www.ncbi.nlm.nih.gov/pubmed/37969712>
204. Ashton-Miller, J.A., *et al.* Functional anatomy of the female pelvic floor. *Ann N Y Acad Sci*, 2007. 1101: 266.  
<https://www.ncbi.nlm.nih.gov/pubmed/17416924>
205. Mahoney, C.K., *et al.* The impact of pregnancy and childbirth on pelvic sensation: a prospective cohort study. *Sci Rep*, 2023. 13: 1535.  
<https://www.ncbi.nlm.nih.gov/pubmed/36707642>
206. Amarenco, G., *et al.* [Perineal neuropathy due to stretching and urinary incontinence. Physiopathology, diagnosis and therapeutic implications]. *Ann Urol (Paris)*, 1990. 24: 463.  
<https://www.ncbi.nlm.nih.gov/pubmed/2176777>
207. Huang, X., *et al.* Psychological factors and pain catastrophizing in men with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS): a meta-analysis. *Transl Androl Urol*, 2020. 9: 485.  
<https://www.ncbi.nlm.nih.gov/pubmed/32420154>
208. Fleming, M., *et al.* Sexuality and chronic pain. *Journal of Sex Education and Therapy*, 2001. 26: 204.  
<https://www.tandfonline.com/doi/abs/10.1080/01614576.2001.11074415>
209. Chen, X., *et al.* The Effect of Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS) on Erectile Function: A Systematic Review and Meta-Analysis. *PLoS One*, 2015. 10: e0141447.  
<https://www.ncbi.nlm.nih.gov/pubmed/26509575>
210. Jacobsen, S.J., *et al.* Frequency of sexual activity and prostatic health: fact or fairy tale? *Urology*, 2003. 61: 348.  
<https://www.ncbi.nlm.nih.gov/pubmed/12597946>
211. Tripp, D.A., *et al.* Prevalence, symptom impact and predictors of chronic prostatitis-like symptoms in Canadian males aged 16-19 years. *BJU Int*, 2009. 103: 1080.  
<https://www.ncbi.nlm.nih.gov/pubmed/19007369>
212. Pereira, R., *et al.* Sexual Functioning and Cognitions During Sexual Activity in Men With Genital Pain: A Comparative Study. *J Sex Marital Ther*, 2016. 42: 602.  
<https://www.ncbi.nlm.nih.gov/pubmed/26548315>
213. Muller, A., *et al.* Sexual dysfunction in the patient with prostatitis. *Curr Opin Urol*, 2005. 15: 404.  
<https://www.ncbi.nlm.nih.gov/pubmed/16205492>
214. Smith, K.B., *et al.* Sexual and relationship functioning in men with chronic prostatitis/chronic pelvic pain syndrome and their partners. *Arch Sex Behav*, 2007. 36: 301.  
<https://www.ncbi.nlm.nih.gov/pubmed/17186130>
215. Latthe, P., *et al.* WHO systematic review of prevalence of chronic pelvic pain: a neglected reproductive health morbidity. *BMC Public Health*, 2006. 6: 177.  
<https://www.ncbi.nlm.nih.gov/pubmed/16824213>
216. ter Kuile, M.M., *et al.* Sexual functioning in women with chronic pelvic pain: the role of anxiety and depression. *J Sex Med*, 2010. 7: 1901.  
<https://www.ncbi.nlm.nih.gov/pubmed/19678881>
217. Collett, B.J., *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 Gynaecol*, 1998. 105: 87.  
<https://www.ncbi.nlm.nih.gov/pubmed/9442168>
218. McCabe, M.P., *et al.* Intercorrelations among general arousability, emerging and current sexual desire, and severity of sexual dysfunction in women. *Psychol Rep*, 1989. 65: 147.  
<https://www.ncbi.nlm.nih.gov/pubmed/2780925>

219. Flor, H., *et al.* The role of spouse reinforcement, perceived pain, and activity levels of chronic pain patients. *J Psychosom Res*, 1987. 31: 251.  
<https://www.ncbi.nlm.nih.gov/pubmed/3585827>
220. Paice, J. Sexuality and chronic pain. *Am J Nurs*, 2003. 103: 87.  
<https://www.ncbi.nlm.nih.gov/pubmed/12544064>
221. Verit, F.F., *et al.* Validation of the female sexual function index in women with chronic pelvic pain. *J Sex Med*, 2007. 4: 1635.  
<https://www.ncbi.nlm.nih.gov/pubmed/17888066>
222. Maruta, T., *et al.* Chronic pain patients and spouses: marital and sexual adjustment. *Mayo Clin Proc*, 1981. 56: 307.  
<https://www.ncbi.nlm.nih.gov/pubmed/7230895>
223. Hetrick, D.C., *et al.* Musculoskeletal dysfunction in men with chronic pelvic pain syndrome type III: a case-control study. *J Urol*, 2003. 170: 828.  
<https://www.ncbi.nlm.nih.gov/pubmed/12913709>
224. Clemens, J.Q., *et al.* Biofeedback, pelvic floor re-education, and bladder training for male chronic pelvic pain syndrome. *Urology*, 2000. 56: 951.  
<https://www.ncbi.nlm.nih.gov/pubmed/11113739>
225. Liao, C.H., *et al.* Chronic Prostatitis/Chronic Pelvic Pain Syndrome is associated with Irritable Bowel Syndrome: A Population-based Study. *Sci Rep*, 2016. 6: 26939.  
<https://www.ncbi.nlm.nih.gov/pubmed/27225866>
226. Zondervan, K.T., *et al.* Prevalence and incidence of chronic pelvic pain in primary care: evidence from a national general practice database. *Br J Obstet Gynaecol*, 1999. 106: 1149.  
<https://www.ncbi.nlm.nih.gov/pubmed/10549959>
227. Drossman, D.A., *et al.* U.S. householder survey of functional gastrointestinal disorders. Prevalence, sociodemography, and health impact. *Dig Dis Sci*, 1993. 38: 1569.  
<https://www.ncbi.nlm.nih.gov/pubmed/8359066>
228. Prior, A., *et al.* Gynaecological consultation in patients with the irritable bowel syndrome. *Gut*, 1989. 30: 996.  
<https://www.ncbi.nlm.nih.gov/pubmed/2759494>
229. Longstreth, G.F., *et al.* Irritable bowel syndrome in women having diagnostic laparoscopy or hysterectomy. Relation to gynecologic features and outcome. *Dig Dis Sci*, 1990. 35: 1285.  
<https://www.ncbi.nlm.nih.gov/pubmed/2145139>
230. Choung, R.S., *et al.* Irritable bowel syndrome and chronic pelvic pain: a population-based study. *J Clin Gastroenterol*, 2010. 44: 696.  
<https://www.ncbi.nlm.nih.gov/pubmed/20375730>
231. Sperber, A.D., *et al.* Development of abdominal pain and IBS following gynecological surgery: a prospective, controlled study. *Gastroenterology*, 2008. 134: 75.  
<https://www.ncbi.nlm.nih.gov/pubmed/18166349>
232. Monnikes, H. Quality of life in patients with irritable bowel syndrome. *J Clin Gastroenterol*, 2011. 45 Suppl: S98.  
<https://www.ncbi.nlm.nih.gov/pubmed/21666428>
233. Canavan, C., *et al.* Review article: the economic impact of the irritable bowel syndrome. *Aliment Pharmacol Ther*, 2014. 40: 1023.  
<https://www.ncbi.nlm.nih.gov/pubmed/25199904>
234. Morgan, C.J., *et al.* Ketamine use: a review. *Addiction*, 2012. 107: 27.  
<https://www.ncbi.nlm.nih.gov/pubmed/21777321>
235. Lorencatto, C., *et al.* Depression in women with endometriosis with and without chronic pelvic pain. *Acta Obstet Gynecol Scand*, 2006. 85: 88.  
<https://www.ncbi.nlm.nih.gov/pubmed/16521687>
236. Howard, F.M. Chronic pelvic pain. *Obstet Gynecol*, 2003. 101: 594.  
<https://www.ncbi.nlm.nih.gov/pubmed/12636968>
237. Fitzgerald, M.P., *et al.* Beyond the lower urinary tract: the association of urologic and sexual symptoms with common illnesses. *Eur Urol*, 2007. 52: 407.  
<https://www.ncbi.nlm.nih.gov/pubmed/17382458>
238. Davis, S.N., *et al.* Is a sexual dysfunction domain important for quality of life in men with urological chronic pelvic pain syndrome? Signs "UPOINT" to yes. *J Urol*, 2013. 189: 146.  
<https://www.ncbi.nlm.nih.gov/pubmed/23164384>
239. Cleeland, C., *The Brief Pain Inventory User Guide*. 2009.  
[https://www.mdanderson.org/documents/Departments-and-Divisions/Symptom-Research/BPI\\_](https://www.mdanderson.org/documents/Departments-and-Divisions/Symptom-Research/BPI_)

[UserGuide.pdf](#)

240. Turk, D.C., *et al.* Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. *Pain*, 2003. 106: 337.  
<https://www.ncbi.nlm.nih.gov/pubmed/14659516>
241. Fall, M., *et al.* Chronic interstitial cystitis: a heterogeneous syndrome. *J Urol*, 1987. 137: 35.  
<https://www.ncbi.nlm.nih.gov/pubmed/3795363>
242. Warren, J.W., *et al.* Evidence-based criteria for pain of interstitial cystitis/painful bladder syndrome in women. *Urology*, 2008. 71: 444.  
<https://www.ncbi.nlm.nih.gov/pubmed/18342184>
243. Rao, S.S., *et al.* Functional Anorectal Disorders. *Gastroenterology*, 2016.  
<https://www.ncbi.nlm.nih.gov/pubmed/27144630>
244. Labat, J.J., *et al.* Diagnostic criteria for pudendal neuralgia by pudendal nerve entrapment (Nantes criteria). *Neurourol Urodyn*, 2008. 27: 306.  
<https://www.ncbi.nlm.nih.gov/pubmed/17828787>
245. McNaughton Collins, M., *et al.* Quality of life is impaired in men with chronic prostatitis: the Chronic Prostatitis Collaborative Research Network. *J Gen Intern Med*, 2001. 16: 656.  
<https://www.ncbi.nlm.nih.gov/pubmed/11679032>
246. Wenninger, K., *et al.* Sickness impact of chronic nonbacterial prostatitis and its correlates. *J Urol*, 1996. 155: 965.  
<https://www.ncbi.nlm.nih.gov/pubmed/8583619>
247. Gerlinger, C., *et al.* Defining a minimal 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. 8: 138.  
<https://www.ncbi.nlm.nih.gov/pubmed/21106059>
248. Litwin, M.S., *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. 162: 369.  
<https://www.ncbi.nlm.nih.gov/pubmed/10411041>
249. Mebust, W., *et al.*, Symptom evaluation, quality of life and sexuality. The 2nd International Consultation on Benign Prostatic Hyperplasia. 1993, Jersey, Channel Islands.  
<https://kohahq.searo.who.int/bib/13112>
250. Lubeck, D.P., *et al.* Psychometric validation of the O'leary-Sant interstitial cystitis symptom index in a clinical trial of pentosan polysulfate sodium. *Urology*, 2001. 57: 62.  
<https://www.ncbi.nlm.nih.gov/pubmed/11378052>
251. Francis, C.Y., *et al.* The irritable bowel severity scoring system: a simple method of monitoring irritable bowel syndrome and its progress. *Aliment Pharmacol Ther*, 1997. 11: 395.  
<https://www.ncbi.nlm.nih.gov/pubmed/9146781>
252. Spiegel, B.M., *et al.* Characterizing abdominal pain in IBS: guidance for study inclusion criteria, outcome measurement and clinical practice. *Aliment Pharmacol Ther*, 2010. 32: 1192.  
<https://www.ncbi.nlm.nih.gov/pubmed/20807217>
253. Wiegel, M., *et al.* The female sexual function index (FSFI): cross-validation and development of clinical cutoff scores. *J Sex Marital Ther*, 2005. 31: 1.  
<https://www.ncbi.nlm.nih.gov/pubmed/15841702>
254. Slieker-ten Hove, M.C., *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: 295.  
<https://www.ncbi.nlm.nih.gov/pubmed/19090583>
255. Wyndaele, J.J., *et al.* Reproducibility of digital testing of the pelvic floor muscles in men. *Arch Phys Med Rehabil*, 1996. 77: 1179.  
<https://www.ncbi.nlm.nih.gov/pubmed/8931532>
256. Davis, S.N., *et al.* Use of pelvic floor ultrasound to assess pelvic floor muscle function in Urological Chronic Pelvic Pain Syndrome in men. *J Sex Med*, 2011. 8: 3173.  
<https://www.ncbi.nlm.nih.gov/pubmed/21883952>
257. Anderson, R.U., *et al.* Painful myofascial trigger points and pain sites in men with chronic prostatitis/chronic pelvic pain syndrome. *J Urol*, 2009. 182: 2753.  
<https://www.ncbi.nlm.nih.gov/pubmed/19837420>
258. Sanses, T.V., *et al.* The Pelvis and Beyond: Musculoskeletal Tender Points in Women With Chronic Pelvic Pain. *Clin J Pain*, 2016. 32: 659.  
<https://www.ncbi.nlm.nih.gov/pubmed/26491938>

259. Yang, C.C., *et al.* Physical Examination for Men and Women With Urologic Chronic Pelvic Pain Syndrome: A MAPP (Multidisciplinary Approach to the Study of Chronic Pelvic Pain) Network Study. *Urology*, 2018. 116: 23.  
<https://www.ncbi.nlm.nih.gov/pubmed/29604315>
260. Antolak, S.J., Jr., *et al.* Therapeutic pudendal nerve blocks using corticosteroids cure pelvic pain after failure of sacral neuromodulation. *Pain Med*, 2009. 10: 186.  
<https://www.ncbi.nlm.nih.gov/pubmed/19222779>
261. Filler, A.G. Diagnosis and treatment of pudendal nerve entrapment syndrome subtypes: imaging, injections, and minimal access surgery. *Neurosurg Focus*, 2009. 26: E9.  
<https://www.ncbi.nlm.nih.gov/pubmed/19323602>
262. Lee, J.C., *et al.* Neurophysiologic testing in chronic pelvic pain syndrome: a pilot study. *Urology*, 2001. 58: 246.  
<https://www.ncbi.nlm.nih.gov/pubmed/11489711>
263. Lefaucheur, J.P., *et al.* What is the place of electroneuromyographic studies in the diagnosis and management of pudendal neuralgia related to entrapment syndrome? *Neurophysiol Clin*, 2007. 37: 223.  
<https://www.ncbi.nlm.nih.gov/pubmed/17996810>
264. Poldrack, R.A., *et al.* Scanning the Horizon: challenges and solutions for neuroimaging research. *Nat Rev Neurosci*, 2017. 18: 115.  
<https://doi.org/10.1038/nrn.2016.167>
265. Salomons, T.V., *et al.* The "Pain Matrix" in Pain-Free Individuals. *JAMA Neurol*, 2016. 73: 755.  
<https://www.ncbi.nlm.nih.gov/pubmed/27111250>
266. Charlanes, A., *et al.* Diffusion-Weighted Magnetic Resonance Imaging: A New Tool for the Diagnosis of Bladder Pain Syndrome/Interstitial Cystitis. *Urol Int*, 2019. 102: 109.  
<https://www.ncbi.nlm.nih.gov/pubmed/30428470>
267. Meares, E.M., *et al.* Bacteriologic localization patterns in bacterial prostatitis and urethritis. *Invest Urol*, 1968. 5: 492.  
<https://www.ncbi.nlm.nih.gov/pubmed/4870505>
268. Nickel, J.C. The Pre and Post Massage Test (PPMT): a simple screen for prostatitis. *Tech Urol*, 1997. 3: 38.  
<https://www.ncbi.nlm.nih.gov/pubmed/9170224>
269. Nickel, J.C., *et al.* How does the pre-massage and post-massage 2-glass test compare to the Meares-Stamey 4-glass test in men with chronic prostatitis/chronic pelvic pain syndrome? *J Urol*, 2006. 176: 119.  
<https://www.ncbi.nlm.nih.gov/pubmed/16753385>
270. Nickel, J.C., *et al.* A randomized, placebo controlled, multicenter study to evaluate the safety and efficacy of rofecoxib in the treatment of chronic nonbacterial prostatitis. *J Urol*, 2003. 169: 1401.  
<https://www.ncbi.nlm.nih.gov/pubmed/12629372>
271. Manganaro, L., *et al.* Diffusion tensor imaging and tractography to evaluate sacral nerve root abnormalities in endometriosis-related pain: a pilot study. *Eur Radiol*, 2014. 24: 95.  
<https://www.ncbi.nlm.nih.gov/pubmed/23982288>
272. Howard, F.M. The role of laparoscopy as a diagnostic tool in chronic pelvic pain. *Baillieres Best Pract Res Clin Obstet Gynaecol*, 2000. 14: 467.  
<https://www.ncbi.nlm.nih.gov/pubmed/10962637>
273. Jacobson, T.Z., *et al.* Laparoscopic surgery for pelvic pain associated with endometriosis. *Cochrane Database Syst Rev*, 2009: CD001300.  
<https://www.ncbi.nlm.nih.gov/pubmed/19821276>
274. Porpora, M.G., *et al.* The role of laparoscopy in the management of pelvic pain in women of reproductive age. *Fertil Steril*, 1997. 68: 765.  
<https://www.ncbi.nlm.nih.gov/pubmed/9389799>
275. Collings, R., *et al.* Effect of investigative laparoscopy on bladder pain syndrome: a prospective cohort trial. *Int Urogynecol J*, 2020. 31: 1583.  
<https://www.ncbi.nlm.nih.gov/pubmed/31240363>
276. Seracchioli, R., *et al.* Cystoscopy-assisted laparoscopic resection of extramucosal bladder endometriosis. *J Endourol*, 2002. 16: 663.  
<https://www.ncbi.nlm.nih.gov/pubmed/12490020>
277. Wyndaele, J.J., *et al.* Cystoscopy and bladder biopsies in patients with bladder pain syndrome carried out following ESSIC guidelines. *Scand J Urol Nephrol*, 2009. 43: 471.  
<https://www.ncbi.nlm.nih.gov/pubmed/19707951>

278. Elcombe, S., *et al.* The psychological effects of laparoscopy on women with chronic pelvic pain. *Psychol Med*, 1997. 27: 1041.  
<https://www.ncbi.nlm.nih.gov/pubmed/9300510>
279. Peters, A.A., *et al.* A randomized clinical trial to compare two different approaches in women with chronic pelvic pain. *Obstet Gynecol*, 1991. 77: 740.  
<https://www.ncbi.nlm.nih.gov/pubmed/1826544>
280. Cole, E.E., *et al.* Are patient symptoms predictive of the diagnostic and/or therapeutic value of hydrodistention? *Neurourol Urodyn*, 2005. 24: 638.  
<https://www.ncbi.nlm.nih.gov/pubmed/16208660>
281. Lamale, L.M., *et al.* Symptoms and cystoscopic findings in patients with untreated interstitial cystitis. *Urology*, 2006. 67: 242.  
<https://www.ncbi.nlm.nih.gov/pubmed/16442603>
282. Ottem, D.P., *et al.* What is the value of cystoscopy with hydrodistension for interstitial cystitis? *Urology*, 2005. 66: 494.  
<https://www.ncbi.nlm.nih.gov/pubmed/16140064>
283. Shear, S., *et al.* Development of glomerulations in younger women with interstitial cystitis. *Urology*, 2006. 68: 253.  
<https://www.ncbi.nlm.nih.gov/pubmed/16904429>
284. Tamaki, M., *et al.* Possible mechanisms inducing glomerulations in interstitial cystitis: relationship between endoscopic findings and expression of angiogenic growth factors. *J Urol*, 2004. 172: 945.  
<https://www.ncbi.nlm.nih.gov/pubmed/15311005>
285. Aihara, K., *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. 16: 947.  
<https://www.ncbi.nlm.nih.gov/pubmed/19817916>
286. Messing, E., *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. 49: 81.  
<https://www.ncbi.nlm.nih.gov/pubmed/9146006>
287. Waxman, J.A., *et al.* Cystoscopic findings consistent with interstitial cystitis in normal women undergoing tubal ligation. *J Urol*, 1998. 160: 1663.  
<https://www.ncbi.nlm.nih.gov/pubmed/9783927>
288. Geurts, N., *et al.* Bladder pain syndrome: do the different morphological and cystoscopic features correlate? *Scand J Urol Nephrol*, 2011. 45: 20.  
<https://www.ncbi.nlm.nih.gov/pubmed/20846081>
289. Johansson, S.L., *et al.* Pathology of interstitial cystitis. *Urol Clin North Am*, 1994. 21: 55.  
<https://www.ncbi.nlm.nih.gov/pubmed/8284845>
290. Jhang, J.F., *et al.* Clinical Relevance of Bladder Histopathological Findings and Their Impact on Treatment Outcomes among Patients with Interstitial Cystitis/Bladder Pain Syndrome: An Investigation of the European Society for the Study of Interstitial Cystitis Histopathological Classification. *J Urol*, 2021. 205: 226.  
<https://www.ncbi.nlm.nih.gov/pubmed/32856961>
291. Ness, R.B., *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. 186: 929.  
<https://www.ncbi.nlm.nih.gov/pubmed/12015517>
292. Corey, L., *et al.* Genital herpes simplex virus infections: clinical manifestations, course, and complications. *Ann Intern Med*, 1983. 98: 958.  
<https://www.ncbi.nlm.nih.gov/pubmed/6344712>
293. Young, H., *et al.* Screening for treponemal infection by a new enzyme immunoassay. *Genitourin Med*, 1989. 65: 72.  
<https://www.ncbi.nlm.nih.gov/pubmed/2666302>
294. Culley, L., *et al.* The social and psychological impact of endometriosis on women's lives: a critical narrative review. *Hum Reprod Update*, 2013. 19: 625.  
<https://www.ncbi.nlm.nih.gov/pubmed/23884896>
295. Souza, C.A., *et al.* Quality of life associated to chronic pelvic pain is independent of endometriosis diagnosis—a cross-sectional survey. *Health Qual Life Outcomes*, 2011. 9: 41.  
<https://www.ncbi.nlm.nih.gov/pubmed/21663624>

296. Barri, P.N., *et al.* Endometriosis-associated infertility: surgery and IVF, a comprehensive therapeutic approach. *Reprod Biomed Online*, 2010. 21: 179.  
<https://www.ncbi.nlm.nih.gov/pubmed/20541976>
297. Heim, L.J. Evaluation and differential diagnosis of dyspareunia. *Am Fam Physician*, 2001. 63: 1535.  
<https://www.ncbi.nlm.nih.gov/pubmed/11327429>
298. Vercellini, P., *et al.* Medical treatment for rectovaginal endometriosis: what is the evidence? *Hum Reprod*, 2009. 24: 2504.  
<https://www.ncbi.nlm.nih.gov/pubmed/19574277>
299. Khan, K.S., *et al.* MRI versus laparoscopy to diagnose the main causes of chronic pelvic pain in women: a test-accuracy study and economic evaluation. *Health Technol Assess*, 2018. 22: 1.  
<https://www.ncbi.nlm.nih.gov/pubmed/30045805>
300. Kaminski, P., *et al.* The usefulness of laparoscopy and hysteroscopy in the diagnostics and treatment of infertility. *Neuro Endocrinol Lett*, 2006. 27: 813.  
<https://www.ncbi.nlm.nih.gov/pubmed/17187014>
301. Walters, C., *et al.* Pelvic girdle pain in pregnancy. *Aust J Gen Pract*, 2018. 47: 439.  
<https://www.ncbi.nlm.nih.gov/pubmed/30114872>
302. Hay-Smith, E.J. Therapeutic ultrasound for postpartum perineal pain and dyspareunia. *Cochrane Database Syst Rev*, 2000. 1998: CD000495.  
<https://www.ncbi.nlm.nih.gov/pubmed/10796210>
303. Cappell, J., *et al.* Clinical profile of persistent genito-pelvic postpartum pain. *Midwifery*, 2017. 50: 125.  
<https://www.ncbi.nlm.nih.gov/pubmed/28419979>
304. Landau, R., *et al.* Chronic pain after childbirth. *Int J Obstet Anesth*, 2013. 22: 133.  
<https://www.ncbi.nlm.nih.gov/pubmed/23477888>
305. Roovers, J.P., *et al.* A randomised controlled trial comparing abdominal and vaginal prolapse surgery: effects on urogenital function. *BJOG*, 2004. 111: 50.  
<https://www.ncbi.nlm.nih.gov/pubmed/14687052>
306. Niro, J., *et al.* [Postoperative pain after transvaginal repair of pelvic organ prolapse with or without mesh]. *Gynecol Obstet Fertil*, 2010. 38: 648.  
<https://www.ncbi.nlm.nih.gov/pubmed/21030280>
307. Reid, F.M., *et al.* How common are complications following polypropylene mesh, biological xenograft and native tissue surgery for pelvic organ prolapse? A secondary analysis from the PROSPECT trial. *BJOG*, 2021. 128: 2180.  
<https://www.ncbi.nlm.nih.gov/pubmed/34473896>
308. Vancaillie, T., *et al.* Sacral neuromodulation for pelvic pain and pelvic organ dysfunction: A case series. *Aust N Z J Obstet Gynaecol*, 2018. 58: 102.  
<https://www.ncbi.nlm.nih.gov/pubmed/29218704>
309. Eisenberg, V.H., *et al.* Ultrasound visualization of sacrocolpopexy polyvinylidene fluoride meshes containing paramagnetic Fe particles compared with polypropylene mesh. *Int Urogynecol J*, 2019. 30: 795.  
<https://www.ncbi.nlm.nih.gov/pubmed/30083941>
310. Kim, K.Y., *et al.* Translabial Ultrasound Evaluation of Pelvic Floor Structures and Mesh in the Urology Office and Intraoperative Setting. *Urology*, 2018. 120: 267.  
<https://www.ncbi.nlm.nih.gov/pubmed/30031831>
311. Sindhwani, N., *et al.* Short term post-operative morphing of sacrocolpopexy mesh measured by magnetic resonance imaging. *J Mech Behav Biomed Mater*, 2018. 80: 269.  
<https://www.ncbi.nlm.nih.gov/pubmed/29455036>
312. Zacharakis, D., *et al.* Pre- and postoperative magnetic resonance imaging (MRI) findings in patients treated with laparoscopic sacrocolpopexy. Is it a safe procedure for all patients? *Neurourol Urodyn*, 2018. 37: 316.  
<https://www.ncbi.nlm.nih.gov/pubmed/28481045>
313. Ford, A.C., *et al.* Irritable Bowel Syndrome. *N Engl J Med*, 2017. 376: 2566.  
<https://www.ncbi.nlm.nih.gov/pubmed/28657875>
314. Nicola, M., *et al.* Defining pain-validation: The importance of validation in reducing the stresses of chronic pain. *Front Pain Res (Lausanne)*, 2022. 3: 884335.  
<https://www.ncbi.nlm.nih.gov/pubmed/36313220>
315. Moseley, G.L., *et al.* Fifteen Years of Explaining Pain: The Past, Present, and Future. *J Pain*, 2015. 16: 807.  
<https://www.ncbi.nlm.nih.gov/pubmed/26051220>

316. Mardon, A.K., *et al.* Recommendations for patient education in the management of persistent pelvic pain: a systematic review of clinical practice guidelines. *Pain*, 2024. 165: 1207.  
<https://www.ncbi.nlm.nih.gov/pubmed/38112691>
317. NICE, Shared decision making: NICE Guideline. 2021.  
<https://www.nice.org.uk/guidance/ng197>
318. Simmons, M., *et al.* Shared decision-making: benefits, barriers and current opportunities for application. *Australas Psychiatry*, 2010. 18: 394.  
<https://www.ncbi.nlm.nih.gov/pubmed/20863175>
319. Saleeb, M., *et al.* Associations between perceptions of shared decision making and health among hysterectomy patients: A prospective observational study. *Int J Gynaecol Obstet*, 2023. 162: 1020.  
<https://www.ncbi.nlm.nih.gov/pubmed/37078494>
320. McGowan, L., *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. 12: 261.  
<https://www.ncbi.nlm.nih.gov/pubmed/17456285>
321. Loving, S., *et al.* Does evidence support physiotherapy management of adult female chronic pelvic pain? A systematic review. *Scand J Pain*, 2012. 3: 70.  
<https://www.ncbi.nlm.nih.gov/pubmed/29913781>
322. Haugstad, G.K., *et al.* Mensendieck somatocognitive therapy as treatment approach to chronic pelvic pain: results of a randomized controlled intervention study. *Am J Obstet Gynecol*, 2006. 194: 1303.  
<https://www.ncbi.nlm.nih.gov/pubmed/16647914>
323. Fitzgerald, M.P., *et al.* Randomized multicenter feasibility trial of myofascial physical therapy for the treatment of urological chronic pelvic pain syndromes. *J Urol*, 2013. 189: S75.  
<https://www.ncbi.nlm.nih.gov/pubmed/23234638>
324. Pandey, M., *et al.* Pelvic-floor relaxation techniques using biofeedback – more effective therapy for chronic prostatitis/chronic pelvic pain syndrome. *Journal of Clinical Urology*, 2020. 13: 454.  
<https://journals.sagepub.com/doi/abs/10.1177/2051415820939450>
325. de las Penas, C., *et al.* Manual therapies in myofascial trigger point treatment: a systematic review. *J Bodyw Mov Ther*, 2005. 9: 27.  
<https://www.ncbi.nlm.nih.gov/books/NBK71861/#d12005009070>
326. Tough, E.A., *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. 13: 3.  
<https://www.ncbi.nlm.nih.gov/pubmed/18395479>
327. Oyama, I.A., *et al.* Modified Thiele massage as therapeutic intervention for female patients with interstitial cystitis and high-tone pelvic floor dysfunction. *Urology*, 2004. 64: 862.  
<https://www.ncbi.nlm.nih.gov/pubmed/15533464>
328. Langford, C.F., *et al.* Levator ani trigger point injections: An underutilized treatment for chronic pelvic pain. *Neurourol Urodyn*, 2007. 26: 59.  
<https://www.ncbi.nlm.nih.gov/pubmed/17195176>
329. FitzGerald, M.P., *et al.* Randomized multicenter clinical trial of myofascial physical therapy in women with interstitial cystitis/painful bladder syndrome and pelvic floor tenderness. *J Urol*, 2012. 187: 2113.  
<https://www.ncbi.nlm.nih.gov/pubmed/22503015>
330. Kellog-Spadt, S., *et al.*, Role of the female urologist/urogynecologist, in Women's sexual function and dysfunction: Study, diagnosis and treatment., I. Goldstein, *et al.*, Editors. 2006, Taylor and Francis: London.  
<https://doi.org/10.1201/9780367800123>
331. Webster, D.C., *et al.* Use and effectiveness of physical self-care strategies for interstitial cystitis. *Nurse Pract*, 1994. 19: 55.  
<https://www.ncbi.nlm.nih.gov/pubmed/7529390>
332. Hayes, R.D., *et al.* What can prevalence studies tell us about female sexual difficulty and dysfunction? *J Sex Med*, 2006. 3: 589.  
<https://www.ncbi.nlm.nih.gov/pubmed/16839314>
333. Berghmans, B. Physiotherapy for pelvic pain and female sexual dysfunction: an untapped resource. *Int Urogynecol J*, 2018. 29: 631.  
<https://www.ncbi.nlm.nih.gov/pubmed/29318334>
334. Fuentes-Marquez, P., *et al.* Trigger Points, Pressure Pain Hyperalgesia, and Mechanosensitivity of Neural Tissue in Women with Chronic Pelvic Pain. *Pain Med*, 2019. 20: 5.  
<https://www.ncbi.nlm.nih.gov/pubmed/29025041>

335. Ghaderi, F., *et al.* Pelvic floor rehabilitation in the treatment of women with dyspareunia: a randomized controlled clinical trial. *Int Urogynecol J*, 2019. 30: 1849.  
<https://www.ncbi.nlm.nih.gov/pubmed/31286158>
336. Rowe, E., *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. 173: 2044.  
<https://www.ncbi.nlm.nih.gov/pubmed/15879822>
337. Kastner, C., *et al.* Cooled transurethral microwave thermotherapy for intractable chronic prostatitis--results of a pilot study after 1 year. *Urology*, 2004. 64: 1149.  
<https://www.ncbi.nlm.nih.gov/pubmed/15596188>
338. Montorsi, F., *et al.* Is there a role for transrectal microwave hyperthermia of the prostate in the treatment of abacterial prostatitis and prostatodynia? *Prostate*, 1993. 22: 139.  
<https://www.ncbi.nlm.nih.gov/pubmed/8456052>
339. Zimmermann, R., *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. 56: 418.  
<https://www.ncbi.nlm.nih.gov/pubmed/19372000>
340. Zeng, X.Y., *et al.* Extracorporeal shock wave treatment for non-inflammatory chronic pelvic pain syndrome: a prospective, randomized and sham-controlled study. *Chin Med J (Engl)*, 2012. 125: 114.  
<https://www.ncbi.nlm.nih.gov/pubmed/22340476>
341. Vahdatpour, B., *et al.* Efficacy of extracorporeal shock wave therapy for the treatment of chronic pelvic pain syndrome: a randomized, controlled trial. *ISRN Urol*, 2013. 2013: 972601.  
<https://www.ncbi.nlm.nih.gov/pubmed/24000311>
342. Moayednia, A., *et al.* Long-term effect of extracorporeal shock wave therapy on the treatment of chronic pelvic pain syndrome due to non bacterial prostatitis. *J Res Med Sci*, 2014. 19: 293.  
<https://www.ncbi.nlm.nih.gov/pubmed/25097599>
343. Franco, J.V., *et al.* Non-pharmacological interventions for treating chronic prostatitis/chronic pelvic pain syndrome. *Cochrane Database Syst Rev*, 2018. 1: CD012551.  
<https://www.ncbi.nlm.nih.gov/pubmed/29372565>
344. Mykoniatis, I., *et al.* Low-intensity shockwave therapy for the management of chronic prostatitis/chronic pelvic pain syndrome: a systematic review and meta-analysis. *BJU Int*, 2021. 128: 144.  
<https://www.ncbi.nlm.nih.gov/pubmed/33434323>
345. Chuang, Y.C., *et al.* Pain reduction realized with extracorporeal shock wave therapy for the treatment of symptoms associated with interstitial cystitis/bladder pain syndrome-A prospective, multicenter, randomized, double-blind, placebo-controlled study. *Neurourol Urodyn*, 2020. 39: 1505.  
<https://www.ncbi.nlm.nih.gov/pubmed/32394478>
346. Sahin, S., *et al.* Acupuncture relieves symptoms in chronic prostatitis/chronic pelvic pain syndrome: a randomized, sham-controlled trial. *Prostate Cancer Prostatic Dis*, 2015. 18: 249.  
<https://www.ncbi.nlm.nih.gov/pubmed/25939517>
347. Qin, Z., *et al.* Acupuncture for Chronic Prostatitis/Chronic Pelvic Pain Syndrome: A Randomized, Sham Acupuncture Controlled Trial. *J Urol*, 2018. 200: 815.  
<https://www.ncbi.nlm.nih.gov/pubmed/29733836>
348. Chang, S.C., *et al.* The efficacy of acupuncture in managing patients with chronic prostatitis/chronic pelvic pain syndrome: A systemic review and meta-analysis. *Neurourol Urodyn*, 2017. 36: 474.  
<https://www.ncbi.nlm.nih.gov/pubmed/26741647>
349. Qin, Z., *et al.* Systematic Review of Acupuncture for Chronic Prostatitis/Chronic Pelvic Pain Syndrome. *Medicine (Baltimore)*, 2016. 95: e3095.  
<https://www.ncbi.nlm.nih.gov/pubmed/26986148>
350. Sun, Y., *et al.* Efficacy of Acupuncture for Chronic Prostatitis/Chronic Pelvic Pain Syndrome : A Randomized Trial. *Ann Intern Med*, 2021. 174: 1357.  
<https://www.ncbi.nlm.nih.gov/pubmed/34399062>
351. Pan, J., *et al.* Acupuncture for Chronic Prostatitis or Chronic Pelvic Pain Syndrome: An Updated Systematic Review and Meta-Analysis. *Pain Res Manag*, 2023. 2023: 7754876.  
<https://www.ncbi.nlm.nih.gov/pubmed/36960418>
352. Nickel, J.C., *et al.* Sexual function is a determinant of poor quality of life for women with treatment refractory interstitial cystitis. *J Urol*, 2007. 177: 1832.  
<https://www.ncbi.nlm.nih.gov/pubmed/17437831>
353. Williams, A.C., *et al.* Psychological therapies for the management of chronic pain (excluding headache) in adults. *Cochrane Database Syst Rev*, 2012. 11: CD007407.  
<https://www.ncbi.nlm.nih.gov/pubmed/23152245>

354. Cheong, Y.C., *et al.* Non-surgical interventions for the management of chronic pelvic pain. *Cochrane Database Syst Rev*, 2014. 2014: CD008797.  
<https://www.ncbi.nlm.nih.gov/pubmed/24595586>
355. Champaneria, R., *et al.* Psychological therapies for chronic pelvic pain: systematic review of randomized controlled trials. *Acta Obstet Gynecol Scand*, 2012. 91: 281.  
<https://www.ncbi.nlm.nih.gov/pubmed/22050516>
356. Li, A.S., *et al.* Psychological management of patients with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS): a systematic review. *Scand J Pain*, 2023. 23: 25.  
<https://www.ncbi.nlm.nih.gov/pubmed/35938980>
357. Ariza-Mateos, M.J., *et al.* Effects of a Patient-Centered Graded Exposure Intervention Added to Manual Therapy for Women With Chronic Pelvic Pain: A Randomized Controlled Trial. *Arch Phys Med Rehabil*, 2019. 100: 9.  
<https://www.ncbi.nlm.nih.gov/pubmed/30312595>
358. Daniels, J.P., *et al.* Chronic pelvic pain in women. *BMJ*, 2010. 341: c4834.  
<https://www.ncbi.nlm.nih.gov/pubmed/20923840>
359. Rosenbaum, T.Y. How well is the multidisciplinary model working? *J Sex Med*, 2011. 8: 2957.  
<https://www.ncbi.nlm.nih.gov/pubmed/22032406>
360. Brunahl, C.A., *et al.* Combined Cognitive-Behavioural and Physiotherapeutic Therapy for Patients with Chronic Pelvic Pain Syndrome (COMBI-CPPS): study protocol for a controlled feasibility trial. *Trials*, 2018. 19: 20.  
<https://www.ncbi.nlm.nih.gov/pubmed/29316946>
361. Meissner, K., *et al.* Psychotherapy With Somatosensory Stimulation for Endometriosis-Associated Pain: A Randomized Controlled Trial. *Obstet Gynecol*, 2016. 128: 1134.  
<https://pubmed.ncbi.nlm.nih.gov/27741200/>
362. Bohm-Starke, N., *et al.* Treatment of Provoked Vulvodynia: A Systematic Review. *J Sex Med*, 2022. 19: 789.  
<https://www.ncbi.nlm.nih.gov/pubmed/35331660>
363. Macea, D.D., *et al.* The efficacy of Web-based cognitive behavioral interventions for chronic pain: a systematic review and meta-analysis. *J Pain*, 2010. 11: 917.  
<https://www.ncbi.nlm.nih.gov/pubmed/20650691>
364. Zarski, A.C., *et al.* Efficacy of internet-based treatment for genito-pelvic pain/penetration disorder: Results of a randomized controlled trial. *J Consult Clin Psychol*, 2021. 89: 909.  
<https://www.ncbi.nlm.nih.gov/pubmed/34843312>
365. Shoskes, D.A., *et al.* Phenotypically directed multimodal therapy for chronic prostatitis/chronic pelvic pain syndrome: a prospective study using UPOINT. *Urology*, 2010. 75: 1249.  
<https://www.ncbi.nlm.nih.gov/pubmed/20363491>
366. Nickel, J.C., *et al.* Treatment of chronic prostatitis/chronic pelvic pain syndrome with tamsulosin: a randomized double blind trial. *J Urol*, 2004. 171: 1594.  
<https://www.ncbi.nlm.nih.gov/pubmed/15017228>
367. Zhao, W.P., *et al.* Celecoxib reduces symptoms in men with difficult chronic pelvic pain syndrome (Category IIIA). *Braz J Med Biol Res*, 2009. 42: 963.  
<https://www.ncbi.nlm.nih.gov/pubmed/19787151>
368. Bates, S.M., *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. 99: 355.  
<https://www.ncbi.nlm.nih.gov/pubmed/17313424>
369. Franco, J.V., *et al.* Pharmacological interventions for treating chronic prostatitis/chronic pelvic pain syndrome. *Cochrane Database Syst Rev*, 2019. 10: CD012552.  
<https://www.ncbi.nlm.nih.gov/pubmed/31587256>
370. Cheah, P.Y., *et al.* Terazosin therapy for chronic prostatitis/chronic pelvic pain syndrome: a randomized, placebo controlled trial. *J Urol*, 2003. 169: 592.  
<https://www.ncbi.nlm.nih.gov/pubmed/12544314>
371. Gul, O., *et al.* Use of terazosine in patients with chronic pelvic pain syndrome and evaluation by prostatitis symptom score index. *Int Urol Nephrol*, 2001. 32: 433.  
<https://www.ncbi.nlm.nih.gov/pubmed/11583367>
372. Mehik, A., *et al.* Alfuzosin treatment for chronic prostatitis/chronic pelvic pain syndrome: a prospective, randomized, double-blind, placebo-controlled, pilot study. *Urology*, 2003. 62: 425.  
<https://www.ncbi.nlm.nih.gov/pubmed/12946740>

373. Evliyaoglu, Y., *et al.* 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: 351.  
<https://www.ncbi.nlm.nih.gov/pubmed/12899226>
374. Tugcu, V., *et al.* A placebo-controlled comparison of the efficiency of triple- and monotherapy in category III B chronic pelvic pain syndrome (CPPS). *Eur Urol*, 2007. 51: 1113.  
<https://www.ncbi.nlm.nih.gov/pubmed/17084960>
375. Chen, Y., *et al.* Effects of a 6-month course of tamsulosin for chronic prostatitis/chronic pelvic pain syndrome: a multicenter, randomized trial. *World J Urol*, 2011. 29: 381.  
<https://www.ncbi.nlm.nih.gov/pubmed/20336302>
376. Nickel, J.C., *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. 93: 991.  
<https://www.ncbi.nlm.nih.gov/pubmed/15142149>
377. Anothaisintawee, T., *et al.* Management of chronic prostatitis/chronic pelvic pain syndrome: a systematic review and network meta-analysis. *JAMA*, 2011. 305: 78.  
<https://www.ncbi.nlm.nih.gov/pubmed/21205969>
378. Cohen, J.M., *et al.* Therapeutic intervention for chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS): a systematic review and meta-analysis. *PLoS One*, 2012. 7: e41941.  
<https://www.ncbi.nlm.nih.gov/pubmed/22870266>
379. Nickel, J.C., *et al.* Alfuzosin and symptoms of chronic prostatitis-chronic pelvic pain syndrome. *N Engl J Med*, 2008. 359: 2663.  
<https://www.ncbi.nlm.nih.gov/pubmed/19092152>
380. Nickel, J.C., *et al.* Predictors of patient response to antibiotic therapy for the chronic prostatitis/chronic pelvic pain syndrome: a prospective multicenter clinical trial. *J Urol*, 2001. 165: 1539.  
<https://www.ncbi.nlm.nih.gov/pubmed/11342913>
381. Lee, J.C., *et al.* Prostate biopsy culture findings of men with chronic pelvic pain syndrome do not differ from those of healthy controls. *J Urol*, 2003. 169: 584.  
<https://www.ncbi.nlm.nih.gov/pubmed/12544312>
382. Alexander, R.B., *et al.* Ciprofloxacin or tamsulosin in men with chronic prostatitis/chronic pelvic pain syndrome: a randomized, double-blind trial. *Ann Intern Med*, 2004. 141: 581.  
<https://www.ncbi.nlm.nih.gov/pubmed/15492337>
383. Nickel, J.C., *et al.* Levofloxacin for chronic prostatitis/chronic pelvic pain syndrome in men: a randomized placebo-controlled multicenter trial. *Urology*, 2003. 62: 614.  
<https://www.ncbi.nlm.nih.gov/pubmed/14550427>
384. Zhou, Z., *et al.* Detection of nanobacteria infection in type III prostatitis. *Urology*, 2008. 71: 1091.  
<https://www.ncbi.nlm.nih.gov/pubmed/18538692>
385. Thakkinstian, A., *et al.* alpha-blockers, antibiotics and anti-inflammatories have a role in the management of chronic prostatitis/chronic pelvic pain syndrome. *BJU Int*, 2012. 110: 1014.  
<https://www.ncbi.nlm.nih.gov/pubmed/22471591>
386. Bonkat, G., *et al.* EAU Guidelines on Urological Infections. *EAU Guidelines*. Edn. presented at the EAU Annual Congress, London 2026, 2026.  
<http://uroweb.org/guideline/urological-infections/>
387. Leskinen, M., *et al.* Effects of finasteride in patients with inflammatory chronic pelvic pain syndrome: a double-blind, placebo-controlled, pilot study. *Urology*, 1999. 53: 502.  
<https://www.ncbi.nlm.nih.gov/pubmed/10096374>
388. Kaplan, S.A., *et al.* A prospective, 1-year trial using saw palmetto versus finasteride in the treatment of category III prostatitis/chronic pelvic pain syndrome. *J Urol*, 2004. 171: 284.  
<https://www.ncbi.nlm.nih.gov/pubmed/14665895>
389. Wagenlehner, F.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. 56: 544.  
<https://www.ncbi.nlm.nih.gov/pubmed/19524353>
390. Cai, T., *et al.* Pollen extract in association with vitamins provides early pain relief in patients affected by chronic prostatitis/chronic pelvic pain syndrome. *Exp Ther Med*, 2014. 8: 1032.  
<https://www.ncbi.nlm.nih.gov/pubmed/25187793>

391. Cai, T., *et al.* The efficacy and tolerability of pollen extract in combination with hyaluronic acid and vitamins in the management of patients affected by chronic prostatitis/chronic pelvic pain syndrome: a 26 weeks, randomized, controlled, single-blinded, phase III study. *Minerva Urol Nephrol*, 2022. 74: 780.  
<https://www.ncbi.nlm.nih.gov/pubmed/33781014>
392. Cai, T., *et al.* The role of flower pollen extract in managing patients affected by chronic prostatitis/chronic pelvic pain syndrome: a comprehensive analysis of all published clinical trials. *BMC Urol*, 2017. 17: 32.  
<https://www.ncbi.nlm.nih.gov/pubmed/28431537>
393. Matsukawa, Y., *et al.* Comparison of cernitin pollen extract vs tadalafil therapy for refractory chronic prostatitis/chronic pelvic pain syndrome: A randomized, prospective study. *Neurourol Urodyn*, 2020. 39: 1994.  
<https://www.ncbi.nlm.nih.gov/pubmed/32648985>
394. Shoskes, D.A., *et al.* Quercetin in men with category III chronic prostatitis: a preliminary prospective, double-blind, placebo-controlled trial. *Urology*, 1999. 54: 960.  
<https://www.ncbi.nlm.nih.gov/pubmed/10604689>
395. Zhang, K., *et al.* The efficacy and safety of *Serenoa repens* extract for the treatment of patients with chronic prostatitis/chronic pelvic pain syndrome: a multicenter, randomized, double-blind, placebo-controlled trial. *World J Urol*, 2021. 39: 3489.  
<https://www.ncbi.nlm.nih.gov/pubmed/33452912>
396. Aboumarzouk, O.M., *et al.* Pregabalin for chronic prostatitis. *Cochrane Database Syst Rev*, 2012. 2012: CD009063.  
<https://www.ncbi.nlm.nih.gov/pubmed/22895982>
397. Pontari, M.A., *et al.* Pregabalin for the treatment of men with chronic prostatitis/chronic pelvic pain syndrome: a randomized controlled trial. *Arch Intern Med*, 2010. 170: 1586.  
<https://www.ncbi.nlm.nih.gov/pubmed/20876412>
398. Nickel, J.C., *et al.* Pentosan polysulfate sodium therapy for men with chronic pelvic pain syndrome: a multicenter, randomized, placebo controlled study. *J Urol*, 2005. 173: 1252.  
<https://www.ncbi.nlm.nih.gov/pubmed/15758763>
399. Parsons, B.A., *et al.* The Benefits and Harms of Botulinum Toxin-A in the Treatment of Chronic Pelvic Pain Syndromes: A Systematic Review by the European Association of Urology Chronic Pelvic Pain Panel. *Eur Urol Focus*, 2022. 8: 320.  
<https://www.ncbi.nlm.nih.gov/pubmed/33526405>
400. Goldmeier, D., *et al.* Treatment of category III A prostatitis with zafirlukast: a randomized controlled feasibility study. *Int J STD AIDS*, 2005. 16: 196.  
<https://www.ncbi.nlm.nih.gov/pubmed/15829018>
401. Nickel, J.C., *et al.* Preliminary assessment of safety and efficacy in proof-of-concept, randomized clinical trial of tanezumab for chronic prostatitis/chronic pelvic pain syndrome. *Urology*, 2012. 80: 1105.  
<https://www.ncbi.nlm.nih.gov/pubmed/23010344>
402. McNaughton, C.O., *et al.* Allopurinol for chronic prostatitis. *Cochrane Database Syst Rev*, 2002: CD001041.  
<https://www.ncbi.nlm.nih.gov/pubmed/12519549>
403. Ziaee, A.M., *et al.* Effect of allopurinol in chronic nonbacterial prostatitis: a double blind randomized clinical trial. *Int Braz J Urol*, 2006. 32: 181.  
<https://www.ncbi.nlm.nih.gov/pubmed/16650295>
404. Sant, G.R., *et al.* A pilot clinical trial of oral pentosan polysulfate and oral hydroxyzine in patients with interstitial cystitis. *J Urol*, 2003. 170: 810.  
<https://www.ncbi.nlm.nih.gov/pubmed/12913705>
405. Foster, H.E., Jr., *et al.* Effect of amitriptyline on symptoms in treatment naive patients with interstitial cystitis/painful bladder syndrome. *J Urol*, 2010. 183: 1853.  
<https://www.ncbi.nlm.nih.gov/pubmed/20303115>
406. Hwang, P., *et al.* Efficacy of pentosan polysulfate in the treatment of interstitial cystitis: a meta-analysis. *Urology*, 1997. 50: 39.  
<https://www.ncbi.nlm.nih.gov/pubmed/9218016>
407. Mulholland, S.G., *et al.* Pentosan polysulfate sodium for therapy of interstitial cystitis. A double-blind placebo-controlled clinical study. *Urology*, 1990. 35: 552.  
<https://www.ncbi.nlm.nih.gov/pubmed/1693797>

408. Fritjofsson, A., *et al.* Treatment of ulcer and nonulcer interstitial cystitis with sodium pentosanpolysulfate: a multicenter trial. *J Urol*, 1987. 138: 508.  
<https://www.ncbi.nlm.nih.gov/pubmed/2442416>
409. van Ophoven, A., *et al.* Safety and efficacy of concurrent application of oral pentosan polysulfate and subcutaneous low-dose heparin for patients with interstitial cystitis. *Urology*, 2005. 66: 707.  
<https://www.ncbi.nlm.nih.gov/pubmed/16230121>
410. Nickel, J.C., *et al.* Pentosan polysulfate sodium for treatment of interstitial cystitis/bladder pain syndrome: insights from a randomized, double-blind, placebo controlled study. *J Urol*, 2015. 193: 857.  
<https://www.ncbi.nlm.nih.gov/pubmed/25245489>
411. Oravisto, K.J., *et al.* Treatment of interstitial cystitis with immunosuppression and chloroquine derivatives. *Eur Urol*, 1976. 2: 82.  
<https://www.ncbi.nlm.nih.gov/pubmed/971677>
412. Moran, P.A., *et al.* Oral methotrexate in the management of refractory interstitial cystitis. *Aust N Z J Obstet Gynaecol*, 1999. 39: 468.  
<https://www.ncbi.nlm.nih.gov/pubmed/10687766>
413. Asklin, B., *et al.* Intravesical lidocaine in severe interstitial cystitis. Case report. *Scand J Urol Nephrol*, 1989. 23: 311.  
<https://www.ncbi.nlm.nih.gov/pubmed/2595329>
414. Giannakopoulos, X., *et al.* Chronic interstitial cystitis. Successful treatment with intravesical idocaine. *Arch Ital Urol Nefrol Androl*, 1992. 64: 337.  
<https://www.ncbi.nlm.nih.gov/pubmed/1462157>
415. Henry, R., *et al.* Absorption of alkalized intravesical lidocaine in normal and inflamed bladders: a simple method for improving bladder anesthesia. *J Urol*, 2001. 165: 1900.  
<https://www.ncbi.nlm.nih.gov/pubmed/11371877>
416. Parsons, C.L. Successful downregulation of bladder sensory nerves with combination of heparin and alkalized lidocaine in patients with interstitial cystitis. *Urology*, 2005. 65: 45.  
<https://www.ncbi.nlm.nih.gov/pubmed/15667861>
417. Nickel, J.C., *et al.* Intravesical alkalized lidocaine (PSD597) offers sustained relief from symptoms of interstitial cystitis and painful bladder syndrome. *BJU Int*, 2009. 103: 910.  
<https://www.ncbi.nlm.nih.gov/pubmed/19021619>
418. Cervigni, M., *et al.* A randomized, open-label, multicenter study of the efficacy and safety of intravesical hyaluronic acid and chondroitin sulfate versus dimethyl sulfoxide in women with bladder pain syndrome/interstitial cystitis. *Neurourol Urodyn*, 2017. 36: 1178.  
<https://www.ncbi.nlm.nih.gov/pubmed/27654012>
419. Parsons, C.L., *et al.* Treatment of interstitial cystitis with intravesical heparin. *Br J Urol*, 1994. 73: 504.  
<https://www.ncbi.nlm.nih.gov/pubmed/8012771>
420. Baykal, K., *et al.* Intravesical heparin and peripheral neuromodulation on interstitial cystitis. *Urol Int*, 2005. 74: 361.  
<https://www.ncbi.nlm.nih.gov/pubmed/15897705>
421. Thilagarajah, R., *et al.* Oral cimetidine gives effective symptom relief in painful bladder disease: a prospective, randomized, double-blind placebo-controlled trial. *BJU Int*, 2001. 87: 207.  
<https://www.ncbi.nlm.nih.gov/pubmed/11167643>
422. Kelly, J.D., *et al.* Clinical response to an oral prostaglandin analogue in patients with interstitial cystitis. *Eur Urol*, 1998. 34: 53.  
<https://www.ncbi.nlm.nih.gov/pubmed/9676414>
423. Cartledge, J.J., *et al.* A randomized double-blind placebo-controlled crossover trial of the efficacy of L-arginine in the treatment of interstitial cystitis. *BJU Int*, 2000. 85: 421.  
<https://www.ncbi.nlm.nih.gov/pubmed/10691818>
424. Ehren, I., *et al.* Effects of L-arginine treatment on symptoms and bladder nitric oxide levels in patients with interstitial cystitis. *Urology*, 1998. 52: 1026.  
<https://www.ncbi.nlm.nih.gov/pubmed/9836549>
425. Barbalias, G.A., *et al.* Interstitial cystitis: bladder training with intravesical oxybutynin. *J Urol*, 2000. 163: 1818.  
<https://www.ncbi.nlm.nih.gov/pubmed/10799190>
426. van Ophoven, A., *et al.* The dual serotonin and noradrenaline reuptake inhibitor duloxetine for the treatment of interstitial cystitis: results of an observational study. *J Urol*, 2007. 177: 552.  
<https://www.ncbi.nlm.nih.gov/pubmed/17222632>

427. Chen, H., *et al.* Efficacy of daily low-dose sildenafil for treating interstitial cystitis: results of a randomized, double-blind, placebo-controlled trial--treatment of interstitial cystitis/painful bladder syndrome with low-dose sildenafil. *Urology*, 2014. 84: 51.  
<https://www.ncbi.nlm.nih.gov/pubmed/24837447>
428. Shiraishi, K., *et al.* High Inguinal Microsurgical Denervation of the Spermatic Cord for Chronic Scrotal Content Pain: A Novel Approach for Adult and Pediatric Patients. *Urology*, 2019. 131: 144.  
<https://www.ncbi.nlm.nih.gov/pubmed/31136771>
429. Lee, J.Y., *et al.* Efficacy of vasectomy reversal according to patency for the surgical treatment of postvasectomy pain syndrome. *Int J Impot Res*, 2012. 24: 202.  
<https://www.ncbi.nlm.nih.gov/pubmed/22622333>
430. Hetta, D.F., *et al.* Pulsed Radiofrequency Treatment for Chronic Post-Surgical Orchialgia: A Double-Blind, Sham-Controlled, Randomized Trial: Three-Month Results. *Pain Physician*, 2018. 21: 199.  
<https://www.ncbi.nlm.nih.gov/pubmed/29565950>
431. West, A.F., *et al.* Epididymectomy is an effective treatment for scrotal pain after vasectomy. *BJU Int*, 2000. 85: 1097.  
<https://www.ncbi.nlm.nih.gov/pubmed/10848703>
432. Sauvan, M., *et al.* [Medical treatment for the management of painful endometriosis without infertility: CNGOF-HAS Endometriosis Guidelines]. *Gynecol Obstet Fertil Senol*, 2018. 46: 267.  
<https://www.ncbi.nlm.nih.gov/pubmed/29510966>
433. Jarvis, S.K., *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. 44: 46.  
<https://www.ncbi.nlm.nih.gov/pubmed/15089868>
434. Kamanli, A., *et al.* Comparison of lidocaine injection, botulinum toxin injection, and dry needling to trigger points in myofascial pain syndrome. *Rheumatol Int*, 2005. 25: 604.  
<https://www.ncbi.nlm.nih.gov/pubmed/15372199>
435. Ho, K.Y., *et al.* Botulinum toxin A for myofascial trigger point injection: a qualitative systematic review. *Eur J Pain*, 2007. 11: 519.  
<https://www.ncbi.nlm.nih.gov/pubmed/17071119>
436. Zermann, D., *et al.* Perisphincteric injection of botulinum toxin type A. A treatment option for patients with chronic prostatic pain? *Eur Urol*, 2000. 38: 393.  
<https://www.ncbi.nlm.nih.gov/pubmed/11025376>
437. Eckardt, V.F., *et al.* Treatment of proctalgia fugax with salbutamol inhalation. *Am J Gastroenterol*, 1996. 91: 686.  
<https://www.ncbi.nlm.nih.gov/pubmed/8677929>
438. Atkin, G.K., *et al.* Patient characteristics and treatment outcome in functional anorectal pain. *Dis Colon Rectum*, 2011. 54: 870.  
<https://www.ncbi.nlm.nih.gov/pubmed/21654255>
439. Chey, W.D., *et al.* Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. *Am J Gastroenterol*, 2012. 107: 1702.  
<https://www.ncbi.nlm.nih.gov/pubmed/22986437>
440. Ruedert, L., *et al.* Bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome. *Cochrane Database Syst Rev*, 2011. 2011: CD003460.  
<https://www.ncbi.nlm.nih.gov/pubmed/21833945>
441. Khanna, R., *et al.* Peppermint oil for the treatment of irritable bowel syndrome: a systematic review and meta-analysis. *J Clin Gastroenterol*, 2014. 48: 505.  
<https://www.ncbi.nlm.nih.gov/pubmed/24100754>
442. Stones, R.W., *et al.* Interventions for treating chronic pelvic pain in women. *Cochrane Database Syst Rev*, 2000: CD000387.  
<https://www.ncbi.nlm.nih.gov/pubmed/11034686>
443. Chaparro, L.E., *et al.* Combination pharmacotherapy for the treatment of neuropathic pain in adults. *Cochrane Database Syst Rev*, 2012. 2012: CD008943.  
<https://www.ncbi.nlm.nih.gov/pubmed/22786518>
444. Remy, C., *et al.* State of the art of paracetamol in acute pain therapy. *Curr Opin Anaesthesiol*, 2006. 19: 562.  
<https://www.ncbi.nlm.nih.gov/pubmed/16960492>
445. Moore, R.A., *et al.* Overview review: Comparative efficacy of oral ibuprofen and paracetamol (acetaminophen) across acute and chronic pain conditions. *Eur J Pain*, 2015. 19: 1213.  
<https://www.ncbi.nlm.nih.gov/pubmed/25530283>

446. Marjoribanks, J., *et al.* Nonsteroidal anti-inflammatory drugs for dysmenorrhoea. *Cochrane Database Syst Rev*, 2010: CD001751.  
<https://www.ncbi.nlm.nih.gov/pubmed/20091521>
447. Brown, J., *et al.* Nonsteroidal anti-inflammatory drugs for pain in women with endometriosis. *Cochrane Database Syst Rev*, 2017. 1: CD004753.  
<https://www.ncbi.nlm.nih.gov/pubmed/28114727>
448. NICE, Neuropathic pain in adults: pharmacological management in non-specialist settings: NICE Guideline. 2020.  
<http://guidance.nice.org.uk/CG173>
449. Saarto, T., *et al.* Antidepressants for neuropathic pain. *Cochrane Database Syst Rev*, 2007. 2007: CD005454.  
<https://www.ncbi.nlm.nih.gov/pubmed/17943857>
450. Lunn, M.P., *et al.* Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. *Cochrane Database Syst Rev*, 2014. 2014: CD007115.  
<https://www.ncbi.nlm.nih.gov/pubmed/24385423>
451. Welsch, P., *et al.* Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia. *Cochrane Database Syst Rev*, 2018. 2: CD010292.  
<https://www.ncbi.nlm.nih.gov/pubmed/29489029>
452. Wiffen, P.J., *et al.* Carbamazepine for acute and chronic pain in adults. *Cochrane Database Syst Rev*, 2011: CD005451.  
<https://www.ncbi.nlm.nih.gov/pubmed/21249671>
453. Public Health England, Report of the review of the evidence for dependence on, and withdrawal from, prescribed medicines. 2020.  
<https://www.gov.uk/government/publications/prescribed-medicines-review-report>
454. Wiffen, P.J., *et al.* Gabapentin for chronic neuropathic pain in adults. *Cochrane Database Syst Rev*, 2017. 6: CD007938.  
<https://www.ncbi.nlm.nih.gov/pubmed/28597471>
455. Horne, A.W., *et al.* Gabapentin for chronic pelvic pain in women (GaPP2): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet*, 2020. 396: 909.  
<https://www.ncbi.nlm.nih.gov/pubmed/32979978>
456. Derry, S., *et al.* Pregabalin for neuropathic pain in adults. *Cochrane Database Syst Rev*, 2019. 1: CD007076.  
<https://www.ncbi.nlm.nih.gov/pubmed/30673120>
457. Sommer, C., *et al.* Opioids for chronic non-cancer neuropathic pain. An updated systematic review and meta-analysis of efficacy, tolerability and safety in randomized placebo-controlled studies of at least 4 weeks duration. *Eur J Pain*, 2020. 24: 3.  
<https://www.ncbi.nlm.nih.gov/pubmed/31705717>
458. Noble, M., *et al.* Long-term opioid management for chronic noncancer pain. *Cochrane Database Syst Rev*, 2010. 2010: CD006605.  
<https://www.ncbi.nlm.nih.gov/pubmed/20091598>
459. Faculty of Pain Medicine, Opioids Aware: A resource for patients and healthcare professionals to support prescribing of opioid 2021.  
<https://fpm.ac.uk/opioids-aware>
460. Sandhu, H., *et al.* What interventions are effective to taper opioids in patients with chronic pain? *BMJ*, 2018. 362: k2990.  
<https://www.ncbi.nlm.nih.gov/pubmed/30262590>
461. SIGN 173, Management of chronic pain (part 1). 2025.  
<https://www.sign.ac.uk/guidelines/management-of-chronic-pain/>
462. Stockings, E., *et al.* Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies. *Pain*, 2018. 159: 1932.  
<https://www.ncbi.nlm.nih.gov/pubmed/29847469>
463. NICE, Cannabis-based medicinal products: NICE Guideline. 2019.  
<https://www.nice.org.uk/guidance/ng144>
464. Moore, R.A., *et al.* Cannabinoids, cannabis, and cannabis-based medicines for pain management: an overview of systematic reviews. *Pain*, 2021. 162: S67.  
<https://www.ncbi.nlm.nih.gov/pubmed/32804833>
465. Baranowski, A., *et al.*, Urogenital Pain in Clinical Practice. 1st Edition ed. 2007, Boca Raton.  
<https://doi.org/10.3109/9781420021196>

466. Li, C.B., *et al.* The efficacy and safety of the ganglion impar block in chronic intractable pelvic and/or perineal pain: A systematic review and meta-analysis. *Int J Clin Exp Med* 2016. 9: 15746.  
<https://e-century.us/files/ijcem/9/8/ijcem0021581.pdf>
467. Krijnen, E.A., *et al.* Pulsed Radiofrequency of Pudendal Nerve for Treatment in Patients with Pudendal Neuralgia. A Case Series with Long-Term Follow-Up. *Pain Pract*, 2021. 21: 703.  
<https://www.ncbi.nlm.nih.gov/pubmed/33522082>
468. Ran, J., *et al.* Efficacy of ganglion impar block combined with pudendal nerve pulsed radiofrequency for pudendal neuralgia management-a randomized clinical trial. *Trials*, 2024. 25: 316.  
<https://www.ncbi.nlm.nih.gov/pubmed/38741220>
469. Conic, R.R.Z., *et al.* Pudendal Neuralgia: A Review of the Current Literature. *Curr Pain Headache Rep*, 2025. 29: 38.  
<https://www.ncbi.nlm.nih.gov/pubmed/39873912>
470. Eker, H.E., *et al.* Management of neuropathic pain with methylprednisolone at the site of nerve injury. *Pain Med*, 2012. 13: 443.  
<https://www.ncbi.nlm.nih.gov/pubmed/22313580>
471. Labat, J.J., *et al.* Adding corticosteroids to the pudendal nerve block for pudendal neuralgia: a randomised, double-blind, controlled trial. *BJOG*, 2017. 124: 251.  
<https://www.ncbi.nlm.nih.gov/pubmed/27465823>
472. Abreu-Mendes, P., *et al.* Effect of Intratrigonal Botulinum Toxin in Patients with Bladder Pain Syndrome/Interstitial Cystitis: A Long-Term, Single-Center Study in Real-Life Conditions. *Toxins (Basel)*, 2022. 14.  
<https://www.ncbi.nlm.nih.gov/pubmed/36356025>
473. Kuo, Y.C., *et al.* Adverse Events of Intravesical OnabotulinumtoxinA Injection between Patients with Overactive Bladder and Interstitial Cystitis—Different Mechanisms of Action of Botox on Bladder Dysfunction? *Toxins (Basel)*, 2016. 8.  
<https://www.ncbi.nlm.nih.gov/pubmed/26999201>
474. Lee, C.L., *et al.* Long-Term Efficacy and Safety of Repeated Intravesical OnabotulinumtoxinA Injections Plus Hydrodistention in the Treatment of Interstitial Cystitis/Bladder Pain Syndrome. *Toxins (Basel)*, 2015. 7: 4283.  
<https://www.ncbi.nlm.nih.gov/pubmed/26506388>
475. Fang, H., *et al.* Clinical effect and safety of pulsed radiofrequency treatment for pudendal neuralgia: a prospective, randomized controlled clinical trial. *J Pain Res*, 2018. 11: 2367.  
<https://www.ncbi.nlm.nih.gov/pubmed/30410389>
476. Fariello, J.Y., *et al.* Sacral neuromodulation stimulation for IC/PBS, chronic pelvic pain, and sexual dysfunction. *Int Urogynecol J*, 2010. 21: 1553.  
<https://www.ncbi.nlm.nih.gov/pubmed/20972541>
477. Cottrell, A.M., *et al.* Benefits and Harms of Electrical Neuromodulation for Chronic Pelvic Pain: A Systematic Review. *Eur Urol Focus*, 2020. 6: 559.  
<https://www.ncbi.nlm.nih.gov/pubmed/31636030>
478. Tutolo, M., *et al.* Efficacy and Safety of Sacral and Percutaneous Tibial Neuromodulation in Non-neurogenic Lower Urinary Tract Dysfunction and Chronic Pelvic Pain: A Systematic Review of the Literature. *Eur Urol*, 2018. 73: 406.  
<https://www.ncbi.nlm.nih.gov/pubmed/29336927>
479. Mahran, A., *et al.* Sacral neuromodulation treating chronic pelvic pain: a meta-analysis and systematic review of the literature. *Int Urogynecol J*, 2019. 30: 1023.  
<https://www.ncbi.nlm.nih.gov/pubmed/30874835>
480. Stelter, B., *et al.* Dorsal Root Ganglion Stimulation for the Treatment of Non-Complex Regional Pain Syndrome Related Chronic Pain Syndromes: A Systematic Review. *Neuromodulation*, 2021. 24: 622.  
<https://www.ncbi.nlm.nih.gov/pubmed/33501749>
481. Mira, T.A.A., *et al.* Hormonal treatment isolated versus hormonal treatment associated with electrotherapy for pelvic pain control in deep endometriosis: Randomized clinical trial. *Eur J Obstet Gynecol Reprod Biol*, 2020. 255: 134.  
<https://www.ncbi.nlm.nih.gov/pubmed/33129015>
482. Chen, Y., *et al.* The diagnostic and therapeutic efficacy of cystoscopy with hydrodistension and random biopsies in clinically suspected interstitial cystitis/bladder pain syndrome. *Eur J Obstet Gynecol Reprod Biol*, 2021. 265: 156.  
<https://www.ncbi.nlm.nih.gov/pubmed/34492610>
483. Smith, C.P., *et al.* Botulinum toxin a has antinociceptive effects in treating interstitial cystitis. *Urology*, 2004. 64: 871.  
<https://www.ncbi.nlm.nih.gov/pubmed/15533466>

484. Kuo, H.C., *et al.* 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. 104: 657.  
<https://www.ncbi.nlm.nih.gov/pubmed/19338543>
485. Pinto, R., *et al.* Trigonal injection of botulinum toxin A in patients with refractory bladder pain syndrome/interstitial cystitis. *Eur Urol*, 2010. 58: 360.  
<https://www.ncbi.nlm.nih.gov/pubmed/20227820>
486. Akiyama, Y., *et al.* Botulinum toxin type A injection for refractory interstitial cystitis: A randomized comparative study and predictors of treatment response. *Int J Urol*, 2015. 22: 835.  
<https://www.ncbi.nlm.nih.gov/pubmed/26041274>
487. Pinto, R., *et al.* Persistent therapeutic effect of repeated injections of onabotulinum toxin a in refractory bladder pain syndrome/interstitial cystitis. *J Urol*, 2013. 189: 548.  
<https://www.ncbi.nlm.nih.gov/pubmed/23253961>
488. Pinto, R.A., *et al.* Intratrigonal OnabotulinumtoxinA Improves Bladder Symptoms and Quality of Life in Patients with Bladder Pain Syndrome/Interstitial Cystitis: A Pilot, Single Center, Randomized, Double-Blind, Placebo Controlled Trial. *J Urol*, 2018. 199: 998.  
<https://www.ncbi.nlm.nih.gov/pubmed/29031769>
489. Evans, R.J., *et al.* Injection location does not impact botulinum toxin A efficacy in interstitial cystitis/ bladder pain syndrome patients. *Can J Urol*, 2020. 27: 10125.  
<https://www.ncbi.nlm.nih.gov/pubmed/32065870>
490. Jiang, Y.H., *et al.* Repeated intravesical injections of platelet-rich plasma improve symptoms and alter urinary functional proteins in patients with refractory interstitial cystitis. *Sci Rep*, 2020. 10: 15218.  
<https://www.ncbi.nlm.nih.gov/pubmed/32939046>
491. Kerr, W.S., Jr. Interstitial cystitis: treatment by transurethral resection. *J Urol*, 1971. 105: 664.  
<https://www.ncbi.nlm.nih.gov/pubmed/4397018>
492. Peeker, R., *et al.* Complete transurethral resection of ulcers in classic interstitial cystitis. *Int Urogynecol J Pelvic Floor Dysfunct*, 2000. 11: 290.  
<https://www.ncbi.nlm.nih.gov/pubmed/11052564>
493. Ko, K.J., *et al.* Comparison of the Efficacy Between Transurethral Coagulation and Transurethral Resection of Hunner Lesion in Interstitial Cystitis/Bladder Pain Syndrome Patients: A Prospective Randomized Controlled Trial. *Eur Urol*, 2020. 77: 644.  
<https://www.ncbi.nlm.nih.gov/pubmed/31959549>
494. Osman, N.I., *et al.* A Systematic Review of Surgical interventions for the Treatment of Bladder Pain Syndrome/Interstitial Cystitis. *Eur Urol Focus*, 2021. 7: 877.  
<https://www.ncbi.nlm.nih.gov/pubmed/32127327>
495. Kim, H.J., *et al.* Efficacy and safety of augmentation ileocystoplasty combined with supratrigonal cystectomy for the treatment of refractory bladder pain syndrome/interstitial cystitis with Hunner's lesion. *Int J Urol*, 2014. 21 Suppl 1: 69.  
<https://www.ncbi.nlm.nih.gov/pubmed/24807503>
496. Shirley, S.W., *et al.* Experiences with colcystoplasties, cecocystoplasties and ileocystoplasties in urologic surgery: 40 patients. *J Urol*, 1978. 120: 165.  
<https://www.ncbi.nlm.nih.gov/pubmed/671623>
497. von Garrelts, B. Interstitial cystitis: thirteen patients treated operatively with intestinal bladder substitutes. *Acta Chir Scand*, 1966. 132: 436.  
<https://www.ncbi.nlm.nih.gov/pubmed/5972716>
498. Webster, G.D., *et al.* The management of chronic interstitial cystitis by substitution cystoplasty. *J Urol*, 1989. 141: 287.  
<https://www.ncbi.nlm.nih.gov/pubmed/2913346>
499. Nurse, D.E., *et al.* The problems of substitution cystoplasty. *Br J Urol*, 1988. 61: 423.  
<https://www.ncbi.nlm.nih.gov/pubmed/3395801>
500. Rossberger, J., *et al.* Long-term results of reconstructive surgery in patients with bladder pain syndrome/interstitial cystitis: subtyping is imperative. *Urology*, 2007. 70: 638.  
<https://www.ncbi.nlm.nih.gov/pubmed/17991529>
501. Peeker, R., *et al.* The treatment of interstitial cystitis with supratrigonal cystectomy and ileocystoplasty: difference in outcome between classic and nonulcer disease. *J Urol*, 1998. 159: 1479.  
<https://www.ncbi.nlm.nih.gov/pubmed/9554337>
502. Linn, J.F., *et al.* Treatment of interstitial cystitis: comparison of subtrigonal and supratrigonal cystectomy combined with orthotopic bladder substitution. *J Urol*, 1998. 159: 774.  
<https://www.ncbi.nlm.nih.gov/pubmed/9474146>

503. Volkmer, B.G., *et al.* Cystectomy and orthotopic ileal neobladder: the impact on female sexuality. *J Urol*, 2004. 172: 2353.  
<https://www.ncbi.nlm.nih.gov/pubmed/15538266>
504. Shaikh, A., *et al.* Pregnancy after augmentation cystoplasty. *J Pak Med Assoc*, 2006. 56: 465.  
<https://www.ncbi.nlm.nih.gov/pubmed/17144396>
505. Elzawahri, A., *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. 171: 1559.  
<https://www.ncbi.nlm.nih.gov/pubmed/15017220>
506. Freiha, F.S., *et al.* The surgical treatment of intractable interstitial cystitis. *J Urol*, 1980. 123: 632.  
<https://www.ncbi.nlm.nih.gov/pubmed/7420547>
507. Zhao, Y., *et al.* Circumcision plus antibiotic, anti-inflammatory, and alpha-blocker therapy for the treatment for chronic prostatitis/chronic pelvic pain syndrome: a prospective, randomized, multicenter trial. *World J Urol*, 2015. 33: 617.  
<https://www.ncbi.nlm.nih.gov/pubmed/24980414>
508. Chaudhari, R., *et al.* Microsurgical Denervation of Spermatic Cord for Chronic Idiopathic Orchialgia: Long-Term Results from an Institutional Experience. *World J Mens Health*, 2019. 37: 78.  
<https://www.ncbi.nlm.nih.gov/pubmed/30209898>
509. Oomen, R.J.A., *et al.* Prospective double-blind preoperative pain clinic screening before microsurgical denervation of the spermatic cord in patients with testicular pain syndrome. *Pain*, 2014. 155: 1720.  
<https://www.ncbi.nlm.nih.gov/pubmed/24861586>
510. Menconi, C., *et al.* Persistent anal and pelvic floor pain after PPH and STARR: surgical management of the fixed scar staple line. *Int J Colorectal Dis*, 2016. 31: 41.  
<https://www.ncbi.nlm.nih.gov/pubmed/26248794>
511. Molegraaf, M.J., *et al.* Twelve-year outcomes of laparoscopic adhesiolysis in patients with chronic abdominal pain: A randomized clinical trial. *Surgery*, 2017. 161: 415.  
<https://www.ncbi.nlm.nih.gov/pubmed/27866713>
512. Yoon, S.M., *et al.* Treatment of female urethral syndrome refractory to antibiotics. *Yonsei Med J*, 2002. 43: 644.  
<https://www.ncbi.nlm.nih.gov/pubmed/12402379>
513. Costantini, E., *et al.* Treatment of urethral syndrome: a prospective randomized study with Nd:YAG laser. *Urol Int*, 2006. 76: 134.  
<https://www.ncbi.nlm.nih.gov/pubmed/16493214>
514. Kaur, H., *et al.* Urethral pain syndrome and its management. *Obstet Gynecol Surv*, 2007. 62: 348.  
<https://www.ncbi.nlm.nih.gov/pubmed/17425813>
515. Ploteau, S., *et al.* [Minimal and mild endometriosis: Impact of the laparoscopic surgery on pelvic pain and fertility. CNGOF-HAS Endometriosis Guidelines]. *Gynecol Obstet Fertil Senol*, 2018. 46: 273.  
<https://www.ncbi.nlm.nih.gov/pubmed/29510965>
516. de Paula Andres, M., *et al.* The current management of deep endometriosis: a systematic review. *Minerva Ginecol*, 2017. 69: 587.  
<https://www.ncbi.nlm.nih.gov/pubmed/28545293>
517. Findekle, S., *et al.* Treatment algorithm for women with endometriosis in a certified Endometriosis Unit. *Minerva Ginecol*, 2020. 72: 43.  
<https://www.ncbi.nlm.nih.gov/pubmed/32153163>
518. Shafik, A. Pudendal canal syndrome as a cause of vulvodinia and its treatment by pudendal nerve decompression. *Eur J Obstet Gynecol Reprod Biol*, 1998. 80: 215.  
<https://www.ncbi.nlm.nih.gov/pubmed/9846672>
519. Baurant, E., *et al.* [Modern algorithm for treating pudendal neuralgia: 212 cases and 104 decompressions]. *J Gynecol Obstet Biol Reprod (Paris)*, 2003. 32: 705.  
<https://www.ncbi.nlm.nih.gov/pubmed/15067894>
520. Possover, M., *et al.* Laparoscopic neurolysis of the sacral plexus and the sciatic nerve for extensive endometriosis of the pelvic wall. *Minim Invasive Neurosurg*, 2007. 50: 33.  
<https://www.ncbi.nlm.nih.gov/pubmed/17546541>
521. Robert, R., *et al.* Decompression and transposition of the pudendal nerve in pudendal neuralgia: a randomized controlled trial and long-term evaluation. *Eur Urol*, 2005. 47: 403.  
<https://www.ncbi.nlm.nih.gov/pubmed/15716208>
522. Robert, R., *et al.* [Pudendal nerve surgery in the management of chronic pelvic and perineal pain]. *Prog Urol*, 2010. 20: 1084.  
<https://www.ncbi.nlm.nih.gov/pubmed/21056388>

523. Duckett, J., *et al.* Mesh removal after vaginal surgery: what happens in the UK? *Int Urogynecol J*, 2017. 28: 989.  
<https://www.ncbi.nlm.nih.gov/pubmed/27924372>
524. Lee, D., *et al.* Transvaginal mesh kits--how "serious" are the complications and are they reversible? *Urology*, 2013. 81: 43.  
<https://www.ncbi.nlm.nih.gov/pubmed/23200966>
525. Shah, K., *et al.* Surgical management of lower urinary mesh perforation after mid-urethral polypropylene mesh sling: mesh excision, urinary tract reconstruction and concomitant pubovaginal sling with autologous rectus fascia. *Int Urogynecol J*, 2013. 24: 2111.  
<https://www.ncbi.nlm.nih.gov/pubmed/23824269>
526. Ramart, P., *et al.* The Risk of Recurrent Urinary Incontinence Requiring Surgery After Suburethral Sling Removal for Mesh Complications. *Urology*, 2017. 106: 203.  
<https://www.ncbi.nlm.nih.gov/pubmed/28476681>
527. Jong, K., *et al.* Is pain relief after vaginal mesh and/or sling removal durable long term? *Int Urogynecol J*, 2018. 29: 859.  
<https://www.ncbi.nlm.nih.gov/pubmed/28695345>
528. Hansen, B.L., *et al.* Long-term follow-up of treatment for synthetic mesh complications. *Female Pelvic Med Reconstr Surg*, 2014. 20: 126.  
<https://www.ncbi.nlm.nih.gov/pubmed/24763152>
529. Ridgeway, B., *et al.* Early experience with mesh excision for adverse outcomes after transvaginal mesh placement using prolapse kits. *Am J Obstet Gynecol*, 2008. 199: 703 e1.  
<https://www.ncbi.nlm.nih.gov/pubmed/18845292>
530. Gyang, A.N., *et al.* Managing chronic pelvic pain following reconstructive pelvic surgery with transvaginal mesh. *Int Urogynecol J*, 2014. 25: 313.  
<https://www.ncbi.nlm.nih.gov/pubmed/24217793>
531. Ferreira, M., *et al.* [Pelvic floor muscle training programmes: a systematic review]. *Acta Med Port*, 2011. 24: 309.  
<https://www.ncbi.nlm.nih.gov/pubmed/22011604>
532. Winstock, A.R., *et al.* The prevalence and natural history of urinary symptoms among recreational ketamine users. *BJU Int*, 2012. 110: 1762.  
<https://www.ncbi.nlm.nih.gov/pubmed/22416998>
533. Belal, M., *et al.* British Association of Urological Surgeons Consensus statements on the management of ketamine uropathy. *BJU Int*, 2024. 134: 148.  
<https://www.ncbi.nlm.nih.gov/pubmed/38778743>

## 8. CONFLICT OF INTEREST

All members of the Chronic Pelvic Pain Guidelines working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is provided below and is also publicly available on the EAU website: <https://uroweb.org/guidelines/chronic-pelvic-pain/panel>.

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