EAU Guidelines on

Chronic Pelvic Pain

D. Engeler (Chair), A.P. Baranowski, B. Berghmans,
J. Birch (Patient Advocate), J. Borovicka, A.M. Cottrell,
P. Dinis-Oliveira, S. Elneil, J. Hughes,
E.J. Messelink (Vice-chair), R.A. Pinto,
M.L. van Poelgeest (Patient Advocate), V. Tidman,
A.C. de C Williams
Guidelines Associates: P. Abreu-Mendes, S. Dabestani,
B. Parsons, J. Tornic, V. Zumstein
Guidelines Office: J.A. Darraugh

European Association of Urology

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1. INTRODUCTION

1.1 Aim

This guideline plays 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. This guideline has been recognised as a cornerstone for important developments that have taken place in the past ten years.

This guideline aims 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 guideline is a useful instrument not only for urologists, but also for gynaecologists, surgeons, physiotherapists, psychologists and pain doctors.

It must be emphasised that guidelines present the best evidence available to the experts. However 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.

Structure and scope

The panel wishes to take advantage of modern methods of delivering guideline information to clinicians dealing with these patients. 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 guideline was changed according to the template used in all other non-oncology guidelines of the EAU. It was recognised that structuring a guideline on chronic pain is quite different from structuring one on another subject. A multi-disciplinary approach is of utmost importance and demands a broad view. In 2016, the guideline was 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.

1.2 Publication history

The EAU Guidelines on Chronic Pelvic Pain were first published in 2003 [1] which formed the basis of a scientific publication in European Urology in 2004 [2]. Also, in the 2003 edition the concept of Chronic Pelvic Pain Syndromes (CPPS) was introduced, which is now referred to as “pain as a disease process”. Partial updates of the Chronic Pelvic Pain Guidelines were published in 2008 and formed the basis for another scientific publication in European Urology in the year 2010 [3, 4]. Two chapters were added at that time: Chapter 5 ‘Gastrointestinal aspects of chronic pelvic pain’ and Chapter 7 ‘Sexological aspects of chronic pelvic pain’. In the 2014 edition minor revisions were made in Chapter 5 ‘Gastrointestinal aspects of chronic pelvic pain’ and Chapter 8 ‘Psychological aspects of chronic pelvic pain’.

For the 2015 edition the panel critically reviewed the sub-chapter on chronic primary bladder pain syndrome (BPS) which is now a comprehensive part of the guideline. The fact that this part was so extensive shows that the roots of talking about abdominal pain and pelvic pain lies in the bladder, where Interstitial Cystitis was one of the first subjects addressed talking about pain in urology. The panel has illustrated this in the publication in European Urology in 2013 [5].

1.3 Available Publications

Alongside the full text version, a quick reference document (Pocket Guidelines) is available in print and as an app for iOS and Android devices. These are abridged versions which may require consultation together with the full text version. This reference document follows the updating cycle of the underlying large texts.

All available material can be viewed at the EAU website. The EAU website also includes a selection of EAU Guideline articles as well as translations produced by national urological associations: uroweb.org/guideline/chronicpelvicpain/.

1.4 Panel composition

The panel of experts responsible for this guideline include five urologists, (one of whom has a sub-specialisation in neuro-urology and one is a sexologist), three consultants in pain medicine, a uro-gynaecologist, a psychologist, a gastroenterologist, a pelvic physiotherapist, health scientist and (clinical) epidemiologist and two patient advocates.

1.5 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 glomerulation on cystoscopy, whereas other bladder pain conditions may have a normal appearance on cystoscopy. These are two different phenotypes. The same is true for 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, auto-immune, or neuropathic). In the absence of well-defined mechanisms, describing the condition by its symptoms, signs and, where possible, by investigations, has been demonstrated to have clinical and research validity in many situations. When pain is the main symptom and pain as a disease process is considered the cause, the condition is often referred to as a pain syndrome - a well-defined collection of symptoms, signs and investigation results associated with pain mechanisms and pain perception as the primary complaint. The World Health Organization (WHO) International Classification of Diseases 11th Revision (ICD-11) uses the term Chronic Primary Pain to distinguish these conditions from pain associated with another diagnosis that they refer 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 BPS. The EAU, the International Society for the study of BPS (known as ESSIC), the International Association for the Study of Pain (IASP) and several other groups have preferred the term BPS. 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 takes into account the emotional, cognitive, behavioural, sexual and functional consequences of the chronic pain.

When defining the phenotype, the terminology used in that definition must also be clear and if necessary, defined. One of the most important guiding principles is that spurious terminology should be avoided. Terms that end in "itis" should particularly be avoided, unless infection and or inflammation is proven and considered to be the cause of the pain [6]. It must be appreciated that 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 sub-divides 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 antiinflammatory 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, as well as hope for relief. It may therefore help in acceptance of the problem as chronic, resolution of unfounded fears about its implications (if not life-threatening), and engagement in therapeutic endeavours, as well as assists in self-management. However, it may lead to accessing information of variable quality associated with the diagnosis or name, and the possibility of generating new concerns about long-term consequences or about the appropriateness of treatment.

IASP definitions
Sub-dividing pain syndromes
There is much debate on the sub-divisions of the pain syndromes within the hierarchical taxonomy. The EAU has led the way in this regard and the guiding principles are as follows [2]:

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 sub-division phenotype should only be used if there is adequate evidence to support its use. For instance, in non-specific, poorly localised pelvic pain without obvious pathology, only the term chronic primary pelvic pain syndrome (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 (Multi-disciplinary Approach to the study of Chronic Pelvic Pain research) has been devised to investigate the importance of these factors and looks at all types of pelvic pain irrespective of the end-organ where the pain is perceived. It also looks at systemic disorder associations, such as the co-occurrence of fibromyalgia, facial pain, or auto-immune 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 [7], modified by Magri *et al*. [8]. In light of these and other publications, the symptom classification table has been updated (Table 1).

The debate in relation to sub-dividing the pain syndromes continues. As more information is collected suggesting that the central nervous system (CNS) is involved, and indeed may be the main cause of many CPPPS conditions (e.g., bladder, genitalia, colorectal or myofascial), therefore 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 change.

ICD classification: purpose and uses
The International Classification of Diseases 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 [9]. The latest version, ICD-11, is available for member states to report with from January 2022.

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 that term Chronic Secondary Pain become Chronic Primary Pain? [10, 11]. Similarly, the contents of recent drafted national institute for health and care excellence (NICE) guidelines [12] (https://www.nice.org.uk/guidance/GID-NG10069/documents/draft-guideline), were found to be contentious as the guidelines considered all Chronic Primary Pain as being essentially the same and the 'biological' nature of the pain appeared to have been missed. Whereas in the final guidelines this may be corrected, it does illustrate the risk behind the term Chronic Primary Pain.

The panel will change the EAU terminology previously used in the 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	Chronic secondary pelvic pain syndrome, formally known as specific disease associated pelvic pain OR Chronic primary pelvic pain syndrome, formally known as pelvic pain syndrome	Urological	Prostate		Suprapubic Inguinal Urethral Penile/clitoral Perineal Rectal Back Buttocks Thighs	ONSET Acute Chronic ONGOING Sporadic Cyclical Continuous TIME Filling Emptying Immediate post Late post TRIGGER Provoked Spontaneous	Aching Burning Stabbing Electric	UROLOGICAL Frequency Nocturia Hesitancy Dysfunctional flow Urgency Incontinence GYNAECOLOGICAL Menstrual Menopause GASTROINTESTINAL Constipation Diarrhoea Bloatedness Urgency Incontinence NEUROLOGICAL Dysaesthesia Hyperaesthesia Allodynia Hyperalgesia SEXUOLOGICAL Satisfaction Female dyspareunia Sexual avoidance Erectile dysfunction Medication MUSCLE Function impairment Fasciculation CUTANEOUS Trophic changes Sensory changes	ANXIETY About pain or putative cause of pain Catastrophic thinking about Pain DEPRESSION Attributed to pain or impact of pain Attributed to other causes Unattributed PTSD SYMPTOMS Re-experiencing Avoidance
				Bladder					
				Scrotal Testicular Epididymal					
				Penile Urethral					
				Post-vasectomy					
		Gynaecological	Vulvar Vestibular Clitoral						
			Endometriosis associated						
			CPPPS with cyclical exacerbations						
			Dysmenorrhoea						
		Gastrointestinal	Irritable bowel						
			Chronic anal						
			Intermittent chronic anal						
		Peripheral nerves	Pudendal pain syndrome						
		Sexological	Dyspareunia						
			Pelvic pain with sexual dysfunction						
		Psychological	Any pelvic organ						
		Musculo-skeletal	Pelvic floor muscle Abdominal muscle Spinal						
			Coccyx Hip muscle						

Hx = History; Ex = Examination; Ix = Investigation; PTSD = post-traumatic stress disorder.

Pain syndromes
The original EAU classification [2] was inspired by the IASP classification [13] 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 men or women. It is often associated with negative cognitive, behavioural, sexual and emotional consequences as well as with symptoms suggestive of lower urinary tract (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 hence 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 sub-divided 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 purpose of 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 new ICD-11 these conditions have new names: the former will be called Chronic Secondary Pelvic Pain and the latter Chronic Primary Pelvic Pain.

The following classification only deals with Chronic Primary Pelvic Pain Syndromes.

EAU Definition of chronic primary pelvic pain syndrome
Chronic primary pelvic pain syndrome (CPPPS) 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 the text below in the 2021 update, CPPS 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), fibromyalgia (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 BPS (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 sub-divide by anatomy and prefer to refer to patients with pain perceived within the pelvis, and no specific disease process, as suffering from CPPPS, sub-divided 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 significant important concomitant symptoms that are relevant to pain, disability and poor QoL. Catastrophic interpretation of pain has been shown to be a particularly salient variable, predicting patients' report of pain, disability, and poor QoL, over and above psychosocial variables such as depression or behavioural factors such as self-reported sexual dysfunction. Many of these biopsychosocial consequences are common to other persistent pain problems but may show varying degrees of importance for any one 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) [14].

Functional considerations for classification

Functional disorders, for the purpose of this document, are pathologies that have arisen secondary to changes in the control mechanisms of an organ or system. That is, they are disorders characterised by disturbance of function. As an example, slow colonic transit is a functional disorder of the bowel - the normal function of the bowel is not occurring as a result of changes in the mechanisms that produce defecation, and 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.

Multi-system sub-division

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 multi-systemic 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 CPPS, 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 women and men. It is usually applied to penile penetration, but is often associated with pain during insertion of any object. It may apply to anal as well as vaginal intercourse. It is classically sub-divided 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	
Primary prostate pain syndrome	Primary prostate pain syndrome (PPPS) 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 lower urinary tract 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 National Institutes of Health (NIH) consensus [15] 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 prostadynia has also been used in the past but is no longer recommended by the expert panel. Please note that some of the authors of the IASP document disagree with this term and suggest that CPPPS of the male is used instead of PPPS, which has been agreed by the majority.

Primary bladder pain syndrome	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 day-time 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 lower urinary tract and sexual dysfunction. PBPS is believed to represent a heterogeneous spectrum of disorders. There may be specific types of inflammation as a feature in subsets of patients. Localisation of the pain can be difficult by examination, and consequently, another localising symptom is required. Cystoscopy with hydrodistension and biopsy may be indicated to define phenotypes. Recently, ESSIC has suggested a standardised scheme of sub-classifications [16] to acknowledge differences and make it easier to compare various studies. Other terms that have been used include “interstitial cystitis”, “painful bladder syndrome”, and “PBS/IC” or “BPS/IC”. These terms are no longer recommended.
Primary scrotal pain syndrome	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 lower urinary tract 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.
Primary testicular pain syndrome	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 lower urinary tract 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
Primary epididymal pain syndrome	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 lower urinary tract 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.
Primary penile pain syndrome	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 lower urinary tract and sexual dysfunction.
Primary urethral pain syndrome	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 lower urinary tract, sexual, bowel or gynaecological dysfunction. Primary urethral pain syndrome may occur in men and women.
Post-vasectomy scrotal pain syndrome	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 lower urinary tract and sexual dysfunction. Post-vasectomy pain may be as frequent as 1% following vasectomy, possibly more frequent. The mechanisms are poorly understood and for that reason it is considered by some a special form of primary scrotal pain syndrome.

Primary Gynaecological Pain Syndromes: external genitalia	
Primary vulvar pain syndrome	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 lower urinary tract, 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 International Society for the Study of Vulvovaginal Disease (ISSVD) has used the term vulvodynia, where we 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.
Primary generalised vulvar pain syndrome	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 diffuse and affects all parts of the vulva. The vulvar vestibule (the part that lies between the labia minora into which the urethral meatus and vaginal introitus open) may be involved but the discomfort is not limited to the vestibule. This pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences. Previous terms have included "dysesthetic vulvodynia" and "essential vulvodynia", but these are no longer recommended.
Primary localised vulvar pain syndrome	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 as a result of provocation (touch, pressure or friction). Primary localised vulvar pain syndrome can be sub-divided into primary vestibular pain syndrome and primary clitoral pain syndrome.
Primary vestibular pain syndrome	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.
Primary clitoral pain syndrome	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.
Gynaecological system: internal pelvic pain syndromes	
Endometriosis-associated pain syndrome	Endometriosis-associated pain syndrome is chronic or recurrent pelvic pain in patients with laparoscopically confirmed endometriosis, and the term is used when the symptoms persist despite adequate endometriosis treatment. It is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction. Many patients have pain above and beyond the endometriotic lesions; this term is used to cover that group of patients. Endometriosis may be an incidental finding, is not always painful, and the degree of disease seen laparoscopically does not correlate with severity of symptoms. As with other patients, they often have more than one end-organ involved. It has been suggested that this phenotype should be removed from the classification because the endometriosis may be irrelevant.
Chronic primary pelvic pain syndrome with cyclical exacerbations	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 similar to that associated with endometriosis/adenomyosis but where no pathology is identified. This condition is different from dysmenorrhoea, in which pain is only present with menstruation.
Primary dysmenorrhoea	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.

Gastrointestinal Pelvic Pain Syndromes	
Irritable bowel syndrome	Irritable bowel syndrome is the occurrence of chronic or recurrent episodic pain perceived in the bowel, in the absence of proven infection or other obvious local pathology. Bowel dysfunction is frequent. 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 lower urinary tract or gynaecological dysfunction. The above classification is based upon the Rome III Criteria [17]: three months of continuous or recurring symptoms of abdominal pain or irritation that may be relieved with a bowel movement, may be coupled with a change in frequency, or may be related to a change in stool consistency. Two or more of the following are present at least 25% of the time: change in stool frequency (> three bowel movements per day or < three per week); noticeable difference in stool form (hard, loose, watery or poorly formed stools); passage of mucus in stools; bloating or feeling of abdominal distension; or altered stool passage (e.g., sensation of incomplete evacuation, straining, or urgency). Extra-intestinal symptoms include: nausea, fatigue, full sensation after even a small meal, and vomiting.
Chronic primary anal pain syndrome	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 lower urinary tract, sexual, bowel or gynaecological dysfunction.
Intermittent chronic primary anal pain syndrome	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.
Musculoskeletal System	
Primary pelvic floor muscle pain syndrome	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 lower urinary tract, 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.
Primary coccyx pain syndrome	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 lower urinary tract, sexual, bowel or gynaecological dysfunction. The term “coccydynia” was used but is no longer recommended.
Chronic Pain Post-Surgery	
Chronic post-surgical pain syndrome	The definition of chronic post-surgical pain is chronic pain that develops or increases in intensity after a surgical procedure and persists beyond the healing process, i.e., at least three months after the surgery. There is a separate category for this in the ICD11 classification.

2. METHODOLOGY

2.1 Methods

For each recommendation within the guidelines there is an accompanying strength rating form, the basis of which is a modified GRADE methodology [18]. Each strength rating form addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [19];

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 of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak' [18]. 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 nature and variability of patient values and preferences.

Additional information can be found in the general Methodology section of this print, and online at the EAU website: http://www.uroweb.org/guideline/. A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

The 2012 full text update was based on a systematic review (SR) 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. Searches covered the period January 1995 to July 2011 and were restricted to English language publications. In 2017, a scoping search for the previous five years was performed and the guideline was updated accordingly.

In 2021, a new section was included on Post-Surgical Pain Syndrome. In addition, the classifications in the Guideline have been amended to reflect ICD-11 released by WHO. The latest version of ICD-11 will be available for member states to report with as from January 2022. For the 2022 print, a scoping search for the previous three years was performed and the guideline was updated accordingly.

2.2 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 actual or potential tissue damage, or described in terms of such damage (IASP Taxonomy).

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, both animal and clinical research have 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 as a result 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 forms the basis of the pain syndrome diagnosis and each individual phenomenon needs to be addressed in its own right through multi-specialty and multi-disciplinary 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 [20] 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 UK study found a prevalence of chronic pelvic pain of 14.8% in women over 25 years [21].

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

Assessing QoL in pelvic pain patients is challenging due to the complex pathology, the multi-faceted nature of the complaints and the overlap between the different pelvic pain syndromes [22, 23]. Pelvic pain syndromes have an impact in terms of QoL [24, 25], depression, anxiety, impaired emotional functioning, insomnia and fatigue [24, 26]. 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 [27]. Quality of life assessment is therefore important in patients with pelvic pain and should include physical, psychosocial and emotional tools, using standardised instruments where possible [25]. Chronic pain is, in many countries, the leading cause of years lost to disability [20], although these figures are dominated by musculoskeletal pain and headache. Chronic pain is often associated with depression and other psychological problems; with loss or reduction of work and of ability to carry out domestic tasks; and, with substantial use of healthcare, often with disappointing outcomes.

*3.1.4 **Costs***

No adequate data on costs were found.

*3.1.5 **Risk Factors and underlying causes***

3.1.5.1 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 rectal hypersensitivity to rectal distension. This model suggests an action of CRH on mast cells. A range of stress-related illnesses have been suggested, e.g., IBS and BPS. There is evidence accumulating to suggest that the sex hormones also modulate both nociception and pain perception. 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 [28]. Asking the patient about these events is important as they have an effect on a patient's psychological wellbeing [29, 30].

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 and animals can be bred to be more prone to apparent chronic pain state. 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 complicated in that developmental, environmental and social factors also influence the situation. 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 [31, 32].

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 [33]. Beliefs about pain contribute to the experience of pain [34] and symptom-related anxiety and central pain amplification may be measurably linked, as in IBS [35], and catastrophic thinking about pain and perceived stress predict worsening of urological chronic pain over a year [33, 36]. Central sensitisation has been demonstrated in symptomatic endometriosis [37] and central changes are evident in association with dysmenorrhoea and increasingly recognised as a risk for female pelvic pain [38]. 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 vs. psychogenic is unscientific. Diagnoses that assign women's pain to psychological origins due to scepticism about the reality or severity of their pain [39, 40] undermines any therapeutic relationship [41]. Pelvic

pain and distress may be related [42] in both men and women [43]; as are painful bladder and distress [36]. In a large population based study of men, CPPPS was associated with prior anxiety disorder [44]. The only SR [45] of risk factors for chronic non-cyclical pelvic pain in women included, as well as 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 somatic problems (OR: 4.83; 95% CI: 2.50-9.33 and 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 women with pelvic pain [46]. It is hard to establish a causal role for sexual abuse or trauma history, anxiety or depression in women with CPPPS [47, 48], as the attribution of current pain to past sexual or physical abuse is associated both with current depression [49] and with current overall physical health [50]. There is some evidence for a specific relationship between rape and CPPPS (and with fibromyalgia and functional gastrointestinal disorders) [51]; and, recent sexual assault may prompt presentation of pelvic pain [46, 52]. Few studies have been found of sexual or physical abuse in childhood and pelvic pain in men, although it has known adverse effects on health [51], but men who reported having experienced sexual, physical or emotional abuse had increased odds (3.3 vs. 1.7) for symptoms suggestive of CPPPS [53]. 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 [53].

3.1.5.2 Underlying causes

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

1. Ongoing acute pain mechanisms [54] (such as those associated with inflammation or infection), which may involve somatic or visceral tissue.
2. Chronic pain mechanisms, which especially involve the CNS [6].
3. Emotional, cognitive, behavioural and sexual responses and mechanisms [55-57].

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. The presence or absence of endometriosis does not seem to change this [58].

Chronic pain mechanisms may include altered resting state neuromotor connectivity, for instance in men with chronic prostatitis/CPPPS [59].

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
Effective painful stimuli	Stretching and distension, producing poorly localised pain.	Mechanical, thermal, chemical and electrical stimuli, producing well localised pain.
Summation	Widespread stimulation produces significantly magnified pain.	Widespread stimulation produces a modest increase in pain.
Autonomic involvement	Autonomic features (e.g., nausea and sweating) frequently present.	Autonomic features less frequent.
Referred pain	Pain perceived at a site distant to the cause of the pain is common.	Pain is relatively well localised and well recognised.
Referred hyperalgesia	Referred cutaneous and muscle hyperalgesia is common, as is involvement of other visceral organs.	Hyperalgesia tends to be localised.
Innervation	Low density, unmyelinated C fibres and thinly myelinated A∂ fibres.	Dense innervation with a wide range of nerve fibres.
Primary afferent physiology	Intensity coding. As stimulation increases, afferent firing increases with an increase in sensation and ultimately pain.	Two fibre coding. Separate fibres for pain and normal sensation.
Silent afferents	50-90% of visceral afferents are silent until the time they are switched on.	These fibres are very important in the central sensitisation process. Silent afferents present, but form a lower percentage.
Central mechanisms	Play an important part in the hyperalgesia, viscero-visceral, viscero-muscular and musculo-visceral hyperalgesia.	Sensations not normally perceived become perceived and non-noxious sensations become painful. Responsible for the allodynia and hyperalgesia of chronic somatic pain.
Abnormalities of function	Central mechanisms associated with visceral pain may be responsible for organ dysfunction.	Somatic pain associated with somatic dysfunction, e.g., muscle spasm.
Central pathways and representation	As well as classical pathways, there is evidence for a separate dorsal horn pathway and central representation.	Classical pain pathways.

Ongoing peripheral pain mechanisms in visceral pain

In most cases of chronic pelvic pain, ongoing tissue trauma, inflammation or infection is absent [60, 61]. 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 [62]. It is for this reason that the early stages of assessment include looking for these pathologies [16]. Once excluded, ongoing investigations for these causes are rarely helpful and indeed may be detrimental.

When acute pain mechanisms are activated by a nociceptive event, as well as direct activation of the peripheral nociceptor transducers, sensitisation of those transducers may also occur; therefore, magnifying the afferent signalling. Afferents that are not normally active may also become activated by the change, that is, there may be activation of the so-called silent afferents. Although these are mechanisms of acute pain, the increased afferent signalling is often a trigger for the chronic pain mechanisms that maintain the perception of pain in the absence of ongoing peripheral pathology (see below) [63].

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

1. Modification of the peripheral tissue, which may result in the transducers being more exposed to peripheral stimulation.
2. There may be an increase in the chemicals that stimulate the receptors of the transducers [64].
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 [65, 66].

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. For instance, with central sensitisation, stimuli that are normally sub-threshold may 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. As a consequence, 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 [67]. Several neurotransmitters and neuromodulators are involved in descending pain-inhibitory pathways. The main ones are the 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 managed as appropriate.

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 [68].

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 [69] 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 [28] of chronic pelvic pain in women dismantled the notion that women without relevant physical findings differ in psychological characteristics from women with relevant physical findings. Women with pelvic pain often have other non-pain somatic symptoms and current or lifetime anxiety and depression disorder [21]; 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 originis of the complaint (‘psychosomatic’ or ‘somatoform’ disorders). Pain studies describe multiple processes

by which pain may spread across sites, or in time, including central sensitisation (see previous section), viscero-visceral cross sensitisation in relation to multiple pain sites [70], activation of the hypothalamic-pituitary axis and dysregulation of serotonergic pathways [71] that can render pain levels responsive to stress. Some pain problems which 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 [72]. Better integration of sexology and mainstream psychology for pelvic pain in both men and women is needed, building on a biopsychosocial formulation [73, 74].

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 [75].

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 3.1.5.1).

There is no evidence that women with CPPPS without physical findings are primarily presenting a psychological problem [28]. Anxiety and post-traumatic stress symptoms are common in some women with CPPPS [40, 76] and with vulvar pain [77], and may account for substantial variance in health status, treatment use and treatment outcome; for instance, women's expectations about vulvar pain on penetration predicted pain, sexual function and sexual satisfaction [78]. Negative investigative findings do not necessarily resolve women's anxieties about the cause of pain [79, 80] and anxiety often focuses on what might be 'wrong'. Depression may be related to pain in various ways, as described above. Until measures are available that are adequately standardised 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 [81, 82]. Reference to the studies of the IMMPACT group [83] 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 [30]. The patient should be asked about adverse life events that may produce these biological responses and affect general psychological well-being [30, 84].

3.1.5.3 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 as a result 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 [63].

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 BPS. Referred pain with hyperalgesia is thought to be due to central sensitisation of the converging viscero-somatic 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. It is not unknown for adjacent muscles of the lower limbs and the thorax to become involved. Pain may be localised to the trigger points but it is more often associated with classical referral patterns. As well as trigger points, inflammation of the ligaments and tendons to the bones (enthesitis) and of the bursa (bursitis) may be found [85]. Certain postures affect the

different muscles in different ways, and as a consequence, may exacerbate or reduce the pain. Stress has been implicated as both an initiator of pelvic myalgia and as a maintenance factor. As a result, negative sexual encounters may also have a precipitating effect [28].

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***

3.2.2.1 Primary prostate pain syndrome

There is only limited information on the true prevalence of 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 [86, 87]. In the literature, population-based prevalence of prostatitis symptoms ranges from 1-14.2% [88, 89]. The risk of prostatitis increases with age (men aged 50-59 years have a 3.1-fold greater risk than those aged 20-39 years).

3.2.2.2 Primary bladder pain syndrome

Reports of PBPS prevalence have varied greatly, along with the diagnostic criteria and populations studied. Recent reports range from 0.06-30% [90-99]. There is a female predominance of about 10:1 [96] but possibly no difference in race or ethnicity [86, 100, 101]. The relative proportions of Hunner's lesion and non-lesion disease are unclear. Incidence in studies has ranged from 5-50% [102-105]. There is increasing evidence that children under eighteen may also be affected, although prevalence figures are low; therefore, PBPS cannot be excluded on the basis of age [106].

3.2.2.3 Sexual pain syndrome

In the 1980s, an association between chronic pelvic pain and sexual dysfunction was postulated. In a review the relationship between Primary Prostate Pain Syndrome and health status, with influence on sexual activity, was addressed [107]. In a Chinese study of men 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 [108, 109]. Erectile dysfunction was prevalent in 27.4% of Italian men aged 25-50 [110], 15.2% among Turkish men (significantly higher than in the control group) [111] and 43% among Finnish men with PPPS [112]. The prevalence of ED was found to be higher in young men with PPPS than in the general population. According to other studies, men with pelvic pain had a higher chance of suffering from ED [113]. 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 [114], while other studies using the same questionnaires were not able to confirm such a correlation [74, 115]. Some studies also report ejaculatory dysfunction, mainly premature ejaculation [108, 109, 116, 117].

In community-based studies in the UK [118], New Zealand [119] and Australia [120], a substantially larger proportion of the women with chronic pelvic pain reported dyspareunia (varying between 29-42%) than women without chronic pelvic pain (varying between 11-14%). Only a few studies have investigated sexual problems within clinical populations [121]. Another study showed that all of the sexual function domains (desire, arousal, lubrication, orgasm, satisfaction, and pain) were significantly lower in women with chronic pelvic pain than in women without chronic pelvic pain [121]. In line with the results of these community based studies, patients with chronic pelvic pain reported more sexual problems such as dyspareunia, problems with desire or arousal and lubrication than women without chronic pelvic pain [121, 122]. One study of patients enrolled in chronic pain treatment programs in England has reported that 73% had pain-related sexual problems [123].

3.2.2.4 Myofascial pain syndromes

The relationship between muscular dysfunction (especially over-activity) and pelvic pain has been found in several studies [124]. Rectal pain treated with pelvic floor muscle therapy is only relieved when patients learn to relax their pelvic floor muscles [125, 126]. The vast majority (92.2%) of men visiting a tertiary centre for pelvic

pain had dysfunction of the pelvic floor muscles. This finding was true regardless of evidence of inflammation (prostatitis or cystitis) [127]. This relationship has been found in chronic prostatitis [128], PBPS [129] and vulvar pain [130]. 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. They are described in Section 3.1.5.1. The underlying causes, including the mechanisms for the different clinical pain syndromes are described here.

3.2.5.1 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 men exposed to one or more initiating factors, which may be single, repetitive or continuous. Several of these potential initiating factors have been proposed, including infectious, genetic, anatomical, neuromuscular, endocrine, immune (including autoimmune), or psychological mechanisms. These factors may then lead to a peripheral self-perpetuating immunological, inflammatory state and/or neurogenic injury, creating acute and then chronic pain. A study showed that chronic but not acute histological inflammation of the prostate was significantly associated with symptomatic progression [131]. Based on the peripheral and the CNS, sensitisation involving neuroplasticity may lead to a centralised neuropathic pain state [132]. 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 [44].

3.2.5.2 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 as yet been implicated. Nevertheless, urinary infections are significantly more frequent during childhood and adolescence, in patients with PBPS in adulthood [133]. Experimental induction of chronic pelvic pain by O-antigen deficient bacterial strains supports the bacterial hypothesis [134]. Pancystitis, with associated perineural inflammatory infiltrates, and mast cell count increase is an essential part of PBPS type 3 C [135], but is rare in non-lesion PBPS [30, 68, 136, 137]. 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 [138-144] and a consequent cytotoxic effect [145, 146]. Basic and clinical studies indicate that autonomic dysfunction with sympathetic predominance may be implicated in PBPS [147, 148].

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 [149-153].

Risk of PBPS correlates with a number of non-bladder syndromes in each patient [154]. Recent work showing non-lesion PBPS to have significantly more FM, migraine, temporomandibular joint disorder and depression than PBPS type 3 C patients, which emphasises, the need for subtyping [155].

3.2.5.3 Primary scrotal pain syndrome

Often scrotal pain is not associated with any specific pathology. Pain is perceived in the testes, epididymis, or the vas deferens. The ilioinguinal, genitofemoral and the pudendal nerves innervate the scrotum [156]. Any pathology or intervention at the origin or along the course of these nerves may result in pain perceived in the scrotum [157].

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 a special form of primary scrotal pain syndrome. Incidence of post-vasectomy pain is 2-20% among all men who have undergone a vasectomy [158]. In men with post-vasectomy pain, 2-6% have

a Visual Analogue Scale (VAS) score > 5 [159]. In a large cohort study of 625 men, 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. the scalpel group 18.8%) [160].

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 [157, 161]. 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 [162]. Inguinal hernia repair can lead to chronic post-surgical pain (CPSP) in up to 10% of patients at six months [163] 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 2/3 of patients [164]. Careful identification and preservation of nerves has been found to be associated with a reduced risk of chronic pain.

3.2.5.4 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 [165, 166]. Another possible mechanism is neuropathic hypersensitivity following urinary tract infection [167]. The relationship with gynaecological and obstetric aspects is unclear. In a small group of patients with urethral pain, it has been found that grand multi-parity and delivery without episiotomy were more often seen in patients with urethral syndrome, using univariate analysis [168].

3.2.5.5 Primary vaginal and vulvar pain syndromes

Pain in the vagina or the female external genital organs is often due to infection or trauma, as a consequence of 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 does 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 are many and include:

- history of sexual abuse;
- history of chronic antibiotic use;
- hypersensitivity to yeast infections, allergies to chemicals or other substances;
- abnormal inflammatory response (genetic and non-genetic) to infection and trauma;
- nerve or muscle injury or irritation;
- hormonal changes.

3.2.5.6 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, respectively. They were deemed easy to insert, but no credence was given as to how safe they were, whether they could be removed should they cause complications, or what to do should they not be effective [169, 170]. Most meshes took less than an hour to implant surgically and most patients were treated as day cases, allowing women to leave hospital quickly and get on with their lives. Therefore, rather than undergo complex traditional surgery, women were offered permanent mesh implants, particularly in the treatment of SUI where they were considered to be the gold standard [171, 172]. However, over the last few years the insertion of mesh has come with significant ‘health and safety warnings’ [173, 174].

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% [175]. They included chronic pain [176, 177], as well as chronic infections [178], erosion into the surrounding organs including the vagina, urethra and bladder, as well as nerve and musculoskeletal damage affecting mobility [176, 177, 179, 180]. All had a significant impact on the patients' QoL.

It is as a result of severely debilitating complications following mesh implantation [176], that the field of mesh removal medicine and surgery has emerged [181].

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 the pain after the operation is very severe and much more than expected after this type of surgery, it can be a sign that there was added trauma to the surrounding organs during the procedure. Most pain is often managed with analgesia, but some women 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 [182], as has been proposed in hernia mesh neuralgia. The impact of the mesh, regardless of site, appears to be similar.

3.2.5.7 Chronic post-surgical pain

Chronic post-surgical pain

Chronic pain may develop following surgical procedures and has a significant impact on the individual. The ICD-11 has recently classified chronic post-surgical pain (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, i.e., at least three months after the surgery [183].

Chronic post-surgical pain may occur in a significant number of patients, and is more prevalent following some operations rather than others. Procedures with a higher risk of CPSP include limb amputation (30-85%), thoracotomy (5-65%) and mastectomy (11-57%) [184].

Risk factors for CPSP include a number of pre-, peri- and post-operative factors. Younger age, female gender, chronic pain pre-operatively elsewhere, higher number of previous operations, use of opioids and a higher post-operative pain score have been found to be associated with a higher risk of CPSP in a prospective cohort of patients undergoing laparoscopy and laparotomies. Older age, malignant indication for surgery, a higher pre-operative mental health score and the use of epidural analgesia in addition to general anaesthesia were protective [185, 186].

There are a number of 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 SR identified only low level evidence to help guide management of affected individuals [187].

The estimated prevalence of CPSP following bariatric surgery is 30% [188]. 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 post-operative pain [189].

Inguinal hernia repair can lead to CPSP in up to 10% of patients at six months [163] and may present with groin and/or scrotal pain.

The incidence of post vasectomy pain ranges from 2-20% [158, 159]. The risk is significantly lower following the no scalpel technique [160].

The incidence of post-surgical pain following hysterectomy is difficult to determine as pain is a common indication for the operation. When defined as CPSP, rates are estimated at 28-30% [190, 191]. Careful case selection and management of patient expectation is therefore important.

The frequency of caesarean section 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) [192], therefore careful counselling is needed in non-emergency cases.

3.2.5.8 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 post-operative scarring may result in nerve injury [193].

Pudendal neuralgia is the most often mentioned form of nerve damage in the literature. Anatomical variations may pre-dispose the patient to developing pudendal neuralgia over time or with repeated low-grade trauma (such as sitting for prolonged periods of time or cycling) [194, 195].

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 hence be trapped; or in other cases, muscle hypertrophy or spasm is implicated.
2. The sacrospinal/sacrotuberous ligaments, possibly accounting for 42% of cases.
3. Within Alcock's canal (medial to the obturator internus muscle, within the fascia of the muscle), possibly accounting for 26% of cases.
4. Multiple levels in 17% of cases.
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. There is a wide age range, as one would expect, with a condition that has so many potential causes. It is suggested that, the younger the patient, the better the prognosis. Essentially, the sooner the diagnosis is made, as with any compression nerve injury, the better the prognosis, and older patients may have a more protracted problem [196-198]. Six out of ten cases are observed in women. 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 [199, 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, 202]. 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 [203].
- The pudendal neuralgia of birth trauma is thought to resolve in most cases over a period of months. However, rarely, it appears to continue as painful neuropathy. Multiple pregnancies and births may predispose to stretch neuropathy in later life. This is more difficult to be certain about [204].
- Child birth and repeated abdominal straining associated with chronic constipation [205] are thought to pre-dispose elderly women to post-menopausal 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 commonest associations with pudendal neuralgia appear to be: history of pelvic surgery; prolonged sitting (especially young men working with computer technology); and postmenopausal older women.

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 men and women.

Men

Chronic pain as well as its treatment can impair our ability to express sexuality. In an England study, 73% of patients with any chronic pain had some degree of sexual problems as a result of the pain [123]. These problems can occur because of several factors. Psychological factors like decrease in self-esteem, depression and anxiety can contribute to loss of libido. Physiological factors like fatigue, nausea and pain itself can cause sexual dysfunction. Pain medications (opioids, and the selective serotonin re-uptake inhibitors [SSRIs]) can also decrease libido [206] 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 [145].

The presence of pelvic pain may increase the risk for ED independent of age [207]. On the other hand, cross-sectional data suggest no improvement of lower urinary tract symptoms (LUTS) by an increased frequency of ejaculation [208]. 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 [117]. 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 [107-109, 208-210]. Sexual dysfunction heightens anger, frustration and depression, all of which place a strain on the patients' relationships. The female partners of men with sexual dysfunction and depression often present with similar symptoms including pain upon intercourse and depressive symptoms. Men with CPPPS have reported a high frequency of sexual relationship dissolution and psychological symptoms, such as depression and suicidal thinking [107, 211]. Primary Prostate Pain Syndrome patients reported substantial sexual and relationship problems [107, 211]. On the other hand, it was found that men with PPPS did not report significantly decreased sexual satisfaction compared to controls [212]. 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.

Women

Chronic pelvic pain leads to substantial impairment in QoL and several sexual dysfunctions [119, 213-215]. It seems reasonable to expect that pain, extreme fatigue, depressive mood and pain drugs will affect women's sexuality. Women with CPPPS reported significantly more pain, depression, and anxiety symptoms and were physically more impaired than women in the control group. In comparison with controls, women with CPPPS reported significantly more sexual avoidance behaviour, non-sensuality, and complaints of "vaginismus" [216]. Patients with CPPPS reported more sexual problems than women with any other type of chronic pain problem [217]. The quality of intimate 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].

Approximately two-thirds of patients in another study reported reduced frequency in their sexual relations as a result of CPPPS [220]. One study demonstrated that CPPPS patients reported worse sexual function with regard to desire, arousal, lubrication, orgasm, satisfaction, and more frequent and severe pain with vaginal penetration than women without 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 their sex life [222]. In a study in patients with back pain, half reported decreased frequency of sex since the onset of chronic pain [123]. The Female Sexual Function Index (FSFI) has been developed as a brief, multi-dimensional self-report instrument for assessing the key dimensions of sexual function in women, which includes desire, subjective arousal, lubrication, orgasm, satisfaction, and pain. Using the FSFI, women with CPPPS reported worse sexual function in all subscales and total score than women without CPPPS. The largest differences between women with CPPPS and 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 women with CPPPS. The FSFI also showed good ability to discriminate between women with and 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 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 showed that 51% of patients with prostatitis and only 7% of controls had any muscle tenderness. Tenderness in the pelvic floor muscles was only found in the CPPPS group [128].

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 [127]. Animal studies on the role of neurogenic inflammation have also elucidated some important phenomena. Irritation of the prostate, bladder and pelvic floor muscles results in expression

of C-fos-positive cells in the CNS. There appears to be convergence of afferent information onto central pathways. Once the central changes have become established, they become independent of the peripheral input that initiated them [225].

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 as a result of these trigger points is aggravated by specific movements and alleviated by certain positions. Positions and movements in which the shortened muscle is stretched are painful. Patients know which activities and postures influence pain. Trigger points can be located within the pelvic floor muscles and in adjacent muscles such as the abdominal, gluteal and 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 [226]. Chronic Pelvic Pain has been shown to be one of the most common functional disorders in women of reproductive age. The monthly incidence rate of CPPPS published by Zondervan *et al*. was 1.58/1000 [227].

*3.3.2 **Prevalence***

Using a vague definition of continuous or episodic pain situated below the umbilicus over six months, one study reported that CPPPS was one of the most common diagnoses in primary care units in Great Britain [227]. 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. The overall prevalence of anorectal pain in a sample of USA householders was 6.6% and was more common in women [228]. Irritable bowel syndrome is associated with common gynaecologic problems (endometriosis, dyspareunia, and dysmenorrhoea) [229]. Fifty per cent of women who presented with abdominal pain to the gynaecologic clinic or were scheduled for laparoscopy due to CPPPS had symptoms of IBS [230]. In a survey from Olmsted county, 20% of women reported CPPPS and 40% of those met the criteria for IBS [22]. This overlap of CPPPS and IBS was associated with an increased incidence of somatisation. Not gynaecological surgical procedures but only psychosocial variables predict pain development without a different incidence of IBS in a prospective and controlled study [231]. Clinical features of pelvic floor dysfunction, gynaecological and psychological features, are related to disordered anorectal function in IBS patients, but do not predict physiological anorectal testing.

*3.3.3 **Influence on 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 in patients with IBS treated at referral centres who have comparable HRQoL scores as patients with other common disorders such as diabetes, end-stage renal disease, and inflammatory bowel disease [232]. Sub-groups of IBS with predominance of diarrhoea or constipation show no difference in HRQoL. Multi-variate analysis shows that HRQoL in patients with IBS is affected by sex and psychological conditions.

*3.3.4 **Costs***

Costs combine direct health-care 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: CPPPS and mechanisms

Summary of evidence	**LE**
CPPPS mechanisms are well defined and involve mechanisms of neuroplasticity and neuropathic pain.	2
The mechanisms of neuroplasticity and neuropathic pain result in increased perception of afferent stimuli which may produce abnormal sensations as well as pain.	1

End-organ function can also be altered by the mechanisms of neuroplasticity 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 multi-disciplinary 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 so as to be able to manage CPPPS comprehensively in a multi-specialty and multi-disciplinary environment with consideration of all their 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.

4.1.1.1 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 [34], or to uncertainties about treatment and prognosis. These 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 colleague.

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 sexological aspects were added [238]. However, it may underassess relevant psychological variables [43]. Generic QoL measures are helpful. If such an instrument is not already used in the clinic, 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]).

4.1.1.2 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 [49]. 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 4.2.3). These subjective outcome measures are recommended for the basic evaluation and therapeutic monitoring of patients in urological practice.

Primary bladder pain syndrome
Primary bladder pain syndrome should be diagnosed on the basis of pain, pressure or discomfort associated with the urinary bladder, accompanied by at least one other symptom, such as daytime and/or night-time increased urinary frequency, the exclusion of confusable diseases as the cause of symptoms, and if indicated, cystoscopy with hydrodistension and biopsy (Table 4) [16].

The nature of pain is key to disease definition:
1. pain, pressure or discomfort perceived to be related to the bladder, increasing 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.

4.1.1.3 Gynaecological aspects
A detailed medical history outlining the nature, frequency and site of pain; 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 as well as 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.

4.1.1.4 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 asked, ideally applying symptom questionnaires for urinary and anorectal symptoms (e.g., Rome III 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 III criteria are as follows and must include all of the following: chronic or recurrent rectal pain or aching, episodes last at least twenty 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 [243, 244].

The 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.

Primary intermittent chronic anal pain syndrome (proctalgia fugax) consists of all the following diagnostic criteria, which should be fulfilled 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 the 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.

4.1.1.5 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 that the main nerve, CNS central sensitisation, and consequently, the involvement of other organs and systems in a regional pain syndrome. Other nerves in the vicinity may also be involved, for example, inferior cluneal nerve and perineal branches of the posterior femoral cutaneous nerve. The musculoskeletal system may become involved, confusing the pain picture as aches and pain 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 meanings to 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 as a consequence, develop a wide range of other aches and pains. Soft seats are often less well-tolerated, whereas sitting on a toilet seat is said to be much better tolerated. If unilateral, sitting on one buttock is common. The pain may be exacerbated by bowel or bladder evacuation.

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

Many of those suffering from pudendal neuralgia complain of fatigue and generalised muscle cramps, weakness and pain. Being unable to sit is a major disability, and over time, patients struggle to stand and they often become bedbound. The immobility produces generalised muscle wasting, and minimal activity hurts. As a consequence of the widespread pain and disability, patients often have emotional problems, and in particular, depression. Patients with chronic pelvic pain are also often anxious and have the tendency to catastrophise. Depression, catastrophising and disability are all poor prognostic markers. Cutaneous colour may change due to changes in innervation but also because of neurogenic oedema. The patient may describe the area as swollen due to this oedema, but also due to the lack of afferent perception.

4.1.1.6 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 certainly should be addressed: lower urinary tract function, anorectal function, sexual function, gynaecological items, presence of pain and psychosocial aspects. One cannot state that there is a pelvic floor dysfunction based only on the history. But there is a suspicion of pelvic floor muscle dysfunction when two or more pelvic organs show dysfunction, for instance a combination of micturition and defecation problems.

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 an integral part of the assessment and undertaken. 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 on the one hand directed towards identification and exclusion of specific diseases associated with pelvic pain, and on the other hand may be used for phenotypic description. Abdominal and pelvic examination to exclude gross pelvic pathology, as well as to 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 that one should assess cutaneous allodynia along the dermatomes of the abdomen (T11-L1) and the perineum (S3), and the degree of tenderness should be recorded. The bulbocavernosus reflex in the male 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 bi-manual examination can generate severe pain so the examiner must proceed with caution. A rectal examination is done to look for prostate abnormalities in male patients including pain on palpation and to examine the rectum and the pelvic floor muscles regarding muscle tenderness and trigger points as well as 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 findings may show high or low anal sphincter resting pressure, a tender puborectalis muscle in patients with the Levator Ani Syndrome, and occasionally increased perineal descent. The tenderness during posterior traction on the puborectalis muscle differentiates between Levator Ani Syndrome and unspecified Functional Anorectal Pain and is used in most studies as the main inclusion criterion. Dyssynergic (paradoxical) contraction of the pelvic muscles when instructed to strain during defecation is a frequent finding in patients with pelvic pain. Attention should be paid to anal or rectal prolapse at straining, and ideally during 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 frequently findings are non-specific. The main pathognomonic features are the signs of nerve injury in the appropriate neurological distribution, for example, allodynia or numbness. Tenderness in response to pressure over the pudendal nerve may aid the clinical diagnosis. This may be elicited by per rectal or per vaginal examination and palpation in the region of the ischial spine and/or Alcock's canal. Muscle tenderness and the presence of trigger points in the muscles may confuse the picture. Trigger points may be present in a range of muscles, both within the pelvis (levator ani and obturator internus muscles) or externally (e.g., the piriformis, adductors, rectus abdominis or paraspinal muscles).

4.2 Supplemental evaluation

If history is suggestive of lower urinary tract, gynaecological, anorectal or other disease of known aetiology, diagnostic work-up should follow respective guidelines.

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

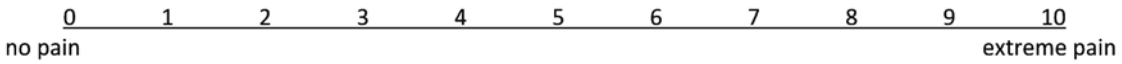
Determination of the severity of pain and associated symptoms, its progression and treatment response can be assessed only by means of a reliable and validated symptom-scoring instrument. These subjective outcome measures are recommended for the basic evaluation and therapeutic monitoring of patients. Pain should always be assessed at presentation and (see below) to identify progression and treatment response. As well as doing this in the clinic, the patient can keep 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 and 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) [57].

Where the primary outcome of treatment is pain relief, it is useful before starting treatment to agree a clinically useful level of relief [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 [56]. 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 IBSSymptom 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 effects on sexual function are ED and premature ejaculation. These can be evaluated by proper questionnaires namely IIEF and PEDT (Premature Ejaculation Diagnostic Tool). In comparison with controls, women with chronic pelvic pain reported significantly more sexual avoidance behaviour, non-sensuality, and complaints of "vaginismus" [205]. The Female Sexual Function Index (FSFI) has been developed as a brief, multi-dimensional self-report instrument for assessing the key dimensions of sexual function in women, which includes desire, subjective arousal, lubrication, orgasm, satisfaction, and pain. The corresponding evidence in men is lacking.

4.2.2 Focused myofascial evaluation

Pelvic floor muscle testing can be done by the medical doctor but a consultation of the pelvic floor by a physiotherapist is a good alternative, but either should have had 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 [253]. Rectal examination is a good way to test the pelvic floor function in men [254]. 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 [255]. In a cohort study of 72 men 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%) [256]. 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 [257, 258].

*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 [259, 260]. 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. Ultrasound avoids any form of radiation, whereas CT guidance involves a significant amount of radiation. Currently, fluoroscopy is probably the imaging technique most frequently used because it is readily available to most anaesthetists that perform the block. Currently, infiltration of the pudendal nerve within Alcock's canal is primarily undertaken with the use of CT. As well as injecting around the pudendal nerve, specific blocks of other nerves arising from the pelvis may be performed.

Electrophysiological studies

These may reveal signs of perineal denervation, increased pudendal nerve latency, or impaired bulbocavernosus reflex [196, 199, 261-263]. 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 CPPS. 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.

MRI

Magnetic resonance 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.

MR 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 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 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.

*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 [266]. Besides sterile pre-massage urine (voided bladder urine-2), PPPS shows $< 10^3$ cfu/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 enhanced cost-effectively by a simple screening procedure, that is, the two-glass test or pre-post-massage test (PPMT) [267, 268]. 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 men [269].

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 [270].

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 which are typical for patients with CPPPS and IBS. Flexible rectosigmoidoscopy or colonoscopy should be considered in patients with anorectal pain to rule out coincidental colorectal pathology.

Laparoscopy for females

Laparoscopy is perhaps the most useful invasive investigation to exclude gynaecological pathology [271, 272] and to assist in the differential diagnosis of CPPPS in women [273, 274]. Often, it is combined with cystoscopy [275, 276] 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 [277]. Integrating somatic and psychological assessment from the start rather than dealing with psychological concerns only after excluding organic causes of pelvic pain is helpful [278].

Cystoscopy and bladder biopsy

Despite controversy on the diagnostic and follow-up value of cystoscopy in PBPS [279-283], the panel believes 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) [284]. 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 [285]. 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 they can be observed without PBPS [286]. Biopsies are helpful in establishing or supporting the clinical diagnosis of both classic and non-lesion types of the disease [139, 165, 284, 287, 288]. Important differential diagnoses to exclude, by histological examination, are carcinoma in situ and tuberculous cystitis.

Table 4: ESSIC classification of PBPS types according to results of cystoscopy with hydrodistension and biopsies [16]

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

[a]Cystoscopy: glomerulations grade 2-3.

[b]Lesion per Fall's definition with/without glomerulations.

[c]Histology showing inflammatory infiltrates and/or detrusor mastocytosis and/or granulation tissue and/or intrafascicular fibrosis.

4.3 Diagnostic algorithm

Figure 1: Diagnosing chronic pelvic pain

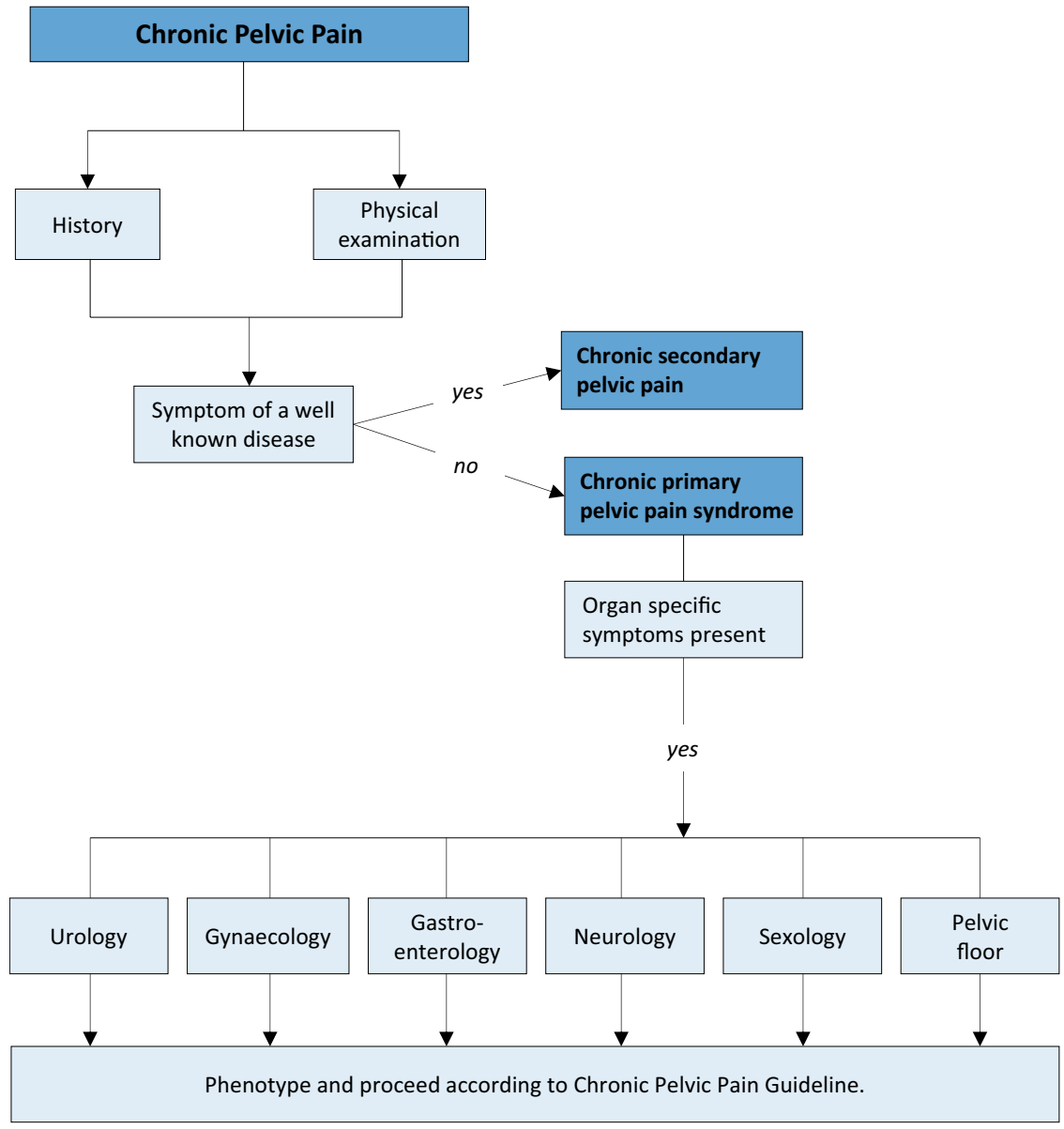


Figure 2: Phenotyping of pelvic pain - UPOINT classification

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, sexological complaints. Gynaecological examination, rectal examination.
Infection	Semen culture and urine culture, vaginal swab, stool culture.
Neurological	Ask for neurological complaints (sensory loss, dysaesthesia). Neurological testing during physical examination: sensory problems, sacral reflexes and muscular function.
Tender muscle	Palpation of the pelvic floor muscles, the abdominal muscles and the gluteal muscles.
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 [273]. Secondary dysmenorrhoea suggests the development of a pathological process, such as endometriosis [272], adenomyosis or pelvic infection, which need to be excluded.

Infection

In pre-menopausal women, 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 [289], as they can cause severe pelvic/vaginal/vulvar pain [290] and are associated with ulcerating lesions and inflammation, which may lead to urinary retention [291]. 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 women's lives [292], with pain more important than physical findings in determining QoL [293]. The precise aetiology is unknown, but an association with infertility is recognised [294]. A diagnosis is usually made when a history of secondary dysmenorrhoea and/or dyspareunia exists [295]. On examination, there is often tenderness in the lateral vaginal fornices, reduced uterine mobility, tenderness in the recto-vaginal septum, and on occasion, adnexal masses. Laparoscopy is the most useful diagnostic tool [296-298]. Adenomyosis is associated with augmented pain during menses [299]. It is diagnosed by an US scan 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 [298]. Female sexual dysfunction is perhaps the commonest presenting problem [301], though increasingly women are reporting other symptoms such as pelvic girdle pain and other genito-pelvic pain of different aetiology [302]. There is often a transient problem with oestrogen deficiency in the post-partum period and during breastfeeding, which can compound this situation. Denervation of the pelvic floor can similarly compound the situation [303].

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 [304]. Prolapse is often a disease of older women, and it is often associated with postmenopausal oestrogen deficiency, which may lead to pain associated with intercourse. Prolapse surgery has entailed the use of non-absorbable mesh (usually in the form of "mesh kits"). Although they may have a role in supporting the vagina, they are also associated with several complications including bladder, bowel and vaginal trauma [305], chronic pain [306] and neuropathy [307]. 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 [308-311].

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. A number of high quality clinical guidelines address this topic [243, 312].

4.5 Summary of evidence and recommendations: diagnostic evaluation

4.5.1 Diagnostic evaluation - general

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

Recommendation	Strength rating
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

Summary of evidence	LE
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 cystoscopic or histologic findings.	2a
Primary bladder pain syndrome Type 3 C 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 EAU 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 men 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 BPS.	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 as a result of injury to one or more of many nerves. The anatomy is complex.	2
There is no single aetiology for the nerve damage and the symptoms and signs may be few or multiple.	1
Investigations are often normal.	2
The peripheral nerve pain syndromes are frequently associated with negative cognitive, behavioural, sexual, or emotional consequences.	1

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
Men who reported having sexual, physical or emotional abuse show a higher rate of reporting symptoms of CPPPS.	2b
Sexual dysfunctions are prevalent in men with PPPS.	2b
In men 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
Women 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 for 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 distress in relation to their pain.	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 it is recommended to actively look for the presence of myofascial trigger points.	Weak

5. MANAGEMENT

The philosophy for the management of chronic pelvic pain is based on a bio-psychosocial model. This is a holistic approach with patients' active involvement. Single interventions rarely work in isolation and need to be considered within a broader personalised management strategy, including self-management. Pharmacological and non-pharmacological interventions should be considered with a clear understanding of the potential outcomes and endpoints. These may well include: psychology, physiotherapy, drugs and more invasive interventions.

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 [313]. 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 [314].

5.1 Conservative management

5.1.1 *Pain education*

It is always valuable to include education about the causes of pain, including eliciting from patients their anxieties about undiscovered pathology and addressing them. Information improves adherence to treatment and underpins self-management, as shown in bladder pain syndrome and in many other painful and non-painful disorders [315].

5.1.2 *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 have been done looking at the effect of physiotherapy in pelvic pain, the treatment of the pelvic floor is only part of the pain management. In a review about physiotherapy in women with pelvic pain, it was concluded that recommendations for physiotherapy should be given with caution [316]. 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 (CBT) [317].

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 musculo-skeletal 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 (RR) 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 [318].

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 [319]. Most studies of dry needling have compared with wet needling. Different SRs 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 [320].

Physiotherapy in PBPS

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 [321]. The role of specific levator ani trigger point injections in women with chronic pelvic pain has been studied [322]. Each trigger point was identified by intravaginal palpation and injected with bupivacaine, lidocaine and triamcinolone. Seventy-two percent of women improved with the first trigger point injection, with 33% being completely pain-free. Efficacy and safety of pelvic floor myofascial physical therapy has been compared with global therapeutic massage in women with PBPS; global response assessment (GRA) 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 women with PBPS [323].

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 [125]. 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 vs. 45% for electrogalvanic stimulation, and 22% for massage. These results were maintained at twelve months with adequate relief after nine sessions of biofeedback in 58% of the whole group (Rome II: “Highly likely” and “Possible Levator Ani Syndrome”), after galvanic stimulation in 27% and massage in 21% of patients. As previously described in dyssynergic defecation, the ability to expel a 50 mL water filled balloon and to relax pelvic floor muscles after biofeedback treatment were predictive of a favourable therapeutic outcome [125]. The pathophysiology of the chronic primary anal pain syndrome is therefore similar to that of dyssynergic defecation, and this favours the role of the pelvic floor muscles in the pathophysiology of both conditions. Other treatment modalities have been less successful.

Treatment of sexual dysfunctions and chronic pelvic pain

Couples often benefit from early referral for relationship and sexual counselling during their treatment course [324]. It needs to be remembered that sexual difficulties will arise as a result of pelvic pain syndromes as well as those disorders potentially being primary. Specific behavioural strategies for women who have urogenital complaints and female sexual dysfunction often include exploring alternatives to sexual intercourse (manual or oral pleasuring), different coital positions (female superior or side lying), and pacing, such as limiting 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 men 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 [324, 325], and increased use of vaginal dilators, fingers or sex toys. Lubricants can also be used and women with signs of vulvovaginal atrophy may benefit from oestrogen cream [326]. Optimising the pelvic floor muscle is indicated when dysfunction is present and will relieve the pain [327-329].

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 [330].

Microwave thermotherapy. In uncontrolled studies significant symptomatic improvement has been reported from heat therapy, for example, transrectal and transurethral thermotherapy [331, 332].

Extracorporeal shockwave therapy. A small sham-controlled double-blind study of four times weekly perineal extracorporeal shockwave therapy (n=30) in men with CPPPS showed significant improvement in pain, QoL, and voiding compared to the control group (n=30), over twelve weeks [333]. Two other randomised shamcontrolled studies, have been published more recently, one comparing ten treatment sessions over two weeks (n=40 vs. n=40) [334], another with four times weekly treatments (n=20 vs. n=20) [335]. Both concluded there was a significant effect in terms of total NIH-CPSI score and pain at twelve weeks. Unfortunately, no long term effects at 24 weeks could be shown in a published follow-up study of the second [336]. 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 [337]. In addition, a recent SR and meta-analysis concluded that extracorporeal shockwave therapy is effective for the improvement of pain and quality of life, but long-term efficacy was non-significant [338]. Recent publications show a potential role for external shock wave lithotripsy applied to the bladder. In a RCT enrolling 54 patients, improvement in the VAS $\geq$ 3 was 57.1% vs. 19.0% (ESWT vs. placebo; P =.011), at 12 weeks post treatment. However, primary endpoint did not reach significance [339].

Acupuncture. In a small three-arm RCT of CPPPS in men, electro-acupuncture was superior to sham treatment and advice and exercise alone [340]. Another RCT comparing acupuncture (n=50) vs. sham-controlled (n=50), once weekly treatment for six weeks showed significant long lasting improvement at 24 weeks in terms of RR and overall symptom scores [341]. Another RCT showed a significant effect for a follow-up of 32 weeks [342]. Two SRs and meta-analyses were published in 2016 analysing seven RCTs on a total of 471 participants comparing acupuncture to sham control or oral medical treatment [343, 344]. Both came to the conclusion 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 recent Cochrane review [337] on non-pharmacological treatment options. However, the durability of this effect is not known.

Posterior tibial nerve stimulation. See section 5.3.2, Neuromodulation.

Transcutaneous electrical nerve stimulation. See section 5.3.2, Neuromodulation.

5.1.3 Psychological therapy

Psychological interventions may be directed at pain itself or at adjustment to pain in terms of function and mood and reduced health-care use, with or without pain reduction. Ideally, treatment follows general principles and practice in the field of chronic pain [345, 346] but these have been neglected in pelvic pain. Two SRs and meta-analyses of the few heterogeneous trials of psychologically based treatment for pelvic pain [347, 348] 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 women with chronic pelvic pain proved superior to manual therapy in reducing those fears and overall pain disability, albeit assessed only by self-report [349]. The importance of multi-disciplinary treatment is emphasised by several reviews [43, 350, 351] of intervention for diverse chronic pains, but standard multi-component psychologically-based programmes for pelvic pains are mostly in the pilot stages [352], with mixed findings so far [353]. For less disabled and distressed patients treatment can be delivered remotely [354].

*5.1.4 **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. Where there is no evidence the reader is directed to the section on analgesics below (Section 5.2.2) where more generic use is discussed. 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 [355]. 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 [356]. Monotherapeutic strategies for the treatment of CPPPS may fail [357], 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.

5.2.1.1 Mechanisms of action

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

5.2.1.2 Comparisons of agents used in pelvic pain syndromes

Primary Prostate Pain Syndrome (PPPS)

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 vs. placebo, but effects were limited to the duration of therapy [358]. In a meta-analysis, two studies of NSAIDs [269, 358] and one with prednisolone [359] 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 glycosaminoglycans, phytotherapy and tanezumab), a significant effect on total NIH-CPSI scores and treatment response rates could be demonstrated. Overall, a moderate treatment effect has been shown for anti-inflammatory drugs, but larger studies are needed for confirmation, and long-term side-effects have to be taken into account.

α-blockers

Positive results from RCTs of α-blockers, i.e. terazosin [360, 361], alfuzosin [362], doxazosin [363, 364], tamsulosin [365, 366], and silodosin [367] have led to widespread use of α-antagonists in the treatment of PPPS in recent years. Whereas one SR and meta-analysis has not reported a relevant effect of α-blockers due to study heterogeneity [368], another network meta-analysis of α-blockers [367] has shown significant improvement in total symptoms, pain, voiding, and QoL scores. In addition, they 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, i.e., clinically perceptive or significant improvement, may be lower than expected from the change in mean symptom scores. Overall, α-blockers seem to have moderate but significant beneficial effects. This probably is not the case for long-standing PPPS patients [369]. Future studies should show if longer duration of therapy or some sort of 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. Unfortunately, culture, leukocyte and antibody status of prostate-specific specimens do not predict antibiotic response in patients with PPS [370], and prostate biopsy culture findings do not differ from those of healthy controls [371]. The only placebo-controlled RCTs of sufficient quality have been done for oral antibiotic treatment with ciprofloxacin (six weeks) [372], levofloxacin (six weeks) [373], and tetracycline hydrochloride (twelve weeks) [374]. The studies have been analysed in meta-analyses [367, 375]. 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 α-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 [375]. 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. 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 [376].

5-α-reductase inhibitors

Although a few small pilot studies with 5-α-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 [377]. In another RCT, finasteride provided better amelioration of symptoms compared to saw palmetto over a one-year period, but lacked a placebo-control arm [378]. 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 [366]. The NIH-CPSI scores decreased significantly in a subgroup of men enrolled in a prostate cancer risk reduction study treated with dutasteride compared to placebo [367]. 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-α-reductase inhibitors cannot be recommended for use in PPPS in general, but symptom scores may be reduced in a restricted group of older men with an elevated PSA [367].

Phytotherapy

Phytotherapy applies scientific research to the practice of herbal medicine. An adequately powered placebo-controlled RCT of a pollen extract (Cernilton) showed clinically significant symptom improvement over a twelve week period in inflammatory PPPS patients (NIH Cat. IIIA) [379]. 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 [380]. In an RCT of patients treated with pollen extract suppositories (n=70) vs. oral ibupofen (n=71) over a period of ten days, the authors could find a clinically significant effect up to six months of follow-up including fewer adverse events in the pollen extract group [381]. A SR and meta-analysis of pollen extract for the treatment of PPPS showed significant improvement in overall QoL [382]. Quercetin, a polyphenolic bioflavonoid with documented antioxidant and anti-inflammatory properties, improved NIH-CPSI scores significantly in a small RCT [383]. In contrast, treatment with saw palmetto, most commonly used for "benign prostatic hyperplasia", did not improve symptoms over a one-year period [378]. In a SR and meta-analysis, patients treated with phytotherapy were found to have significantly lower pain scores than those treated with placebo [367]. 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 [384], 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 [385].

Pentosane polysulphate is a semi-synthetic drug manufactured from beech-wood hemicellulose. One study using oral high-dose (3 x 300 mg/day) demonstrated a significant improvement in clinical global assessment and QoL over placebo in men with PPPS, suggesting a possible common aetiology [386].

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 α-blocker (doxazosin) was effective in treatment-naïve patients, but not superior to an α-blocker alone [364].

Botulinum toxin type A (BTX-A) for the treatment of CPPPS is an off-label use, but a recent SR identified two RCTs and one non-randomised comparative study assessing intraprostatic BTX-A injections (100-200 units) for treatment of PPPS [387]. 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 in two low-power placebo-controlled studies failed to show a benefit [359, 388]. More recently, a placebo-controlled phase IIa study of tanezumab, a humanised monoclonal antibody that specifically inhibits the pain mediating neurotrophin, nerve growth factor, failed to demonstrate significant effect [389] and should only be used in clinical trials.

Allopurinol
There is insufficient evidence for the use of allopurinol in PPPS [390, 391].

Primary Bladder Pain Syndrome (PBPS)

Treatments of significant value for PBPS

Anti-histamines
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 [392] and H2 [393] receptor subtypes, with variable results. A prospective placebo-controlled RCT of hydroxyzine or oral pentosane polysulphate did not show a significant effect [394].

Amitriptyline
Amitriptyline is a tricyclic antidepressant. Several reports have indicated improvement of PBPS symptoms after oral amitriptyline [395]. Amitriptyline has been shown to be beneficial when compared with placebo plus behavioural modification [396]. Drowsiness is a limiting factor with amitriptyline, nortriptyline is sometimes considered instead.

Pentosane polysulphate
Pentosan polysulphate is a semi-synthetic drug manufactured from beech-wood hemicellulose. Subjective improvement of pain, urgency, frequency, but not nocturia, has been reported [397, 398]. Pentosane polysulphate had a more favourable effect in PBPS type 3 C than in non-lesion disease [399]. 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 [400, 401].

Immunosuppressants
Azathioprine treatment has resulted in disappearance of pain and urinary frequency [402]. Initial evaluation of cyclosporin A (CyA) [403] and methotrexate [404] 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 bio-availability 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 [405].

- **Local anaesthetics**

There are sporadic reports of successful treatment of PBPS with intravesical lidocaine [406, 407]. Alkalisation of lidocaine improves its pharmacokinetics [408]. Combination of heparin, lidocaine and sodium bicarbonate gave immediate symptom relief in 94% of patients and sustained relief after two weeks in 80% [409]. Intravesical instillation of alkalised lidocaine or placebo for five consecutive days resulted in significantly sustained symptom relief for up to one month [410].

- **Hyaluronic acid and chondroitin sulphate**

These are described to repair defects in the GAG layer. Despite the fact that 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. A recent RCT seems to reinforce the case for GAG layer replenishment, however it lacks a placebo arm [411]. A meta-analysis confirms usefulness of GAG layer replenishment. However most retrieved studies are non-randomised and with scarce numbers [412].

- **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 [413]. Kuo reported another trial of intravesical heparin for three months in women with frequency-urgency syndrome and a positive potassium test. Symptomatic improvement was reported in 80% of PBPS patients [414]. 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 twelve months [415].

- **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 [400].

Treatments of limited value for PBPS

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 [416].

Prostaglandins

Misoprostol is a prostaglandin that regulates various immunological cascades. After three months of treatment with misoprostol, fourteen out of 25 patients had significantly improved, with twelve showing a sustained response after a further six months [417]. The incidence of adverse drug effects was 64%.

L-Arginine

Oral treatment with the nitric oxide (NO) synthase substrate L-arginine decreases PBPS-related symptoms [418, 419]. Nitric oxide is elevated in patients with PBPS [420]. However, others have not demonstrated symptomatic relief or changes in NO production after treatment [421, 422].

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 [423]. However, an effect on pain has not been reported.

Duloxetine (a serotonin-noradrenaline re-uptake inhibitor antidepressant with a licence for the management of neuropathic pain) did not significantly improve symptoms of PBPS [424]. Administration was safe, but tolerability was poor due to nausea. Based on these preliminary data, duloxetine cannot be recommended for treatment of PBPS.

Primary Scrotal Pain Syndrome (PSPS)

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

In men 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 [192, 425].

For scrotal pain post vasectomy, affected men may find that reversal of vasectomy can cure symptoms especially in those in whom patency is achieved [426]. 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 [427]. The evidence for epididymectomy is poor but if considered, is less likely to provide benefit if the epididymis has a normal sonographic appearance [428].

Chronic gynaecological pain

It is difficult to compare the wide variation of drugs from an efficacy and safety perspective as they have such diverse uses/indications. In those gynaecological patients where chronic pelvic pain is unrelated to any of the well-defined conditions, it is often difficult to determine a therapeutic pathway other than a multi-disciplinary chronic abdomino-pelvic pain management plan. A Cochrane review suggests there may be some evidence (moderate) supporting the use of progestogens [347]. Though efficacious, physicians need to be knowledgeable of progestogenic side effects (e.g., weight gain, bloatedness - the most common adverse effects) which 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, their efficacy remains limited. The quality of evidence is generally low and drawn from single studies [347]. Gonadotropin-releasing hormone on the other hand 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 [429].

Pelvic Floor, Abdominal and Chronic Anal Pain

Botulinum toxin type A (pelvic floor)

Pelvic floor muscle over-activity 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 women with pelvic floor muscle overactivity as defined by a vaginal resting pressure > 40 cm H_2O 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 [430]. A recent SR 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 [387].

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 [431]. Reviews do not support the injection of BTX-A into trigger points [432].

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 thirteen patients with CPPPS, BTX-A was injected into the external urethral sphincter. Subjectively, eleven patients reported a substantial change in pain symptoms, from a score of 7.2 to 1.6 on a VAS [433].

Intermittent chronic primary anal pain syndrome

Due to the short duration of the episodes, medical treatment and prevention is often not feasible. Inhaled β-2 adrenergic agonist salbutamol was effective in an RCT in patients with frequent symptoms and shortened pain duration [434]. Other treatment options are topic diltiazem and BTX-A [435]. 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) in order 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 µg 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 [436]. 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.

Delta-9-tetrahydrocannabinol (THC) shows only equivocal evidence of analgesic effects in chronic primary abdominal pain. In a recently published phase II trial, no difference was found between THC tablet and a placebo tablet in reducing pain outcome in patients with chronic abdominal pain [437].

*5.2.2 **Analgesics***

If the use of simple analgesics fails to provide adequate benefit, then 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 [438], 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 [439]. 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. Unfortunately, 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.

5.2.2.1 Mechanisms of action

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

5.2.2.2 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 [440]. 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 [441]. 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 [442], 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 [443] then the evidence is lacking for NSAIDs despite their common use.

At a practical level, if NSAIDs are considered for use, 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 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 dependance-forming. In the UK, NICE has reviewed the pharmacological management of neuropathic pain [444]. 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 [58].

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 [445], suggesting that they are effective for neuropathic pain. Amitriptyline is the most commonly used at doses from 10-75 mg/day (sometimes rising to 150 mg/day). This is titrated against benefit or side-effects and should be taken at night [444]. Nortriptyline and imipramine are used as alternatives.

Other Antidepressants

Duloxetine is a SNRI antidepressant licensed for use in depression, SUI and neuropathic pain. There is evidence of benefit in diabetic neuropathy and fibromyalgia at a dose of 60 mg/day [446, 447]. 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 looking more particularly at pelvic pain. Individual agents have been systematically reviewed. Their use is suggested in the NICE Neuropathic Pain Guidelines [444].

Carbamazepine has a long history of use in neuropathic pain. Evidence exists for its benefit [448]. Trials trend 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 [449]. A formal assessment of efficacy against benefit and side-effects (both pain and QoL) is required with the patient in order 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 [450, 451]. This demonstrates good evidence for posterpatic neuralgia and diabeltic neuropathy but evidence for other neuropathies is limited. A double-blind RCT looking at CPPPS in women with no obvious pathology demonstrated no benefits but higher levels of side effect [451].

Pregabalin is a commonly used neuromodulator with good evidence of efficacy in some neuropathic conditions [452]. The dose for benefit is in the range of 300-600 mg/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 whom 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 multi-dimensional management plan.

Opioids
Over recent years opioids have been used extensively for managing 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 [453]. 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 effect [454]. There is clear evidence of harm including effects on the endocrine and immune systems as well as a growing understanding of opioid-induced hyperalgesia [455]. 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 [456].

Opioids should only be used in conjunction with a management plan with consultation between clinicians experienced in their use. It is suggested that a pain management unit should be involved along with the patient and their primary care physician. 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 [455].

The risk of harm increases substantially at doses above 120 mg/day morphine equivalence [455] and guidance suggests regular (at least annual) review for patients with over 50 mg/day morphine equivalence and pain specialist involvement above 90 mg/day morphine equivalence [457].

There are well-established guidelines for the use of opioids in pain management as well as considering the potential risks [455, 457]. Opioid reduction and optimisation should be undertaken where opioids are not providing clear measurable benefit. There is also information available online for patients [455]. Opioids Aware is a web-based resource 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. https://fpm.ac.uk/opioids-aware.

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 [458-460] 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 [461]. 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 these interventions for chronic non-malignant pain [462].

Pudendal Neuralgia

The role of injections may be divided into two. First, an injection of local anaesthetic with or without steroids at the sight of nerve injury may produce a therapeutic action [463, 464]. 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 [260, 465-472].

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. Currently, fluoroscopy is probably the imaging technique most frequently used because it is readily available to most anaesthetists that perform the block. Currently, infiltration of the pudendal nerve within Alcock's canal is primarily undertaken with the use of CT. As well as injecting around the pudendal nerve, specific blocks of other nerves arising from the pelvis may be performed. Pulsed radio frequency stimulation has been suggested as a treatment [473]. 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 [474].

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 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 [475]. Its role in overactive bladder (OAB) and faecal incontinence is more robust but is limited for pain. Two SRs have evaluated neuromodulation techniques for CPPS [476, 477]. Both studies concluded that neuromodulation may be effective in reducing pain and improving QoL in patients with CPPS; 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 SR identified twelve studies of TENS in chronic pelvic pain conditions including four RCTs [476]. All RCTs demonstrated a significant reduction in pain following twelve 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 with regard to 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 dysmenorrhea 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 men with CPPPS and another demonstrating a prolonged significant improvement in women 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 use in an outpatient setting. Two SRs have shown that PTNS is effective in reducing pain in patients with CPPPS [476, 477]. Three RCTs identified 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 SR 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 demonstrated in two of 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. Re-operation 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 SR review in 2018 identified fourteen 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/BPS 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. This is mainly supported by level 2b studies. Randomised prospective studies are warranted to compare SNS vs. other modalities for chronic pelvic pain treatment. Further studies are needed to compare antegrade vs. retrograde approaches [478].

Other neuromodulation techniques

A variety of other techniques of neuromodulation for patients with CPPPS were identified by SRs [476, 479]. These techniques include intravaginal electrical stimulation for women 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 men 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. Neuromodulaution in combination with hormonal treatment in deep endometriosis may have some benefit [480].

*5.3.3 **Surgery***

Primary Bladder Pain Syndrome (PBPS)

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.

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 [481]. Treatment with hydrodistension and hydrodistension plus intravesical BTX-A has been compared [482]. 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 [483]. Over 50% reported continued benefit nine months after the first treatment. When re-treatment was needed, similar results were obtained. Adverse effects of BTX-A administration for IC/PBPS were significantly less than for OAB syndrome, namely in increased post-void residual volumes and decreased voiding efficiency [484]. Recent RCTs have reported benefits and long efficacy of BTX-A administration [485-488], but a summary estimate for overall change in pain following BTX-A injections was not possible in a recent SR [387]. Conflicting data on results hinders issuance of a clear guideline for the use of Botox in PBPS phenetypes. Despite this, the American Urological Association (AUA) guidelines panel has upgraded BTX-A treatment from fifth to a fourth line treatment [489].

Results of treatment with intravesical plasma rich (PRP) injections are also being explored. A recent prospective trial, showed that patients with GRA (global response assessment) ≥ 2, had success rates at one month and at three months after the 4th PRP injection, of 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. Since the 1970s, resection and fulguration have been reported to achieve symptom relief, often for more than three years [491-493]. Prolonged amelioration of pain and urgency has been described for transurethral laser ablation as well [494].

Open Surgery for PBPS

Primary bladder pain syndrome is benign and does not shorten life, thus operative procedures rank last in the therapeutic algorithm. There is no evidence that it relieves pain. Surgery for PBPS is only appropriate as a last resort for patients with refractory disease. Major surgery should be preceded by thorough pre-operative evaluation, with an emphasis on determining the relevant disease location and subtype. If surgery is considered, the panel's advice is to refer the patient to a specialist centre experienced in managing CPPPS with a multi-disciplinary team approach.

Four major techniques are common:

1. Urinary diversion without cystectomy is performed to minimise the duration and complexity of surgery, but complications related to the retained bladder commonly occur. Reports that un-resected PBPS bladders cease to induce symptoms after loss of contact with urine are scarce [103, 495].
2. Supratrigonal cystectomy with bladder augmentation represents the most favoured continence-preserving surgical technique particularly in younger patients [496]. Various intestinal segments have been used [497-499]. After orthotopic bladder augmentation, bladder emptying may be incomplete so intermittent self-catheterisation may be required. A study on female sexuality after cystectomy and orthotopic ileal neobladder showed pain relief in all patients and improvement in sexual function items in women who remained sexually active [500]. Pregnancies with subsequent lower-segment Caesarean section have been reported after ileocystoplasty [501].
3. Subtrigonal or simple cystectomy refers to removal of the entire bladder at the level of the bladder neck. This approach has the benefit of removing the trigone as a possible disease site, but at the cost of requiring ureteric re-implantation. Trigonal disease is reported in 50% of patients and surgical failure has been blamed on the trigone being left in place [502], especially in patients with non-lesion type disease [503, 504]. However, in a previous study all patients were rendered symptom-free by supratrigonal resection compared to 82% of those undergoing subtrigonal cystectomy. Voiding dysfunction is most likely to occur following trigonal resection and patients considering augmentation and especially substitution procedures must be capable of accepting, performing and tolerating self-catheterisation [505].
4. Cystectomy with formation of an ileal conduit 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 [506].

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) vs. 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 auto-immunity to the prostate gland. They reported an improvement in total NIH-CPSI score and subdomain scores at twelve 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 have to 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 hemorrhoidopexy 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 health care costs as compared to laparoscopy alone [511].

Primary Urethral Pain Syndrome

There is no specific treatment that can be advised. Management should be multi-disciplinary and multi-modal [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]. The majority of publications on treatment of primary urethral pain syndrome have come from psychologists [167, 514].

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 [514].

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 vs. sham surgery [272, 515]. Increasingly treatment algorithms are being developed using a multi-disciplinary approach, although none have thus far been proven clinically [516]. 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 the approach of choice probably depends upon the nature of the 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 [198, 260, 517-520]. Currently, there has been only one prospective RCT (transgluteal approach) [519]. This study 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, providing the diagnosis was clear-cut, most patients were grateful to have undergone surgery but many still have symptoms that need management.

Chronic Pelvic Pain and Prolapse/Incontinence Mesh

Removing an existing mesh is a complex procedure [521]. Each patient is approached on an individual basis depending on the type of mesh and extent of complications [522]. The complexity of surgery often involves removal of dense scar tissue, reformation of inflamed vaginal skin and surgical reconstruction of the urethra and bladder [523]. Such surgery requires specialist skills, best provided within a multi-disciplinary tertiary setting. Possible complications as a result of this surgical removal include bleeding, infection, damage to surrounding organs as well as LUTS, persistent chronic pain and recurrent SUI, which occurs after mesh removal [524].

Removal of mesh, whilst complex, does have beneficial outcomes generally, which are also durable particularly for chronic pain [525]. However, the long-term consequences after the mesh is removed still can include, not only chronic persistent pain but also autoimmune responses and complex neuropathies affecting the pelvis and lower limbs [526, 527]. Some of these can be treated effectively using a multi-disciplinary pain medicine approach [528]. 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. They include behavioural change, physiotherapy (for SUI and Grade I-II uterovaginal prolapse) or traditional surgical techniques. Studies have shown that over 70% who committed to physiotherapy for SUI often did not need any further intervention [529]. Many clinicians are reverting to conservative measures first, before re-considering surgery. Clinicians are also now retraining in traditional continence surgical techniques, which 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.

5.4 Summary of evidence and recommendations: management

5.4.1 Management of primary prostate pain syndrome

Summary of evidence	LE
Phenotypically directed treatment may improve treatment success.	3
α-blockers have moderate treatment effect regarding total pain, voiding, and QoL scores in PPPS.	1a
Antimicrobial therapy has a moderate effect on total pain, voiding, and QoL scores in PPPS.	1a
Non-steriodal 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

Recommendations	Strength rating
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 (NSAIDs) in PPPS, but long-term side-effects have to be considered.	Weak

5.4.2 Management of primary bladder pain syndrome

Summary of evidence	LE
There is insufficient data for the long-term use of corticosteroids.	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 BCG is not effective in PBPS.	1b
Transurethral resection (coagulation and laser) may be effective in PBPS type 3 C.	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 multi-disciplinary assessment including pain management.	Strong
Offer transurethral resection (or coagulation or laser) of bladder lesions, but in PBPS type 3 C 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 (CBT or supportive psychotherapy) can improve pain and 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 using 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 multi-disciplinary approach to pain management in persistent disease states.	Strong
All patients who have developed complications after mesh insertion should be referred to a multi-disciplinary 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-galvanic 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
Neuropathic pain guidelines are well-established. Use standard approaches to management of neuropathic pain.	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 his/her 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 multi-disciplinary 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
Where there is a history or suspicion of drug abuse, involve a psychiatrist or psychologist with an interest in pain management and drug addiction.	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 some time with the caregiver who understands the nature of their pain. First evaluation should take place after about six weeks to see if the treatment has been successful or not. When necessary adaptations are made and a next evaluation is planned.

6.1.1 *Treatment has not been effective*

6.1.1.1 *Alternative treatment*

In cases where the treatment initiated did not have enough effect, an alternative approach is advised. The first thing to do is a thorough evaluation of the patients' or care providers' adherence to the treatment that was initiated. Ask the patient if they have 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 thing to do is to read the reports of other caregivers, for example, the physiotherapist and the 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 had been terminated by the patient, ask the patient why they made that decision. Check if the patient has understood the idea behind the therapy that had been prematurely stopped.

6.1.1.2 *Referral to next envelope of care*

If patients and doctors conclude that none of the therapies given showed enough effect, then referral to a next envelope of care is advised. Unfortunately, the terminology used to describe the nature and specialisation level of centres providing 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 is working with a multi-disciplinary team and nationally recognised as specialised in pelvic pain. Such a centre will re-evaluate what has been done and when available, provide specialised care.

6.1.1.3 *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 that a caregiver is available for supporting the self-management strategies. Together with this caregiver, the patient can optimise and use the management strategies.

*6.1.2 **Treatment has been effective***

In cases where treatment has been effective, the caregiver may pay attention 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 he/she has learned during the former treatment. By doing so they will have the best chance of preventing the re-development of pelvic pain syndromes.

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8. CONFLICT OF INTEREST

All members of the EAU Chronic Pelvic Pain Guidelines working panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of conflict of interest. This information is publically accessible through the European Association of Urology website https://uroweb.org/guidelines/.

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